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ABSTRACT BOOK

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EPNS23-2946 Oral
Neurogenetic Disorders

Midbrain Gene Therapy for AADC Deficiency

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Objective: Aromatic L-amino acid decarboxylase (AADC) deficiency is a neurodevelopmental disorder characterized by congenital deficiency of dopamine and serotonin. It presents in infancy with hypotonia, hypokinesia, oculogyric crises (OGC), dystonia, autonomic dysfunction, and global developmental delay. Here we describe interim findings from a Phase 1/2 dose escalation trial to evaluate the tolerability of MR-guided delivery of adeno-associated virus serotype 2 (AAV2)-hAADC to the bilateral midbrain in children and young adults with AADC deficiency.

Methods: Twenty-eight individuals (15 female, 13 male; median age 8.0 years, range 4-27 years) received AAV2-AADC (dose 4.2 x 1011-1.5 x 1012 vector genomes(vg)) delivered in a single infusion of up to 300 microliters per hemisphere, targeting the substantia nigra pars compacta and ventral tegmental area. Changes in symptoms and motor function were assessed by caregiver log, neurologic examination and systematic review of home videos for attainment of motor milestones. Changes in dopamine metabolism were assessed by analysis of CSF homovanillic acid (HVA).

Results: Results were analyzed for 17 subjects who were followed for at least 12 months (range: 12-45 months). OGC improved in all subjects and resolved completely in 14/17 (82%) after gene delivery. All subjects had severe motor function impairment at baseline, with inability to sit without support. Motor function improvement was observed across the age spectrum. By 12 months post-surgery, head control was attained by 16/17 (94%) of subjects, and independent sitting by 80% (4/5) under age 7 years and 42% (5/12) age 7 years or older at time of surgery. Two subjects (baseline ages 4.8, 4.9 years) walked independently by 24-36 months. All subjects experienced improvements in mood, sleep, and feeding tolerance. CSF HVA increased from <20% of the lower limit of normal at baseline, to 24-100% at 6-12 months post-gene transfer (median increase 87 nmol/L, range 30-190), consistent with increased brain dopamine synthesis. All subjects tolerated the surgical procedure well. Post-treatment dyskinesia was experienced by all subjects, peaking between 6 and 12 weeks after surgery and improving over 6-12 months.

Conclusions: Midbrain AAV2-AADC gene delivery has now been performed in a total of 35 individuals. The procedure is safe and produces consistent and sustained improvements for up to 5 years in oculogyric crises, mood, sleep, and motor function in patients with AADC deficiency.

Keywords:
gene therapy, neurotransmitter disease, parkinsonism

EPNS23-2620 Oral
Movement Disorders

N-acetyl-L-leucine Improves Symptoms and Functioning in Niemann-Pick disease type C (NPC) and GM2 Gangliosidosis (Tay-Sachs & Sandhoff): Results from Two Parallel, Multi-National, Rater-Blinded Clinical Trials

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Objective: Niemann-Pick disease type C (NPC) and GM2 Gangliosidoses (Tay-Sachs and Sandhoff diseases) are rare, neurogenerative, lysosomal storage disorders with no or limited available treatments. The modified aminoacid N-acetyl-leucine has been associated with positive symptomatic and neuroprotective effects in animal and cellular models of NPC and GM2 gangliosidosis, as well as in observational case series.
The presented clinical trials aimed to investigate the safety and efficacy of N-acetyl-L-leucine (NALL) in the symptoms of patients with GM2 gangliosidosis or NPC from 6 years of age.

Methods: We conducted two multicenter Phase IIb studies (IB1001-201 and IB1001-202). Patients with a genetically confirmed diagnosis of NPC or GM2 gangliosidosis were evaluated before treatment initiation, after 6 weeks of treatment with oral NALL (IB-1001, 4 g/day in patients older than 13 years, weight-adjusted dosing for patients 6-12 years), as well as after a wash-out period of 6 weeks after treatment. We assessed changes on the Clinical Impression of Change in Severity (CI-CS) scale by blinded raters, who compared randomized pairs of videos from each patient, while they were performing a predetermined ataxia screening test. The tests were either the 8-Meter Walk Test (8MWT) or the 9-Hole Peg Test (9HPT). SCAFI and SARA scores, as well as quality of life measurement scales, were also assessed.

Results: 33 NPC subjects aged 7 to 64 years, and 30 GM2 subjects aged 6 to 55 were recruited, respectively. NPC patients showed a statistically significant improvement in CI-CS ($p=0.029$), in SARA ($p<0.001$) as well as the three SCAFI dimensions (9HPT $p=0.084$, 8MWT $p=0.065$, PATA $p=0.076$). Patients with GM2 gangliosidosis showed a statistically significant improvement in CI-CS ($p=0.044$), in SARA ($p<0.001$), as well as in the PATA test (PATA $p<0.001$). We did not detect any clinically significant side effects.

Conclusions: NALL rapidly improved symptoms, functioning and quality of life in 6-weeks in patients with NPC and GM2 gangliosidosis. The effect was reversed after a 6-week, wash-out period. High consistency and statistical significance between the primary and secondary endpoints demonstrate a clinically meaningful improvement with NALL. NALL was well-tolerated, and no drug-related serious adverse events were reported, demonstrating a favourable risk/benefit profile.

Keywords:
NPC, GM2 gangliosidosis, Tay-Sachs, Sandhoff, ataxia, acetyl-leucine, NALL

EPNS23-2203 Oral
Movement Disorders

Pediatric de novo movement disorders in the context of SARS-CoV-2

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Objective: In the third year of the COVID-19 pandemic, mortality rates decreased, but the risk of neuropsychiatric disorders remained the same. The prevalence of COVID-19-associated neuropsychiatric impairments, including movement disorders, was estimated to be 3.8% of pediatric cases. Additionally, a rising incidence of functional movement disorders during the COVID-19 pandemic was recently compared to the "Charcot's Era at the Salpêtrière". We now aim to provide information on pediatric COVID-19-associated nonfunctional de novo movement disorders beyond epidemiological data.

Methods: In this study, we first report on a 10-year-old girl with striking hemichorea after SARS-CoV-2 infection. We performed immunostainings on unfixed murine brain with patient CSF to identify anti-neuronal/-glial antibodies. We further performed a scoping review in MEDLINE.

Results: We identified intrathecal autoantibodies in the patient's CSF binding unknown antigens in murine basal ganglia. The child received immunosuppressive therapy and recovered completely. In a scoping review, we identified further 32 children with de novo movement disorders after COVID-19. Whereas in a minority of cases, movement disorders were a symptom of known clinical entities (e.g. ADEM or Sydenham's chorea), in most children, the etiology was suspected to be of autoimmune origin without further assigned diagnosis. Two neurologic systems seemed to be targets of autoimmunity: (i) the cerebellum and (ii) the basal ganglia. (i) Children with COVID-19-ataxia (79 %) presented with different characteristics (older age, less favorable outcome) compared to the well-known condition of postinfectious acute cerebellar ataxia/cerebellitis. (ii) Hyperkinetic movement disorders (21 %) were choreiform in most cases. Besides 14 % of spontaneous recovery, immunosuppressive therapy was necessary in most children (79 %). 57 % of patients fully recovered after therapy and in approximately one third a partial recovery was described.

Conclusions: Infection with SARS-CoV-2 can trigger de novo movement disorders in children and adolescents, likely through post-viral humoral autoimmunity. Most children presented with signs of COVID-19-ataxia and fewer with -chorea. Our data suggest that patients benefit from immunosuppression, especially steroids. Despite treatment, one third of patients recovered only partially, which makes up an increasing cohort with neurological sequelae to be dealt with in the future.

Keywords:
movement disorder, COVID-19, SARS-CoV-2, ataxia, chorea

EPNS23-2162 Oral or e-Poster
Movement Disorders

Plasma Neurofilament Light Chain Levels Are A Potential Biomarker In AP-4-Associated Hereditary Spastic Paraplegia And Differentially Elevated Across Phenotypic Clusters

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Objective: To examine neurofilament light (NfL) and glial fibrillary acidic protein (GFAP) as potential plasma biomarkers in patients with AP4-associated hereditary spastic paraplegia (AP4-HSP) and to investigate whether these were correlated with disease severity.

Methods: Plasma neurofilament light (pNfL) and glial fibrillary acidic protein (pGFAP) were measured in plasma samples of 46 patients and 46 age- and sex-matched controls using ultra-sensitive Simoa assays. Patients were systematically assessed using the AP-4-HSP natural history study questionnaire, the Spastic Paraplegia Rating Scale (SPRS) and the SPATAX Disability score (SPATAX). Classification performance based on pNfL was assessed through receiver operator characteristics (ROC) analysis and area under the curve (AUC) calculation. Spearman's rank correlation coefficient and multivariate linear regression analyses adjusting for age and sex were used to evaluate association between pNfL and functional scores or dichotomous clinical findings. Unsupervised clustering based on clinical data was performed using Gower's distance and the partitioning around medoids (PAM) algorithm.

Results: While pGFAP levels did not significantly differ in patients and controls ($p = 0.55$), pNfL was significantly increased in patients and showed promising performance as a disease marker, allowing to differentiate between patients and controls ($p = 3.0e-10$, AUC = 0.87). No correlation with established scores for disease severity and functioning were observed, however, pNfL levels were significantly associated with three clinical findings ('unsupported walking not achieved' [$p = 0.009$], 'generalized-onset seizures' [$p = 0.024$] and 'history of status epilepticus' [$p = 0.036$]). Phenotypic cluster analysis revealed a patient subgroup with severe generalized-onset seizures and neurodevelopmental stagnation, who had significantly higher pNfL levels compared to other patients ($p = 2.5e-6$).

Conclusions: The present study identifies pNfL as a promising potential biomarker for patients with AP4-HSP, thereby providing the basis for future longitudinal studies and increasing clinical trial readiness. The study also highlights the importance of comprehensive phenotyping for the evaluation of biomarker-symptom associations, in particular for disorders with marked phenotypic pleiotropy, such as hereditary spastic paraplegia.

Keywords:
hereditary spastic paraplegia, AP-4, biomarker, neurofilament light, plasma, phenotypic clustering

EPNS23-2148 Oral or e-Poster
Movement Disorders

Eladocagene exuparvovec gene therapy improves motor development in patients with aromatic L-amino acid decarboxylase deficiency

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Objective: Aromatic L-amino acid decarboxylase (AADC) deficiency is caused by mutations in the dopa decarboxylase gene leading to reduced AADC enzyme activity; it is characterized by motor impairments and inability to attain developmental milestones. Eladocagene exuparvovec is a recombinant adeno-associated viral vector serotype 2 carrying the coding sequence for human AADC deficiency. Its efficacy was investigated in 3 studies (AADC-CU/16.01 [n=8], AADC-010 [n=10], and AADC-011 [n=12]) in patients aged 18-102 months.

Methods: Eladocagene exuparvovec was infused bilaterally in the putamina of 30 children with AADC deficiency. Data were extracted on July 15, 2022. Patients were followed for up to 132 months and assessed for motor milestone attainment using the Peabody Developmental Motor Scale, 2nd edition (PDMS-2). Specific motor skill items of the PDMS-2 were used to assess key motor milestones including head control (partial or full), sitting (supported or independently), standing (with/away from support;), and walking (with/without assistance; up stairs; taped line). Motor milestones and development were measured every 3 months for 1 year following gene therapy, then every 6 months for up to 5 years and yearly after 5 years.

Results: At baseline, no patients had mastered head control or more advanced milestones. At year 1 of follow-up, patients were gaining the following skills (n): partial head control (26), full head control (15), sitting unassisted (7), and supported standing (2). Progression of development was noted at years 5 and 10. By year 5 of follow-up, more advanced milestones were developing (n): full head control (24), sitting unassisted (21), assisted walking (5), walking to toy (4), or walking up stairs (3). These abilities were maintained for as long as 11 years after gene therapy.

Conclusions: The data indicate that eladocagene exuparvovec can provide a durable, positive impact on motor development in patients with AADC deficiency.

Keywords:
Rare disease, AADC deficiency, movement disorder

EPNS23-2568 Oral or e-Poster
Movement Disorders

SGCE-Myoclonus dystonia diagnostic criteria: the pediatric gap in a childhood onset condition

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Objective: Objectives: Myoclonus dystonia (MD) is a childhood onset movement disorder mostly caused by a genetic defect in SGCE. Current diagnostic criteria are established according to clinical data of adult SGCE-MD patients. As a result, these criteria are difficult to apply in early stages of the disease. The aim of this study is to propose diagnostic criteria for SGCE-MD suitable also for children.

Methods: Methods: A cross sectional study in a large SGCE-MD pediatric cohort of forty-eight patients (15.2±12 years) with childhood-onset (2.8±1.8 years) to investigate the presence of current diagnostic criteria.

Results: Results: Four main clinical signs were identified in this study in most of the patients: Action myoclonus in upper limbs or neck 70% (27/41 patients), action specific dystonia during gait 67% (20/30 patients) or during writing 83% (35/42 patients), normal neurodevelopment 94% (45/48) and onset of symptoms in the first decade 100% (48/48). A positive family history was present in more than a half of the patients 66% (32/48 patients). No other motor disturbances in addition to myoclonus and/or dystonia were observed and no brain lesions on MRI related to clinical symptoms were identified in any patient (48/48). In the whole group, 22 patient accomplished 5/5 criteria, 19 patients only 4/5 and 5 patients 3/5.

Conclusions: Conclusions: According to our results, we propose the following signs to suspect a SGCE-MD with a high probability: (1) Action myoclonus in upper limbs or neck; (2) Action specific dystonia when walking, running or writing; (3) Normal neurodevelopment; (4) Onset of symptoms in the first decade; (5) A positive family history. Exclusion criteria proposed are: (1) Other motor disturbances in addition to myoclonus and/or dystonia were observed; (2) Lesions related to clinical symptoms in brain MRI were identified in any patient. Other criteria proposed in adulthood, like alcohol responsiveness or spontaneous remission of limb dystonia during adolescence, should not be applied to children. A limitation of this study is the lack of data of psychiatric signs, which are known to be highly comorbid signs in this disease. According to proposed criteria, fulfilling all these signs has only 48% (22/46) of sensitivity. Sensitivity rises at 89% (41/46) if at least four out of five criteria are identified. The rest of the patients fulfilled at least three out of five clinical criteria. Future studies in a SGCE mutation-negative MD group are needed to evaluate specificity.

Keywords:
Myoclonus-dystonia; diagnosis; action dystonia; childhood-onset dystonia

EPNS23-2212 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

Genetic variants in the patients with developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep

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Objective: Developmental epileptic encephalopathy with spike-and-wave activation in sleep (DEE-SWAS) and epileptic encephalopathy with spike-and-wave activation in sleep (EE-SWAS) are characterized by cognitive, language, behavioral, and motor regression. The duration and etiology are the most important predictors of cognitive outcome. Genetic etiology detection vary between 6-23% in DEE/EE-SWAS cohorts and highly heterogeneous; microdeletion/duplication syndromes and single gene defects- most commonly GRIN2A followed by potassium channel defects. Hence we aimed to share our patients' known and newly diagnosed genetic variations.

Methods: Genomic DNA was isolated from peripheral blood using the QIAamp DNA Blood Mini QIAcube Kit (Qiagen, Hilden, Germany) as per the manufacturer's instructions. All coding regions in the human genome were sequenced to 150 bp at both ends (pair-end) on the Illumina NovaSeq Platform using the Agilent SureSelect V5 kit (Agilent, Santa Clara, CA, USA). The raw data analyzed with the Qiagen Clinical Insight data analysis platform. Variant classification was done according to the guidelines of the American College of Medical Genetics and Genomics.

Results: This retrospective study included 28 patients (18 boys, 10 girls) aged between 5.8-16.5 with a mean of 11 years. The age of onset of epilepsy ranged from 8 months to 8 years (mean:4.9 years). Clinically absence, focal tonic or clonic, generalized tonic clonic, hypomotor,atonic and non convulsive status were seen in decreasing order. Spike wave index was >85% except two patients. Dysmorphic findings, autism spectrum disorder were accompanied in four patients and attension deficit hyperactivity disorder in three. In this cohort, genetic alterations were found in 7 of 28 cases (25%). Eight different variants were detected in 7 genes (SCN8A, ADGRV1, SCN1A, DLG4, SLC12A5, GRIN2A, TET3). Two of these variants were pathogenic, 4 were likely pathogenic and 2 were variants of uncertain significance (VUS). 37.5% of the variations (ADGRV1, DLG4, SLC12A5) were novel.

Conclusions: Pathogenic/likely pathogenic variations were detected in DLG4, TET3, SLC12A5 and SCN8A genes that were not previously reported. Half of the novel genetic defects detected in this study are related to ion channels/transporters, which are well known to be associated with the epilepsy phenotype. In this study, the relationship of SCN8A, DLG4, SLC12A5 and TET3 genes with DEE/EE-SWAS was revealed for the first time.

Keywords:
epileptic encephalopathy with spike-and-wave activation in sleep, DLG4,GRIN2A, SCN8A, SLC12A5, TET3

EPNS23-2917 Oral
Epilepsy: Medical & Surgical Treatment

Challenges in conducting an academic international European multicentre trial: What we can learn from the RESCUE ESES trial

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Objective: Randomised controlled trials (RCTs) are the "gold-standard" for safety and effectiveness assessments and international trials have the theoretical potential of enrolment of many patients within a relatively short period. RCTs in rare diseases are particularly challenging. Epileptic encephalopathy with spike wave activation in sleep (EE-SWAS) is a rare childhood epilepsy syndrome which can lead to devastating developmental deficits if untreated. Evidence on the most effective treatment in EE-SWAS is lacking and a group of European experts designed a multicentre trial to reflect existing medical practices. We present the challenges conducting an academic pragmatic international multicentre trial.

Methods: A European multicentre randomised controlled trial in children with EE-SWAS (RESCUE ESES) was performed between 2013 and 2022 and aimed to compare the effects of treatment with either corticosteroids or clobazam in 130 children with EE-SWAS aged 2 to 12 years.

Results: Trial initiation was delayed at many sites by the need to address heterogeneous procedures and requests by ethical committees and competent authorities working under different regulations and cultural conditions. Approval of the study protocol and documents, and the clinical trial agreements between the sponsor and the participating centres, was very time consuming. Although for routine clinical care both study drugs are readily available, these drugs had to be imported and labelled specifically for the trial at several study sites. Initially, principal investigators of 21 centres intended to participate. Complying with regulatory requirements sometimes proved to be practically unfeasible and 5 sites were never initiated. Although pre-trial feasibility survey results suggested that more than sufficient patients would meet inclusion criteria, actual recruitment was hampered for many reasons, including parental or doctor's treatment preferences. Eventually only seven sites enrolled patients. Despite repeatedly extending the study, enrolment was stopped prematurely for feasibility reasons after inclusion of only 45 patients.

Conclusions: Investigator-driven RCTs in rare diseases are highly challenging. The lessons learned in this trial are of importance to all centres taking part in international multicentre studies. We strongly advocate to simplify and harmonise regulations, and centralise regulatory assessment of investigator-driven trials. This would encourage much needed comparative effectiveness research in rare diseases.

Keywords:
RCT, international, European, trial, EE-SWAS, ESES, treatment, methodology

EPNS23-2255 Oral

Epilepsy: Medical & Surgical Treatment

30 years experience of stiripentol shows efficacy and safety in Dravet patients under 2 years of age

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Objective: To evaluate the efficacy and safety of stiripentol (STP) when initiated below 2 years of age in patients with Dravet syndrome (DS), based on a real world experience of 30 years (y) in France.

Methods: Four cohorts French databases were retrospectively included: French Reference center for Rare Epilepsies cohorts (CREER-1 1991-2004 and CREER-2 2005-2021), STP temporary authorization for use (TAU) (2003-2007), and STP post-marketing survey (PMS) (2007-2012). We extracted the data on tonic-clonic seizures (TCS) frequency and duration (available in CREER-1 and CREER-2), adverse events (AE) and antiseizure medications at three steps: before STP initiation (3 month-baseline), at short-term (< 6 months on STP) and long-term (last visit on STP before 7y).

Results: Overall population comprised 131 patients. Stiripentol was initiated at a median (med) age of 13m, at a dose ranging from 35mg/kg/day to 74mg/kg/day (med=50mg/kg/day), in adjunction to valproate (med=24mg/kg/day) and clobazam (med=0.5mg/kg/day) in 93% of cases. At short-term (med age=16m) TCS frequency had significantly decreased (p< 0.01), both for prolonged TCS (5-30min) and status epilepticus (>30min), with respectively 55%;61% responders and 39%;55% seizure free. At long-term (med age=41m) long-lasting TCS continued to decline (p=0.03 vs short-term, down to 67%;71% responders and 62%;67% seizure free). Hospitalizations dropped from 91% to 43% and 12% at short- and long-term. Stiripentol did not avoid the natural emergence of short TCS (<5min) at long-term; additional therapies (mostly topiramate) did not stop them neither. Three patients (2%) died from SUDEP. Three patients discontinued stiripentol for adverse events (AE) while 55% reported at least one AE, mostly loss of appetite/weight (21%), sleep disorders (11%), somnolence (11%), agitation/irritability (7%), and hypotonia (5%). Respectively 5 and 4 patients had asymptomatic neutropenia and thrombopenia. Noteworthy, stiripentol use significantly improved since the 2000s (CREER-2 vs CREER-1): earlier initiation, lower stiripentol doses, better safety with maintained efficiency.

Conclusions: Initiating stiripentol in infants with DS is safe and beneficial, avoiding recurrent status epilepticus, long-lasting seizures and hospitalizations in the first years where these events are highly frequent with a negative impact on patients, families and health economy.

Keywords:

dravet ; syndrome ; stiripentol ; epilepsy ; seizure ; real world ; early ; treatment ; below 2 ; tonic ; clonic ; rare disease ; neuropediatry ; neurology ; pediatry ; drug resistent ;

EPNS23-2957 Oral
Epilepsy: Diagnosis and Investigations

Diagnostic and prognostic significance of serum interleukins in Electrical Status Epilepticus in Sleep (ESES) syndrome

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Objective: To study serum interleukin-6(IL-6), interleukin-8(IL-8) and interleukin-10(IL-10) levels in Electrical status epilepticus in sleep (ESES)syndrome, drug refractory epilepsy (DRE) and well controlled epilepsy (WCE). To analyze the prognostic ability of interleukins in ESES.

Methods: Children (2-12 years) with immunotherapy naïve ESES (spike-wave index(SWI) in sleep more than 50%) were enrolled. Age matched children with DRE (resistant to two antiseizure drugs with preserved cognition and behavior) and WCE (seizure free for >1 year with preserved cognition & behavior). Participants with recent febrile illness (within one week of enrollment were excluded. Valid psychometric tools were used to asses cognition and behavior. Serum Il-6, Il-8 and IL-10 levels were compared between the groups using Kruskal Wallis test; multiple comparison were performed by Dunn's test with Bonferroni correction. Children with ESES were initiated on immunotherapy with five-day intravenous methylprednisolone pulse followed by oral steroids 2mg/kg for 6 weeks and tapering over next 6 weeks. Outcome in ESES group was assessed six-months post therapy in form of change in seizure frequency, SQ/IQ and behavioral scores. Electroclinical responders were defined as seizure reduction by 50% (when active seizures present) with mean change in SQ by 5 points with improvement in atleast one domain of childhood behavior checklist by 5 points alongwith a 25% reduction in SWI on sleep EEG. Mean change in serum Interleukin levels one month from baseline was compared between responders and non responders.

Results: Twenty children with ESES, 18 with DRE and 18 with WCE were enrolled. Age and distribution of structural and non structural etiology was evenly distributed across groups. Serum IL-6(pg/ml){(ESES: 3.775(IQR 2.205, 11.28); DRE: 3.01 (IQR 2.04, 4.56); WCE: 1.655 (IQR 1.27, 2.29), p=0.0065} and IL-8(pg/ml) {(ESES: 103.2(IQR 34.01, 200.82); DRE: 19.595(IQR 16.54, 39.7); WCE: 18.97 (IQR 16.54, 21.91) p =0.0002} was significantly different between the three groups. In ESES group 12/20(60%) showed electroclinical response to steroids. Responders had a significant reduction in IL6 levels(pg/ml){4.045(IQR 2.605, 18.96) to 1.13 (IQR 054, 1.74)} compared to non responders {3.12 (IQR 1.655, 5.27) to 4.37 (IQR 2.83, 9.855)} (p =0.0069).

Conclusions: Proinflammatory cytokines (IL-6 and IL-8) are significantly elevated in ESES compared to DRE and WCE. Serum IL-6 reduces significantly in children responding to steroid therapy.

Keywords:
ESES, drug refractory epilepsy, proinflammatory cytokines, interleukin-6, steroid therapy

EPNS23-2451 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

Effect of ganaxolone on behaviours in children with the CDKL5 Deficiency Disorder

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Objective: CDKL5 deficiency disorder (CDD) is a rare developmental epileptic encephalopathy. A phase 3 randomized, placebo-controlled trial found that ganaxolone, a neuroactive steroid recently approved by FDA for the treatment of seizures associated with CDD, significantly reduced major motor seizure frequency (MMSF) in children with CDD. This post-hoc analysis explored whether ganaxolone was associated with improved behaviours.

Methods: Children (2-19 years) with genetically confirmed CDD and >=16 major motor seizures per month were enrolled. Ganaxolone or placebo was administered TID over a 17-week period. Behaviour was measured with the Anxiety, Depression and Mood Scale (ADAMS) in five domains: Manic/Hyperactive Behaviour, Depressed Mood, Social Avoidance, General Anxiety, and Compulsive Behaviour (decreased scores indicate improvement). Scores were compared using ANCOVA, adjusted for age, sex, number of anti-seizure medications, baseline 28-day MMSF, and baseline developmental skills and behaviour scores.

Results: 101 children with CDD (39 clinical sites, 8 countries) were randomized. Median (IQR) age was 6 (3-10) years, 79.2% were female, and 50 received ganaxolone. After 17 weeks of treatment, Manic/Hyperactive scores were on average 1.27 points (95%CI -2.38,-0.16, p=0.025) lower for children in the ganaxolone group than in the placebo group. Post-treatment Compulsive Behaviour scores were 0.58 points (95%CI -1.14,-0.01, p=0.046) lower in the ganaxolone group. Depressed Mood, Social Avoidance and General Anxiety scores were similar between the two groups.

Conclusions: Non-seizure outcomes can contribute to the success of anti-seizure interventions. Along with better seizure control, children who received ganaxolone had improved behavioural scores in select domains compared to those receiving placebo.

Funding: This work was supported by Marinus Pharmaceuticals, Inc.; editorial support provided by Orion.

Keywords:

CDKL5, CDKL5 Deficiency Disorder, CDD, ganaxolone, behaviour, children, non-seizure outcomes

EPNS23-2895 Oral
Epilepsy: Medical & Surgical Treatment

Corticosteroids versus clobazam in epileptic encephalopathy with spike wave activation in sleep; results of the RESCUE ESES Trial

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Objective: Epileptic encephalopathy with spike wave activation in sleep (EE-SWAS) is associated with acquired cognitive and behavioural deficits. Based on mostly small and retrospective studies, corticosteroids and clobazam are considered the most effective pharmacological treatments to improve neurodevelopmental outcome. This European multicentre randomised controlled trial aimed to compare cognitive outcome 6 months after starting treatment with either corticosteroids or clobazam.

Methods: Patients were eligible if they were 2-12 years, were diagnosed with EE-SWAS within 6 months prior to inclusion and had not been treated with clobazam or corticosteroids. After informed consent they were randomly allocated to treatment with oral clobazam (range 0.5-1.2 mg/kg/day) or corticosteroids (either 1-2mg/kg/day orally or 20mg/kg/day intravenously for 3 days every 4 weeks). Primary outcomes were 1) responder rate (improvement of > 11.25 IQ points, i.e. 75% of SD), 2) change in total IQ and 3) change in cognitive sum score (Z-score based on tests covering 6 cognitive domains) after 6 months of treatment. Secondary outcomes were the sleep induced epileptic activity index (SWI) on EEG, the incidence of seizures and safety. Data is analysed by the intention-to-treat principle. Based on power calculation we aimed to include 130 patients.

Results: Between 2012 and 2022, only 45 patients could be included (22 in corticosteroid and 23 in clobazam arm) and the trial was terminated prematurely for feasibility reasons. 6 months after inclusion, responder rate was 5/22 in the corticosteroid group versus none of those who started with clobazam (p=0.024, Barnard's unconditional test). Mean delta total IQ was higher in the corticosteroid group (mean difference 5.6, CI 0.3 - 10.8, p=0.039). The difference in mean cognitive sum score was 0.24 (CI 0.04 - 0.51 p=0.092). SWI did not significantly differ (p=0.715), neither did the incidence of seizures (36.4% vs. 42.9% resp., p=0.760). Adverse events occurred in a similar proportion of patients in both groups (63.6% vs. 69.6% resp., p=0.758).

Conclusions: Although the number of children included did not meet the predefined minimum, comparing the two treatments in 45 eligible patient suggested that responder rate and increase in IQ was significantly higher in the group that started on corticosteroids. The clinical relevance of this effect is not certain, but suggests that early initiation of steroid treatment is beneficial.

Keywords:
epilepsy, EE-SWAS, neurodevelopment, corticosteroids, clobazam, RCT

EPNS23-2285 Oral
Neurogenetic Disorders

NEXT GENERATION SEQUENCING EXPERIENCE IN PEDIATRIC NEURO-GENETIC DISORDERS ACROSS 5 YEARS : A DUAL-CENTER PROSPECTIVE OBSERVATIONAL STUDY

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Objective: Inception of Next-generation sequencing (NGS) as a clinical diagnostic test has revolutionized the approach of pediatric neuro-genetic disorders, creating unprecedented opportunities to integrate genomic data into the clinical diagnosis and management. This study aims to elucidate the impact of genetic testing and to investigate the diagnostic utility of NGS in neurology.

Methods: This is a dual-center prospective observational study done across 5 years (Jan 2018 - Dec 2022)from two tertiary-care centers in India. Patient attributes were set out on Microsoft Excel 2016(v16.0). 3400 patients were observed to have a strong genetic etiology from a total of 31332 children under 18 years who underwent treatment from neurology out-patient and in-patient services . Among these only 212 patients could afford an NGS based testing. On the basis of their predominant clinical presentations, cases were assorted into seven phenotypes (Neuro-developmental , ASD/ADHD , Epilepsy , Neuro-degenerative/regression, Neuromuscular ,Movement disorder and mixed/other)and the genomic variants were tabulated accordingly.

Results: Predominant developmental delay and epilepsy phenotypes together accounted for 72 % of all cases. Mean age at testing was 3.6 years with male preponderance (2.2:1).History of consanguinity was ascertained in 43 patients (20%). Among the 212 patients, 48 underwent clinical exome sequencing ,161 -Whole exome sequencing and 3-focused clinical exome. Pathogenic variants were tracked down in 54, likely pathogenic in 56, variants of uncertain significance (VUS) in 92 patients and no variants in 10. Among the VUS,62 patients had reverse phenotyping match on clinical correlation and the rest had no correlation. Re-analysis was done in 4 patients .Parental Sanger sequencing was done in 12 patients . Pre-natal testing could be done in only 6 patients. Autosomal dominant disorders were sort out in 87 ,autosomal recessive in 102, X-linked recessive in 6, and X-linked dominant in 7. Other clinical parameters like dysmorphism , seizure type, incidence of refractory seizures, neuro-imaging correlates , surgical interventions ,precision medicine and outcome measures were also analyzed.

Conclusions: This study obtained robust estimates of the spectrum of genomic variants in pediatric neuro-genetic disorders and also their key epidemiological ,clinical, radiological and outcome measures, which provides an additional evidence to the current literature.

Keywords:
Next generation sequencing, pediatric neurology, genetics , exome sequencing

EPNS23-2721 Oral or e-Poster
Neurogenetic Disorders

Prime editing to genetically repair POLG mutations in patient-derived fibroblasts

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Objective: Point mutations in the POLG gene cause one of the most severe forms of intractable epilepsy. Current anti-seizure medications are ineffective and many children die within months to years after seizure onset, usually due to status epilepticus or liver failure. Gene therapy holds promise to directly target the root of the disease. We aimed to prepare for human gene correction therapies by using the recently developed gene editing technique prime editing to repairing disease-causing mutations in fibroblasts of patients with POLG-related disease.

Methods: We designed guide RNAs using in-silico prediction algorithms and tested their efficacy for prime editing of the p.A467T POLG mutation, the most common pathogenic variant resulting in POLG-related disease. Patient-derived fibroblasts were transfected with CRISPR prime editing plasmids along with these guide RNAs and a mutation-specific dual-fluorescent prime editing and enrichment reporter. Using Sanger sequencing, we assessed gene editing efficiency and unwanted bystander edits. We analysed various functional readouts, including mtDNA levels, mitochondrial density, oxidative phosphorylation, and mitochondrial complex levels.

Results: With one of the prime editing guide RNAs, we were able to correct the p.A467T mutation in 81-100% of patient-derived fibroblasts after selection for transfected cells. We observed no unwanted editing of other nucleotides near the target site. Repaired cells showed an improvement in functional readouts of phenotypic repair.

Conclusions: We show that prime editing can be effective in repairing disease-causing mutations in the POLG gene in vitro. Although several hurdles still need to be overcome before in vivo gene editing will be possible, we expect that this approach will pave the way towards eventual causal treatment of patients suffering from POLG-related disease as well as other severe monogenic disorders.

Keywords:
POLG, epilepsy, gene therapy, prime editing, precision therapy, metabolic

EPNS23-2746 Oral or e-Poster
Neurogenetic Disorders

Joint analysis of multiple trio genomic datasets for the discovery of novel dominant epilepsy genes

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Objective: The epileptic encephalopathies (EEs) and epilepsy with co-morbid intellectual disability (ID) are groups of epilepsy characterized by refractory seizures and developmental regression. Both groups have been shown to have underlying monogenic causes, often due to dominant de-novo variants, but also recessive genetic forms. However, despite state-of-the-art testing, a significant proportion of people with epilepsy with ID and EE (roughly 50%, depending on type) do not receive a molecular diagnosis, suggesting there are additional, yet to be identified genetic causes of these epilepsies. We set out to identify novel epilepsy with ID and EE genes by centralizing genetic datasets on patients including their parental datasets using whole-exome and genome sequencing technology (WES/WGS).

Methods: For inclusion in this study, the participants must have provided consent for gene discovery research, have clinical phenotypes based on HPO terms with EE or epilepsy with ID, and have trio samples of WGS or WES available. Trio-based WES/WGS were from the FutureNeuro Research Centre (141 trios), the Epilepsy Genetics Initiative (29 trios), Epi4K/EPGP (337 trios), and the UK 100,000 Genomes Project (269 trios). The bioinformatics workflow using GATK4.2.0 were used for the variant calling steps. Statistical model using denovolyzeR were utilized to identify genes with a significant excess of de-novo variants (DNVs).

Results: A total of 776 trios were included in the final analysis. We identified 23 genes with significant excess of DNVs and being observed in more than one unrelated patients, of which 19 were established monogenic causes of epilepsies. Among the potentially novel genes, damaging *MAST4* variants are observed in three unrelated patients. All *MAST4* patients had epilepsy and a similar developmental phenotype.

Conclusions: Combining genetic and phenotypic data, we report the significant enrichment of de-novo variants within our combined collection of over 2,000 individuals who underwent WES/WGS. We implicate de novo variants in *MAST4* as a cause of epilepsy with ID.

Keywords:
epileptic encephalopathies, intellectual disability, genomics, MAST4

EPNS23-2233 Oral
Neurogenetic Disorders

SEVERITY OF GNAO1-RELATED DISORDERS IS UNDERPINNED BY MECHANISTIC CHANGES IN G PROTEIN FUNCTION

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Objective: Developmental and epileptic encephalopathy 17 (OMIM #615473), caused by variants in the GNAO1 gene, is characterized by epilepsy, intellectual disability, hypotonia and movement disorders. Neither a genotype-phenotype correlation nor a clear severity score have been established for this disorder. Therefore, the objective of this prospective, observational study was to develop a severity score for GNAO1-related disorders and to delineate the correlation between the underlying molecular mechanisms and clinical severity.

Methods: Sixteen individuals with GNAO1-related disorders harboring 12 distinct missense variants, including four novel variants (p.K46R, p.T48I, p.R209P, p.L235P) were examined with repeated clinical assessments, video-EEG monitoring and brain MRI. The molecular mechanisms (receptor-mediated activation of the G protein, trimer formation, dominant negative activity and receptor interaction) of each variant were delineated using a molecular deconvoluting platform.

Results: The patients displayed a wide variability in the severity of their symptoms. This heterogeneity was well represented in the GNAO1-related disorders severity score, with a broad range of scoring. Patients with the same variant had comparable severity scores, indicating that differences in disease profiles are not due to inter-patient variability but rather to unique disease mechanisms. Moreover, we found a significant correlation between clinical severity score and molecular mechanisms.

Conclusions: The clinical score proposed here provides further insight into the correlation between pathophysiology and phenotypic severity in GNAO1-related disorders. We found that each variant has a unique profile of clinical phenotypes and pathological molecular mechanisms. These findings will contribute to the development of pharmacological interventions for GNAO1-related disorders. Additionally, the severity score will facilitate standardize categorization of patients and assessment of response to therapies in development.

Keywords:
GNAO1, developmental and epileptic encephalopathy, movement disorders, epilepsy, missense

EPNS23-2570 Oral
Neurogenetic Disorders

Natural history modelling of STXBP1-related disorders

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Objective: Individuals with STXBP1-related disorders present with developmental delay, epilepsy, abnormalities of movement, and behavioral features. To date, there is limited data on the natural history and the impact of epilepsy on developmental trajectories - limiting the understanding of endpoints for future clinical trials.

Methods: We conducted a cross-sectional retrospective study, in which caregivers and clinicians of individuals with STXBP1-related disorders completed standardized questionnaires containing clinical histories, diagnostic findings, and developmental outcomes. Individuals were recruited in collaboration with international clinical centers and the German family support group.

Results: Our cohort consisted of 73 individuals with STXBP1-related disorders, including 46 previously unreported individuals. The median age at inclusion was 5.3 years (IQR 3.4-8.5 years) with the oldest individual at 43.8 years. 54/73 (74%) individuals had a history of epilepsy and 20/71 (28%) had epileptic spasms. 24/51 (47%) individuals were seizure free at the time of study inclusion. Neurodevelopmental abnormalities were present in all but one individual. 30/62 (48%) individuals were able to walk independently with a median age of 32 months at which the milestone was reached (IQR = 18-41 months, n = 25). 17/58 (29%) individuals communicated verbally. Individuals without a history of epilepsy presented with a similar onset and spectrum of clinical features but had higher functional motor levels (GMFCS, median 3 vs. 4, $p < 0.01$) than individuals with epilepsy. Of individuals who had seizures, individuals with epileptic spasms were less likely to walk independently compared to individuals with other seizure types (6% vs. 59%, $p < 0.01$). Individuals with an earlier seizure onset were more likely to require assisted ambulation ($p = 0.03$) and to communicate nonverbally ($p = 0.04$). However, we did not find a correlation between genotype and developmental outcomes.

Conclusions: We mapped clinical features and developmental trajectories of STXBP1-related disorders, comparing individuals with and without a history of epilepsy. These findings describe the spectrum of outcomes in STXBP1-related disorders across clinical subgroups, providing prognostic insight for comprehensive family consultations and a framework for interpreting future interventional studies in STXBP1-related disorders.

Keywords:
epilepsy, epileptic spasms, STXBP1, neurodevelopmental disorders, neurogenetics

EPNS23-2829 Oral
Movement Disorders

Highlighting the Dystonic Phenotype Related to GNAO1

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Objective: Most GNAO1 mutations have been associated with a severe phenotype: a developmental epileptic encephalopathy or a neurodevelopmental disorder with predominant chorea which could exacerbate, with or without seizures.
The aim was to characterize the clinical and genetic features of patients with mild GNAO1-related phenotype with prominent movement disorders (MD).

Methods: We included patients diagnosed with GNAO1-related movement disorders of delayed onset (>2 years). Patients experiencing either severe or profound intellectual disability or early-onset epileptic encephalopathy were excluded.

Results: Twenty-four patients and 1 asymptomatic subject were included. Mean age at disease onset was 6.6 years (range: 0.25-47). Initial manifestations included developmental delay (13), with hypotonia in 4 patients, dystonia (10), myoclonus or seizures (1). All patients showed dystonia as prominent MD. Mean age of dystonia onset was 10.1 years (range: 2-47). Dystonia was segmental (brachio-cervical) in 11, generalized in 13; oromandibular dystonia with dysarthria was reported in 19 patients. Dystonia was combined with parkinsonism in 7 subjects, with myoclonus in 3, with chorea in 2; dystonia was associated with mild to moderate ID in 12 patients.
Dystonia was non-progressive in 11. Only 3 patients presented an acute exacerbation of dystonia and 3 others presented epileptic seizures between the age of 4 and 19 years.
Movement disorders response to medication, including anticholinergic drugs, levodopa, tetrabenazine, amantadine, clonazepam, or methylphenidate, was poor. Six patients received pallidal deep brain stimulation (DBS), with improvement for 5 of them.
Most of the variants identified were novel; two variants recurred in multiple families (11/20), suggesting that mild phenotypes could be related to specific mutations.

Conclusions: We highlighted a mild GNAO1-related phenotype, including adolescent-onset dystonia, broadening the clinical spectrum of this condition. GNAO1 mutations should be considered as a cause of adolescent or adult-onset nonprogressive dystonia, particularly in the presence of a speech involvement, even in the absence of acute exacerbation, seizures, or ID.

Keywords:
GNAO1; dystonia; mild phenotype

EPNS23-2793 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

Vigabatrin-associated brain MRI changes and clinical symptoms in infants with tuberous sclerosis complex

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Objective: The multicentre EPISTOP trial demonstrated that preventive treatment with vigabatrin (VGB) in infants with tuberous sclerosis complex (TSC) reduces the risk and severity of epilepsy. Previous small retrospective studies have reported vigabatrin-associated brain abnormalities on MRI (VABAM), seen mostly on T2 and DWI sequences. The clinical impact of VABAM is largely unknown. We evaluated the association between VGB and specific brain MRI changes in a large and homogenous TSC cohort, and assessed to what extent VABAM-related symptoms were reported in infants with TSC.

Methods: The Dutch TSC Registry and the EPISTOP cohort provided retrospective and prospective data from 69 TSC patients on VGB before the age of two, and 23 TSC patients without VGB. 29 age matched non-TSC epilepsy patients not receiving VGB were included as controls. VABAM, specified as T2/FLAIR hypertensity or diffusion restriction in predefined brain areas, were examined on brain MRIs before (within first year of life), during (around age 2 years), and after VGB (around age 4 years), and once in the control group (around age 2 years). For the evaluation of clinical symptoms, a larger cohort of 80 TSC patients with less strict MRI date criteria was used. The following symptoms were considered possibly VABAM-related: dyskinetic movement disorders, ataxia, bradycardia, respiratory distress and acute encephalopathy.

Results: Prevalence of VABAM in TSC patients receiving VGB was 36.2%. VABAM-like changes were also observed in 13.0% of TSC patients without VGB and in 13.8% of the controls. VGB treatment was significantly associated with VABAM (OR 3.65; 95%CI 1.50-9.94). Refractory epilepsy did not impact this association (p=0.70). In all 14 patients with VABAM for whom post treatment MRIs were available, VABAM resolved after VGB discontinuation. In TSC infants on VGB, prevalence of symptoms was 11.8% in patients with VABAM and 6.5% in those without, indicating that VABAM were not significantly associated with clinical symptoms (OR 1.91; 95% 0.39-10.30).

Conclusions: VABAM are common in TSC patients treated with VGB, however T2/FLAIR hyperintensities in these predefined areas were neither exclusive for VGB nor for TSC. These MRI changes may be explained by abnormal myelination, possibly related to seizures or other antiseizure medication. Furthermore their presence was not associated with clinical symptoms. This study confirms the notion that anti-seizure effects of VGB outweigh the risk of clinical symptoms related to VABAM.

Keywords:

tuberous sclerosis complex, vigabatrin, brain MRI abnormalities

EPNS23-2509 Oral or e-Poster
Neurogenetic Disorders

Recurrent variants in subunits of the Human Mediator complex affect brain development and lead to severe neurodegenerative and neurodevelopmental disorders.

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Objective: The mediator (MED) multisubunit-complex modulates the activity of the transcriptional machinery, and genetic defects in different MED subunits (17, 20, 27) have been implicated in pediatric neurological and neurodegenerative diseases. In our study, we identified genetics deficits in three other subunits of the complex (11, 22, 28). The first aim of our study is to characterise the neurodevelopmental and neurodegenerative disorders associated with deficits in human mediator complex, under the name of "neuroMEDopathies". The second aim is to understand the pathway that leads to the dysfunction and to neurodegeneration.

Methods: We performed exome or genome sequencing in the affected families. Deep clinical and brain imaging evaluations were performed by clinical pediatric neurologists and neuroradiologists. The functional effect of the candidate variant was assessed using reverse transcriptase polymerase chain reaction and western blotting. Animal models (knock-out and knock-in zebrafish and/or drosophilas) were generated using clustered regularly interspaced short palindromic repeats/Cas9. Activator-bound Mediator was purified from mutant and wild-type human fibroblast cell lines and mediator subunit composition was analysis through AP-MS.

Results: The disease caused by mutations in MED11, MED22 and MED28 is characterised by microcephaly, profound neurodevelopmental impairment, brain atrophy and degeneration, and variable presence of seizures, dystonia and movement abnormalities. Animal models recapitulate the phenotype. AP-MS and Pro-Seq experiment are still ongoing, but we expect to see an alteration in the structure or stability of the whole human mediator complex, as predicted by computational studies performed in our lab.

Conclusions: Deficits in several MED subunits share overlapping clinical features and severely affect brain development. Different mutations may affect the binding efficiency to other MED subunits and to the transcription machinery, thus implicating the MED-complex stability and function in brain development and neurodegeneration.

Keywords:
Mediator complex, Brain developmental, Neurodegeneration

EPNS23-2967 Oral
Neurocutaneous Syndromes

CORTICAL GYRIFICATION INDEX IN A COHORT OF TUBEROUS SCLEROSIS COMPLEX PATIENTS: A RETROSPECTIVE MONOCENTRIC STUDY

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Case study: Background. Gyrification brain abnormalities are considered a prognostic marker of early neurodevelopmental alterations and a predictor of poor outcome in psychiatric disorders. Tuberous Sclerosis Complex (TSC) is an autosomal dominant genetic multisystemic disorder in which the neurological and neuropsychiatric involvement is present in about 90% of cases.
Objectives. To evaluate brain gyrification in a group of patients with TSC, identifying possible differences when compared with a control group; analyze the possible correlations between brain gyrification and the clinical and neuroradiological variables in patients with TSC; evaluate the possible prognostic role of gyrification for neurological and neuropsychiatric outcomes in patients with TSC.
Methods. Retrospective analysis of a pediatric population of 45 patients (20 males, 25 females) affected by TSC, with average age, at last magnetic resonance imaging (MRI), of 14 ± 6.3 years (range 4-31 years). For each patient we evaluated the clinical characteristics, including in particular the neurological and neuropsychiatric phenotype, and the brain MR images (in particular volumetric T1 sequences). Gyrification index (GI) was measured using the CAT12 software.
Results. Patients showed significantly higher gyrification when compared with healthy controls both on the left and the right hemisphere. Significant correlations were found between gyrification and clinical and neuroradiological variables in TSC patients such as: age of onset of epilepsy, intellectual disability, TSC-associated Neuropsychiatric Disorder (TAND) and number of cortical tubers.
Conclusions. Gyrification differs greatly between TSC patients and healthy controls and could play a role in determining the patient's outcome. Gyrification and number of cortical tubers showed a clear correlation; this was expected because tubers determine a profound alteration of the cortical structure. Nevertheless, we found that some TAND categories (behavioral, psychiatric and psychosocial) had a more accurate correlation with the gyrification index. For this reason, gyrification index and number of tubers might have an independent prognostic role in TSC patients.
Further studies are needed to identify specific pathological patterns of gyrification; local gyrification index could be used to screen earlier and more carefully for some TAND in children with TSC.

Keywords:
Tuberous Sclerosis Complex, TAND, gyrification, neuroimaging

EPNS23-2523 Oral
Neurodevelopmental Disorders

Seven new cases of ZBTB11-related disorder with a focus on movements disorders

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Objective: ZBTB11 encodes the transcriptional regulator Zinc Finger (Znf) and Broad-complex, Tramtrack, Bric-à-brac (BTB) Domain containing 11. Variants in these gene have been associated to Intellectual developmental disorder, autosomal recessive 69 (OMIM#618383) in 23 reported patients.

Methods: We report seven additional cases of ZBTB11-related disorders, describing five novel pathogenic variant, and review previously published cases of MRT69. We focus on the movement disorders and describe the outcome of one case after internal Globus Pallidus deep brain stimulation.

Results: Seven affected individuals (three males, four females) from four families, including two consanguineous families, showed mild to moderate intellectual disability, motor developmental regression, bilateral cataracts, and complex movement disorders. All patients had normal birth parameters, whereas all of them showed impaired language or motor developmental delay. Hypotonia was prevalent in childhood but evolved into hypertonia with limb contractures as individuals aged. Complex movement disorders included orofacial and limb dystonia, myoclonus, and coarse and resting tremor. One patient exhibited acute right myoclonus dystonic status, requiring urgent deep brain stimulation at 16 years of age, with a favorable response, recovery of independent walking, the ability to eat, and improvement of the myoclonus. In this cohort, only one patient showed combined malonic and methylmalonic aciduria (CMMMA) previously associated with this disorder. Brain MRI showed T2W hyperintensity and atrophy of basal ganglia. Four novel missense variants (c.2009T>C/ p.Met670Thr, c.2517G>C/p.Arg839Ser, c.2618A>G/p.Tyr873Cys and c.2708G>A/p.Arg903His) and one novel frameshift variant (c.999dup/ p.Arg334Thr*13) in the ZBTB11 (NM_014415.4) gene were identified by whole exome sequencing of affected individuals.

Conclusions: Our description of seven patients establishes bi-allelic ZBTB11 variants as a cause of a human disorder characterized by variable combinations of neurodevelopmental delay, intellectual disability, complex movement disorders, cataracts, and CMMMA. Our study adds the phenotype of complex movement disorder and the response to deep brain stimulation. Finally, this study also expands the mutation spectrum of the condition.

Keywords:
ZBTB11, dystonia, myoclonus, deep brain stimulation

EPNS23-2247 Oral or e-Poster
Neurogenetic Disorders

Biallelic MED27 variants lead to variable ponto-cerebello-lental degeneration with movement disorders

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Objective: MED27 is a subunit of the Mediator multiprotein complex, which is involved in transcriptional regulation. Biallelic MED27 variants have recently been suggested to be responsible for an autosomal recessive neurodevelopmental disorder with spasticity, cataracts, and cerebellar hypoplasia. The objective of this study is to further delineate the clinical phenotype of MED27-related disorder by characterizing the clinical and radiological features of 54 affected individuals from 27 unrelated families with biallelic MED27 variants.

Methods: Utilizing exome sequencing and extensive international genetic data sharing, 36 unpublished affected individuals from 15 independent families with biallelic missense variants in MED27 have been identified. Follow-up and hitherto unreported clinical features were obtained from the published 12 families. Brain MRI scans from 34 cases were reviewed. The associations between clinical and neuroradiological findings were evaluated by the chi-squared and Fisher exact test. Statistical significance was set at = 0.05. Statistical analyses were performed using SPSS Statistics software, v26 (IBM, Armonk, NY, USA)

Results: The condition is characterised by global developmental delay/intellectual disability, ranging from mild to profound (100%), bilateral cataracts (88%), infantile hypotonia (72%), microcephaly (63%), gait ataxia (63%), dystonia (59%), variably combined with epilepsy (53%), limb spasticity (52%), facial dysmorphism (37%), and premature mortality (16%). Brain MRI revealed cerebellar atrophy (100%), white matter volume loss (76.4%), pontine hypoplasia (47%) and basal ganglia atrophy with signal alterations (44.1%). Previously unreported 36 affected individuals had six homozygous pathogenic missense MED27 variants, five of which were recurrent. An emerging genotype-phenotype correlation was observed. Our series suggests an underlying neurodegenerative process that prompts us to define the cerebellar involvement as "atrophy" rather than "hypoplasia" in MED27-related NDDs.

Conclusions: This study provides a comprehensive clinical-radiological description of MED27-related disease, establishes genotype-phenotype and clinical-radiological correlations, and suggests a differential diagnosis with syndromes of cerebello-lental neurodegeneration and other disorders resulting from defects in the MED complex. We propose a term "MEDopathies" for all the monogenic disorders resulting from defects in different subunits of the MED complex.

Keywords:
Mediator complex, gene transcription, neurodevelopmental disorders, dystonia, cerebello-lental degeneration, cerebellar atrophy

EPNS23-2865 Oral or e-Poster
Neuropsychiatric Disorders

Fear conditioning is preserved in very preterm-born young adults despite increased anxiety levels

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Case study: Objective: Very preterm birth (less/ equal 32 weeks of gestation) is associated with an increased risk for anxiety disorders. Abnormal brain development may result in disordered fear learning processes, which may be exacerbated by environmental risk factors and persist in adulthood.
Methods: We tested the hypotheses that very preterm-born young adults displayed higher levels of fear conditioning, less differentiation between threat, CS+, and safety, CS-, signals and stronger resistance to extinction relative to term-born controls. A group of 37 very preterm-born young adults without major cerebral lesions (less/ equal intraventricular hemorrhage grade II, IVH) and norm intelligence and 31 age- and sex-matched term-born controls performed a differential fear conditioning paradigm on two consecutive days. Acquisition and extinction training were performed on day 1. Recall and reinstatement were tested on day 2.
Results: Preterm-born participants showed significantly higher levels of anxiety in the Depression-Anxiety-Stress-Scale-21 questionnaire. The fear conditioning outcome measures, skin conductance response amplitudes and anxiety ratings, were overall higher in the preterm-born group compared to controls. Acquisition, extinction, recall and reinstatement of differential conditioned fear responses, CS+ > CS-, however, were not significantly different between the groups.
Conclusion: Although very preterm-born young adults were on average more anxious than their term-born peers, we did not detect significant abnormalities in the acquisition of learned differential fear responses. Likewise, extinction learning and return of fear in recall and reinstatement were not significantly altered. Small differences, however, may become more obvious using a simpler differential learning paradigm with no change in contexts and a single CS+. Abnormalities in preterms may also be more prominent in preterms who have developed more pronounced anxiety disorders. Findings need to be confirmed in future studies in larger preterm populations and using less complex fear conditioning paradigms.

Keywords:
Prematurity, anxiety, fear, classical conditioning, associative learning

EPNS23-2591 Oral or e-Poster
Neuropsychiatric Disorders

Serum and CSF IL-17 dosage in pediatric patients with acute neuropsychiatric disorders: a monocentric prospective study

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Objective: Acute neuropsychiatric disorders are heterogeneous conditions resulting from the interaction between genetic, epigenetic, neurobiological and environmental factors, that can be caused by a variety of metabolic, toxic, infectious, inflammatory, genetic and psychiatric diseases. Among autoimmune and post-infectious forms Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS, in which a direct pathogenetic role of group A streptococcus [GAS] has been proposed), have gained interest in the past decade. Studies on murine models have shown that GAS might produce neuroinflammation through a T-Helper-17 and Interleukin-17 (IL17) mediated response, which seems to be related to the blood-brain barrier (BBB) functions.

Methods: In this study we analyze serum and cerebrospinal fluid (CSF) IL-17 concentrations in a cohort of pediatric patient affected by acute neuropsychiatric disorders. We prospectively enrolled patients diagnosed with acute onset or acute relapse of neuropsychiatric disorder in the period 2016-2020. IL-17 was determined by means of quantitative sandwich enzyme immunoassay technique (Human IL17 Immunoassay, R&D Systems, Minneapolis, MN), and values were compared to a population of healthy controls (n=15).

Results: 61 subjects were included in the study (69% males, median age at onset 6.6 years). Final diagnosis was PANDAS (52%), PANS (12%), complex TIC disorder (13%), Tourette's syndrome (2%), NMDAR encephalitis (2%), unclassified acute neuropsychiatric disorder (20%). Median time from symptoms onset and IL17 determination was 27.15 months. Median IL-17 concentrations were higher in the study population compared to controls, both on serum (12.1 vs 0.01 pg/mL, $p<0.0001$) and CSF (14.9 vs 0.1 pg/mL, $p< 0.0001$). IL-17 tended to increases in pubertal age (>10 years) both on serum ($p=0.05$) and on CSF ($p=0.04$). Median IL-17 was higher in the CSF than in serum ($p=0.003$), with a marked significance in the PANDAS/PANS group (21.6 vs 12.6 pg/mL, $p<0.001$).

Conclusions: Our results suggest a role of IL-17 as a possible biomarker in acute neuropsychiatric disorders in childhood, particularly for PANDAS and PANS patients. Further studies are necessary to validate its potential diagnostic and prognostic implications and the actual pathogenic role of IL-17 in these disorders.

Keywords:
Pediatrics, T-helper 17, Streptococcus, interleukin

EPNS23-2652 Oral or e-Poster
Neurodevelopmental Disorders

Application of transcranial magnetic stimulation in children with psycho-speech delayed with autism spectrum

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Objective: Study of the impact of various transcranial magnetic stimulation (TMS) programs on cognitive, communicative and behavioral functions in children with psycho-speech developmental delay in the autism spectrum (SSD AS).

Methods: TMS was carried out from January 2021 to May 2022 in 950 children with mental retardation and autistic features of various origins. The age of the patients ranged from 2 to 16 years. Among them, the largest number of patients was of age of 4-6 years (33.2%), and 2 to 4 years (30.0%), this is the age when the symptoms of delayed speech development are most clearly manifested.

Results: Each child was examined by a neurologist before conducting TMS. Most of these children underwent an EEG examination before the TMS procedure. Parents filled out a questionnaire at the beginning of treatment and one month after treatment. Depending on the TMS treatment regimen, patients were divided into 2 groups: the 1st group received 10 sessions of 12 minutes each for the DLPFC zone on the right and left, the 2nd group received 20 sessions for the DLPFC zone on the left and Broca's zone projection on the left. All children took 2-3 courses with an interval of 1-3 months. The frequency of stimuli was choosen individually depending on behavioral manifestations and the presence of seizures in history - from 0.2 to 1.0 Hz (safe low-frequency stimulation in children with epilepsy).
Results: A positive effect was noted in 85% of patients, of which 30% in children of the 1st group and 55% in children of the 2nd group - reduction of stereotypes and echolalia, improved understanding of requests, the appearance of a pointing gesture, improved eye contact, improved emotions, changes taste preferences.
Most often, positive effects were observed in of 2-4 and 4-6 y.o. groups, which is associated with the plasticity of the formation of functional centers during this period.

Conclusions: Despite the wide range of causes of SSD AS, positive effects were noted in most children. The effectiveness of the method depends on many factors, including the zone of influence and the duration of treatment. Further research is needed to develop a generally accepted treatment protocol for these children.

Keywords:
transcranial magnetic stimulation, autism spectrum , psycho-speech developmental delay

EPNS23-2269 Oral or e-Poster
Neuropsychiatric Disorders

The Association of Electroencephalogram Abnormalities with Clinical Symptoms and Neuropsychiatric Comorbidities in Children with Attention-Deficit Hyperactivity Disorder

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Objective: Attention-Deficit Hyperactivity Disorder (ADHD) is a neuro-developmental disorder that is characterized by inattention, hyperactivity and impulsivity. This study proposed for investigating the association of electroencephalogram (EEG) abnormalities with clinical symptoms and comorbidities in ADHD children.

Methods: We've conducted a retrospective study by reviewing the medical records of newly diagnosed ADHD children since Jan 2020 to Dec 2022 in our pediatric clinics. All ADHD children had been scored for core symptoms by SNAP-IV parent-rating and teacher-rating scales. Most of these ADHD children also received resting EEG evaluations both in awake and sleep status. ADHD children were classified into two groups according to the existence of EEG abnormalities, such as focal or generalized discharges and background slowing. Then the comparison of statistical differences between the demographic data, SNAP-IV parent-rating and teacher-rating scores, and other neuropsychiatric comorbidities were performed. The statistical analysis included nonparametric Mann-Whitney U test and Fisher's exact test.

Results: We've recruited 63 newly diagnosed ADHD children with complete SNAP-IV parent-rating/teacher-rating scales and resting EEG studies. These 63 ADHD children were divided into two groups due to the results of EEG studies, with 35 (55.6% in normal EEG group and 28 (44.4%) in abnormal EEG group. The abnormal EEG group showed older average age (8.8±2.4 vs 7.4±2.3 yr, p=0.02) and more neuropsychiatric comorbidities, such as Tourette syndrome/tic disorders, autistic spectrum disorder(ASD) and epilepsy (78.6% vs 51.4%, OR: 3.88, 95%CI: 1.2-12.7, p=0.02). However, no children with normal EEG developed into epilepsy. These two groups revealed no statistical differences in inattention, hyperactivity-impulsivity and oppositional scores both in SNAP-IV parent-rating and teacher-rating scales. Most common EEG abnormalities in ADHD children were focal epileptiform discharges (92.9%). Only 3 children (10.7%) revealed generalized spike-waves during sleep status.

Conclusions: Our study showed EEG abnormalities seemed to have no significant correlation with SNAP-IV parent-rating and teacher-rating scales, indicating that EEG abnormalities were more likely associated with other neuropsychiatric comorbid disorders. We've suggested that EEG could be used as a supportive tool for evaluating children with ADHD, especially those comorbid with suspected neuropsychiatric disorders.

Keywords:
ADHD, EEG, SNAP-IV, Neuropsychiatric comorbidities

EPNS23-2400 Oral
Neurodevelopmental Disorders

Holter of Movement provides first digital outcome measure qualified by a regulatory agency

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Objective: Quantifying movement disorders is challenging, as clinical condition of patients may fluctuate, which can create discrepancy between hospital-based assessment and patient's condition.
Using sensors based on magneto inertial technology, we developed a Holter of movement able to identify and measure continuously and accurately patients movements during real life in uncontrolled environment. The sensors were initially validated in ambulant patients with Duchenne Muscular Dystrophy (DMD).

To validate and gather regulatory approval of a digital outcome measure, the 95th centile Stride velocity (SV95C) in patients with DMD. The SV95C represent the 5% most rapid strides performed by an individual during at least 50 hours.

Methods: SV95C properties were studied in 125 ambulant DMD patients, aged 5 to 14 years, from 6 different natural history studies and clinical trials and from patients attending routine clinic appointments. An additional study included healthy controls in a controlled environment.

Results: In controlled environment, stride velocity measured by the magneto inertial sensor diverges from gold standard motion-capture by a median error of 0.01 cm/s, and the divergence between six-minute-walking test (6MWT) measured by physiotherapists or by trajectory reconstruction was < 0.5%. In uncontrolled environment, reliability of SV95C during two consecutive 50 hours recording period was 0.97. We did not find any influence of compliance, or time of recording on the SV95C. We observed a significant difference of -7.34 ± 9.19% between week-end and week days. SV95C fully discriminated DMD and controls in the different age groups. SV95C demonstrated sensibility to positive change in patients put on steroids, and sensibility to negative change due to disease progression that significantly outperformed hospital-based assessment such as 6MWT or North Star Ambulatory Assessment.

Conclusions: SV95C became the first digital outcome approved by a regulatory agency as a secondary outcome in 2019, and has received a positive qualification opinion as a primary endpoint. Public consultation for final qualification is ongoing. Wearable technologies open a completely new field of opportunity in neuromuscular diseases and movement disorders. We currently develop similar approaches in diseases such as Angelman syndrome, multiple sclerosis and several other neuromuscular disorders.

Keywords:
outcome measure, movement quantification, Duchenne Muscular Dystrophy

EPNS23-2727 Oral or e-Poster
Neurogenetic Disorders

Biallelic variants in ARHGAP19 cause mixed demyelinating and axonal polyneuropathy

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Objective: Rho GTPases are members of the large superfamily of small GTPase proteins considered as molecular switches in various cellular events. One of the major regulators of Rho GTPases are Rho GTPase-activating proteins (GAPs). RhoGAPs stimulate intrinsic GTPase activity of Rho GTPases therefore acting as negative regulators of Rho pathway. One of the Rho effectors, the serine/threonine protein kinase ROCK, has important role in actin organisation, cell migration regulation, cell cycle control, and cell adhesion.
By using next generation sequencing we identified 16 individuals from 14 unrelated families with biallelic variants in Rho GTPase-activating protein 19 (ARHGAP19) presenting with young age of onset progressive weakness in lower limbs, difficulty in walking and foot deformities. Nerve conduction studies reveal mixed demyelinating and axonal polyneuropathy.

Methods: We are using various approaches to model these variants; in-vitro GAP assays to assess if the GAP activity is affected by expression of proteins carrying ARHGAP19 mutations, complemented by an in-vivo Drosophila melanogaster model to test for movement, lifespan and neuromuscular junction integrity; in silico approach to gain an understanding of protein structure changes and its implications.

Results: Ongoing studies such as the in-vitro GAP assays show that ARHGAP19 has GAP activity towards RhoA but not Rac1 or Cdc42. Three of the mutations found in patients are being tested for their GAP activity and preliminary data suggest a loss of the GAP activity in a frame shift mutation.
Visualisation of the endogenous expression pattern of ARHGAP19 ortholog in fly, RhoGAP54D, suggest the protein is expressed in perineural or subperineural glia in the fly brain. Preliminary results indicate that RNAi knockdown of RhoGAP54D in flies reduces both overall movement and startle responses to light-dark transitions.

Conclusions: This is a first association of ARHGAP19 with neurological disease and deep phenotyping analysis in conjunction with the in-vivo animal model and the in-vitro GAP assay will help highlight he importance of the gene in early human brain development and function.

Keywords:
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EPNS23-2547 Oral

Quality of Life in Children with Neurological Disorders

Neuromuscular scoliosis - A practical pathway to optimize peri-operative health and guide decision making for children for surgical intervention

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Objective: Neuromuscular scoliosis is a common feature in children with severe neurological impairment (SNI), which includes those with cerebral palsy, neuromuscular disorders or slowly progressive neurodegenerative disorders. Increased survival of these children means that they live longer with associated medical complexity and acquired musculoskeletal complications. Surgical correction of neuromuscular scoliosis is the mainstay of treatment. There is good evidence to show improved quality of life and high satisfaction rates after the surgery. However, the complication rates post-surgery are high. There are currently no published practice guidelines or care pathways for children with SNI who are undergoing scoliosis corrective surgery. In response to a critical post-operative incident at our institute, and the high complication rates, we established an inter-disciplinary service.

Methods: We describe our neuromuscular scoliosis service and the step by step processes that are followed when potential candidate for surgery is identified. Firstly, a detailed medical assessment clinic with a paediatrician, respiratory physician and nurse consultant is completed and we follow a proforma aimed to optimise medical care pre and post-surgery. This includes management of comorbidities such as respiratory health, nutrition, epilepsy, pain and anxiety. A boarder discussion with the family and child about their beliefs and fears is also conducted. Then, we present the candidate at a collaborative meeting which is attended by an inter-disciplinary team including surgeons, paediatricians, respiratory physicians, anaesthetists, intensivists and nurse consultants.

Results: Important decisions are made such as whether the surgery should proceed, the planned surgical approach, whether an intensive care admission is required and whether or not to extubate to non-invasive ventilation. A fundamental part of the decision process is to consider the ethical impact of the surgery on the child. We take time to place the family and child at the centre and to provide shared decision making to identify the right candidate for the right surgery. Details of the decision process are then discussed with the family.

Conclusions: There is a rising need for surgical interventions for children with SNI. This inter-disciplinary model is a costly service. However, these pathways provide guidance for optimisation of the health pre and post-surgery for children with SNI, and provide a clear space for broader ethical decision making.

Keywords:

Severe Neurological Impairment, neuromuscular scoliosis

EPNS23-2147 Oral
Neuromuscular Disorders

Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in DMD

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Objective: Delandistrogene moxeparvovec (SRP-9001) is an investigational gene transfer therapy developed to address the root cause of Duchenne muscular dystrophy (DMD) through targeted skeletal and cardiac muscle expression of SRP-9001 dystrophin protein, which contains key functional domains of dystrophin. This study aimed to evaluate functional data in patients with DMD ≥4 to ≤8 years of age at Year 1 following infusion of delandistrogene moxeparvovec versus a propensity-score-weighted external control (EC) cohort.

Methods: Ambulatory patients with DMD ≥4 to ≤8 years of age received a single intravenous infusion of delandistrogene moxeparvovec ($1.33x10^{14}$ vg/kg, linear standard quantitative polymerase chain reaction).

The dataset included patients treated with clinical process delandistrogene moxeparvovec material (Study 101, Phase 1/2a; NCT03375164 and Study 102, Phase 2; NCT03769116) and intended commercial process delandistrogene moxeparvovec material (ENDEAVOR, Phase 1b; NCT04626674). Data were compared with a propensity-score-weighted EC cohort (N=131), comprised of natural history and external clinical trial data from three studies. The primary endpoint was 1-year change from baseline in North Star Ambulatory Assessment (NSAA) total score. Exploratory endpoints included the effect on key timed function tests 1 year post-treatment. Collective safety data available from Study 101, Study 102 and ENDEAVOR are also presented.

Results: The integrated analysis evaluated functional data from 52 patients, including patients from Study 101 (N=4), Study 102 (n=28) and Cohort 1 of ENDEAVOR (n=20). Results showed a statistically significant difference of 2.4 points ($P<0.0001$) in NSAA change from baseline to Year 1 in treated patients versus the EC cohort (n=105). In a collective safety analysis from the three studies, there were no adverse events that led to study discontinuation and no deaths.

Conclusions: Delandistrogene moxeparvovec demonstrated a clinically meaningful and statistically significant difference versus a propensity-score-weighted EC cohort in change from baseline in NSAA total score at Year 1, suggesting a beneficial modification of the DMD disease trajectory. Collective safety data were consistent and manageable across studies.

Keywords:
Duchenne muscular dystrophy, gene therapy, clinical trials, gene transfer

EPNS23-2215 Oral
Neurodevelopmental Disorders

Small-Fiber-Neuropathy - Normal reference values of small nerve fiber density in children and association with neurodevelopmental disorders

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Objective: Small fiber neuropathy (SFN) describes the degeneration of mildly or unmyelinated nerve fibers and causes neuropathic pain and autonomic dysfunction. Gold standard for the diagnosis is a skin punch biopsy from the lower leg and the quantification of the intraepidermal nerve fiber density (IENFD). In Parkinson's disease, SFN is already present in the early stages. Whether neurodevelopmental disorders (NDDs) in childhood are likewise associated with SFN is largely unknown. The IENFD is age-dependent and declines with age.
In children, the IENFD reference values have not been systematically assessed.
In this study, we are determining the IENFD reference values and we are investigating if the IENFD is reduced in children with NDDs.

Methods: Skin biopsies from control children without a chronic disease are drawn from surgical crop margins during orthopedic surgery from the lower leg. Skin biopsies from children with acquired or genetic NDD are drawn in the setting of elective interventions after local anesthesia. IENFD is quantified by immunofluorescence.

Results: From 01-12/2022 we have analyzed N=96 skin samples (control N=26, acquired-NDD N=12; genetic-NDD N=44, unclear etiology N=14).
In controls, the median IENFD (10.7/mm) is in the range of the IENFD of young adult men (10.9/mm). The median IENFD is significantly higher in younger than in older children (< 5 years: 22.2/mm vs > 5 years: 10.0/mm). The preliminary calculated 5th age-dependent cutoff value for the diagnosis of SFN is 8/mm for < 5years and 7/mm for >5 years. The IENFD in children with acquired cerebral palsy (e.g. after encephalitis) is in the range of control children (median 11.8/mm). In contrast, in 40% of children with genetic NDDs (e.g. AGA, YARS1, MT-ATP6, MEF2C, FDXR, SCL52A3) the IENFD is significantly reduced. In 50% of patients with unclear etiology we also detected a reduced nerve fiber density. As a reduced nerve fiber density might be a marker of genetic etiology, we initialized exome sequencing and found pathogenic variants in a subset of patients.

Conclusions: The age-dependent reference values will help in the diagnosis of SNF in patients with NDDs, but also with other pain disorders. SFN might help as a biomarker to differentiate between genetic and acquired NDDs. SFN might be an under-recognized cause of neuropathic pain in children with NDDs and diagnosing SFN might guide symptomatic treatment with e.g. gabapentin. We are still in the recruiting phase and expect to have analyzed N=120 samples by 06/2023.

Keywords:
Small fiber neuropathy, neuropathy, neurodevelopmental disorders, biomarker, neuropathic pain, autonomic dysfunction, cerebral palsy, genetic etiologiy

EPNS23-2389 Oral or e-Poster
Neuromuscular Disorders

Direct utility of natural history data in analysis of clinical trials: Propensity matched comparison of MOXIe Extension to FA-COMS patients as an assessment of the efficacy of Omaveloxolone in Friedreich ataxia

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Objective: The natural history of Friedreich Ataxia (FA) is being investigated in a multi-center longitudinal study designated as the Friedreich Ataxia Clinical Outcome Measures Study (FA-COMS). To understand the utility of this natural history dataset in analysis of clinical trials, we performed a propensity-matched comparison of the data from the open-label MOXIe Extension (omaveloxolone) with that from FA-COMS.

Methods: All MOXIe Extension patients who had at least one post-baseline assessment were matched to FA-COMS patients using logistic regression to estimate propensity scores based on multiple covariates: sex, baseline age, age of FA onset, baseline modified Friedreich Ataxia Rating scale (mFARS) score, and baseline gait score. Selection of covariates was based on clinical relevance (i.e., factors considered prognostic for disease progression) and availability. The change from baseline in mFARS at Year 3 for the MOXIe Extension patients compared to the matched FA-COMS patients was analyzed as the primary efficacy endpoint using mixed model repeated measures analysis.

Results: Data from the MOXIe Extension show that omaveloxolone provided persistent benefit over three years when compared to an untreated, rigorously matched cohort from FA-COMS. At each year, and in all analysis populations, patients in the MOXIe Extension experienced a smaller change from baseline in mFARS score than the matched FA-COMS patients. In the Primary Pooled Population (136 patients in each group) by Year 3, patients in the FA-COMS matched set progressed 6.6 points whereas patients treated with omaveloxolone in MOXIe Extension progressed 3 points (difference = -3.6; nominal p value = 0.0001). Thus, progression in mFARS was slowed by 55% with omaveloxolone treatment relative to the patients in the FA-COMS data set.

Conclusions: These results suggest a clinically meaningful slowing of FA progression with omaveloxolone, and consequently detail how propensity-matched analysis may contribute to the understanding of the effects of therapeutic agents. This supports the potential value of the FA-COMS dataset in the evaluation of FA clinical trials.

Keywords:
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EPNS23-2027 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Impact of Cardiac Injury on the Clinical Outcome of Children with Convulsive Status Epilepticus

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Objective: Objectives: the aim of this study was to determine the impact of cardiac injury on clinical profile, cardiac evaluation and outcome in patients hospitalized with convulsive status epilepticus (CSE).

Methods: Materials and methods: this prospective observational study included 74 children with CSE. Cardiac injury was evaluated and defined using combination of cardiac troponin, electrocardiography (ECG) and echocardiography. Clinical outcome and mortality rates were compared in patients with and without cardiac injury.

Results: Results: A total of 74 patients with CSE were included in the study.
Thirty-six (48.6%) patients demonstrated markers of cardiac injury. ECG changes occurred in 45.9% and echocardiographic signs of left ventricular systolic and diastolic dysfunction reported in 5.4% and 8.1%, respectively. The mean length of hospital stays and need for ICU admission were significantly higher in patients with cardiac injury compared to others. One third of patients with cardiac injury needed mechanical ventilation and this was significantly higher than patients without ($p = 0.042$). hypotension and/or shock developed in 25% of cardiac injury patients and most of them required inotropic support; this was significantly higher than others without markers of cardiac injury. The overall mortality in cardiac injury group was higher (13.9% vs. 2.6%); however, this difference was not statistically significant.

Conclusions: Conclusion: Markers of cardiac injury were common and associated with poor clinical outcome and higher risk of mortality in patients with CSE, so extensive routine cardiovascular evaluation is essential in these patients.

Keywords:
cardiac injury; convulsive status epilepticus; mortality; outcome

EPNS23-2589 Oral
Infections and Inflammatory Diseases

Gram-negative bacillary meningitis in the neonatal intensive care unit: the clinical characteristics and risk factors of adverse outcomes

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Objective: We aimed to describe the clinical features of Gram-negative bacillary (GNB) meningitis in young infants and investigate the risk factors associated with final adverse outcomes of neonatal GNB meningitis.

Methods: From 2003 to 2020, all neonates (aged less than 90 days old) with bacterial meningitis who were hospitalized in four tertiary-level neonatal intensive care units (NICU) of two medical centers in Taiwan were enrolled. Multivariate logistic regression analysis was performed to investigate the independent risk factors of final adverse outcomes.

Results: During the study period, a total of 153 neonates with bacterial meningitis were identified and enrolled. GNB accounted for 51.6% (n=79) of all neonatal bacterial meningitis, with E coli to be the most common GNB pathogens. Among neonates with GNB meningitis, 69.6% (n=55) had neurological complications, and 26 (41.3%) of 63 survivors had neurological sequelae at discharge. Neonates with GNB meningitis were significantly more preterm and had a lower birth weight than those with group B streptococcus (GBS) meningitis. The overall final mortality rate was comparable between neonates with GNB and GBS meningitis. After multivariate logistic regression analysis, neonates with thrombocytopenia, seizure at onset of meningitis, and respiratory failure were independently associated with final adverse outcomes.

Conclusions: Nearly half of all neonates with GNB meningitis were associated with final adverse outcomes. Given the high mortality and morbidity rates in neonates with complicated GNB sepsis, further studies for early identification of specific strains, risk factors and genetic mechanisms that will cause GNB meningitis are urgently needed in the future.

Keywords:
neonatal meningitis, neurological sequelae, GBS, mortality

EPNS23-2262 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

The predictive values of status epilepticus scoring models for outcome characteristics in the childhood population

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Objective: Various scoring models have been developed to predict the characteristics of the outcome of status epilepticus (SE). However, a few of these scoring models have been used in a pediatric population with SE. In this study, we retrospectively evaluated the predictive value of a set of available scoring models for outcome characteristics of SE in a large single-center cohort.

Methods: The study cohort included 240 children with SE who were followed up at the Emergency Department and Pediatric Intensive Care Unit of Ege University Children's Hospital between January 2019 and September 2022. The Status Epilepticus in Pediatric Patients Severity Score (STEPSS), the modified Status Epilepticus in Pediatric Severity Score (mSTEPSS), and the END-IT Score (encephalitis, nonconvulsive status epilepticus, diazepam resistance, neuroimaging abnormalities, and tracheal intubation) were used to predict outcomes. These three scoring systems were calculated and correlated with three different outcome characteristics: (1) in-hospital mortality, (2) progression to refractory and super-refractory SE, and (3) the Pediatric Overall Performance Category (POPC) scale for the functional outcome at three months post-discharge. The areas under curves (AUC) were calculated for the scores of outcome characteristics.

Results: One hundred patients (41.7%) progressed to refractory or super-refractory SE, including eight with new-onset refractory status epilepticus. 30% of the patients were intubated, and 16% required tracheostomy in the pediatric intensive care unit. In-hospital mortality was 2.5%. A poor functional outcome was defined in 64 (26.7%) with a POPC score. The END-IT provided a moderate predictivity for in-hospital mortality, refractory/super-refractory SE, and poor functional outcome with the AUCs: 0.815, 0.715, and 0.720, respectively. However, the STEPSS and mSTEPSS yielded a weak predictivity for functional decline prediction with POPC score (AUCs:0.592 and 0.590, respectively).

Conclusions: The END-IT score is useful and accurate in predicting short-term mortality and poor functional outcome in children with SE. However, the other scoring models (STEPSS and mSTEPSS) did not provide high predictive values for the outcomes. This could be attributed to the cohort characteristics such as etiologic distribution, clinical conditions, and multifaceted SE care. More prospective studies with a large number of patients are needed to find out how accurate the scoring models shown at the bedside are.

Keywords:
status epilepticus, scoring model, outcome

EPNS23-2717 Oral or e-Poster

Infections and Inflammatory Diseases

Long-term follow up MR-imaging in children with transverse myelitis

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Objective: Background: We recently described the magnetic resonance imaging (MRI) presentation of children with transverse myelitis (TM) at first event of an acquired demyelinating syndrome (ADS). We revealed important and unique features depending on the underlying disease entity: myelin oligodendrocyte glycoprotein associated disorders (MOGAD), multiple sclerosis (MS) and antibody (ab) negative children.
Objectives: To compare the MRI features at onset and long-term follow up of children with MOGAD, MS and seronegative children.

Methods: In this prospective study, 60 children from 27 different European medical centres with TM as part of MOGAD (n=29), MS (n=15) and in seronegative children (n=16) were included. They had a complete data set with clinical symptoms, cerebrospinal fluid testing, serial MOG- and Aquaporin-4 ab testing and MRI studies at onset as well as follow up MRI studies up to 24 months. A grading system consisting of 4 grades (grade 1 = complete resolution; grade 4 = no resolution at all) was used to compare the degree of lesion resolution over time in the different disease entities.

Results: In our previous study we could show that children with TM as part of different disease entities have special features in regard to the MRI presentation such as longitudinally extensive transverse myelitis (LETM) and leptomeningeal enhancement in children with MOGAD.
In the follow up study we further found important differences in regard to resolution of lesions over time in the three different subgroups. All children with MOGAD showed a significant resolution of the initially detected lesion over time. There was a significant difference of MRI grades before versus after twelve months of onset ($p<0.002$). In contrast, the majority of children with MS had no or only a slight improvement (grade 3, 4) and no child had a complete lesion resolution within 24 months (grade 1). The group of seronegative children was more heterogeneous with radiological findings ranging from complete resolution after six months (grade 1) to no change at all after 24 months (grade 4). A special feature in children with MOGAD was the complete resolution of lesions as early as six weeks but not later than twelve months (grade 1).

Conclusions: Children with TM and antibodies to MOG show an excellent radiological resolution compared to children with MS and seronegative children.

Keywords:
Transverse Myelitis, Neuroinflammation, MOG, Magnetic Resonance Imaging

EPNS23-2528 Oral or e-Poster
Neurological Emergencies in Children

Neurological management of Status Epilepticus in the pediatric Emergency Room: an eleven-years retrospective analysis.

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Objective: Status Epilepticus (SE) in the pediatric age represents a medical and neurological emergency with risk of brief- and long-term sequelae. The aim of the present study was to (1) retrospectively evaluate the diagnostic and therapeutic approach to SE in the emergency room (ER) of a tertiary care center for pediatrics and pediatric neurology; (2) describe the long-term outcome of these events.

Methods: The present monocentric, retrospective study included episodes of SE diagnosed and treated between 2010 and 2021 by consultant pediatric neurologists in the pediatric ER. The clinical features and management of SE were analyzed. The risk of admission to the Intensive Care Unit (ICU) was evaluated using the Pediatric Early Warning Signs (PEWS) score. The SE in Pediatric patients Severity Score (STEPSS) and the PEDSS outcome prediction score were calculated.

Results: 142 episodes of SE were included within a cohort of 101 patients (mean age: 5 years old). Remote symptomatic etiology was the most frequent (39%), followed by febrile SE (25%). Ninety-one percent of the episodes were classifiable as Convulsive SE (CSE). Video-electroencephalography (v-EEG) was available in 34% of SE in the ictal phase. Nonconvulsive SE (NCSE) and de novo episodes were treated less frequently ($p=0.004$) and with higher delay ($p=0.01$) than CSE and SE occurring in people with epilepsy or history of previous SE. Time to v-EEG and time to therapy administration were directly related to SE's total duration ($Rho=0.6279$ and $Rho=0.64$).
V-EEG recording also helped to identify and treat NCSE occurring after CSE in 30% of registered CSE.
Appropriate color-tagging during triage allowed a timely treatment of SE with shorter duration ($p=0.0043$). High scores on PEWS were associated with higher odds of admission to pediatric ICU in this cohort ($p=0.011$). No significant correlation was found between STEPSS scores and response to treatment ($p=0.24$).

Conclusions: The present study highlighted triage and v-EEG recording play a pivotal role in order to allow a rapid diagnosis and timely treatment of SE in the pediatric ER setting, especially in case of episodes with subtle motor features (NCSE occurring alone or after CSE). The predictive role of STEPSS and PEDSS score has been explored. The PEWS score may be helpful to predict the risk of admission to ICU in pediatric patients with SE. Further studies are needed to improve the approach to SE in the real-life setting.

Keywords:
Status Epilepticus, Emergency Room, Pediatric, Seizures, EEG, PEWS, STEPSS, PEDSS, Management

EPNS23-2124 Oral or e-Poster
Neurological Emergencies in Children

The association between neuro-radiologic parameters and outcome in children with Acute Liver Failure (ALF): a national cohort study

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Objective: Pediatric Acute Liver Failure (PALF) is a rare, life-threatening condition in children, necessitating liver transplantation (LTx) in absence of spontaneous recovery. In the pre-transplant period, the neurological condition can deteriorate rapidly, resulting in morbidity and mortality. In individual patients, obtaining pre-transplant insights into the (ir)reversibility of the neurological condition has been notoriously difficult, hampering medical and surgical decision making. Therefore, we aimed to investigate pre-transplant neurological parameters in relation to outcome.

Methods: We performed a retrospective, observational cohort study of PALF patients with hepatic encephalopathy (HE) grade III-IV, admitted between 1993-2020. According to neurologic parameters and cerebral MRI descriptions, we subdivided patients into three groups: (1) intact pupillary and brainstem reflexes; (2) absent pupillary and/or brainstem reflexes without radiologically proven brain herniation; (3) radiologically proven brain herniation. Primary outcome was defined as survival within 1 year after discharge. We compared the groups for pre-transplant neurological parameters and neurological outcome after treatment.

Results: We included 47 patients, of whom 27/47 (57%) ultimately underwent LTx. Survival rates were 73% (24/33), 43% (3/7) and 14% (1/7) for group 1, 2 and 3, respectively. Survival rates were higher in the LTx group vs. the no-LTx group (74% (20/27) vs. 30% (6/20); p=.006). After LTx, 16/21 patients from group 1 survived with no neurological impairment (14/16) or moderately severe impairment (2/16). From the no-LTx group, 8/12 patients survived, 7 with no neurological impairment and 1 with moderately severe impairment. Absent pupillary reflexes and/or absent brain stem reflexes were not necessarily associated with poor outcome in the LTx group, as 3/3 patients survived with full neurological recovery. All 4 patients from the no-LTx group died. Radiologically proven brain herniation (beginning or advanced) was the only parameter associated with subsequent mortality (6/7) or minimally conscious state (1/7) in both treatment groups.

Conclusions: In patients with PALF and grade III-IV HE, radiological signs of brain herniation are associated with subsequent mortality or severe neurological damage, irrespective of subsequent LTx. Absent pupillary reflexes and/or absent brain stem reflexes do not exclude full neurological recovery after LTx in our cohort and should therefore be interpreted with great caution.

Keywords:
pediatric acute liver failure, liver transplantation, pupillary reflexes, neurological outcome, brain herniation

EPNS23-2597 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

OUTCOME PREDICTORS OF SEIZURE FREEDOM/DRUG FREEDOM AFTER EPILEPSY SURGERY IN A PEDIATRIC SERIES

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Objective: to evaluate the pre-surgical variables associated with seizure freedom/drug freedom in children and adolescents with epilepsy who underwent resective surgery or lobar disconnection

Methods: monocentric retrospective study on epileptic patients who underwent epilepsy surgery. Inclusion criteria: age < 18 years, focal non-hemispheric epilepsy, follow-up > 3 years. Exclusion criteria: age > 18 years, follow-up < 3 years, insufficient data, previous surgical treatment in other centers, palliative surgery, hemispherotomy, hypothalamic hamartomas. Using logistic regression, we evaluated the correlation between semiological, EEG, brain MRI variables and the post-surgical outcome. We grouped patients based on pathology and evaluated the outcome in terms of seizure freedom/drug freedom.

Results: 125 patients (61% M), mean age 13.3 years (3,54-26), age at surgery 9 years (median 9, range 0,5-17,9), mean follow up 4,7 years. Seventy-five (58%) were drug resistant before surgery. EEG showed no interictal epileptic discharges (IEDs) in 36/125 (29%), focal or diffuse IEDs in 79/125 (63%), bilateral independent IEDs in 11/125 (9%). 115/125 (92%) had a clear or subtle brain MRI lesion. Histology: 21/125 (17%) FCD I, 28/125 (22%) FCD II, 53/125 (42%) LEAT, 11/125 (9%) HS, 12/125 (10%) other. Eighty-five patients (68%) were seizure-free and drug-free at last follow-up. Patients with FCD I and other lesions are less likely to become seizure free/drug free than patients with LEAT and FCD II. Predictors of seizure freedom/drug freedom were higher age at onset (p 0.004), shorter disease duration (p 0.001), absence of IEDs (p 0.017) or other than bilateral independent IEDs (p 0.048), positive MRI (p 0.004), lobar/sublobar lesion (p 0.002), no drug resistance (p 0.008). We did not find significant relationship with other variables such as lateralizing or localizing signs, closeness to eloquent areas, seizure frequency before surgery, temporal epileptogenic zone.

Conclusions: Our study underlines the role of IEDs and brain MRI as predictors of outcome in epilepsy surgery in the pediatric population. As already reported in literature, we documented the association between a worse surgical outcome and higher age at surgery, longer disease duration, drug resistance. Data regarding not only predictors of seizure freedom but also drug freedom after surgery are lacking. We reported a good outcome and a long follow-up in our series, suggesting that early withdrawn of ASMs does not influence surgical outcome.

Keywords:

epilepsy surgery - seizure freedom - drug freedom - pre-surgical predictors - pediatric patients

EPNS23-2126 Oral
Epilepsy: Medical & Surgical Treatment

MONARCH and ADMIRAL Interim Analyses: Phase 1/2a Studies Investigating Safety and Drug Exposure of STK-001, an Antisense Oligonucleotide (ASO), in Children and Adolescents with Dravet Syndrome (DS)

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Objective: DS is a severe and progressive genetic developmental and epileptic encephalopathy that typically begins in the first year of life. Approximately 85% of cases are caused by heterozygous, loss of function, de novo mutations in the *SCN1A* gene, which encodes the voltage-gated sodium channel type 1 α subunit ($Na_v1.1$) protein. DS is characterized by high seizure frequency (SF) and severity, intellectual disability, ataxia/motor abnormalities, and a high risk of sudden unexplained death in epilepsy. STK-001 is an investigational ASO treatment designed to upregulate $Na_v1.1$ protein expression in the brain by leveraging the wild-type (non-mutant) copy of *SCN1A* to restore physiological $Na_v1.1$ levels, thereby potentially reducing both SF and non-seizure comorbidities.

Methods: MONARCH (NCT04442295) and ADMIRAL (2020-006016-24) are ongoing, open-label, multi-center studies in US and UK of patients with DS aged 2-18 years assessing safety, tolerability, plasma PK and CSF exposure of intrathecally (IT) administered ascending doses of STK-001. Patients have disease onset <12 months old with recurrent seizures and a genetically confirmed *SCN1A* variant. Patients are grouped by age (2-12 and 13-18 years) and SF is observed for 28 days before dosing. Patients are followed for 6 months after last dose. Adverse events (AEs) are monitored continuously, with plasma and CSF collected for STK-001 exposure at multiple times.

Results: As of 11AUG22, 55 patients received ≥ 1 dose of STK-001 (10 to 45mg/dose). All treatment-emergent adverse events related to study drug were non-serious and mild or moderate. 74.1% (20/27) of patients treated with 3 doses of STK-001 experienced a reduction from baseline in convulsive SF as measured from Day 29 after 1st dose to 3 months post last dose. 55.2% median reduction was observed in patients treated with 45mg (n=6). SF reductions occurred on a background of anti-seizure medications, including fenfluramine. Dose-dependent increase in plasma and CSF exposure was observed, and following repeat dosing, CSF STK-001 accumulation was observed.

Conclusions: Data to date indicate that STK-001 was well-tolerated and overall potential benefit-risk remains favorable in single and multiple doses up to 45 mg/dose. These data support continued development of STK-001 as the first potential disease-modifying approach to treat DS. Together with the OLEs, these data will help inform future clinical studies of STK-001.

Keywords:
mRNA, splicing, trial, United Kingdom, TANGO, United States,

EPNS23-2447 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

Long-term cognitive consequences of self-limited epilepsies of childhood

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Objective: The self-limited epilepsies of childhood are common and were historically considered benign. We sought to determine whether cognitive function in young adults who experienced self-limited epilepsy as children and are now seizure-free and unmedicated differs to the general population.

Methods: We performed a cross-sectional population-based study using data obtained from a national compulsory program for military conscription from 1980-2018. Participants were defined as having a self-limited epilepsy of childhood if they had a previous diagnosis of epilepsy but were > 5 years following the last seizure and > 2 years without anti-seizure medication. The main outcome was the odds ratio for having low cognitive function defined as being >1.5 SD below the mean in those with previous self-limited epilepsy of childhood vs. their peers without a history of epilepsy, using an unadjusted multinominal regression model. Separate analyses were performed for three sub-periods to assess potential impact of changes in management over time. A similar analysis was performed in participants following remission of a non-neurological chronic disease of childhood, asthma.

Results: Following exclusion criteria, 2,124,871 men and women aged 16 to 19 years were included in the analysis, of whom 3,452 (0.16%) met the criteria of having had a self-limited epilepsy of childhood. 346 (10.0%) participants from the self-limited epilepsy group had low cognitive function vs. 160,133 (7.5%) in the other participants. The odds ratio of having low cognitive function in the self-limited epilepsy of childhood group was 1.43 (95% CI 1.28-1.59, p<.001). Correcting for gender and socioeconomic status did not attenuate the statistical significance and was unchanged during the three sub-periods. We did not demonstrate similar findings in the resolved asthma cohort.

Conclusions: Cognitive outcomes in young adults with previous self-limited epilepsies of childhood are more likely to be poor compared to peers with no history of epilepsy. Our results support that this is not merely due to the burden of dealing with chronic illness and stresses the need to avoid the term "benign" for these epilepsies. Further research should delineate the role of seizure burden vs. other possible contributing factors such as long-term effects of anti-seizure medications or genetic variations in epilepsy patients.

Keywords:
epilepsy cognition

EPNS23-2279 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Early predictors of remission in newly diagnosed children with epilepsy: a prospective study

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Objective: Early prediction of treatment outcome in epilepsy continues to be a major challenge. The purpose of this study is to identify predictive factors of a two-year remission (2YR) in a large cohort of children with new-onset seizures based on baseline clinical characteristics, initial EEG and brain MRI findings. A secondary objective is to compute remission rates according to the classification of epilepsies.

Methods: A prospective cohort of 677 children with newly-diagnosed epilepsy, initiated on treatment with antiseizure medication and with a follow-up of at least two years was evaluated. 2YR was defined as achieving at least two years of complete seizure freedom while on treatment. Multivariable analysis was performed with the Cox proportional hazards model and recursive partition analysis was used to develop a decision tree. P-values<0.05 were considered significant.

Results: The median age at time of seizure onset was 6.7 years and the median follow-up was 7.3 years. 548 (80.9%) achieved a 2YR during the follow up period, with the highest yield in children with self-limited focal epilepsy (97.5%) and the lowest in those with developmental epileptic encephalopathy (48.4%). Multivariable analysis found the presence and degree of developmental delay (DD), detection of an epileptogenic lesion on brain MRI and a higher number of pretreatment seizures were significantly associated with a lower probability of achieving a 2YR. Recursive partition analysis found that the presence and severity of DD were the most important predictors of remission. An epileptogenic lesion was a significant predictor variable only in children with no evidence of DD, and a high number of pretreatment seizures was a predictive factor in children with no DD and absence of an epileptogenic lesion.

Conclusions: Seizure remission can be predicted to some extent at the time of initial evaluation, allowing timely selection of children requiring close follow-up, consideration for neurosurgical intervention, or investigational treatments trials.

Keywords:

Children with epilepsy, remission, epileptogenic lesion, developmental delay, number of pretreatment seizures

EPNS23-2818 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Interictal epileptiform discharges stratify focal cortical dysplasia type I and II in intracranial EEG

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Objective: Surgical treatment of pharmacoresistant focal epilepsy related to focal cortical dysplasia (FCD) targets completely removing the epileptogenic lesion. However, a large proportion of the patients have no visible MRI changes despite technical progress in neuroimaging. The delineation of the lesion boundaries still depends on stereo-EEG (SEEG) examination and resection size on the prediction of FCD type I or II (extensive or limited). The cytoarchitectonic background of FCD suggests different manifestations in electrophysiological activity. We hypostatise the interictal epileptiform discharges (IEDs) as the most occurred interictal activity that can reflect FCD types.

Methods: Six hours of awake (3h) and sleep (3h) interictal SEEG of 44 patients with FCD (n=19 type I, n=25 type II) were analysed for IED detection and identify episodes of IEDs recruited into repetitive discharges (RDs). Average IED rate, inter-discharge interval and IEDs periodicity within RD episodes, and average and maximal RD duration were compared between FCD type I and II.

Results: Patients with FCD type II had a significantly higher IED rate ($p<0.005$), a shorter inter-discharge interval within RD episodes ($p<0.003$), sleep influence on decreased RD periodicity ($p<0.036$), and longer RD episode duration ($p<0.003$) than patients with type I. A Bayesian classifier can stratify FCD types with 82% accuracy.

Conclusions: Temporal characteristics of IEDs recruited to RDs reflect the histological findings of FCD subtypes from SEEG and can predict FCD types I and II for surgery planning purposes.

Keywords:
focal cortical dysplasia, epilepsy, interictal epileptiform discharges, type stratification

EPNS23-3000 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Initial phenotype in children with focal cortical dysplasia and low-grade epilepsy-associated tumors: first results of Time to Operate Study

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Objective: to determine the initial phenotype in children with malformations of cortical development (MCD), with emphasis on focal cortical dysplasia (FCD) and low-grade epilepsy-associated tumors (LEAT).

Methods: We retrospectively evaluated 78 clinical characteristics in surgical cohorts of paediatric patients with histological diagnosis of MCD or LEAT operated between 2010 and 2020 in three epilepsy surgery centers (MUH, Prague; UMC, Utrecht; GOSH, London). Identifiers characterized the initial clinical presentation of patients and their diagnostic findings at the time of epilepsy onset. Time intervals between important milestones (e.g. seizure manifestation to the diagnosis, to the referral to the epilepsy surgery centre, to the epilepsy surgery) were analyzed.

Results: We retrospectively assessed 37 children with FCD I, 51 with FCD IIa, 126 with FCD IIb, 36 with FCD IIIb, and 188 with LEAT. Mean age at first seizure was lower in FCDs (type I 49±43 months, IIa 29±34, IIb 36±37) in comparison to FCD IIIb (73±59) and LEATs (70±59). Altogether 24% of patients had diagnostic delay (>2 weeks) after the epilepsy onset (17±25 months). Daily seizures at the time of epilepsy onset were common (>65% of patients) in children with FCD IIa and IIb. Patients with FCD I and IIa had a developmental delay before epilepsy onset more frequently (in 32 and 33% of cases, respectively) than those with FCD IIb, IIIb, and LEAT (<15%). Initial EEG findings were not available in 24% of cases, however, reported ones were abnormal in over 74% of cases. The presence of focal rhythmic discharges appears to be a diagnostic biomarker in a subgroup of children with FCD IIa (33%) and IIb (24%). The first brain MRI was evaluated as normal in 48% of patients with FCD I whereas tumors were almost always diagnosed from the very first MRI. The sensitivity of MRI in determining the associated FCD IIIb in LEATs was low. Best pooperative seizure outcomes were seen in children with LEATs, FCD IIIb, and IIb (86, 78, and 80% of cases seizure-free at 2 years follow-up) compared to 66% in FCD I and 75% in FCD IIa.

Conclusions: With these preliminary results of an ongoing multicentric study, we were able to describe, compare and contrast the initial clinical course of FCD type I, type II and LEAT. We were able to describe, compare and contrast the initial clinical course of FCD type I, type II and LEAT. Several gaps in current clinical practice were identified. Our ultimate goal is to facilitate the diagnostic process in this patient's group.

Keywords:
epilepsy surgery, MCD, FCD, LEAT, preoperative evaluation, phenotype

EPNS23-2220 Oral or e-Poster
Movement Disorders

The clinical and genetic spectrum of autosomal-recessive TOR1A-related disorders

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Objective: TOR1A-associated arthrogryposis multiplex congenita 5 (AMC5) is a rare neurodevelopmental disorder arising from biallelic variants in TOR1A. While less than 15 individuals with TOR1A-AMC5 have been reported in detail, a systematic investigation of the full disease-associated spectrum of autosomal-recessive TOR1A-related disorders has not been conducted.

Methods: Clinical characteristics, imaging findings, and genetic information of 56 affected individuals from 39 families with biallelic variants in TOR1A were systematically analyzed using standardized Human Phenotype Ontology terminology and in silico prediction tools.

Results: Median age at last follow-up was 3 years (0-24 years). Most individuals presented with congenital flexion contractures (95%) and developmental delay (80%). Motor symptoms were reported in 79% and included lower limb spasticity, pyramidal signs, and gait disturbances. Facial dysmorphism was an integral part of the phenotype, with key features being a broad/full nasal tip, narrowing of the forehead and full cheeks. Analysis of disease-associated manifestations delineated a phenotypic spectrum ranging from normal cognition and mild gait disturbance to congenital arthrogryposis, global developmental delay and inability to walk. In a subset, the presentation was consistent with fetal akinesia deformation sequence with severe intrauterine abnormalities. Survival was 71% with higher mortality in males. Death occurred at a median age of 1.2 months (1 week - 9 years) due to respiratory failure, cardiac arrest, or sepsis. Brain MRIs identified non-specific neuroimaging features, including a hypoplastic corpus callosum (72%), foci of signal abnormality in the subcortical and periventricular white matter (55%), diffuse white matter volume loss (45%), mega cisterna magna (36%) and arachnoid cysts (27%). The molecular spectrum included 22 variants, defining a mutational hotspot in the C-terminal domain of the Torsin-1A protein. Genotype-phenotype analysis revealed an association of missense variants in the 3-helix bundle domain to an attenuated phenotype, while missense variants near the Walker A/B motif as well as biallelic truncating variants were linked to early death.

Conclusions: This systematic cross-sectional analysis of a large cohort of individuals with biallelic TOR1A variants across a wide age-range delineates the clinical and genetic spectrum of TOR1A-related autosomal-recessive disease and highlights potential predictors for disease severity and survival.

Keywords:
AMC5; arthrogryposis multiplex congenita 5; biallelic variation; NDD; Torsin-1A

EPNS23-3009 Oral or e-Poster
Neurogenetic Disorders

Biallelic pathogenic variants in ITFG2 are associated with a a syndromic megalencephalic neurodevelopmental syndrome

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Objective: The mechanistic target of rapamycin complex 1 (mTORC1) is a central regulator of cell growth that responds to diverse environmental signals and is deregulated in many human diseases, including cancer and neurodevelopmental disorders. KICSTOR is a four-member (KPTN, SZT2, ITFG2 and c12orf66) protein complex involved in the lysosome-associated negative regulation of mTORC1 signalling. KPTN and SZT2 have already been implicated in neurodevelopmental disorders mainly characterized by global developmental delay, intellectual disability, epilepsy, macrocephaly and facial dysmorphisms (MIM 615620 and MIM 615463). Integrin-alpha FG-GAP repeat containing protein 2, or ITFG2, is one of the four subunits of the KICSTOR protein complex.

Methods: The affected individuals were identified by screening genomic datasets from several diagnostic and research genetic laboratories internationally, as well as using GeneMatcher. After obtaining signed informed consent forms, clinical data and DNA samples were collected from participating families and used under research project approved by the Review Boards and Bioethics Committees at University College London Hospital and the other participating institutions. Either whole exome sequencing (WES) or whole genome sequencing (WGS) was performed at different diagnostic or research laboratories. The candidate variants were confirmed after filtering and interpretation according to the ACMG Guidelines, and segregation analyses was done by Sanger sequencing. Knockouts and knockins in zebrafish were generated by CRISPR/Cas9.

Results: We report a total cohort of 37 affected individuals from 22 unrelated families, presenting with a neurodevelopmental disorder characterized by global developmental delay, intellectual disability, macrocephaly, facial dysmorphisms and variable presence of autistic features. Sixteen variants were detected, including eight truncating variants, six missense variants and two splice variants. Interestingly, two of the missense variants were detected within multiple families, suggesting there might be a shared ancestral haplotype within these families. Knock-out and knock-in zebrafish model recapitulates the phenotype, presenting with craniofacial abnormalities and severe motor deficits.

Conclusions: We implicate ITFG2 as a new disease causing gene related to a novel syndromic megalencephalic neurodevelopmental syndrome.

Keywords:
KICSTOR, mTOR, Megalencephaly, Intellectual disability

EPNS23-2302 Oral
Neurogenetic Disorders

Analysis of progression and specific patterns of brain atrophy in CLN2 patients receiving standard of care ICV-ERT with Cerliponase alfa

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Objective: Neuronal ceroid-lipofuscinosis type 2 (CLN2) is a neurodegenerative lysosomal storage disease caused by mutations in the TPP1 gene, encoding the lysosomal enzyme tripeptidyl peptidase 1 (TPP1). Affected children show first clinical symptoms between 1.5 and 4 years of age, including language developmental delay, seizures, psychomotor decline and loss of vision. As the disease primarily affects the central nervous system, neurodegeneration is reflected by a rapidly progressive loss of gray matter which can be quantified using MRI volumetric analysis. Currently, the only approved treatment consists of intraventricular enzyme replacement therapy (ICV-ERT) with recombinant human TPP1 (Cerliponase alfa). Clinical trials have shown that this treatment slows down the loss of motor and language function as measured using disease specific clinical scoring systems.

Methods: In our study, we followed 29 CLN2 patients receiving ICV-ERT as standard of care outside clinical trial settings and collected longitudinal data on disease progression for up to 55 months: These data consisted of MRI scans every 6 months as well as the Hamburg LINCL Scale, the Weill-Cornell LINCL Scale, Denver Developmental test and CLN2 Movement Disorder Inventory as clinical follow-up parameters. For MRI volumetric analysis we used the Freesurfer Software followed by a non-linear mixed effects regression. Partial Least Square analysis was used to analyse the correlation between clinical parameters and brain volumetric measures. Global gray matter loss was contextualized with metabolic, transcriptomic, structural and functional network data of healthy cohorts (Allen Human Brain Atlas).

Results: Analyses revealed that the overall loss of cortical gray matter in treated patients (4.5 % per year) was less than in pre-published natural history cohort (12.5% per year). Moreover, we could identify patterns of brain atrophy as well as of clinical disease progression which strongly correlated with each other. Contextualization analyses showed that brain regions with high levels of interconnection, with high oxygen and high glucose metabolism are most severely affected by brain atrophy.

Conclusions: These data show that brain volumetric analysis in MRI scans is a valuable and sensitive follow-up parameter for analysis of disease progression and treatment efficacy. Moreover, contextualization results suggest that TPP1 deficiency affects especially highly active neurons and provide novel insights into the pathophysiology in CLN2 disease.

Keywords:
neuronal ceroid lipofuscinosis (NCL; CLN); enzyme replacement therapy (ERT); cerliponase alfa; magnetic resonance imaging (MRI), neuroimaging, brain volumetry

EPNS23-2787 Oral or e-Poster
Neurogenetic Disorders

Expanding clinical and molecular spectrum of IL-6 signal transduction disorders reveals variable immunodeficiency and neurodevelopmental features with dysregulated autophagy and intracellular trafficking

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Objective: Cytokine receptors on cell surfaces include transmembrane interleukin-6 signal transducers that regulate cellular differentiation, proliferation, and host defense against intruding organisms during infection. Biallelic variants in cytokine receptor genes *IL6ST* and *LIFR* are associated with Stüve-Wiedemann syndrome (SWS), characterized by neurodevelopmental disorders, dysautonomia, bone abnormalities, and innate errors of immunity. Monoallelic variants are increasingly found with isolated phenotypes (urinary tract anomalies, Hyper-IgE syndrome). The pathomechanism, metabolic dysregulation, and phenotypic variability remain largely elusive.

Methods: We investigated detailed clinical, imaging, molecular, and immune cellular features from the largest cohort of patients with biallelic and monoallelic IL-6 signal transduction disorders reported to date. We complemented our analysis by a reverse genetic approach including proteomic data and experimental findings from primary patient cells, murine cellular assays, and transgenic mice.

Results: Based on detailed characterization of 85 patients with biallelic and monoallelic *LIFR* and *IL6ST* variants, we identified a wide clinical, molecular, and imaging spectrum. Genotype-phenotype studies suggested tentative correlations between clinical severity and residual protein expression. Characteristic findings of SWS showed variable progression, even in monoallelic disorders. Novel phenotype expansions mimicking congenital disorders of autophagy included hypopigmentation, epilepsy, and movement disorders. We characterized one patient with a homozygous LIFR:p.Cys270Gly mutation and lethal course of COVID-19 infection in more detail. Murine cellular assays with LIFR:p.Cys270Gly indicated reduced STAT3, STAT1, and ERK phosphorylation, and flow cytometry revealed lower LIFR presentation on the cell surface. We detected significant downstream dysregulation of autophagy and intracellular trafficking in proteomic investigations from primary LIFR:p.Cys270Gly patient cells, isolated out of bronchoalveolar lavage fluid, and from a transgenic mouse model with selective inhibition of Il6st in astrocytes.

Conclusions: Impaired IL-6 signal transduction reveals downstream dysfunction of autophagy and intracellular trafficking that may explain several features of the phenotype expansion in SWS. This novel pathomechanism in cytokine receptor disorders may serve as a basis for therapy development for an important emerging group of monogenic neuroimmunological disorders.

Keywords:
neuroimmunological disorders, dysautonomia, COVID-19, autophagy, intracellular trafficking, cellular assays, transgenic mice

EPNS23-2638 Oral
Neurogenetic Disorders

The genetic spectrum of congenital ocular motor apraxia type Cogan

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Objective: The term congenital ocular motor apraxia (COMA), coined by Cogan in 1952, designates the incapacity to initiate voluntary eye movements performing rapid gaze shift, so called saccades. While regarded as a nosological entity by some authors, there is growing evidence that COMA designates merely a neurological symptom with etiologic heterogeneity.

Methods: In 2016, we reported an observational study in a cohort of 21 patients diagnosed as having COMA. Thorough re-evaluation of the neuroimaging features of these 21 subjects revealed a previously not recognized molar tooth sign (MTS) in 11 of them, thus leading to a diagnostic reassignment as Joubert syndrome (JBTS). Specific MRI features in two further individuals indicated a Poretti-Boltshauser syndrome (PTBHS) and a tubulinopathy. In eight patients, a more precise diagnosis was not achieved. We pursued this cohort aiming at clarification of the definite genetic basis of COMA in each patient.

Results: Using a candidate gene approach, molecular genetic panels or exome sequencing, we detected causative molecular genetic variants in 17 of 21 patients with COMA. In nine of those 11 subjects diagnosed with JBTS due to newly recognized MTS on neuroimaging, we found pathogenic mutations in five different genes known to be associated with JBTS, including KIAA0586, NPHP1, CC2D2A, MKS1, and TMEM67. In two individuals without MTS on MRI, pathogenic variants were detected in NPHP1 and KIAA0586, arriving at a diagnosis of JBTS type 4 and 23, respectively. Three patients carried heterozygous truncating variants in SUFU, representing the first description of a newly identified forme fruste of JBTS. The clinical diagnoses of PTBHS and tubulinopathy were confirmed by detection of causative variants in LAMA1 and TUBA1A, respectively. In one patient with normal MRI, biallelic pathogenic variants in ATM indicated variant ataxia telangiectasia. Exome sequencing failed to reveal causative genetic variants in the remaining four subjects, two of them with clear MTS on MRI.

Conclusions: Our findings indicate marked etiologic heterogeneity in COMA with detection of causative mutations in 81% (17/21) in our cohort and nine different genes being affected, mostly genes associated with JBTS. We provide a diagnostic algorithm for COMA.

Keywords:
Congenital ocular motor apraxia; Cogan syndrome; Joubert syndrome; molar tooth sign; ciliopathy; Poretti-Boltshauser syndrome

EPNS23-2250 Oral or e-Poster
Neurogenetic Disorders

Whole exome and whole genome sequencing for the diagnosis of rare paediatric neurological disorders

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Case study: Introduction: Rare diseases affect a very small percentage of the population (5 out of 10 000 people in Europe). Most of them have neurological symptoms and about 90% of those affect children. The average time from the first symptom to diagnosis is at least three to five years and up to 50% of patients remain undiagnosed. Genetic testing plays an important role in discovering and identifying the underlying disease mechanism. Next generation sequencing techniques, like whole exome sequencing (WES) and whole genome sequencing (WGS) quickly became a first-line diagnostic approach for undiagnosed genetic disorders.

Materials and Methods: In our study we examined 70 undiagnosed patients with neurological features. Their age ranges from 6 mounts to 16 years. WES was applied on 32 patients and 38 patients were tested through WGS. WES and WGS were performed on an BGISEQ-500 platform in our partner laboratory - BGI. We performed individual bioinformatics analysis on WES and WGS data based on every patient clinical phenotype. The classification of the variants was performed using ACMG criteria.

Results: We identified pathogenic/likely pathogenic variants in 38 out of 70 patients, which were correctly diagnosed. Variants with unknown significance were detected in 22 patients as potential candidates associated with their phenotype. For them we recommended family segregation analysis for re-classification of identified VUS. After performed bioinformatic analysis ten remained without diagnosis, and re-analysis of the data after one year was recommended.

Conclusion: The application of WES and WGS has revolutionized the diagnosis of rare pediatric disorders. The results ended the diagnostic odyssey of 38 of our patients and added valuable genetic knowledge about pediatric neurologic disorders in our country. Fifty-four percent of our patients received a genetic diagnose, among them children with ultra-rare diseases like: TH deficiency, Knobloch syndrome, Smith-Kingsmore syndrome, Cockayne syndrome, type B, Walker-Walburg syndrome, Basilicata-Akhtar Syndrome, Alazami-Yuan syndrome etc. For many of these disorders there is no treatment available, but the diagnosis allows families to understand the condition, enables prevention and prognosis of the course of the disease.

Keywords:
WES, WGS, paediatric neurological disorders, ultra-rare diseases

EPNS23-2659 Oral
Epilepsy: Diagnosis and Investigations

Complex clinical and genetic characteristics of a single-center cohort of pediatric patients with focal cortical dysplasia type I and epilepsy

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Objective: Focal cortical dysplasia type I (FCD type I) is still an enigmatic entity - patients vary in their clinical course, and its genetic cause is still unknown. We aimed to characterize clinical course and describe genetic findings of a large surgical cohort of pediatric patients with FCD type I.

Methods: We included paediatric patients who underwent epilepsy surgery in Motol Epilepsy Center for focal drug-resistant epilepsy with histopathological diagnosis of isolated FCD type I according to the current FCD classification (n=28). Preoperative evaluation always included a detailed description of a clinical course, scalp EEG, MRI and neuropsychological examination; SPECT, PET and SEEG if necessary. DNA isolated from blood and brain tissue was tested by whole-exome sequencing (WES).

Results: Histopathology verified FCD type IA in 61%, FCD type IB and IC represent 21% and 18% resp. Epilepsy started before 6 years of age in 75%. Daily seizures were observed in 78% of patients and 4/28 had a status epilepticus. Developmental delay or cognitive decline during the epilepsy course was observed in 22 patients (79%). Localized continual or intermittent EEG slowing was described in 26 patients (92%). Interictal epileptiform abnormity was mostly multiregional (18/28). Normal or nonspecific findings on MRI were in 12/28, and 10/12 (83%) of them underwent SEEG. Focal resection was done in 16 patients (57%), multilobar in 7 (25%), hemispherotomy in 4 (14%) and lobar in 1 patient. Postoperatively, 71% of children are seizure-free (Engel 1). Molecular-genetic testing of blood-derived DNA was done in 19/28 patients, and somatic WES in 14/28. In one patient, we identified a somatic variant in *RARS1* gene (c.1761G>T, chr5:g.168517950G>T, p.Lys587Asn) with VAF 2,53%. We also identified in one patient a germline variant in gene *Rb1* (c.1815-1G>A, chr13:g.49030339G>A).

Conclusions: We present a unique cohort of paediatric patients with FCD type I. Utilizing complex multimodal diagnostic approach, they can achieve favorable postsurgical outcomes. We identified a somatic variant in *RARS1* gene previously not associated with MCD and a germline variant in *Rb1* gene which can regulate neuronal migration. In both of these findings, however, functional studies are necessary.

Keywords:
focal epilepsy; focal cortical dysplasia type I; preoperative evaluation, molecular-genetic testing

EPNS23-2633 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

Effect of Fenfluramine on Generalized Tonic-Clonic Seizures in Rare Epilepsy Syndromes: A Review of Published Studies

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Objective: We aim to describe the effectiveness of fenfluramine (FFA) on generalized tonic-clonic seizures (GTCS) or tonic-clonic seizures (TCS) in patients with rare epilepsy syndromes.

Methods: Reports of patients treated with FFA for seizures associated with rare epilepsy syndromes were identified and subsequently included if FFA was used for convulsive seizure control. The studies selected described a change in the frequency of GTCS, TCS, or major motor seizures. Case reports or studies where the reduction in GTCS or TCS was unclear were excluded. Initial FFA doses, duration of treatment (exposure), and reduction in GTCS/TCS are reported. Descriptive statistics were used for the analysis.

Results: We included data from 13 studies: 4 randomized-controlled trials (RCTs), 4 observational studies, 4 open-label studies, and 1 case series. A total of 561 patients were enrolled and treated with FFA for DS (n=360), LGS (n=176), Sunflower syndrome (n=10), CDKL5 deficiency disorder (n=6), SCN8A-related disorder (n=3), and other developmental and epileptic encephalopathies (DEEs; n=6). Of these, 396 (70.6%) patients experienced GTCS or TCS at baseline. Patients were generally initiated on 0.2 mg/kg/day FFA added to their baseline standard-of-care regimen and titrated per protocol or by physician discretion. Mean or median treatment duration (exposure) ranged from 12 weeks up to 16 years. In 3 studies, the reduction in GTCS or TCS was included as part of the overall seizure type evaluated. A reduction in frequency of GTCS or TCS was observed in most FFA-treated patients. In 8 studies (including the 4 RCTs), the median percent reduction in GTCS ranged from 45.7% to 90.8%. Among 8 studies providing data, 7 reported at least half of the patients experienced >=75% reduction in GTCS or TCS frequency; 5 studies reported that more than half of patients were GTCS-free after FFA treatment.

Conclusions: These results indicate that FFA led to a clinically significant reduction in GTCS or TCS frequency in patients with rare epilepsy syndromes. Further research is needed to determine the impact of FFA on sudden unexpected death in epilepsy (SUDEP) in those patient populations. Funded by UCB Pharma.

Keywords:

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EPNS23-2723 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Exome sequencing reveals novel candidate variants in patients with malformations of cortical development and focal epilepsy

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Objective: Despite emerging reports on novel genes implicated in pathogenesis of malformations of cortical development (MCD), a significant proportion of patients remain without genetic cause. We aimed to detect novel genetic variants in genes involved in neurogenesis in a cohort of patients with MCD and focal epilepsy investigated in a tertiary centre for epilepsy and epilepsy surgery.

Methods: A database of 165 blood-derived DNA samples obtained from patients investigated for focal epilepsy and/or MCD was filtered for variants in 7547 genes involved in neurological pathways and phenotypes published in a paper by Lai et al., 2022. The respective patients underwent targeted gene panel sequencing and/or exome sequencing. We prioritised for loss-of-function variants with less than 1% frequency in gnomAD (genomes and exomes).

Results: Approximately 256 thousand variants were identified (before prioritization). We identified one splice-site and one frameshift deletion variant in ATP6V0B : NM_001294333.1(ATP6V0B):c.258del p.(Lys87Argfs*58) and NM_004047.5(ATP6V0B):c.68-5T>A p.? , both previously unreported, in patients with strikingly similar phenotype. Both patients suffered from drug-resistant focal epilepsy originating in insular cortex, with normal cognitive development and normal neurological findings, otherwise healthy; both were MRI-negative. They both underwent epilepsy surgery, including stereoEEG study; in neither of them were we able to ascertain histopathological diagnosis. Both patients are seizure-free after surgery, still on anti-seizure medication. ATP6V0B encodes for ATPase H+ transporting V0 subunit b, and Meo-Evoli et al. found that ectopic expression of ATP6V0B increased mTORC1 activity, a know pathway involved in FCD pathogenesis. In both cases, the variant was inherited from an unaffected parent. No other LoF, missense or splicing variants in ATP6V0B, absent from controls, were identified in our database.

Conclusions: We identified two LoF variants in ATP6V0B in patients with drug-resistant focal insular epilepsy. We hypothesise a potential role of ATP6V0B, possibly in combination with a second-hit variant present in brain tissue. Functional studies to ascertain the role of these variants are warranted.

Keywords:

ATP6V0B, focal cortical dysplasia, insular epilepsy

EPNS23-2971 Oral
Epilepsy: Diagnosis and Investigations

PredictSNP^{NEURO}: Structure- and Sequence-Based Bioinformatics Analysis of Mutations in Protein Targets Related to Epilepsy

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Objective: Understanding the effect of mutation on protein function is essential in medicine for the treatment of various diseases. Nowadays, precision medicine is increasingly applied to treat individual patients based on their specific predispositions. With fast and cheap sequencing methods, we can identify variations in an individual's genetic code and preselect altered proteins that could be causing a disease. Methods of structure- and sequence-based bioinformatics can be efficiently used to analyze these variations on a molecular level, explain the effect of mutation on protein function, and even suggest potential treatment strategies. Recently, we developed a web server, PredictSNP^{ONCO}, for the analysis of mutations in cancer-related proteins (https://loschmidt.chemi.muni.cz/predictsnp-onco). The web server provides fully provides automated computational workflow combining bioinformatics, molecular modelling, and machine learning to evaluate the effect of mutation and to select potential drugs.

Methods: In the next step, we will update our workflow to analyze proteins related to epilepsy, including calcium and sodium channels and GABA receptors. First, we will download and prepare the structures of relevant target proteins. Second, the workflow will build the mutant proteins, structurally and sequentially compare the wild-type protein with its variants, and evaluate changes in protein stability, structure, and function. A subsequent virtual screening will evaluate changes in the binding of potential inhibitors from a list of all FDA/EMA-approved drugs. The calculated results will be supplemented with data from bioinformatics databases, like UniProtKB, and will be quickly available in an interactive graphical user interface. The results will be further analyzed by a predictor based on machine learning. For the analysis of transmembrane channels, some modifications of the workflow need to be introduced. Besides the preparation of novel protein targets and search in relevant databases, analysis of ligand transport by an in-house developed tool CaverDock will be implemented.

Results: The goal is to provide clinicians with aggregated data from multiple computational tools and databases to identify problematic mutations, analyze their effects, and suggest potential inhibitors in a drug-repurposing manner.

Conclusions: PredictSNP^{NEURO} will be designed as a fully automated web server with an intuitive graphical user interface for non-experts in computer modeling.

Keywords:
web server, bioinformatics, effect of mutation, structure analysis

EPNS23-2287 Oral

Epilepsy: Medical & Surgical Treatment

SURGICAL TECHNIQUE DOES NOT DETERMINE SEIZURE OUTCOME AFTER HEMISPHEROTOMY

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Objective: We aimed to assess determinants of seizure outcome following pediatric hemispherotomy in a contemporary cohort.

Methods: We retrospectively analyzed the seizure outcomes of 457 children who underwent hemispheric surgery in five European epilepsy centers between 2000 and 2016. We identified variables related to seizure outcome through multivariable regression modeling with missing data imputation and optimal group matching and further investigated the role of surgical technique by Bayes factor (BF) analysis.

Results: 177 (39%) children underwent vertical and 280 (61%) lateral hemispherotomy. 344 (75%) children achieved seizure freedom at a mean follow-up of 5.1 years (range 1 to 17.1). We identified acquired etiology other than stroke (odds ratio (OR) 4.4, 95% confidence interval (CI) 1.1-18.0), hemimegalencephaly (OR 2.8, CI 1.1-7.3), contralateral MRI findings (5.5, CI 2.7-11.1), prior resective surgery (OR 5.0, CI 1.8-14.0), and left hemispherotomy (OR 2.3, CI 1.3-3.9), as significant determinants of seizure recurrence. We found no evidence for an impact of the hemispherotomy technique on seizure outcome (the Bayes factor for a model including the hemispherotomy technique over the null model was 1.1), with comparable complication rates for different approaches.

Conclusions: Knowledge about independent determinants of seizure outcome following pediatric hemispherotomy will improve the counseling of patients and families. In contrast to previous reports, we found no statistically-relevant difference in seizure-freedom rates between the vertical and horizontal hemispherotomy techniques when accounting for different clinical features between groups.

Keywords:

hemispheric surgery; hemispherotomy; pediatric epilepsy; seizure outcome

EPNS23-2996 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Establishing PROMs in medication management of rare genetic epilepsies: What are the best medications in 228 SYNGAP1 patients?

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Objective: A major problem with rare diseases is that there is often little structured data on the efficacy of drugs, as individual institutions only care for a small number of patients. In addition, in rare diseases, it is often not known what the main goals and problems of drug therapy are. To solve these problems, we developed the data collection topics together with the patients' parents and collected drug efficacy data worldwide with the patients' parents (PROMs - Patient Reported Outcome Measures). We started with one pilot disease, SYNGAP1-related developmental and epileptic encephalopathy (SYNGAP1).

Methods: In order to cover a large collective and thus obtain better statistical power, a multilingual online platform for patient collaboration and data collection was developed. The online questionnaire system was based on REDCap. In the survey, we asked parents' subjective evaluation of the effect of medication in SYNGAP1. We worked out with the parents that in addition to the effect on seizures, the effects and side effects on behavior, development, and sleep are of very great interest in SYNGAP1. Thus the parents indicated the effect on seizures, behavior, development, and sleep on a scale from -50 to +50.

Results: We received 228 complete data sets from at least 15 countries, representing 20% of the known SYNGAP1 patients worldwide. Of these, we collected data on 49 medications. To motivate parents, we have displayed the survey results immediately. We evaluated data only on drugs for which at least seven responses were available.
The best effects in the area of seizures were achieved by the drugs valproate, ethosuximide and clobazam, lamotrigine and CBD; In the behavioral area THC, statins and CBD; in the developmental area carbamazepine, statins and CBD and in the sleep area melatonin, THC, and clonidine.

Conclusions: Valproate, which is by far the most frequently used medication, and ethosuximide achieve a very good anticonvulsant effect, but have only a slight positive effect in the other three areas.
The drugs levetirazetam and perampanel had small positive effects on seizures but such negative ratings on behavior, sleep, and development that their use seems questionable.
Carbamazepine had unexpected ratings: on average, it seemed to worsen seizures minimally, but there was a very significant improvement in development. We believe we may be able to elucidate this effect in the future with a correlation with the different genetic SYNGAP1 mutations.

Keywords:
SYNGAP1, therapy, rare genetic epilepsies, AED

EPNS23-2573 Oral or e-Poster
Neurodevelopmental Disorders

Cognitive, Motor and Social Development of Toddlers Aged 12 To 36 Months Old during the Covid-19 Pandemic in the National Capital Region, Philippines: A Single Tertiary Hospital Study

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Objective: During the first three years of life, rapid growth ensues to facilitate development. With lockdown restrictions, toddlers during the COVID-19 pandemic had significantly reduced environmental stimulation, leading to missed opportunities for learning and play. Studies revealed declining scores in children's developmental assessments since the pandemic started. This was the first study in the Philippines to describe the cognitive, motor and social development of children aged 12 to 36 months during the COVID-19 pandemic, using the Early Childhood Care and Development (ECCD) Checklist. This study also identified factors correlated with increased risk of developmental delay.

Methods: A descriptive cross sectional study was done among children aged 12 to 36 months. The ECCD Checklist was administered to determine the children's risk of developmental delay. Descriptive statistics determined the demographics. Factors correlated with developmental delay determined using Chi-square test, Multiple Logistic Regression and Odds Ratios, (CI=95%, alpha=0.05).

Results: 145 children aged 12 to 36 months were included (mean=25.28±7.078 months). Compared to pre pandemic data, more children (25.5%, n=145) were identified at risk for delays in one or more developmental domains. The odds of toddlers being at risk of developmental delay increased by two-fold among those with daily screen time of an hour or longer (p=0.033, OR=3.055). 73.1% (n=145) of toddlers had daily screen time of an hour or longer, contrary to AAP recommendations. Though 61.4% (n=145) had less than an hour of daily informal study sessions, 93.1% (n=145) had daily physical activity of an hour or longer despite lockdowns.

Conclusions: During the COVID-19 pandemic, more toddlers were at risk for developmental delay, with odds increased with longer screen time. These findings may guide educational sectors in formulating interventions to prevent delays as we continue online classes in the Philippines. All this to help children adapt better as the country moves through the new normal.

Keywords:
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EPNS23-2217 Oral
Neurodevelopmental Disorders

DEVELOPMENTAL OUTCOME OF BABIES BORN DURING THE COVID-19 PANDEMIC

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Objective: Introduction: As paediatric neurologists, to better understand an abnormal developmental course when we see it in our patients, we must know what constitutes normal neurodevelopment. Early in the Covid-19 pandemic there was speculation about the impact of mass isolation and mask-wearing on infant development.

Aims: To look at neurodevelopmental outcomes in a Covid-19 pandemic birth-cohort.

Methods: Methods: We report on a longitudinal prospective observational cohort study of infants born into the Covid-19 pandemic. At 12- and 24-months of age, parents completed developmental questionnaires [developmental milestones, Ages-and-Stages(ASQ), and Language Development Survey (LDS)]. Results were compared to a pre-pandemic birth cohort. A subset of infants were assessed at 18-months using eye-tracking technology(Tobii Pro/X3-120), to look at gaze preference in masked and unmasked adults.

Results: Results: 365 infants born between March and May 2020 were recruited to the cohort study.

At 12-months we compared milestones for pandemic and pre-pandemic cohorts; in logistic analyses infants in the pandemic cohort had significant differences in having one definite and meaningful word, pointing and crawling compared to the pre-pandemic cohort.

At 24-months of age infants in the pandemic and pre-pandemic cohorts had similar developmental outcomes in most domains on ASQ (fine motor, problem solving, personal and social) except communication and gross motor where children from the the pandemic cohort had lower scores compared to a pre-pandemic cohort, and communication where children from the pandemic cohort were more likely to fall under standardized cut-offs. In addition, children born in the pandemic cohort had fewer average words on the LDS compared to previously reported birth cohorts.

In the eye-tracking task when parents or strangers wore a mask, infants demonstrated less interest in the mouth.

Conclusions: Conclusion: Fewer pandemic-born infants have achieved communication milestones at 12- and 24-months compared to a pre-pandemic cohort. 18-month-old infants paid little interest in the mouth and face when looking at masked adults. Further work will determine if mask wearing is linked to language attainment. Universal developmental screening and appropriate timely intervention is extremely important for pandemic-born infants.

Keywords:
Normal neurodevelopment

EPNS23-3014 Oral or e-Poster
Infections and Inflammatory Diseases

Post-Covid-19 Immune-mediated encephalitis in children: case series and literature review

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Case study: OBJECTIVES
Immune-mediated encephalitis is a rare complication of SARS-CoV2 infection at all ages (overall incidence of 0.5%).This condition presents extreme clinical variability: it highlights the importance of a standardized diagnostic-therapeutic algorithm.
METHODS
We conducted: (a) a systematic review (from January 2020 to December 2022) searching on Pubmed and Google Scholar databases including all paediatric patients (aged 0 to 18 years) with post-Covid-19 encephalitis; we aimed to analyze demographic data, clinical manifestations, laboratory and instrumental findings, therapy and prognosis; (b) a clinical, laboratory and imaging prospective study in a cohort of 8 children seen and prospectively followed-up at our Center.
RESULTS
A total of 25 affected children were analyzed from 17 studies and compared with our cohort. The mean age at onset in the literature was 9.3 years (SD ± 4,26) vs. 5,8 years (SD ± 2,08) in our cohort; the clinical presentation ranged from mild to severe neurological manifestations, in the literature vs. our series:headache(4/25 vs. 1/8);tonic-clonic seizures(6/25 vs. 3/8);tics-like motor disorders,ataxia, dysarthria(8/25 vs. 3/8);irritability or psychiatric disorders(3/25 vs. 3/8); altered mental status (2/25 vs. 4/8). Brain MRI showed T2 hyperintensities in the middle portion of the posterior corpus callosum (12/25 vs. 1/8), in the subcortical parietal/temporal/frontal white matter (8/25 vs. 7/8) and in the limbic system (2/25 vs. 2/8), and leptomeningeal enhancement in unilateral areas (3/25). The remnant 4/25 reported cases in literature showed normal brain MRI patterns, vs. no negative cases in our cohort. Autoantibodies were tested both in serum and on CSF: it showed positivity to anti-MOG (3/25), anti-basal ganglia (1/25), anti-NMDAR (1/25) antibodies; autoantibodies were absent in our cohort.The prognosis was good in most children after treatment with IVIG, high-dose methylprednisolone, and/or rituximab with complete recovery (15/25 vs. 5/8), partial recovery (10/25 vs. 3/8).
CONCLUSIONS
The latency of onset of neurological manifestations following Covid-19 infection suggests the role of SARS-CoV2 as a possible autoimmune trigger. Diagnosis is crucial for early therapeutic choice.The triad of corpus callosum, subcortical white matter and leptomeningeal involvement aided the diagnostic work-up in our experience. The prompt use of immunomodulating-therapies allows a good prognosis despite the severity of the clinical condition.

Keywords:
post-covid19; encephalitis; autoimmune encephalitis

EPNS23-2299 Oral
Sleep Disorders

Screen exposure and sleep: how the COVID-19 pandemic influenced children and adolescents - a questionnaire-based study

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Objective: COVID-19 pandemic has drastically increased the exposure to electronic devices in children, influencing their lifestyle and their sleep. This study was conducted to explore the relationship between the augmented screen exposure and sleep habits in children during and after the pandemic

Methods: Using the "Google Forms" tool, we created an online questionnaire addressed to parents of children and adolescents aged 2-18 years. We explored the use of screens before and during/after the lockdown and assessed the presence of sleep disturbances through the Sleep Disturbance Scale for Children (SDSC), referring to the period before and during/after COVID-19 pandemic.

Results: We collected 1084 valid questionnaires (median age 8.5±4.1 years). We observed a significant increase in screens exposure for school (72%) and for leisure (49.7%) during the pandemic. We reported an increased sleep disturbances prevalence from 22.1% before the pandemic to 33.9% during the outbreak ($p<0.001$). Even before the pandemic, the highest risks for sleep disorders were related to daily screen time for school reasons (OR 1.65, $p <0.001$) and total screen time after 6 pm (OR 1.59, $p <0.001$). The augmented exposure to screens for any reasons during the pandemic was significantly related to an increase of sleep disorders, especially regarding the increased exposure after 6 pm (OR 1.67, $p <0.001$).

Conclusions: The augmented use of electronic devices was recognized to be a significant predisposing factor in increasing the rate of sleep disorders during and after the pandemic, thus sleep hygiene recommendations should be highlighted to promote correct sleep habits.

Keywords:
COVID-19, pandemic, screen use, electronic device, sleep, children

EPNS23-2783 Oral or e-Poster
Infections and Inflammatory Diseases

High incidence of cerebrovascular lesions in pediatric COVID-19 during omicron outbreak - a MRI study

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Objective: The incidence of pediatric hospitalization was significantly increased since the spread of omicron variant of COVID19. A change of characteristics in respiratory and neurological symptoms have been reported. The abnormalities on MRI in children with omicron-related neurological manifestation haven't been reported. Vasculitis of various sized vessels have been proposed as an important mechanism of neurological involvement in COVID. We performed a retrospective, cross-sectional study to characterize the MRI abnormalities in children with an emphasis on the change of cerebral vasculatures.

Methods: We retrospectively collected clinical and MRI data of 31 children with neurological symptoms during the acute infection and abnormalities on MRI during an outbreak of omicron variant. The prevalence of clinical diagnosis, MRI abnormalities, and cerebral vascular abnormalities were analyzed.

Results: Total 15 (48.4%) of the 31 patients had abnormalities on MRI. The diagnosis in children with MRI abnormalities included encephalitis/encephalopathy (N=11, 73.3%), ischemic stroke (N=3, 20 %), hemorrhage (N=2, 13.3%), and Alice in wonderland syndrome (N=1, 6.7%). MRI abnormalities included two diffuse cortical T2 and/or DWI hyperintensity, lesions in the globus pallidus, thalamus, pons, subthalamic region, cerebral peduncle, brainstem, cerebellum, and splenium of corpus callosum. Twelve of 15 patients (80%) with MRI abnormalities had abnormal MR angiography (MRA). Involved vessels included anterior cerebral arteries (ACA) (N=2), middle cerebral arteries (MCA) (N=7), posterior cerebral arteries (PCA) (N=2), and internal carotid arteries (ICA) (N=3).

Conclusions: A high incidence of vascular abnormalities was observed in children with neurological involvement, suggesting vascular involvement is an important mechanism of neurological manifestation in omicron variant.

Keywords:
COVID-19, MRI, cerebral vascular disease

EPNS23-2495 Oral or e-Poster
Neuropsychiatric Disorders

The impact of the COVID-19 pandemic on the incidence of Somatic Symptom Disorders in children and adolescents: a retrospective study

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Objective: In the early 2020 the SARS-CoV-2 infection rapidly spread around the world becoming pandemic. In addition to the risks related to the infection, there has been growing concerns about the psychological impact of the pandemic. Somatic Symptom Disorders (SSDs) are the physical manifestation of psychoemotional distress, presenting with disabling symptoms that severely impact on daily activities. The pandemic has been a great stressor and a potential risk factor for the development of SSDs: we therefore assess the impact of COVID-19 on the incidence and manifestations of SSDs in our department in the last 5 years.

Methods: We conducted a retrospective study from Jan 2016 to Aug 2021 on patients admitted to the Pediatrics Department. All children with SSDs (according to DSM-V diagnostic criteria) were included. Exclusion criteria were: age < 5 and >18 years, lack of a defined final diagnosis, isolated headache disorder. Data were collected from electronic medical records. The study period was divided in a pre-pandemic period (Jan 2016 to Feb 2020) and a pandemic period (Mar 2020 to Aug 2021).

Results: We included 30 patients (66% females, median age 12 years). 53% had a diagnosis of Conversion Disorder, followed by Brief Somatic Symptom Disorder (23%), Somatic Symptom Disorder (20%), and Factitious Disorder (3%). 76% were adolescents (>10 years). The annual hospitalization rate of SSD raised from 3 to 8.5 in the pandemic period ($p<0.05$), and 53% of all hospitalizations occurred during the second pandemic "wave" (Nov 2020 - Jul 2021). 87% of the patients were admitted from the emergency department. Despite the psychological origin of the disorders, and because SSDs remain a diagnosis of exclusion, multiple investigations were conducted: blood exams (97%), EEG (73%), brain MRI (53%), EKG (40%), brain CT-scan (20%), lumbar puncture (17%) and electromyography/neurography (7%). None of the invasive test showed abnormal results. 83% of the cases required a multidisciplinary approach.

Conclusions: The increased incidence of SSDs in the pediatric population reflects the overall negative impact of the pandemic on mental health. While institutions should be aware of this impact in the post-pandemic era, to implement prevention strategies and protect the psychological health of children and adolescents, health care providers must consider SSDs in young patients with acute somatic symptoms and provide optimal support while limiting unnecessary investigations.

Keywords:
COVID-19; pandemic; SARS-CoV-2; Somatic Symptom Disoders; SSD; SSDs; mental health; psychological health; neuropsychiatric disorders; children; adolescents

EPNS23-2462 Oral
Neurometabolic Disorders

What are the current challenges for the treatment of diseases with approved cell & gene therapy?

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Objective: There are currently 21 approved cell & gene therapies in the EU. It has been reported that for a rare disorder that has an approved cell/gene therapy only 30% of patients are diagnosed and only 15% of them receive the treatment.
Since pharmaceutical companies report a lower number of patients treated compared to the estimated numbers, an important topic is how to ensure the timely availability of approved treatment and include it in the standard therapeutic procedure. To determine the key administration processes from the determination of the patient's diagnosis to finding the treatment (identification of the treatment centre, suitability assessment, treatment plan, approval of costs and final implementation).

Methods: Admin processes for 4 different cell & gene therapies in 11 diagnostic and treatment centres in Europe were evaluated from diagnosis to treatment. Input was mapped and collected from 138 stakeholders responsible for the process. During the implementation, emphasis was placed on the fulfilment of standard legal and quality requirements.

Results: A total of 28 treated patients were evaluated. It took 6 to 18 months, with an average of more than 12 months, from diagnosis to initiation of the therapy.
A total of 36 different processes were required from diagnosis to treatment.
27 logistic processes (75%) were required for cell and gene therapy requirements.
21 processes (58%) required more than 100 hours to establish patient diagnostic and referral centres to coordinate physicians with external stakeholders. This required significant and unplanned health care professional resources, mainly the attending physicians.

Conclusions: The timing of treatment is unpredictable and the window for its implementation is short, so the situation often requires rapid action. Cell & gene therapy needs high specific skills and coordination of projects and treatments in a European environment. Successful treatment requires many additional processes, time, various stakeholders and approvals from patients to payers. One of the solutions could be building up a network of experts and presentation of diagnostic and eligibility criteria to shorten the time to initiate the treatment. In the case that the diagnostic or reference centre does not have an in-house cell & gene therapy team, an experienced external team can manage the coordination.

Keywords:
cell & gene therapy, reference centre, eligibility, processes, cross-country treatment

EPNS23-2155 Oral or e-Poster
Neurometabolic Disorders

Real-world clinical outcomes of intraventricular cerliponase alfa in CLN2 disease: Comparison with a historical cohort

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Objective: To assess real-world safety and effectiveness of cerliponase alfa in children with neuronal ceroid lipofuscinosis type 2 (CLN2) disease treated outside of the clinical trial setting.

Methods: The analysis population included cerliponase alfa-treated patients with CLN2 disease and matched untreated natural history (NH) controls enrolled in the DEM-CHILD registry. Treated patients had initiated cerliponase alfa outside of a clinical trial and had at least 6 months of follow-up. In the primary analysis, treated patients and NH controls were matched 1:1 based on two criteria: baseline age (±12 months) and score on the combined motor-language (ML) domains of the CLN2 clinical rating scale. Rate of decline in ML score, time to unreversed 2-point decline or ML score of 0, and time to unreversed ML score of 0 were assessed. Treatment-related adverse events (AEs) were assessed for all cerliponase alfa-treated patients.

Results: A total of 24 cerliponase alfa-treated patients were eligible for inclusion, with a mean (standard deviation, SD) follow-up time of 106.7 (64.1) weeks. 21 treated patients (mean [SD] age: 4.7 [1.9] years; 11 females, 10 males) were successfully matched with 21 NH control patients (mean [SD]: 4.7 [1.9] years; 5 females, 16 males). Matched mean (SD) baseline ML score was 3.9 (1.6). Treated patients had a mean (SD) rate of decline in ML score of 0.46 (0.43) points/48 weeks compared with 1.88 (1.45) points/48 weeks in the NH controls (mean difference: 1.42; 95% CI 0.74, 2.10; p=0.0003). Compared with NH controls, treated patients had a reduced risk of an unreversed 2-point decline or ML score of 0 (hazard ratio [HR] 0.08; 95% CI 0.02, 0.28; p<0.0001) and unreversed ML score of 0 (HR 0.07; 95% CI 0.01, 0.40; p=0.003). In the treated safety population (n=24), 16 patients (67%) had any treatment-related AE (mostly Grade 2), with pyrexia (50%), vomiting (33%), and nausea (21%) the most common. Device-related infection and device leakage were reported in 3 patients (13%) and 2 patients (8.3%), respectively.

Conclusions: Cerliponase alfa in children with CLN2 disease slowed deterioration in motor and language function in the real-world setting and had an acceptable safety profile. These findings are consistent with those reported previously in the clinical trial setting.

Keywords:
Cerliponase alfa, CLN2, efficacy, safety, real-world data, registry

EPNS23-2499 Oral
Neurometabolic Disorders

Tolerability and efficacy of L-serine in patients with GRIN-related encephalopathy

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Objective: GRIN-related disorders are a group of rare paediatric encephalopathies caused by to de novo GRIN variants, encoding for the ionotropic glutamate NMDA receptor subunits. We evaluated L-Serine efficacy for the treatment of patients with GRIN genetic variants leading to hypofunctional (loss-of-function: LOF) NMDA receptors.

Methods: This is a phase 2A, 52-weeks, multicenter, interventional, non-randomized, open label study. Children > 2 years with GRIN LOF pathogenic variants, received L-Serine 250 mg/kg/day during the first 2 weeks and 500 mg/kg/day later on. Primary endpoints were changes from baseline in a series of neurodevelopment tests and detection of possible adverse events. Tests applied were: Vineland (VABS-v2), Bayley (BSID), WISC-V, Gross Motor Function-88 (GMFM-88), Sleep Disturbance Scale for Children (SDSC), Pediatric Quality of Life (PedsQL) v4.0 and EEG. Assessments were performed 3 months and 1 day before starting treatment and 3-6-12 months after the beginning of the supplement.

Results: Twenty-four patients (13 males /11 females, mean age 9,8 years (SD 4,8; range 4-18 years) were recruited. Thirteen patients (54,2%) were GRIN2B, 6 GRIN1, and 5 GRIN2A variants carriers. Clinical phenotype showed: 91% intellectual disability (62% severe), 85% behavioral problems, 79% movement disorders and 62% with epilepsy history.
L-serine treatment was associated with significant improvement in the raw scores on the VABS-2 for expressive ($p < 0,001$), personal ($p = 0,002$), community ($p < 0,001$), interpersonal relationships ($p = 0,004$), and gross motor ($p = 0,011$) subdomains. GMFM-88 total score ($p < 0,001$) and PedsQL score ($p = 0,005$) at the earliest timepoint (month 3) and throughout the 52-week treatment period also improved. Greater improvements were seen in children older than 6 years and carriers of GRIN2A pathogenic variant. L-serine normalized EEG pattern in 4 children, and the frequency of seizures in one clinically affected child. One patient discontinued treatment, due to irritability, self-aggression, insomnia after 2 weeks of treatment. No major side effects were reported.

Conclusions: L-serine produced significant and steady improvements in the adaptive behavior, motor function and quality of life, starting after 3 months of treatment and increased in the subsequent evaluations. These findings reinforced the beneficial effects of L-serine as a safe and well-tolerated treatment option in patients with GRIN variants leading to LOF NMDA receptors.

Keywords:
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EPNS23-2916 Oral or e-Poster
Neurometabolic Disorders

Capturing different disease severity of brain Tyrosine Hydroxylase deficiency (THD) in human iPSC-derived cerebral organoids

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Objective: Tyrosine hydroxylase deficiency (THD) is a neuropediatric inherited metabolic disorder characterized by the lack of the enzyme tyrosine hydroxylase (TH), an important source of dopamine in the brain. Symptoms can resemble those of a movement disorder (Type A) or also include those of a severe widespread brain disorder (Type B). The Type A form shows marked improvement when treated with L-Dopa, while patients with patients with Type B are unresponsive to treatment and experience cognitive impairment. Here, we aim to study the genotype-phenotype relationship in human disease-relevant cell types using three-dimensional models obtained from the severe variant of the disease (type B) and the corrected one.

Methods: We generated different types of iPSC-derived brain organoids from THD-B patient, its isogenic counterpart healthy control and performed phenotypical and functional analyses.

Results: We showed that ventral midbrain organoids (vmO) from THD-B iPSC exhibit less dopaminergic neurons, less expression of tyrosine hydroxylase (TH) protein and lower levels of DA when compared to control vmO. Moreover, THD-B and control cortical organoids (CO) exhibited the presence of ventricular zone-like structures comprised of proliferative neural progenitor cells (NPC) and distinct subtypes of mature cortical neurons around them. Calcium dynamic studies showed differential activity patterns between THD-B and control cortical organoids, thus suggesting the existence of altered neural function in THD-B context.

Conclusions: Our iPSC-based THD model provides a valuable tool to investigate the unknown pathogenic mechanisms of THD and to screen for drugs as well as for the development of novel therapies that may help for the management of all THD patients.

Keywords:
Organoids, THD-iPSC model

EPNS23-2330 Oral
Neurometabolic Disorders

Peripheral nerve conduction speed is decreased in children and adolescents with diabetes mellitus type 1, dependent and independent of metabolic management

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Objective: Background/Aim: Nerve conduction speed (NCS) abnormalities are considered to be early signs of diabetic peripheral neuropathy (DPN). We investigated which determinants impact the NCS and how it is related to markers of metabolic control in children and young adults with type 1 diabetes mellitus (T1DM).

Methods: Method: Fifty-three children aged five to 23 years suffering from T1DM were recruited into this study, which was conducted prospectively at the Children's Hospital of Eastern Switzerland from March 2016 to June 2022. Metabolic control parameters were recorded and a cross-sectional nerve conduction study analyzing three motor nerves and one sensory nerve was performed. Data were compared to a control population of healthy children of the same height and the height-adjusted NCS (dNCS) was analysed.

Results: Results: For all four nerves under investigation, a statistically significant decrease in the NCS of approximately 3-5 m/s was found compared to the controls and independent of metabolic management; the peroneal nerve being the most sensitive. The dNCS of the peroneal nerve correlated significantly negatively with the glycated haemoglobin (HbA1c), especially with the long-term mean of glycated haemoglobin and highly significantly negatively with the standard deviation of mean glucose (SD), but there was only a trend for association with the time in range (TIR).

Conclusions: Interpretation: DPN should be screened by using the height-adjusted NCS. Most T1DM patients show a reduced NCS and good metabolic control only attenuates this comorbidity. High glucose variability clearly increases the risk of neuropathy, together with but also independently of the mean plasma glucose level. We suspect the metabolic control-independent decrease of dNCS to be due to a lack of C-peptide.

Reference: https://www.medrxiv.org/content/10.1101/2022.12.08.22283120v1

Keywords:
Type 1 diabetes mellitus, peripheral neuropathy, decreased nerve conduction speed, long-term HbA1c, glucose variability, height, height-adjusted, C-peptide

EPNS23-2154 Oral or e-Poster
Neurometabolic Disorders

Eladocagene exuparvovec gene therapy increases Bayley-III cognitive and language raw scores in patients with aromatic L-amino acid decarboxylase deficiency

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Objective: Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare, life-limiting, autosomal recessive genetic disorder of the central nervous system. Mutations in the dopa decarboxylase (*DDC*) gene result in patients with AADC deficiency experiencing impaired cognitive and motor development. Here, the impact on cognitive and language development in children with AADC deficiency was assessed following gene therapy treatment with eladocagene exuparvovec, which was recently approved for use in the EU and UK.

Methods: Eladocagene exuparvovec was infused bilaterally in the putamina of 22 children with AADC deficiency in two single-arm, open-label clinical trials (AADC-010 [n = 10] and AADC-011 [n = 12]). The Bayley Scales of Infant and Toddler Development 3rd Edition (Bayley-III) was used to measure cognitive and language, both receptive and expressive, scores for patients. Patients were assessed every 3 months for 1 year following gene therapy, then every 6 months for 5 years and then annually up to 84 months. A repeated measures model was employed to calculate the least squares (LS) mean change from baseline (CFB), with baseline score and age at gene therapy as covariates, and study and time as main effects.

Results: At baseline, raw mean (95% CI [confidence interval]) cognitive Bayley-III scores were 12.4 (10.6-14.2) for the 22 patients, who had a mean age of 40.9 months (standard deviation [SD]: 25.6). This corresponds to a developmental age equivalent of a 3.0-month-old infant (SD: 1.0). The LS mean for CFB in raw cognitive score at 3 months was 1.6 (95% CI: -1.1-4.3; n = 22). This increased to 11.9 (95% CI: 9.1-14.7; n = 19) at 12 months and 22.7 (95% CI: 19.5-25.9; $p < 0.0001$; n = 11) at 60 months. Increases in LS mean for CFB were also observed for expressive language score (1.0 [95% CI: -0.4-2.5; n = 22] at 3 months, 2.8 [95% CI: 1.3-4.3; n = 19] at 12 months and 6.5 [95% CI: 4.7-8.2; $p < 0.0001$; n = 11] at 60 months) and receptive language score (1.8 [95% CI: 1.0-2.6; n = 22] at 3 months, 4.5 [95% CI: 3.7-5.3; n = 19] at 12 months and 7.3 [95% CI: 6.3-8.3; $p < 0.0001$; n = 11] at 60 months).

Conclusions: Gradual and sustained increases were observed in CFB in Bayley-III cognitive scale and language scale domains following treatment with eladocagene exuparvovec.

Keywords:
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EPNS23-2338 Oral
Epilepsy: Diagnosis and Investigations

Epilepsy in children with cerebral palsy: can evolve and be self-limited

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Objective: This study aimed to determine seizure prevalence, epilepsy syndromes and seizure outcomes in a homogenous group of children with cerebral palsy due to vascular injury, namely ischaemia or haemorrhage.

Methods: We studied a population-based cohort of children with cerebral palsy due to prenatal or perinatal vascular injuries, born between 1999-2006. Each child's MRI was reviewed to characterise patterns of grey and white matter injury. Children with a likely genetic cause were excluded, given the inherent association of some genetic disorders with epilepsy. Medical chart reviews were conducted, parent interviews completed, and electroencephalograms were re-analysed to determine epilepsy syndromes and seizure outcomes.

Results: Included were 256 children, 93 (36%) of whom had one or more febrile or afebrile seizures beyond the neonatal period. Eighty-seven (34%) had epilepsy. Children with childhood seizures were more likely to have a history of neonatal seizures, have spastic quadriplegic cerebral palsy, and function within Gross Motor Function Classification System level IV or V.

We diagnosed most children, 56/93 (60%) with self-limited focal epilepsy of childhood (SeLFE), as they had electroclinical features of this syndrome. The other epilepsy syndromes diagnosed were focal epilepsy - not otherwise specified in 28, infantile spasms syndrome in 11, Lennox-Gastaut syndrome in three, and genetic generalised epilepsies in two. Nine children had febrile seizures. No epilepsy syndrome was assigned in seven children as they had no electroencephalogram completed. Epilepsy syndromes evolved during childhood to another syndrome for 21 children. Of the 56 children with SeLFE, ictal symptomatology usually manifested with a mix of autonomic and brachio-facial motor features. Occipital and/or centro-temporal spikes were identified on EEG. Of those with SeLFE, 42/56 (75%) had been seizure-free for at least 2 years. Of the 93 children with seizures, at last follow-up (mean age 15 years), 61/91 (67%) had not had a seizure in over 2 years, highlighting that a favourable seizure outcome is possible.

Conclusions: Children with cerebral palsy and seizures can be assigned specific age-dependent and self-limited epilepsy syndromes, despite the current ILAE classification precluding a diagnosis of SeLFE in children with a brain lesion. Our findings have important implications for treatment and prognosis of epilepsy in cerebral palsy, and for research into the pathogenesis of SeLFE.

Keywords:
cerebral palsy, epilepsy, self-limited

EPNS23-2715 Oral or e-Poster
Miscellaneous

EPILEPSY and THE WHO INTERSECTORAL GLOBAL ACTION PLAN IN SUB-SAHARAN AFRICAN CHILDREN

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Objective: The Intersectoral Global Action Plan (IGAP) 2022-2031 aims to increase access to epilepsy care in developing countries mainly at primary care level. Nearly 80% of the 50 million people with epilepsy live in low- and middle-income countries. In sub-Saharan Africa (SSA) 2/3 of people with epilepsy (PWE) have no access to treatments, the majority are children. There is 1 neurologist every 2 millions inhabitants and almost no child neurologists: more than 90% of PWE are managed by health care providers (HCP) whose education is insufficient. In SSA there are more than 26 millions HIV+ people and HIV is a risk factor for epilepsy. IGAP also calls to integrate care for epilepsy with other highly prevalent conditions as HIV. Teleneurology can help reaching IGAP goals by offering neurologists advices to SSA HCP. This requires enhanced education in paediatric neurology to HCP. We report on the effect that HCP education and training have on teleconsultations.

Methods: The Disease Relief through Excellent and Advanced Means (DREAM) is a public health program operating in 10 SSA countries. In Malawi and Central African Republic (CAR) DREAM follows 18836 patients: 81.6% are HIV+.Thanks to the Global Health Telemedicine (GHT) platform voluntary European adult and paediatric neurologists send their advices to HCP in Malawi and CAR DREAM centres. The Italian Society of Neurology, the C.Besta Neurologic Institute and the Mariani Foundation give their support to the program. In 2021 two video-electroencephalograms were installed; in the last 2 years 12 face-to-face education and training courses have been delivered to local HCP. Several sessions from remote were also offered. Integrating epilepsy and HIV care was part of the program.

Results: Since the epilepsy program was started in 2020 the number of PWE under care has much increased and now they are 1064 - 5,6% of the total population. Clinical characteristics of PWE were: median age 19,8 years, 68,6% younger then 18 years; only 11% were older then 40 years. In the last 2 years the number of teleconsultations for epilepsy was 1617, 815 in 2022; 267 EEG were also sent.

Conclusions: Education and training to SSA HCP enhances teleconsultations to European epilepsy specialists. This is an essential tool to improve access to care to children in SSA primary care, ie to reach IGAP goals.

Keywords:
Intersectoral Global Action Plan (IGAP) 2022-2031, epilepsy care in developing countries, Epilepsy, Sud Saharian Children

EPNS23-2381 Oral or e-Poster
Neurogenetic Disorders

Neurogenetic Conditions in Children with Cerebral Palsy (CP) Mimics

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Objective: Neurogenetic conditions with motor or movement features that present in early childhood are commonly misdiagnosed as CP; these are referred to as CP mimics. Our objectives were to identify, describe clinical manifestations of, and delineate the neuroradiological, neurophysiological, and genetic findings in cases of CP mimics in the cohort of CP patients referred to the tertiary paediatric neurology clinic at Chelsea and Westminster Hospital (CWH).

Methods: A retrospective study of 822 patients (0-16 years) referred by general paediatricians to the paediatric neurology clinic at CWH with a CP diagnosis between April 2016 and April 2022 was conducted by reviewing the clinical notes, electronic records, neuroradiology, neuro-physiology, and neurogenetic reports.

Results: Out of 822 referrals, 6 cases were identified as CP mimics (male to female ratio of 2:1, age range of 0-21 months, and all non-Caucasian): 2 with quadriplegia, 1 with dystonic-spasticity, 1 with diplegia, 1 with paraplegia, and 1 with generalised hypotonia. All patients had global developmental delay. 83% patients had infantile seizures (focal / spams) and poor feeding, 67% dysmorphic features, acquired microcephaly, visual impairment and later childhood epilepsy, 50% dystonia and PEG feeding, and 30% central apnoeas, hearing loss and progressive degenerative disorders. The imaging features in all cases were atypical for a non-progressive perinatal injury and raised the possibility of an alternative underlying pathology. The spectrum of abnormalities included diffuse white matter signal change, extensive structural malformations, and progressive global atrophy. On EEG, 1/6 had a severe epileptic encephalopathy, 1/6 had focal epileptic discharges, 1/6 had photosensitivity, and the rest had no significant abnormalities. In 4/6 patients a neurogenetic diagnosis was established, with mutations in the PPPT2CA, SCN2A, MAST1, and CLTC genes. In 2/6 cases the genetic reports are awaited.

Conclusions: Though rare, our case series study highlights the need to consider further investigation, often including genetic testing, if there is clinical suspicion of a CP mimic. It also highlights the importance of increasing awareness of CP mimics among clinicians. Identification of a neurogenetic cause may substantially alter the prognosis, need for genetic counselling, and treatment options. It may also streamline the use services for a patient previously diagnosed with CP, including early referral for a palliative care, where appropriate.

Keywords:
Cerebral Palsy Mimics, neuro-genetic conditions, neuro-degenerative conditions, gene mutations, MRI brain changes

EPNS23-2420 Oral
Cerebrovascular Disorders

Tertiary centre experience of management of children presenting with Chiari 1 malformation and papilloedema

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Objective: Chiari malformation type I(CM1)is herniation of one/both cerebellar tonsils >5mm below McRae's line or 3-5 mm descent with syringomyelia. The association between Chiari and IIH is not well-understood.We reviewed all patients with CM1 referred to a tertiary IIH service over a three-year period with respect to the diagnostic challenges and management.

Methods: Database review of 183 children referred into the IIH service between 2018-2021 with 62 confirmed cases of IIH.

Results: Seven children were identified who were seen in the IIH service for concerns about headache and/or papilloedema and radiology showing CM1.Five out of seven children were female and mean age at presentation was 10.6 years(SD-2.8).BMI was >98th centile in five children.The presenting complaints were headache with transient visual-obscuration in two, headache with nausea in four and asymptomatic in one. None had occipital/CM1 headache phenotype.All children had papilloedema and the neurological examination was otherwise normal,with MRI suggestive of CM1 in all seven children.Three children required 24 hours invasive intracranial pressure(ICP)monitoring due to worsening papilloedema and headache.ICP was raised in one(spiked up to 25mmHg)and normal in two children(3 &3.4mmHg).Six children had grade1 papilloedema at diagnosis,resolved on follow-up in four and showed improving trend in rest two.One child had grade2/3 papilloedema which spontaneously resolved on follow-up.Two children evolved to have migraines and tension-type headaches on follow-up,controlled with paracetamol/ibuprofen.One child was treated with acetazolamide.None required neurosurgical interventions.

Conclusions: Establishing the cause and effect in IIH with CM1 is challenging. Sustained pressure elevation in IIH leads to cerebellar herniation,resulting in acquired tonsillar ectopia. Alternatively,posterior fossa compression due to progressive CM1,can elevate the intracranial pressure,causing change in CSF dynamics with venous sinus obstruction,leading to papilloedema and IIH symptoms. Detailed headache phenotyping,confirmation of papilloedema, neuroimaging and ICP measurement may help to distinguish between these two disease mechanisms.As shown in our cohort, most children presenting with papilloedema and CM1 respond to conservative management and do not require neurosurgical decompression.Careful monitoring of mild papilloedema and appropriate management of headaches avoids invasive diagnostics and unnecessary medical treatment.

Keywords:
IIH, chiari

EPNS23-2321 Oral or e-Poster
Basic Science

Expression pattern of epsilon-sarcoglycan (SGCE) isoforms in brain

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Objective: Mutations in epsilon-sarcoglycan (SGCE) cause myoclonus-dystonia (MD), a rare childhood-onset movement disorder. SGCE is expressed in a wide range of tissues, although its exact role is still unknown. Previous studies have focused on the canonical isoform (e-SG1) and a brain-specific isoform (e-SG2) of the protein. A second brain isoform (e-SG3) was first discovered in mice. It contains a PDZ-motif, which would allow it to interact with postsynaptic protein scaffolds, such as PSD-95. However, there is almost no data of this isoform in the human brain. Therefore, the fact that at least one brain isoform exists in humans implies that it may participate in specialized functions in the central nervous system and its alteration could be related to MD.

Thus, objectives are:
1.Analyze the expression pattern of SGCE isoforms in the mouse and human brain.
2.Design a specific antibody to study e-SG3 in the human brain.

Methods: Expression was tested in post-mortem samples from control subjects not affected by MD and in wild-type C57BL/6 adult mice. We studied brain regions with high expression of SGCE according to the Allen Brain Atlas (mouse cerebellum, hippocampus, cortex, olfactory bulb and human cerebellum) and other regions that may be involved in MD (human caudate nucleus and putamen and mouse striatum). The expression of e-SG1 and brain e-SG2 and e-SG3 was studied by qPCR and Western Blot. To study e-SG3 in the human brain, we designed a specific antibody that recognizes the C-terminal region of the protein. Statistical analysis was performed using one-way ANOVA and t test.

Results: First, we observed that SGCE was widely distributed in the brain, in agreement with published data. However, a high biological variability was observed in the human samples, at both RNA and protein level. We also observed the expression of the transcripts that encode e-SG2 and e-SG3 brain isoforms in all the human regions tested. To study whether these transcripts were truly expressed, we used specific antibodies designed against these isoforms. Hence, we saw for the first time the expression of e-SG3 in the human brain regions tested.

Conclusions: This study has analyzed the expression pattern of SGCE, and identified for the first time the presence of e-SG3 in the human brain. Using this study as a starting point, we will explore the expression of SGCE isoforms in further brain regions and subcellular compartments, hypothesizing that they may play an important role in the correct functioning of the synapse.

Keywords:
Myoclonus-dystonia, epsilon-sarcoglycan, Isoform

EPNS23-2569 Oral
Basic Science

Mitotic defects in human ASPM microcephaly

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Objective: Primary Microcephaly (PM) is a rare genetic neurodevelopmental disorder that affects brain growth responsible for intellectual disability of variable severity and epilepsy. PM can result from mutations in more than two hundred genes encoding proteins involved in centrosome duplication / cohesion, spindle pole positioning, mitotic division, DNA replication and repair. Among these genes, the spindle pole encoding gene ASPM (Abnormal Spindle like Microcephaly), is the most frequently mutated. Reduction in brain volume in ASPM-PM reaches 50%, affecting equally the cerebral cortex and the white matter. Mouse or ferret mutants studies have suggested that spindle orientation defects of neural progenitors (NP) could be the main mechanisms underlying ASPM-PM was a premature differentiation of neural progenitors (NP) pool owing to their exhaustion explained spindle orientation defects leading to a switch from symmetric to asymmetric divisions of NP. However, little is still known about how ASPM mutations affect human NP' proliferation and tissue organization during early brain development.
Our objectives are to identify defects in NP' division, differentiation and survival at the origin of ASPM-PM using brain organoids.

Methods: Neuroepithelial rosettes and 3D organoids were generated from fibroblast of 2 patients carrying ASPM mutations differentiated into NP using a neural induction protocol based on SMAD inhibition. Healthy and isogenic controls of both patients' iPSCs were also obtained using the CRISPR-Cas9 technology. NP' division, differentiation and survival were assessed by immuno-labeling and confocal microscopy imaging.
Statistical tests used for the comparisons were Student's t test and 1 or 2-way ANOVA analyses with post-test comparison and Bonferroni adjustment.

Results: ASPM neuroepithelial rosettes and brain organoids were much smaller in size, and showed tissue disorganization. We confirm defects in spindle orientation of NP in ASPM brain organoids. In addition, NP display defects in spindle morphology, a high frequency of mitotic defects and chromosome segregation errors that were absent in healthy and isogenic controls.

Conclusions: Our results reveal that beside the known defects in spindle orientation, abnormal mitotic figures and chromosome segregation errors specifically affect ASPM-mutated NP and may be at the origin of ASPM-PM.

Keywords:
primary microcephaly, ASPM, brain organoids

EPNS23-2100 Oral
Fetal and Neonatal Neurology

Serum Orexin-A as a potential biomarker in hypoxic-ischemic encephalopathy

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Objective: To investigate whether serum orexin-A concentration is a reliable biomarker in determining hypoxic-ischemic encephalopathy (HIE) severity and/or an independent diagnostic test for the efficiency of therapeutic hypothermia (TH).

Methods: The study was designed as a prospective case control study. Thirty-three neonates with a gestational age of 36 weeks or greater who were followed-up with the diagnosis of HIE in the neonatal intensive care unit were included. A detailed physical examination, clinical scoring systems (Thompson scoring and Sarnat & Sarnat staging systems) , amplitude-integrated and video electroencephalogram (EEG) records, and brain magnetic resonance imaging (MRI) were used to determine the severity of the disease. Serum orexin-A levels of the patients in the first six and 72-96 hours were measured by ELISA method. The data were analyzed using SPSS 28 statistical software.

Results: Mean serum orexin-A level of the patients received TH (n=19) were 197.2±58.1 pg/mL and 274.1±258.8 pg/mL in the first six hours and 72-96 hours, while mean serum orexin-A level of those not received TH (n=14) were 290.9±138.2 pg/mL and 194.7±51.5 pg/mL in the first six hours and 72-96 hours, respectively. The difference between first and second measurements was significantly lower in patients received TH comparing to the patients not received TH (p=0.002). There was a strong inverse relationship between the difference of two measurements and therapeutic hypothermia treatment (p=0.01; r= -0.54). More, Sarnat stage 3 patients had significantly higher mean serum orexin-A levels (567.7±640.8 pg/mL) comparing to Sarnat stage 1 and 2 patients in 72-96 hours (209.9±73.1, 203.2±40.2; p=0.008).

Conclusions: This is the first clinical study investigating the role of serum orexin-A levels in the course of HIE as a potential biomarker and the possible relations between serum orexin-A levels and the efficiency of TH. The study revealed that TH treatment is associated with higher serum orexin-A levels in neonates with HIE, and serum orexin-A levels show the severity of the disease in patients with moderate-to-severe encephalopathy. Serum orexin-A level could be a useful biomarker in the follow-up and treatment of HIE.

Keywords:
Hypoxic-ischemic encephalopathy, therapeutic hypothermia, asphyxia, neonate, orexin-A.

EPNS23-2999 Oral
Fetal and Neonatal Neurology

Improving the neurological examination of a sick, term newborn

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Objective: 1) To review the confidence of UK paediatricians on the neurological examination in unwell newborn babies
2) To describe paediatricians' attitudes towards the examination
3) To design a new neurological examination to assist the assessment of sick term newborn babies.

Methods: Phase one: An explanatory sequential mixed methods approach. A survey on attitudes to the neonatal neurological examination was sent to all UK neonatal units and members of the British Paediatric Neurology Association. Volunteers were sought for semi-structured interviews. Thematic analysis was used to interpret qualitative data.

Phase two: Using the data from phase one, a new neurological examination was designed for sick term newborn babies by a panel of perinatal neurologists and a graphic designer. Focus groups with paediatricians were performed to discuss the examination.

Results: One hundred ninety-three surveys were returned. The median range for confidence was 4 (IQR3-5). Twenty-three interviews occurred. Most interviewees did not feel confident performing or interpreting the neurological examination in unwell neonates. Many units had a culture of seeing it as low priority, did not see its relevance in the acute management of unwell neonates. A few interviewees worked in units with a positive culture towards the neurological examination who used adapted standardised examinations and provided training. 72% of questionnaire responders wanted a new standardised neurological examination designed for the unwell neonate, which should be short, utilise pictures from the Hammersmith Neonatal Neurological Examination, contain an assessment of consciousness, and to be developmentally appropriate and achievable in unwell, ventilated neonates. Participants wanted a schematic to aid interpretation.

We designed a proforma for a neurological examination. Focus groups assisted with layout, removal of unnecessary sections, and added important information we had not included. Participants thought the examination would standardise the examination and improve confidence and interpretation. We present our new examination.

Conclusions: Most paediatricians reported they did not feel confident performing a neurological examination in a newborn baby, had received little training, and did not know what to do or how to interpret the findings. We present a new proforma that paediatricians reported would help to standardise the approach and assist with interpretation.

Keywords:
Neonatal neurology, Examination, Diagnostics, Qualitative research

EPNS23-2426 Oral or e-Poster
Fetal and Neonatal Neurology

Clinical profile, Outcomes and Predictors of Drug-Resistant Epilepsy in Children after Neonatal Seizures

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Objective: To study the clinical profile, etiologies, and outcomes, of neonatal seizure and evaluate the predicting factors for drug-resistant epilepsy in children after neonatal seizures.

Methods: We reviewed the medical records for clinical information and outcomes for patients who developed seizures during NICU admission from January 2008 to December 2018. Baseline characteristics, investigation, treatment, and outcome were collected until the last follow-up visit. All had been followed up at our hospital for at least one year.

Results: One hundred and fifty-three patients were identified, 93 boys (60.8%) and 130 (85%) full-term newborns. The median (interquartile range; IQR) age of seizure onset was 3.5 hours (1 hour-29 days). Automatism was the most common presenting seizure type 115 (75.2%). The most common etiologies of seizures were hypoxic-ischemic encephalopathy (HIE) (69%), intracranial/intraventricular hemorrhage (6.2%), arterial ischemic stroke (3.8%), meningitis/sepsis (3.1%), structural brain malformations (2.3%), inborn errors of metabolism (1.5%), miscellaneous (12%), and unknown (2.1%). Thirty-three patients (20.9%) were lost to follow-up. The median (IQR) follow-up time was 22 months (1- 10.4 years). Thirty-five (29.4%) developed epilepsy at the median (IQR) age of 7 months (3 - 45 months). Developmental impairment was present in 40 (33.3%). Developmental delays, abnormal neurological examination at discharges, and non-ambulation at follow-up were associated with postnatal epilepsy ($p < 0.05$). Seven (33.3%) were diagnosed with drug-resistant epilepsy. Four had a history of severe HIE. Genetic testing (epilepsy panel) was done in three. One was positive for GNAO1 and one for STXBP1. Markedly abnormal brain imaging and multiple seizure types in the first year of life are predictors of drug-resistant epilepsy following neonatal seizures ($p < 0.05$). Age of seizure onset did not correlate with drug-resistance epilepsy later in life ($p=0.067$).

Conclusions: Our study shows hypoxic-ischemic encephalopathy is the most common cause of neonatal seizures. One-third of newborns who had neonatal seizures subsequently develop epilepsy. Abnormal neurological examination at discharges, developmental delays, and non-ambulation was associated with subsequent epilepsy. Most of the patients with post-natal epilepsy developed recurrent seizures within two years of life. Markedly abnormal brain imaging and multiple seizure types in the first year of life were predictors of drug-resistant epilepsy

Keywords:
Neonatal seizure, post-natal epilepsy, drug-resistance epilepsy

EPNS23-2923 Oral or e-Poster

Fetal and Neonatal Neurology

MRI-Trio: A New Diagnostic Approach for the Evaluation of Fetuses with Brain Anomalies - preliminary results

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Objective: A multidisciplinary approach combined with fetal neuroimaging and genetic analysis frequently enables accurate parental counselling regarding the neurodevelopmental outcome of the fetus with brain anomalies. However, in many cases the outcome cannot be precisely deciphered.
The repeated presentation of brain abnormalities in subsequent pregnancies without an unequivocal genetic diagnosis, has led us to hypothesize that an autosomal dominant disorder inherited from a healthy parent was the possible cause. Therefore, we decided to refer the parents for a brain MRI (pMRI), to investigate whether one of them had similar findings to those observed in the fetus.

Methods: In this retrospective study, we reviewed the charts of pregnant women who underwent a fetal MRI between 2008-2022 at Tel Aviv Sourasky Medical Center(TASMC) and were followed during their pregnancies at two Fetal Neurology Clinics: Wolfson Medical Center and TASMC. Inclusion criteria were: 1) fetal MRI (fMAI), 2) pMRI performed as part of the prenatal evaluation 3) prenatal counseling following pMRI results.

Results: 52 women met the inclusion criteria, mean age 32±4.8 years, mean gestational age at fMRI was 32±2.8 weeks.

The main causes of referral for parental MRI were: isolated disorders of the corpus callosum (iDCC) (30.8%), multiple brain anomalies (46.2%), isolated periventricular pseudocysts (iPVPC) and midline anomalies (5.8% each), isolated malformation of cortical development (iMCD) (3.8%). Twenty-one women had a history of a previous termination of pregnancy (TOP). Information on 36 pregnancy outcomes is currently available.

75 parents underwent MRIs. In 32 cases (61.5%) the pMRIs were normal. Pregnancies were terminated in 12 of these cases: 5 multiple anomalies; 3 iDCC; 1 PVPC, 1 midline anomaly, 1 cerebellar, and 1 MCD each. 3 children developed typically, 2 had atypical development. Information is currently not available (NA) for 15 pregnancies.

In 20 cases (38.5%) one of the parents had an abnormal MRI with similar findings as the fetus. Nine of them developed typically (3 with iDCC and multiple anomalies each; 1 with PVPC, MCD, PVNH each). Three children with multiple anomalies had atypical development, 2 underwent TOP. Information is not NA for 6 pregnancies.

Conclusions: The addition of parental MRI improved the counselling accuracy when the parents had similar findings as their fetuses and prevented wrongful pregnancy terminations. This was observed mostly in fetuses with iDCC and multiple brain anomalies.

Keywords:

Parental MRI, Brain Abnormalities, Fetal

EPNS23-2797 Oral or e-Poster

Fetal and Neonatal Neurology

Neurodevelopmental outcomes of prenatally diagnosed corpus callosum dysgenesis

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Objective: Advanced prenatal imaging via sonography and MRI have enabled diagnosis of subtler anomalies of the corpus callosum (CC) other than complete agenesis. Determining neurodevelopmental outcomes of these cases is important for prognostication in fetal neurology counselling.

Methods: This is a retrospective study that included children referred to a fetal-neurology clinic due to CC dysgenesis. Maternal, prenatal, and postnatal infant data were collected and analyzed. Patients with additional brain anomalies and complete agenesis of corpus callosum were excluded.

Results: Thirty patients were identified with prenatally diagnosed isolated dysgenesis of CC, of whom 29/30 (97%) had late fetal MRI at more than 30 weeks gestational age. One patient was diagnosed by sonography only. Dysgenesis features of CC included partial agenesis (13/30, 43%), short CC (10/30, 33%), pericallosal lipomas (5/30, 16%) and thick CC (1/30, 3%).
In utero genetic testing included chromosomal microarray analysis in 20/30 (66%) children, all with normal results; whole exome sequencing in 15/30 (50%), one of them with abnormal results of a MED12 mutation (received postnatally).
Postnatal imaging using sonography was performed in 27/30 (90%) patients, and MRI in 18/27 (66%).
Median age at follow-up was 12 (interquartile range 6-18) months. In 24/30 (80%) neurological examination was normal. Six patients showed neurological findings at examination: mild Hypotonia (4/6), postnatal microcephaly and hypertonia without pyramidal signs (1/6) and dysmorphic features (1/6). Neurodevelopmental evaluation was normal in 23/30 (76%) patients; abnormal development included mild gross motor delay in 5/30 (16%), moderate global developmental delay in one patient (same patient with postnatal microcephaly who did not undergo any genetic testing), and another child with suspected communication disorder. None of the patients exhibited seizures.

Conclusions: In our cohort of prenatally diagnosed CC dysgenesis as an apparently isolated finding, neurodevelopmental outcome was favorable in 76-80% and 13-17% showed mild findings such as hypotonia and mild motor delay. Further follow up is required to affirm these findings. Larger cohorts and prospective studies are needed to ascertain neurodevelopmental outcomes of children with CC dysgenesis, to provide accurate counseling during pregnancy to expectant families.

Keywords:

fetal, corpus callosum, neurodevelopment

EPNS23-2210 Oral or e-Poster

Infections and Inflammatory Diseases

MOG ANTIBODY TITRES IN RELAPSING DISEASE: IMPLICATIONS TO CLINICAL PRACTICE

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Objective: Myelin oligodendrocyte glycoprotein IgG (MOG-IgG) of titres 200 or more are considered positive/diagnostic for MOG associated disease(MOGAD). Early reports suggest patients who become seronegative are less likely to relapse but some patients showed otherwise. To compare relapsing paediatric MOGAD patients who remain persistently seropositive versus those who are reported as seronegative on follow-up.

Methods: Single centre retrospective review of clinical and paraclinical data of patients with relapsing MOGAD who had ongoing long term follow-up, and at least two serum samples tested for MOG-IgG by live cell-based assay.

Results: Amongst 41 patients with MOGAD, 15 (36.5%) had a relapsing course [mean relapses 3.6 (range 2-9); mean follow-up duration 78.5(range 11- 168)months] with 11 being persistently seropositive over mean of 5.6(range 0.92-14)years [7 females; mean 8.3(range 4-11)years; mean time to first relapse 22.9 (range 2-72)months] and 4 having at least one relapse after a negative result [2 females; mean 10.5(range 7-14)years; mean time to first relapse 52.2(range 8-120)months]. Both seropersistent and seroconverting groups did not differ on presentation and subsequent demyelinating phenotypes, both clinically and radiologically. Seroconverting group had mean 5.7 ± 2.25 relapses with annualized relapse rate (ARR) of 0.63 ± 0.382. Seropersistent group had a mean of 2.9± 0.59 relapses with ARR of 0.85 ± 0.484. Mean time to seropersistent relapse was 43.6 months (N=25, range 2-120) versus seroconverting relapses 85.7 months (N=7; range 60-121). Mean number of relapse prior to becoming seronegative was 3 (range 2-5). 4/7(57%) of seronegative relapses had titres of 1:100. Disease modifying therapies were commenced in 11/15 patients after the second clinical event. This was not different between seropersistent and seroconverting groups. 55% (6/11) of the seropersistent group vs 75% (3/4) of the seroconverting group were on monotherapy with mycophenolate mofetil(MMF) or azathioprine. Two patients (one each from seroconverting and seropersistent group) were on combination therapy of IVIG and MMF. Overall, despite the seronegative status, follow-up extended disability status scale was worse.

Conclusions: Paediatric MOGAD patients can relapse after a seronegative test result, most of whom still have detectable serum MOG-IgG but below the diagnostic cut-off. It may be useful for titres to be included in MOG-Ab results to support clinical interpretation, particularly in relapsing disease.

Keywords:

relapsing MOG-Ab disease; Low MOG-Ab titres

EPNS23-2344 Oral
Neurogenetic Disorders

Treatment with Baricitinib and Anifrolumab in a patient with malignant atrophic papulosis and Interferon alpha/beta receptor malfunction

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Case study: Objectives. Atrophic papulosis (synonym Köhlmeier-Degos disease) is an extremely rare disease of unknown cause mostly diagnosed by disseminated, characteristic skin lesions. Its systemic variant (malignant atrophic papulosis, MAP) is a multisystemic vasculopathy including in 20-60% the central nervous system. In patients with a central nervous system involvement MAP progresses quickly and is lethal within 2-3 years in most patients. Until now, no effective therapeutic approaches have been identified.
Methods. Whole exome sequencing (WES) was performed with DNA from a patient and her parents to elucidate the genetic cause of MAP. Clinical workup (skin/ brain biopsies, brain imaging) and extensive blood tests including assessment of the interferon signature was performed repeatedly.
Results. The 9-year-old-girl presented with MAP symptoms, including skin lesions, cognitive decline, progressive flaccid tetraparesis, focal-onset seizures, glaucoma, optic nerve atrophy and hearing impairment. WES identified a heterozygous de-novo nonsense variant c.830G>A (p.W277*) in the interferon- alpha/beta receptor subunit 1 gene (IFNAR1, NM_000629.2), resulting in a truncated, soluble protein and an overactivated receptor function. Baricitinib, a downstream Janus kinase inhibitor, initially lead to a clinical stabilization. After a partial radiological progression, hydroxychloroquine and subsequently cyclophosphamide were added, but were unable to prevent disease progression. Given the identified IFNAR1 variant and the hypothesized increased activation of a soluble aberrant protein, the monoclonal IFNAR1 antibody anifrolumab was applied as a monthly infusion in addition to daily oral baricitinib. This led to a rapid neurological stabilization and normalization of the previously highly elevated interferon signature.
Conclusions. This case presents for the first time that MAP can be caused by a variant in the IFN pathway with an elevated interferon signature linking it to monogenetic type I interferonopathies. Further, we present data that targeted therapeutic inhibition of this pathway with baricitinib and anifrolumab can stabilize disease progression and normalize the hyperinflammatory state.

Keywords:
malignant atrophic papulosis, interferonopathy, targeted therapy

EPNS23-3013 Oral or e-Poster
Infections and Inflammatory Diseases

Dynamic MRI Lesion Evolution in paediatric MOG-Ab associated disease (MOGAD)

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Objective: MOGAD presents as a monophasic and relapsing disease course. Both radiological lag with worsening of the MRI during clinical recovery and dramatic lesion resolutions have been reported.Our aim is to correlate MRI changes lesion evolution over time and correlate with patients' clinical state.

Methods: Clinical and paraclinical features were reviewed in children (<18yr) with MOGAD from 8 tertiary paediatric neurosciences centres in the UK between 2014-2022.

Results: 558 MRI scans from 235 patients and 457 attacks were available for analysis. Median age at presentation was 6.8yrs (IQR 4.0-10.4), 103 (43.8%) were male and 58 (40.3%) were non-Caucasian. At final follow-up (median period 4.42 years, IQR2.28-7.74) 85/235 (34.8%) had a relapsing disease course. (Median relapses number 3, IQR (2-4)).

At onset, brain lesions were seen in 140/235 (59.6%), spine in 54/235 (23.0%), optic nerve in 104/235 (44.5%) and gadolinium enhancing lesions in 58/107 (54.2%).

MRI was normal in 13 (5.5%) at first scan; Within 1 month all 13 developed lesions on subsequent MRIs and 4 of them had further new asymptomatic lesions (radiological lag).
New asymptomatic lesions (< 1 month, not associated with clinical picture/relapse) following first clinical event were seen in 18/41 (43.9%) with persistent contrast enhancement in 8/41 (19.5%).

Of 118 patients who had elective scanning following first attack, 7 relapsed clinically within 120 days. Complete lesion resolution was reported in 20/74 (27.0 %) within 120 days following 1st acute attack, 12/85 (24%, to final follow up) after 2nd acute attack, and 4/51 (21.1%) following 3rd acute attack and none following further relapses. Partial resolution of MRI lesions was seen in 20/68 (29.4%) monophasic patients and 16/86 (18.6%) relapsing patients after the first follow-up scan (p >0.5).

Conclusions: Lesions in paediatric MOGAD are dynamic and timing of MRI scanning may reveal different regional involvement. Unlike in multiple sclerosis, a significant number of MOGAD patients will have complete lesion resolution at first follow-up, although the ability to repair is reduced in patients with multiple relapses.

Keywords:
MOGAD , neuroinflammation

EPNS23-2062 Oral or e-Poster

Infections and Inflammatory Diseases

Brain volume measurement in children with radiologically isolated syndrome

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Objective: Radiologically isolated syndrome (RIS) is defined as T2-white matter lesions suggestive of multiple sclerosis (MS), identified incidentally in magnetic resonance imaging (MRI) scans performed for other reasons than symptoms suggestive of MS. We have already shown that pediatric MS patients have a significant volume loss at first clinical presentation. The aim of this study is to assess brain volumes of children with RIS at time of diagnosis and follow up after two years.

Methods: Children with pediatric RIS (pedRIS) who fulfilled the diagnostic criteria proposed by Makhani were included in the study (e.g. a. incidental findings on MRI, b. ovoid, well-circumscribed, and homogenous foci). Whole brain volume was assessed using FSL SIENAX based on MPRAGE sequences and compared to children from the NIH Paediatric MRI Data Repository. Clinical follow up data were collected from all patients. Group differences were analyzed using Kruskal-Wallis and Mann-Whitney-U-Test.

Results: 21 children (17 female/4 male) with a median age of 13,26 years (range: 6,8 - 17,6) were included. Total median MRI lesion count on brain MRI was 9 (range: 2-25). 7/17 children who received a spinal MRI had spinal lesions. 16/21 patients had positive OCBs. 9/21 patients developed a first clinical event with a median of 0,9 years after pedRIS diagnosis. All RIS patients who developed MS had risk factors like OCBs and/or spinal lesions. Additionally, we observed that these patients tend to have more pronounced volume loss compared to RIS patients without MS (RIS-MS: 1651493,867mm^2 vs. RIS non-MS 1700057,283 mm^2). Furthermore, brain volume measurements of RIS patients at onset did range between brain volumes of healthy controls and pediatric MS patients at first clinical episode. Follow up brain volume measurements are pending.

Conclusions: Our study shows that RIS patients have reduced brain volumes compared to healthy controls which is less pronounced than in pediatric MS patients. Further analyses are pending assessing brain volume loss overtime in particular in children with risk factors for MS.

Keywords:

Radiologically isolated syndrome, multiple sclerosis, brain volume

EPNS23-2790 Oral or e-Poster
Infections and Inflammatory Diseases

Clinical utility of chemokine C-X-C motif ligand 13 levels in cerebrospinal fluid for the recognition of neuroinflammation

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Objective: C-X-C motif ligand 13 (CXCL13) chemokine is a crucial chemokine for B-cell recruitment to the CNS. Its increased intrathecal levels in cerebrospinal fluid (CSF) has been observed in patients with multiple sclerosis and other noninfectious inflammatory central nervous system disorders, and strikingly in neuroborreliosis. We aimed to determine the diagnostic relevance of CXCL13 in the recognition of neuroinflammation in comparison with CSF white blood cell counts (WBC), and in the context of clinical diagnoses.

Methods: CXCL13 level in samples from 142 paediatric patients with various (mostly non-infectious) inflammatory CNS diseases and 61 controls were analysed; 27 children also had samples after recovery and another 12 children multiple samples from different time periods of their illness. All CSF samples were routinely tested; WBC, oligoclonal bands (OCB) and CSF/serum albumin ratios (Qalb) were included. Luminex multiple bead technology and enzyme-linked immunosorbent assay were used to determine the CXCL13 level. Receiver operating characteristic curve (ROC) were constructed for analysis of control and patient samples from acute phase of their disease and prior any therapy (symptomatic samples) to determine the area under curves (AUC), and the sensitivity for thresholds that assure high (> 95%) specificity for neuroinflammation. The ROC were constructed with 1) using all symptomatic samples (n=142) and 2) using selected symptomatic samples with CSF WBC count < 5cells/uL (n=71). Other non-parametric tests were also performed.

Results: Compared with the control CSF samples, CXCL13 level was increased in all symptomatic CSF samples; the level decreased after recovery ($p < 0,0001$). CXCL13 level correlated with CSF WBC, OCB and Qalb ($p < 0,001$). The AUCs were 0,877 (CI 0,831 - 0,922) for CSF WBC and 0,885 (CI 0,84 - 0,929) for CSF CXCL13 level (all symptomatic samples included). The CSF level of CXCL13 above 13,27 pg/mL assured 95% specificity for neuroinflammation with 72,5% sensitivity (all symptomatic samples included), respectively with 60% sensitivity with selected symptomatic samples (CSF WBC < 5 cells/uL). CXCL13 levels varied by diagnosis and showed individual dynamics in patients with multiple samples.

Conclusions: In CSF, the level of CXCL13 was comparable biomarker of neuroinflammation to WBC counts. The increased CSF level of CXCL13 can help to recognised neuroinflammation in uncertain clinical cases with CSF WBC < 5 cells/uL.

Keywords:
CXCL13 chemokine, neuroinflammation, cerebrospinal fluid

EPNS23-2621 Oral or e-Poster
Infections and Inflammatory Diseases

Treatment of Sydenham's chorea and its relationship with disease course and outcome: an individual patient data meta-analysis of 1017 cases

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Objective: To assess treatment strategies and their relationship with disease course and outcome in Sydenham's chorea (SC).

Methods: Systematic literature review in multiple databases (Pubmed, Embase, CINHAL, Cochrane) including all cases of SC with individual data. Primary outcomes evaluated were time to complete chorea resolution at first event and monophasic vs. relapsing disease course (including only cases with follow-up of at least 12 months, or relapse at any time). Modified Rankin Scale (mRS) score was recorded as provided in the original paper or assessed by the investigators when possible. Mann-Whitney U, chi-square and Fisher's exact tests were applied as appropriate.

Results: 1017 patients with SC were included (70.0% [685/979] females). Median onset age was 10 years (IQR 8-12, 95.6% [967/1012] <18 years). 52.5% (211/402) had infectious symptoms preceding SC onset. 30.1% (199/662) had hemichorea. 65.2% (268/411) had psychiatric symptoms, most frequently emotional lability, anxiety, hyperactivity-attention difficulties and irritability. mRS score at nadir was 4 or higher in 33.2% (122/370). Carditis was detected in 53.4% (468/876) and joint involvement in 26.3% (232/881).
Full chorea resolution after the first event occurred in 89.0% (263/297 with follow-up of at least 12 months). In these, median chorea duration was 2.0 months (IQR 1.0-4.0). Resolution was faster in patients with prodromal infection (median 1.2 vs. 2.5 months, p<0.001), patients administered antibiotics at prodromal infection (1.0 vs. 2.0 months, p=0.026) and patients administered corticosteroids (1.2 vs. 2.0 months, p=0.027). Slower resolution was associated with abnormal MRI (4.0 vs. 2.0 months, p=0.049) and formal psychiatric diagnosis during SC (3.0 vs. 1.7 months, p=0.007).
44.5% (271/609) relapsed. Factors at first event associated with reduced odds of relapse included treatment with corticosteroids (OR 0.18, 95% CI 0.10-0.33, p<0.001), valproate (OR 0.33, 95% CI 0.18-0.60, p<0.001) and antibiotics (OR 0.50, 95% CI 0.34-0.73, p<0.001). ESR elevation (OR 2.36, 95% CI 1.26-4.43, p=0.007) and carditis (OR 1.46, 95% CI 1.03-2.07, p=0.032) were associated with increased odds of relapse.

Conclusions: Comparison based upon combining data from studies taking place in different conditions and at different times must be treated with caution, particularly with therapies that are relatively new in SC, but it appears that corticosteroids are associated with shorter chorea duration and 5.6-fold reduced odds of relapse in SC.

Keywords:
Sydenham's chorea, immunotherapy, corticosteroids, outcome, relapse, metanalysis

EPNS23-2241 Oral or e-Poster
Neurometabolic Disorders

Atidarsagene Autotemcel (Autologous Hematopoietic Stem Cell Gene Therapy [HSC-GT]) Preserves Cognitive and Motor Development in Early-Onset Metachromatic Leukodystrophy with up to 11 years follow-up

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Objective: Metachromatic leukodystrophy (MLD) is a rare neurometabolic disorder due to deficiency of arylsulfatase A (ARSA), causing progressive demyelination, motor and cognitive decline, and early death. We present long-term results from 39 patients with early-onset MLD (19 late-infantile [LI], 20 early-juvenile [EJ]) treated with HSC-GT (atidarsagene autotemcel, "arsa-cel").

Methods: Arsa-cel consists of autologous CD34+ cells transduced ex vivo with a lentiviral vector encoding for the human ARSA gene. Following myeloablative busulfan conditioning, arsa-cel was administered intravenously. Patients were treated across two monocentric prospective clinical trials and expanded access programs; safety and efficacy outcomes were integrated and compared to an untreated natural history (NHx) cohort of 43 early-onset MLD patients followed at the same center.

Results: Median follow-up was 6.15 years (range 0.64-11.03). All patients achieved stable engraftment of gene-corrected cells and restoration of ARSA activity to normal or supranormal levels in the hematopoietic system and cerebrospinal fluid, sustained throughout follow-up. Most patients treated while pre-symptomatic (PS) or early-symptomatic (ES, able to walk independently, without cognitive decline) maintained normal or near-normal cognitive development at last follow-up (17/18 PS-LI; 8/8 PS-EJ; 8/11 ES-EJ). In contrast, NHx patients experienced severe cognitive impairment. Verbal communication was also preserved in most treated patients, whereas most NHx patients lost all speech. The risk of experiencing severe motor impairment or death was significantly reduced in PS-LI ($p<0.001$), PS-EJ ($p=0.049$) and ES-EJ ($p<0.001$) patients vs. NHx. Notably, 25/26 PS patients retained the ability to walk at last follow-up, and 9/11 ES-EJ patients had slowed progression of motor decline vs. NHx. Brain MRI total scores stabilized at substantially lower levels over time in treated patients vs. NHx, indicating stabilization or slowed progression of brain demyelination and atrophy. There were no serious adverse events related to arsa-cel, no malignancies, and no evidence of abnormal clonal expansion or replication-competent lentivirus. Three patients died (2 ES-EJ from disease progression, 1 PS-EJ from cerebral stroke), all considered unrelated to arsa-cel.

Conclusions: These results demonstrate that arsa-cel is generally well-tolerated and effective for preserving cognitive and motor function and slowing disease progression in most early-onset MLD patients.

Keywords:
metachromatic leukodystrophy, gene therapy, hematopoietic stem cell gene therapy, clinical trials

EPNS23-2766 Oral
White Matter Diseases

Preliminary Results from CAN*aspire*, a First-in-Human Phase 1/2 Controlled Open-Label Study of BBP-812, a Recombinant AAV9-h*ASPA* Vector for the Treatment of Canavan Disease

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Objective: Canavan Disease (CD) is an ultra-rare leukodystrophy caused by mutations in the *ASPA* gene leading to brain accumulation of N-acetylaspartic acid (NAA) and profound early-onset impairment of psychomotor development. The objective of the CAN*aspire* study is to evaluate the safety and pharmacodynamic and clinical activity of BBP-812, a systemically administered recombinant broad-tropism AAV9 h*ASPA* vector for the treatment of CD.

Methods: CAN*aspire* (NCT04998396) is a multi-center Phase 1/2 first-in-human dose escalation/dose expansion trial evaluating safety, pharmacodynamic activity (NAA levels), developmental skills and quality of life over a 1-year acute and 4-year long-term follow-up period in infants and young children with CD. Clinical outcome assessments include the disease-specific Canavan Disease Rating Scale (CDRS) that ranks the severity of 11 characteristic neurological and developmental manifestations of CD, as well as a battery of performance-based and parent-reported pediatric motor and developmental scales. These assessments mirror those in the retrospective and prospective CD natural history study CAN*inform* that is conducted in parallel, enabling use of CAN *inform* data as an untreated control and for establishment of a primary clinical endpoint. Eligibility criteria for the CAN*aspire* gene therapy trial include a confirmed genetic, biochemical and clinical diagnosis of CD, age ≤ 30 months, absence of clinically meaningful medical co-morbidities or manifestations of advanced CD, and negative anti-AAV9 antibody titers.

Results: Pre-treatment magnetic resonance imaging (MRI) showed extensive abnormalities in white matter, globi pallidi, thalami and cerebellum as well as elevated NAA on MR spectroscopy (MRS) and in cerebrospinal fluid (CSF) and urine. Findings from the first 4 participants have shown evidence of tolerability as well as NAA decreases of 70-90% in CSF, 42-87% in urine, up to 75% in brain (right frontal white matter) by MRS, and stabilization or improvement in CDRS scores. Most adverse events (AEs) have been mild or moderate with no treatment-related serious AEs or AEs requiring halting the BBP-812 infusion or study withdrawal.

Conclusions: CAN*aspire* is the first clinical trial of a systemically administered gene therapy candidate for CD. Preliminary data from 4 participants have supported the overall tolerability of this approach and have demonstrated reduced NAA levels in urine, CSF and brain along with initial signs of clinical efficacy after BBP-812 treatment.

Keywords:
Canavan disease, gene therapy, AAV9, N-acetylaspartate, NAA, aspartoacylase, ASPA, MRI, MRS

EPNS23-2238 Oral
White Matter Diseases

Preliminary results of X-Linked Adrenoleukodystrophy Newborn Screening in Italy

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Objective: X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder, caused by variants in the ABCD1 gene. The main phenotypes observed in affected males are: Addison disease, a primary adrenal insufficiency that must be promptly treated with hormone replacement therapy in case of impaired adrenal hormones; adrenomyeloneuropathy, characterized, as main symptoms, by spastic paraparesis, sensory-motor peripheral neuropathy, sphincter disturbances and sexual dysfunction; and cerebral ALD (cALD), a relentless progressive cerebral disease, typically associated with rapid clinical deterioration and, if untreated, death. The standard treatment for cALD is haematopoietic stem cell transplantation, which is not able to recover white matter degeneration but stabilize and avoid further degeneration if performed early in the disease.
Early diagnosis is therefore crucially important for a timely treatment in case of cerebral signs or adrenal insufficiency, and for this reason, several countries have already implemented X-ALD in their newborn screening programs (NBS) through the assessment of C26:0-lysophosphatidylcoline (C26:0-LPC).

Methods: In June 2021, we launched a pilot study for the implementation of X-ALD in the Italian NBS program. It is based on a 3-tier approach that includes the quantification of C26:0-LPC values and other metabolites in dried blood first by FIA-MS/MS and then by the liquid chromatography-tandem mass spectrometry (UHPLC -MS/MS) and a targeted NGS genetic confirmation.

Results: We here present the preliminary data for the period between June 2021 and December 2022. Among 76770 newborn patients, 35273 were examined. Through the first Tier 443 patients tested non-negative and 118 of them resulted still non negative after re-test. Among these, 5 tested positive at the second Tier test and they all resulted carriers of pathogenic variants in ABCD1 gene.
Genetically confirmed patients underwent a specific disease monitoring protocol, created based on literature data and personal direct experience, to promptly start a specific treatment if, and when, first signs of brain damage or adrenal insufficiency appear.

Conclusions: The introduction of X-ALD into NBS would significantly change the natural history of the disease. Results from our pilot study and from the others conducted internationally will form the basis for framing how to introduce X-ALD into the current Italian NBS program, in order to offer all newborns early diagnosis, follow-up and timely treatment.

Keywords:
X-linked adrenoleukodystrophy, X-ALD, Newborn Screening, ABCD1, early diagnosis, timely treatment

EPNS23-2252 Oral or e-Poster
White Matter Diseases

Phenotypic features in 18 patients with hypomyelinating leukodystrophy 14 (UFM1 gene)

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Objective: UFM1-associated hypomyelinating leukodystrophy 14 (HLD14, OMIM #617899) represents a severe neurodegenerative disorder with neonatal/early infantile onset with autosomal recessive inheritance. In Europe, HLD14 was described exclusively in patients with Roma ethnicity so far. We present a overview of the phenotypic features in 18 patients.

Methods: In patients with suggestive clinical findings, targeted Sanger sequencing of a promoter region in the UFM1 gene was performed (reference sequence: NM_001286704.1, dbSNP rs747359907).

Results: In 18 patients of Roma ethnicity (11 males, 7 females), the homozygous pathogenic variant c.-273_- 271delTCA in the UFM1 gene was confirmed. The children were born at 36th to 40th gestational week, with a birth weight range from 1700 to 3910 g (avg. 2878 g), birth length range from 44 to 53 cm (avg. 47 cm) and head circumference 33 cm (available in 2 patients). The first symptoms typically appeared between 2 and 3 months of age, initially manifested by axial hypotonia along with rapid development of spastic quadriparesis (18/18), developmental delay at the level of the 1st trimenon (18/18), biphasic stridor (14/18), and general dystrophy with progressive microcephaly (18/18). All anthropometrical parameters declined to values under -2.00 SDS in the 6th month of life in 17/17 patients. With disease progression, extreme values were observed with weight 5500 g, i.e., -9.27 SDS, and length 63 cm, i.e., -7.60 SDS in the 29th month of life. Epilepsy or EEG abnormalities evolved in 5/18 and dystonic opisthotonus in 9/18 patients. The respiratory insufficiency with the need of tracheostomy (7/18) and artificial pulmonary ventilation (2/18) was present as well as the need for a PEG tube due to pseudobulbar palsy (8/18). Inconstantly, hearing loss and blindness were reported. Brain MRI and MR Spectroscopy signs corresponded to significantly delayed supratentorial white matter myelinization. The course of the disease was adverse with early mortality (avg. time of death 16 months, range 3 to 29 months).

Conclusions: The carrier frequency is > 3,3 % in the Roma population in various European countries. The pathogenic variant in the promoter region may escape panel or exome sequencing [Hamilton et al., 2017]. HLD14 accentuates the particularity of the genetic disorders in Roma subpopulation and calls attention to the need for a population-specific approach both in the clinical and scientific settings.

References: Hamilton EMC et al. Neurology. 2017;89(17):1821-1828.

Keywords:
leukodystrophy, hypomyelinating, UFM1 gene, infantile, founder mutation

EPNS23-2646 Oral or e-Poster
White Matter Diseases

Unraveling pediatric genetic white matter disorders: Preliminary results from a tertiary referral center

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Objective: We aimed to retrospectively review patients in the pediatric age group with white matter lesions on magnetic resonance imaging (MRI) and display the clinical and molecular background of genetic white matter disorders.

Methods: This study included patients aged between 0-18 years with white matter lesions on MRI who were admitted to a tertiary center between January 2010-June 2022. Patients were identified retrospectively by scanning MRI reports for the words "leukodystrophy" and "white matter disease".

Results: Two hundred and twenty-one patients with white matter lesions on MRI were evaluated. After exclusion of 32 patients because of missing data, 189 patients were evaluated. The male/female ratio was 127/62. Consanguinity was reported in 55.6%. The age of the patients at the time of admission was 0-221, median 52.9 months. The most common complaints at admission were developmental delay (n=50, 26.5%), gait problems (n= 33, 17.5%), seizures (n= 24, 12.7%), and regression (n=23, 12.2%). Symptoms were static in 44 (23.3%) patients and progressive in 77 (40.7%). Among 84 (44.4%) patients with a definite diagnosis, X-linked adrenoleukodystrophy was the most common group with 18 patients (21.4%), followed by metachromatic leukodystrophy (12 patients, 14.3%), glutaric aciduria type 1 and Nieman Pick type C with 5 patients each (6%). One patient was found to have a novel splice site DNAJC3 mutation. The diagnosis was confirmed by whole exome sequencing (WES) in 31 patients (36.9%), targeted gene analysis in 19 patients (22.6%), and chromosome analysis from fibroblast culture in one patient. Twenty-nine patients did not undergo genetic testing. Molecular diagnosis of 47 (56%) patients were complemented by biochemical tests and/or recognition of MRI pattern. Initial WES analysis was not diagnostic in 11 out of 31 patients ; no pathogenic variant was detected in one, while variants of unknown significance detected in 10 patients were not compatible with the phenotype.

Conclusions: Diagnosis in white matter diseases is challenging. Considering patients who underwent molecular genetic testing diagnostic yield was 52.5%. This clearly indicates introducing further diagnostic and genomic approaches in order to bridge the gap in terms of genetic counseling, proactive management and future individualized treatments.

Keywords:
leukodystrophy, genetic white matter disorders

EPNS23-2505 Oral
Miscellaneous

Novel gene therapy approach corrects manifestations of Infantile Krabbe Disease. FBX-101 is a Phase I/II Intravenous AAV Gene Replacement Therapy after infusion of transplanted Umbilical Cord Blood

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Objective: Infantile Krabbe disease (IKD) is a severe neurodegenerative disorder caused by galactocerebrosidase (GALC) deficiency which leads to death by 2 years. For 20 years, umbilical cord blood transplantation (UCBT) has been used to treat asymptomatic newborns with survival into late teen years. However, due to progressive peripheral neuropathy, motor function deteriorates. FBX-101 is an AAVrh10-GALC gene therapy given intravenously during the myelo/immune ablation for UCBT preventing safety concerns related to immune response against the vector's capsid and potentially increasing AAV transduction. In addition, UCB donor cells are naïve to AAVrh10 and carry normal GALC, avoiding the antibody response to the transgene. FBX-101 is designed to "rescue" peripheral nerve disease not addressed by HSCT. Asymptomatic patients are diagnosed because of family history or through newborn screening (NBS), available in 10 states across the US.

Methods: RESKUE is a first-in-human, open-label Phase 1/2 dose-escalating trial to evaluate safety and efficacy of FBX-101 during UCBT for subjects with IKD. Cohort 1 receives a single FBX-101 IV infusion at a low dose (3.0x1013 vg/kg) post-UCBT. The post-administration evaluation period is 2 years, with 3 years of additional follow-up. Motor development is measured using the PDMS-II. Diffusion tensor imaging (DTI) measures white matter integrity in subjects and compares it to historical controls receiving only UCBT.

Results: Two subjects identified through NBS have been enrolled and received FBX-101 at a dose of 3.0x1013 vg/kg at 25 and 29 days post UCB infusion, respectively. The diagnosis of infantile Krabbe was based on mutations, elevated psychosine, abnormal auditory brainstem responses, and muscle tone abnormalities. FBX-101 was well tolerated, with no treatment-related serious adverse events up to Day 365 and Day 180, respectively. No antibodies to AAVrh10 have developed. The subjects engrafted with full chimerism. We report an 80 fold increase in plasma GALC and 6-10 fold increase in CSF GALC following gene transfer, and motor skills within normal and above the range of UCBT-only treated patients. Both subjects have normal brain white matter integrity.

Conclusions: Administration of FBX-101 during UCBT represents a novel gene therapy strategy that is well tolerated with no adverse events. FBX-101 leverages the myelo/immune-ablated environment of UCBT, resulting in efficient AAV transduction, increasing GALC activity and supporting brain and motor development.

Keywords:
Krabbe, gene therapy, AAV, transplant, UCBT, HSCT

EPNS23-2894 Oral or e-Poster
Neuromuscular Disorders

Transient increase of Neurofilament light serum concentrations following gene replacement therapy in patients with Spinal Muscular Atrophy

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Objective: Neurofilament light chain (NfL) concentrations in serum have been proposed as a biomarker for monitoring treatment response in Spinal Muscular Atrophy (SMA). But NfL data following gene replacement therapy (GRT) with Onasemnogen-Abeparvovec (OA) are limited.

Methods: We conduct a multicenter, retrospective observational study.

Results: NfL serum concentrations were determined longitudinally in 54 children younger than age 4 years (56% SMA type 1, 35% SMA type 2, 7% presymptomatic) receiving OA. 36 patients were previously treated (57% Nusinersen, 7% Risdiplam). Mean NfL serum concentration before GRT was 99 ± 191,95 pg/ml, increased to 420 ± 341,62 pg/mL 30 days after GRT, and declined constantly thereafter to 79 ± 74,63 pg/mL after 6 months. During this time, 80% patients experienced improvement in motor function.

Conclusions: We found a paradoxical transient increase of NfL serum concentrations after GRT in children with SMA despite improvement of motor function. We hypothesize that this does not reflect disease progression, but rather mirrors a physiological neuronal inflammatory response directed against the adenovirus infection

Keywords:
Neurofilament light chain; SMA; Onasemnogen-Abeparvovec; Nusinersen; Risdiplam

EPNS23-2106 Oral or e-Poster
Neuromuscular Disorders

Health Outcomes Impacting Quality of Life in Spinal Muscular Atrophy Type 1 Following Onasemnogene Abeparvovec Gene Replacement Therapy

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Objective: Spinal muscular atrophy (SMA) type 1 is a rare genetic neuromuscular disease causing rapid deterioration of voluntary motor and bulbar function when untreated. Although several trials of SMA disease-modifying therapies have been conducted, limited evidence exists for associating post-treatment improvements in health outcomes to patient and/or caregiver health-related quality of life (HRQOL). This study assessed the health outcomes of symptomatic SMA type 1 infants treated with onasemnogene abeparvovec, a one-time gene replacement therapy. We sought to assess health outcomes including pulmonary and nutritional interventions, swallow function, speaking ability, hospitalization rate, and motor function as indirect HRQOL-related measures for SMA type 1 patients treated with onasemnogene abeparvovec.

Methods: We conducted a pooled *post-hoc* analysis of symptomatic SMA type 1 infants (<6 months; two *SMN2* copies) treated with onasemnogene abeparvovec in the START, STR1VE, and STR1VE-EU trials conducted between 12/2014 and 09/2020. Patients were followed for 18 to 24 months post-treatment.

Results: This analysis included 65 patients. By study completion: 36 (55%) patients did not require noninvasive ventilation. 60/61 (98%) patients had stable or improved swallow function demonstrated by clinical swallowing assessment, and 49 (75%) fed exclusively by mouth; 26/27 (96%) patients were able to speak. Mean percentage of time hospitalized was 4.3%. Mean unadjusted annualized hospitalization rate was 1.6 (range=0-14), with a mean length of stay/hospitalization of 7.4 (range=2.0-20.5) days. 52 (80%) patients achieved full head control, 38 (58%) sat without assistance, and five (7.7%) patients walked independently.

Conclusions: Onasemnogene abeparvovec treatment of patients with symptomatic SMA type 1 preserves respiratory and bulbar function, reduces hospitalization and nutritional support requirements, and improves motor function. This contrasts with the natural history of progressive respiratory failure and early death. Reduction in respiratory interventions, hospital readmissions, preservation of bulbar function, and continued achievement of motor milestones might be associated with improved HRQOL. Reduced health care utilization and care requirements could potentially alleviate patient/caregiver burden, suggesting further HRQOL benefit.

Keywords:
disease-modifying treatment, health-related quality of life, onasemnogene abeparvovec, spinal muscular atrophy

EPNS23-2622 Oral or e-Poster
Neuromuscular Disorders

Real-world data on the efficacy of gene replacement therapy in spinal muscular atrophy (SMA)

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Objective: Limited data from clinical trials and observational studies are available on the use of gene replacement therapy in SMA with onasemnogene abeparvovec (Zolgensma®), especially for patients >24 months, >8.5 kg body weight or after pre-treatment with nusinersen or risdiplam.

Methods: We conduct a protocol-based, prospective observational study at 30 neuromuscular centres in Germany, Austria and Switzerland, including (pre)symptomatic patients with SMA treated with Zolgensma® and followed-up for 12 or 24 months. We analyse motor function scores (CHOP INTEND, HFMSE and motor milestones) as well as nutritional and respiratory data.

Results: To date, >250 SMA patients have been treated with gene replacement therapy in the D-A-CH region. Statistical analysis is ongoing at the time of abstract submission. Planned is the presentation of time-to-event analyses with Kaplan-Meier curves with regard to the primary endpoints free sitting and free walking and the secondary endpoints ventilation and tube feeding as well as a presentation of CHOP INTEND and HFMSE scores.

Conclusions: This study investigates the efficacy of gene replacement therapy in the largest cohort worldwide according to a standardised protocol. The results will be significant for future consultations, especially for patients for whom insufficient trial data are available.

Keywords:
Spinal muscular atrophy; SMA; gene therapy; efficacy

EPNS23-2204 Oral or e-Poster
Neuromuscular Disorders

Apitegromab in SMA: Analysis of Correlates of Patient Reported Outcomes and Motor Function Increases in 24 Month TOPAZ Data

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Objective: Apitegromab is an investigational, fully human, monoclonal antibody that specifically binds to pro- and latent- forms of myostatin, an inhibitor of muscle growth and strength, thereby directly targeting muscle atrophy in patients with SMA. TOPAZ is a phase 2, 3-cohort study (NCT03921528) of Types 2/3 SMA patients dosed with IV apitegromab Q4W for 12-months with 3 successive 12-month extension periods. In the nonambulatory Type 2 SMA cohort (nusinersen started before age 5; n=20) patients on nusinersen were randomized to receive 2 or 20mg/kg apitegromab for the first 12-month treatment period. During the first extension period, patients initially assigned to the 2mg/kg dose were switched over to the 20mg/kg dose. In a separate nonambulatory Type 2/3 cohort (nusinersen started at age > 5; n=15), patients on nusinersen received 20mg/kg apitegromab. In these 2 nonambulatory cohorts, 46% of patients achieved a 3 or more point increase in HFMSE and 50% achieved a 2 or more point increase in RULM at 24-months.

Methods: Patient reported outcomes that measure fatigue, endurance and impacts to activities of daily living were assessed by PEDICAT and PROMIS measures in the TOPAZ study.

Results: Analyses of patient reported outcomes and their association with motor function scales in the nonambulatory cohorts will be presented. The patient populations, including exploratory analyses (e.g., age, mobility, weight) will be considered together with motor function scales and patient reported outcomes over 24 months.

Incidence and severity of AEs were consistent with the underlying patient population and nusinersen therapy throughout the 24-month treatment period with no safety risks identified.

Conclusions: Apitegromab has the potential to be the first muscle-targeted therapy to address motor function impairment affecting patients with SMA and further exploration of its impact on Quality of Life (QoL) is warranted.

Keywords:
apitegromab, SMA, myostatin, muscle, TOPAZ, muscle targeted, SAPPHIRE

EPNS23-2558 Oral or e-Poster
Neuromuscular Disorders

One thousand patients in the French Spinal Muscular Atrophy Registry. What have we learnt from the use of innovative therapies, in particular of gene therapy?

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Objective: Spinal Muscular Atrophy (SMA) is the most lethal genetic disease in children. SMA France Registry (NCT04177134) was set up in 2020 to collect real-life data after the arrival of new therapies: Nusinersen (Ns, 2016), Onasemnogene abeparvovec gene therapy (GT, 2019) and Risdiplam (Rs, 2020). It includes all types of severities, treated or not, died or alive. The objective was to describe the characteristics of SMA population treated in France and to analyze GT tolerance, efficacy and prognostic factors.

Methods: Observational registry collecting retrospective and prospective data: epidemiology, natural history, effect of interventions and treatments, and impact of the disease.

Results: 1001 patients (504 children, 497 adults) are currently registered (64 centers). Patients are: SMA1 (23%), SMA2 (41%), SMA3 (35%). Two infants with family antecedents were diagnosed presymptomatically (SMAp). 78% patients were treated (506 Ns, 219 Rs, 62 GT). 107 patients had more than one treatment: 102 switched from Ns to Rs (32 SMA1, 56 SMA2, 14 SMA3); 4 from Ns to GT (SMA1), 1 GT had one year later Rs (SMA1). In the follow-up, 98 patients (23 treated) did not survive (82 SMA1, 10 SMA2, 5 SMA3). Follow-up 18 months post GT was available in 41 infants (2 SMAp, 32 SMA1, 5 SMA2). The mean values at treatment were 8 months (0.6-17) and 7.5 Kg (3-11). Mean CHOP-Intend score pre-GT was 30 (11-59) and at last visit 51 points (33-66). 74 % increased >4 . The best prognostic motor function indicator was the pre-GT CHOP-intend score (< 15; >15-30;>30-45;>45), independently of the age of treatment, SMA types or SMN2 copies. Both SMAp remain asymptomatic at 1 and 3 years. One death due to thrombotic microangiopathy prompted the collection of exhaustive blood data in all GT treated infants. Analysis of the 'biological module' shows increase of liver enzymes (80%) and thrombocytopenia (20%) in the 2 first weeks post-GT. Steroid doses were increased to improve GT tolerance.

Conclusions: The SMA French Registry has already recruited a thousand patients. Our results show that motor prognosis in infants treated by GT depends on the motor function at baseline, rather than the SMA type or the age at treatment. The exhaustivity and quality of the data collected in this national real-life registry allows a better understanding of the disease, the efficacy and/or the adverse effects of innovative therapies.

Keywords:
Spinal Muscular Atrophy, French SMA Registry, Nusinersen, Onasemnogene abeparvovec gene therapy, Risdiplam

EPNS23-2142 Oral or e-Poster
Neuromuscular Disorders

Seroprevalence and Half-life of Pre-existing Anti-adeno-associated Virus Serotype 9 (AAV9) Antibodies in Neonates

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Objective: Onasemnogene abeparvovec is a one-time AAV9 vector-based gene replacement therapy for the treatment of spinal muscular atrophy. Safety and efficacy of onasemnogene abeparvovec for patients with elevated anti-AAV9 antibody titers (>1:50) are not established. Neonates may have elevated anti-AAV9 antibody concentrations because of transplacental maternal transfer, but titers generally decrease after birth. The seroprevalence and half-life of passively acquired anti-AAV9 antibodies in newborns are unknown. We aimed to establish the seroprevalence and half-life of maternally transferred anti-AAV9 antibodies in neonates.

Methods: AAV9 IgG titers were measured with an enzyme-linked immunosorbent assay (ELISA) in 795 patients aged 0-12 months. AAV9 IgG concentrations of 13 neonates with at least two longitudinal samples and initial titers ≥1:100 were measured with a novel, more quantitative ELISA assay (Viroclinics Biosciences) to express AAV9 IgG concentrations in EU/mL and to calculate half-lives. Additional samples were tested to express IgG concentrations relative to AAV9 IgG titers.

Results: For neonates aged 0-1 month, the prevalence of elevated antibody titers was 14% (n=22/160). The prevalence was 2% for patients aged 2-3 months (n=4/178), and this continued to decrease during the first year of life. For the 13 patients with multiple samples, antibody concentrations waned for all patients according to first-order kinetics. The half-life of the antibodies was estimated to be 18-59 days. An AAV9 IgG titer of ≤1:50 was equivalent to a concentration of <203 EU/mL.

Conclusions: Concentrations of anti-AAV9 antibodies acquired via transplacental maternal transfer decrease in newborns following first-order kinetics. To follow the decline of elevated anti-AAV9 antibody titers to concentrations that permit onasemnogene abeparvovec dosing, retesting should be considered at 4 weeks for patients with initial titers ≥1:200, and at 8 weeks for initial titers ≥1:400. Initially elevated anti-AAV9 antibodies in newborns do not preclude onasemnogene abeparvovec administration.

Keywords:
AAV9, disease-modifying treatment, onasemnogene abeparvovec, spinal muscular atrophy

EPNS23-2979 Oral
Cerebrovascular Disorders

Comparison of Three Methods for Estimation of Infarct Volume in Children with Arterial Ischemic Stroke of Childhood

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Objective: Background Several volumetric techniques have been used to measure stroke volume for the prediction of outcome following pediatric ischemic stroke. Accurate stroke volume measurement requires manual segmentation which is time-consuming, so information on prognosis cannot be easily and quickly obtained in acute settings.
Aim: to evaluate the accuracy and reliability of 3 different volumetric techniques: Modified Pediatric Alberta Stroke Program Early Computed Tomography Score (modASPECTS), the simplified volumetric estimation using the ABC/2 formula, and segmentation.

Methods: 197 children with the diagnosis of arterial ischemic stroke (AIS) recorded in 2 different registries (prospective registration and retrospective analyses) from 2000 to 2021 who had diffusion-weighted images (DWI) in the acute phase entered the study. For the modASPECTS the ischemic lesion was scored on DWI images with a maximum of 23 points in each hemisphere; Lesion size with the ABC/2 formula was measured by placing linear diameters in three perpendicular axes on the slice where the lesion on DWI appeared largest, and the product of the three diameters was divided by two; 3D slicer volumetric software program was used for the segmentation.

Results: Results: There was a highly significant association between all three techniques for measuring stroke size: Segmentation had a higher correlation to the ABC/2 (Spearman's rho=0.97, p<0.000), than to the modASPECTS (Spearman's rho=0.77, p<0.000); the high correlation was defined between ABC/2 and modASPECTS (Spearman's rho=0.74, p<0.000).

Conclusions: Feasible methods such as modASPECTS and/or ABC/2 could replace technically demanding and time-consuming methods of volumetry such as segmentation.

Keywords:
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EPNS23-2821 Oral or e-Poster
Miscellaneous

Incidence and characteristics of epilepsy after acute central nervous system complications in pediatric hematopoietic stem cell transplantation: a multicenter study

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Objective: Seizures are a frequent and often severe symptom of acute central nervous system (CNS) complications among patients undergoing pediatric hematopoietic stem cell transplantation (p-HSCT). Evidence on the long-term development of epilepsy in this population is scarce. The aim of the study is to better define seizures characteristics and outline incidence, features and predictive factors of epilepsy developing in the aftermath of acute CNS complications of p-HSCT.

Methods: All acute CNS complications of p-HSCT occurring between 2000 and 2020 where retrospectively collected using electronic medical charts of four tertiary care centers for pediatric hematology and neurology. In patients with seizures, demographic, clinical, therapeutical and prognostic data including long-term outcomes were analyzed. Epilepsy was defined as the occurrence or re-occurrence of unprovoked seizures after p-HSCT.

Results: 122 events of acute p-HSCT-related CNS complications in 120 patients (42 females, 78 males, mean age at p-HSCT: 10 years old) were included. 29 patients (24.2%) already had neurological conditions at the time of transplantation (mainly CNS disease localization). Posterior reversible encephalopathy syndrome (PRES - 44.0%) and CNS infections (12.5%) were the most frequent complications. Prophylaxis with anti-seizure medications was administered during conditioning regimen to 35 patients (29%). Seizures occurred in 80 patients (66.6%), of which 20 developed status epilepticus (16.6%). 17 patients (14%) finally developed epilepsy (classified as structural focal epilepsy in all of them).

Conclusions: We focused on patient with p-HSCT-related acute CNS complications to determine the incidence and features of long-term epilepsy in this cohort. Our data confirm that seizures are a common and potentially severe manifestation of acute CNS complications in p-HSCT, ad that one in seven children with CNS complications will eventually develop epilepsy. The identification of specific risk factors for epilepsy among children and adolescents undergoing HSCT entails several preventive, therapeutic and prognostic implications that will be thoroughly discussed.

Keywords:
Hematopoietic stem cell transplantation; CNS complications, acute symptomatic seizures

EPNS23-2221 Oral or e-Poster
Cerebrovascular Disorders

The neurovascular rarity of Bow-Hunter's syndrome and three paediatric cases from a single tertiary centre.

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Objective: Bow Hunter's Syndrome (BHS) is a rare vascular phenomenon, which manifests with distinctive symptoms of posterior circulation ischaemia, resulting from the reversible occlusion of the vertebral artery (VA) either due to bony abnormalities or due to cervical instability during head rotation.

Methods: We describe 3 cases of paediatric BHS cases and suggest two different approaches with and without use of hard neck collar, depending on whether the affected VA is fully occluded or not and the on state of the contralateral VA.

Results: A 6-year-old boy presented with left hemiparesis, ataxia and dysarthria. His MRI shows posterior circulation infarcts of varying chronology. His vasculitis, thrombophilia and viral screens were unremarkable. He was discharged on prophylactic aspirin but represented one month later with worsening ataxia. His repeat MRI brain confirmed multiple new posterior circulation infarcts. Cervical CT showed no bony abnormalities and a Digital Subtraction Angiography (DSA) showed a left VA thrombus. A subsequent dynamic DSA demonstrated complete occlusion of the left VA on head turn to the right at 90° with 2 thrombi and impingement of the Right VA on head turn to the left, confirming the diagnosis of BHS. He was managed with a hard neck collar, enoxaparin and aspirin and underwent cervical fixation.

A 15-year-old boy developed headache, vomiting, dizziness, ataxia and left-sided neck pain. His MR brain confirmed a right cerebellar infarct and dissection of the right VA and his cervical CT showed an adjacent bony fragment, linked to the dissection. He received Enoxaparin and Aspirin. His repeat MR angiogram showed persistent occlusion of the right VA with a patent left VA and required no neurovascular intervention.

A 7-year-old boy presented with left hemiparesis with no preceding history of trauma. His MR brain showed posterior circulation infarcts of varying chronology. Imaging showed evidence of a right VA dissection without bony abnormalities. His DSA confirmed right BHS secondary to C1-2 instability. He is currently managed with aspirin and hard neck collar and is awaiting a cervical fixation.

Conclusions: The presence of recurrent posterior circulation strokes in the absence of trauma, vasculopathy, cardiac causes, and infection should raise a high suspicion of BHS. The gold standard diagnostic modality for BHS is dynamic DSA with head turn, as conventional DSA might not reveal the dynamic compression of the VA during neck rotation.

Keywords:
Bow Hunter, posterior circulation strokes, DSA

EPNS23-2448 Oral or e-Poster
Cerebrovascular Disorders

Lyme disease with cerebrovascular involvement in childhood

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Case study: Objective: Lyme neuroborreliosis (LNB) is caused by infection of spirochetes Borrelia burgdorferi genospecies complex sensu lato and is frequent in the Czech Republic. Typical clinical manifestations of LNB are lymphocytic meningitis, cranial neuritis, radiculoneuritis and rarely LNB presents as a cerebrovascular insult (CVI) in terms of vasculitis. To date, published systematic reviews about CVI of borrelial etiology are based on data of adult patients and in the minority involve children patients.
Method: Case reports of four pediatric patients (F:M = 2:2; age 7, 7, 10 and 13 years), who were admitted to the Department of Pediatric Neurology in our hospital and diagnosed with CVI caused by LNB. Each patient underwent in the acute phase the following: 1) neurological examination, 2) electroencephalography (EEG), 3) magnetic resonance imaging (MRI) of the brain with gadolinium administration including T2- and diffusion weighted, fluid attenuated inversion recovery, time of flight angiography and black blood sequences; in the last one the signal from flowing blood is suppressed and gadolinium enhancement of the vessel wall can indicate the pathology and 4) cerebrospinal fluid (CSF) and blood withdrawals for multiple laboratory testing.
Results: All children presented with decreased level of consciousness. In addition, three of them had acute hemiparesis and one child suffered from headache. All patients had abnormal EEG reports that mostly showed slow waves.
Brain imaging was abnormal in all cases, but the vascular pathology was detected only in three of them. Ischemic brain lesion was observed in two out of that three patients and the posterior circulation was mostly affected. One patient with acute hemiparesis had no detectable vascular pathology or ischemic lesion. CSF workout was abnormal in all patients, it revealed pleocytosis (median 219 cells/uL, range 100-768), blood-brain barrier dysfunction and intrathecal synthesis of specific borrelial antibodies. All patients were treated with antibiotics and anticoagulants; two received intravenous steroids. Three out of four patients completely recovered.
Conclusion: We demonstrate the importance of complex laboratory testing in children with CVI symptoms to reveal possible infectious etiology and vasculitis. The screening of LNB and especially in endemic areas is crucial for correct therapy management and global prognosis of these patients.

Keywords:
Lyme neuroborreliosis, cerebrovascular insult in childhood

EPNS23-2960 Oral or e-Poster
Cerebrovascular Disorders

Spontaneous perinatal intracranial hemorrhage-clinical, neuro-imaging and etiological correlates

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Objective: To characterize clinical, neuroimaging data and etiology of spontaneous perinatal intracranial hemorrhage (spICH) not related to prematurity.

Methods: A prospective, single-center study of 86 consecutive cases with spICH identified in the fetal/neonatal period between 2014-2022. Perinatal history, clinical presentation and neuroimaging data were reviewed. ICH mechanism was determined based on neuroimaging.

Results: Among 86 cases of spICH, 41 (47.7%) were diagnosed postnatally [median age-2.5 day (IQR 1,8 days)], and 45 (52.3%) were diagnosed antenatally at a median age of 27.5 weeks' gestation (IQR 24,33). Forty (62.5%) patients were symptomatic in the perinatal period and presented at a median age of 2.5 days (IQR 1,8) whereas 10 (15.6.%) had presumed spICH and presented at a median age of 4.5 months (4, 8.5). Seventeen (37.7%) underwent termination of pregnancy (TOP). Types of hemorrhage were as follows: IVH (n=65, 75.6%), PVHI (n=52, 60.5%), subpial (n=10, 11.6%), parenchymal (n=9, 10.5%), subdural (n=7, 8.1%). Fifty-three (61.6%) patients had more than one type of hemorrhage. IVH of all grades and PVHI (mainly frontal) were more commonly identified in patients diagnosed prenatally ($p<0.001$, $p=0.047$ respectively), whereas subpial hemorrhage was exclusively diagnosed post nataly ($p<0.001$). PVHI was mainly unilateral (80.8%) and was left-sided in 46.2%. No difference in terms of mode of delivery, maternal age, parity status, gestational age at birth and birth weight between different types of hemorrhage or timing of diagnosis. The origin of hemorrhage was germinal matrix in 41 [prenatal cases (n=30, 67%] post-natal cases [n=11, (27%), $p<0.001$], Choroid plexus in 46 (53%) [prenatal cases (n=27, 60%, post-natal cases [n=19, (46.3%], hemorrhagic transformation of venous infarction [8 (9.3%)], vascular malformation in 2 (2.3%), bleeding diathesis and congenital tumor (one each) and unknown (n=20, 23.3%). Family history of coagulopathy were associated with primary parenchymal ($p=0.047$) or subpial hemorrhage ($p=0.026$) and post-natal IVH ($p=0.025$). Genetic workup was performed in 36 (42%) cases, of whom 15 (41.6%) had a genetic diagnosis underlying the hemorrhage. Most (80%) patients with genetic diagnosis had an antenatal bleeding and 8 (53%) underwent TOP.

Conclusions: In our cohort with spICH, germinal matrix was the most common origin in fetuses compared to choroid plexus in post-natal hemorrhage. Family history of coagulopathy was associated with parenchymal or subpial hemorrhage.

Keywords:
Hemorrhage, IVH, PVHI, Prenatal

EPNS23-2170 Oral or e-Poster
Cerebrovascular Disorders

Visuospatial processing skills following unilateral arterial ischemic stroke in childhood

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Objective: Due to the rare occurrence of childhood stroke, its impact on later cognitive functioning remains unclear. Even though it has been posited that children recover better than adults do, recent studies suggest that childhood stroke can negatively affect a wide range of cognitive domains, such as attention, language, and processing speed. We examined the effect of neurologic characteristics on visuoconstructive abilities and visual memory in childhood stroke patients.

Methods: 17 children with a single unilateral arterial ischemic stroke (10 left hemispheric (LH), seven right hemispheric (RH), age range 7y0mo-17y5mo) participated in this retro- and prospective study. The Rey Osterrieth Complex Figure (ROCF) was evaluated quantitatively and qualitatively using the 36-point scoring system and the Developmental Scoring System. Two-sample t-tests and the Mann-Whitney U test were employed to examine group differences. To detect potential associations between continuous variables, Spearman's rank correlation was used. To analyze the effect of neurologic data on cognitive outcome, significance of correlations was set based on a Bonferroni correction factor ($\alpha = .05/7 = .007$).

Results: We found that lesion laterality and age at stroke impacted patients' ability to recall certain elements of the ROCF. The LH stroke patients included less internal details than the RH stroke patients, both immediately after copying the figure ($U = 13.0$, $p = .032$) and after a 20-minute delay ($U = 10.0$, $p = .015$). Moreover, patients with a stroke onset before the age of five years remembered fewer structural elements than patients with a stroke onset after the age of five years ($r_s = .66$, $p = .004$). Finally, the qualitative scoring method better differentiated between individuals and between groups than the quantitative method.

Conclusions: Our findings support the notion that the left hemisphere is more involved in local-level processing of visual material than the right hemisphere and that patients with later stroke onset can better recall visual material than patients with earlier stroke onset, providing evidence for the early vulnerability thesis. These findings have important clinical implications. Whereas LH and RH stroke patients may need different types of cognitive training, children with very early stroke onset may need more support overall. Finally, assessing the ROCF qualitatively may help clinicians in pinpointing a child's cognitive deficits and tailoring therapy to their specific needs.

Keywords:
childhood stroke, cognitive development, early vulnerability, visual memory, visuoconstruction

EPNS23-2271 Oral or e-Poster
Neurogenetic Disorders

The added value of systematic reanalysis of exome sequencing data in pediatric neurology practice

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Objective: Whole exome sequencing (WES) has obtained an important place in the diagnostic process of identifying the cause of pediatric neurological disorders suspected to have a genetic origin. Between 2011 and 2015, in a cohort of 150 patients referred to a tertiary centre for pediatric neurology in whom we suspected a genetic cause for their pediatric neurological problem (intellectual disability, movement disorder, epilepsy and/or neuromuscular disorder), we were able to establish a definite diagnosis in 31% of patients (N= 47) using whole exome sequencing, compared to 7% of patients using standard diagnostics (all other available diagnostics except whole exome sequencing).

Methods: Five years after the first analysis, we looked again at the 103 patients from this cohort in whom we could not make a definitive diagnosis in 2015. Initially, we looked whether new diagnostics had been performed at the request of parents and referring physicians in the intervening 5 years. 7 patients got a definitive diagnosis in this way. Then we looked whether new information was available on previously found mutations in the DNA that were not related to a known human disease in 2015, but were in 2020. 10 patients received a definitive diagnosis in this way. Afterwards we reanalyzed all exome data with current bioinformatics systems, this led to 6 new definite diagnoses. Of all patients who still did not have a diagnosis after this re-evaluation, resequencing took place using the latest whole exome sequencing technique (TWIST), this led to another 9 new diagnoses

Results: A total of 32 new diagnoses were able to be made using this systemic reanalysis, increasing the diagnostic yield of the WES from 31% (N= 47) to 53% (N= 79).

Conclusions: Thus, it is important to re-evaluate the data after several years in patients with a suspected genetic diagnosis without a definitive diagnosis after whole exome sequencing studies, as this gives a real chance to make a definite diagnosis.

Keywords:
whole exome sequencing, re-analysis

EPNS23-2842 Oral or e-Poster
Movement Disorders

High prevalence and early onset of Parkinsonism signs in a series of patients with Rett syndrome

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Objective: Although parkinsonism has been reported in Rett syndrome(RTT) detailed descriptions regarding onset age,spectrum of symptomatology and long-term outcome has been scarcely reported. This work aims to detect and analyze hypokinetic rigid syndrome (HRS)signs in a series of 12 patients with Rett syndrome(RTT) (MECP2 mutations).

Methods: Descriptive study of 12 patients with RTT with an age range at the assessment between 11 and 19 years(mean age 15,33± 2,64).Anamnesis,retrospective study of medical history,genetic information,physical examination and video filming protocol were performed.Rett Clinical Severity Scale(RCSS)and UPDRS Scales were applied.

Results: The mean age at which RTT symptoms began was 12.17±5.99 months. Neurodevelopmental regression occurred at a mean age of 20.3±0.85 months.HRS signs were first detected at a mean age of 14,4±3.34 years.Patients presented rigidity 91.7%,hypomimia 83.3%,hypokinesia 83.3%,rest tremor 58.3% and dystonia 41.7%. Eleven out of 12 patients showed some degree of extrapyramidal rigidity more evident in patients at age of 13 years and elder. Rest tremor and dystonic postures were observed in patients from age 13 to 19.Hypomimia and hypokinesia were observed in all age ranges(from 8 to 19).Patients with higher severity of rigidity were those with a higher severity RTT score (RCSS) (p=0.039).Other symptoms do not present a correlation with RCSS score(p=0.05).The evolution of HRS symptoms and signs was progressive and slow in 4 patients and 8 had a static clinical picture. Brain MRI studies did not add significant information. The study of neurotransmitters in CSF was performed only in 3 patients.One patient presented decreased HVA and 5-HIAA levels (dopaminergic and serotoninergic metabolites respectively). Another patient presented an isolated decrease of 5-HIAA levels. Genetic mutations did not correlate with the presence or severity of HRS signs.

Conclusions: In RTT Parkinsonism signs are already present in childhood, therefore earlier than reported in previous studies.Our series shows a high percentage of HRS symptoms compared to other reports.This could be due to the fact of looking carefully and specifically for these type of symptoms.As a consequence of these findings we could suggest that HRS seems to be a cause of early onset parkinsonism and belong to the natural evolution of RTT motor disorders without correlation with the clinical severity of the patients(except for rigidity).Early therapeutic interventions(L-Dopa or similar)are advisable.

Keywords:
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EPNS23-2411 Oral or e-Poster
Neurogenetic Disorders

Rapid whole genome sequencing in paediatric neurological disorders during hospitalization: a single-centre prospective study

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Objective: Rapid genomic testing (2-3 weeks) facilitates the diagnosis of around 30% of critically ill children, influencing clinical outcomes. Our objective was to evaluate the diagnostic and therapeutic utility of rapid whole-genome sequencing (WGS) in hospitalized children with a suspicion of genetic etiology.

Methods: An 18-month prospective, single-centre study of 71 consecutively paediatric patients with acute or progressive neurological and/or multisystemic symptoms, that required hospitalization in ward, neonatal unit or intensive care. A specialized paediatric clinical team initially assessed their eligibility and each family received a detailed genetic counselling consultation, provided by a registered genetic counsellor, before recruitment. Trio WGS was performed on germline DNA and pathogenic variants were filtered and reported by extensive bioinformatic analysis.

Results: We identified pathogenic or likely pathogenic variants in 24/71 patients (33.8%) hospitalized in ward (58%), neonatal unit (25%) or intensive care (17%). Of those, 21 presented with neurological symptoms (87.5%), with a mean age of four years (11/21 were <6 months; range newborn-13 years). In five patients with refractory seizures, trio WGS revealed variants in SCN1A, DEPDC5, DDX3X, PPP3CA and POLR2A genes. Three patients with ALG1, GLRA1 and HIBCH variants presented with neonatal encephalopathy. Congenital or early-onset hypotonia was related to variants in PLP1, SCN4A and RYR1 genes. Progressive symptoms such as ataxia, cognitive decline or psychosis were associated to variants in CLN6, FXN, SACS and SHANK3 genes. Of those with suspicion of malformation syndromes with psychomotor delay, six patients were diagnosed with mutations in TELO2, GATAD2B, FAM111A, NSD1, SMARCA4 and PTEN genes. A genetic diagnosis was achieved in a mean of 20 days (range 8-33). We performed a genetic counselling in the 21 families according to the pattern of inheritance: de novo (10), autosomal recessive (7), familial autosomal dominant (2) and X-linked (2). Specific treatment was changed in six patients after the genetic diagnosis.

Conclusions: Our approach has allowed a prompt molecular diagnosis in more than one third of the cases. It avoided the diagnostic odyssey, facilitated a fast genetic counselling and lead to treatment and care adjustments.

Keywords:
whole genome sequencing; genetic diagnosis; genetic counselling; neurological disorders

EPNS23-2483 Oral or e-Poster
Movement Disorders

Clinical and genetic characterization of a paediatric series of 28 patients with hereditary spastic paraplegia

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Objective: Hereditary spastic paraplegia (HSP) is a genetically and clinically heterogeneous group of disorders in which the main clinical feature is progressive lower extremity spastic weakness. Most of the HSP data reported in the literature correspond to adults series, and there have been only a few studies in children.

Methods: We conducted a clinical study of paediatric patients followed in the paediatric neurology consultation, who met clinical criteria for the diagnosis of HSP. Demographic and clinical characteristics were reviewed and analyzed using descriptive statistics. All patients were assessed by the same clinician using a standard protocol. Imaging, neurophysiological and genetic studies were reviewed.

Results: We identified 28 unrelated patients with HSP of onset in the paediatric age, of whom 19 are males (68%). Age at onset was below 2 years old in 25 patients (89%), mainly presenting with a delay in gait acquisition or an abnormal gait pattern, such as toe gait. Thirteen presented with pure phenotype, and 12 had complex presentations. Most complex phenotypes were progressive (10) and the most common associated symptoms were dystonia, cognitive deficits and muscle atrophy. Three patients had marked asymmetry. Upper limbs were mildly involved in 14 patients (50%), with hyperreflexia in 9, fine motor skills impairment in 7 and dystonia in 5. A genetic diagnosis was established in 19 patients (68%). The most common pathogenic variantes were found in SPAST gene (SPG4) in 4, in ATL1 (SPG3A) in 2 and in KIDINS220 in 2. The remaining had pathogenic variants in NIPA1, KIF5A, BSCL2, SLC15A2, B4GALNT1, KIF1A, AP4B1, ENTPD1, UBAP1, PI4KA, and ALS2 genes. Nine (32%) had de novo mutations, including three patients with SPG4 who presented complex phenotypes. VOUS in relevant genes were found in 6, WES was negative in 2 and NGS gene panel in 1.

Conclusions: We present a highly clinically and genetically heterogeneous series of paediatric onset HSP patients. Paediatric patients mostly present with delayed motor milestones or abnormal gait patterns in toddlerhood. Substantial phenotypic variation can occur between individuals with the same SPG type. The absence of family history should not exclude the diagnosis of HSP, as mutations are often de novo.

Keywords:
hereditary spastic paraplegia; childhood onset; spasticity

EPNS23-2737 Oral or e-Poster
Neurogenetic Disorders

Pathogenic variants in the KIF1A gene are a significant cause of spastic paraplegias and neuropathies in the Czech Republic

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Objective: KIF1A is a neuron-specific member of the kinesin-3 family essential for the axonal transport. Biallelic pathogenic variants in the KIF1A gene are the cause of hereditary sensory neuropathy type 2 (HSAN2). Pathogenic variants in the KIF1A are known also as the cause of hereditary spastic paraplegias (SPG) - both recessive and dominant. SPG could be a part of a complex dominantly inherited KIF1A syndrome. The evaluation of KIF1A variants' causality is challenging because of ambiguous modes of inheritance and a broad spectrum of caused phenotypes. The majority of described variants in the KIF1A gene is of missense type. The mode of inheritance does not strictly correlate with the type of variant (truncating/missense). The loss of function variants are inherited in autosomal recessive pattern, while those with autosomal dominant inheritance have more likely the dominant negative effect.

Methods: Approx. 300 patients with hereditary neuropathies/hereditary spastic paraplegias from the Czech Republic screened by exome sequencing .

Results: We diagnosed 12 patients with one heterozygous missense variant in the KIF1A gene as the only possible disease-causing variant.In two cases the do-novo occurrence was confirmed, both patients presented with early onset of the disease, rapid progression and complex phenotype. All diagnosed KIF1A patients followed the autosomal dominant pattern of inheritance and in all cases the causal variant was localised in the gene's protein domain. The age of onset and clinical manifestation were highly variable, including even psychiatric impairment. The ambiguity and variability of KIF1A phenotypes makes the diagnostics and variants' causality interpretation much complicated. Some KIF1A pathogenic variants arose de novo, which is not usual in neuropathies and spastic paraplegias, and these cases are connected with more severe course of disease. The presence of causal variants in the gene's protein domain seems to be crucial for pathogenicity.

Conclusions: Pathogenic variant in KIF1A gene are significant cause of spastic paraplegias, neuropathies in the Czech Republic, inherited in autosomal dominant pattern. The KIF1A spastic paraplegias (SPG30) even count for one of more common types among AD SPGs. The final number of KIF1A patients could be still underdiagnosed. However, the variants' causality should be carefully considered and the larger segregation analysis in the family is necessary.

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Keywords:
KIF1A gene, de novo occurence, AD spastic paraplegias, AD neuropathies, variable phenotype

EPNS23-2546 Oral or e-Poster
Sleep Disorders

Sleep problems in children with fetal alcohol spectrum disorder (FASD) versus Children with attention deficit hyperactivity disorder (ADHD).

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Case study: Background/Objective: Fetal alcohol spectrum disorder (FASD) covers a broad spectrum of cognitive-behavioral manifestations (secondary ADHD, among others) and dysmorphologies, because of prenatal exposure to alcohol. Sleep problems associated with FASD are a poorly explored area.
The objective of the present study is the characterization of the sleep pattern of a population of children with FASD with secondary ADHD, in relation to that of a homonymous population with primary ADHD.

Methods: We compared two populations with ADHD. On one side 170 patients (117 males) with primary ADHD (DSM-5 criteria); 100 of them had combined ADHD presentation, and 70 had the inattentive one ADHD presentation (mean age was 11 years). On the other hand, 100 patients (73 males) with FASD and secondary ADHD (mean age of 10 years). Sleep disorders were studied using the Sleep Disturbance Scale for Children (SDSC). It suggests sleep disturbance if the global cut point accounting for the different subscales is greater or equal to 39.

Results: Regarding the population of children with primary ADHD, a total of 33 patients (19.4%) had an overall SDSC score greater or equal to 39. Meanwhile the population of children with FASD and secondary ADHD, a total of 28 patients (28%) had an overall SDSC score greater or equal to 39. In relation to SDSC subscales, the population with primary ADHD presented: "disorders of initiating and maintaining sleep" (DIMS): 28 pt. (84.9%), "respiratory disorders" (RDS): 0 pt. (0%), "arousal disorders" (AD): 1 pt. (3%), "alterations transit wake-sleep" (AWS): 9 pt. (27.3%), "excessive daytime sleepiness" (EDS), 17 pt. (51.5%), and "hyperhidrosis during sleep" (HS): 2 pt. (6%). Regarding the SDSC subscales, the population with secondary ADHD (FASD children) presented: DIMS: 23 pt. (82%), RDS: 5 pt. (17%), AD: 2 pt. (7%), AWS: 9 pt. (32%), EDS: 9 pt. (32%), and HS: 4 pt. (14%).

Conclusions: Sleep problems in both populations are more frequent in males. The population of patients with FASD has a slightly higher percentage of sleep disorders compared to primary ADHD (28% vs. 19%). The most compromised subscales in both populations were problems related to sleep initiation and maintenance, EDS, and AWS. A greater presence of breathing problems during sleep was observed in FASD, while the population with ADHD showed a greater tendency towards EDS.

Keywords:
ADHD, FASD, Sleep disturbance, Sleep Disturbance Scale for Children (SDSC)

EPNS23-2817 Oral or e-Poster
Sleep Disorders

Sleep apnea as the only clinical manifestation of Chiari malformation

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Case study: 12-year-old girl presenting with sleep apnea -respiratory pauses of approximately 10 seconds duration several times a night, recorded by parents. Nocturnal polysomnography was performed, in which 206 apneas and 12 hypopneas were observed, all of them of a central nature with an apnea-hypopnea index of 27. In the last year the patient had sporadically reported episodes of mild neck pain, without other associated clinical manifestations: no headache, no vomiting, no dysesthesia.
Given the central origin of the apneas, a craniomedullary magnetic resonance was requested to rule out neuroanatomical abnormalities, observing a herniation of the cerebellar tonsils through the foramen magnum (descended 28 mm, at C2 level) and also part of the medulla oblongata, with cervical compression, compatible with Chiari malformation 1.5. Urgent evaluation by Neurosurgery was requested, proceeded to surgical correction by suboccipital craniectomy and C1 laminectomy. After surgery, she presented complete resolution of sleep apnea episodes, with normal follow-up polysomnography (apnea-hypopnea index 0.6). In the control MRIs, a good postoperative evolution was observed, without Chiari recurrences. The patient has not presented episodes of neck pain again, and never presented the usual Chiari symptoms such as headache, vomiting or dysesthesia.
The relationship between Chiari malformation and sleep-related breathing disorders should be taken into account, especially the presence of central apneas which, in some cases like the one we present, may be the only consistent clinical manifestation, and require polysomnography and MRI for a proper diagnosis.

Keywords:
Chiari malformation, Chiari, sleep apnea

EPNS23-3002 Oral or e-Poster
Sleep Disorders

Theory of Mind impairment in childhood Narcolepsy type 1: a case-control study

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Objective: Narcolepsy type 1 (NT1) is a central disorder of hypersomnolence characterized by excessive daytime sleepiness, cataplexy, and rapid eye movement sleep-related manifestations.
There is general agreement regarding neural correlates of NT1 that seem related to anatomical and functional abnormalities in the hypothalamic region. Concerning cataplexy, it is well known that emotional stimuli can trigger cataplexy attacks. Authors focused on the neurobiological correlates of emotions. Indeed, cataplexy seems to depend on dysfunctional hypothalamic-amygdala interactions triggered by positive emotions.
Several neurophysiological studies suggest an alteration in emotional processing consequent to the impaired function of the amygdala and hypothalamus, but there is no clinical evidence in line with this. Thus, NT1 patients may show an alteration in a more complex cognitive ability related to emotional processing, namely Theory of Mind (ToM).
This study aims to assess the ability of ToM in children with NT1.

Methods: Twenty-two NT1 patients (6 females, mean age 11.02, SD 1.54) and 22 healthy controls matched for age and sex underwent a neuropsychological evaluation to assess the visual and verbal ToM abilities, emotion recognition, pragmatics, and any symptoms of anxiety and depression. Specific scales in everyday use in clinical practice were used to assess the clinical characteristics of patients with NT1.
A Mann-Whitney U test and a Spearman's rank-order correlation were conducted to test for differences between the two groups and to assess the relationship between ToM skills and clinical measures.

Results: Children with narcolepsy showed impairment in ToM visual (p=0.009) and verbal (p=0.005) skills compared to healthy controls.
Correlation analyses showed more significant ToM verbal and visual skills impairment in patients with greater disease severity assessed by the Pediatric Narcolepsy Severity Scale (PNSS; p=0,035 and p=0,012 respectively) and daytime sleepiness assessed by the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD; p=0,025 and p=0,038 respectively).

Conclusions: Our study demonstrates a selective impairment in the ToM domain in children with NT1.
Our hypothesis is that childhood-onset NT1 may interfere with the normal development of ToM and that subsequently ToM abilities may modulate the severity of NT1 symptoms by providing greater ability to avoid cataplexy. Further longitudinal studies assessing how the trajectory of NT1 and ToM skills interact over time are needed.

Keywords:
narcolepsy; theory of mind; cataplexy; emotional processing;

EPNS23-2327 Oral
Neuropsychiatric Disorders

Sleep Spindle Analysis in Autism Spectrum Disorder

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Objective: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and reciprocal interaction accompanied by stereotyped, restricted, and repetitive patterns of behavior. Considering the relationship between neural maturation and changes in sleep spindle activity, it has been suggested that sleep spindles can be used as a potential index of neural maturation. There are conflicting findings regarding sleep spindles in children with autism spectrum disorder (ASD). We hypothesized that the spindle characteristics of children with autism were different from the control group. These differences may explain neurodevelopmental deficiencies in these patients.

Methods: Sleep EEGs of 30 ASD patients aged 2-13 years diagnosed by child psychiatry and 30 healthy controls in the same age group were evaluated in terms of sleep spindles. Patients and controls were divided into two groups as 2-5 years old and over 5 years old. Spindle amplitude, frequency, duration, density and activity were compared.

Results: ASD patients, 11 were girls (36.7%), 19 were boys (63.3%), 11 of the control group were girls (36.7%), 19 were boys (63.3%). The mean amplitude, mean frequency and mean duration of the spindles did not differ significantly between the ASD patients and the control group. Median spindle count (11.5 vs 20; p=0.005), median spindle density (2.3 vs 3.6; p=0.008) and median spindle activity (52 vs 67; p=0.024) were lower in ASD patients compared to the control group. A positive correlation was found between spindle density and spindle activity (r=0.348; p=0.044) and duration (r=0.354; p=0.047) in ASD patients. Median spindle count (14 vs 21; p=0.023), median spindle density (2.8 vs 4.2; p=0.022), and median spindle activity (55.3 vs 72.4; 0.032) in male ASD patients compared to the control group were low.

Conclusions: Our results revealed that sleep spindles in ASD patients have different characteristics compared to healthy children. As a result, with current and advanced evaluations of sleep spindles, treatment can be started with a cheap and easy method early in ASD patients, and the destructive effects of the disease can be intervened relatively earlier, and sleep spindles can be used as a marker. More detailed and advanced studies on sleep are required in this patients.

Keywords:
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EPNS23-2699 Oral
Sleep Disorders

Childhood narcolepsy - clinical and social long-term outcome

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Objective: Narcolepsy is a chronic neurological disorder that often begins in adolescence. The aim of our retrospective study was to evaluate the clinical course and impact of narcolepsy with cataplexy (NT1) and narcolepsy without cataplexy (NT2) on the social relationships of patients.

Methods: Forty patients (17 males, mean age 23.0±6.9 years, age at disease onset 13.0±4.1 years, age at diagnosis 15.0±4.0 years, mean follow-up period 8.5±7.5 years) were invited to a clinical interview to summarize their neurological and psychiatric complaints and to complete the Narcolepsy Severity Scale (NSS), Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scale (HADS) and a questionnaire regarding the impact of narcolepsy on their social interactions, education, employment (if relevant) and partner relationships. Most patients (n=31) were diagnosed with NT1. Fisher's exact test and a two-sample t-test were used for statistical analyses.

Results: Regarding clinical complaints, the NT1 group showed a more severe disease course (NSS) with higher subjective sleepiness (ESS) and higher depression score (HADS) than the NT2 group ($p<0.05$ in all evaluated parameters). Narcolepsy was reported as the cause of educational failure in 57.5% of respondents. At the age of 20 years only 65.6% of subjects completed secondary school, and at the age of 25 years, only 38.5% of subjects reported being currently enrolled in and/or completed education at the university level. Employment difficulties were reported by 40.5%, and the professional position did not match achieved education in more than one third of cases. Most respondents (15 of 27 older than 20 years) had no satisfactory partnerships and prioritized single life due, at least partially, to narcolepsy. Despite adequate treatment, 29 % of NT1 patients older than 18 years received financial disability assistance. Regarding psychiatric comorbidities, 8 patients (20%) were treated for depression or general anxiety disorder, 6 subjects (15%) for behavioral development disorder (attention deficit hyperactivity disorder; n=4, Asperger syndrome; n=2). Schizophrenia occurred in two NT1 subjects during adulthood.

Conclusions: Narcolepsy diagnosed in childhood and adolescence severely impairs social functioning in young adult life. This impact affects education and employment as well as partner relationships. Psychiatric comorbidities associated with narcolepsy may additionally contribute to negative social outcomes.

Keywords:
Childhood narcolepsy, long-trerm outcome, clinical course, social functioning

EPNS23-2356 Oral or e-Poster
Sleep Disorders

Polysomnographic Profile and Sleep Abnormalities in Children Diagnosed with Celiac Disease before the Initiation of Gluten Free Diet

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Objective: The study assessed the presence of sleep abnormalities in children who had recently been diagnosed with celiac disease (CD) and not started a gluten free diet (GFD).
The children's polysomnographic profiles were also characterized and further compared with healthy children of the same age.

Methods: This prospective cross-sectional study involved 46 pediatric subjects (aged 1-19 years) who had recently been diagnosed with CD and not started a GFD. The control group consisted of 32 healthy children (aged 2-17 years). All children underwent anthropometric measurement, laboratory testing and standard overnight observation with in-laboratory video-PSG.

Results: No significant differences in the basic demographic and anthropometric parameters between the celiac and control group were observed. Significantly prolonged sleep latency (SOL) was evident in the celiac subjects (21.89 ± 20.77 min. vs. 10.99 ± 7.94 min., p = 0.02), with a probability of prolonged SOL of 4.23-fold greater (OR = 4.23; 95% CI 1.1 - 16.22) than the healthy controls, especially in the subgroup of older celiac patients. No significant differences in the sleep period time (SPT), total sleep time (TST), wake during sleep (WASO), sleep efficiency (SE) and sleep stage distribution and cyclization were found. The respiratory rates during sleep indicated a significantly increased incidence of central sleep apnea (CSA) in celiac subjects (4.41 ± 6.55 vs. 1.56 ± 1.85, p = 0.04) and related central apnea-hypopnea index (CAHI) (0.54 ± 0.78 vs. 0.19 ± 0.24, p = 0.03) with a 3.16-fold greater probability of pathological central AHI (OR = 3.16; 95% CI 1.02 - 9.77) than the control group. An increased incidence of CSA in the subgroup of younger celiac patients compared to younger healthy controls was especially evident.

Conclusions: The findings of the study suggest a difference in sleep architecture and an increased incidence of CSA in children with untreated CD, but additional research is required to verify the results.

Keywords:
polysomnography, celiac disease, children, central sleep apnea

EPNS23-2111 Oral or e-Poster
Neuromuscular Disorders

Safety and efficacy of ataluren in nmDMD patients from Study 041, a phase 3, randomized, double-blind, placebo-controlled trial

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Objective: Study 041 (NCT03179631) is an international, phase 3, randomized, double-blind, placebo-controlled 72-week ataluren trial in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) followed by a 72-week open-label period. Here, we describe efficacy and safety results from the placebo-controlled phase.

Methods: Boys with nmDMD aged ≥5 years, on corticosteroids, and with a 6-minute walk distance (6MWD) ≥150m were eligible. The primary objective was to determine ataluren's effect on ambulatory function, assessed by the 6-minute walk test. Boys were randomized 1:1 to ataluren:placebo. The intention-to-treat (ITT) population comprised randomized boys who received ≥1 dose of study treatment. Predefined subgroups included boys with baseline ≥300m 6MWD and ≥5s stand from supine (primary) and those with baseline 300-400m 6MWD. For the analysis of efficacy endpoints, a mixed model for repeated measures was employed to interpret results. Time to 10% persistent worsening in 6MWD was evaluated using a log-rank test and Kaplan-Meier analysis.

Results: Ataluren and placebo groups in the ITT population and key subgroups were balanced according to enrolment age, baseline 6MWD, corticosteroid use and time to stand from supine. Significant differences in mean 6MWD change from baseline and rate of change favoured ataluren in the ITT population (14.4m; 0.20m/week; p=0.0248) and 300-400m 6MWD subgroup (24.2m; 0.34m/week; p=0.0310), representing a 21% and 30% slowing of the decline rate in 6MWD in these groups, respectively. There were significant treatment benefits in time to 10% worsening of 6MWD. The number of ITT patients who lost ambulation receiving placebo was almost double that of those receiving ataluren. Ataluren was well tolerated, had no probable drug-related serious adverse events (AEs), and AE frequency (85.3%) was similar to placebo (84.7%).

Conclusions: Treatment with ataluren delayed decline in loss of motor function, and therefore disease progression, compared with placebo in patients with nmDMD. Favourable safety results consistent with the known safety profile of ataluren were also demonstrated. Therefore, Study 041 confirms ataluren's favourable benefit-risk profile as shown in previous clinical and real-world evidence studies.

Keywords:
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EPNS23-2780 Oral or e-Poster
Movement Disorders

GENOTYPIC AND PHENOTYPIC FEATURES OF A SERIES OF PATIENTS WITH A GENETIC DIAGNOSIS OF HYPEREKPLEXIA: BEYOND EXAGGERATED STARTLE RESPONSE

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Objective: Hereditary hyperekplexia is caused by mutations which affect glycinergic neurotransmission. It presents from birth with exaggerated startle response to sudden visual, auditory or tactile stimuli, and tends to improve with age.

Objective: to describe the genotypic and phenotypic findings from ten patients with a diagnosis of hyperekplexia.

Methods: Observational, descriptive, retrospective multicenter study.

Results: Ten patients were included, two of them siblings, with symptoms of early onset easy-provoked startle responses to somatosensory and/or acoustic stimuli (first days or weeks of life). Three patients presented neonatal apneas (one also after neonatal period). Family history: epilepsy in 4/10 and easy-provoked startle response to stimuli: 6/10.

Genetic testing detected the likely pathogenic or pathogenic variants *SLC6A5* (p.Pro318GlnfsX11) in patients 1 and 2 (siblings), *GLRB* (p.Trp493Ser) in patient 3, *GLRB* (p.Val256Met) in patient 4, *GLRA1* (p.Arg299Gln) in patient 5, *SLC6A5* (p.Gly452Ala) in patient 6, *SLC6A5* (319delC, 1994delT) in patient 7, *GLRA1* (p.Tyr230Ter) in patient 8, and *GLRA1* (p.Tyr307Cys) in patient 9. Patient 10 showed the variant of unknown significance *GLRA1* (p.Arg369Cys).

Phenotypes: Patient 10 was excluded from this description because he suffered a cardiorespiratory arrest due to apnea at age 1 month and as consequence a severe spastic-dystonic cerebral palsy; basal hypertonia: 9/9 (transitory in 5); epileptic seizures: 2/9 (absence seizures plus bilateral clonic seizures in one patient, generalized tonic seizures in another); neurodevelopmental delay: 7/9; motor delay: 4/9; hypokinesia: 2/9; impairment of language development: 7/9; cognitive impairment: 2/9; attention difficulties and/or motor restlessness: 6/9; autism spectrum disorder -ASD- traits: 2/9; conduct disorder: 1/9; sleep disorders: 2/9. Severe cognitive impairment with absence of expressive language in adulthood: 1. Seven of 9 patients received treatment with clonazepam with partial or complete response.

Conclusions: We highlight the presence of common language developmental disorders and attention difficulties in our patients, including a very severe phenotype with lack of expressive language in adulthood, and the finding of ASD traits in two cases. The presence of epileptic seizures in two patients is also remarkable, together with a family history of epilepsy in 40% of the cases. Apneas can be fatal.

Keywords:
hyperekplexia, apnea, epilepsy, attention difficulties, developmental language disorders

EPNS23-2605 Oral or e-Poster
Neuromuscular Disorders

Multiomics Profiling of Spinal Muscular Atrophy (SMA)

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Objective: Spinal Muscular Atrophy (SMA) is a rare neuromuscular disease caused by mutations in the survival motor neuron (SMN1) gene. Symptoms include progressive muscle atrophy due to loss of motor neurons. If untreated, SMA is described as the most common genetic cause of infant death. Since 2016, SMA patients can be treated by commercially available intrathecal treatment with the antisense oligonucleotide Nusinersen, thereby leading to alternative splicing of the SMN2 gene and significant improvement of motor function and clinical outcome.

Methods: In this prospective study (ethics vote number: 31-162 ex 18/19, Medical University of Graz, Austria) we employed metabolomics, lipidomics as well as proteomics to investigate the composition of sequentially collected CSF samples of 13 patients with SMA (7 female and 6 male) for biochemical variations in response to treatment with Nusinersen, compared to 14 age- and sex- matched controls. Proteomics analysis was performed using the software MaxQuant and Perseus for statistical analysis. The programs Compound Discoverer (Thermo Scientific) and Lipid Data Analyzer (version 2.8.3) were used for metabolomics and lipidomics, respectively. Univariate and multivariate analysis was performed using the program R.

Results: By combining results of the multi-omics approach, we were able to detect over 800 proteins and 400 small molecules in CSF samples of our cohort. In pre-treatment samples we found decreased levels of the neurotransmitter acetylcholine, the phospholipid phosphatidylethanolamine, plasmalogens and sphingomyelin in SMA patients compared to healthy controls. In contrast, CSF of children with SMA showed increased levels of the signaling lipid sphingosine as well as its precursor serine compared to controls. Analysis of follow-up samples is pending.

Conclusions: Results of multi-omics profiling from pre-treatment CSF samples indicate a changed lipid metabolism in SMA patients compared to healthy controls.

Keywords:
Proteomics, Metabolomics, Lipidomics, Rare Diseases, Biomarker

EPNS23-2282 Oral
Movement Disorders

Seven new cases of developmental encephalopathy 64 associated with RHOBTB2 variants and a review of literature

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Case study: Objectives. RHOBTB2 (Rho Related BTB Domain Containing 2) interacts with the cullin-3 protein, a ubiquitin E3 ligase required for mitotic cell division, and has been associated with epileptic encephalopathy, early infantile, 64, autosomal dominant (OMIM#618004) in 30 reported patients.
Methods. We report seven additional cases of RHOBTB2-related encephalopathy, describe a novel pathogenic heterozygous variant, and review previously published cases of RHOBTB2-associated encephalopathy.
Results. Patients (4 males, 3 females) had a mean age of 8,9+-7,3 years (Mean+-SD). All patients presented with seizures before one year of age, including focal seizures, tonic-clonic seizures, nonfebrile status epilepticus, and febrile status epilepticus. The patients showed a good response to CBZ, OXC, and TPM treatment. Movement disorders presented between 4 months and 14 years of age, and included kinesigenic paroxysmal dyskinesia, generalized choreodystonia, brief dystonia attacks, stereotypies, hemiplegic episodes, and ataxia. There was an improvement in the movement disorder with CBZ or OXC treatment. Three patients showed acute encephalopathic episodes at ages 4 and 6 (2 patients), that showed improvement after methylprednisolone. MRI showed transient FLAIR abnormalities during these episodes as well as myelination delay, thin corpus callosum, and brain atrophy. One patient harbored a novel RHOBTB2 variant (c.314G>A/p.Gly105Glu)
Conclusion. RHOBTB2-related disorders are characterized by early-onset epilepsy, movement disorders, developmental delay or intellectual disability, acquired microcephaly, and episodes of acute encephalopathy. At a young age, focal dystonia as well as acute encephalopathic episodes and episodes of tongue protrusion or vasomotor disorders are critical clues to diagnosis. Patients responded favorably to TPM, CBZ, or OXC treatment.

Keywords:
RHOBTB2, oxcarbamazepine, epileptic encephalopathy, acute encephalopathy, movement disorders, kinesigenic paroxysmal dyskinesia

EPNS23-2063 Oral or e-Poster
Neuromuscular Disorders

Updated demographics and safety data from patients with nonsense mutation Duchenne muscular dystrophy receiving ataluren in the STRIDE Registry

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Objective: Duchenne muscular dystrophy (DMD) is a severe neuromuscular disorder caused by a lack of functional dystrophin. Ataluren promotes readthrough of an in-frame premature stop codon to produce full-length dystrophin and is indicated for the treatment of patients with nonsense mutation (nm)DMD. Strategic Targeting of Registries and International Database of Excellence (STRIDE; NCT02369731) is an ongoing registry providing real-world data on ataluren use in nmDMD patients.

We aimed to describe the demographics of the STRIDE population and interim safety results, as of January 31, 2022, the latest data cut-off date.

Methods: Data from enrolled patients are collected at the consent date; for patients who initiated ataluren as part of a commercial or early access program before enrollment, data for the period prior to enrollment are obtained retrospectively. Patients will be followed up for greater than or equal to 5 years or until study withdrawal.

Results: As of January 31, 2022, 306 patients had been enrolled in STRIDE in 14 countries and received at least one ataluren dose. Total mean (standard deviation [SD]) exposure to ataluren was 1623 (586.3) days; equivalent to 1359.8 patient-years. Safety outcomes were consistent with the known safety profile of ataluren. Forty-three of the 306 boys discontinued the study. Of the 306 boys enrolled, 290 had genetically confirmed nmDMD. Most patients were white (213/290 [73.4%]) and the mean (SD) age at consent date was 10.2 (4.2) years (n=290). Mean (SD) age at first symptoms was 2.8 (1.7) years (n=273); at nmDMD confirmation it was 5.1 (3.2) years (n=281). Median time between first symptoms and nmDMD confirmation was 1.4 years (n=269). Most patients used concomitant corticosteroids (261/290 [90.0%]).

Conclusions: STRIDE is the first drug registry for nmDMD patients. The interim registry data suggest ataluren has a favorable safety profile when used in routine clinical practice, consistent with that shown in clinical trials.

Keywords:
Rare disease, Duchenne muscular dystrophy (DMD), patient registry

EPNS23-2560 Oral or e-Poster
Movement Disorders

Natural history study of SGCE-myoclonus dystonia in childhood

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Objective: The prognosis of children with SGCE-myoclonus dystonia (SGCE-MD) is uncertain, with some children improving during childhood and others requiring deep brain stimulation in adulthood, after many years of disease progression. We aim to describe the natural history of SGCE-MD using rating tools for disease monitoring.

Methods: This is a longitudinal study in two cohorts of patients with SGCE-MD from Spain and the Netherlands. We included patients aged < 25 years with a follow-up >24 months who were video-recorded following a standardized protocol. We excluded patients that underwent deep brain stimulation during the study period. Two examiners blinded for the age of the patients at the time of the assessment scored patients in consensus. Disease progression was analyzed using a modified version of the Writer's Cramp Rating Scale (WCRS) in patients >6 years, the Gait Dystonia Rating Scale (GDRS) during walking and running in all ages, and the Unified Myoclonus Rating Scale (UMRS) questionnaire. Values obtained on first evaluations (FE) and last evaluations (LE) were compared using Wilcoxon signed rank test.

Results: We included 37 patients (age at FE 10±4.5 years, range 2-21) with a mean follow up of 4.1±1 year. A total of 58 video-recordings were obtained from 31 patients.
Writing dystonia was present in 19/19 patients, of whom 4 were left-handed. A sensory trick (touching the writing hand with the contralateral hand) was used by 4 patients. We observed an increase in WCRS scores over time (FE 15,7±6,9 vs LE 18,9±6,7; p-value=0.004).
Gait dystonia was observed in 11/23 patients, and the majority (9 patients) used sensory tricks (self-touching, hands in pockets, holding hands). Non-significant changes in GDRS scores were observed on follow-up (for walking: FE 2±3,4 vs LE 1,4±2,6; for running: FE 4,6±5 vs LE 4,4±4,8). Regarding the UMRS disability questionnaire (n=33), patients perceived a worsening of symptoms during the study period (FE 4,4±3,5 vs LE 6,4±4,5; p-value=0.003), being significant for writing (p-value=0.007) and walking (p-value=0.012). No sex differences were observed.

Conclusions: This is the first natural history study in children and young adults with SGCE-MD. Using task-specific rating scales, we observed that severity of writing dystonia increased over time, whereas no changes were demonstrated on gait dystonia. In agreement with these results, patients also perceived a worsening of functional capability during the study period.

Keywords:
myoclonus dystonia; SGCE; MD; natural history

EPNS23-2898 Oral or e-Poster
Movement Disorders

SMA: treatment of a group of Ukrainian children.

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Case study: Objectives.
The term spinal muscular atrophy (SMA) is applied to a diverse group of genetic disorders that all affect the spinal motor neuron. The different forms of SMA are associated with numerous gene mutations and significant phenotypic variability. SMA is usually categorized by pattern of weakness and mode of inheritance. The most common form is autosomal recessive proximal SMA or 5q-SMA and is due to a homozygous deletion or mutation of the Survival Motor Neuron 1 (SMN1) gene. The distribution of SMA in Ukraine is the same as in the world.
Methods.
Our observation group included 24 children diagnosed with SMA. The diagnosis was confirmed by PCR test SMN1 exon 7/8 copy number by qPCR. 23 children have a homozygous SMN1 mutation, 1 child has heterozygous. All children in the group do not have any copies of the SMA 1 gene. 10 children were examined for the presence of SMA2 copies: 7 children have 2 copies of SMA2, 3 children - 3 copies of this gene.
Results.
Since 2020, 2 drugs for the treatment of SMA have been registered in Ukraine - it is a disease-modifying therapy (drugs stimulate the production of the SMN protein).
15 children (12 from 2020 and 3 from 2021) started taking risdiplam (Evrysdi): 6 children with type I and 8 children with type II. 3 children started therapy with risdiplam at the age of 6 months.
Starting from 2021, nusinersen (Spinraza) therapy has been started in our hospital. The group included 9 children: 6 have type II SMA and 3 - type III.
All children develop with positive dynamics, gain weight and move better. In 2 children against the background of influenza, lung ventilation was used. All children are alive.
Conclusions.
We plan to evaluate the effectiveness of therapy with the help of tests after the stabilization of the situation in Ukraine.
Since October 2022, a pilot project has been launched in Kyiv to conduct expanded neonatal screening, thanks to which it will be possible to identify children diagnosed with SMA even before the onset of the first symptoms, which will allow treatment to be started as early as possible.

Keywords:
SMA, Evrysdi, Spinraza

EPNS23-2788 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Clinical course and treatment outcome in children with Rasmussen Encephalitis

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Case study: Objectives: Rasmussen encephalitis (RE) is a progressive, neuro-inflammatory disease causing progressive hemiparesis, cognitive impairment, and unilateral brain atrophy. Its etiopathogenesis is not fully understood and treatment remains challenging. The goal of this study is to evaluate the electroclinical characteristics, management, and disease course in children with RE.
Methods: We conducted a retrospective, descriptive study in nine patients (six girls and three boys) with RE followed between 2009 and 2021. The diagnosis was made based on clinical, video-EEG and brain MRI findings. Selected patients had a PET study.
Results: The mean age of onset of RE was 7.9 (2-14) years, mean current age, 15.9 (8-27) years, and mean follow-up, 54 (6-96) months. The left hemisphere was affected in 7/9 patients. Focal motor seizures were the initial symptom in all patients. One had hyperactivity and learning difficulties prior to seizures. Five patients had epilepsia partialis continua. Six patients developed hemiparesis and two, hemiplegia. The EEG revealed interictal slowing, epileptic abnormalities, and clinical and/or electrographic seizures consistent with the affected hemisphere in all patients.
Treatment included corticosteroids and intravenous immunoglobulin (IVIg) in six patients; rituximab in two; tacrolimus in three and IVIg alone in three patients. One patient went through COVID-19 infection without any significant complications. Two patients underwent anatomic hemispherectomy and another had left temporal lobectomy prior to hemispherectomy. Hemispheric surgery was not performed in the rest of the patients due to various causes (preserved motor functions, language dominance and family decision).
At the latest follow-up, all patients continued to have refractory seizures except for three patients, two of whom having hemispheric surgery.
Conclusion: Immunomodulatory treatment is known to modify the disease course, however, unilateral hemispheric surgery with either removing or disconnecting the affected hemisphere remains the best treatment option for management of seizures in patients with RE. Of note, the left hemisphere was affected in the majority of our patients which warrants further discussion.

Keywords:
Refractory seizure, Rasmussen Encephalitis , Outcome

EPNS23-2635 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Fenfluramine Responder Analysis and Numbers Needed to Treat: Post-Hoc Pooled Analysis of Two Phase 3 Studies in Dravet Syndrome

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Objective: To conduct a post-hoc responder analysis of pooled data from 2 identical phase 3 trials of fenfluramine (FFA) in Dravet syndrome (DS) to estimate the number-needed-to-treat (NNT) to reach clinically meaningful response thresholds (NCT02682927; NCT02826863).

Methods: DS patients aged 2 to 18 years were randomized to placebo (n=88), FFA 0.7 mg/kg/day (n=88), or 0.2 mg/kg/day (n=85) added to their baseline standard-of-care regimen. Monthly convulsive seizure frequencies (MCSFs) during treatment were compared to the 6-week baseline period in each group and were used to calculate the NNT (1/[FFA responder rate-placebo responder rate]).

Results: Clinically meaningful reductions in MCSF (>=50%) occurred in 70% and 42% of patients treated with FFA 0.7 mg/kg/day or FFA 0.2 mg/kg/day, respectively, compared with 9% in the placebo group. Similarly, profound reductions in MCSF (>=75% reduction) occurred in 49% and 26% of patients treated with FFA 0.7 mg/kg/day or FFA 0.2 mg/kg/day, respectively, compared with 3% in the placebo group. The NNTs to reach clinically meaningful or profound response thresholds were 1.6 and 2.2 in the FFA 0.7 mg/kg/day group and 3.0 and 4.3 in the 0.2 mg/kg/day group.

Conclusions: For every 2 to 4 patients treated with FFA, one patient achieved a >=50% or >=75% reduction from baseline in MCSF. With no head-to-head comparative trials in therapies approved for DS, these results may be used to guide clinical treatment decisions. Funded by UCB Pharma.

Keywords:
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EPNS23-2860 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

Epilepsy Surgery in Children with Tuberous Sclerosis - a Single Center Study

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Objective: In this study we have reviewed data of a large surgical cohort of pediatric patients with tuberous sclerosis complex (TSC) evaluated and operated in Motol Epilepsy Center, Prague. Our aim was to characterize their phenotype, diagnostic findings and outcomes in order to facilitate identification of surgical candidates in this group of patients.

Methods: We have retrospectively evaluated clinical, electrophysiological and neuroimaging data of all pediatric patients with TSC operated in our tertiary epilepsy surgery center. The inclusion criteria were 1) confirmed clinical diagnosis of TSC, 2) resective epilepsy surgery performed in Motol Epilepsy Center, 3) age at time of surgery 0-19 years. Surgical outcome was assessed only in patients who had at least one year of follow-up.

Results: In total 31 patients (14 girls, 17 boys) operated from February 2004 to October 2022 met the inclusion criteria. The onset of epilepsy was in infancy or neonatal period (up to 48 hours after birth) in the majority of patients (25/31). The seizure burden was high - 28/31 patients had daily seizures and 19/31 had (among other seizure types) spasms. Although the majority of patients (23/31) had normal initial development, 19/30 displayed intellectual disability at time of the evaluation (the assessment was impossible in one patient due to a language barrier). Age at time of surgery ranged from 4 months to 19 years (median 5.6 years), the duration of epilepsy was from 3.5 months to 18.7 years (median 4.4 years). MRI revealed cortical tubers affecting multiple lobes of one hemisphere in 2/31 patients. In the remaining 29 patients tubers affected both hemispheres. Ten patients had two-step surgery with long-term invasive monitoring from intracerebral electrodes. The extent of resection ranged from focal (19/31) to lobar (5/31) and multilobar (7/31). Seventeen patients have been rendered seizure-free (to January 2023, median follow-up 7.9 years), including seven cases both seizure- and ASM-free. The complications occurred in 4 patients and two children had permanent consequences. Outcome was unavailable in 6 patients (4 less than 1 year after the surgery, 2 cases lost to follow-up).

Conclusions: Epilepsy is an early and debilitating complication affecting many children with TSC. In selected patients with TSC epilepsy surgery has a superior efficacy and safety compared to pharmacotherapy and thus should be considered early despite a widespread MRI and frequently also EEG findings.

Keywords:

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EPNS23-2216 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

EXPANDING THE PHENOTYPE OF SCN8A-LOF EPILEPSY AND RELATED DISORDERS

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Case study: OBJECTIVES

Our aim is to describe the phenotype of patients carrying SCN8A variants with loss-of-function (LOF) effect, through the description of a large cohort, expanding the clinical phenotype and obtaining data for early differential diagnosis and precision therapy management.

METHODS

From our database of 692 individuals with SCN8A-related disorders, we selected those carrying variants with confirmed LOF effect (truncating variants or previously tested with functional studies).
Detailed demographic, genetic and electro-clinical data were collected, including information about psychomotor development, neurological examination, epilepsy, and response to anti-seizures medications (ASMs).

RESULTS

Sixty patients were included, with a median age of 12 years (range: 18 months-42 years).
Epilepsy was reported in 33/60 (55%), with a median age at onset of 2 years, 9 months (range: 1 month-14 years); 30% had generalized epilepsy (GE), 16.7% severe developmental and epileptic encephalopathy (DEE), 5% myoclonic epilepsy, unclassified in 3.3%.
Seizure types included absences (42%), generalized tonic-clonic-seizure (TCS) (42%), clonic-myoclonic/hemiclonic (18%), atonic (6%), tonic (3%). Three patients presented status epilepticus. Among epileptic patients EEG was normal in 2 (6.5%), and showed epileptiform discharges in 25 subjects, either generalized (55%), focal (36%), or multifocal (29%).
Seizure-freedom was achieved in 12/33 (36.4%) patients either in monotherapy with ETS (2), LEV (2), VPA (4) or in combination of TPM-LTG (1), VPA-LTG (2) or LEV-TPM (1). One is no longer taking ASMs. Sodium Channel Blockers (SCB) induced seizure worsening in 2, partial seizure control in 7 cases and complete seizure control in 2 patients in add-on with other ASMs.
Forty-nine/60 had intellectual disability (ID), either severe/profound (15%), mild-moderate (52%), or global developmental delay (15%). Normal cognition was reported in 10 (17%). Behavioral problems and/or autism were reported in 47% of patients.
Patients harbored 46 different variants (16 missense, 30 truncating/frameshift); 26/60 (43%) occurred de novo.

CONCLUSION

We report detailed genotype-phenotype correlations in a large cohort of subject with LOF-SCN8A-diseases. Four main phenotypes have emerged, namely generalized epilepsy, myoclonic epilepsy, DEE and neurodevelopmental disorders without epilepsy.

Keywords:

SCN8A, epilepsy, deep-phenotyping, DEE

EPNS23-2081 Oral
Epilepsy: Diagnosis and Investigations

Home-video EEG long term telemetry in a pediatric setting

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Objective: Pediatric video-EEG monitoring is a standard procedure in epilepsy clinic, usually performed as an in-house procedure. Hospitalization for pediatric video-EEG is sometime not mandatory and is a burden to the child and family. Ambulatory or home video-EEG monitoring had evolved the wake of telehealth, with a portable cordless EEG machine and camera.
Our goal was to check the feasibility of ambulatory video-EEG in a pediatric population.

Methods: We performed a prospective pilot study of twenty ambulatory video-EEG in children. Quality of EEG and video recording were assessed on a 5-point scale. Demographic, clinical and quality data were compared to a similar group undergoing in-house video-EEG monitoring.
Statistical analysis was performed with the SPSS software (IBM®SPSS® version 27). Numeric parameters were compared using the unpaired t test or the Mann Whitney U ranking test. Nominal parameters were compared using the Chi square test or Fisher exact test.

Results: 20 children aged 2.1-17.2 years (mean 9.57±1.01), 12 females (60%), underwent ambulatory video-EEG. There were more children with intellectual disability/ autism in the ambulatory-EEG group as compared to inhouse group: 12 patients (60%) vs 5 (25%) ($p<0.05$*, Fisher exact test). Patients with developmental and epileptic encephalopathy were overrepresented in the ambulatory group (7 i.e., 35% vs 0), while self-limited childhood epilepsy in the inhouse group (5 i.e., 25% vs 0) ($p< 0.05$*, Chi square). The reasons for referral were seizure localization/classification in 11 patients (55%), paroxysmal event classification in 5 (25%) and quantification of sleep epileptic activity in 4(20%), similar to the control group (40%, 40% and 20% respectively, $p >0.05$, Chi square). The quality of the EEG recording was higher compared to inhouse tests: median 5 [IQR 3.25-5] vs 4[IQR 3-4] ($p<0.05$*, Mann-Whitney U test). The quality of video recording was lower compared to inhouse recordings: median 3[IQR 2.25-4] vs 5[IQR4-5] ($p<0.01$**, Mann-Whitney U test).

Conclusions: Home video-EEG monitoring is a new option of long-term pediatric EEG monitoring, especially for children with special needs.

Keywords:
home EEG, telemedicine, ambulatory EEG

EPNS23-2672 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Epilepsy surgery in Long-term Epilepsy Associated Tumors (LEATs) - a retrospective study of 73 children

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Objective: LEATs are low-grade tumors with high incidence of pharmacoresistant epilepsy. LEATs can be associated with other structural pathological findings, mainly with focal cortical dysplasias, which are denominated as FCD type IIIb. LEATs represent the second most common neuropathological finding in epilepsy surgery cohorts. However, there is a lack of data about correlations at clinical and histological level.

Methods: We analyzed age at seizure onset, pharmacoresistance, findings of diagnostic tests used in presurgical evaluation, surgical approach (age at surgery, duration of epilepsy, use of invasive EEG) and outcome (minimal follow-up 2 years) of 73 children with isolated LEATs or FCD type IIIb. We also statistically compared histological findings (isolated LEATs vs. FCD IIIb.) in terms of the above-mentioned parameters.

Results: In the whole cohort of 73 children, median age at seizure onset was 6,0 years (range 0,12-16,8). 72,6% of patients were pharmacoresistant. Median age at surgery was 10,08 years (range 2,01-18,96) and median duration of epilepsy before surgery was 1,87 years (range 0,02-16,13). Majority of LEATs resp. FCD IIIb. (56,8%) were localized in the temporal lobe, 39,2% were extratemporal, and in 4,1% multilobar including temporal lobe. We routinely use intraoperative ECoG; moreover, long-term invasive EEG was used in four cases (5,5%). Six patients (8,2%) underwent a reoperation. Of the total cohort, only two patients (2,7%) were classified as Engel II-IV two years after surgery and 97,3% were seizure-free. 39,7% of patients (29 children) had isolated LEATs and 60,3% (44 children) FCD IIIb. Median age at seizure onset was 7,5 years (range 0,8-16,0) in the first subgroup and 7,27 years (range 0,12-16,8) in the second ($p=0,97$). 62,1% of children with isolated LEATs and 79,5% of children with FCD IIIb. were pharmacoresistant ($p=0,10$). Extratemporal localization was more frequent in the subgroup of isolated LEATs (69% vs. 20,5% in the FCD IIIb. subgroup, $p<0,001$). Of the six reoperated patients, three had a FCD IIIb. and three an isolated LEAT. One child in each group was classified as Engel II-IV two years after surgery.

Conclusions: Epilepsy surgery is highly effective in children with LEATs, with no significant differences between isolated LEATs and cases associated with FCD IIIb. In terms of clinical presentation, we found more frequent extratemporal localization of isolated LEATs compared with FCD IIIb.

Keywords:
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EPNS23-2263 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Highly significant ≥75% and ≥80% responder rates with stiripentol in Dravet syndrome patients: Data from the STICLO pivotal trials

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Objective: The effectiveness of stiripentol (STP) for treating seizures associated with Dravet syndrome was demonstrated in two phase 3 double-blind placebo-controlled trials (STICLO-France and STICLO-Italy). This work takes the benefit of the data collected during these two clinical trials and analyses the efficacy results of the pooled studies.

Methods: Efficacy results were analysed in Intent to Treat (ITT) and Per Protocol (PP) populations, in terms of percentage change from baseline in seizure frequency and responders (≥50% reduction in seizure frequency). Seizure reductions ≥75%, ≥80% and 100% (seizure free) were also calculated.

Results: Following the 2-month treatment period, STP administration led to an 84.4% median decrease in generalized tonic-clonic seizures (GTCS), compared to -5.8% in the placebo group ($p<0.0001$) in ITT analysis. In PP, STP group experienced an 87.5% median decrease in GTCS compared to -6.5% in the placebo group ($p<0.0001$).
In ITT and PP, 69.7% and 74.2% of the STP-treated patients were responders respectively, while they were only 6.5% and 8% in the placebo group ($p<0.0001$).
Also, 54.6% and 51.6% of the STP-treated patients had a ≥75 % and a ≥80 % decrease in frequency of GTCS respectively, compared to 3.2% in the placebo-treated patients ($p<0.0001$ in both cases) in ITT. In PP, 58.1% and 54.8% of the STP patients had a ≥75 % and a ≥80 % decrease in frequency of GTCS respectively, compared to 4.0% and 4.0% in the placebo group ($p<0.0001$ in both cases).
Finally, 36.4% and 38.7% of STP-treated participants remained free of GTCS during the second month in the ITT and PP respectively, versus none in the placebo group ($p=0.0002$ and $p=0.0005$).

Conclusions: Results of the pooled studies demonstrate the strong reduction in seizures on STP and confirms the highly significant difference with the placebo-treated patients. Reducing frequency of GTCS may alleviate burden of the disease.

Disclosures:
Study supported by Biocodex. This abstract has been adapted from an abstract previously submitted to the American Epilepsy Society (AES) 2022 Annual Meeting.

Keywords:
dravet ; syndrome ; stiripentol ; palcebo ; efficacy ; epilepsy ; seizure ; RCT ; randomized ; clinical ; trial ; early ; treatment ; responder ; rate ; tonic ; clonic ; rare disease ; neuropediatry ; neurology ; pediatry ; drug resistent ;

EPNS23-2871 Oral or e-Poster
Neuromuscular Disorders

Efficacy and safety of widely available nusinersen programme in Polish children under the age of 2 years.

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Objective: Spinal muscular atrophy (SMA) is a devastating progressive neuromuscular disorder. Most frequently, the symptoms appear in infants and young children but SMA is increasingly diagnosed in presymptomatic children due to newborn screening programmes (NBS). In Poland, NBS has been introduced in 2021. Recently, disease-modifying therapies have been introduced in SMA. Starting from 2017 until September, 2022, nusinersen was the only reimbursed therapy for SMA in Poland and it was available for all SMA patients, regardless of their age, SMA severity or SMN2 gene copies. At the beginning, both newly diagnosed patients and patients with long history of the disease and severe complications were included in the treatment programme. Currently, new diagnoses prevail. Here we present the results of nusinersen treatment in Polish children who started treatment under the age of 2 years.

Methods: Baseline data, including the type of SMA, SMN2 gene copies and functional status, as well as response to treatment measured in the CHOP-INTEND scale at the last follow-up were analysed. First follow-up functional examination was performed after 5 nusinersen doses.

Results: Between 2017 and 2022, 114 children started nusinersen therapy under the age of 2 years. There were 17 presymptomatic cases, 72 children with SMA1, 23 with SMA2, and 2 with SMA type 3. Seven presymptomatic children had 2 copies, 9- 3 copies, and 1 - 4 copies of SMN2 gene. One SMA1 patient had 1 copy, 57 - 2 copies, 12- 3 copies, 1 - 4 copies, and 1- 5 copies of SMN2 gene. Three patients with SMA2 had 2 copies, 19-3 copies, and 1 - 4 copies of SMN2 gene. Two patients with SMA type 3 had 2 copies of SMN2 gene. The baseline CHOP-Intend score ranged from 22 to 61 in presymptomatic cases, from 0 to 56 in SMA1 cases, from 22 to 57 in SMA type 2 patients and from 50 to 60 in SMA type 3. Eleven patients dropped out from the programme: 4 patients died and 7 change therapy. 69 patients received at least 5 nusinersen doses. The mean change in CHOP-INTEND score in SMA1 was +20 points, in SMA2 - +12.2 points, in SMA3 - +13 points and +16.5 in presymptomatic patients. In the presymptomatic patients, 6 out of 7 reached at lest 60 points. One patient with SMA1 deteriorated.

Conclusions: Early SMA treatment is associated with significant improvement in children under the age of 2, regardless of their baseline functional status and SMA type.

Keywords:
spinal muscular atrophy, nusinersen, treatment

EPNS23-2864 Oral or e-Poster
Neuromuscular Disorders

Two years of newborn screening for spinal muscular atrophy in Poland

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Objective: Spinal muscular atrophy (SMA) is a severe genetic condition, that can be successfully treated with targeted therapies (Nusinersen, Ridiplam, ZolgenSMA). It fulfills all criteria to be included in newborn screening testing (NBS). Therefore, a huge effort is taken to implement such testing, especially in countries that cover the cost of the treatment. Herein, we present our two-year experience with NBS-SMA, including the pilot study.

Methods: After a short pilot study since January 2021, the SMA was added to the National Newborn Screening Programme in April 2021 and subsequently covered all districts in Poland. Since 03.2022, all newborns with opt-in signed, are tested for SMA (>99% of individuals). Standard dried blood spots are used for DNA extraction. We use SALSA MC002 SMA Newborn Screen test (based on PCR-HRM technique, MRC-Holland) as a first-tier test to detect newborns with the homozygous deletion of exon 7 of the *SMN1* gene. The second-tier test is based on MLPA technique (P021 kit).

Results: Since January 2021, about 417000 newborns were screened and SMA has been confirmed in 57 children that were admitted to regional centres for clinical examination and further therapy. The results of the first-tier test and MLPA verification from blood spots were available on the 8th day of life (mean: 9.2±4.5; 3 days since registration in the central database). On the day 14th (mean 15.8±6.0; 9 days since registration), the results of the verification MLPA test were ready. The treatment was implemented as soon as possible. Most of the children having 2 or 3 *SMN2* copies (respectively, 17 and 24 individuals) were treated with Nusinersen or Ridiplam under clinical trial, and since September 2022 there is a possibility to treat them also with ZolgenSMA. Two children with 1 *SMN2* copy were identified and they both were symptomatic at birth and had a heart defect. Four and 5 *SMN2* copies, were identified in 11 and 3 children, respectively. They are under careful observation and in case of disease progression the treatment was or would be implemented.

Conclusions: The PCR-HRM method was successfully used in NBS-SMA and our procedure allowed to quickly identify positive patients that can be treated with available therapies. The calculated prevalence of SMA is about 1/7300 in Polish population.

The project was partially supported from Institute of Mother and Child intramural grant 510-18-17.

Keywords:
SMA, newborn screening, spinal muscular atrophy, SMN1, SMN2, targeted therapy

EPNS23-2580 Oral or e-Poster
Neurodevelopmental Disorders

Newborn Screening for Metachromatic leukodystrophy in Germany- A prospective Study

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Objective: Metachromatic leukodystrophy (MLD) is a rare, fatal autosomal-recessive genetic disorder caused by insufficient activity of the enzyme arylsulfatase A (ARSA) that results in intra-lysosomal accumulation of the ARSA substrate galactosylceramide I3-sulfate (sulfatide), inevitably leading to progressive demyelination and neurodegeneration in the CNS and PNS. There are three variants of MLD commonly described in the literature: late-infantile MLD, juvenile MLD, and adult MLD. Children affected by MLD display progressive neurologic symptoms, including ataxia, seizures, and quadriplegia, culminating in severe disability and early death. MLD diagnosis is often delayed or missed thus detection at birth is critical. A new gene therapy approved by EMA in 2020 is now available and established in the treatment center for MLD in Tübingen recently. The availability of the first therapy has emerged the need for a strategy to implement MLD in current NBS projects.

Methods: We have initiated a prospective pilot newborn screening study with the integration of sulfatide profiling in Dried Blood Spots. Using a specific consent form, sulfatide profiling indicative of MLD is now performed in addition to the German national screening panel.

Results: Since starting in October 2021 over 60.000 samples were successfully analyzed. The study duration is planned for 12 months with a possible extension for up to three years. C16:0, C16:0-OH, and C16:1-OH are measured by means of a fast UHPLCMS/MS method that facilitates analysis times of <2min per sample. In potential positive cases with elevated sulfatide levels, genetic confirmatory testing (ARSA, SUMF1, and PSAP genes) will follow. The technical robustness and precision are good and comparable or even superior to those of other tests used in newborn screening.

Conclusions: The false positive rate has been found to be acceptable. Besides a couple of carriers for ARSA and PSAP, first positive case with two potentially pathogenic mutations has been identified. This is the first worldwide MLD case identified through NBS program.

Keywords:
MLD, NBS, biomarkers, sulfatides

EPNS23-2151 Oral or e-Poster
Miscellaneous

Universal Genomic Newborn Screening for early, treatable, and severe conditions: Baby Detect

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Objective: Newborn screening (NBS), historically performed in a biochemical and metabolic technique, has greatly improved the management of many serious and treatable diseases. Building on the success of the NBS for Spinal Muscular Atrophy initiated in 2018, we started the Baby Detect pilot program in September 2022. Baby Detect aims to screen for 126 serious, treatable, and early-onset genetic diseases. 21 neurologic diseases - caused by mutation in 52 genes - are included in the current panel. The list of gene was established with the support of the Liege paediatric community.
Objectives: This prospective study aims to study the feasibility and acceptability of newborn genetic screening to screen up to 40,000 newborns per year progressively in 3 years for virtually all the early onset severe diseases that can benefit from treatment or a pre-symptomatic clinical trial. The primary outcome is the percentage of parents accepting the proposed screening in comparison with the number of mothers approached for consent.

Methods: Information for parents was conducted during the pregnancy and soon after delivery using flyers, videos, a website, and verbal information. On the first day of the child's life, almost all parents were approached by a member of the team to present the study. If they agreed, they would fill in an electronic consent form (paper consent is also possible). In case of refusal, we tried to find out the reasons for the refusal briefly.

Results: As of December 27th, 823 families have been approached, and 752 consented, indicting an acceptability rate of 91%. The refusals do not seem to be linked to a fear of a genetic test, but rather to a lack of knowledge and understanding of the project and the risks. The most common reasons for refusal were "in my family we don't have any diseases", "it didn't exist before, why always add things", "it's not mandatory, I don't do it". The buy in by the gynecologists and midwifes community was high.
During the congress, we will disclose the most recent figures and the identified cases.

Conclusions: This genomic NBS received strong support from local IRB, local health professionals involved in pregnancy and the neonatal care, with good acceptability (91%) from parents. We will extend the project more widely by opening up to other maternity hospitals in the coming months. Other information materials are being made available (flyer in other languages, videos with the sponsorship of a famous sportsman...) with the aim to improve acceptability.

Keywords:
Newborn screening; universal genomic

EPNS23-2692 Oral
Neuromuscular Disorders

New variants in *MYBPC1* gene: Phenotypic spectrum of congenital myopathy and arthrogryposis

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Objective: *MYBPC1* gene encodes the slow skeletal Myosin Binding Protein-C expressed in striated muscles. Variants in the *MYBPC1* gene are associated with congenital myopathy (CM) or distal arthrogryposis type 1 (DA1) with autosomal dominant inheritance and with lethal congenital contracture syndrome type 4 (LCCS4) with autosomal recessive inheritance. However, only few cases have been reported so far and exact pathophysiology is still unclear.

Methods: Two patients with symptoms of CM and one patient with symptoms of DA1 were referred to our Center. Clinical examination of patients and their parents was performed, followed by next-generation sequencing (NGS) and muscle MRI.

Results: The patients with CM showed facies myopathica, hypotonia, muscle weakness with maximum on the upper limbs (UL), static acral limb and tongue tremor. In one of the patient and in his mother previously published missense variant *MYBPC1* (NM_002465.4):c.776T>C, p.(Leu259Pro) was found. Splicing variant *MYBPC1*:c.832+2_832+3del, unpublished so far, was found in the second patient and in his father. Both affected parents showed gentle symptoms similar with their descendants however with much lower intensity and with improvement over time. The muscle MRI of lower limbs (LL) in the affected parents showed rather normal findings with gentle changes in the posterior muscle group.
The patient with DA1 showed dystrophic habitus, craniofacial stigmatization, contractures of UL and LL, general muscle weakness with maximum on the proximal parts. The NGS revealed two heterozygous variants in the *MYBPC1*:c.2486_2492del, p.(Lys829Ilefs*7) and c.2663A>G, p.(Asp888Gly) in trans position, each parent being a carrier for one of the variants with no clinical symptoms manifested.

Conclusions: Our results show that CM is inherited AD with improvement of the clinical symptoms over time, acral limb and tongue tremor being significant symptoms of the disease. The phenotype of the patient with missense variant p.(Leu259Pro) resembles that case published previously. The case of the patient with the variant c.832+2_832+3del is the first case reported so far when a splicing variant manifested with the phenotype of CM.
Concerning the patient with the DA1 phenotype, cases of DA1 with AD inheritance and LCCS4 with AR inheritance has been published, however this is the first case with AR inheritance with less severe phenotype of DA1 reported so far.
Our results further broaden the spectrum of both AR and AD inheritance for *MYBPC1*.

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Keywords:
MYBPC1, congenital myopathy, arthrogryposis, acral limb tremor, tongue tremor, muscle weakness

EPNS23-2121 Oral or e-Poster
Neuromuscular Disorders

Outcomes in Patients with Spinal Muscular Atrophy and Four or More *SMN2* Copies Treated with Onasemnogene Abeparvovec: Findings from RESTORE

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Objective: Onasemnogene abeparvovec (OA) is a one-time gene replacement therapy for spinal muscular atrophy (SMA). While clinical trials of OA included patients with two or three *SMN2* gene copies, patients with four or more copies may be treated in clinical practice. Natural history and outcomes following SMA treatment have not been well-characterized for these patients. We sought to describe clinical outcomes after OA monotherapy for patients with four or more *SMN2* copies in RESTORE, a comprehensive, noninterventional SMA registry.

Methods: We evaluated baseline characteristics, and post-treatment motor function, motor milestone achievement, use of ventilatory/nutritional support, and adverse events (AEs) (as of May 23, 2022, data cut). Patients evaluable for motor function or milestone achievement had two or more assessments, with at least one occurring after OA administration.

Results: Nine children with four *SMN2* copies and five with four or more copies were included. All 14 cases were identified by newborn screening in the United States and treated presymptomatically. Median age at OA administration was 3.5 (range, 1-11) months. All six children with evaluable motor milestone assessments achieved new milestones. All four children evaluable for CHOP INTEND maintained/achieved the maximum score of 64 points. One child was evaluable for HINE-2 and achieved a ≥2-point increase. One child was evaluable for HFMSE and achieved a ≥3-point increase. Six children with recorded AE data had one or more treatment-emergent AE. Two children reported AEs ≥Grade 3 (one had otitis media and one with history of fetal stroke had seizure ~3.5 months post-OA). No deaths or use of ventilatory/nutritional support were reported.

Conclusions: Patients with four or more *SMN2* gene copies attained improvements in motor function and achieved new milestones after treatment with OA. SMA presentation with four or more *SMN2* copies is heterogeneous, and laboratory determination of *SMN2* copy number may be unreliable, highlighting the importance of early identification and intervention to optimize outcomes for all SMA patients.

Keywords:
disease-modifying treatment, onasemnogene abeparvovec, registry, spinal muscular atrophy, survival motor neurons

EPNS23-2103 Oral or e-Poster

Fetal and Neonatal Neurology

Fetal temporal sulcus depth asymmetry predicts language development

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Objective: In most humans, the superior temporal sulcus (STS) shows a rightward depth asymmetry. This asymmetry can not only be observed in adults, but is already recognizable in the fetal brain. As the STS lies adjacent to brain areas important for language, STS depth asymmetry may represent an anatomical marker for language abilities. We were thus interested in the prognostic value of STS depth asymmetry in healthy fetuses for later language abilities, language localization, and language-related white matter tracts.

Methods: In this retro- and prospective study, we invited children whose mothers were transferred to fetal MRI diagnostics due to clinical reasons 6-13 years ago and whose fetal MRIs were subsequently diagnosed as normal. In 38 healthy children (age 6-13 years, mean 8.85, SD 1.98, 14 girls), a neuropsychological examination, a functional magnetic resonance imaging (fMRI) for language localization, and diffusion tensor imaging to identify language-related white matter bundles were performed. Multiple linear regressions were carried out to test if fetal STS depth laterality predicted language abilities and language-related white matter tracts 6-13 years later, and Spearman correlations were used to investigage the association of fetal STS depth asymmetry with later neural language localization.

Results: On the group level, the mean depth of the right fetal STS was significantly larger than its left counterpart ($t=6.494$, $p<.001$). In the individual fetal measurements, STS depths were right-lateralized in 69%, bilateral in 28%, and left lateralized in 3% of the fetuses. Less right lateralization of the fetal STS depths was significantly associated with better language abilities, with fetal STS depth asmmetry explaining 45% of variance in vocabulary ($p<.001$), 43% of variance in verbal fluency ($p=.001$), and 48% of variance in verbal memory ($p<.001$) 6-13 years later. Furthermore, less right fetal STS depth asymmetry correlated with increased left language localization and a greater volume of the left superior longitudinal fasciculus during childhood.

Conclusions: We hypothesize that earlier and/or more localized fetal development of the left temporal cortex is accompanied by an earlier development of the left STS and is favorable for early language learning. If the findings of this pilot study hold true in clinical populations, fetal STS asymmetry has the potential to become a diagnostic biomarker of the maturity and integrity of neural correlates of language.

Keywords:

fetal MRI; language development; STS depth; fMRI; DTI; cognition

EPNS23-2796 Oral or e-Poster
Fetal and Neonatal Neurology

EXPANDING THE SPECTRUM OF NEONATAL-ONSET AIFM1-RELATED MITOCHONDRIAL ENCEPHALOPATHY

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Case study: Objectives: to present a novel phenotype associated with a variant in the X-linked AIFM1 gene.
Methods: We report on a new-born child who presented with seizures on his first day of life. We performed EEG recordings, Brain MRI scans, Brain MR Spectroscopy, metabolic screening, echocardiogram, whole exome sequencing, and skin biopsy.
Results: The proband was born to non-consanguineous parents at term. Emergency C-section was performed due to not reassuring CTG. APGAR score was 6/6, his weight 2670 gr. He presented with drug-resistant, electro-clinical, multifocal seizures. Venous gas analysis initially revealed mild acidosis (pH 7.17). Lactate levels (12 mmol/L), CPK (1671 UI/L), LFT (AST/ALT > 5 x ULN), and renal function were initially abnormal but later normalized. Uric acid and ammonia were normal. Brain MRI on day 1 revealed swelling of both hemispheres with diffuse signal alteration, highly T2 hyperintense and T1 hypointense, with diffusion restriction, widespread in the white matter and in part of the cortex, which mimicked hypoxic-ischaemic encephalopathy. Subsequent EEG changes (progression to suppression burst pattern), evolution of MRI changes, and the presence of persistently high lactate peak on MR spectroscopy pointed to a metabolic disorder. Metabolic screening and repeated echocardiograms were unremarkable. Clinically, there were no dysmorphic features. The child was mildly lethargic. He did not present as a floppy infant and muscle tone was slightly increased. We observed frequent tremors and elicited brisk reflexes. Antigravity strength was normal but spontaneous movements were qualitatively and quantitatively poor. Next-generation sequencing analysis revealed a variant (NM_004208.4) c.5T>C; p.(Phe2Ser) in the AIFM1 gene, which is absent in reference population databases and described as putatively pathogenic. Analysis on cultured fibroblast to demonstrate respiratory chain abnormalities are ongoing. At 2 months, the child is alive and orally-fed. Neuro exam has not significantly changed.
Conclusions: Pathogenic variants in AIFM1 have been associated with a wide spectrum of clinical presentations including mitochondrial encephalopathies with basal ganglia involvement, peripheral neuropathy with ataxia and deafness, and early-onset motor neuron disease. This is the first case associated with diffuse white matter involvement with relative sparing of basal ganglia, in the absence of clinical signs suggestive of myopathy or motor neuron disease.

Keywords:
AIFM1; neonatal encephalopathy; mitochondria; neonatal seizures

EPNS23-2000 Oral or e-Poster
Fetal and Neonatal Neurology

Omega-6 and Omega-3 Fatty Acid-derived Oxylipins in Placental Tissue and Their Relationship with Neonatal Head Circumference at Delivery

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Objective: Polyunsaturated fatty acids (PUFA) are critical for infant neurodevelopment, but specific mechanisms remain unknown. PUFAs exert their effects through metabolism to oxylipins including multiple classes of specialized pro-resolving meditators, however associations between these metabolites and neurodevelopmental outcomes are not well understood. Furthermore, placental concentrations of PUFA metabolites and infant neurodevelopment have not been explored despite the role of the placenta in developmental programming. The objective of this study was to perform advanced lipidomics to identify placental oxylipins and investigate their relationship with newborn head circumference (a surrogate measure of fetal brain development).

Methods: Maternal subjects were enrolled at the time of delivery and placental samples were collected. Liquid chromatography-tandem mass spectrometry was used to quantify oxylipin levels in placental tissue. Metabolites measured included those derived from omega (n)-3 PUFA (e.g. eicosapentaenoic acid, EPA and docosahexaenoic acid, DHA) and n-6 PUFA (e.g. arachidonic acid). A Food Frequency Questionaire was administered to quantify PUFA intake; newborn head circumference was measured according to established protocols. Spearman correlation coefficients were used to assess associations between placental metabolite levels and infant head circumference at birth. A p-value of <0.05 was considered significant.

Results: A total of 121 women were enrolled. Mean intakes of n-3 PUFAs were below established guidelines (250-500 mg) at 110 mg/day. Metabolites of the n-6 PUFAs arachidonic acid (DiHET) and linoleic acid (DiHOME) were positively associated with newborn head circumference ($r=0.32$, $p=0.03$; $r=0.32$. $p=0.04$, respectively) and head circumference percentile ($r=0.39$, $p=0.01$; $r=0.37$, $p=0.01$, respectively). Maternal levels of multiple n-3 PUFA EPA and DHA metabolites (HEPE, DiHOME, HDHA) were positively associated with placental concentrations

Conclusions: PUFA metabolites may influence fetal head circumference in utero. Low maternal intakes of n-3 PUFA in the population may have influenced the production of downstream metabolites resulting in inadequate concentrations to produce measurable effects. It is possible these metabolites could be used as future biomarkers of neonatal head growth and neurological development in utero.

Keywords:
neonatal, polyunsaturated fatty acids, head circumference, placenta, oxylipins,

EPNS23-2784 Oral or e-Poster

Fetal and Neonatal Neurology

Is Parental Counselling Accurate at a Multidisciplinary Fetal Neurology Clinic?

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Objective: To evaluate the accuracy of parental counselling given at a multidisciplinary Fetal Neurology Clinic (FNC) regarding fetuses with brain anomalies, by assessing the child's neurodevelopmental outcome.

Methods: Retrospective cohort study done between the years 2020-2022. The study compares the counselling given to parents who visited the fetal neurology clinic at Wolfson Medical Center in the years 2012-2017, and the child's neurodevelopmental outcome. Neurodevelopment was assessed using the Vineland-II Adaptive Behavior Scales and in cases where the child was seen at the FNC follow up clinic, the evaluation was included.

Results: 66 children aged 3 to 9 were included in the study. In 90.91% of cases, the counselling matched the neurodevelopmental outcome. Only in 6 cases (9.09%) the counselling differed. One child displayed a significant developmental impairment, compared to a low-risk counselling, and 5 developed within the norm, while the prognosis given at the clinic suggested a high risk of global developmental delay. The mean result of the children's cognitive assessment was in the normal range (86-130, average 98.73, median 101).

Conclusions: The counselling given at the multidisciplinary Fetal Neurology Clinic is mostly consistent with the neurodevelopmental outcome, presumably due to the vast experience and knowledge of the medical experts at the FNC.

Keywords:

MRI, ultrasound, brain anomalies, prenatal diagnosis, fetal neurology, neurodevelopment.

EPNS23-2601 Oral
Infections and Inflammatory Diseases

The clinical and molecular characteristics, therapeutic interventions and outcomes of neonates with group B Streptococcus meningitis

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Objective: Group B Streptococcus (GBS) meningitis is associated with high mortality and morbidity rates in neonates, especially those with neurological complications. We aimed to characterize the clinical and molecular characteristics and risk factors for adverse outcomes of neonates with GBS meningitis.

Methods: All neonates with GBS meningitis who were hospitalized in a tertiary-level neonatal intensive care unit in Taiwan between 2003 and 2020 were enrolled. The GBS isolates underwent serotyping, multilocus sequence typing (MLST) and antibiotic susceptibility testing. Neonates with GBS meningitis were compared with those of uncomplicated GBS bacteremia.

Results: During the study period, a total of 48 neonates and young infants (aged less than 6 months old) with GBS meningitis were identified and enrolled. All of them had concurrent GBS bacteremia and sepsis, and more than half (54.2%, n=26) had septic shock. Among neonates with GBS meningitis, 35 (72.9%) had neurological complications, 17 (40.5%) of 42 survivors had neurological sequelae at discharge, and the mortality rate was 12.5%. When compared with a total of 140 neonates with GBS sepsis but without meningitis during the study period, the overall mortality rate was relatively higher. Serotype III GBS isolates accounted for the majority of neonates with GBS meningitis (68.8%, n=33), followed by type Ia (20.8%, n=10) and type Ib (8.3%, n=4) GBS isolates. The majority (89.7%) of the type III GBS isolates belong to sequence type 17. There was a significantly higher antimicrobial resistance rate among the type Ib and type III GBS isolates. After multivariate logistic regression analysis, neonatal GBS meningitis with septic shock and respiratory failure were independently associated with final adverse outcomes.

Conclusions: 25.5% of all neonates with GBS sepsis had meningitis and they were associated with a higher mortality rate and neurological complications. Because of the high rate of neurological sequelae, further studies that aim to develop predictive model for early identification of GBS meningitis and novel therapeutic strategies are urgently needed in the future.

Keywords:
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EPNS23-2870 Oral or e-Poster
Fetal and Neonatal Neurology

Assessing neonatal conscious levels: preliminary results a neonatal coma score

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Objective: Reduced consciousness is a part of many neonatal conditions, but there is no accepted score for assessing neonatal consciousness. We devised a neonatal coma score (NCS). Our objectives were to
1) Determine the normal NCS for well term babies
2) Assess interobserver agreement
3) Collect preliminary data on how the NCS changes with gestational age (GA)
4) Look for evidence the NCS could detect deterioration in clinical practice.

Methods: Phase one - Well term neonates were recruited from two major UK cities (Sheffield and Leeds) at the time of newborn examination by 2 health care professionals. The range of scores was studied and intra-observer agreement calculated using intraclass correlation coefficients (ICC).

Phase two - Neonates admitted to the neonatal unit in Sheffield were recruited. The nurses were asked to record the NCS up to 4 times a day. We studied how the NCS changed with corrected GA when participants were well, and compared values between extremely, very, and moderately late preterm and term participants using Kruskal-Wallis Test with $p<0.05$ considered significant. We sought evidence of how the NCS changed when participants became unwell.

Results: Phase one - 150 participants (82 girls, 68 boys) were recruited with a median GA at birth of 39w and 4d (IQR 39weeks 0days - 40weeks 3days) and time of assessment 23hrs (IQR 18-25hours). 98% scored 13 or more, and 94% scored 14 or 15. ICC was 0.78 (95% CI 0.70 - 0.84).

Phase two - 101 participants (57 boys and 44 girls, median GA at birth 31w and 6d (IQR 28w 4d to 34w 4d)) were recruited. Median length of follow-up was 14 days (IQR 5-30 days). When combined with the term participants, 1627 datapoints were obtained from 242 participants. The NCS increased with GA. There was significant difference in values between groups of GA. We present evidence of the NCS changing when preterm children deteriorated.

Conclusions: The NCS has strong agreement between observers. The majority of term newborns have a score of 13 or more. The NCS changes with corrected GA, and it changed when neonates were deteriorating and improving. Future work is needed to validate the NCS and determine its usefulness in clinical practice.

Keywords:
Neonatal neurology, Consciousness, Coma score, Clinical Examination

EPNS23-2516 Oral or e-Poster
Fetal and Neonatal Neurology

Neurodevelopmental Outcome after Nosocomial Sepsis in Preterm Neonates

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Objective: This study aimed to compare the ND outcome at 18 months of age using Bayley Scales of Infant and Toddler Development (Third Edition) (BSID III) in preterm infants exposed to nosocomial sepsis during NICU admission and non exposed preterm infants.

Methods: This was a retrospective study at the Follow up clinic of Neonatal Unit at Mansoura University Children Hospital, from January 2017 to August 2018.Target infants (Two groups):
A. Exposed group to nosocomial sepsis.
B. Non exposed group to nosocomial sepsis.

All infants were examined and three domains of neurodevelopment were assessed: cognitive function, language and motor function (Aylward, 2013). The examination was done at the age of 18 months corrected age. The examination was done once using Bayley Scales of Infant and Toddler Development (III) (Bayley, 2006).

Results: of 61 ex-preterm infants aging 18 months who were admitted to the NICU of MUCH during the period (October 2015 to February 2017). 30 had a confirmed nosocomial sepsis . Male infant and low birth weight , Low APGAR score were significantly higher in the nosocomial group.
In our cohort, among the infants with bacterial LOS, gram-negative organisms accounted for 60% of the cases; Klebsiella (33.3%), E-coli (20.0%), Pseudomonas (3.3%) and Enterobacter (3.3%).
Regarding culture result for sepsis group gram positive bacteria Staphylococci accounted for 16.7% of cultures.

The neurodevelopmental delay was greater in sepsis group than non sepsis group in all examined functions and the difference was significant and sepsis cases represented about 2/3 of cases that had neurodevelopmental impairment.
This study also found that there are other risk factors that can impair ND beside sepsis, these factors include male sex, decrease GA, LBW, multigravida mothers, irregular ANC, low Apgar score at 5 minutes, long duration of hospital stay, need for supplemental oxygen, central line insertion, low SES and infection with gram positive organisms.
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Conclusions: This study showed that, neurodevelopmental impairment was significantly increased among neonates who developed neonatal sepsis despite treatment with effective antibiotic therapy. Due to the high risk of adverse outcomes after the development of neurologic complications, it is important that physicians can highly alert the possibility of bacteremia-related neurologic complications after bacteremia, and aim to detect neurological complications early .

Keywords:
Neurodevelopmental outcome, infection, nosocomial, preterm

EPNS23-2224 Oral or e-Poster
Cerebrovascular Disorders

Deep medullary veins thrombosis: a systematic literature review.

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Objective: Deep medullary veins (DMVs) thrombosis is a rare cause of brain damage in both preterm and full-term neonates. Diagnosis is challenging due to the low level of suspicion and the scarce availability of MRI in acute settings. With this study we aimed to collect data on clinical and radiological presentation, treatment and outcome of DMVs thrombosis.

Methods: We conducted a systematic literature review on DMVs thrombosis in neonates.
The search was carried out in Pubmed, Clinical Trial Gov, Scopus and Web of Science by two independent researchers, up to date to November 2022; any discrepancies between them were resolved by consensus or by consultation with a third senior investigator.

Results: 75 published cases of DMVs thrombosis were identified and analyzed. We did not notice a clear prevalence of preterm neonates. Neonatal distress, respiratory resuscitation or need for inotropes during the first week of life were present in 34/75 (45%) of patients. Signs and symptoms at presentation included: seizures (38/75, 48%), apnea (27/75, 36%), lethargy or irritability (26/75, 35%), poor feeding and weight loss (19/75, 25%). At MRI, performed between 0-48 days after birth, fan-shaped linear T2-hypointense lesions were documented in all cases. Edema or ischemia of corpus callosum was the main collateral finding on MRI (77%). Treatment was not mentioned in any of the studies included. Although the reported mortality is low (2/75, 2.6%), a large proportion of patients develop neurological sequelae (major neurodevelopmental impairment in 32% of cases, epilepsy in 18%).

Conclusions: DMVs thrombosis is still rarely identified in the literature, even if possibly under-recognized. It presents with seizures and aspecific systemic signs/symptoms that often cause diagnostic delay. The high rate of morbidity, which determines important social and health costs, requires further in-depth studies aimed at defining an earlier diagnosis and at developing evidence-based prevention and therapeutic strategies.

Keywords:
Deep medullary vein thrombosis, neonatal, perinatal thrombosis, deep cerebral venous system

EPNS23-2230 Oral or e-Poster
Cerebrovascular Disorders

Lemierre syndrome in children: prevalence of neurological complications

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Objective: Lemierre syndrome is a severe condition associating cervical and/or cerebral venous thrombosis (CCSVT) in an infectious setting, well described in adults. Pediatric characteristics are scarcely reported. We aimed to study the type and rate of early and late neurological complications, and outcomes in a large sample of pediatric patients with Lemierre syndrome.

Methods: This regional bicentric retrospective study (catching area of 12 million people, 2.3 million children) included pediatric patients (< 18 years old) admitted with a diagnosis of Lemierre syndrome (LS) defined by the association of (i) a head or neck infection, (ii) an adjacent CCSVT and, (iii) at least one criteria of severe condition (extensive CCSVT, cerebral/meningeal/osteoarticular infection, pulmonary/abdominal septic emboli, cervical/cerebral arteritis), from Jan 2016 to May 2022. Clinical, biological, and radiological parameters were recorded at presentation, during the early phase (first 21 days), the late phase (>21 days), and follow-up. Late outcome was evaluated using the modified Rankin Scale (mRS) 6 months after LS onset.

Results: Fifty-nine children were included, 33 boys (56%), with a median age of 4.5 years old. Because of their initial severity, the majority of patients (n=48/59, 83%) were admitted in a pediatric ICU. Otogenic infection was more frequent in children younger than 2 years old (n=15/18), whereas sinus or cervical infection was more frequent in older patients (n=23/41), p<0.01. Early-onset neurological complications (first 21 days) occurred in one third of patients (n=17/59, 29%): cerebrovascular (radiological arteritis n=9, arterial ischemic stroke n=5), infectious (subdural empyema n=5, cerebral abcess/cerebritis n=3), or symptomatic intracranial hypertension (n=1), with a median delay of 5 days. Two patients (3%) died during this early phase. Neurological complications were associated with older age (p< 0.05). Late-onset complications (>21 days) occured in 4/59 patients (6%), including a giant carotid artery aneurysm; 9/35 patients (25%) had significant long-term sequelae (mRS 1 or higher).

Conclusions: Lemierre syndrome is a severe condition in children also. The rate of early neurological complications, especially cerebrovascular, is even higher than reported in adults, and long-term consequences are frequent. Strategies to prevent cerebrovascular complications need to be initiated from the acute phase in addition to antimicrobial therapies.

Keywords:
cerebral venous thrombosis, Lemierre syndrome, arteritis, stroke

EPNS23-2951 Oral or e-Poster
Cerebrovascular Disorders

Long-term neurodevelopmental outcome of perinatal spontaneous intracranial hemorrhage in term-born neonates- a tertiary-care, single-center prospective study

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Objective: To characterize the neurodevelopmental outcome of spontaneous perinatal intracranial hemorrhage (spICH).

Methods: A prospective, consecutive single- center cohort of longitudinally followed children with spICH identified in the fetal or neonatal period between 2014-2022. The presence of cerebral palsy, neurodevelopmental disabilities and remote epilepsy were documented. Neurodevelopmental outcome was rated using the Pediatric Stroke Outcome Measure (PSOM) and the modified-Rankin scale (mRS).

Results: Of 64 subjects included, 41 (64.1%) were diagnosed postnatally and 23 (35.9%) were diagnosed antenatally IVH was the most common bleeding type (n=44, 68.8%) followed by PVHI (33, 51.6%), subpial (10, 15.6%), parenchymal (8, 12.5%) and subdural (6, 9.4%). IVH was more common in patients diagnosed prenatally (p=0.025). Mean clinical follow-up time was 5.6±2.8Y. Half of the patients developed post hemorrhagic hydrocephalus (PHH) (n=32, 50%), of whom 24 (75%) underwent at least one neurosurgical procedure. Mortality rate was 1.6% (n=1). Twenty-four patients had cerebral palsy (CP) [hemiparesis-15/24 (62.5%), quadriparesis-6/24 (5%), GMFCS-2 (9/24, 37.5%)]. Fifteen (23.4%) patients had remote epilepsy, most of them (93%) had IVH and or PVHI. Epilepsy was more common in patients with PHH (p=0.01). Three had autism (4.7%), 19 (29.7%) had vision impairment. PSOM scores were available for 52 patients at a median age of 2.75 years (IQR 1.6,5). According to the PSOM, 22 (42.3%) patients were classified as normal, 8 (15.4%) as mild, 8 (15.4%) as moderate, and 14 (26.9%) as severe. Patients with higher IVH grade (p=0.026), PHH (p=0.006), vermis or brainstem bleeding, Wallerian degeneration (p=0.017), basal ganglia involvement (p<0.01), abnormal myelination in the posterior limb of internal capsule (p=0.02), had a higher PSOM (p=0.05) and a higher rates of cerebral palsy. Timing of hemorrhage or the presence of PVHI did not predict worser outcome according to PSOM but PVHI was associated with higher rates of CP (p<0.001).

Conclusions: In our cohort, spICH was associated with high rates of PHH and long term neurologic deficits according to PSOM. Neuroradiological markers predicted poor long-term neurodevelopmental outcomes.

Keywords:
IVH, PVHI, Perinatal, Hemorrhage

EPNS23-2005 Oral
Cerebrovascular Disorders

Clinical improvement of a toddler with COVID-19 focal cerebral arteriopathy possibly due to intra-arterial nimodipine

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Case study: In the pediatric population, stroke is an infrequent but severe complication of COVID-19. Overall, pediatric stroke is rare, affecting 1.3-1.6 per 100,000 children per year in developed countries. Mortality rates range from 7% to 28%, making stroke one of the top 10 causes of death in the pediatric population. Despite the neural plasticity present in children, about half of those affected by stroke have persistent disability to various degrees. Focal cerebral arteriopathy (FCA), an acute unilateral intracranial arteriopathy, is one of the most common causes of arterial ischemic stroke in a previously healthy child. It manifests as narrowing of the distal internal carotid artery and its distal branches.

The present report describes a toddler diagnosed at our medical center with FCA most likely induced by SARS-CoV-2 infection. Head magnetic resonance imaging (MRI) including MR angiography (MRA) and MR perfusion (MRP) revealed a subacute infarct core with restricted diffusion in the right basal ganglia and corona radiata, surrounded by a large penumbra encompassing most of the right MCA territory. Severe stenosis of the right MCA was apparent on MRA. After parental consent was obtained, the child was referred for diagnostic cerebral angiography. Severe focal stenosis was noted in the M1 segment of the right MCA with delayed filling of M2 branches and no evidence of an occluding thrombus. Nimodipine, a dihydropyridine calcium channel antagonist, was injected into the right MCA. Following injection of a bolus of contrast medium, significant amelioration of the right M1 stenosis was noted in addition to an increase in anterograde flow and disappearance of the leptomeningeal collaterals. After the procedure, the child was treated with oral nimodipine at a maintenance dose for an additional 5 days, in addition to intravenous methylprednisolone and Oral aspirin as well. The patient was discharged from the hospital after 8 days with completely normal ambulation and nearly symmetric use of both upper extremities, with no hand preference.

The present report describes a toddler with FCA most likely induced by SARS-CoV-2 infection who showed significant clinical improvement that may be related to injection of intra-arterial nimodipine. The efficacy and safety of intra-arterial nimodipine administration by well trained invasive neuroradiologists warrants further investigation.To our knowledge, this is the first reported use of nimodipine in this setting.

Keywords:
Focal cerebral arteriopathy , nimodipine, Coronavirus disease 2019 (COVID-19)

EPNS23-2883 Oral or e-Poster
Cerebrovascular Disorders

Successful mechanical thrombectomy in an 11-year-old boy with an acute ischemic stroke associated with MIS-C (Multisystem Inflammatory Syndrome in Children).

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Objective: MIS-C (Multisystem Inflammatory Syndrome in Children) is a rare post-infectious hyperinflammatory condition, which typically occurs in paediatric patients two to eight weeks after SARS-CoV-2 infection. Both, COVID-19 and MIS-C, are associated with an increased risk of thromboembolic events, especially in patients who develop severe ventricular dysfunction or coronary artery aneurysms. Thromboembolic events not only include deep vein thrombosis, central venous sinus thrombosis and pulmonary embolism, but also thrombosis in cerebral arteries, causing acute ischemic stroke.

Methods: We describe the case of a previously healthy 11-year-old-boy, presenting to our emergency department with therapy-refractory fever lasting for six days, abdominal pain, vomiting and swelling of cervical lymph nodes eight weeks after symptomatic SARS-CoV-2 infection.

Results: Laboratory findings were conclusive with MIS-C and echocardiography revealed reduced left ventricular output, consistent with acute ventricular dysfunction. Immediately after admission to our paediatric intensive care unit treatment with antibiotics, intravenous immunoglobulin, methylprednisolone, enoxaparin, oral aspirin and an IL-1 antagonist has been established. On the following day the patient suddenly developed central facial paralysis, dysarthria and left-sided hemiparesis. Computed tomography (including an angiography) was performed immediately revealing middle cerebral artery occlusion with early signs of an acute ischemic stroke in the right temporal lobe. Because of the acute onset of symptoms and the immediate detection of the arterial thromboembolism the decision to perform a mechanical thrombectomy was made. Only 24 hours after the successful intervention the patient was free of neurological symptoms with complete recovery within 14 days.

Conclusions: Thromboembolic events in patients with acute SARS-CoV-2 infections and in those with MIS-C are scarce but potentially life threatening. An early detection of symptoms as well as an immediate and intensive treatment is necessary to reduce morbidity and mortality. To our knowledge this is one of the first patients with MIS-C and ischemic stroke, who was successfully treated with mechanical thrombectomy, underlining once more the importance of early recognition and intervention.

Keywords:
Acute Ischemic Stroke, Mechanical Thrombectomy, SARS-CoV-2, MIS-C

EPNS23-2450 Oral or e-Poster
Cerebrovascular Disorders

Basal ganglia stroke in children after minor head trauma

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Objective: Ischemic lesion of the basal ganglia in children after the minor head trauma (MHT) is a rarely described event with the occurrence frequency of less than 2% of all cerebral infarctions in childhood. To analyze cases of ischemic lesion of the basal ganglia in children after the MHT.

Methods: 124 pediatric patients with cerebral infarction were analyzed. Ischemic lesion of the basal ganglia after the MHT was found in 17 (13%) patients.

Results: Out of 17 patients 11 (65%) were boys and 6 (35%) - girls. The median age at stroke was 1.4 years [IQR 1.0; 2.0]. 8 (47%) patients had an ischemic lesion on the right, 9 (53%) - on the left. The median time from the moment of the MHT to clinical manifestations of stroke was 60 minutes [IQR 5; 90]. According to the PedNIHSS scale in the acute period 2 (12%) patients had mild neurological deficit (1-4 points); 15 (88%) - moderate (5-15 points), moderate-heavy and heavy - 0 cases. General cerebral symptoms such as headache, nausea were observed only in one patient. In addition to the MHT, 10 (58%) patients had other possible etiological factors for the stroke: 2 (11.5%) patients had patent foramen ovale (PFO), 2 (11.5%) - PFO and hyperhomocysteinemia; 2 (11.5%) - PFO and iron deficiency anemia, 1 (6%) - hyperhomocysteinemia and iron deficiency anemia, 2 (11.5%) - hereditary thrombophilia (heterozygous Leiden mutation), 1 (6%) - iron deficiency anemia. Follow-up time after stroke was 46 months [IQR 19; 65]. Currently, according to the PedNIHSS scale, 7 (41%) patients have mild neurological deficit (1-4 points); 10 (59%) patients do not have any symptoms. A stroke recurrence was observed in one patient with PFO - it occurred in the basal ganglia in the opposite side in one year after the first episode and also after the MHT.

Conclusions: According to our data, basal ganglia stroke in children after the MHT occurs in 13% of cases, however, we do not exclude the role of concomitant factors that were observed in 10 (58%) out of 17 patients.

Keywords:
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EPNS23-2492 Oral or e-Poster
Infections and Inflammatory Diseases

PROGNOSTIC RELEVANCE OF QUANTITATIVE AND LONGITUDINAL MOG ANTIBODY TESTING IN PATIENTS WITH MOGAD: A MULTICENTER RETROSPECTIVE STUDY

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Objective: IgG antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) define a subset of associated disorders (MOGAD) distinct from aquaporin-4 IgG associated neuromyelitis optic spectrum disorders and multiple sclerosis. MOGAD can have a relapsing course in 40-50% of patients. The utility of retesting MOG-IgG over time and measuring their titers is uncertain. We aimed to evaluate the clinical relevance of longitudinal MOG-IgG titer measurement as relapse predictor in patients with MOGAD.

Methods: This is a retrospective multicenter Italian cohort study, involving 34 Italian centers and 102 pediatric and adult patients. We recruited patients with MOGAD and available longitudinal samples (at least one >3 months after disease onset) between 2018 and 2021. We tested them with a live cell-based assay with endpoint titration (1:160 cut-off) in two referral laboratories. Samples were classified as "attack" [within 30 days since a disease attack] and "remission" [more than 31 days after attack].

Results: We included 102 patients with MOGAD (57% adults and 43% pediatric) with a total of 354 samples (83% from remission and 17% from attack). Median titers were higher during attacks (1:1280 vs 1:640, p=0.001). Median onset titers were higher than remission titers in both adults and pediatric patients. Median onset titers did not correlate with attack-related disability, age or relapses. Remission titers were higher in relapsing patients (p=0.02). 59.8% of the patients remained persistently positive, while 40.2% descended below the cut-off at least once during follow-up, with no differences between adult and pediatric patients (p=0.59). When considering the first remission sample available for each patient, titers >1:2560 were predictors of relapsing course in survival (log rank, p<0.001) and multivariate analysis (p<0.001, HR: 10.9, 95%CI 3.4-35.2), even when separately considering adults and children. MOG-IgG negative seroconversion associated with a 95% relapse incidence rate reduction (IRR: 0.05, p<0.001).

Conclusions: Early identification of relapse risk factors for MOGAD is crucial to define prognosis and choose the best treatment strategies. Longitudinal MOG-IgG titer measurement could be a useful tool, as persistent MOG-IgG positivity and high remission titers associate with an increased relapse risk. More data on longitudinal MOG-IgG titers might be useful in the future to stratify

patients to be treated with long term immunosuppressive therapy.

Keywords:
MOG antibodies, demyelinating disorders, antibody titers, relapses

EPNS23-2576 Oral or e-Poster

Infections and Inflammatory Diseases

Subacute sclerosing panencephalitis - upcoming changes of phenotype over the last decade

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Objective: Subacute sclerosing panencephalitis (SSPE) is a rare, progressive disease with poor outcomes. Anti-measles vaccination contributed to decreasing the number of SSPE patients, but not to eradication. Our study aims to evaluate how SSPE has changed over the last three decades and investigate why vaccinated children suffer SSPE.

Methods: A retrospective study included SSPE patients treated during the last three decades. The patients are divided into two groups: treated before and after 2010. Diagnosis of SSPE was based on Dyken's criteria. ELISA tests were used for At-Measles-Ab in serum and CSF. The treatment included ASM, corticosteroids, IVIG, isoprinosine, ribavirin, and interferon-alpha.

Results: Thirty-three children with SSPE have been treated in Institute during the last three decades: 27 pts before 2010, and 5 pts after 2010. Two patients were suffering a fulminant form in the group treated before 2010, while all five cases treated afterward had a fulminant SSPE. The last group was more precisely investigated, and we found two were not vaccinated, while three were immunized according to a regular schedule. All of the patients were previously healthy, immune-competent children, with normal global development. The age of measles infection was in the range from 0.5-26 (mean12.5) months, while the onset of SSPE was in the range from 2.5 to 16 years (mean age 8.1 years). The latency period from measles infection to SSPE onset was in the range of 1.8 - 7 years (mean 4.32 years). Progressive motor and cognitive decline, behavior changes, movement disorders, myoclonic jerks, and different types of seizures were observed in clinical presentation in all patients. Two patients experienced epilepsia partialis continua, and one child had opsoclonus. In all patients, the index titer of IgG anti-measles antibodies in the serum vs. CSF is reduced, and oligoclonal bands were positive in CSF. The course was extremely fulminant with the lethal outcome within three months from initial symptoms in four cases.

Conclusions: Scheduled measles vaccination of children contributed to decreasing frequency but not eradicating SSPE. The reason is that the children suffered from measles before the planned vaccination. In aiming to eliminate SSPE, weaning of vaccine-derived immunity, and re-vaccination of girls at fertile age are recommended. We like to increase the awareness of upcoming changes in disease phenotype since we found domination of fulminant SSPE form during the last decade.

Keywords:

SSPE, measles, fulminant SSPE

EPNS23-2186 Oral or e-Poster
Infections and Inflammatory Diseases

Opsoclonus-myoclonus-ataxia syndrome: Two children with interesting similarities and literature review

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Objective: Opsoclonus-myoclonus-ataxia syndrome (OMAS/ OMS) is a rare autoimmune neurologic disorder particularly affecting infants and toddlers. There is a strong association with neuroblastoma, but increasingly, reports about other related disorders emerge, even COVID-19.

Methods: Here we report two cases of OMAS diagnosed in the same centre over a time span of several weeks. Both children were less than 2 years old, were diagnosed with adrenal neuroblastoma of different histology and received Meningococcal B vaccination (MenBV) prior to OMAS-onset. Several videos and imaging examples highlight the diagnostic and therapeutic course of our patients. Additionally, we present an overview about the recent literature including revised diagnostic criteria, recommendations for diagnosis and monitoring as well as a discussion about the various therapeutic approaches summarised in the current review of the 'International OMS study group'.

Results: The first patient was diagnosed with neuroblastoma of the adrenal gland confirmed by biopsy at 6 months of age. The tumor size regressed without intervention under a watch and wait strategy. The patient developed severe ataxia and opsoclonus at 12 months, several days after MenBV. The second patient developed progressive ataxia and tremor with only mild signs of opsoclonus at 20 months, remarkably several days after MenBV, too. In the context of an extensive tumor search, a very small, catecholamine-negative atypical nodular ganglioneuroblastoma of the adrenal gland was found. Both children started four-weekly dexamethasone pulse therapy and underwent complete tumor resection. Due to insufficient treatment-response as judged by the OMS rating score, the first patient received additional rituximab therapy. After one year of therapy and an additional six months of follow up both patients achieved a complete remission and are devoid of any OMAS-symptoms.

Conclusions: OMAS is a rare but severe condition that is clinically diagnosed. Early diagnosis followed by immediate and effective therapy is thought to be important for prognosis; however, substantial evidence for this hypothesis is still lacking. The presented cases followed by a literature review will enable attendees to recognize OMAS as a differential diagnosis and to initiate appropriate diagnostic and therapeutic approaches.

Keywords:
Opsoclonus-myoclonus-ataxia syndrome, OMAS, OMS, Neuroblastoma, Meningococcal B vaccination, autoimmune disease

EPNS23-2524 Oral
Infections and Inflammatory Diseases

Pediatric MOGAD presenting with fulminant idiopathic intracranial hypertension

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Objective: Clinical presentation of fulminant idiopathic intracranial hypertension (IIH) is characterized by headache and distinct decrease of vision within days. Children with MOG-associated disease (MOGAD) can also present with bilateral profound visual loss due optic neuritis (ON).
Our aim is to delineate a subgroup of MOGAD patients with clinical presentation suggestive of fulminant IIH.

Methods: In this observational, retrospective case series we describe pediatric patients with MOGAD presenting with headache, papilledema and vision loss, who were misleadingly diagnosed and treated for IIH. Patients were assigned by physicians contributing patients for our BIOMARKER study from different European countries.

Results: Six patients (median age 7y, range 4-14y; f:m = 4:2) with a temporary diagnosis of IIH and MOG-antibodies (titer >1:160) were included. Vision loss was present in all patients, in addition to headache (n=5), nerve palsy leading to impairment of eye movement (n=3), vomiting (n=2) and tiredness (n=2). In two patients further neurological symptoms occurred during disease course (ataxia, limb weakness). Ophthalmological findings showed bilateral papilledema in all patients and decreased visual acuity (VA) was recorded in five patients (range VA: <20/630 - 20/32). In three patients cerebral MRI showed additional signs of IIH like inward convexity in optic disc localization. In four patients a reliable CSF opening pressure was tested, which revealed elevated levels (range: 38-60cm H2O). Acetazolamid was administered in four patients. Two patients received the indication for a ventriculoperitoneal drainage, in one patient a VP shunt was implanted. Repetitive lumbar puncture was performed in one patient. Subsequently, intravenous Methylprednisolone was administered in all patients either due to worsening of symptoms, positive MOG-ab titer or MRI lesions indicating inflammatory processes. Recovery was good, 2/6 patients still had visual residuals after a median follow-up of 22 months (range: 13-36months).

Conclusions: Children with MOG-positive bilateral ON presenting with papilledema and loss of vision are at risk of being misdiagnosed as fulminant IIH. The misdiagnosis is supported by lumbar puncture, showing an elevated opening pressure - resulting from underlying inflammatory processes. Correct diagnosis is mandatory with important treatment implication.

Keywords:
MOGAD, idiopathic intracranial hypertension, bilateral optic neuritis, pseudotumor cerebri

EPNS23-2938 Oral or e-Poster

Infections and Inflammatory Diseases

Hyponatremia in acute encephalitis syndrome in children: its frequency and effect on the outcome

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Objective: Hyponatremia has been reported in various central nervous system infections like tuberculous meningitis and found to be associated with poor outcome. So far, no study has been conducted on hypontremia in acute encephalitis syndrome (AES) in children. This study was planned to study proportion of hyponatremia in acute encephalitis syndrome (AES) in children, its association with clinical and lab parameters and effect on outcome.

Methods: This was a prospective observational study done at tertiary care teaching hospital. Institutional ethical clearance and informed consent from parents was taken. Patients between 6 months and 12yrs of age who presented with acute onset (7 days) of fever and neurological manifestation that included new onset seizures and/ or change in mental status (duration of altered sensorium >12 hrs) were included. A detailed history and examination was conducted, blood and CSF investigations and serum electrolytes were done in all AES cases, neuroimaging was done in a few cases. Hyponatremia was the main outcome variable of interest, defined as serum sodium of less than 135 mmol/L. Clinical, lab parameters and mortality were compared between hyponatremic and non hyponatremic patients.

Results: 200 children with AES were included in the study over 18 months duration. Hyponatremia was found in 24.5% cases. Mortality was significantly higher in children with hyponatremia (24.5%) in comparison to non hyponatremic patients (9.3%), p=0.02. No significant association was seen with the occurrence of fever duration, seizures, and focal deficits. No significant association was seen with other GCS at admission, meningeal signs and CNS examination. Hepatomegaly was seen more (36.7%) in children with hyponatremia, p value- 0.012.. Hypocalcemia (p value- 0.002) and hypoalbuminemia (p value- 0.007) was seen more in children with hyponatremia. Uraemia (p value- 0.03) was seen more in children without hyponatremia. CBC, LFT and CSF examination didn't show any significant association. The most common aetiology was scrub typhus, positive in 12.2% children with hyponatremia, 8.6% children without hyponatremia, followed by dengue, JE, chikungunya and malaria.

Conclusions: Hypernatremia was found in one fourth cases and it was associated with significantly higher mortality in AES. Monitoring and timely correction of hyponatremia is prudent in AES.

Keywords:

Acute encephalitis syndrome, hyponatremia

EPNS23-2265 Oral or e-Poster
Infections and Inflammatory Diseases

Autoimmune-related epilepsy in childhood autoimmune encephalitis: Definition with scoring models, treatment modalities, and outcomes

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Objective: Acute symptomatic seizures secondary to autoimmune encephalitis (AIE) are common initial symptoms and could propagate to autoimmune-related epilepsy (ARE) in the following phases of the disease. Several scoring models are suggested for identifying ARE. In this study, we aimed to define ARE according to the proposals of the ILAE Autoimmunity and Inflammation Taskforce in a pediatric cohort with AIE, to evaluate clinical parameters and therapeutic modalities for ARE, and to assess the predictive value of two scoring models for ARE identification.

Methods: This retrospective study included 23 pediatric AIE patients (seropositive:15, seronegative:8) who were followed up in the Ege University Pediatric Neurology Clinic between 2013 and 2022. We used the Antibody Prevalence in Epilepsy (APE), and the Response to Immunotherapy in Epilepsy (RITE) scores to predict ARE.

Results: Anti-seizure medication (ASM) was applied to 21 (91%) patients. Seizures were the initial symptom in 19 (83%) patients. The remaining two patients had active epileptiform discharges on electroencephalography without clinical seizures. The most preferred ASMs were levetiracetam (85.7%), diphenylhydantoin (38%), and valproic acid (38%). 29% of the cohort achieved seizure control with monotherapy. Polytherapy was applied in 9 of 13 patients (69%). Immune-related status epilepticus (SE) was defined in 6 patients (26%).
Pulse methylprednisolone therapy was given to all patients as first-line therapy. In addition, IVIG was added to 18 (78.3%) patients. Twelve (%52,2) patients had second-line immunotherapy (rituximab or cyclophosphamide). We defined a favorable outcome in 56% of he cohort at 12 months of follow-up. However, ARE is described in 6/23 (26%) patients. The presence of status epilepticus at admission was significantly associated with developing ARE (p=0.019).
ARE was defined in an equal proportion of patients (91.5%) with two scores (APE and RITE). The mean of RITE score was statistically higher in the seropositive AIE group than the seronegative group (10.3±2.7 vs. 7.5±1.2, p=0.005). However, there was no statistical significance for APE scores between the two groups.

Conclusions: The presence of SE at the time of AIE diagnosis was significantly associated with the development of ARE. Scoring models for identifying ARE may be applied to the pediatric age group. Additional new immunotherapies with monoclonal antibodies or interferon receptor antibodies might be considered in the second-line immunotherapy.

Keywords:
autoimmune-related epilepsy, autoimmune encephalitis, RITE, APE

EPNS23-2471 Oral
Infections and Inflammatory Diseases

Comparison of acute flaccid myelitis and transverse myelitis in children and evaluation of diagnostic criteria

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Objective: Acute flaccid myelitis (AFM) and transverse myelitis (TM) are serious conditions that may be difficult to differentiate, especially at onset of disease. In this study we compared clinical features of pediatric AFM and TM and evaluated current diagnostic criteria, aiming to improve early and accurate diagnosis.

Methods: Data of two cohorts of children with either enterovirus D68-associated AFM or clinically diagnosed TM were retrospectively compared regarding presenting clinical features, performed additional investigations and outcome. Current diagnostic criteria for AFM and TM were applied to evaluate their specificity.

Results: Children with AFM (n=21) compared to those with TM (n=36) were younger (median 3 vs. 10 years), more often had a prodromal illness (100% vs. 39%), predominant proximal weakness (69% vs. 17%) and hyporeflexia (100% vs. 44%), and less often had sensory deficits (0% vs. 81%), bowel and/or bladder dysfunction (12% vs. 69%) and hyperreflexia (0% vs. 44%). On MRI, brainstem involvement was more common in AFM (74% vs. 21%), while supratentorial abnormalities were only seen in TM (0% vs. 40%).
When omitting the criterion of a sensory border, 11/15 (73%) children with AFM fulfilled the diagnostic criteria for TM. Of children with TM, 4/33 (12%) fulfilled the diagnostic criteria for probable/definite AFM.

Conclusions: While there is considerable overlap between AFM and TM in children, we found important early differentiating clinical and diagnostic features. Meeting diagnostic criteria for AFM in children with TM and vice versa, underlines the importance of thorough clinical examination and early and accurate diagnostic studies.

Keywords:
Acute flaccid myelitis, transverse myelitis, enterovirus D68, diagnostic criteria

EPNS23-2779 Oral or e-Poster
Neurogenetic Disorders

Epg5 links autophagic clearance and epileptogenesis in Drosophila and Vici Syndrome patients

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Objective: Epilepsy is a common neurological condition that arises from dysfunctional neuronal circuit control due to either acquired or innate disorders. Autophagy is an essential neuronal housekeeping mechanism, which has been linked to epileptogenesis when impaired. The precise molecular mechanisms underlying this association remain uncertain. Vici Syndrome (VS) is the paradigmatic congenital autophagy disorder in humans due to recessive variants in the EPG5 gene, encoding ectopic P-granules autophagy tethering factor 5 with a crucial role in effective autophagic clearance. VS is characterized by a wide range of neurodevelopmental, neurodegenerative, and neurological features, including epilepsy.

Methods: We investigated a transgenic epg5-deficient Drosophila melanogaster model to study the role of epg5 in development, ageing, and epileptogenesis. We also provide complementary clinical data from EPG5-mutated patients.

Results: Our data indicate that autophagic clearance and seizure-like behaviors correlate and are commonly regulated, suggesting that seizures occur as a direct consequence of autophagy defects and age-dependent neurodegenerative progression in epg5 mutants, in the absence of evident neurodevelopmental abnormalities. Moreover, the seizure phenotype in epg5-deficient Drosophila melanogaster appears to be amenable to fasting. We provide complementary evidence from EPG5-mutated patients, demonstrating progression of seizure activity and EEG abnormalities over time consistent with predictions from animal models. This observations provide insights into the intricate relationship between primary autophagy defects and epileptogenesis, and suggest autophagy-stimulating diets as a potential therapeutic approach to control EPG5-related seizures.

Conclusions: These findings expand the clinical, genetic, and pathophysiological understanding of EPG5-related epilepsy and grant insights into age-dependent pathomechanisms in congenital disorders of autophagy.

Keywords:
epilepsy, epileptogenesis, congenital disorders of autophagy, Drosophila melanogaster

EPNS23-2802 Oral or e-Poster
Neurogenetic Disorders

Gender effect in children with rare autosomal genetic mutations linked to autism

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Objective: Autosomal genetic mutations may affect males and females at same rate. Clinical differences may be present as a result of epigenetic effects and environmental influences such as age of diagnosis and intervention.
Objective: to examine gender influence on the developmental phenotype among children with rare autosomal genetic mutations linked to autism, with or without intellectual disability or global developmental delay. Even though the examined mutations are autosomal and not sex-linked we assumed that epigenetic factors, environmental impac, and diagnostic bias may influence the phenotype differently in females versus males.

Methods: We examined the developmental phenotype in a retrospective cohort of 32 children with a rare genetic mutation linked to autism and intellectual disability that were followed between 2012 and 2021 at one tertiary center.

The cohort comprised of 11 girls and 21 boys with at least two years of longitudinal follow-up. The main domains examined were initial concerns, age of initial referral, clinical diagnosis and diagnostic stability, the trajectory of language, motor, and communication development, long-term comorbidities at follow-up visits, severity of autism and of intellectual disability.

Results: Boys were first referred to a developmental assessment much earlier than girls at a mean age of 3.71 months (SD=3.033 as compared to 10.5 months (SD=11.1) (U=26, p value=0.001).

Boys were genetically diagnosed about two years earlier than girls- at average age of two years with SD=12.36 monthsas compared to girls at almost four years of age with SD=40.01) (u=18.0, p value=0.002).

Significant gender differences (P value=0.03) were found at all severity levels of intellectual disability (P value=0.026).

The risk of severe intellectual developmental disability was higher in girls, with a relative risk of 1.9 (95% CI, 1.24-2.91).

Conclusions: Gender influence was found to be significant in autosomal genetic disorders linked to autism and to intellectula disabilities.

Mein defferences were found in the age of the initial referral, the age of genetic diagnosis which were advanced by average of two years in girls, and the level of intellectual disability with lower IQ range in girls.

A protracted diagnostic process was found in girls in girls despite a significantly lower intellectual level. Earlier diagnosis of autism and intellectual disability in girls may prompt earlier intervention and improve developmental trajectory.

Keywords:
mutation, gender, autism, intellectual disability

EPNS23-2651 Oral or e-Poster
Neurogenetic Disorders

Examining the Correlation Between Neurofilament Levels and Clinical Features in a Friedreich Ataxia Cohort from the Czech Republic

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Objective: Friedreich's ataxia (FA) is the most common autosomal recessive hereditary ataxia caused by a mutation in the FXN gene characterized by ataxia, dorsal root syndrome, scoliosis, cardiomyopathy, and other symptoms. Neurofilaments, structural proteins which play a key role in the maintenance of axonal caliber and axonal integrity, may be an interesting biomarker of neurodegeneration in FA. To better understand the role of neurofilaments in the pathogenesis of FA, we conducted a study to examine the relationship between phosphorylated neurofilament heavy chain (pNFH) and neurofilament light chain (NFL) and clinical features in a well-characterized FA patient cohort.

Methods: In the Center of Hereditary Ataxias in Prague were recruited 40 FA patients (mean age 33, range 8-72, 6 of them age bellow 18) between August 2021 and June 2022 and underwent clinical assessment using the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) protocol at the baseline (T0) and in one year follow-up (T1) on the same day that blood samples were collected and frozen. The blood samples for gene testing were collected at T0. Blood samples from 14 age matched healthy controls (HC) served as a reference (mean age 34). Plasma pNFH levels were measured by an enzyme-linked immunosorbent assay, ELISA.

Results: Preliminary results from the T0 examination showed higher levels of pNFH (mean 48 pg/ml, range 9-202) in FA patients compared to HC (mean 15 pg/ml, range 10-18). Patients with a faster average progression of ataxia according to the scale for the assessment and rating of ataxia (SARA) had higher levels of pNFH, while patients with higher mobility impairment had lower pNFH levels. Both patients with better performance on the functional 9-hole peg test and patients with a younger age at initial examination had higher levels of pNFH.

Conclusions: Current literature and our preliminary results suggest that neurofilament levels in FA patients are significantly increased compared to HC and in the early stages of the disease. They gradually decrease with increasing age and more severe disability and faster progression. After the T1 assessments in April 2023 are completed, we will have the opportunity to compare levels of pNFH (ELISA) and NFL (measured by a single molecule array, SIMOA) at both T0 and T1 and examine the correlations between these biomarker levels and clinical data at both time points.

Keywords:
Friedreich Ataxia, Neurofilaments, Neurogenetic Disorder, Movement Disorder, pNFH, NLF

EPNS23-2504 Oral
Neurogenetic Disorders

Neurological and Cognitive outcome in children with microcephalic dwarfism

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Objective: Microcephalic dwarfism is a rare, autosomal recessive genetic disease, including Seckel, Bloom, and MOPDII syndromes. Whereas growth defect and genetic diagnosis (mutations in ATR, RBBP8, CENPJ, CEP152, CEP63, CEP135, NIN, DNA2, TRAIP, NSMCE2, BLM, LIG4, PLK4, and PCNT genes) of these children are well described, neurodevelopmental and cognitive abilities, as well as their autonomy capacities in adulthood are nearly not described.
Our objectives are to characterize brain growth and to assess motor, language, and cognitive development of the most common forms of microcephalic dwarfism.

Methods: In this retrospective study we describe growth parameters, developmental skills and intellectual abilities of 2 groups of patients with microcephalic dwarfism and known molecular diagnosis (CENPJ, CEP152, CEP135, BLM, LIG4, PLK4 and PCNT):
1) 575 patients reported in the literature
2) 18 patients from our series
Statistical tests used for the comparisons were Student's t test and 1-way ANOVA analyses with post-test comparison and Bonferroni adjustment.

Results: Weight, height and head circumference (HC) growth retardation worsen with age. HC is the most impacted growth parameter in the 212 children for whom HC was available at follow up ($p<0.0001$). HC reduction depended on the genotype ($p<0.0001$), patients with CENPJ, PLK4 and CEP152 mutations having the smallest HC among the studied genotypes.
Developmental skills of these children showed:
-Delay in walking for 5/17 patients from whom data were available
-Delay in language development for 7/13 patients from whom data were available
Mean full IQ of the 27 assessed patients was 74 (standard deviation [SD] 20.28, range 45-88). Intellectual disability was severe in 7 patients, moderate in 10, and mild in 10, with a significant difference according to genotype, CENPJ, PCNT and PLK4 patients being more severely affected than others. Scores on the Vineland Adaptive Behavior Scales obtained from 6 patients were homogeneous according to the different domains understudy.

Conclusions: This study allows for the first time to characterize kinetics of brain growth, neurodevelopmental skills and cognitive abilities of children affected by microcephalic dwarfism and suggest disparities between patients depending on the genotype.

Keywords:
microcephalic dwarfism, CENPJ, CEP152, CEP135, BLM, LIG4, PLK4, PCNT mutations, intellectual disability

EPNS23-2506 Oral or e-Poster
Neurogenetic Disorders

The Natural History of Ataxia-Telangiectasia (N-HAT): a national population study

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Objective: To describe the natural history of ataxia-telangiectasia (A-T), a rare autosomal recessive incurable multisystem disease, from presentation and diagnosis throughout the life course of a national population in order to define the critical stages, and suggest targets for future clinical trials.

Methods: This is a population-based retrospective longitudinal and cross-sectional observational study. Participants were identified through the national paediatric and adult A-T clinics, from 2001 and 2012 respectively. Ethical approval was obtained for an opt-out consent. Data were collected from the clinical notes of participants for every clinic visit, typically every 1-2 years, and entered into a bespoke database. Descriptive statistical analysis was undertaken: Fisher's exact for categorical data and Mann-Whitney U for continuous data.

Results: 173/178 (83 male) were recruited; 126 with classical A-T and 47 people with mild variant A-T. 5/178 (3%) opted-out of the study.

162/173 (94%) were symptomatic at diagnosis, 5 were asymptomatic, in 6 this was not recorded. The most common symptom was gait abnormality. The median age of first symptom in the classical group (n=103) was 1.25 (IQR 1.00-1.50) years and in the variant group (n=39) was 3.00 (IQR 1.50-7.00) years ($p<0.001$).

The median age of onset of gait ataxia in the classical group (n=84) was 1.33 (IQR 1.08-1.50) years and in the variant group (n=23) was 3.00 (IQR 1.50-8.00) years ($p<0.001$). The median age of first wheelchair use in the classical group (n=36) was 9.83 (IQR 8.08-11.00) years and in the variant group (n=16) was 13.00 (IQR 10.50-19.33) years ($p=0.002$).

38 participants had a gastrostomy inserted (32 classical, 6 variant) at an overall median age (n=34) of 12.14 (IQR 9.92-21.74) years.

25 malignancies were reported in the classical group, median age (n=23) at diagnosis 13.42 (IQR 8.17-19.92) years, and 13 in the variant group, median age (n=13) of diagnosis 38.66 (IQR 28.71-48.09) years ($p<0.001$).

36 deaths were reported in the classical group at a median age (n=32) of 19.38 (IQR 13.32-27.45) years, and 7 in the classical group, median age (n=6) of 49.69 (IQR 34.99-52.55) years ($p=0.003$).

Conclusions: This study has generated a high quality natural history of A-T. Understanding the natural history allows the treatment of potentially devastating complications early. The hypotheses generated from these observations will inform future clinical trials to improve the quality of life of people with A-T.

Keywords:
ataxia-telangiectasia, A-T, ataxia

EPNS23-2458 Oral or e-Poster
Neurogenetic Disorders

CEP192, another CEP family member associated with microcephaly?

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Case study: The centrosomal protein family or CEP family is the active component in centrosome maturation, centriole biogenesis and cell cycle progression control. Pathogenic variants in multiple CEP family genes are established causes of primary microcephaly (CEP138, CEP152, CEP215). We propose another CEP family member, CEP192, to be associated with primary microcephaly. CEP192, located on chromosome 18p11.21, is a pericentriolar protein required for nucleation of centrosomal microtubules during mitosis. CEP192 plays a dual role. Firstly, together with Aurora A, CEP192 is responsible for recruiting gamma-tubulin and microtubule nucleators which are essential for correct centrosome maturation. The second key function of CEP192 is centriole duplication. CEP192 and CEP152 are both responsible for recruitment of Polo-like kinase 4 (Plk4), a regulator of centriole duplication. Depletion of CEP192 and CEP152 results in impaired centriole segregation by impaired Plk4 recruitment. Both mechanisms of centriole maturation and duplication are essential for the tightly-regulated mitotic process.

At our centre, we found two compound heterozygous variants in CEP192, one missense- and one splice variant, in a three-year-old male patient with profound microcephaly (-3,9 SD), failure to thrive, global developmental delay and oesophageal dysmotility. Trough international collaboration, six more patients were identified carrying compound heterozygous variants in CEP192. Microcephaly was present in 6/7 cases, with an average of -4.7 SD (mean of available OFC measurements), developmental delay in 4/7 cases and oesophageal motility disorders (dysmotility, achalasia) in 3/7 cases. Functional studies of CEP192 are ongoing. We propose that pathogenic variants in CEP192 are associated with a new developmental syndrome characterized by microcephaly, developmental delay,
failure to thrive and oesophageal motility disorders.

Keywords:
CEP192, microcephaly, developmental delay

EPNS23-2234 Oral or e-Poster
Neuromuscular Disorders

Evolution of respiratory related outcomes and treatment in Duchenne muscular dystrophy

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Objective: For patients with Duchenne muscular dystrophy (DMD) the respiratory function is affected due to progressive loss of respiratory muscles and thoracic and spinal deformity. This leads to chronic respiratory failure and increased risk of pneumonia or secretion stagnation causing acute respiratory failure. The aim of this study is to describe the respiratory-related comorbidities including debut and treatment and their effects on life expectancy and cause of death in patients with DMD.

Methods: This is a retrospective nation-wide study exploring the life expectancy, leading causes of death and co-morbidity in patients with DMD, born since 1 January 1970 who died by 31 December 2019. The patients were identified via the National Quality Registry for Neuromuscular Diseases, the National Registry for Respiratory Failure, pathology laboratories, medical clinics, as well as the network for neuromuscular diseases. Information regarding age and cause of death was retrieved from the Cause of Death Registry and cross-checked with medical records, along with start of co-morbidities and treatment.

Results: Of 129 patients who deceased during the study period, 49 died from respiratory failure at a median age of 23.4 years. 82 of 117 patients had at least one episode of pneumonia by the age of 17.9 years (median). Early loss of ambulation, history of pneumonia, and scoliosis over 20° were more commonly found in patients who died from respiratory failure compared to other causes of death, pneumonia being the only significant risk factor (p=0.049). 53 of 121 patients started mechanical in- and exsufflation (MI-E) at a median age of 20.3 and 90 of 126 patients started mechanical ventilation at a median age of 19.3 years. For patients born in the 1980's; 67 % of patients who had mechanical ventilation also had a MI-E prescribed, compared to 83 % of patients born in the 1990's. Median age for start of mechanical ventilation was 19.3 years for patients born in the 1980's and 18.6 years for patients born in the 1990's while age at start of MI-E was 23.4 and 17.4 years, respectively. Multivariate analyses of risk- and protective factors and time-to-event analyses for cause of death and lifespan are ongoing.

Conclusions: The usage of respiratory-related treatments is increasing over time and initiated at younger ages. Disease severity and comorbidities such as pneumonia should be taken into consideration for early initiation of treatments.

Keywords:
DMD, respiration, comorbidites, cause of death

EPNS23-2149 Oral
Neuromuscular Disorders

A Phase 2 clinical trial evaluating the safety and efficacy of delandistrogene moxeparvovec in patients with DMD

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Objective: Delandistrogene moxeparvovec (SRP-9001) is an investigational gene transfer therapy developed to address the root cause of Duchenne muscular dystrophy (DMD) through targeted skeletal and cardiac muscle expression of SRP-9001 dystrophin protein, which contains key functional domains of dystrophin. This study aimed to evaluate the safety and efficacy of delandistrogene moxeparvovec compared with placebo in patients with DMD aged ≥4 to <8 years.

Methods: Study 102 (NCT03769116; N=41) is a Phase 2 prospective study in patients with DMD aged ≥4 to <8 years. Part 1 was a 48-week, randomised, double-blind, placebo-controlled period. In Part 2 (48 weeks), patients randomised to placebo in Part 1 received delandistrogene moxeparvovec. Part 3 is an ongoing, ≤212-week, open-label follow-up period. Mean change in North Star Ambulatory Assessment (NSAA) total score was calculated.

Results: Overall maintenance of the mean NSAA total score was observed 96 weeks after delandistrogene moxeparvovec treatment, when functional decline is expected based on natural history. Mean NSAA total score increased by 1.3 points at 48 weeks post-treatment in patients who received placebo in Part 1 and delandistrogene moxeparvovec in Part 2 (aged >5 to <9 years at dosing). In a post hoc analysis, a statistically significant difference of 2 points in mean NSAA total score change from baseline was observed in patients treated in Part 2 versus the propensity-score-weighted external control group (P=0.0009).

SRP-9001 dystrophin expression was achieved in all patients treated with delandistrogene moxeparvovec 12 weeks post-treatment. Patients treated in Part 1 continued to express SRP-9001 dystrophin 60 weeks post-treatment.

The most common treatment-related treatment-emergent adverse events (AEs) were vomiting, decreased appetite, and nausea. There were no discontinuations due to an AE and no deaths. No new safety signals have been observed in Study 102.

Conclusions: Findings from Study 102 reinforce that delandistrogene moxeparvovec has a favourable benefit-risk profile, with no new safety signals observed. Overall maintenance of motor function was observed over 2 years following delandistrogene moxeparvovec treatment.

Keywords:
Duchenne muscular dystrophy, gene therapy, clinical trials, gene transfer

EPNS23-2139 Oral or e-Poster
Neuromuscular Disorders

A Real-World Analysis of an XLMTM Patient Cohort from the MTM and CNM International Patient Registry

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Objective: X-linked myotubular myopathy (XLMTM) is a rare genetic neuromuscular disorder for which there are limited real-world data. We aimed to describe demographic and clinical characteristics of male patients with XLMTM in the Myotubular Myopathy (MTM) and Centronuclear Myopathy (CNM) Patient Registry.

Methods: We performed a cross-sectional analysis of a genetically confirmed, living male patient cohort with XLMTM from the international MTM and CNM Patient Registry. As the data are patient-entered, some analyses had different denominators due to varying response rates for certain questions. Results were de-identified and reported at the aggregate level from patients' most recent data entry. Analyses were not performed for response rates ≤2 patients. Data lock was on July 22nd, 2022.

Results: A total of N=88 patients were included. Mean age was 11.7 years (range: 0 to 59 years). Mean age at genetic report was 4.1 years (range: 0 to 46 years) for n=73 responding patients. Fifty-four of 85 responding patients (63.5%) had received a muscle biopsy. Best motor milestone reported by patients (n=79) was 43.2% unable to sit or walk without support, 7.4% able to walk supported, 16.1% able to sit on their own, 21.0% able walk on their own, and 12.4% unknown. Of 88 patients, most (73.9%) reported requiring ventilation at birth; approximately 45.5% reported currently utilizing ventilation ≥16 hours/day, 25.0% utilized <16 hours/day, including while sleeping and awake, 9.1% utilized ventilation <16 hours/day, but only while sleeping, and 10.2% did not utilize ventilation. Of 82 responses, 58.5% reported feeding tube only, 30.5% reported no feeding tube, and 11% reported a gastric or nasal tube with some oral feeding. Of 81 responses, 55.6%, 4.9%, and 29.6% reported using a wheelchair all the time, some of the time, and never, respectively.

Conclusions: The MTM and CNM Patient Registry provides a unique opportunity to examine real-world data in patients with XLMTM with evidence of varying severity. Data suggest that the disease burden of XLMTM is substantial, with most patients experiencing limited motor function and requiring respiratory support at birth and in daily life. Use of assistive devices and gastric or nasal tubes was common. Limitations include varying response rates, missing data, and the cross-sectional nature of this analysis.

Keywords:
XLMTM, myotubular myopathy, myopathy, neuromuscular, patient registry, real-world

EPNS23-2670 Oral or e-Poster
Neuromuscular Disorders

Inhibition of nonsense-mediated mRNA decay may improve stop codon read-through therapy for Duchenne muscular dystrophy

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Objective: Duchene muscular dystrophy is a are genetic neuromuscular disorders that affect skeletal and cardiac muscle resulting from mutations in the dystrophin gene, coding for dystrophin protein. Read-through therapies hold great promise for the treatment of genetic diseases harboring nonsense mutations, such as DMD, as they enable complete translation of the affected gene. However, to date most read-through drugs have only moderate success in the clinic. One possible explanation for the limitation of these therapies for DMD is that they rely on the presence of mutant dystrophin mRNAs.
Mutant mRNAs containing premature termination codons (PTCs) are identified by the cellular surveillance mechanism, nonsense-mediated mRNA decay (NMD) process, and are degraded. Here, we show that the combination of read-through drugs together with known NMD inhibitors have a synergistic effect on the levels of nonsense-containing mRNAs, among them the mutant dystrophin mRNA. This synergistic effect may enhance read-through therapies efficacy and improve the current treatment for patients.

Methods: Patient-derived skin fibroblasts were collected from two BMD patients, one harboring an in-frame duplication of exons 2-7 and one with an in-frame deletion of exons 45-49, and three DMD patients, with nonsense mutations in exon 11,53 and 66. Dystrophin mRNA levels were analyzed using qPCR.
Studies were approved by the Hadassah Medical Center Helsinki Committee.

Results: We show that dystrophin mRNA levels in BMD/DMD patient-derived fibroblasts are unstable and undego degradation via nonsense mediated decay pathway. We show that the combination of read-through drugs (PTC124) together with known NMD inhibitors (5'-Aza cytidine and amlexanox) have a synergistic effect on the levels of nonsense-containing mRNAs, among them the mutant dystrophin mRNA. This synergistic effect may enhance read-through therapies efficacy and improve the current treatment for patients.

Conclusions: The combination of read-through drugs together with known NMD inhibitors have a synergistic effect on the levels of nonsense-containing mRNAs, among them the mutant dystrophin mRNA. This synergistic effect may enhance read-through therapies efficacy and improve the current treatment for patients.

Keywords:
Duchenne muscular dystrophy , Nonsense mediated decay ,Readthrough

EPNS23-2507 Oral or e-Poster
Neuromuscular Disorders

Survival in Eteplirsen-treated vs Duchenne Muscular Dystrophy Natural History Patients: An Indirect Treatment Comparison Using Real-world Data

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Objective: Eteplirsen results in attenuation of ambulatory and pulmonary decline in patients with Duchenne muscular dystrophy (DMD) vs natural history (NH) controls. However, impact on survival is unknown. This study assessed the impact of eteplirsen therapy on survival of patients with DMD.

Methods: Using real-world data collected by Sarepta's patient support program, survival of patients receiving eteplirsen as part of routine care was compared with DMD NH data (2 US-based and 2 European studies). Kaplan-Meier curves were digitized, generating reproduced individual patient data. Survival age was compared between eteplirsen-treated patients and DMD NH controls using unadjusted Kaplan-Meier curves, log-rank tests, Cox models, and parametric specifications. Time from treatment initiation to death was compared in a simulation randomly matching each eteplirsen-treated patient still alive at age of treatment initiation with up to 15 DMD NH controls, adjusted for baseline age and age-treatment interaction.

Results: Among 579 patients, the mean age at eteplirsen initiation was 11.9 years (range 1.0-35.0) and mean exposure was 3.7 years (0.0-8.6). Median age at death was higher for eteplirsen-treated patients vs DMD NH controls (32.8 vs 27.4 years, log-rank $P<0.0001$), resulting in prolonged median survival of 5.4 years for eteplirsen-treated patients. Hazard of death appeared 66% lower for eteplirsen-treated patients vs DMD NH controls (HR 0.34, 95% CI [0.23, 0.50], $P<0.001$). Mortality rates were lower for eteplirsen-treated patients vs DMD NH controls across all 5-year segments, ranging from 5 to 45 years. Younger initiation and longer treatment exposure were independently associated with longer survival. Results were robust to different combinations of DMD NH controls.

Conclusions: Real-world data from patients treated with eteplirsen had significantly longer survival compared with reproduced patient-level data on DMD NH controls, with a median difference of at least 5.4 years. These data suggest eteplirsen may prolong survival in patients with DMD across a wide age range.

Keywords:
eteplirsen, DMD, real-world

EPNS23-2140 Oral or e-Poster
Neuromuscular Disorders

Ataluren preserves motor function in nmDMD patients from Study 041, a phase 3, randomized, double-blind, placebo-controlled trial

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Objective: Study 041 (NCT03179631) is an international, phase 3, randomized, double-blind, placebo-controlled 72-week ataluren trial in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) followed by a 72-week open-label period. Here, we describe the effects of ataluren on motor function as assessed by the North Star Ambulatory Assessment (NSAA).

Methods: Boys with nmDMD aged ≥5 years, on corticosteroids for ≥12 months and with a 6-minute walk distance (6MWD) ≥ 150m were eligible and randomized 1:1 to ataluren:placebo. The intention-to-treat (ITT) population comprised randomized boys who received ≥1 dose of study treatment. Key subgroups included 1) boys with baseline ≥300m 6MWD and ≥5s supine-to-stand time and 2) boys with baseline 300-400m 6MWD. Change from baseline to week 72 NSAA total score was a secondary endpoint. A revised NSAA was used consisting of 16 activities (head lift was excluded), each scored as 0, 1, or 2, and summed to give a total score. Transformation of the total score to a linear scale was additionally performed. A mixed model for repeated measures was employed to compare the change from baseline between ataluren and placebo.

Results: Ataluren and placebo groups were balanced according to enrolment age, baseline 6MWD, corticosteroid use and supine-to-stand time. A significant difference between the ataluren and placebo groups, favouring ataluren, was observed in the ITT population for both the total and linear NSAA score change from baseline (0.9, p=0.0235 and 2.3, p=0.0246, respectively), representing 19.0% and 19.3% decreases in decline compared to placebo, respectively. This was consistent with results for the primary endpoint of slope change in 6MWD. The difference in change from baseline in NSAA score for numerically favoured treatment with ataluren compared with placebo in subgroup 1 (≥300m 6MWD and ≥5s supine-to-stand time) and showed a significant difference following treatment with ataluren compared with placebo in subgroup 2 (300-400m 6MWD subgroup [3.3, p =0.0419]).

Conclusions: These results from Study 041 demonstrate that ataluren preserves the ability to perform the NSAA, and therefore preserves motor function in patients with nmDMD.

Keywords:
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EPNS23-2134 Oral or e-Poster
Neuromuscular Disorders

Baseline Characteristics and Interim Safety in RESPOND: A Phase 4 Study in Children with Spinal Muscular Atrophy Treated With Nusinersen After Onasemnogene Abeparvovec

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Objective: Onasemnogene abeparvovec (OA) is an adeno-associated viral (AAV) vector gene therapy for spinal muscular atrophy (SMA) in children age <2 years. Animal models and limited human postmortem studies have demonstrated incomplete transduction of motor neurons by the AAV9 vector. Nusinersen has the potential to increase SMN protein in untransduced motor neurons, which may provide additional clinical benefit to individuals with SMA. We provide baseline characteristics and interim safety findings from RESPOND (NCT04488133), a single-arm study evaluating nusinersen in children with SMA previously treated with OA ≥2 months previously.

Methods: RESPOND study participants have ≥1 *SMN2* copy, are age ≤36 months, nusinersen-naïve, and have suboptimal clinical status at baseline. Suboptimal clinical status (investigator-determined) includes ≥1 of these domains: motor function, respiratory support, swallowing/feeding ability, other. Participants receive the approved 12-mg nusinersen regimen: 4 loading doses followed by maintenance doses every 4 months. Recruitment is ongoing.

Results: As of 15 August 2022, 34 children were enrolled and dosed. Median time from OA treatment to first nusinersen dose was 6.9 (range: 3-31) months. At baseline, 28/34 children demonstrated suboptimal clinical status in ≥2 domains after OA treatment; motor function (n=33) and respiratory function (n=22) were most common. Baseline HINE-2 total score (mean ± SD) was 6.7 ± 5.7 (n=33). Median duration on nusinersen was 183 (range: 1-540) days. Thirty of 34 participants had 2 *SMN2* copies. Adverse events (AEs) were typical of SMA; the most common were upper respiratory tract infection (n=6) and viral upper respiratory tract infection (n=5). Two participants had mild proteinuria considered nusinersen-related, which resolved. Nine participants had serious AEs; all were considered unrelated to nusinersen and resolved. No deaths or post-lumbar puncture syndrome events occurred. Additional data will be presented.

Conclusions: In RESPOND, the majority of enrolled children previously treated with OA had suboptimal clinical status in ≥2 domains. Interim safety findings were overall consistent with nusinersen's safety profile. Funding: Biogen.

Keywords:
spinal muscular atrophy, nusinersen, onasemnogene abeparvovec, study design, clinical trial

EPNS23-2466 Oral or e-Poster
Neurodevelopmental Disorders

Parental anxiety after extremely preterm birth and its relationship with neuromotor development and perinatal risk factors

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Objective: Understanding psychological effects of preterm birth on parents after discharge from the NICU is important, because it may impact their well-being. Prematurity itself can have negative effects on a child's neurodevelopment, but research into the association between postnatal neuromotor functioning and parental anxiety is scarce. Differences between mothers and fathers may exist. We aimed to compare anxiety levels in parents of extremely preterm infants with those of working adults throughout the first two years after NICU discharge, and to investigate the differences between mothers and fathers. Secondly, we aimed to examine associations between neuromotor functioning, perinatal risk factors and parental anxiety.

Methods: From a cohort of 280 infants (GA < 30wks and BW < 1000g) born between 2015 and 2022, 189 parents completed the State-Trait Anxiety Inventory (STAI) at 6, 12 and/or 24 months. STAI-scores consist of two sets of 20 statements evaluating how respondents feel 'right now' (State) and how people 'generally feel' (Trait). Neuromotor functioning was assessed using the motor optimality score revised (MOS-R) at 3 months corrected age. Perinatal risk factors included GA, intraventricular hemorrhage (IVH) and bronchopulmonary dysplasia (BPD). A series of variance analyses, paired samples t-tests, and bivariate correlations were used to evaluate the study aims.

Results: Mothers and fathers did not report elevated levels of state anxiety, and the scores decreased over time. Trait anxiety was only elevated in mothers at 6 and 12 months. Mothers had higher state anxiety at 6 months and trait anxiety at 6 and 12 months than fathers ($p=0.005$, $p<0.001$, and $p<0.001$, respectively). Parental anxiety levels did not associate with MOS-R, GA or IVH. State and Trait scores of mothers at 12 months were significantly associated with BPD ($r=0.183$, $p=0.041$ and $r=0.177$, $p=0.049$).

Conclusions: Anxiety levels of mothers and fathers after NICU discharge are generally comparable to those of working adults. State anxiety decreased between 6 and 24 months, indicating increased confidence. Only at 6 months, maternal state anxiety was higher than paternal state anxiety. Parental anxiety was not primarily associated with infant neuromotor development or perinatal risk factors, except for higher levels of maternal anxiety of infants with BPD at 12 months. It can be considered reassuring that the majority of parents did not experience increased levels of anxiety throughout the two years after NICU discharge.

Keywords:
Anxiety, State-Trait Anxiety Inventory, STAI, Motor optimality score revised, MOS-R, Neuromotor functioning, Neurodevelopment, Perinatal risk factors, Extremely preterm infants, NICU, Intraventricular hemorrhage, IVH, Bronchopulmonary dysplasia, BPD

EPNS23-2778 Oral or e-Poster
Neurodevelopmental Disorders

Morphological and functional MRI findings in congenital hemiplegia linked to better motor function

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Case study: Objectives: Patients with congenital hemiplegia suffer from different degree of motor impairment. There is emerging data from neuroimaging studies, but still no clear clinical or imaging indicators that can predict the motor function of the patient. In order to expand the knowledge of possible link between motor function and lesion's morphological characteristics, white matter microstructural changes and functional reorganization in the motor cortex, we performed the following study.
Methods: We performed MRI with 3D T1 imaging and evaluation of lesion's volume, type by MRICS and presumed time of occurence; fMRI with motor paradigm for the paretic and non-paretic hand and tractography in 44 patients with congenital hemiplegia (mean age 15 years 7 months), devided in 3 groups according to their MACS-level (1-3). Analysis of the intergroup differences was used to seek for possible indicators for better hand function.
Results: Analysis of the structural characteristics of the brain lesion showed strong correlation between better hand function and smaller lesion volume size and no association with lesion type and time of occurence. FMRI analysis of motor paradigm with the paretic hand found significantly greater activation in the ipsilesional hemisphere in inferior parietal and frontal regions in MACS 1 vs MACS 3 patients and significantly greater activation in the contralesional hemisphere in the postcentral gyrus in MACS 2 vs MACS 3. FMRI analysis of motor paradigm with the non-paretic hand found no significant activation difference between the groups. TBSS analysis registered significantly higher FA values in the ipsilesional hemisphere: in the subcortical white matter, pyramidal tract (corona radiata, posterior limb of internal capsule, external capsule and crus cerebri), posterior thalamic radiation, knee and body of corpus callosum, superior et inferior longitudinal fasciculus in patients with MACS 1 compared to MACS 3.
Conclusion: Better motor function of the paretic upper limb in patients with congenital hemiplegia is associated with: smaller lesions (regardless of the type and time of occurrence of the lesion); increased ipsilelional cortical activation during active movement of the paretic hand, and better microstructure of the white matter both in and outside the corticospinal tract.

Keywords:
Congenital hemiplegia, morphometry, tractography, fMRI

EPNS23-2968 Oral or e-Poster
Neurodevelopmental Disorders

Designing and validation of a neurodevelopmental test for five-year-old (NDT5) children

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Case study: Objectives: To construct and validate a Neurodevelopmental Test for Five-Year-old (NDT5) children.
Methods: The first step of the study included design of the test and its application to 5-years old children visiting 51 randomly chosen different kindergartens in 18 cities and 21 villages in five country regions from January 2012 to January 2014. The second study step was to calculate the predictive validity based on the language and mathematics results on the national examination after 4th grade of elementary school (at 11 years of age) of the same children.
Results: 426 children of mean age 63.5 months (SD-3.7) and male to female ratio 1:1.02 were examined. Each test results was scored according to percentage of children that fulfill it. A cut off point of X+1SD was established. The reliability (test-retest and interrater variability) of the final score was very high (kappa from 0.81 to 1). The internal consistency of test domains varied from satisfactory to excellent (Cronbach from 0.48-0.86). Based on factor analysis, a short version of the test was created with 40 items grouped in five domains- motor development, language development, articulation, perception (non-verbal intelligence) and behavior. The 4th grade exam results of 352 children were correlated with their 5-years test results. Significant moderate correlations were found between the following variables: short version final results and academic results; language domain test results and national language exam grades; non-verbal intelligence test results and mathematics grades. A significant but weaker correlation was found between language domain test results and either mathematics exam grades or overall average grades.
Conclusions: Easy to use short screening test that covers reliably all developmental domains is provided free of charge and standardized for national use. The 5-years age is suitable as it allows detailed neurodevelopmental examination and two-years window for intervention before scolarisation.

Keywords:
developmental assessment tool, developmental screening, standardization and validation

EPNS23-2218 Oral or e-Poster
Infections and Inflammatory Diseases

Effects of velmanase alfa on pulmonary function in paediatric and adult patients with alpha-mannosidosis

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Objective: Alpha-mannosidosis (AM) is an ultra-rare progressive lysosomal storage disorder. Clinical presentations vary and include reduced pulmonary function (PF). Velmanase alfa (VA) is a recombinant human alpha-mannosidase enzyme replacement therapy authorized for AM in Europe and other regions. Patients with AM experience progressive decline of PF and pneumonia is the most common cause of death in adults. We investigated effects of VA on PF with age-adjusted data for paediatric and adult patients with AM. We frame PF response to VA in AM relative to 2 approved drugs for idiopathic pulmonary fibrosis (IPF): pirfenidone (PFD) and nintedanib (NTD). While a different disease, IPF can provide guidance on framing meaningful improvement in PF in AM.

Methods: We analysed data from rhLAMAN-05 (NCT01681953; randomized, placebo [PBO]-controlled trial) and rhLAMAN-10 (NCT02478840; open-label, long-term, integrated efficacy trial of rhLAMAN-02/03/04/05). We calculated mean absolute changes in forced vital capacity (FVC% predicted) from baseline to 52 weeks in overall, paediatric, and adult groups; framed effect size of age and disease with IPF for PFD and NTD; and conducted an integrated pooled analysis of mean absolute changes in age-adjusted FVC% predicted from baseline to Month 12 and last observation (up to 48 months).

Results: In rhLAMAN-05 (N=25), adjusted mean absolute difference for FVC% predicted favoured VA (n=12) over PBO (n=9) in overall (+5.91; p=0.278), paediatric (+6.2), and adult (+5.0) groups; overall mean FVC improvement for VA vs PBO was 270 ml (p>0.05). For a meaningful improvement benchmark, albeit for a different disease (IPF), mean FVC% predicted improved vs PBO by 4.4 (p< 0.05), 0.6 (p >0.05), and 2.9 (p<0.05) in 3 PFD studies and mean FVC improved vs PBO by 94, 125, and 131 mL in 3 NTD studies. Mean FVC gains of VA vs PBO in rhLAMAN-05 were meaningful relative to 2 approved IPF therapies. In the rhLAMAN-10 (N=33) integrated analysis population, mean FVC% predicted improved from baseline to Month 12 (+6.6) and last observation (+8.1; mean: 29.3 months, max: 48 months); both p<0.05.

Conclusions: Both paediatric and adult patients with AM showed more notable PF improvement with VA compared with PBO. VA resulted in non-age-dependent improvements in mean PF vs PBO. Longer term VA therapy showed statistically significant improvement in PF, assessed by mean FVC% predicted, and these improvements are meaningful when framed by approved IPF therapies.

Keywords:
Alpha-mannosidosis, velmanase alfa, pulmonary function, interstitial lung disease

EPNS23-2156 Oral or e-Poster
Neurodevelopmental Disorders

Pathogenetic Insights in Developmental Coordination Disorder: a Unique Condition or part of a Movement Disorder Spectrum?

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Objective: Developmental Coordination Disorder (DCD) is a neurodevelopmental condition characterized by non-progressive incoordination not attributable to intellectual, visual, or neurological impairments and interfering with daily functioning. Movement disorder features can be observed as part of the motor phenotype. Until now, the pathogenesis of DCD remains unclear. Recent genome wide association studies suggested genetic underpinnings in DCD, but comprehensive knowledge about potentially implicated genes is still lacking. In the present study, we aimed to provide an overview of the genes and loci previously associated with DCD, and to explore and compare the underlying pathogenetic mechanisms in DCD and in other movement disorders.

Methods: First, we identified genes and loci with copy-number variations (CNV) associated with DCD according to the diagnostic criteria, by reviewing the literature using Malacards, DISEASES and PubMed. Second, we explored the pathogenetic mechanisms underlying the DCD-associated genes through brain-specific gene co-expression, biological pathway enrichment, temporal and tissue-specific gene expression analyses. Third, we compared these results with previous findings in other movement disorders in literature.

Results: In literature, 12 genes were associated with DCD and met the diagnostic criteria. One gene from the CNV-locus 16p11.2, *TLCD3B*, was predicted to be functionally similar to the 12 DCD-associated genes. The significantly enriched biological pathways were related to nervous system development, neural signaling and cellular organization processes. The expression patterns of the 12 DCD-associated genes were not specific for any central nervous system structure, nor for any time point during brain development (until the age of 18 years). These pathogenetic mechanisms were previously reported in ataxia and dystonia. 12 co-expressed genes, functionally similar to the DCD-associated genes, overlapped with known ataxia, dystonia, and myoclonus genes.

Conclusions: This is the first study to provide a comprehensive review of all 12 genes associated with DCD. Interestingly, we identified one extra gene, *TLCD3B*, which might be functionally associated with DCD. Our pathogenetic data in DCD indicates a resemblance with previously described mechanisms in other movement disorders, such as ataxia, dystonia, and myoclonus. This raises the question whether the motor phenotype of DCD could be regarded as part of a movement disorder spectrum, instead of being a unique disorder.

Keywords:
Developmental Coordination Disorder; DCD; Genetics; Copy Number Variations; TLCD3B gene; Movement Disorders.

EPNS23-2559 Oral
Neurodevelopmental Disorders

Diagnostic yield in Autism Spectrum Disorders and Intellectual Disability of molecular genetics and cytogenetic testing

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Case study: Objectives: To describe a series of 61 patients suffering from autism spectrum disorders (ASD) and intellectual disability (ID), to compare the diagnostic yield of the different available genetic testing and attempt to identify some clinical features that may be correlated with diagnostic efficiency.
Methods: single center retrospective observational study. Family history and medical records were reviewed. Statistical data analysis was performed by using nonparametric tests (Odds Ratio -OR- and Fisher's Exact Test) and calculating frequency distribution of the different clinical features and diagnostic yield for each kind of genetic testing.
Results: in our series we found 70.5% of males, 83.6% of the total of subjects suffering from ID and 59% had had a diagnosis of ASD. Genetic diagnosis was achieved in the 41% of patients and in the 21.6% of them it was done by chromosomal microarray (CMA). Subsequently performing gene panel testing and/or whole exome sequencing (WES) an increase in the diagnostic yield of 6.6% and 8.2% was found, respectively. No patient was diagnosed in our series by FMR1 testing approach. The median for intelligence quotient (IQ) in our series was 69 and the mean age at genetic diagnosis when it was accomplished was 9.8 years old (CI 95% 7.9-11.7 years old). 40.4 % of subjects had an abnormal EEG, but only 16.4% had experienced seizures. Familial history of neurodevelopmental disorders was observed in 15%. Dysmorphic features were presented in 36.7% and abnormal brain MRI in 17.5%. There was no relationship between diagnosis yield for any of genetic testing performed and clinical features of the patients such us microcephaly, epilepsy nor dysmorphic features.
Conclusions: despite the small size of our series in order to do general recommendations, our results would encourage to include the new molecular genetic testing strategies based on the massive sequencing techniques. We would recommended it at least in the neurodevelopmental disorders cases in which we could not accomplish a diagnosis after follow the current recommended diagnosis approach based on FMR1 and CMA testing. Maybe is time to modified practice guidelines for diagnosis in neurodevelopmental disorder which are current since 2013.

Keywords:
autism spectrum disorders, intellectual disability, whole exome sequencing (WES), chromosomal microarray (CMA)

EPNS23-2901 Oral
Neurodevelopmental Disorders

MITOCHONDRIAL MODULATION WITH LERIGLITAZONE AS A POTENTIAL TREATMENT FOR RETT SYNDROME.

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Objective: Rett syndrome is an untreatable neurodevelopmental disease affecting 1:10,000 girls, usually due to MECP2 mutations. It is characterized by a regression in the neuronal development following a normal postnatal growth, resulting in the loss of acquired capabilities such as speech, purposeful usage of hands and arousal of epileptic crises. Alterations in mitochondrial homeostasis are part of a complex pathophysiology, shaping it as an attractive target for the treatment of the disease. We have studied the effect of Leriglitazone (LGZ), an FDA and EMA-designed orphan drug, in the modulation of mitochondrial performance in the context of Rett syndrome and its potential use to modify Rett's phenotype.

Methods: We first proved that mitochondrial dysfunction in Rett patients' fibroblasts was potentially corrected with Leriglitazone. We defined the alterations in mitochondrial homeostasis through measurement of mitochondrial shape (both ultrastructure and network parametrization through electronic and confocal microscopy), dynamics (by measurement of fission-fusion proteins) and energy metabolism function (by evaluating ATP production through a luciferine-luciferase assay, reactive oxygen species production and metabolism). Then, we treated Rett mice models and evaluated LGZ effect on brain mitochondrial homeostasis, in terms of both mitochondrial function and phenotypic correction.

Results: We proved that treating the cells with LGZ resulted in the correction of energy metabolism and oxidative stress alterations. Based on these positive results, we moved forward to study a female Rett murine model. We confirmed mitochondrial function were area-dependent, and especially relevant in hippocampus and cerebellum. Prolonged treatment of Rett mice resulted in a correction of the mitochondrial performance, both in ATP production and oxidative stress. It also exerted an anti-inflammatory effect, measured both in the presence of microglia in cortex and through a multiplex cytokines panel. Moreover, it derived in an amelioration of the mice phenotype, particularly evident in their motor coordination, explorative activity, and general health, with no adverse effects observed.

Conclusions: Our studies confirm mitochondrial modulation through Leriglitazone as a potential treatment for Rett syndrome along with other diseases with mitochondrial implication, constituting the pre-clinical evidence introductory to a clinical trial.

Keywords:
Rett; Neurometabolism; Treatments

EPNS23-2478 Oral or e-Poster
White Matter Diseases

Hippocampus and thalamus atrophy are features of RNASET2 deficient cystic leukencephalopathy

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Objective: Cystic leukencephalopathy is caused by loss-of-function mutations in RNASET2. It is an autosomal recessive disease that causes severe intellectual disability, motor impairment, and spasticity, and is characterized by brain anomalies, such as multifocal white matter lesions, subcortical cysts and intracranial calcifications, that cannot be distinguished from those caused by congenital cytomegalovirus brain infection. Recently, hippocampal accentuated brain atrophy was described in a mouse model with RNASET2 deficiency. We analyzed which subcortical structures are affected by atrophy in patients with RNASET2 deficient leukencephalopathy.

Methods: Structural MR-images (T1-, T2-weighted) of 4 patients with RNASET2 deficient leukencephalopathy and 51 healthy controls were processed with the Freesurfer (V 7.2.0) SAMSEG algorithm. Subcortical structures and white matter lesions were semi-automatically re-segmented with ITK-Snap.

Results: Patients with RNASET2 deficient leukencephalopathy show bilateral hippocampus and thalamus atrophy. Thalamus atrophy correlates with the volume of white matter lesions.

Conclusions: Hippocampus and thalamus atrophy, which are present in neurodegenerative diseases such as Alzheimer's disease or multiple sclerosis (MS), can also be found in patients with RNASET2 deficiency. It is discussed that thalamus atrophy resembles disruption of cortico-thalamic connectivity by axonal transection in MS patients. Network mediated processes could also drive neurodegeneration in monogenic leukencephalopathies, like RNASET2 deficient leukencephalopathy, and should be further addressed by research.

Keywords:
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EPNS23-2764 Oral
Neurometabolic Disorders

Influence of fingolimod treatment on disease outcome and MRI brain volumes in children with CLN3

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Objective: To assess the effects of fingolimod treatment on the disease progression in children with CLN3 in an open label observational study.

Methods: Children with CLN3 were included and treated with Fingolimod over a period of at least one year. MRI studies including MPrage sequences at onset of treatment and after one year in addition to standardized cognitive testing were performed. The Hamburg JNCL score was applied at baseline and at clinical visits after 6 and 12 months. Serum NFL measurements were performed at the same intervals. Fingolimod treatment was monitored by measuring absolute lymphocyte count and liver enzymes every 1-3 months and ophthalmologist consultations every 3-6 months.

Results: 10 children with genetically confirmed CLN3 were included (7 females, 3 males, age 5-16 years) including two siblings who are not yet affected by the disease. Treatment with Fingolimod - adapted to the weight of the child- was well tolerated. None of the patients had side effects such as increased rate of infections and raised lever enzymes. In general absolute lymphocyte count was within the target range of 300-500 lymphocytes/µl. NFl serum levels were mildly elevated in 9/10 children before treatment (median: range 30- 79 pg/ml). Follow-up values are pending. Preliminary findings suggest that progressive visual impairment is not ameliorated by the treatment of fingolimod but clinical scores including cognitive function, motor and language skills and epilepsy have remained stable over the observation period (range x to x months).
5 patients had a normal MRI at baseline and 5 patients had already signs of mild cerebral and/or cerebellar brain atrophy. The results of whole brain volume measurement at baseline and after one year of treatment are still pending.

Conclusions: Our results indicate that Fingolimod is well tolerated and may alleviate the disease progression in CLN3 patients probably by influencing the secondary immunological reactions

Keywords:
NCL3, Fingolimod

EPNS23-2205 Oral or e-Poster
Neurometabolic Disorders

Update on a two-part, international, real-world, observational registry of participants diagnosed with aromatic L-amino acid decarboxylase deficiency (AADCd) with or without treatment with eladocagene exuparvovec

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Objective: Aromatic L-amino acid decarboxylase deficiency (AADCd) is a rare autosomal-recessive neurotransmitter disorder resulting in severe neurodevelopmental impairment; information about clinical presentation, prognostic factors, and treatment patterns is limited. AADCAware is a 2-part registry; Part A describes the natural history of AADCd in patients receiving standard of care. Part B assesses long-term safety and effectiveness of eladocagene exuparvovec on motor function. Demographics and baseline characteristics of patients in Part A of AADCAware, up to November 2022, are described.

Methods: AADCAware is an international, multicentre, longitudinal, real-world, observational registry of patients with AADCd. In Part A, participants are followed up annually for a minimum of 5 years. Motor development status was assessed using the Peabody Developmental Motor Scale-2.

Results: Of the 36 participants initially enrolled, 34 participants formed the study population after two patients lacking clinical information were excluded. AADCd diagnosis was confirmed by genetic testing (33/34, 97.1%), plasma AADC enzyme activity analysis (22/34, 64.7%), CSF metabolite analysis (17/34, 50.0%), or a combination of these tests. At enrolment, the study population had a median (min, max) age of 4 (1, 41) years and were predominately White (White, 23 [69.7%]; Asian, 4 [12.1%] or Other, 5 [18.2%]). Median (min, max) ages at: onset of first symptoms, genetic molecular diagnosis and AADC enzymatic activity diagnosis were 3 (0, 12), 12 (3, 384) and 24 (4, 384) months, respectively. Median (min, max) duration between age at diagnosis and age at onset of symptoms was 9.0 (0.0, 381.0) months. Of 22 participants with available PDMS-2 data, 17 (77.3%) had not developed full head control and 18 (81.8%) were unable to sit unassisted or stand or walk with support. Only 4/22 (18.2%) participants had achieved all four major motor milestones at enrolment. One patient achieved full head control only. Oculogyric crises were very common, experienced by 32/34 patients (94.1%) prior to study enrolment. To date, 8/34 (23.5%) patients discontinued Part A of the study when they received eladocagene exuparvovec treatment, 24/34 (70.6%) participants remain in the study, 2/34 (5.9%) participants died.

Conclusions: The majority of participants failed to achieve all 4 major motor milestones (18/22, 81.8%) indicating extremely poor quality of life and a substantial need for basic daily life support.

Keywords:
AADC deficiency, oculogyric crisis, gene therapy, delayed diagnosis

EPNS23-2239 Oral or e-Poster
White Matter Diseases

Classification update of Type I Alexander disease

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Objective: Alexander disease (AxD) is a rare progressive leukodystrophy caused by autosomal dominant mutations in the Glial Fibrillary Acidic Protein (GFAP) gene. It is traditionally classified according to age at onset as neonatal, infantile, juvenile or adult presentation. More recently two other classification system has been proposed, both based on clinical features at onset and brain MRI findings. One distinguishing two main presentations, AxD type I and AxD type II, the second one defining three main phenotypes, cerebral, intermediate and bulbo-spinal AxD. Recently, we proposed an update of the Type I/II classification, based not only on presenting signs and symptoms but also on disease course over time. With the current study we aimed at applying it to a large series of patients through a literature revision

Methods: A literature review was conducted in PubMed for articles published between 1949 to date. We included only patients fulfilling criteria for type I AxD, with a genetically confirmed diagnosis, and of whom there was available information about age and symptoms at onset, developmental milestones and loss of motor and language skills.

Results: Clinical data from 205 patients affected with pediatric-onset AxD were retrospectively reviewed. Among these, we identified 65 patients fulfilling inclusion criteria. We revised available clinical information and we assessed their disease evolutionary trajectories over time

Conclusions: Our results confirm that patients with Type I AxD might be classified into four subgroups (Ia, Ib, Ic, Id) basing on follow up data. In fact, despite the great variability of phenotypes in AxD, there are some shared trajectories of the disease evolution over time

Keywords:
Alexander disease, GFAP, leukodystrophy

EPNS23-2153 Oral or e-Poster
Neurometabolic Disorders

Cerebellar atrophy is the MRI hallmark of late-onset Tay-Sachs disease and alpha-mannosidosis

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Objective: The characteristic MRI findings can help in early diagnosis of patients with lysosomal storage diseases (LSD). Our aim was to evaluate the neuroradiological findings in late-onset Tay-Sachs disease (LOTS) and alpha-mannosidos (AM).

Methods: Sixteen brain MRIs from 16 patients with LOTS and 22 MRIs acquired in 13 untreated AM patients were assessed and compared to age- and sex- related controls.

Results: Pontocerebellar atrophy was a constant finding in patients with LOTS. Other findings included mild thinnig of corpus callosum (38%), cortical atrophy (19%) and supratentorial abnormalities of signal intensity (13%). Cerebellar atrophy was common also in AM patients (62%). Other findings in AM patients included focal and/or diffuse hyperintense signals in the cerebral white matter (85%), cortical atrophy (62%), corpus callosum thinning (23%), enlargement of perivascular spaces in white matter (38%), widening of perioptic CSF spaces (62%), enlargement of cisterna magna (85%). The most frequent non CNS-abnormalities were diploic space thickening (100%), mucosal thikcening (69%) and sinus hypoplasia (54%).

Conclusions: Profound pontocerebellar atrophy is the hallmark neuroradiological abnormality in patients with LOTS. Altough the median age at symptom onset was 21,5 years (6-33 years) in 40% of patients the disease onset was in childhood. White matter changes and cerebellar atrophy are the characteristic brain MRI features of AM.

Keywords:
late-onset Tay-Sachs disease, alpha-mannosidosis, neuroimaging findings, cerebellar atrophy

EPNS23-2866 Oral or e-Poster
Neurometabolic Disorders

Inherited glycosylphosphatidylinositol (GPI) deficiency disorders - phenotype and genotype heterogeneity in a cohort of Polish patients.

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Objective: Glycosylphosphatidylinositol (GPI) is a glycolipid anchoring over 150 different proteins to the cell membrane. This GPI-anchor is an important part of receptors, plays crucial role in molecules adhesion, embryogenesis and neurogenesis. Its biosynthesis, attachment and processing require proteins encoded by over 30 genes. Mutations in some of these genes can result in decreased cell surface presentation of GPI-anchored proteins and lead to relatively new subclass of congenital disorders of glycosylation termed inherited GPI deficiency disorders (IGDs).GPI deficiencies are inherited in an autosomal recessive pattern, with the exception of PIGA mutations, which are X-linked recessive. The aim of this study was to investigate phenotype and genotype heterogeneity in a cohort of Polish patients with these disorders.

Methods: A retrospective cohort study of Polish patients with IGDs. Molecular diagnosis was established based on whole exome sequencing. All identified variants were confirmed by Sanger sequencing.

Results: A total of 30 Polish patients (50,0% female) were included in this analysis. There were 11 patients with PIGN, 10 with PIGT, 6 with PIGV and 3 with PIGA variants. All patients presented developmental delay. Other common symptoms included hypotonia (96,7%), ophthalmological disorders (83,3%) such as strabismus, nystagmus or visual impairment and epilepsy (76,7%). Majority of patients presented with seizures within the first 2 years of life. The incidence of seizures was higher in patients with the PIGN and PIGT variants (81,8% and 80,8%, respectively) compared with individuals with PIGV and PIGA variants (66,7%). Several patients presented also joint contractures (26,7%), dysphagia (26,7%), failure to thrive (20%), cardiac (20%), renal (23,3%) and fingers (13,3%) anomalies, as well as hearing impairment (16,7%). Hyperphosphatasia was diagnosed only in patients with PIGV (83,3%) and PIGA (33,3%) variants. The main brain MRI finding was cerebellar atrophy (50,0%).

Conclusions: The neurological symptoms are predominant manifestation of inherited GPI deficiencies. We should consider this group of diseases in patients with developmental delay, hypotonia, seizures and multiorgan involvement, especially if cerebellar atrophy is present.

Keywords:
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EPNS23-2328 Oral or e-Poster
White Matter Diseases

Cognitive performance and psychological symptoms in adolescents with multiple sclerosis: the role of the treatment

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Objective: Multiple Sclerosis (MS) is a rare condition in pediatric age. Cognitive decline is a common feature among children and adolescents with MS and involves verbal and visuo-spatial memory, processing speed, attention and executive functions. Impairment in cognitive skills may affect academic, familiar and social functioning. Data on the role of the different therapeutic approaches on cognitive ability in pediatric age are sparse. We evaluated: 1) the impact of treatment received on patients' cognitive performance in one year follow up; 2) the association between cognitive profile, fatigue, psychological symptoms and treatment received.

Methods: In this retrospective study, thirty-seven adolescents with MS were included (13 boys, 24 girls; mean onset age=14; ± 2.05). The cognitive profile was assessed by Rao's Brief Repeatable Battery (SDMT, CLRT, LTS, SPART, PASAT and LWG subtests). The Fatigue Severity Scale (FSS), Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 Questionnaire (GAD-7) were used to explore fatigue, depression and anxiety. Seventeen patients received infusion treatment (n= 12 Natalizumab; 4 Ocrelizumab; 1 Rituximab) and 20 received non-infusion treatment (n= 2 Glatiramer Acetate; 6 Interferon beta 1a; 2 Dimethyl Fumarate; 10 Fingolimod). Every patient underwent a baseline evaluation (T1) and second evaluation (T2).

Results: Our data showed a general improvement in several subtests of the Rao battery (p=<0.05). Thirty patients (81%) obtained higher scores in processing speed (SDMT) in T2 compared with T1 (p=< 0.001). Higher mean scores emerged in both patients receiving infusion treatment (p=0.053) and non-infusion treatment (p=0.006). Moreover, our data showed an improvement in short-term verbal memory (SRT- LTS, p=0.003), short-term spatial memory (SRT, p=<0.001) and executive functions (LWG, p=< 0.001). A positive association between fatigue and SDMT in T2 was found (p=0.029). A large percentage of patients showed depression (61%) and anxiety (70%) symptoms in the second evaluation. No difference (T1 vs T2) according to the treatment in fatigue and psychological symptoms was found.

Conclusions: Our study demonstrates a positive influence of medical treatment on cognitive performance in pediatric SM. Given the impact that MS can have on emotional development, a special attention should be paid to young patients' psychological symptoms.

Keywords:
Multiple sclerosis; Adolescents; Cognitive performance; Psychological symptoms.

EPNS23-2059 Oral or e-Poster
Neuropsychiatric Disorders

Double-blind randomized clinical trial on effect of mobile neurofeedback in ADHD and neurotypical children: an exploratory study and theta-phase gamma-amplitude coupling analysis

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Objective: The purpose of this study was to determine the therapeutic effect of mobile neurofeedback (MNF) in attention-deficit/hyperactivity disorder (ADHD) and neurotypical children compared to sham mobile neurofeedback.

Methods: A total of 168 subjects were assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version Korean Version (K-SADS-PL-K) and were assigned to one of the three groups: ADHD MNF-medication (n=72), ADHD MNF alone (n=35), and Neurotypical (NT, n=61). Within each group participants were randomly assigned to the MNF active or sham control groups, and a double-blinded randomized sham-controlled trial was conducted. We recorded the absolute and relative EEG power in 19 channels and conducted the theta-phase gamma-amplitude coupling (TGC) analysis. TGC, which reflects the degree of neuronal interactions between functional systems, provides information about an individual's attentional network. The MNF program was conducted three days a week, twice a day, for 10-20 minutes for 12 weeks. All participants completed EEG test before and after the 3-month MNF program.

Results: In the EEG analysis collected before MNF intervention, the NT group had higher TGC scores in almost all brain regions than the other two ADHD groups. In comparison before and after 3 months of MNF intervention: (a) In the ADHD (MNF-medication) group, active MNF increased TGC of Fp2, F3, F4, F8, P4, O1, and O2; whereas sham MNF decreased TGC of C4 and Cz. (b) In the ADHD (MNF alone) group, both active and sham MNF showed mixed results, and a certain direction could not be confirmed. (c) In the NT group, active MNF showed no significant change, while sham MNF decreased TGC of P7, Cz, and O2.

Conclusions: MNF alone group did not show a significant effect compared to sham control. However, MNF intervention as an additive therapy to ADHD medication can induce neurophysiological changes, which can be confirmed by TGC. In addition, given that TGC decreases after sham MNF intervention in NT children, neurofeedback intervention that does not give proper feedback may cause damage, so caution is needed.

Keywords:
ADHD, mobile neurofeedback, double-blind randomized clinical trial, theta-phase gamma-amplitude coupling

EPNS23-2519 Oral or e-Poster

Quality of Life in Children with Neurological Disorders

Subjective Burden of Endocrinological Complications of Duchenne Muscular Dystrophy

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Objective: Endocrinological complications are common in Duchenne muscular dystrophy (DMD). We aimed at mapping and describing the subjective burden of these complications, their surveillance protocols, and treatment.

Methods: Patients willing to participate in a prospective study to monitor endocrinological complications in DMD were asked to give their opinion about the presence, treatment, and surveillance of secondary osteoporosis (SO), delayed puberty, and short stature, and their treatment. This was done via an online structured questionnaire using the Survio.com website. The boys were encouraged to fill in the forms themselves, but some forms were answered for the boys by their care-taker. The answers were then summarised as a number of patients who chose the predefined answers and graphically presented using Microsoft Excel. For comparing two groups, Fisher exact test was used, with $p < 0,05$ considered significant.

Results: There were 27 respondents, 7 (26 %) of whom were boys with DMD themselves ("patients") and 20 (74 %) care-takers ("parents"). Only 5 (19 %) boys suffered from severe backpain, which was not asociated with the presence of vertebral fracture ($p = 0,54$). The treatment of SO by Zoledronic acid (ZA) was well tolerated and reduced back pain. Delayed puberty was considered an important issue for 5 (18 %) of boys, all of them older than 12 years. Five participants were treated for delayed puberty, 3 of them reported positive effects, the other two did not observe any effects yet. Of the studied endocrinological complications, secondary osteoporosis and bone health was considered by far the most important, chosen by 19 (70 %) respondents, followed by short stature (n = 6, 22 %) and delayed puberty (n = 2, 7 %). The patients did not mind the time spent in hospitals required for the screening and treatment of endocrinological complications. The parents were more prone to chose neutral answers than the patients, especially considering puberty ($p = 0,01$).

Conclusions: Bone health is the most crucial issue for our DMD patients. The surveillance protocols are well tolerated. Back pain is not always associated with vertebral fractures. Treatment by ZA, as well as pharmaceutical induction of puberty, are well tolerated. Delayed puberty is a tabuisised theme and deserves more discussion. The boys seem less hesitant in answering the questions about their health which should be addressed when making treatment decisions.

Keywords:
Duchenne muscular dystrophy, secondary osteoporosis, short stature, puberty

EPNS23-2585 Oral or e-Poster

Quality of Life in Children with Neurological Disorders

Factors influencing the quality of life of school children with epilepsy

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Objective: Quality of life (QOL) of children with epilepsy (CWE) and factors affecting it have received considerable attention. However, considerably less emphasis is placed on the associated developmental and psychiatric comorbidities which could have a significant impact on QOL. The aim of this study is to investigate the influence of various factors potentially affecting QOL with emphasis on these comorbidities.

Methods: The study involved children with epilepsy (n=104) with duration of epilepsy of 5.6 ± 3.7 years (range of 1-14.5 years). The inclusion criteria were: 1) age between 8 and 15 years, 2) attending a mainstream primary school. To evaluate the QOL, we used the previously validated 23-item Czech version of CHEQOL - 25 having four scales (1. interpersonal and social impact, 2. fears, worries and interests of CWE, 3. intrapersonal and emotional impact, 4. epilepsy as a child's secret) and total score ranging from 23 to 92 points. Psychiatric comorbidities were evaluated with the 27-item Children's Depression Inventory and the 14-item anxiety scale of the Piers Harris Questionnaire. Diagnostics of Attention deficit hyperactivity disorder (ADHD) and learning disorders (LD) was based on assessment by an experienced child psychologist and performed in accordance with Czech standards. 60-item Raven's matrices were used to measure nonverbal intelligence. Medical factors as seizure frequency and type, duration of epilepsy etc. were also evaluated.

Results: Total score of QOL were significantly higher for children performing better in the nonverbal intelligence test ($p = 0.007$). It was found that CWE having LD and/or ADHD had significantly lower QOL ($p<0.001$) in all scales compared to CWE without these conditions. The total score of QOL was 62.30±12.12 in the prior group compared to 74.54±11.32 in the latter. A very strong relationship was found between QOL and depression and also anxiety ($p< 0.001$ in both cases). Among the medical factors, neither the number of AEDs nor seizure frequency was statistically significant in any of the scales or in the total QOL score ($p >0.05$). Duration of epilepsy was near threshold for the total score of QOL ($p=0.049$).

Conclusions: These results suggest that developmental and psychiatric comorbidities could have a greater impact on QOL than medical factors. The findings provide a better understanding of QOL of CWE and the results could be helpful for assessing QOL in patients undergoing epilepsy surgery.

Keywords:

Quality of life, children with epilepsy, Attention deficit hyperactivity disorder, learning disorders,

EPNS23-2065 Oral or e-Poster

Quality of Life in Children with Neurological Disorders

Concerning weight trajectories indicate a need to optimise weight management after brain injury: a retrospective review of paediatric records

List of authors:

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Objective: Optimal nutrition following acquired brain injury (ABI) is critically important to ensure ideal neurological and physical healing and more favourable long-term outcomes. The complex interplay between the injury, its sequelae (e.g., physical limitations, emotional disturbance, and neuroendocrine problems) and the environment are related to altered eating behaviour and nutrition-related outcomes including overweight and obesity. Despite significantly and disproportionately contributing to disability in children, the literature and management guidelines for nutritional support of these children is limited. We hypothesised that there would be an increased prevalence of overweight and obesity in children with ABI followed through a state-based paediatric rehabilitation service.

Methods: After consent, a retrospective chart review was performed (n=132), documenting demographic, injury, and anthropometric data. Families also completed health service delivery, family burden, and quality of life questionnaires. Body mass index (BMI), BMI percentile, and weight category were compared pairwise. BMI percentile change within 4 years of injury was analysed by linear mixed model. Logistic regression analysis was used to assess factors influencing malnutrition states.

Results: 104 children participated (56% male), with an average age at injury of 6.3 (SEM 4.9) years. Brain injury aetiology was acquired (66%) or traumatic (34%). At follow up, 75% of carers felt the ABI affected the whole family. Clinical problems included decreased mobility (42%), behavioural (32%), and speech/language, oromotor, or oropharyngeal dysfunction (18%). 63% of participants were malnourished (19% underweight, 44% overweight or obese). There was a significant increase in BMI (0.66, $p<0.01$) and BMI percentile (4.38, $p<0.01$) 1-year post-injury. Age at injury, lower quality of life, and male sex were associated with malnutrition post-injury ($p<0.05$).

Conclusions: Children with ABI demonstrated a high degree of medical and psychosocial complexity contributing to altered weight outcomes. Compared to the national average in children (25%), a higher proportion become overweight or obese with resulting risks for future non-injury related chronic disease. Further, a significant proportion of ABI children were underweight, reflecting the medical complexity of this group. There is a need for comprehensive, consumer co-designed interventions to maximize healthy lifestyles and optimal weight management for children with acquired brain injury.

Keywords:

Paediatric neurology, behaviour, nutrition, physical activity, quality of life, rehabilitation

EPNS23-2681 Oral

Quality of Life in Children with Neurological Disorders

Glycopyrrolate For Drooling in Children with Neurodisability

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Objective: Drooling is a symptom that reduces quality of life and there is a growing literature for the use of glycopyrrolate in its management. For all that, the information flow with glycopyrrolate remains inconsistent, and drooling is often poorly controlled in children with neurodisability. Here we reported, the patients diagnosed with drooling and treated with glycopyrrolate in our clinic were retrospectively

Methods: Seventy-five children with neurodisability who had never received medication for drooling included between 1/1/2020-1/1/2022. Children were received glycopyrrolate 1 mg tablet. Dose was increased over 4 weeks to achieve optimum symptom control with minimal side-effects; steady dose then continued to 12 weeks (min:1mg/day; max:3 mg/day). Subjective saliva production was registered with Drooling Impact Scale (DIS) score, Drooling Severity and Frequency Scale (DSFS). DIS, DSFS and quality of life (QoL) questionnaire; adverse events were questioned at the beginning, at week-4 and 12.

Results: All data of 50 patients out of 75 patients were complete. Fifteen of the patients had autism and neuromotor retardation, and 35 had cerebral palsy. The age range of 50 patients included in the study was 3y 6mo-17y 11months. DIS showed a significant increase at 12 weeks after treatment in comparison with the pre-treatment values (21.84±5.17 and 80.22±8.01, p=0.001).) Participant scores on the DSFS varied from 7 to 9 points (median = 8) prior to glycopyrrolate, and from 2 to 5 (median = 3) at the week 12 (Z =-6,213; $p < 0.001$). Participant scores on QoL Scale varied from 1 to 2 points (median = 1) at the beginning, and from 2 to 4 (median = 3) following treatment (Z = -6,144; $p < 0.001$). There were no predictable and non-predictable side-effects that required drug discontinuation in any of the patients. There were no permanent side effects, but temporary constipation and flushing side effects were observed at the first month of the drug

Conclusions: This study is one of the few studies showing that glycopyrrolate is effective and safe in patients with cerebral palsy as well as in children with neurodisability such as autism

Keywords:

Autism, cerebral palsy, drooling, glycopyrrolate

EPNS23-2072 Oral or e-Poster
Neuropsychiatric Disorders

The Efficacy of Addition of Atomoxetine to Speech Therapy on the Stuttering Severity of Children Aged 4-12 Years; a Double-Blind Controlled Randomized Clinical Trial

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Objective: Stuttering is a common problem at all ages and it is thus required to treat this problem since childhood. Atomoxetine is currently used for the treatment of attention deficit hyperactivity disorder (ADHD) and can also be effective for the treatment of stuttering due to its selective inhibition of norepinephrine reuptake and dopaminergic properties. Therefore, this randomized clinical trial (RCT) aimed to evaluate the effect of Atomoxetine on children's stuttering.

Methods: Children aged 4-12 years, diagnosed with stuttering, who referred to pediatric neurology clinic, were randomly divided into experimental (N=50) and control (N=50) groups. One group received atomoxetine plus speech therapy and the other group only speech therapy. Both groups completed the Stuttering Severity Questionnaire (SSI4) at baseline (on the first visit) and three months after the intervention.

Results: Most (67%) were boy; 24% aged < 60mo,46% 60-95mo,and 30% >95mo. About half (52%) had a positive family history of stuttering. Stuttering severity was highest at ages of 60-95mo, in left-handed children,those who used formula,and those who felt insecure in the family; but was not different based on child's sex, concomitant ADHD, multilingualism, facial or movement tics, based on sleeping hours, and using teats. Mean stuttering severity reduced in both groups (P<.001) with a greater decrease in the experimental group, compared to the control group (P=.011).

Conclusions: Atomoxetine,plus speech therapy, is effective for the treatment of children's stuttering and can be used as a complementary treatment strategy in these patients.

Keywords:
Stuttering; Speech Therapy; Atomoxetine

EPNS23-2522 Oral or e-Poster
Neuropsychiatric Disorders

Features of tissue energy metabolism in children with autism

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Objective: to substantiate the expediency of energy-tropic therapy (ETT) in children with autism spectrum disorders

Methods: 34 children from 3 to 12 years old, 27 boys and 7 girls, were examined. Autism (A) was manifested by speech and motor disorders, stereotypes, and behavioral disorders. In blood leukocytes, the activity of energy metabolism enzymes was determined: succinate dehydrogenase (SDH),glycerophosphate dehydrogenase (GPDH), glutamate dehydrogenase (GDH), lactate dehydrogenase (LDH). Psychological research was carried out according to the following methods: "10 words" (Luria); proof test (Vexler); technique "10 words" for visual stimuli.
All children received Risperidone and intermittent courses for 5 months of levocarnitine, coenzyme Q10, acetylaminosuccinic acid solution, thiamine, pyridoxine, cyanocobalamin.

Results: 28 children (87.5%) with (A) showed signs of mitochondrial dysfunction. Of these, 12 (37.5%) had a violation of the activity of two enzymes, 13 (40.6%) - three, and 3x (9%) - four enzymes. A decrease in the activity of GPDH was in 18 (56%), GDH - in 19 (59%); an increase in LDH activity was noted in 21 (66%). SDH activity was reduced in 9 (28%) and increased in 13 (40.6%)children .
When assessing the clinical manifestations of (A) in children after a course of complex ETT, a change in indicators was noted: an improvement in behavior in the form of a decrease in the severity of stereotypes by 25%, a decrease in motor anxiety by 12.5%, an increase in cognitive functions by 57%, an improvement in concentration by 20%, an increase the volume of active speech, relative to the original figures.
After the use of EET, normalization of the activity of SDH enzymes, and an increase in GFDG and GDH are noted.
The best results of EET were established in the group of children with initially reduced values of SDH activity than in the group with an increase in the activity of SDH.

Conclusions: impaired mitochondrial activity is an important link in the pathogenesis of (A). The addition of ETT to the ongoing treatment with psychotropic drugs increases the effectiveness of therapy and improves the prognosis of the course of the disease.

Keywords:
energy metabolism, autism, energy-tropic therapy

EPNS23-2815 Oral or e-Poster
Miscellaneous

General Paediatric vs Paediatric Headache Clinics: a comparison using national performance indicators

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Objective: The National Institute of Health and Care Excellence (NICE) mandated our hospital review children's headache management. The aim of this study was to compare the management of children with headache attending a tertiary paediatric neurology headache clinic (SHC) to those attending routine general paediatric secondary care clinics (GPC), using national quality standards (QS42) based on established NICE guidelines (CG150).

Methods: We compared three retrospective clinical audits, of anonymised clinical data from paper and electronic medical records of samples of children and young people under the age of 18 years seen for headache.

The following quality standard criteria were used:
QS 1. People diagnosed with a primary headache disorder have their headache type classified as part of the diagnosis
QS 2. People with a primary headache disorder are given information on the risk of medication overuse headache
QS 3. People with tension-type headache or migraine are not referred for imaging if they do not have signs or symptoms of secondary headache
QS 4. People with migraine are advised to take combination therapy with a triptan and either a non-steroidal anti-inflammatory drug (NSAID) or paracetamol.
A Clinical Global Impression of change (CGIc) was used to assess the 1 year outcome as "improved", where data allowed.
The clinical audits were a mandated part of continuing Quality Improvement at our hospital, so Research Ethics Committee approval was therefore not required.

Simple descriptive statistics were used.

Results: Patient episodes meeting quality standards, and improving:

QS 1. GPC 17/35 (49%); SHC 82/82 (100%)
QS 2. GPC 5/35 (14%); SHC 47/76 (62%)
QS 3. GPC 10/16 (63%); SHC 13/18 (72%)
QS 4. GPC 3/8 (38%); SHC 63/66 (95%)
CGIc. GCP 15/19 (79%); SHC 20/28 (71%).

Conclusions: Although the clinic populations were different: the SHC only consisted of tertiary patients referred by general paediatricians or other secondary care specialists, so were more likely to have failed GPC care, all the quality standards were more often met in the SHC and the GPC. Outcomes, as expected, were better in the GPC, although were good in the SHC considering patients had failed secondary care.

Even though retrospective and not robust, the data is informative, and the first to our knowledge that attempts such a comparison.

This highlights a knowledge gap between the GPCs and SHC that can be addressed by developing general paediatricians with expertise in paediatric headache, undertaking general paediatric headache clinics.

Keywords:
NICE Quality Standards, Migraine, Service Delivery, Children

EPNS23-2446 Oral or e-Poster
Miscellaneous

OnabotulinumtoxinA for treatment of chronic migraine in adolescents: the experience of an Italian third level headache center.

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Case study: Objectives.
Migraine is the main cause of headache in children and can evolve into chronic forms in up to 5% of cases, causing severe disability. BoNT-A for the treatment of chronic migraine in adults represents one of the strategy with the greatest efficacy and safety data. We have few data on the use of BoNT-A in children or adolescents. The present study aims to describe the experience with BoNT-A for the treatment of chronic migraine in adolescents.
Methods: All patients under the age of 18 treated with BoNT-A at the headache center of the Bambino Gesù children hospital from November 2018 to the present were included in the analysis. The patients received the BoNT-A following the PREEMPT protocol. The following parameters were considered: demographic characteristics, number of injections received, adverse effects and treatment efficacy. For the latter parameter, the subjects were classified as responders if a reduction in the monthly frequency of attacks was greater than 50%, partial responders if between 30 and 50% and non-responders if < 30%.
Results: The treated population consisted of 37 females and 9 males with a mean age of 14.7 ± 1.5 standard deviation (SD) years. Patients had a mean disease duration from onset to BoNT-A initiation of 29.3 ± 9.1 SD months. Before starting the BoNT-A, 58.7% of the subjects had attempted prophylactic therapy with other drugs. The mean duration of follow up was 17.6 ± 13.7 SD months. The mean number of BoNT-A injections were 3.4 ± 3 SD. Five patients discontinued the therapy after the first administration because they could not tolerate the injections. No patient who continued the therapy reported major side effects. One patient reported neck muscle weakness lasting 5 days, 3 patients reported injection site redness or mild edema lasting approximately 24 hours. The 68% of subjects responded to treatment within the first three administrations of the BoNT-A. Proceeding with the number of administrations, a progressive improvement in frequency is observed. Non responder were 63%, 34%,31%, 29% and 14% respectively at first, second, third, four and fifth injection. Partially responder were 31%, 36%,24%,14% and 19% while responder were 6%, 30%, 45%, and 57%.
Conclusions: this case series shows that the treatment of chronic migraine can also make use of the toxin in the pediatric age, proving to be both effective in reducing the frequency of attacks and associated with an excellent safety profile.

Keywords:
migraine, chronic, therapy, onabotulinumtoxinA, childhood

EPNS23-2930 Oral
Miscellaneous

Spinal neurostimulation (SNS) - neuromodulation in the treatment of chronic pain syndrome resistant to pharmacotherapy

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Objective: To present epidural spinal neurostimulation (SNS) as rational indication for the treatment approach in children with chronic regional and generalized chronic global (nociceptive) pain syndrome its efficiency and role in neuromodulation resolving chronic pain and restoring functional abilities of affected extremities.

Methods: We present two children with chronic nociceptive pain syndrome.In both patients investigations including orthopedic, rheumatologic, psychologic tests, bone X rays, brain and spinal MR scans, immunologic tests, repeated cerebrospinal fluid exams, were not informative initially and on follow ups, including panel for genetic neuropathies.

Results: A 14-year-old girl since the age of 8 manifested allodynia with signs of chronic regional pain syndrome type 1 in wrist and afterwards knee region, pharmacoresistant to analgesics and immunotherapy, signs of local autonomic dysfunction and trophic changes of the skin, loss of function of the right arm and left leg, becoming non-ambulant. Electromyoneurography (EMNG) was normal. Nerve biopsy showed inflammatory infiltrates and loss of small unmyelinated C fibers in skin biopsy.
A boy now at the age of 17 y manifested at the age of 9 with clinical signs of acute encephalopathy with headache, photophobia, ataxia, development of paraparesis, sphincter incontinence and intensive radicular pain, especially in the extremities. EMNG and nerve biopsy, revealing demyelinated axons and increased fibrosis were compatible with chronic demyelinating polyneuropathy. Treatment was maintained with IVIG and steroids without functional improvement.
Seven and eight years after the onset of symptoms and signs of chronic pain syndromes in both children, epidural SNS was implanted percutaneously under X-ray control, followed by regression of pain up to 100% (in girl) with complete recovery of motor function, local skin changes and normal intraepidermal nerve fiber density in skin biopsy. A boy, became ambulant improving motor functions of the lower extremities with partial recovery of sphincter control and up to 75% pain control, and continued with treatment of chronic demyelinating polyneuropathy.

Conclusions: SNS as minimally invasive neurosurgical method in children may achieve pain control, restitution of trophic tissue changes restoring motor function, and (less often) sphincter control, enabling reduction of polypharmacotherapy and improving of quality of life of family and children with chronic nociceptive pain syndrome

Keywords:
spinal neurostimulation, neuromodulation, chronic nociceptive pain syndrome, pharmacoresistant

EPNS23-2128 Oral
Miscellaneous

A comparative study of Levetiracetam and Phenobarbital for Neonatal Seizures As a 1st line treatment

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Objective: We aimed to evaluate the use of intravenous levetiracetam as the 1st-line treatment of neonatal seizures compared with phenobarbital.

Methods: The study was conducted on 104 neonates (0-28 days) with clinical seizures after inclusion criteria. They were assigned in equal ratio into 2 groups; one included neonates who received phenobarbitone (PB), and the other included neonates who received levetiracetam (LEV). Neonates were loaded with 20 mg/kg of intravenous drug-A (phenobarbitone) or drug-B (levetiracetam). In persistent seizures, a second loading dose of the same drug was given. Crossover to other drugs occurred if seizures persisted after the 2nd dose of the same drug. The proportion of neonates who achieved cessation of seizures following the 1st or 2nd loading dose of either drug-A or drug-B (PB or LEV) was the main outcome measure provided that they remained free of seizure for the following 24 hours.

Results: After one or two doses of Levetiracetam or Phenobarbitone, clinical seizures stopped (and remained seizure-free for 24 hours) in 41 (78.84%) and 34 (65.38%) patients, respectively (P 0.01). Neonates in the LEV group showed better seizure control than neonates in the PB group (RR 0.57; 95% CI (0.17, 0.80). We did not report any adverse drug reactions in the LEV group. However, 12 (23.07%) neonates developed adverse drug reactions in the PB Group.

Conclusions: Levetiracetam is considered an effective and safe drug as a first-line AED in neonatal seizures.

Keywords:
Anti-epileptic drugs, seizure, management, neonate, 1st line.

EPNS23-2998 Oral or e-Poster
Miscellaneous

Electroneurography (ENG) in the characterization of the paediatric chemotherapy-induced peripheral neuropathy (CIPN): a monocentric retrospective study.

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Objective: CIPN is an important dose-dependent side effect of many first-line chemotherapeutics used in paediatric oncology, especially vinca alkaloids. Electroneurography (ENG) is essential to guide the diagnosis and distinguish the type of neuropathy. Nevertheless, most studies of large populations in the literature include the study of single nerves, mainly sensory.
With this monocentric study, we aimed to investigate the role of ENG in characterising CIPN in a paediatric population. Moreover, to identify any relationships between neurophysiologic findings and clinical and demographic variables.

Methods: We retrospectively enrolled paediatric patients with solid or hematologic malignancies, symptomatology suggestive of peripheral neuropathy, and confirmation of CIPN through ENG investigation performed between 2016 and 2022. The standard neurophysiological investigation in our clinic included the study of the median, ulnar, tibial, peroneal, and sural nerves (both sensory and motor). Clinical, demographic, and neurophysiological data were collected and analysed using descriptive statistics, and Z-scores for amplitude, latency, and conduction velocity. Mann-Whitney test was used for comparison between groups.

Results: The cohort included 21 children (17 males/4 females). The mean age at ENG was 9.7 years. Most of the patients underwent chemotherapy for acute lymphoblastic leukaemia. Vincristine was the main administered neurotoxic drug but also Vinblastine, Brentuximab, and Methotrexate alone had been used. 69% of the patients presented with mixed sensory-motor symptomatology, 31% with only motor symptoms. Nevertheless, ENG suggested mixed axonal neuropathy in 92%. One child presented with acute inflammatory demyelinating polyradiculoneuropathy (AIDP). All patients had at least one highly pathological Z-score in the lower and upper limbs ENG. No differences appeared in relation to age or sex.

Conclusions: ENG of both sensory and motor components of the upper and lower limbs is essential to characterize neuropathy and avoid false negatives in paediatric CIPN. Children may report symptoms less accurately than adults. In those cases, comprehensive ENG allowed a more accurate characterization than just the reported symptomatology. Moreover, although the majority of CIPN is axonal, AIDP can occur, and complete ENG plays a key role in identifying it, in order to guide treatment and improve long-term outcomes.

Keywords:
ENG; CIPN; AIDP; chemotherapy; neuropathy

EPNS23-2868 Oral or e-Poster
Miscellaneous

Evaluation of the Cognitive Functions in Children with Coeliac Disease

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Objective: About 2-10% of coeliac disease (CD) patients present neurological manifestations, adults more than children. Ataxia, neuropathy, headache are well-known complications, but cognitive aspects have not been studied in detail, particularly in children. We aimed to determine cognitive functions and the effect of gluten-free diet (GFD) in children with CD.

Methods: Children with CD diagnosed in Pediatric Gastroenterology between September 2013-September 2017 and age-sex matched healthy controls were included. CD patients were tested for plasma anti-tissue transglutaminase IgA (IgA-tTG) and anti-endomisial IgA (IgA-EMA) as markers monitoring adherence to GFD at the time of cognitive evaluation. Patients negative for both antibodies (n=20/42) formed the GFD-adherent group and those positive for either antibody, the GFD non-adherent group. The Turkish version of Wechsler Intelligence Scale for Children-Revised (WISC-R) comprising 10 core and 2 supplemental subtests: Verbal (Information, Similarities, Arithmetic, Comprehension, Vocabulary, Digit Span) and Performance (Picture Completion, Picture Arrangement, Block Design, Object Assembly, Coding, Mazes) were applied. Groups were compared using Kruskal-Wallis test.

Results: Forty-two children with CD (F/M: 26/16), mean age 12.1 (6-16) years and 30 matched controls were evaluated. Mean WISC-R full scale scores were lowest in the GFD non-adherent patients (p= 0.003), as well as verbal scale (p=0.001) including all subsets, performance scale (p=0.007) and its picture arrangement subtest. Scores were higher in GFD adherent patients and highest in healthy controls.

Conclusions: Cognitive impairment has been reported previously in adults with CD (1). We showed similar results in children with CD in association with adherence to diet. An effect of systemic inflammation on cognitive functions, "brain fog", nutritional deficiencies concerning iron, vitamins B12, D and folate may all take part in cognitive dysfunction. Nutrient intake affects neurotransmitter synthesis in experimental studies, but no association between cognition and nutritional state was observed shown in adult CD (2). We did not analyse nutrient intake and metabolism in our groups. Further research on the pathogenesis, clinical effects, and outcome of cognitive functions in CD is warranted.

Keywords:
Coeliac disease, cognitive functions, children

EPNS23-3008 Oral or e-Poster
Neurocutaneous Syndromes

Arterial Spin-Labeling Perfusion Imaging in the Early Stage of Sturge-Weber Syndrome

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Objective: Sturge-Weber syndrome is a rare congenital neuro-oculo-cutaneous disorder. Although the principal mechanism of Sturge-Weber syndrome is characterized by a leptomeningeal vascular malformation, few data regarding perfusion abnormalities of the brain parenchyma are available. Therefore, the aim of this study was to assess the diagnostic performance of arterial spin-labeling perfusion imaging in the early stage of Sturge-Weber syndrome before 1 year of age until 3.5 years of age. We hypothesized that a leptomeningeal vascular malformation has very early hypoperfusion compared with controls with healthy brains.

Methods: We compared the CBF using arterial spin-labeling perfusion imaging performed at 3T MR imaging in the brain parenchymal regions juxtaposing the leptomeningeal vascular malformation in patients with Sturge-Weber syndrome (n ¼ 16;3.5 years of age or younger) with the corresponding areas in age-matched controls with healthy brains (n ¼ 58). The analysis was performed following two complementary methods: a whole-brain voxel-based analysis and a visual ROI analysis focused on brain territory of the leptomeningeal vascular malformation.

Results: Whole-brain voxel-based comparison revealed a significant unilateral decrease in CBF localized in the affected cortices of
patients with Sturge-Weber syndrome (P , .001). CBF values within the ROIs in patients with Sturge-Weber syndrome were lower than those in controls (in the whole cohort: median, 25 mL/100g/min, versus 44 mL/100g/min; P , .001). This finding was also observed in the group younger than 1 year of age, emphasizing the high sensitivity of arterial spin-labeling in this age window in which the diagnosis is difficult.

Conclusions: Arterial spin-labeling perfusion imaging in the early stage of Sturge-Weber syndrome can help to diagnose the disease by depicting a cortical hypoperfusion juxtaposing the leptomeningeal vascular malformation.

Keywords:
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EPNS23-2472 Oral
Neurocutaneous Syndromes

cerebral blood flow in children with tuberous sclerosis assessed by arterial spin labeling magnetic resonance imaging may be related to cognitive performance

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Objective: We aim to study the longitudinal changes in tubers and whole-brain perfusion using arterial spin labeling (ASL) in infants and children with tuberous sclerosis complex (TSC) and to correlate the results with EEG slow waves activity and neurodevelopmental outcome.

Methods: Retrospective longitudinal study of children with TSC who had at least 3 ASL-MRI, a clinical and a neuropsychological evaluation and an EEG (awake-sleep)within 2 months of the MRI. The cerebral blood flow (CBF) values were calculated in tuber segmentation masks, and tuber:cortical CBF ratios were used to study tuber perfusion. Logistic regression analysis was performed to identify which initial tuber characteristics (CBF value, volume, location) in the first MRI predicted tubers subsequently associated with EEG slow waves. Whole-brain and lobar CBF values were extracted for all patient scans and age-matched controls. CBF ratios were compared in patients and controls to study longitudinal changes in whole-brain CBF.

Results: We included 13 children who had 3 to 6 serial ASL-MRI scans between 2 months and 7 years of age (53 scans in total). Perfusion was lower in tubers associated with EEG slow waves compared with other tubers. Low tuber CBF values around 6 months of age and large tuber volumes were predictive of tubers subsequently associated with EEG slow waves. Patients with severe developmental delay had more extensive and severe global hypoperfusion than those with slight or no developmental delay.

Conclusions: Dynamic changes in tuber and brain perfusion occur over time. Perfusion is significantly reduced early in tubers associated with EEG slow waves. Whole-brain perfusion is significantly reduced in patients with severe neurodevelopmentaldelay.

These results were recently published : Rutten, C., Fillon, L., Kuchenbuch, M. et al. The longitudinal evolution of cerebral blood flow in children with tuberous sclerosis assessed by arterial spin labeling magnetic resonance imaging may be related to cognitive performance. Eur Radiol 33, 196-206 (2023). https://doi.org/10.1007/s00330-022-09036-3

Keywords:
TSC, ASL-MRI, neurodevelopment, brain perfusion

EPNS23-3012 Oral or e-Poster
Neurocutaneous Syndromes

Seizures and epilepsy are not a prominent feature of neurofibromatosis type 1 (NF1)

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Case study: Background:Neurofibromatosis type 1 (NF1) is an autosomal dominant disorders, with a prevalence of 1/4000 individuals. Most reviewers have unquestioningly accepted that epilepsy is one of the most common neurological complications in NF1, and still there is no agreement on its prevalence in NF1.
Objective:To better define the prevalence of seizures and epilepsy and their clinical, laboratory, and imaging features and outcome in NF1 and to try to establish a genotype-phenotype correlation.
Methods - A prospective (years 1998-2022), single-center study in two referral populations: 1) children and adults with NF1 (1.244 patients); and 2) children with neurological problems.
Results:37/1244 patients (17M, 20F; aged 4-44 years) had NF1 and seizures and/or epilepsy. The calculated population-based:(1) prevalence of febrile seizures (FS) in NF1 was 1.35%,in line with the general population frequency (1-3%); (2) prevalence of epilepsy in NF1 was 2.9% [lower than the life-time frequency of seizures in the general population (3%)]; (3) prevalence of infantile spasms (IS) in children with NF1 (0.76%) was higher than the reported frequency in the general population (0.02% - 0.05%);(4) frequency of NF1 in the IS series (0.62-0.90%) was lower than the estimated frequencies in the literature (1.5-3.0%). Patients presented with: (a) focal aware and impaired awareness seizures; (b) generalized tonic-clonic seizures;(c) generalized non-motor seizures. The EEG findings at diagnosis showed no alterations in 13/37 cases; the remnant were: hypsaritmia (3/37), focal spikes/waves complexes (7/37), generalized spikes waves (10/37). Only in three cases, we recorded brain malformations (polymicrogyria; opercular and paracentral lobular polymicrogyria of the Foix-Chavany-Marie spectrum). Three of the 37 children with NF1 and epilepsy (9.9%) had an underlying tumor. Germ-line mutations were identified in all subjects. DNA analysis revealed NF1 gene mutations without genotype-phenotype correlation.
Conclusions - This is the longest prospective, follow-up study; and the first genotype-phenotype study on seizures and/or epilepsy in NF1. According to the present findings, febrile and non-febrile seizures and epilepsy are not prominent features of NF1. Even though the combination of IS and NF1 does not seem to be coincidental, it is certainly an unusual event in NF1. DNA analysis revealed NF1 gene mutations without genotype-phenotype correlation.

Keywords:
Neurofibromatosis type 1; epilepsy; genetics

EPNS23-2533 Oral or e-Poster
Neurocutaneous Syndromes

Absence of the Focal Areas of Signal Intensity (FASI) on the brain MRI examination in Legius syndrome

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Objective: Legius syndrome (LGSS) is a rare autosomal dominant hereditary neurocutaneous disorder, that was differentiated from neurofibromatosis von Recklinghausen type I (NF1) due to
pathogenic variants in the SPRED1 gene (15q14). Similarly to the NF1, LGSS also presents with café-au-lait macules on the skin and sometimes intertriginous freckling (numerous small brown spots similar to freckles). However, there are no other diagnostic symptoms of NF1 present in LGSS, such as optic glioma, neurofibromas, Lisch nodules or bone dysplasia. Clinical contradistinction from NF1 is important for the diagnosis of LGSS, but the molecular genetic confirmation is necessary.
Hypersignal areas on T2-weighted MRI images in typical localisations in the brain (Focal Areas of Signal Intensity, FASI) are another common clinical finding in children with NF1. Nevertheless, presence of FASI is rare in LGSS.
The aim of this study is to compare the incidence of FASI in LGSS and NF1 to further distinguish between these two clinical entities and thus evaluate the clinical and diagnostic significance of the absence of FASI in LGSS.

Methods: We have examined the group of 15 children with LGSS and the group of 130 children with NF1. All children had clinically and molecularly diagnosed LGSS or NF1, every child underwent MRI examination of the brain and the Focal Areas of Signal Intensity (FASI) findings on these scans were evaluated. Independency of FASI presence on the diagnosis was tested using the Fisher's exact test.

Results: FASI was found in 116/130 (89%) NF1 children and no FASI were detected in LGSS group 0/15 (0 %). FASI presence is significantly dependent on the type of diagnosis (p=8, 1e-13).

Conclusions: We suggest the absence of a FASI finding on MRI examination of the brain of patients with Legius syndrome as the important clinical and diagnostic feature of this disorder.

Keywords:
Legius syndrome. Neurofibromatosis von Recklinghausen type I (NF1). MRI examination of the brain. Focal areas of signal intensity (FASI).

EPNS23-2928 Oral or e-Poster
Neurocutaneous Syndromes

Selumetinib therapeutic effects and safety at different time points in NF1 patients with plexiform neurofibromas

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Objective: Neurofibromatosis type 1 (NF1) is a multisystemic neurocutaneous syndrome characterized by an altered function of the MAP-kinase pathway resulting in tumor predisposition, with about 50% risk of developing plexiform neurofibromas (PNF). PNF mainly grow during infancy and cause pain, disfigurement, functional loss, and possible threat to life by gaining malignant potential. In 2019 selumetinib, a MEK 1/2 inhibitor, was approved by US FDA for the treatment of PNF in children with NF1.

Methods: Pediatric patients affected by inoperable PNF and treated with selumetinib for at least six months at were enrolled. Clinical data, laboratory results, the volume of PNF, and adverse effects were prospectively collected in a digital database. Each PNF MRI was segmented in slices and volume calculated using a free open-source image analysis software (Horos). Statistical analysis was performed (Wilcoxon test, Spearman's correlation coefficient) searching for correlations among drug efficacy, age at NF1 diagnosis or at first PNF occurrence, age at the start of selumetinib, and adverse effects. Moreover, considering PNF volumes at baseline and after 6 months (T6), the intraobserver agreement was evaluated using the graphical method by Bland and Altman.

Results: 7 patients with a mean age of 12.3 years at the start of the treatment were included, of whom five presenting a disfiguring PNF. 3/7 children had a one-year-long follow-up, one an 18-month-long. No correlation was found between the age of each patient at the start of treatment and the volumetric variation in the main PNF. Comparing volumes at T6 vs baseline, in 5/6 cases (83%) a reduction was detected, in three over 20%. Wilcoxon test demonstrated a significant reduction in volume. Intraobserver agreement was sufficient, according to Bland and Altman graphical methods. The most reported adverse effects was perionyxis/paronychia (57%), with 2 patients requiring minor surgery; facial and/or body acne and cutaneous xerosis affected 43% patients each, while maculopapular rash, thinning of the hair and increased effluvium 29%. No cardiac, ophthalmological, pulmonary, or severe gastrointestinal adverse events were observed.

Conclusions: We confirm the therapeutic efficacy of selumetinib on PNF, with adverse effects being mainly mild and limited to the skin. Volumetric assay of the lesions through open-source software showed sufficient reliability. Prospective data collection will let further statistical analysis

Keywords:
Neurofibromatosis; plexiform neurofibromas; selumetinib; MEK-inhibitors; adverse effects; volumetric analysis

EPNS23-2167 Oral or e-Poster
Neurocutaneous Syndromes

Frequency of epilepsy appearance after discontinuation of preventive epilepsy treatment in TSC

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Objective: Preventive treatment with vigabatrin (VGB) improves epilepsy outcome and neurodevelopment in patients with tuberous sclerosis complex (TSC). Studies have shown the positive effect of pharmacotherapy during the treatment. However, knowledge about the longstanding impact after successful treatment discontinuation is insufficient. This study evaluates the long-term outcomes of preventive therapy with vigabatrin after pharmacotherapy cessation.

Methods: We performed a retrospective review of children diagnosed with TSC and treated preventively in the first 2 years of age with VGB. The data were collected from two clinical centers: the Department of Neurology and Epileptology, The Children's Memorial Health Institute, and the Department of Child Neurology, the Medical University of Warsaw in Warsaw, Poland.
The inclusion criteria were: 1/ Patients with TSC who received preventive treatment with VGB within 24 months of age, 2/ Discontinuation of the treatment with all antiseizure medication (ASM), 3/ Follow-up at least 12 months after treatment discontinuation.
The exclusion criteria were: 1/ Patients who required any antiepileptic treatment, had active epilepsy after preventive treatment, 2/ Follow-up after VGB discontinuation less than 12 months.

Results: Seventeen patients were included in the study, 8 females and 9 males. All participants were treated preventively with VGB due to paroxysmal epileptiform activity on EEG.
VGB was introduced at the median age of 175 days (8-766 days). All patients had a median treatment duration of 2.9 years (1.7-6.7 years).
During the preventive treatment period with VGB, 15 out of 17 (88.2%) children remained seizure-free. In 2 infants, despite the treatment, seizures appeared but dissolved after drug modification. In those who remained seizure-free till 24 months of age or had controlled seizures for at least two years, the decision of drug withdrawal was taken (17 children).
After discontinuation of antiepileptic treatment, patients underwent control visits. Follow-up after drug withdrawal was 2.5 years (median) (1.2-12.3 years). During this follow-up, epilepsy was reported in 1 out of 17 (5.9%) children. Sixteen out of 17 (94.1%) remained seizure-free and treatment-free.

Conclusions: In most patients with TSC, seizure control continues after discontinuation of the preventive treatment with vigabatrin during median follow-up. However, the median observation time in the study was 2.5 years, and the results require further studies.

Keywords:
tuberous sclerosis complex, epilepsy, preventive treatment, vigabatrin, children

EPNS23-2854 Oral or e-Poster
Neurocutaneous Syndromes

Selumetinib-induced cutaneous reactions in children: a single-center interventional study

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Objective: Neurofibromatosis type 1 (NF1) affects nearly 1 in 3000 individuals worldwide. Plexiform neurofibromas (pNF), congenital benign peripheral-nerve tumors, occur in around 50% of NF1 patients and carry a 15% lifetime risk to progress to malignancy. Surgical approaches are often not successful in tumor eradication. Selumetinib is an oral selective inhibitor of mitogen-activated protein kinase 1/2 (MEKI), recently approved for the treatment of symptomatic inoperable pNF in children. Cutaneous reactions (CR) are the most common side effects of this therapy in children. Among them, paronychia is the most represented. Most of the literature regarding the management of CR describes the adult experience and very few recommendations regard pediatric patients. The aim of this study was to determine the frequency and spectrum of CR in a pediatric cohort receiving selumetinib and to propose a management algorithm for a prompt and effective treatment of selumetinib-induced paronychia in children.

Methods: A single-center interventional study was conducted enrolling 18 children treated with selumetinib for symptomatic inoperable pNF from January 1, 2020, to August 1, 2022. Full body skin examination and photographs of dermatologic findings were included at the initial visit; a follow-up skin examination was recommended every three months.

Results: All children presented at least one CR; the most frequent side effect was paronychia, reported by 13 patients (72.2%), of whom 4 (30.7%) classified as grade 3 according to the National Cancer Institute's common terminology criteria for adverse events, version 5.0 (CTCAE). The paronychia treatment algorithm presented here showed the potential to reduce the severity of selumetinib-induced paronychia, increasing the quality of life and the tolerance to this therapy.

Conclusions: This study shows that CR are common in children treated with selumetinib. Although rarely life-threatening, CR may impact the quality of life and lead to low adherence to selumetinib therapy, all of which may affect clinical outcomes. Future studies should include a clinical trial to validate this algorithm and optimize care for NF1 children with selumetinib-induced CR.

Keywords:
Neurofibromatosis type 1; MEK inhibitors; drug response; pediatric oncology;

EPNS23-2655 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Gain-of-function and loss-of-function GABRG2 variants lead to distinct clinical phenotypes in patients with neurodevelopmental disorders

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Objective: Objective: Patients harboring GABRG2 variants have been associated with a broad phenotypic spectrum ranging from simple febrile seizures to developmental and epileptic encephalopathies (DEE). GABRG2 variants have been shown to feature a loss-of-function (LoF) effect, due to reduced neuronal GABAergic activity. No in vitro studies have shown gain-of-function (GoF) effect yet. We describe a clinical, genetic and functional evaluation of patients carrying GABRG2 variants.

Methods: Methods: Patients were ascertained via an international network using detailed demographic, genetic and electro-clinical data. We compared GABAA receptors containing wild-type versus variant GABRG2 subunits using whole-cell voltage clamp electrophysiological recordings.

Results: Results: 39 unpublished patients were included harboring 27 different variants (15 of which were missense) and functionally characterized. Twenty variants showed a LoF effect and two showed a GoF effect. Seven patients harboring five variants with no changes in GABA sensitivity and/or reduced maximum currents were omitted from further analysis. Clear distinct phenotypic differences emerged between GoF and LoF variants. The most severely affected children (n=2) were GoF, with epilepsy onset within 3 months of life, high risk of severe developmental delay (DD), severe DEE, focal seizures with multifocal EEG and severe global hypotonia. A third patient with a variant causing a mild GoF showed only mild DD, mild global hypotonia and autism. Twenty-nine patients were LoF and showed seizure onset between 3 months and 10 years, with febrile seizures only reported in 3/29 (10%) and epilepsy in 26/29 (90%: generalized in 73%, focal + generalized in 19% and focal in 8%): 42% had genetic epilepsy with febrile seizures +, 23% DEE, 8% myoclonic atonic epilepsy, 4% myoclonic absence epilepsy, 4% childhood absence epilepsy, 4% juvenile absence epilepsy and 15% unclassified epilepsy. They also presented with psychiatric and behavioral disturbances in 48%, mild hypotonia in 7% and developmental delay in 34% (mild in 70%). Normal cognition was reported in 19 (66%).

Conclusions: Conclusions: GABRG2 LoF variants are associated with a phenotypic spectrum ranging from febrile seizures to DEE. In addition, our study provides evidence of GABRG2 GoF variants, identifying distinct phenotypic features, from those related to LoF variants.

Keywords:

GABAA receptor; GABRG2; genetic epilepsies; gain of function

EPNS23-2615 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Different modularity of irritative network in focal cortical dysplasia type I and II

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Objective: Surgical treatment of intractable focal epilepsy is based on completely removing the epileptogenic network. Almost half of the patients with focal cortical dysplasia (FCD) have no visible MRI changes despite technical progress in neuroimaging. The decision of resection size in these cases depends on stereo-EEG (SEEG) monitoring and presumption of FCD type I or II (respectively extensive or limited) which is challenging mainly in MRI-negative cases. Structural behaviour of FCD types I and II anticipate the difference between the functional organization of the epileptic network determined by the occurrence of interictal epileptiform discharges (IEDs).

Methods: Six hours of awake (3h) and sleep (3h) interictal SEEG of 44 patients with FCD (n=19 type I, n=25 type II) were analyzed. IEDs were automatically detected and sorted using a previously published technique due to an area of origin into independent sub-regions of an irritative network. Interactions within the network were described by the Markov model as the probability of IEDs transition between sub-regions. Network topology was parametrized by modularity, global effectivity, global clustering coefficient, and global persistence.

Results: Comparison of network topology proved higher modularity in FCD type I than II ($p<0.01$) although the number of sub-regions is statistically similar. Designed generalized linear model (GLM) demonstrated the ability to stratify FCD types with 61 ± 15% (median 67%) accuracy in cross-validation testing (80% training, 20% testing, 10.000 iterations) most specifically for the combination of wakefulness and sleep recordings.

Conclusions: Higher modularity represents a more heterogenous organization of irritative zone that reflects a more diffuse character and partially cognitive-functional of FCD type I lesions. Computational analysis of IEDs interactions within epileptic networks brings new biomarkers which potentially can stratify FCD types I and II pre-surgically.

Keywords:
Focal cortical dysplasia, Epilepsy, Markov chain, Irritative zone

EPNS23-2861 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

NEW CLASSIFICATION OF PAEDIATRIC EPILEPSY IDENTIFIES NEEDS AND OPPORTUNITIES IN CARE

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Objective: There is a paucity of studies reporting the epilepsy spectrum using the new ILAE classification systems in everyday clinical practice. To identify gaps and opportunities in care we evaluated a cohort applying the newer epilepsy classification systems, including aetiology and co-morbidity, and the utility of molecular diagnosis to identify available precision therapies.

Methods: Cross sectional retrospective study of all children with epilepsy (16 years and younger) attending a second level unit (2017-2022). Data collection and analysis of each case was standardised to ensure a systematic approach and application of the new ILAE categorisation and terminology. Ethics approval was obtained.

Results: Among 356 children, epilepsy was classified as focal (46.5%), generalised (38.9%), combined (5.9%), and unknown (8.7%). Epilepsy syndrome was determined in 39.4%, comprising 23 different syndromes, most commonly SeLECTS (8.2%), CAE (7.3%), JAE (5.6%) and ISS (5.9%). New aetiology-specific syndromes were identified (e.g CDKL5-DEE). Aetiology was genetic in 59.6%, with molecular diagnosis confirmed in 19.2% (12.7% monogenic, 6.5% chromosomopathy/CNV), and 40.3% presumed genetic. Remaining aetiology included structural (18.8%), infectious (2%), metabolic (1.7%) and unknown (34.9%). Encephalopathy categorisation was determined in 51% (DE in 38.8%; DEE in a further 11.8%, and pure EE in 0.6%), associated with a range of co-morbidities categorised as global delay (29%), severe neurological impairment (16.3%), isolated delay (13%) and neuropsychiatric (e.g. ASD)(23.4%). Molecular based "precision therapy" was deemed available in 21/356 (5.9%) patients, with "molecular precision" approach utilised in 13/356 (3.7%), and benefit noted in 6/356 (0.2%) of overall cohort [or 6/68 (8.8%) of the molecular cohort] as mostly transient (or for e.g. in SCN1A-DEE by drug avoidance).

Conclusions: Applying the new classification identifies major neurodevelopmental comorbidity (~53%), and a large genetic aetiology (~60%). Review of the unknown category prompts consideration to define a further proportion as genetic within the ILAE classification. We identified interesting phenotype expansions in some molecular diagnosis, but very few meaningful molecular based "precision therapies". There is a monumental gap between aetiological identification, and impact of meaningful therapies, reflecting major challenges in the provision of routine epilepsy care.

Keywords:

ILAE, epilepsy, genetic aetiology, precision therapy

EPNS23-2801 Oral
Epilepsy: Diagnosis and Investigations

Cognitive and behavioral evaluation of children with self-limited epilepsy with centrotemporal spikes (SeLECTS): the correlation with diffusion tensor imaging findings

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Objective: Self-limited epilepsy with centrotemporal spikes (SeLECTS) may cause cognitive and behavioral disturbances. Diffusion tensor imaging (DTI) studies have been used to investigate the microstructural tract abnormalities that might be associated with cognitive and behavioral disturbances.

Methods: A comparative study was designed as patients with SeLECTS (n=26) and age-matched healthy subjects (n=24). Demographic data and EEG findings of the cases were recorded. A semi-structured psychiatric interview (Kiddie Schedule for Affective Disorders and the Lifetime Version), the Wechsler Intelligence Scale for Children-IV (WISC-IV), the Behavior Rating Inventory of Executive Function (BRIEF), the Bender Visual Motor Gestault Test, the Trail Making Test (TMT), the verbal fluency test, and the Attention Deficit/Hyperactivity Disorder (ADHD) DSM-IV based Diagnostic Screening and Rating Scale were applied. The correlation between psychometric test results and DTI parameters, including fractional anisotropy (FA), median diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), was investigated.

Results: The mean FA values of the SeLECTS group was significantly lower in superior longitudinal fasciculus ($p=0.03$) and arcuate fasciculus ($p=0.01$) of the right hemisphere compared to the healthy subjects. Although WISC-IV results were found to be lower in the patient group, statistical significance was not found ($p=0.06$). A statistically significant negative correlation was found between the rotation and perseveration errors of the Bender Gestault test and FA values in the prefrontal tract of the corpus callosum ($p=0.04$, $p=0.008$). The organization of materials (OoM) part of the BRIEF test was found to be significantly lower in the SeLECTS group ($p=0.016$) and it was negatively correlated with the FA values ($p<0.05$) and positively correlated with the MD and AD values ($p<0.05$). The semi-structured psychiatric interview detected ADHD in 11/26 of SeLECTS group and 1/24 in the control group ($p=0.005$). ADHD tests and FA values showed significant negative correlation in the arcuate fasciculus and longitudinal fasciculus ($p<0.05$).

Conclusions: Children with SeLECTS had certain DTI abnormalities (FA, MD, AD, and RD) in the presence of cognitive and behavioral disturbances. The combined use of psychometric tests and DTI parameters in prospective longitudinal studies with a large number of patients might provide valuable clinical predictors for cognitive and behavioral disturbances in children with SeLECTS.

Keywords:
SeLECTS, diffusion tensor imaging, psychometric test

EPNS23-2542 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Prospective cohort study: Annual variation in hypsarrhythmia onsets under six months of age

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Objective: To determine the timing of events and surrogate markers for early detection of infantile epileptic spasm syndrome (IESS), due to possible seasonal risk factors at 43 Degrees Latitude North, from 2016 to 2022.

Methods: Six Year prospective cohort study (N-80) to detect abnormal EEG changes prior to hypsarrhythmia (HYPS). Newborns with congenital, genetic or non-genetic risk factors for IESS were studied with bi-monthly 1-hour scalp EEG recordings from 2 to 12 months in a tertiary pediatric hospital. The 10-20 system of electrode placement was used to extract ten second artifact-free epochs with 19 electrodes in wake and N2 NREM sleep. R-Index was calculated with the Laplacian estimate followed by Hilbert Transform analysis of 3, 6, 11 and 15 Hz EEG activity (Nenadovic et al 2018). The number of HYPS/ spasm onsets under 6 months was compared to that occurring between 7 to 12 months of age. The number of Spring-Summer date of births compared to that of the Fall-Winter births. We ascertained the time of biological conception, birth and HYPS onset in pre-term versus full-term patients with medical risk factors for IESS (Goswami et al 2022). We classified the evolution of HYPS types according to Philippi et al 2008 and considered the epidemiological latitude variability for IESS (Jia et al 2018). We used Chi square for group comparisons and ANOVA for repetitive measures of variance, with a p value < 0.05 for statistical significance.

Results: We obtained a 36% prospective catch ascertainment with 29 confirmed IESS cases: 24/29 term (82%) and 5/29 pre-term (18%). There were 12/29 male (41%) and 17/29 female (59%). Estimated dates of biological conception were higher in March-October with 21/29 (72%) compared to April-September 8 (28%). Date of births between October-March were also higher with 18/29 (62%) compared to April-September 11/29 (38%). Eighteen out of 29 (62%) HYPS/spasm onsets occurred under 6 months compared to 7 to 12-months of age 11/29 (38%). And there were 19/29 HYPS onsets (65%) between October-March compared to April-September 10/29 (35%), (Chi-square: 11.91, df= 4, p= 0.0179). HYPS evolved from paroxysmal focal or generalized slow activity into HYPS Type 1 to Type 3 within 8 weeks, with the wake/sleep R-Index f-ratio of 110.386, $p < 0.0001$.

Conclusions: Chronobiological circannual risk factors may contribute to lower the seizure thresholds of term newborns to develop hypsarrhythmia under 6 months of age.

Keywords:

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EPNS23-2455 Oral or e-Poster
Sleep Disorders

Sleep in complex childhood epilepsies: a prospective comparative EEG and questionnaire study in a large cohort

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Objective: The burden of childhood epilepsy is greater than just seizures: aetiology, comorbidities and medication all affect cognition and behaviour, and thus quality of life. But sleep disturbance also plays a role: It has long been established that sleep and epilepsy have a bidirectional relationship. In children with drug-resistant epilepsy and intellectual disability, research on the influence of sleep is limited. We aim to better understand the multifactorial interaction between sleep, epilepsy and co-morbidities in a large cohort of children with epilepsy.

Methods: Sleep was assessed using a comprehensive sleep questionnaire validated in children with intellectual disabilities (SQ-SP, Maas et al., 2011). In-hospital full scalp sleep EEG, EOG and chin EMG were collected from all patients. Macrostructure was scored manually and by a machine learning algorithm. Microstructural features with potential roles in cognition and behaviour, such as decrease in slow wave activity, spindle frequency and density, phasic and tonic REM sleep, were analysed.

Results: 154 children aged between 4 and 18 years were included, of which 50 had drug-resistant epilepsy, 67 were well controlled and 37 had no diagnosis of epilepsy. Age and gender were evenly distributed among the groups. Prevalence of intellectual disability was significantly higher in the drug-resistant group ($p < 0.001$). Prevalence of ASD, ADHD and cerebral palsy was not statistically different between the groups ($p > 0.05$). Sleep stages were scored in 49 patients. REM percentage was significantly lower ($p = 0.011$) in drug-resistant patients compared with well-controlled patients. Questionnaire results ($n = 136$) showed higher daytime sleepiness scores ($p = 0.016$) and a higher composite sleep index ($p = 0.041$) in drug-resistant patients compared with well-controlled patients.

Conclusions: We present a comparative sleep study in children with epilepsy, with the largest cohort of drug-resistant patients to our knowledge. Questionnaire results show more frequent and severe sleep problems compared with well-controlled epilepsy patients. Macrostructural EEG results will need to be complemented by sleep microstructure. Further research will focus on investigating potential sleep biomarkers for cognitive and behavioural impact.

Keywords:
sleep, EEG, drug-resistant epilepsy, macrostructure, microstructure, machine learning

EPNS23-2806 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Evaluation of Clinical Phenotype and Treatment Responses of KCNQ2 Related Epilepsies: Single Center Experience

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Objective: : Developmental and epileptic encephalopathies (DEE) are a heterogeneous group of diseases that cause deterioration in cognitive and behavioral functions due to epileptic activity. One of the genetic etiologic causes is mutatin KCNQ2 gene; which encodes the Kv7.2 subunit of voltage-gated Kv7 potassium channels. Pathogenic variants of KCNQ2, cause either Self-limited (familial) neonatal epilepsy (SeLNE), Self-limited (familial) infantile epilepsy (SeLIE), Self-limited familial neonatal infantile epilepsy (SeLFNIE) and KCNQ2-DEE. We aimed to determine the characteristics of KCNQ2 variants, clinical phenotype and long-term outcome in children with KCNQ2-related epilepsy.

Methods: KCNQ2 heterozygous variants was detected in 20 of 91 patients whose epilepsy gene panel was studied in our hospital between 2017-2021. Characteristics of KCNQ2 mutations, electroclinical features, clinical course, and response to the treatment were analyzed.

Results: Twenty-one different variants in twenty patients were identified with a variant detection rate of 22.3%. Sixteen of them KCNQ2 gene were evaluated as pathogenic or likely pathogenic. The age range of the patients was between 8 months and 12 years. Seven of 16 (43.75%) patients with different pathogenic variants were KCNQ2-DEE. 10 patients followed as SeLNE, SeLIE, SeLNIE have normal neuromotor development and are seizure-free. The age of onset of seizures was earliest on postnatal 1st day and at latest 36 months, and the most common first seizure types were tonic seizures. Initial EEGs of KCNQ2- DEE patients were suppression burst pattern in five patients and slow and disorganized background with multifocal epileptiform discharges in two patients. Only two patients with KCNQ2-DEE achieved seizure-free status with sodium channel blockers treatment and one case responded well to the ketogenic diet.

Conclusions: Patients with KCNQ2 variants have variable phenotypes. KCNQ2-related disorders represent a process of overlapping neonatal epileptic phenotypes, ranging from mild-end self-limited familial neonatal epilepsy (SLFNE) to severe-end DEE. For therapies targeting the Kv 7.2 channel or the KCNQ2 gene itself, deep clinical phenotyping and identification of treatment responses will be important.

Keywords:

Epilepsy, KCNQ2 encephalopathy, Neonatal seizures

EPNS23-2944 Oral or e-Poster
Basic Science

Seizure activity and hypoxia differentially regulate endogenous neurotrophic Activin A and Neuroglobin expression in the immature mouse brain

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Objective: Activin A, a multifunctional growth and differentiation factor, and Neuroglobin, an oxygen-dependent heme protein, were suggested as novel oxygen-dependent neuroprotectants. Both endogenous cytoprotective factors which are partially under control of hypoxia-inducible transcription factors (HIFs) are strongly up-regulated in various forms of acute brain injury including traumatic, hypoxic and ischemic lesions. Here, we were interested in regulatory effects of seizure-induced excitotoxicity and acute hypoxia on Activin A system and Neuroglobin in the developing mouse brain to determine their neuroprotective role during early brain development.

Methods: We analyzed effects of acute pilocarpine-induced seizures in the brain of neonatal C57BL/6 wild-type mice (P10) on age- and region-specific mRNA (real-time RT-PCR) and protein expression (IHC) of Neuroglobin (Ngb), Activin A (AcvA) and its receptors (Activin A receptor type IB, ActRIB; Activin A receptor type IIA, ActRIIA; Activin A receptor type IIB, ActRIIB), after regeneration periods of 6-72 h. Additional, P7-mice were subjected to acute hypoxia (FiO_2 8 % O_2 for 6 h) using the established mouse model of acute neonatal hypoxic brain injury and the prolyl hydroxylase inhibitor (PHI) FG-4497 (60-100 mg/kg, i.p.) stabilizing cerebral accumulation of HIFs.

Results: (mean ± SEM) Acute seizure-induced excitotoxicity led to significant effects on Ngb and AcvA system regulation. Ngb mRNA expression increased in response to acute seizure activity over time (6h: 4.75 ± 0.78, 12 h: 10.53 ± 1.71; vs controls 6h: 6.23 ± 1.15, 12h: 8.12 ± 0.56, $p<0.01$), exceeding the expected age-related increase. Similar up-regulation was confirmed in response to hypoxia and FG-4497 compared to controls (Ngb mRNA ratio 0.20 ± 0.01 vs. 1.47 ± 0.22, $p<0.01$). Gene expression of AcvA significantly decreased within 6 h of regeneration in response to seizures compared to controls ($p<0.01$), whereas mRNA levels of specific receptors were unaffected. In contrast, in response to hypoxia and high-dose FG-4497 significant up-regulation of AcvA, ActRIB and ActRIIB was detected compared to controls.

Conclusions: Present results indicate the differential regulation of Neuroglobin and Activin A in relation to the time and type of injury and their role as potential biomarkers of excitotoxic and hypoxic injury of the developing brain.

Keywords:
Activin A, Neuroglobin, NGB, seizures, hypoxia, neuroprotection, immature brain

EPNS23-2708 Oral or e-Poster
Basic Science

DPP-IV inhibition and remyelination: an experimental study using sitagliptin and the cuprizone-induced mouse model of multiple sclerosis

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Objective: Dipeptidyl peptidase IV (DPP-IV) inhibitors have been suggested to improve some demyelinating diseases, such as multiple sclerosis (MS). DPP-IV is expressed in several tissues and some of its substrates, such as glucagon-like peptide-1 (GLP-1) and neuropeptide Y (NPY), hold the potential to exert neuroprotective and neurotrophic properties. The aim of this study was to evaluate whether sitagliptin, a DPP-IV inhibitor, could enhance GLP-1 and NPY availability in the central nervous system and, consequently, alleviate demyelination and/or foster remyelination, using the cuprizone-induced mouse model of MS.

Methods: Six groups of 8-week-old C57BL/6J mice (n=10 each) were tested: two under vehicle treatment during 5 and 7 weeks (CTRL W5 and CTRL W7) to serve as controls for the demyelination (W5) and remyelination (W7) phases. Two other groups under cuprizone (CPZ) administration for 5 weeks (CPZ W5), one of them followed by suspension of cuprizone for further two weeks (CPZ W7) to evaluate remyelination. The last two groups were subjected to the same CPZ protocols accompanied by sitagliptin treatment between week 2.5 and the end of studies. The cerebellum (CB) and the right hemisphere (RH) were used to evaluate markers of myelination (protelipid protein [PLP] and myelin basic protein [MBP]), keyplayers of the DPP-IV pathway (DPP-IV, NPY, NPY-1R and GLP-1R), as well as parameters of inflammatory and redox status profiles (TNF, IL-1beta, Sod-1, Sod-2, NRF2, and iNOS).

Results: At W5, sitagliptin was able to significantly reduce mRNA expression of DPP-IV and GLP-1R in the CB and RH regions of the brain, as well as to reduce mRNA expression of NPY-1R in the RH. In addition, sitagliptin may have decreased neuroinflammation and oxidative stress. However, it was unable to prevent demyelination, given the incapacity to prevent the CPZ-evoked downregulation of mRNA expression of PLP and MBP, as well as the reduction of kluver-barrera staining. At W7, sitagliptin also reduced the mRNA expression of markers of DPP-IV pathway and of inflammation and oxidative stress, such as IL-1beta, Sod-1, Sod-2 and NRF2. Sitagliptin not only was unable to accelerate remyelination and even caused its inhibition, when compared with the CPZ W7 group.

Conclusions: Sitagliptin failed to prove efficacy in preventing demyelination and/or promoting remyelination in the CPZ-intoxication mouse model of MS, which might be due to the expressive anti-inflammatory effect demonstrated.

Keywords:
Sitagliptine, Cuprizone, Multiple Sclerosis, Remyelination

EPNS23-2469 Oral
Basic Science

A SCN2A loss-of-function variant causing early infantile onset encephalopathy

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Objective: Pathogenic variants in SCN2A coding the voltage-gated sodium channel Nav1.2 are known to cause a phenotypic spectrum including epileptic encephalopathy and intellectual disability or autism without epilepsy. Classically, early infantile onset encephalopathies are well respondent to sodium channels blockers, assuming gain-of-function (GOF) mutation of the channel. We evaluated the expression and functional effect of a SCN2A: c.4976C>T (p.A1659V) pathogenic variant found at a mosaic state in two infants non-respondent to carbamazepine.

Methods: The SCN2A pathogenic variant was identified through Next Generation Sequencing (NGS) and the mutation was inserted by site-directed mutagenesis in the Pir cmv SCN2A plasmid encoding for Nav1.2. HEK293 cells transfected with WT and mutated (A1659V) SCN2A were stained with anti-PanNaV antibody for immunofluorescence or lysated for Western blot assay. The immunofluorescences were acquired both at the epifluorescence and confocal microscopy. For functional characterization, Nav1.2 WT and A1659V mutant were expressed in HEK293 cells and membrane currents were evaluated by whole-cell patch-clamp technique. Cells were stimulated with constant pulse-potentials ranging from -60 to +30 mV, Δ =10 mV, holding potential was -90 mV ($n \geq 12$ experiments).

Results: SCN2A A1659V mutation does not impact on channel expression as shown by western blot and immunofluorescence assays. Whole-cell conductance (GNa) was calculated as GNa = I/(V - Erev), where I is the measured peak current, V is the step potential, and Erev is the calculated sodium reversal potential predicted by linear regression of the I-V curve for each cell. To calculate voltage dependence of activation, normalized GNa was plotted against voltage and fitted with the Boltzmann function $G/Gmax = (1 + \exp[(V - V1/2)/k]) - 1$, where V1/2 indicates the voltage at half-maximal activation and k is a slope factor describing voltage sensitivity of the channel. Expression of A1659V induced a smaller current respect to WT channel. The quantitative analysis of A1659V activation properties show a shift of V1/2 about 10 mV towards more negative potentials and a time constant slower than the WT channel.

Conclusions: SCN2A loss-of-function mutations may cause a severe phenotype like GOF mutation but with no response to sodium channel blockers. Functional characterization may direct clinical interventions and expand funotype-phenotype correlations.

Keywords:
channelopathies; epilepsy; genetics

EPNS23-2600 Oral
Basic Science

Investigation of Mitochondrial Dysfunction in Childhood Migraine

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Objective: The aim of our study was to determine the role of mitochondrial dysfunction in the etiopathogenesis of childhood migraine patients and to determine the role of CGRP (calcitonin gene-related peptide), FGF-21 (fibroblast growth factor-21), GDF-15 (growth/differentiation factor 15) and NOS (nitric oxide). synthase) levels in the diagnosis and treatment of migraine.

Methods: A group of 32 patients (25 girls, 7 boys) and 26 healthy Control Groups (17 girls, 9 boys) who were followed up with the diagnosis of migraine who applied to Düzce University Research and Practice Hospital Pediatric Neurology Outpatient Clinic were included in the study. Serum CGRP, FGF-21, GDF-15 and NOS levels were measured in the ictal and interictal period in the patient group and at the time of admission in the healthy control group. The levels obtained in the ictal and interictal periods of the patient group were compared with each other. In addition, the levels in both ictal and interictal periods of the patient group were compared with the control group.

Results: In our study, a statistically significant difference was found for serum CGRP and FGF-21 levels in the ictal and interictal periods in the patient group ($p<0.001$ and $p=0.001$, respectively). On the other hand, as a result of the comparison of the patient group with the control group, serum GDF-15 and CGRP levels in both ictal and interictal periods were found to be statistically significantly higher in the patient group compared to the control group (ictal period $p<0.001$ and $p=0.001$, respectively)(interictal period $p<0.001$ and $p<0.00$, respectively)

Conclusions: The result of our study supports the existence of mitochondrial dysfunction in the pathogenesis of migraine in childhood.In addition, measurement of serum CGRP and GDF-15 in migraine patients can be used as a biomarker in the diagnosis and may contribute to new treatments to be developed in the prophylaxis of migraine.

Keywords:
migraine, mitochondrial dysfunction, childhood, CGRP, FGF-21, GDF-15, NOS

EPNS23-2159 Oral or e-Poster
Basic Science

Damage to Cerebellar Outflow Tracts Leads to Severe Dystonia, which can be Alleviated by Thalamic Neuromodulation via Deep Brain Stimulation

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Objective: Dystonia resulting from brain injury, referred to as secondary dystonia, is often refractory to interventions that are successful in primary dystonias. A subset of these acquired dystonias result from lesions to the cerebellar network, a pathophysiology which is relevant to dystonic cerebral palsy. The present study aims to model this form of acquired dystonia in the mouse, and test whether neuromodulation of brain network nodes upstream of the cerebellum can alleviate the dystonia.

Methods: Using stereotactic coordinates, a metal electrode was targeted to the bilateral superior cerebellar peduncles, delivering a 1600uAmp charge for 60 seconds to produce bilateral electrolytic lesions. Sham lesioning in which the electrode was targeted but no charge was delivered was used as control. Subsequent to lesion induction, dystonia was evaluated using the dystonia rating scale and nuchal electromyography. Deep brain stimulation was then used on lesioned and control animals to determine whether modulation of the broader network would affect the phenotype.

Results: Lesion targeting of the bilateral superior cerebellar peduncles was confirmed using nissl staining. Compared to the sham surgeries, bilateral lesions of the superior cerebellar peduncles produced overt and visibly severe dystonia. Subsequent 130Hz stimulation of the bilateral centrolateral thalamic nuclei significantly reduced the dystonia compared to the sham lesion mice in which electrodes were targeted but not used to deliver stimulation.

Conclusions: The various characterized forms of dystonia- genetic, structural, and idiopathic alike- are increasingly recognized to result from aberrant function of a common underlying dystonia network, which involves the basal ganglia, cerebellum, thalamus, and sensorimotor cortex. Here, we find that structural lesioning of the cerebellar outflow tracts is sufficient to produce severe dystonia. Furthermore, we find that deep brain stimulation of the upstream and convergent node in the dystonia network, the thalamus, is sufficient to alleviate the severity of the dystonia. This model may help inform our etiologic understanding of secondary dystonia in the pediatric population and open new avenues for neuromodulatory interventions in this notoriously difficult to treat population.

Keywords:
Cerebellum, dystonia, deep brain stimulation

EPNS23-2685 Oral or e-Poster
Basic Science

A glance at genes regulating sialylation in epileptic human brain tissue

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Objective: Background. In humans, glycoproteins and glycolipids forming cell surface are often terminated with sialic acids (SA). In sialylation, cytidine monophosphate N-acetylneuraminic acid synthetase (CMAS) synthetises SA while neuraminidases cleaves SA from glycoconjugates. Animal studies demonstrate that changes in neural cell sialylation are linked to neurological diseases, such as epilepsy. However, there is no data about human neural cell sialylation in epileptic human brain tissue. Objective. To characterise expression of genes that regulate sialylation in epileptic human brain tissue.

Methods: Human cortical and hippocampal tissues were resected from subjects who had only epilepsy or seizures along with other brain diseases (tumours, hippocampal sclerosis, cysts). Seizure free cortical access tissue was considered as non-epileptic control. RNA was extracted with RNA Purification Kit, RNA integrity was verified using Agilent 2100 Bioanalyzer with RNA 6000 LabChip kit, copy DNA was synthetized using First-Strand cDNA Kit. Neuraminidase 1 (NEU1), neuraminidase 3 (NEU3), neuraminidase 4 (NEU4), CMAS, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene expression was assessed with TaqMan real-time quantitative reverse transcription PCR using commercial primers. Comparative gene expression analysis (2^-delta-deltaCT) and statistical analysis was performed with SPSS 29.0, $p<0.05$ set as statistically significant.

Results: In total, nine cortical and three hippocampal samples from nine subjects were analysed. Adult subjects age ranged from 23 to 61 (median 29) years old, one sample was from paediatric 10-month old subject. In epileptic tissue vs. control, expression of NEU1 (1.13-fold change (FC) SD 0.27) and CMAS (1.07-FC SD 0.20) were similar ($p>0.05$). Epileptic tissue had lower expression of NEU3 (0.72-FC SD 0.22) and NEU4 (0.30-FC SD 0.06) vs. control and expression of NEU4 was significantly lower than NEU3 ($p<0.001$). Expression of NEU4 in epileptic tissue was significantly higher in female subjects (0.33-FC SD 0.04) vs. male (0.25-FC SD 0.04; $p=0.023$) and in paediatric subject (0.41-FC) vs. adults (0.28-FC SD 0.04; $p=0.036$).

Conclusions: Epileptic and non-epileptic human tissue had similar expression of CMAS, a pivot enzyme for SA synthesis. Desialylation regulating enzymes NEU3 and NEU4 were significantly less expressed in epileptic tissue. Epileptic tissue of paediatric and female subjects had significantly higher expression of NEU4 than of adult and male subjects.

Keywords:
Epilepsy; Gene expression; Glycocalix; Sialic acid; CMAS; NEU

EPNS23-2055 Oral
Basic Science

It's easier to relearn skills than learn them for the first time after injury: empirical evidence informing the Age at Injury debate

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Objective: The effect of age at injury on outcomes after brain injury have been long debated. Some argue that greater "plasticity" of the immature brain allow for better outcomes. On the contrary Hebb argued that "an early injury may prevent the development of some intellectual capacities that an equally extensive injury, at maturity, would not have destroyed", i.e. that it may be easier to preserve or recover function established before injury than acquire it for the first time after injury, which would imply poorer outcomes for younger children.

It is difficult to address the question empirically because injury etiology, size, extent and the presence of co-morbidities such as epilepsy are all to an extent also age-dependent and thus threaten to confound observational studies.

Methods: We used two datasets of Gross Motor Function Measure (GMFM) observations: one from a population-based sample of children with cerebral palsy (CP, n=537) and the other a cohort of children with brain injury sustained at later ages in a residential rehabilitation facility (acquired brain injury, ABI, n=74). The GMFM has 66 items of which can be rated from zero ("cannot attempt the task at all") through to 3 ("can perform the task easily") We performed separate, identical de novo Item Response Theory ("Rasch") analyses in these datasets, extracting and comparing the derived item difficulty estimates for the two populations.

Where direct comparison was possible GMFM items were also mapped to the Denver Developmental Screening Test to generate estimates of ages of skill acquisition in typically developing children

Results: Regression plots of the 198 item difficulty estimates (difficulty of achieving a 1, 2 or 3 for each of 66 GMFM items) showed strong correlation (adjusted r2 0.89, $p<<0.0005$) but significant bias with harder items, typically acquired at later ages, being achieved more readily by ABI children than CP children

Conclusions: Results support the Hebbian perspective of effects of injury in an immature brain: that at least in the context of gross motor function it is easier to maintain or recover a previously established function than to learn it for the first time in an already-injured brain. This argues for a more cautious prognosis for outcome after injury at a very young age.

This study also provides validation of the use of the GMFM in an ABI population

Keywords:
Gross Motor Function Measure (GMFM); Age at injury; rehabilitation; plasticity; Rasch analysis; Item Response Theory

EPNS23-2914 Oral or e-Poster
White Matter Diseases

Factors affecting the choice of immunomodulatory therapy in patients with pediatric multiple sclerosis from the perspective of the patient and caregiver.

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Objective: Immunomodulatory therapy radically changed the image of a patient suffering from multiple sclerosis. Treatment strategies indicate that the early control of disease activity is crucial to avoid disability and despite the risk of side effects the use of highly effective drugs is highly justified. The choice of disease-modifying therapy is therefore a challenge in clinical practice.

Methods: A survey was conducted among pediatric patients treated for multiple sclerosis in western Poland assessing the main factors that guide the patients and also their caregivers when faced with the choice of the best therapy.

Results: Most of the examined patients chose oral preparations for treatment. The most important factor that determined this choice was the way of drug administration.
Among the patients who chose the drug in the form of a subcutaneous injection the most important factor that determined the choice was the risk of possible side effects during the therapy.
Patients who chose ocrelizumab used as part of a clinical trial, at intervals favorable to the patient, followed the frequency of administration of the drug when deciding on treatment.
The range of side effects in each type of therapy was also analyzed.
Despite the occurrence of side effects none of the patients found this as a difficulty in the treatment.
Most of the patients believed that the treatment did not impair their daily functioning.
It was also examined what guided the caregivers of children with multiple sclerosis when choosing the appropriate drug.
Parents clearly more often chose the effectiveness and safety of therapy as one of the main factors determining the choice of the drug and the way of administration was less important but it was the most important factor for patients in choosing the drug.
Patients and parents were satisfied with the treatment. Factors determining satisfaction from the therapy were most often the effectiveness of treatment (no relapses in the course of therapy, stable picture of changes in magnetic resonance imaging) and ease of administration of the drug (most often it concerned oral drugs).

Conclusions: The most important factor influencing the choice of therapy among pediatric patients turns out to be the way of drug administration and the impact on everyday functioning, and for their caregivers the paramount value determining the choice is the effectiveness and safety of therapy. Fortunately, current treatment gives patients a wide range of options to choose the most personalized therapy.

Keywords:
multiple sclerosis, therapy

EPNS23-2786 Oral or e-Poster
White Matter Diseases

Leukodystrophy-Like Presentation in a Male Patient. A Case of Allan-Herndon-Dudley Syndrome

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Case study: Objective
The mutations in SLC16A2 gene encoding a monocarboxylate-transporter-8 (MCT8) have been implicated in a rare X-linked endocrine and neurodevelopmental disorder known as Allan-Herndon-Dudley syndrome (AHDS), formerly called MCT8 deficiency. The loss of the gene function can occur through various mechanisms. The milder forms manifest as mild to moderate global developmental delay and dysthyroidism. The severe forms though are characterized by profound early-onset hypotonia, nystagmus, dystonic movements, and progressive spastic quadriplegia as well as thyropathy. The subsequent health complications are numerous and may lead to an early death. Until present, there has been no effective treatment discovered for this condition.
The pathognomonic diagnostic sign for AHDS is the co-existence of a brain hypomyelination and abnormal thyroid-hormon profile. In affected individuals the MRI shows cortical atrophy and bilateral hypomyelination pattern in a young age, the latter showing a progressive improvement over time. Abnormal thyroid function is reflected by an increased free T3, low T4, and regular to high TSH levels in the serum. A free T3/T4 ratio, higher than 0,75 supports the diagnosis.
With this report of an additional case of an AHDS we would like to enhance the clinical phenotype of this rare disorder and underline the leading diagnostic clues.
Method
Retrospective study of the clinical course of the patient, who was hospitalized several times in our tertiary center, due to the worsening of his condition.
Case Report
We report an insidious clinical course (history, MRI, thyroid-hormone profile) of the recently deceased 20 years old male patient with genetically confirmed hemizygous SLC16A2 mutation. He presented with medical condition initiating a hypomyelinating leukodystrophy.
Conclusion
The concurrent presentation of a delayed cerebral myelination and thyroid dysfunction in a male child with developmental disorder should raise an index of suspicion for mutations in the SLC16A2 gene. Even in the case of increased access to advanced sequencing technologies, a thyroid-hormone profile is a helpful and easy to apply screening-marker in daily practice. The early diagnosis is crucial, since some of these patients can present with serious progression of the disease, causing high mortality rates and requiring intensive sociomedical support. Furthermore, the established diagnosis enables a genetic counseling of the affected families.

Keywords:
MCT8 deficiency, SLC16A2, Allan-Herndon-Dudley syndrome, MRI, hypomyelination, leukodystrophy, thyroid-hormon profile.

EPNS23-2782 Oral or e-Poster
White Matter Diseases

Distinct MRI pattern of cerebellar abnormality in VPS11 hypomyelinating leukodystrophy

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Objective: Pathogenic biallelic variants in VPS11 (vacuolar protein sorting 11) gene cause a severe form of hypomyelinating leukodystrophy (HLD) with evidence of lysosomal impairment.
As MRI pattern recognition is an essential diagnostic tool for HLD we reviewed the neuroimaging features of patients with VPS11-related HLD aiming to better delineate the cerebellar findings in this disorder.

Methods: Three male patients harboring c.2536T>G, p.Cys846Gly VPS11 homozygous variants (mean age of 4.6±2.1 years) were identified in the leukodystrophy clinic at Dana-Dwek Children's Hospital between June 2019-December 2022. Clinical, molecular and neuroimaging data were collected and reviewed. Brain MRI imaging were analysed: anatomic structures and lesion characteristics were systematically assessed and were compared to MRI scans of a cohort of 16 patients with molecularly confirmed HLD.

Results: Clinical manifestation included: global developmental delay, microcephaly, progressive visual impairment, spastic dystonic quadriplegia, and epilepsy in all, and hearing impairment in 2/3. Brain MRIs were performed at a mean age of 12.6 months (range 10-15 months) and revealed (i) diffuse reduced myelination with prevalent supratentorial involvement and (ii) thin corpus callosum in all subjects. All 3 patients were noted to have (iii) a distinct peculiar cerebellar abnormality with foliar anomalies in the inferior and posterior hemispheric regions associated with focal absence of the cerebellar cortex in the middle-anterior hemispheric portions. In addition, mild reduction of the volume of the inferior cerebellar vermis was present in all cases. When we compared these three MRI features to the cohort of HLD without mutations in VPS11, diffuse hypomyelination was observed in 3/3 vs 16/16, thin corpus callosum 3/3 vs 5/16 (p=0.058) and none of them demonstrated similar cerebellar folia abnormality 3/3 vs 0/16 (p=0.001).

Conclusions: Here we report distinct cerebellar imaging features in patients with VPS11 variants. These distinct features may aid in the clinical setting to distinguish VPS11 hypomyelinating leukodystrophies among hypomyelinating disorders.

Keywords:
VPS11 variants, hypomyelination, leukodystrophy, cerebellar abnormality

EPNS23-2631 Oral or e-Poster
White Matter Diseases

Myelin oligodendrocyte glycoprotein antibody disease (MOGAD) presenting with raised intracranial pressure and aseptic meningitis in a 7 year old child

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Case study: -Background

Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is the most recently defined inflammatory demyelinating disease of the central nervous system.

The clinical manifestations of MOGAD are heterogeneous, ranging from isolated optic neuritis or myelitis to multifocal CNS demyelination. A critical element of reliable diagnosis is detection of pathogenic serum antibodies MOG. MRI imaging can also help in differentiating MOGAD from other neuroinflammatory disorders.

-Case Presentation
A previously well south Asian 7-year-old boy presented with a 3-month history of nonspecific frontal headache without features suggestive of raised intracranial pressure. There were minimal systemic features: loose stools for one month, reduced appetite and fatigue. Systems examination and growth parameters were normal. Neurological examination was normal except for mild bilateral optic nerve swelling; there was no meningism. Further investigations included unremarkable routine blood tests, normal MRI brain imaging and a lumbar puncture with an opening pressure of 32cm of H2O, cerebrospinal fluid (CSF) white cells 68 (mainly lymphocytes), oligoclonal bands negative and normal chemistry. In view of ongoing clinical concerns, MRI brain 4 weeks later identified abnormal T2 signal bilaterally in the thalami with subtle bright areas in the subcortical white matter of the right parietal and frontal lobes. The changes were consistent with an acute demyelinating process. Subsequently Myelin Oligodentrocyte (MOG) antibodies were positive in the serum. He was treated with a course of oral prednisolone with an immediate improvement in symptoms. Follow up imaging taken 4 months later was normal.

Myelin Oligodendrocyte antibody disorder (MOGAD) is an inflammatory, demyelinating disorder of the central nervous system in children and adults. The course maybe monophasic or relapsing. The clinical phenotypes of MOGAD are heterogeneous and expanding. Recently, pyrexia of unknown origin and aseptic meningitis (without encephalopathy) have been reported at presentation with imaging changes appearing later in the disorder (ref Udani). To our knowledge, this is the first child reported with such a presentation in the United Kingdom. Paediatricians and child neurologists should be aware of this milder phenotype as treatment with corticosteroids is indicated.

Keywords:
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EPNS23-2364 Oral
White Matter Diseases

The Epidemiology of Acquired Demyelinating Syndromes in Latvian Children

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Objective: Acquired demyelinating syndromes (ADS) are immune-mediated demyelinating disorders of the central nervous system. ADS may have monophasic disease course or have relapses and are associated with specific antibodies leading to spectrum of different diagnosis. The aim of the study was to determine and evaluate different ADS incidence and demographic characteristics in Latvian children population.

Methods: This was a retrospective study and included Children's Clinical University Hospital (CCUH) patients with diagnosed ADS starting from 2010 till 2022, that represents all children in Latvia with ADS diagnosis. Clinical and demographic data were collected from medical history data system.

Results: Within a 12 year-period there were 28 children diagnosed with ADS. The annual incidence rate of ADS in this time period was 1.39/ 100 000 children. However, the majority 60.7% (n=17) received ADS diagnosis in the last 4-year period. Mean age of the study group was 13.8 ± 3.8 years, there was equal gender distribution (14 males /14 females). The majority 57% (n=16) were diagnosed with pediatric onset multiple sclerosis (POMS), followed by clinically isolated syndrome (CIS) in 10% (n=3), acute disseminated encephalomyelitis (ADEM) in 10% (n=3), transverse myelitis (TM) in 10% (n=3) and MOG antibody associated disease (MOGAD) in 7% (n=2); 1 patient received diagnosis of unspecified ADS. There was one patient, who initially was diagnosed with ADEM, however in follow-up fulfilled POMS criteria. Both MOGAD patients had relapsing disease course with multiphasic ADEM phenotype. Data showed that patients with ADEM/ MOGAD (n=5) are younger than POMS/ CIS (n=19), (mean 9.7 ± 4.6 years vs mean 15.2 ± 2.5; $p > 0.05$). Furthermore, there was female predominance in POMS/CIS group compared to MOGAD/ADEM group (11/19 females vs 1/5 females).

Conclusions: The incidence of ADS in Latvian children has increased in the last 4 years, most likely due to improved diagnostics and increased awareness. The incidence rate of ADS is consistent with that found in the literature. The most common ADS in Latvian children is POMS, followed by ADEM/ MOGAD. Older children and more commonly females are diagnosed with POMS/ CIS compared with ADEM/MOGAD.

Keywords:
Acquired demyelinating syndromes, POMS, ADEM, MOG

EPNS23-2232 Oral or e-Poster
White Matter Diseases

FURTHER PHENOTYPIC EXPANSION OF NUBPL-RELATED LEUKODYSTROPHY

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Case study: Objectives: Mitochondrial Leukodystrophies represent a heterogenous group of conditions. Some MRI features are typically observed and can be useful hints to the diagnosis. Biallelic mutations on NUPBL have been recognized as cause of a paediatric onset mitochondrial leukodystrophy characterized by onset at the end of the first year of life with motor delay or regression and cerebellar signs, followed by progressive spasticity. Early MRIs show white matter abnormalities with predominant involvement of fronto-parietal regions and corpus callosum. A striking cerebellar involvement is usually observed. Later MRIs show cerebellar involvement evolving to global atrophy and progressive involvement of brainstem. We report on a new patient who further expand the phenotypic spectrum of the disease and we perform a systematic literature revision.
Content: a 16 months old boy had onset during the first months of life with failure to thrive and mild neuromotor developmental delay. At the age of 8 months he presented with a rapid neurological deterioration with marked irritability, truncal hypotonia, pyramidal signs, swallowing difficulties. He lost postural control and was no longer able to smile or babble. Brain MRI showed a diffuse white matter abnormalities with bilateral cystic degeneration at the level of corona radiata. A mitochondrial leukodystrophy was suspected, muscle histological examination was normal while spectrophotometric measurement of OXPHOS complexes showed a marked reduction of complex I activity on both muscle and cultured fibroblast. Next Generation Sequencing (NGS) of a panel of genes associated with mitochondrial disorders demonstrated two heterozygous missense variants in NUBPL.
Conclusion: The phenotypic spectrum of NUBPL associated leukodystrophy is larger then previously thought. Clinical onset can be earlier and more severe and extraneurological involvement can be observed. Brain white matter can be diffusely abnormal, can progressively worsen and cystic degeneration can be present. Thalami can be involved. Basal ganglia can also become involved during disease evolution.

Keywords:
NUBPL, mitochondrial leukodystrophy, leukoencephalopathy, cystic degenration

EPNS23-2329 Oral or e-Poster
White Matter Diseases

Epilepsy and Multiple Sclerosis - a Clinical Conundrum

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Case study: Objectives: Multiple sclerosis (MS) and epilepsy are apparently 2 different pathophysiological entities, but they can certainly cooccur; our aim is to discuss the adversities of diagnosis of epileptic seizures with onset before or during MS through this case series.
Methods: We retrospectively scanned the hospital database for patients with confirmed MS and with history of epileptic seizures hospitalized in the last 5 years. We excluded patients with possible MS. We comprised data for 5 patients, including personal and family history, MRI imaging, EEG recordings.
Results: Out of the 5 patients, 3 are male. 2 out of 5 patients had epilepsy onset before MS diagnosis, in early to middle childhood, 1 with self-limited focal epilepsy of childhood and another with generalized epilepsy with focal features. The remaining patients exhibited prolonged symptomatic seizures during the course of MS. Valproate was used in 3 cases, levetiracetam in 1 case, intrarectal diazepam in 2 cases. Seizure control was obtained for 4 cases, only one of these requiring moderate-term antiseizure medication; 1 case developed polymorphic seizures over time, with flairs of uncontrolled seizures before each relapse. 2 patients feature particular ictal symptoms: on one hand short, frequent dystonic contractions, possibly non-epileptic, requires clonazepam and carbamazepine to become free of seizures, on the other conversive fits - considered a drug resistant epilepsy and requires treatment with valproate, clonazepam, carbamazepine. None have abnormal existing MRI before the onset of epileptic seizures. All have psychiatric and cognitive disturbances, and all have an aggressive course of disease, with MS onset <12 years; they all eventually require fingolimod, or even immunosuppressants as is the case for 1 patient.
Conclusions: This study highlights a possible bidirectional connection between MS and epilepsy in the pediatric population. It is now known that epilepsy and MS can accumulate lesions in both the gray and white matter, and in the context of MS seizures can exacerbate demyelination; our records show an aggressive burden of disease, onset < 12 years notwithstanding. Hence, MS lesions can become epileptogenic and require treatment. The MS clinical spectrum may include typical ictal symptoms, as seen in genetic epilepsies, but also atypical fits, pertaining to movement or conversive disorders; it is crucial to discern early in order to treat accordingly.

Keywords:
epilepsy, child, movement disorder, multiple sclerosis, conversive disorder

EPNS23-2541 Oral or e-Poster
White Matter Diseases

POLR1C pathogenic mutation finding in a neurologically asymptomatic patient with typical MRI brain abnormalities

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Case study: Objectives: To describe the case of a patient who, despite having brain lesions related to a pathogenic POLR3-related leukodystrophy mutation classically associated with neurological deficits, remained asymptomatic from a neurological standpoint.
Methods: We hereby present the case of an 8-year-old female who was referred to neuropediatrics due to unilateral left temporal hemianopia paroxysmal episodes, atypical for this disease. Her parents were consanguineous, first cousins. She had a normal perinatal history and psychomotor development. Her personal history included sporadic episodes of headache without alarm criteria, as well as celiac disease, myopia magna, hypodontia, delayed puberty and short stature. However, she had good academic performance and the neurological examination was unremarkable.
Results: The MRI exhibited diffuse and symmetric deep supratentorial white matter signal abnormalities with an anteroposterior gradient. As a result, a genetic leukodystrophy panel was run, revealing a pathogenic homozygous mutation in POLR1C: c.836G>A (p.Arg279Gln). Both parents were found to be heterozygous carriers.
Conclusions: This case underline the clinical and genetic heterogeneity of this disease. Additional genetic, epigenetic and/or environmental factors possibly influence the clinical outcome and phenotypic expression.

Keywords:
POLR1C, leukodystrophy, hypodontia, asymptomatic

EPNS23-2223 Oral or e-Poster
White Matter Diseases

The B side of intrathecal methotrexate. Case report

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Case study: Objectives
Methotrexate-induced Transient Encephalopathy is a rare neurological complication that affects patients receiving high-dose methotrexate (MTX), mainly in the context of intrathecal chemotherapy for onco-hematological malignancies. Sometimes clinical onset might mimic a stroke. Urgent neuroimaging and close monitoring are in most cases mandatory, including airway protection and Intensive Care Unit admission.

There is scarce evidence about specific therapies reducing MTX neurotoxicity. Herein we report a stroke-like case of methotrexate-induced neurotoxicity.

Methods
A 11-years-old girl with diagnosis of high risk lymphoblastic leukemia type B, receives a cycle of intrathecal therapy based on MTX, hydrocortisone, and cytarabine, as prophylaxis for central nervous system (CNS) involvement. Three days later, she developed rapidly progressive right hemiparesis plus paresthesias, later aphasia and drowsiness.

Code Stroke was activated and consecutive MRI and MR angiography were performed. No vascular anomalies or signs of ischemic or hemorrhagic stroke were shown. Nodular asymmetric white matter lesions in both centrum semiovale and corona radiata were revealed. Lesions shown high-intensity signal in T2 and FLAIR sequences, and marked restricted diffusion without gadolinium enhancement, compatible with cytotoxic edema.

Results
Radiologist concluded probable acute toxic leukoencephalopathy in relation to previous treatment with methotrexate.
Patient was moved to Intensive Care Unit. Theophylline and dextromethorphan was administered. Most symptoms improved within 30 hours, whereas slight paresis of the right lower limb took four more days to resolve. One month later, she was settled for next cycle of intrathecal chemotherapy. This time theophylline and dextromethorphan were given during the 48 hours before and after the infusion. Patient did not experience disease recurrence.

Conclusions
Methotrexate-induced Transient Encephalopathy may course with acute neurological deficit, in those cases, differential diagnosis between a stroke must be done. According to literature, deficits are mostly transient and resolution is complete. Due to the high benefit of MTX intrathecal as prophylaxis of CNS relapse in several hematologic malignancies, and the low rate of neurotoxicity recurrence, this complication should not stop following cycles from being administered.

Keywords:
methotrexate, encephalopathy, white matter lesions, intrathecal therapy, lymphoblastic leukemia

EPNS23-2498 Oral or e-Poster
White Matter Diseases

Pediatric Neuromyelitis Optica Spectrum Disorder: Case Series and Literature Review

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Objective: NMOSD is a central nervous system (CNS) inflammatory demyelinating disease characterized by recurrent inflammatory events that primarily involve optic nerves and the spinal cord, but also affect other regions of the CNS, including hypothalamus, area postrema and periaqueductal gray matter. The aquaporin-4 antibody (AQP4-IgG) is specific for NMOSD. Recently, myelin oligodendrocyte glycoprotein antibodies (MOG-IgG) have been found in a group of AQP4-IgG negative patients. NMOSD is rare among children and adolescents, but early diagnosis is important to start adequate therapy.

Methods: In this report, we present cases of seven pediatric patients with NMOSD and we review the clinical and neuroimaging characteristics, diagnosis, and treatment of NMOSD in children.

Results: This is a narrative review in which we have included original studies and case reports exclusively on pediatric patients with
NMOSD.
After the initial identification of 757 papers, we selected for the final analysis 41 manuscripts.

Conclusions: We have reviewed recent literature to provide a tool for diagnosing and treating children with NMOSD. These case reports are an example of the diagnostic and therapeutic complexity of pediatric NMOSD. Our cases, although limited in number, offer a wide range of personalized therapeutic strategies for the individual patient. Furthermore, our series also discusses AQP4-negative patients, unlike the other reviews that focus on AQP4-positive pediatric patients.

Keywords:
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EPNS23-2456 Oral or e-Poster
White Matter Diseases

Clinical and metabolic manifestations in Canavan disease - results from the PeriNAA study

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Objective: Canavan disease (CD) is a rare, severe autosomal-recessively inherited neurodegenerative leukodystrophy. It is caused by mutations in the aspartoacylase (ASPA) gene and consecutive accumulation of N-acetylaspartate (NAA), which results in impaired myelin development and function. Diagnosis is made by elevated NAA levels in the urine, blood, magnetic resonance spectroscopy, and molecular genetic confirmation. To date, no causal treatment exists to prevent progressive neurodegeneration and premature death. The physiological role of aspartoacylase and NAA is not yet fully understood. There is increasing evidence that it also plays a non-negligible role in the metabolism outside the brain.

Methods: The present study is conducted in the context of a research project (PeriNAA) funded by the German government to gain better knowledge of disease manifestations of CD outside the nervous system by retrospective analysis of clinical and laboratory data. We aim for a comprehensive understanding of the function of NAA in cellular metabolism and signaling using dynamic computational models.

Results: We report on clinical and metabolic manifestations in 44 CD patients with balanced sex (21 female, 23 male). The median age at symptom onset was three months (range 0-7) and six months at diagnosis (range 0-40). The most common pathologic variant was p.A305E, both in homozygous (n=14) and compound heterozygous (n=17) carriers. In six patients, only one known mutation was found. The most common symptoms at disease onset were: developmental delay (n=32; 73%), macrocephalus (n=21; 48%), nystagmus (n=21; 48%), and hypotonia (floppiness; n=20; 45%). Remarkably, two patients with an attenuated disease courses spared macrocephalus, whereas all other patients developed a head circumference of above the 97th percentile. In 28% (5/18) of the patients, beta-hydroxybutyrate levels were elevated in urine. The blood gas analyses showed decreased HCO3 (11/24; 46%) and pCO2 levels (8/14; 57%) and elevated lactate levels (10/14; 71%). The pH was normal or slightly decreased (6/14; 43%) in the patients.

Conclusions: Besides broadening the basis of clinical knowledge of CD our findings indicate that metabolic acidosis with respiratory compensation may play a role in disease manifestation or pathophysiology of CD. Further studies including further elucidation of pathophysiologic mechanisms of the disease are needed.

Keywords:
Canavan disease, leukodystrophy, disease manifestations, N-acetylaspartate, periNAA

EPNS23-2246 Oral or e-Poster
White Matter Diseases

An open-label trial of bioavailable-form curcumin on patients with Pelizaeus-Merzbacher disease

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Objective: Two preclinical studies on mouse models of Pelizeaus-Merzbacher disease (PMD) revealed potential therapeutic effect of curcumin. Here, we examined the effect of curcumin in PMD patients.

Methods: This study was approved by IRB of NCNP. We conducted an open-label oral administration of bioavailable form curcumin on 9 genetically confirmed PMD patients (5-20 years; mean 11 years) for 12 months (low doses for 2 months followed by high doses for 10 months). We evaluated changes in clinical symptoms as the primary endpoint using two scales, Gross Motor Function Measure (GMFM) and PMD Functional Disability score (PMD-FDS). The level of myelination by brain magnetic resonance imaging (MRI) and electrophysiological state by auditory brainstem response (ABR) were evaluated as the secondary endpoint. Safety and tolerability of oral curcumin were also examined.

Results: Increase in both GMFM and PMD-FDS were noted in 5 and 2 cases, respectively, but overall no statistically significant improvement was demonstrated. We found no clear improvement in their brain MRI and ABR. There were no adverse events associated with oral curcumin administration.

Conclusions: We failed to demonstrate significant therapeutic effects of curcumin after 12 months study period. Its tolerability and safety were confirmed. This study did not exclude the possibility of therapeutic effect of curcumin, and a trial with longer period should be considered in comparison with disease natural history.

Keywords:
Pelizaeus-Merzbacher disease, curcumin, treatment, hypomyelinating leukodystrophy

EPNS23-2623 Oral or e-Poster
White Matter Diseases

Clinical and genetic characteristics of KARS-related leukoencephalopathy

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Objective: Leukodystrophies are genetic disorders of the central nervous system white matter, which are most often incurable and often follow a progressive course with premature death. It has recently been reported that abnormalities in aminoacyl t-RNA synthetase (ARS) genes are linked to various unique leukodystrophies and leukoencephalopathies. Aminoacyl t-RNA synthetase (aa-RS) proteins are fundamentally known as the first enzymes of translation, catalyzing the conjugation of amino acids to cognate tRNAs for protein synthesis. It is known that certain aa-RSs have multiple noncanonical roles in both transcription and translation, and their disruption results in varied and complicated phenotypes.

Methods: We clinically and genetically studied seven patients (six boys and one girl; aged 2 to 12 years) from five unrelated families who all showed the same phenotypes of severe developmental delay or arrest, hypotonia, deafness and inability to speak. The subjects further developed intractable epilepsy and nystagmus with increasing age. They demonstrated characteristic laboratory data, including increased lactate and/or pyruvate levels, and imaging findings, including calcification and abnormal signals in the white matter and pathological involvement of the corticospinal tracts. To investigate pathogenic variants, we performed whole-exome sequencing and Sanger sequencing, enzyme assay and in vivo study using Xenopus embryos.

Results: Through whole-exome sequencing, we discovered genetic abnormalities in lysyl-tRNA synthetase (KARS). All patients harboured the specific variants of KARS either in the homozygous state or compound heterozygous state. Moreover, similarly disrupted LysRS proteins showed reduced enzymatic activities and abnormal central nervous systems in Xenopus embryos. Additionally, LysRS acts as a noncanonical inducer of the immune response and has transcriptional activity. We speculated that the complex functions of the abnormal LysRS proteins led to the severe phenotypes in our patients. These specific KARS pathologic variants are novel shared by all patients in the homozygous or compound-heterozygous state.

Conclusions: This common position may play an important role in the development of severe progressive leukodystrophy. Further research is warranted to further elucidate this relationship and to investigate how specific mutated LysRS proteins function to understand the broad spectrum of KARS-related diseases.

Keywords:
KARS gene, leukoencephalopathy, epilepsy, intracranial calcification

EPNS23-2173 Oral or e-Poster
White Matter Diseases

A novel mutation in the ABCD1 gene of a Greek boy with X-linked adrenoleukodystrophy: case report

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Case study: Background: X-linked adrenoleukodystrophy(X-ALD), is the most common peroxisomal neurodegenerative disorder in the world, resulted from the defect in the ATP-binding cassete protein subfamily D1(ABCD1) gene. ABCD1 gene locates in chromosome Xq28 and codes the adrenoleukodystrophy protein (ALDP). ALDP is an ATP-binding transport protein involved in active transport of very long chain fatty acids (VLCFAs) from the cytosol into the peroxisomes. Therefore, a dysfunction of ALDP induces an accumulation of VLCFAs in all tissues . This accumulation often leads to a neurodegenerative disorder in the nervous system's white matter, axons, adrenal glands, and testes.
Results: We report one case of a 9-year old male with a progressive central nervous condition and adrenal failure. The patient had a normal development with the exception of a speech delay, until he reached 9 years old when he suddenly showed psychomotor regression, walking difficulties, slow slurred speech and drooling.The neurological examination revealed hemiparesis of the right side of the body, , cerebellar ataxia, and dysarthria. MRI images were consistent with active demyelination: a high bilateral asymmetrical signal intensity was detected in T2 and Flair within the parietal-occipital area and the splenium of corpus callosum. The lesions may also involved the pyramidal tracts, the internal capsules and then extended in the white matter of the centrum semiovale. Serum cortisol and ACTH levels revealed that the adrenal glands were affected. VLCFAs analysis revealed high levels of C24/C22 and C26/C22 ratio in plasma. DNA sequence analysis of the ABCD1 gene revealed a novel hemizygous mutation: c.1178C>G (p.Thr393Arg. This mutation was of unknown clinical significance. Based on the clinical symptoms, neurologic signs, imaging, adrenal insufficiency and elevated plasma VLCFA, we suggest this mutation as a new pathogenic variant.
Conclusions: we identified here a novel mutation in the ABCD1 gene in a Greek patient causing X-linked adrenoleukodystrophy.

Keywords:
missense mutation, ABCD1, ALDP, VLCFAs, X-linked Adrenoleukodystrophy

EPNS23-2629 Oral or e-Poster
White Matter Diseases

Neurodegenerative Langerhans cell histiocytosis presenting as a mimic of Leukodystrophy

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Case study: Objectives: Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia with highly variable clinical presentation. We aim to describe a case of neurodegenerative Langerhans cell histiocytosis (ND-LCH) presenting as a mimic of Leukodystrophy.

Methods: A 6.10-year-old typically developed boy, presented at the age of 4.4 years with subacute progressing ataxia. Examination revealed spastic ataxic gait, tremor, dysarthria, with maximal SARA (scale for assessment and rating of taxia) score of 14/40, and optic disc pallor with minimal disc elevation. Brain MRI demonstrated prominent patchy white matter T2 hyperintensities, suggestive of a leukodystrophy. Chromosomal microarray, whole exome and whole genome sequencing were negative. Brain MRI pattern was assessed and reviewed and discussed among white matter experts.

Results: Brain MRI findings included: diffuse nonhomogenous white-matter hyperintensities involving corpus callosum, basal ganglia and deep white-matter and hyperintense signal involving the cerebellum and brainstem (FLAIR and T2); bulky choroid-plexuses; and a torcular mass (T1 with gadolinium enhancement). ND-LCH was suspected according to MRI pattern and neurological presentation with progressive cerebellar syndrome, although with no extra- neurological manifestations. Lumbar puncture revealed elevated pressure of 47 cmH2O and normal CSF level of protein, cell count, and lactate. BRAF-V600E mutation was detected in cell free DNA of CSF. Mass biopsy was not performed due to parents preferences. A diagnosis of central nervous system (CNS) LCH was made. Treatment with BRAF-V600E inhibitor vemurafenib resulted in marked radiologic and clinical improvement with a follow up of 2 years, SARA score at last assessment reduced to 5.5/40.

Conclusions: LCH-ND is a rare presentation of LCH with a neurodegenerative syndrome and a specific leukoencephalopathy-like pattern and can present without systemic involvement. ND-LCH should be in kept in mind in the differential diagnosis of CNS demyelination mimics, as prompt diagnosis and treatment is crucial.

Keywords:
Leukodystrophy, Neurodegenerative, Langerhans cell histiocytosis

EPNS23-2677 Oral or e-Poster
White Matter Diseases

The Spectrum of Paediatric Acquired Demyelinating Syndromes: A Single Centre Observation

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Objective: Paediatric acquired demyelinating syndromes (ADS) consist of a broad spectrum of immune-mediated demyelinating diseases of the central nervous system. MOG-abs have been identified in a variety of demyelinating syndromes, with a predominance in paediatric patients. Monophasic MOGAD presentations consist of demyelinating syndromes, including acute disseminated encephalomyelitis (ADEM), optic neuritis (ON) and/or transverse myelitis (TM), NMOSD-like phenotype, encephalitis like phenotype, whereas relapsing forms could also affect paediatric population. In this study, we aimed to identify patients with ADS, their demographic data, clinical features and treatment regimens, and outcome of longitudinal follow-up.

Methods: We conducted a retrospective chart review of all patients who were followed up with a diagnosis of ADS in Antalya Training and Research Hospital Paediatric Neurology clinic between January 2016 and September 2022. Demographic, clinical, laboratory and neuroimaging data of ADS patients were collected from e-records. Then, we identified patients who had a positive value for either AQP4 or MOG-abs.

Results: A total of 37 patients found to have a diagnosis of a demyelinating syndrome, 20 were female, with a median disease onset age of 15 years. Presenting symptoms in these 37 patients included impaired vision (11; 29,7%), headache (7; 18,9%), hemiparesis (5; 13,5%), speech disturbances (3; 8,1%), seizures (3; 8,1%), weakness of any limb (4; 10,81%), altered mental status (3; 8,1%), ataxia (2; 5,4%), dizziness (2; 5,4%), and had a final diagnosis of MS (13; 35,1%), RIS (7; 18,9%), ADEM (7; 18,9%), MOGAD (4; 10, 8%), TM (3; 8,1%), ON (2; 5,4%), CIS (1; 2,7%). Median time from first symptom to diagnosis was, 3 weeks for MOGAD. Waiting time for MOG-abs test result was the reason for the delay. Ten and twelve patients had positive results for oligoclonal bands and IgG index, respectively. Four patients had a positive MOG-abs results whereas no AQP4-ab was picked up. None of our patients had relapses during follow-up of median 3 years. Steroids, intravenous immunoglobulin, or plasma exchange were used in early stages of disease, 11 patients received Interferon Beta-1a and 2 fingolimod treatment. Two patients showed moderate deficit.

Conclusions: Variety of diseases which previously considered similar are established with discoveries of new biomarkers. As in ADS, we need biomarkers, in order to have a better understanding and differentiation of disorders with similar presenting symptoms.

Keywords:
demyelinating syndromes, fingolimod, interferon Beta-1a, MOGAD, multiple sclerosis,

EPNS23-2880 Oral
Basic Science

The Effect of Sodium Imbalance and Seizure on Hippocampal Damage in Rats

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Objective: An increase in the number and duration of epileptic seizures is associated with an increased risk of severe damage particularly in the hippocampal region. Hyponatremia and hypernatremia are electrolyte disorders commonly encountered in clinical practice. Low extracellular osmolality due to low sodium causes cell swelling, edema, deterioration in adaptation, and loss of myelination. As the number and duration of seizures increase, the risk of hippocampal damage increases. We aim to shown that all of natremia levels is supplemented wright approach to algorithm of seizures

Methods: A total of 100 Wistar-Albino rats aged 8-10 weeks weighing 250-350 g were included. Of these rats, 40 of them were treated with hyponatremia, 40 of hypernatremia, and 20 were normonatremic and all the rats were followed up for four to five days. Immunohistochemical Staining in Hippocampal Neurons and TUNEL Staining in Hippocampus were performed using Electron Microscopy with the markers including neuronal nuclear antigen/brain-derived/Neurotrophic Factor/S100/GFAP/myelin basic protein/allograft inflammatory factor/sodium/catalase/glutathione peroxidase.

Results: Hippocampal damage was greater in the hyponatremia group compared to other groups and was found to cause injury and vacuolization in myelinated axons.CA1 region affected in hippocampus changebility of sodium and seizure. TUNEL positive pyrimidal line cells increased apoptosis in hyponatremia groups. The duration and severity of the seizures were greater and the transition periods of the phases were shorter in the chronic hyponatremia and especially neuronal dejeneration and asrocyts death compared to the others group ($p<0.005$). Elektron microscopic was shown swelling and neuronal death, loss of myelination in choric hyponatremia.

Conclusions: There is no study in the literature reporting on how hippocampal damage occurs in the coexistence of these relationship of seizure and natremia. In the project presented, the number, duration, severity, and effects of a possible seizure on hippocampal damage in the presence of serum sodium imbalance were investigated. To this end, the duration and severity of seizures in the group with acute/chronic hyponatremia were greater, which was shown histopathologically as well. In conclusion, the importance of protecting hyponatremia against the effects of cerebral edema etc. indicated that the damage caused by even chronic hyponatremia should be included in the approach and support algorithm for seizures,natremia levels.

Keywords:
epilepsy,rat, sodium, approch, elektron microscpy, damage

EPNS23-2771 Oral or e-Poster
Basic Science

Neurological complications in children with acute lymphoblastic leukemia.

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Objective: Until the 1970s, more than half of children with acute lymphoblastic leukemia had complications from the central nervous system at all stages of therapy, as well as during remission. At the beginning of the 1970s, intrathecal prophylaxis and cranial irradiation of children with hemoblastoses were started, which led to a decrease in patients with neuroleukemia, prolongation of their life, and also an improvement in the quality of life of young patients. However, the use of intrathecal therapy, cranial irradiation began to lead to other neurological complications in the form of neurotoxicity in more than 80% of cases. Nowadays, neurotoxicity occurs in 3-13% of cases in children with ALL. Some of the most common neurological complications from both leukemia itself and drugs are stroke, Posterior Reversible Encephalopathy Syndrome (PRES), peripheral neuropathies, and neurocognitive deficits.

Methods: From September to December 2022, we observed 9 patients with acute lymphoblastic leukemia, who had neurologic deficits.

Results: Of these, 4 (44%) had PRES syndrome, which was confirmed radiologically and was manifested by headaches, convulsions, visual impairment, mental status disorders. MRI of the brain in T2 FLAIR mode showed damage to the white matter of the occipital region, which was characteristic of PRES syndrome. The pathogenesis of this condition is still unknown.
One patient had a hemorrhagic stroke during the induction phase (radiologically confirmed) when thrombocytopenia was noted in the form of single platelets.
Two patients (22%) were observed with epilepsy, in one of them, seizures were drug-resistant and continued at the stage of remission. Seizures were secondarily focal in nature. On MSCT, both patients showed calcifications in the basal ganglia, which were regarded by the radiologist as Fahr's disease.
In the last 2 (22%) patients, meningoencephalitis of cytomegalovirus etiology was noted against the background of agranulocytosis, the clinical picture was dominated by impaired consciousness with hyperkinesis, the diagnosis was made using MRI.

Conclusions: Our studies show a variety of CNS lesions in acute lymphoblastic leukemia. In all cases, MRI played a fundamental role in confirming the diagnosis, which allowed us to differentiate diseases similar in clinical presentation, such as PRES, stroke, meningoencephalitis.

Keywords:
PRES syndrome, acute lymphoblastic leukemia, neurological complications

EPNS23-2182 Oral or e-Poster
Cerebrovascular Disorders

Ischemic strokes due to arteriopathy secondary to Varicella Zoster Virus

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Case study: In children and adults, Varicella Zoster Virus (VZV) is a not uncommon cause of stroke. VZV vasculopathy in children appears to affect large vessels primarily, usually affects the A1 or A2 segments of the anterior cerebral artery (ACA), or the M1 or M2 segments of the medial cerebral artery (MCA) manifesting as TIA or stroke within 12 months of chickenpox
Methods
We report the case of a 10-year-old girl with migraine known to have focal segmental arteriopathy due to VZV. During 3 months, her hemicraneal headaches increases daily with difficulty speaking autolimited and vomiting, she has chickenpox 10 months ago. We reviewed recent studies of stroke associated with VZV vasculopathy and compare with our patient
Results
MRI angiography shows residual lesions (2) dependent on the distal territory of the left MCA. Small spotlights in the post-bifurcation M1 segment.
Resonance controls shows discrete, and short course of the M1 segment of the MCA left middle with decreased signal. Signal decreased in the proximal segment of the left anterior temporal artery.
Angiography: No angiographic signs suggestive of vasculitis were observed. A decrease in caliber at the beginning of the lower division of the left MCA is striking, in a segment of about 8 mm that presents a filiform caliber although with good distal filling, and which also does not seem to correspond to the territory where the lesion is located in the resonance.
Echocardiogram, blood and metabolic studies, with antibodys (ANA, ANCA, TPO, aquaporin 4, Tg), were normal. Serology were negative except IgG VZV, VEB and CMV positive.
In CSF PCR-amplified VZV DNA and herpes family, IgG, oligoclonal bands, albumin, Ac NMDA LGI1, CASPR2, DPPX, R-AMPA (GluR1), AQP4/MOG, myelin-associated oligodendrocyte were normal. IgG VZV was positive
Conclusions:
Diagnosis is confirmed either by the presence of VZV DNA or anti-VZV antibodies in CSF.
With the diagnosis of ischemic arterial infarcts in the subacute phase and clinically asymptomatic (headaches dissapeared), dependent on the distal territory of the left MCA, non-arteriosclerotic segmental focal arteriopathy due to VZV
Our patient was a migrant and was not vaccinated. She could be protected by vaccine from infection and therefore from secondary stroke
The onset of stroke or TIAs in children with varicella in recent months should alert the clinician to the possibility of VZV vasculopathy.

Keywords:
stroke, varicella zoster infection, headache

EPNS23-2941 Oral or e-Poster
Cerebrovascular Disorders

PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM - FROM ONSET TO OUTCOME

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Objective: The primary angiitis of of the central nervous system (PACNS) is a rare disease, affecting patients of all ages, with an average incidence estimated at 2.4:100.000 persons/year. In this paper we relate the difficulties encountered in the diagnosis and treatment of a boy, previously without neurologic history, who at 8 years old, presented multiple, recurrent acute ischemic strokes involving small vessels territory, secondary to a PACNS.

Methods: We made a retrospective analysis of the case file, the blood and cerebrospinal fluid workup and the imaging investigations.

Results: Based on the clinical picture we suspected a vasculopathy, so we performed various blood tests including a complete blood count, hepatic and renal markers, blood sugar level, coagulation disorders screening, an autoimmune and vasculitis screening which were all negative, only the inflammatory markers were constantly elevated. Also, the Magnetic Resonance Angiography was within normal range. Considering all these results, we suspected a small vessel vasculitis, so we performed a conventional angiography, which revealed a diffuse alternation in small arteries diameter with segments of stenosis with segments of normal diameter. There was no sign of systemic vasculitis. Based on these arguments, we established the positive diagnosis of PACNS. We initiated the treatment with immunosuppressants agents, which consisted in monthly administration of Cyclophosphamide for a period of 6 months, followed by daily Mycophenolate mofetil for 18 months. In present, at 3 years from onset, the patient is free of treatment and without neurologic deficits or disease relapses.

Conclusions: In conclusion, when you have clinical, paraclinical and imagistic arguments for PACNS, it is essential to start quickly the adequate treatment in order to have the best outcome.

Keywords:
primary angiitis, CNS, vasculitis, conventional angiography, treatment

EPNS23-2554 Oral or e-Poster
Cerebrovascular Disorders

Stroke After Bee Sting in a Child

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Objective: Local allergic reactions are frequently seen after a bee sting. Serious clinical findings can be rarely observed in sensitive individuals. We present a 14 year old boy who developed basilar artery thrombosis after bee sting.

Methods: The patient's clinical complaints, examination findings, laboratory and imaging results, follow-up and treatment results were evaluated.

Results: Six hour later after bee sting, symptoms started with blurred vision, headache, dizziness, and vomiting. Neurologic examination revealed gait and speech abnormalities, left central facial paralysis, oculomotor and abducens cranial nerve palsies and confusion. Brain magnetic resonance imaging showed ischemic areas with limited diffusion in the cerebellar hemispheres and in the upper part of the vermis, in the anterior part of the right half of the mesencephalon. Brain computer tomography angiography showed thrombosis in basiler and bilateral superior cerebellar arteries. Exclusive examinations for thrombosis did not reveal a pathologic finding. The patient was treated with low molecular weight heparin and acetylsalicylic acid. The patient was discharged with mild sequelae of left eye ptosis.

Conclusions: Although allergic reactions related to bee stings are frequently reported in childhood, rare presentations such as venous sinus thrombosis and stroke should be considered in case of unexpected neurological signs and symptoms. The exact mechanism of thrombosis in cases occury after bee sting is unknown.

Keywords:
child, bee sting, thrombosis, stroke

EPNS23-2019 Oral or e-Poster
Cerebrovascular Disorders

Relation of Post-stroke Headache to Cerebrovascular Pathology and Hemodynamics

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Objective: Despite the high prevalence of cerebrovascular stroke, headache attributed to ischemic strokes is often undertreated and overlooked. The aim is to detect the relation of a post-stroke headache to cerebrovascular pathology and changes in hemodynamics through a high-resolution duplex ultrasound examination.

Methods: This is a case-control study that was conducted in Kasralainy hospital, Cairo University, and Al-Azhar University hospitals from January 2021 to August 2021.The study was conducted on 239 patients who presented with an acute ischemic stroke. Patients were subdivided into two groups; Group I included patients with headache attributed to ischemic stroke (cases) and Group II included headache-free stroke patients (controls). History included headache characteristics and risk factors. Clinical and radiological examination were preformed to detect the type of stroke. Ultrasound duplex examination of the extracranial and intracranial cerebrovascular system was carried for both groups

Results: Group I included 112 patients , Group II included 127 patients . Post-stroke headache was more frequent in patients with posterior circulation infarction (58%). Post-stroke headache was reported within 7 days post-stroke in (61.6%) of patients. Pre-stroke headache was an independent predictor for post-stroke headache occurrence (OR=28.187, 95%CI; 6.612-120.158, P<0.001). Collateral opening and various degrees of intracranial vascular stenosis were strong predictors of headache occurrence (OR=25.071, 95% CI; 6.498-96.722, P<0.001).

Conclusions: Post-stroke-headache is a common phenomenon especially in patients with pre-stroke headache, history of old stroke, posterior circulation infarction, and large artery disease. This headache was of moderate-intensity with clinical characteristics of tension-type. The intracranial cerebrovascular pathological changes including opening of the collateral channels and variable degrees of stenosis of cerebrovascular systems were implicated in the production of that headache.

Keywords:
Post-stroke headache; cerebrovascular; hemodynamics; duplex ultrasound.

EPNS23-2657 Oral or e-Poster
Cerebrovascular Disorders

Pediatric neurovascular complication of SARS-CoV-2 infection: A Single Center Case-Series

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Case study: SARS-CoV-2 virus causing Coronavirus disease 2019 (COVID-19) like other coronaviruses mainly targets the respiratory system. In symptomatic patients, the most common manifestation is fever, fatigue, cough, and headache. Severe forms can present with pneumonia, acute respiratory distress syndrome, acute cardiac dysfunction, and multiorgan failure. Some studies have indicated an association between COVID-19 and neurovascular conditions. These studies report mainly adult patients with a severe course of the infection. SARS-CoV-2 infects the host through its CoV spike glycoprotein, which binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in the lungs, heart, and kidneys and in endothelial cells. In general, pathophysiological processes after COVID-19 infection can cause vascular affliction and microvascular dysfunction and coagulation abnormalities.
It is broadly believed that children usually have a mild case of SARS-CoV-2 infection. However, in connection with the prolong COVID-19 pandemic, we are more likely to see health conditions that have rarely been seen before and that share a common history of recent COVID-19. These cases are intended to present that the course of this infection may not always be benign and a longer period will be needed to assess the consequences of the infection. Further studies will certainly be needed to address the pathophysiological basis in an effort to ensure its optimal diagnostics and treatment in children.
This article presents a case series of 3 children who were diagnosed with cerebrovascular disease and whose common denominator was current or previous infection with SARS-CoV-2

Keywords:
Brain vasculopathy; COVID-19; Children; SARS-CoV-2; Stroke.

EPNS23-2303 Oral or e-Poster
Cerebrovascular Disorders

CLINICO-ETIOLOGICAL PROFILE OF PEDIATRIC STROKE FROM A TERITIARY CENTER AMIDST COVID-19 PANDEMIC

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Objective: There has been a sizeable spurt of pediatric stroke cases in the past 3 years due to the Covid-19 pandemic. Early recognition of pediatric stroke should lead to more rapid neurological consultations ,imaging, treatment and improved outcomes. This study delves into various parameters like demographic data , presenting features, etiology ,mode of investigations ,management and outcome of these children

Methods: This is a single-center prospective-observational study from a tertiary care center in India . All patients under 18 years admitted with primary diagnosis of stroke between November 2019 and November 2022 were included.

Results: A total of 21 cases were included (Arterial stroke in 14,venous strokes in 6 and one case of hemorrhagic stroke). Mean age at onset of symptoms was 4 years (0-13 years) with male preponderance (2.5:1).

Arterial ischemic stroke accounted for 66.6% (14/21 cases) with MCA territorial predominance. The major presenting clinical feature of arterial ischemic strokes were hemiparesis(100%) and facial nerve palsy(71%).Various etiologies established were Moya-Moya disease in 3,presumed perinatal stroke in 2,Childhood Primary Angitis of CNS (cPACNS) in 2,Neurological Sjogren syndrome(Anti-Ro51+) in 1,Pneumococcal vasculitis in 1,Inherited thrombophilia-2 (Protein C resistance) in 1 and idiopathic in 4 cases. Covid-19 infection was not associated with any of these arterial stroke cases.

Venous strokes (CVST)were seen in 6 of 21 cases accounting for 28.6%. Encephalopathy and signs of raised ICT were the presenting features in majority of these cases. Superior sagittal sinus was involved in two cases, transverse sinus in three and thalamic vein in one. Covid-19 infection with MISC in 67 % of venous strokes.

One case of hemorrhagic stroke secondary to SLE associated CNS vasculitis.

Enoxaparin & Aspirin in 4/14 arterial strokes, Enoxaparin & Warfarin in 5/6 venous strokes and Dabigatran in one. Steroids in all cases of CNS vasculitis and pulse cyclophosphamide in cPACNS.

Mortality in 2 arterial strokes, decompressive craniectomy in one ,recurrence in 3 (Moya-Moya-2,cPACNS-1)

Conclusions: This study obtained robust estimates of the spectrum of etiologies in pediatric stroke. While the overall trends in pediatric stroke rates by age-group were generally consistent, there was a large variation in incidence of CNS vasculitis and Covid-19 associated venous strokes. Further research is warranted to examine if this pattern is observed in other geographic regions.

Keywords:
Pediatric Stroke, Etiology, Covid-19

EPNS23-2476 Oral or e-Poster
Cerebrovascular Disorders

Secondary intracranial hypertension following sinus and jugular vein thrombosis in a four-year-old girl

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Case study: Objectives: Description of a previously healthy four-year-old girl experiencing unilateral mastoiditis (as complication of an acute otitis media), transverse and sigmoid sinus and internal jugular vein thrombosis, and secondary intracranial hypertension.
Methods: This case report describes the clinical course, treatment regime and outcome in a child finally diagnosed with secondary intracranial hypertension.
Results: Our patient reported right-sided earaches for five days, was diagnosed having an acute otitis media and treated with amoxicillin/clavulanic acid per os. Increasing ear- and headaches, persisting fever, and reduced vigilance led to a cranial MRI three days later which revealed mastoiditis, and transverse and sigmoid sinus and internal jugular vein thrombosis. The child was referred to our tertiary center for complication-free mastoidectomy, further treatment with ceftriaxone and clindamycin intravenously for the following three weeks, and heparinization for five days followed by rivaroxaban per os.
The girl's general condition improved, and inflammation parameters decreased. Two days later, the patient developed double and blurred vision due to bilateral abducens paresis, and ophthalmologic evaluation showed bilateral papilledema. Due to ongoing heparinization, lumbar puncture (LP) to evaluate CSF pressure was postponed, but treatment with acetazolamide was started with 50mg/kg/d. In the following days, vigilance decreased, and we decided to perform a diagnostic and therapeutic LP, revealing a CSF pressure of 60cm H2O. General condition of our patient improved significantly in the following days but decreased again after a week. LPs were repeated four times showing CSF pressures of 53, 60, 60 and 35cm H2O after one, two, four, and six weeks after first LP. Each time, 15ml CSF were withdrawn. After the second LP, acetazolamide was gradually increased to 100mg/kg/d. More than two months later, our patient does not report any headaches or other neurological symptoms while taking and is still taking acetazolamide. Follow-up cranial MRI is scheduled in five weeks.
Conclusions: Sinus and jugular vein thrombosis and associated secondary intracranial hypertension are rare complications of mastoiditis. Repeated lumbar punctures and highly dosed acetazolamide might be necessary to prevent operative procedures for intracranial hypertension like lumbo- or ventriculoperitoneal shunts.

Keywords:
intracranial hypertension; sinus and jugular vein thrombosis; mastoiditis

EPNS23-2874 Oral or e-Poster
Cerebrovascular Disorders

Internal carotid artery thrombosis following blunt head trauma: a pediatric case report

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Objective: Stroke is a clinical picture that expresses partial cerebral injury and neurological findings as a result of sudden occlusion or rupture (hemorrhage) in cerebral arteries or veins.
Unlike stroke in adults, which is mainly caused by atherosclerosis and thromboembolism, the pathogenesis of Acute Ischemic Stroke (AIS) in childhood is poorly understood. So there is a delay in diagnosis, and cases may still be underdiagnosed or misdiagnosed.We wanted to present a case of carotid, internal carotid artery thrombosis who applied to our emergency department with hemiplegia.

Methods: A six-year-old female patient was admitted to our emergency department with blunt head trauma. She was discharged after her neurological examination, and routine blood and imaging tests (cranial computed tomography) were standard.Shortly after discharge, she was admitted to our hospital again with focal seizures and left hemiplegia.Due to a history of blunt trauma, Diffusion-Weighted Imaging (DWI) and cranial magnetic resonance (MRI) examinations were performed.

Results: Diffusion-weighted imaging (DWI) and Apparent diffusion coefficient (ADC) taken with the suspicion of acute cerebral infarction showed a large infarct area in the right middle cerebral artery region.The right internal carotid artery (ICA) could not be visualized on MR angiography.After a short time, it is seen that the patient's clinical findings improve.We observed a dramatic and rapid development of some collateral flow after the onset of acute ischemic stroke.

Conclusions: Given the better plasticity of the brain in children, the prognosis of AIS in children is generally considered more favourable than in adults.The absence of focal insufficiency in the child despite extensive vessel thrombosis supports this view.

Keywords:
Acute Ischemic Stroke ,Diffusion-Weighted Imaging, Plasticity,Hemiplegia, Dramatic and rapid development

EPNS23-2161 Oral or e-Poster
Cerebrovascular Disorders

The importance of a multidisciplinary approach to pediatric stroke

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Case study: Introduction
Pediatric stroke is defined as stroke occurring in patients between one month and 18 years of age.About 10% of pediatric strokes affect vertebro-basilar circulation.The wide range of clinical presentations and low incidence of this disorder lead to diagnostic delays in children. We present the case of a five-year-old boy with basilar artery occlusion, treated by mechanical thrombectomy with excellent recovery.
Case report
A 5-year-old boy presented with acute hemiparesis of the left side of body, and a gradually deteriorating neurological state. Disease started day before with headache, leg pain and pain behind left eye. Initial brain CT was unremarkable.Hours after, his condition was worsening. A brain MRI scan showed a right pontine stroke, a right infarct at posteroparietal region, infarction on left thalamus, and complete occlusion of basilar artery and right posterior cerebral artery.Multidisciplinary team (pediatric neurologist, invasive neuroradiologist, neurosurgeon and anesthesiologist)decided that for child is lifesaving to do mechanical thrombectomy. Sixteen hours after the symptom onset, thrombectomy was done, which led to the complete recanalization of basilar artery. After the endovascular treatment, the patient was transferred to the neuropediatric intensive care unit under the continuous monitoring of vital parameters. We conducted a wide etiological study of the stroke. We have found positive serology for COVID IgG RBD, low protein S and on transesophageal echocardiography interatrial defect and thrombus in left atrial appendage.Genetics for coagulopathies (about 500 genes) were negative. Additionally, enoxaparin was started. The patient was discharged from our hospital on day 26 after the stroke, with discrete neurological deficit. In the 3 months of the neurological follow-up examination, there was a symmetrical activity of all the extremities. The MRI showed a normal perfused basilar artery without signs of new ischemia.
Conclusion
The non-specific clinical presentation, variable risk factors and pathogenesis of pediatric stroke made diagnostic uncertainty and management dilemmas. As a consequence, stroke is under-recognized in children and there can be marked delays in diagnosis. It's crucial to change approach in decision to make brain MRI/MRA to assist in the diagnostic work up, so we hope to empower the assessing pediatrician to make confident decisions and ultimately lead to better outcomes for pediatric stroke patients.

Keywords:
Pediatric stroke, occlusion, basilar artery, thrombectomy

EPNS23-2584 Oral or e-Poster
Cerebrovascular Disorders

Chickenpox - not as benign. A case presentation of paediatric ischemic stroke due to varicella vasculopathy

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Case study: Objectives:
The purpose is to present a common stroke risk factor in the paediatric population - vasculopathy due to the varicella-zoster virus.
Methods:
Case study of a 5 years old boy from Belarus that moved to Poland a year before symptoms presentation.
Results
A previously healthy child was brought to the emergency room due to the sudden onset of left limb paralysis and left facial nerve paralysis that started 20 hours before admission. PedNIHSS was assessed at 5 pts. No changes in D-dimer levels nor other basic laboratory tests were seen. The extended medical history interview showed that 7 months prior to the symptoms' onset child had chickenpox. The boy was not vaccinated against VZV.
In initial computed tomography ischemic focus with secondary edema in the semioval center was seen. Magnetic resonance imaging (MRI) and arteriography showed cortical arteriopathy of the right internal carotid artery (ICA), the medial cerebral artery (MCA), and the A1 part of the anterior cerebral artery (ACA) with contrast enhancement of the walls in addition to small ischemic changes in frontal, parietal, and occipital lobes on the right side. Antibodies against VZV in blood were confirmed.
The child was treated with acetylsalicylic acid and prednisone, early rehabilitation was introduced. In the following days, improvement in the neurological state was observed. At the hospital discharge, only a subtle weakness in the left limbs was present.
The boy was readmitted to the ward 3 months later for follow-up. Further clinical improvement was seen. The control MRI showed only subtle asymmetry of left/right ICA, improvement of peripheral endings of MCA, and stable changes in the right ACA. Only slight post-contrast enhancement of MCA and ICA was seen.
Regardless of the probable infectious cause of the stroke, the patient was screened for additional risk factors. Homozygotic mutation of both MTHFR genes was found (c.677C>T/ c.665C|>T/p)
Conclusions
Smallpox is a common risk factor for paediatric acute ischemic stroke that should be taken into account in patients with characteristic symptoms and history. In our opinion, early steroid treatment should be considered. In addition, we would like to emphasize that normal D-Dimer in children does not exclude stroke and that since paediatric ischemic stroke often proves to be multifactorial screening for additional risk factors is recommended.

Keywords:
paediatric ischemic stroke, varicella zoster, vasculopathy, arteriopathy

EPNS23-2940 Oral or e-Poster
Cerebrovascular Disorders

Acute Ischemic Stroke and Life-threatening Cerebral Edema in Two Pediatric Patients

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Case study: Introduction: Acute ischemic stroke (AIS) is one of the important causes of mortality and morbidity in children. Cerebral edema is a serious complication of AIS which may lead to increased intracranial pressure and herniation.
Methods: We present two pediatric cases of acute ischemic stroke who developed cerebral edema.
Results: Case- 1: A previously healthy 9-year-old girl was admitted to an outside center after falling from a slide. She had right-sided weakness. Initially, her doctors suspected brain hemorrhage, but brain computerized tomography (CT) scan showed no hemorrhage. Then, she was referred to our hospital. She underwent brain magnetic resonance imaging (MRI) which revealed acute ischemic infarct in left middle cerebral artery (MCA) territory, subsequently, low molecular weight heparin (LMWH) therapy was started. On the 4th day, she experienced generalized tonic-clonic seizure, hypertension and anisocoria; brain CT showed significant cerebral edema and midline shift. The patient underwent decompressive craniectomy and hyperosmolar therapy. She received anti-seizure treatment. She was hospitalized for 33 days and discharge with modified rankin scale (mRS) score 4.
Case- 2: A previously healthy 4.5-year-old girl had a generalized tonic-clonic seizure and developed right-sided weakness after the seizure, then referred to our hospital. On admission, confusion, aphasia and right hemiparesis were noted. She underwent brain MRI which revealed acute ischemic infarct in left MCA territory, then, LMWH therapy was initiated. Control brain CT revealed moderate cerebral edema and midline shift though she experienced no clinical worsening. She received hyperosmolar therapy. No decompressive craniectomy was required. Following a resumption of intravenous heparin, LMWH was switched. The patient was discharged with mRS score 2.

Conclusion: Cerebral edema after AIS is a life-threatening emergency. Difficulties in recognizing cerebral edema may cause a delay in treatment initiation. Qureshi et al. showed most of the patients experienced neurological deterioration due to cerebral edema within 48 hours of AIS. We repeated imaging in the first patient as clinical findings progressed, but in the second patient after 48 hours with no new findings, so we were able to capture brain edema at an earlier stage in latter. Our findings support not only close clinical but also radiological follow-up is essential due to the risk of developing cerebral edema in AIS.

Keywords:
acute ischemic stroke, cerebral edema, outcome

EPNS23-2809 Oral or e-Poster
Cerebrovascular Disorders

Cryptosporidium gastroenteritis and cerebral venous sinus thrombosis: two case reports.

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Case study: Introduction
Cerebral venous sinus thrombosis (CVST) is a rare entity in children. Known risk factors include otitis and mastoiditis, acute systemic illness with severe dehydration, bacterial sepsis and inherited prothrombotic disorders. Currently, cryptosporidium infections have only been known to result in CVST through severe dehydration. However the presence of other genetic or acquired risk factors may lower the threshold for the development of CVST. We present two cases of Cryptosporidium gastroenteritis with secondary CVST.

Case reports
Case 1: An 8year-old boy was hospitalized with a Cryptosporidium gastroenteritis and acute prerenal kidney failure. From then on, he complained of increasing headaches. After two weeks, he also suffered from diplopia. Clinical examination showed a left-sided n.VI paresis and papilledema grade 1. Intracranial pressure was 50 cmH2O. Magnetic Resonance Imaging (MRI) of the brain showed a cerebral venous sinus thrombosis in the right sinus transversus and sinus sigmoideus extending to the confluens sinuum and the vena of Labe. Treatment with low molecular weight heparin (LMWH) and acetazolamide was started. Prothrombotic screening showed a heterozygous prothrombin G20210A mutation, a known prothrombotic risk factor. Immunological screening was normal. Currently, he is treated with Rivaroxaban. Acetazolamide has been stopped. Now, the boy is symptom free.

Case 2: A 12year-old boy was hospitalized with anorexia and vomiting due to a Cryptosporidium infection. He suffered from mild dehydration and asthenia. During hospitalization he developed progressive frontal headaches and pain in his left lower leg. MRI of the brain showed a right-sided dural sinus thrombosis with vasogenous edema and a secondary right temporal hemorrhage. A venous thrombosis in the left leg was seen by doppler ultrasound. The patient was started on LMWH, which was subsequently switched to Rivaroxaban. Screening for prothrombotic risk factors was negative. Nowadays he is symptom free.

Conclusion:
Cryptosporidium gastroenteritis can be complicated by CVST in children who are affected by severe dehydration. We report two patients with a Cryptosporidium gastroenteritis who developed CVST with only mild dehydration. Basic immunological screening was normal. For one patient, an additional risk prothrombotic risk factor was detected. Our findings support the recommended screening for inherited prothrombotic risk factors in children presenting with CVST.

Keywords:
Cryptosporidium, Cerebral venous sinus thrombosis

EPNS23-2948 Oral or e-Poster
Cerebrovascular Disorders

Difficulties in cardiac evaluation and management of cryptogenic arterial ischemic in children - a case series

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Objective: The aim of this paper is to highlight the importance of a complete cardiac evaluation in children with arterial ischemic stroke (AIS) and the difficulties regarding in establishing and treating children with cryptogenic AIS.

Methods: We made a retrospective analysis of the cases files.

Results: We present 3 clinical cases of adolescents hospitalised in our department between February 2021 and December 2022 for AIS. P1, 12 years old female, with chronic kidney disease and multiple venous malformations presented two AIS of medium caliber arteries, in different territories: M2 segment of medium cerebral artery in February 2021, respectively A2 segment of anterior cerebral artery in November 2022, under antiplatelet medication. In her case, the cardiac ultrasonography, which was initially considered as normal, revealed a patent foramen ovale (PFO) after the second episode. P2, 16 years old male, presented an AIS in the M4 segment of medium cerebral artery in March 2022 and he also described a transient episode with aphasia and paresthesia about 1 year before the acute cerebrovascular event. His cardiac evaluation revealed a PFO, which was surgically corrected. The third patient, P3, 17 years old female, with no notable medical history, presented an AIS in October 2022, involving the posterior circulation (basilar artery thrombosis), and her cardiac evaluation also described a PFO that was later surgically corrected. For these 3 cases there was not identified other etiology for the AIS.

Conclusions: A complete cardiological assessment, performed in a specialized center, is indicated in the case of children with AIS, especially in cryptogenic strokes. In these 3 cases, the probable stroke's etiology was represented by PFO, and 2 out of 3 cases were surgical corrected, hoping to prevent the recurrence. The third case is on the waiting list for cardiac surgery. There are no clear international protocols regarding the surgical correction of PFO in cryptogenic stroke in children. The decision is made individually for each case, in multidisciplinary team, depending on the risk based on the clinical history, PFO diameter, PFO shunt and others.

Keywords:
cryptogenic, stroke, cardiac

EPNS23-2792 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Clinical findings from the study of pediatric patients with mutations in the KCNQ2 gene collected from three university neurological clinics in Athens-Greece

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Objective: The aim of the study was to record and attempt to correlate the clinical phenotype with the electroencephalographic paternities and the genotype of pediatric patients with a mutation in the KCNQ2 gene.

Methods: A retrospective qualitative study of neonatal and pediatric population harboring KCNQ2 epileptic encephalopathies was performed. The data was collected by 3 Pediatric University Clinics in Athens Greece during a period of 7 years

Results: Patients were divided in 2 clinical groups, those with Epileptic encephalopathy-EE (7/11) and those with Benign epilepsy-BE (4/11). Age range of seizure onset was 1-60 days with 81.8% of patients developing their first seizure within the first week of life and 18,2% beyond the neonatal period. Within the BE group 100% presented as focal epilepsy exhibiting asymmetrical tonic posturing, often accompanied by autonomic features), whereas in EE group 57% presented with the above clinical phenotype, 14% with salam spasms, and 28% with generalized myoclonic jerks. EEG at onset showed Burst suppression in all patients within the EE group. On follow up 14% patient continued to show a burst suppression pattern, The remaining 43% exhibited multifocal epileptiform discharges, 14% showed findings consistent with migrating epileptic discharges and 14% hypsarrythmia. EEG in patients within the BE group was overall normal. In the BE group all patients were seizure free at the last follow up. Within the EE group, 29% had seizure remission, while 71% presented therapy resistant seizures at their last follow up. Carbamazepine or oxcarbamazepin were tried in all of the EE group once genetic results confirmed KCNQ2 mutation, but only 2/7 responded, and only in one as monotherapy

Conclusions: With this study we aim to reveal that clinical and laboratory factors may contribute in predicting psychomotor outcome in patients with KCNQ2 mutations. The EEG Burst Suppression patter and the Frame shift mutation in the genotype increased the odds of developing psychomotor retardation by 33%, whereas the incidence of undergoing the first epileptic crisis >30 days by 30%. If the gene mutation is predicted to affect either transmembrane or extracellular part of the channel the risk of developing severe form of EE is increased. Although carbamazepine has been proposed as a targeted therapy for patients with mutations in the KCNQ2 gene, it did not have the anticipated results in our study group.

Keywords:

Epilepsies, KCNQ2

EPNS23-2538 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

What do doctors think when they think about seizures?

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Objective: Seizures are common and distressing presentations in childhood, which frequently result in hospital admission and which may herald an epileptic disorder. Accurate seizure recognition by clinicians is an important skill. However, experience of epilepsy is highly variable amongst doctors, and seizure misdiagnosis rates are high in secondary and tertiary centres.
In this study, we conducted a structured evaluation of doctor's EEG requests for children with suspected seizure. We aimed to understand how doctors conceptualise seizures based on the information provided and examine how key elements relate to test outcome.

Methods: We carried out a retrospective analysis of EEG referrals from general paediatric and paediatric emergency departments for first-time seizure presentation in children presenting between 2018 and 2020. Clinical seizure descriptors were coded and systematically examined for all referrals. A word cloud was developed for free text entries on the EEG referral form. Chi-square and Fisher's exact testing was used to examine the relationship between specific seizure descriptors and EEG outcome.

Results: 302 EEG requests were analysed. Children's median age was 3.4 years (range 0-16).
Motor features were described in the majority of referrals (64%), most commonly jerking/clonic movements followed by stiffening/increased tone. Sensory symptoms were described in only 6% referrals; affective and behavioural phenomena in 15 (5%).
Lateralizing signs were described in a minority (21%) although regional descriptors were provided in 78%.
Autonomic signs or colour change were described in 60 cases (20%). Isolated altered awareness or loss of consciousness was described in 34 referrals (11%). No semiology was documented in 16%.
Duration of the presenting ictus was recorded in just over half of referrals. Post-ictal clinical change was documented in 83 referrals (27%).
Epileptiform abnormalities were significantly more likely in children whose referrals had documented lateralizing signs, post ictal features, and which specified afebrile onset.

Conclusions: Seizure referrals from emergency and general paediatric doctors emphasise motor manifestations. Sensory symptoms are rarely described in relation to paediatric seizures and emotional and affective symptoms are rarely detailed. Granular semiological detail of seizure duration, evolution and post-ictal features, is frequently lacking. Such detail is useful, however, and predicts for EEG abnormality when provided.

Keywords:
seizure, diagnosis, EEG request referrals

EPNS23-2706 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

An application study of a refractory epilepsy screening tool for Lennox-Gastaut syndrome (REST-LGS) in pediatric neurology traniees

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Objective: The objective of this study is to assess the drug-resistance epilepsy cases with The Refractory Epilepsy Screening Tool for Lennox-Gastaut Syndrome (REST-LGS) and to identify its utility in the early definiton of LGS cases.

Methods: Using the modified Delphi Consensus, we applied the REST-LGS criteria, which consists of 8 criteria (4 major: upper than 2 seizure types, seizure onset under 12 years, history of electroencephalography (EEG) with generalized slow spike-wave discharges under 2.5 Hz, cognitive impairment since childhood; 4 minor: persistent seizures despite trial of upper than 2 antiseizure medications, history of vagal nerve stimulation, ketogenic diet or epilepsy surgery, seizure-related helmet use/head or face injuries, history of other EEG abnormalities), which are considered as potential indicators of LGS, to the patients we previously followed in our clinic with diagnoses of LGS, Doose syndrome, and refractory epilepsy. The data of 115 patients whose clinical evaluation was performed by a pediatric neurology mentor (HT) were reviewed with these criteria by pediatric neurology fellows (CBO-YA) with diagnostic blindness.

Results: Of 115 patients, two were excluded due to a lack of data or insufficient follow-up time. In a preliminary diagnostic evaluation of 113 patients, 49 were classified as Doose, 43 as LGS, and 21 as refractory epilepsy. When the application of the REST-LGS tool were applied, 108 of 113 patients (95.5%) met 1 to 4 major criteria. 11 of the 49 patients in the Doose syndrome group had upper than 3 major criteria and upper than 2 minor criteria. We thought that the differential diagnosis of Doose-LGS should be strongly reevaluated with clinical and electroclinical follow-up. The REST-LGS tool supported the diagnosis of LGS, as upper than 3 major criteria and upper than 2 minor criteria were met in 41 of 43 patients with a preliminary diagnosis of LGS. According to the REST-LGS tool, 52 of 113 refractory epilepsy patients should be strongly considered LGS.

Conclusions: Defining major/minor criteria in REST-LGS may be helpful in identifying patients with LGS. Thus, it reduces the risk of misdiagnosis and increases the chance of early treatment of the syndrome.

Keywords:

Refractory epilepsy, LGS, screening tool

EPNS23-2689 Oral
Epilepsy: Diagnosis and Investigations

Chalk that wrote by itself: case of focal epilepsy with ictal prosopagnosia?

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Objective: Prosopagnosia is rarely observed as an ictal symptom in focal epilepsy.

Methods: We present the case report of eleven-year-old boy whose dominant ictal symptom was a disturbance of recognition of familiar persons. Patient had suffered from focal epileptic seizures since the age of nine years. Seizures were focal cognitive with impairment of consciousness and progressing to bilateral tonic-clonic. Patient described not seeing familiar persons in the scene during seizures: "Mom, I can't see you". He saw a chalk that wrote by itself on a school blackboard, but he didn't see a teacher. He could see the car's gear lever moving during the ride, but he couldn't see his mother.

Results: Three ASMs were tested with an incomplete effect. MR, Video-EEG, PET, neuropsychological and fMRI examinations confirmed the epileptogenic lesion in the left temporal lobe basally. He was indicated for epilepsy surgery, due to drug resistance and cognitive deterioration (especially difficulties in learning the native and foreign languages). We performed a tailored temporo-basal resection on the left guided by multimodal neuroimaging and intraoperative electrocorticography. Histological analysis of the resected brain tissue proved ganglioglioma (WHO grade I) with FCD3B dysplasia in the adjacent cortex. The boy is now seizure-free for 10 months after surgery. His school performance and speech fluency have improved.

Conclusions: Prosopagnosia is described when specific areas are disturbed, namely fusiform gyrus (fusiform face area) and lower occipital gyrus (occipital face area). Temporal pole is also significantly involved in this visual function. We discuss the person recognition disorder in the context of complex visual disturbance including agnosia, neglect syndrome, and anopia.

Keywords:
epilepsy, seizures, neurosurgery, prosopagnosia

EPNS23-2611 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

The effects of SARS-CoV-2 infection and vaccination on disease course in children with epilepsy

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Objective: Background: Over the past year, a spectrum of neurological syndromes among patients with COVID-19 were reported. However, most of the reports do not specifically describe the effects of the infection on the course of epilepsy. Moreover, there is very little data on the effects of vaccination on the course of epilepsy. We conducted a cross-sectional study to evaluate the adverse events profile of the mRNA-based anti-COVID vaccination and to characterize the epilepsy course after acute infection with SARS-CoV-2

Methods: We conducted an observational cross-sectional study. The patient or their parent who visited our pediatric epilepsy center were offered to fill out an anonymous questionnaire on the effects of COVID-19 and the adverse events of the anti-COVID-19 vaccine. We included children with known epilepsy between the ages of 5 and 18 years. The questionnaire documented the date and clinical manifestations of each SARS-CoV-19 infection, dates and adverse events of each dose of the vaccination, and relevant clinical and demographic information

Results: One hundred and sixty patients with a mean age of 11.2 years completed the questionnaires. Seizures during the acute infection occurred in 17%, and the majority were a-febrile, with otherwise mild disease. No seizure exacerbation was noted over the week following 93 vaccination doses. The vaccination rate was lower than in the general population, especially in children under 12 years

Conclusions: In contrast to the minimal risk for seizure exacerbation following the vaccination, the risk for seizure exacerbation during an infection is substantial. Clinicians should reassure patients, parents, and caregivers regarding the low risk of seizures with anti-Covid-19 vaccination

Keywords:

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EPNS23-2268 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

In utero seizures - prediction of genetic epilepsy

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Case study: A girl aged 2 months has been admitted to the hospital because of repetitive tonic seizures with apnoea lasting for 10 sec, adversion to the right side and cyanosis. In the interictal period she showed good interactions and good skills appropriate to the age, but occasionally she had repeated movements - opening of the mouth, upgaze and nystagmus

The girl was full-term baby, born by Cesarean section, Apgar score was 8 and 9. Weight at birth was 3600g. She was sleepy after birth and developed seizure on 22nd hour of life - tonic episode with tremor. Interictally - hyperesthesia. She had 7 seizures during 2 first days of her life, was admitted to the ICU. EEG showed epileptiform activity over fronto - central - temporal region bilaterally. The girl had been diagnosed with neonatal seizures and after short trial of B6 was put on phenobarbital. MRI showed areas with blurred borders bilaterally periventriculary . Seizures stopped on phenobarbital (10mg/kg/day) so in 2 weeks the dose was tapered to 5 mg/kg/day.
Mother reported that she experienced a sort of trembling of the fetus in utero from 27 week of gestation
On admission phenobarbital had been increased to the previous dose but without success, levetiracetam failed too. Seizures repeated very often so the girl needed intensive care, there she developed refractory SE (resistant to diazepam, intravenous valproates).
Despite the absence of the genetic test result the most frequent genetic epilepsy of the period was suspected and iv phenytoin was introduced. Seizures stopped and the girl was put on carbamazepine (25 mg/kg per day) She is seizure free since then and acquires her milestones with some delay, occasionally she has dystonic movements
Genetic test results came in 2 weeks after introduction of carbamazepine (sequence analysis and deletion/duplication testing of the 1769 genes - multi-panel testing). It showed pathogenic variant in KCNQ2 c.1687G>A (p.Asp563Asn) .

Conclusion. In utero seizures are reported rarely and should be suspicious for KCNQ2 -related seizures

Keywords:
epilepsy, KCNQ2, carbamazepine

EPNS23-2795 Oral
Epilepsy: Diagnosis and Investigations

Epilepsy in children: Difficulties in diagnosis in Kazakhstan.

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Objective: Epileptic seizures can begin at any age - from the newborn period to old age. Convulsions are most common in children under 5 years of age, approximately half of all convulsions that occur in a person over his entire life occur at this age. It is at this age that the need for an adequate diagnosis of the disease is very high. Since with incorrect, long, ineffective, expensive diagnostics, and incorrect treatment, the number of resistant forms of epilepsy and the disabled people increases.

Methods: As part of the prospective research work on the topic: "The role of genetic factors in the development of epilepsy in young children in the Kazakh population" a preliminary analysis of the data of children with epilepsy under the age of 5 years and the absence of morphological brain damage confirmed by MRI of the brain was carried out. In total, the data of 404 children diagnosed with epilepsy were analyzed.

Results: We noted a significant predominance in the clinical picture of focal seizures - in 78% of cases. Also, according to our data, the incidence is highest in the first year of life. The onset of seizures occurred in patients in the first year of life - in 63.25% of cases. At the same time, it was noted that in our study, in 74.2% of cases, the age of the onset of generalized seizures falls at the age of 0-12 months. Infantile spasms occur in 9% of cases. Also, febrile seizures were noted in 10% of cases, which were diagnosed as epilepsy.

Conclusions: The prevalence of generalized seizures in the first year of life, the low frequency of infantile spasms, the presence of febrile seizures diagnosed as epilepsy shows us the lack of accuracy in diagnosis, as well as a large number of additional research methods. This increases the necessity to optimize diagnostic tactics.

Keywords:
epilepsy, epidemiology, Kazakhstan

EPNS23-2836 Oral

Epilepsy: Diagnosis and Investigations

A retrospective review of drug resistant epilepsy in children in South Africa

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Objective: Epilepsy is one of the commonest neurological conditions in children. Most children with epilepsy respond to anti-seizure medications (ASMs) but approximately 30% of children develop drug resistant epilepsy (DRE). DRE is defined as "the failure of adequate trials of two tolerated, appropriately chosen and used ASMs".

This study aimed to describe the clinical characteristics, aetiological factors and possible risk factors for DRE.

Methods: This was a single-centre, retrospective study at a quaternary level paediatric neurology centre. Data of children with DRE was extracted from a database of children with epilepsy identified between January 2015 and December 2019.

Age of diagnosis, gender, seizure types, aetiology, side effects to drugs, response to treatment, investigations and outcome variables were captured and analysed.

Results: 539 children with epilepsy were identified and 138 (25.6%) had DRE. 44(18.7%) were females and 94(30.8%) males (p-value = 0.002 and OR 1.93 (CI 1.29- 2.91)). 115 (24.1%) were African and 17 (34.7%) Indian. The mean age at diagnosis was 3.2 years. Of the children with DRE 52(32.3%) were between 1- 2 years old (p-value= 0.09, OR 1.53 (CI 0.94 - 2.5)).

Forty-nine (35.5%) patients with DRE had mixed seizures, 37(26.8%) had generalized tonic clonic seizures, 18(13.0%) focal seizures, 12(8.7%) epileptic spasms, 4(2.9%) atonic seizures and 2 (1.4%) tonic seizures. The aetiology was unknown in 65 (47.1%) patients, acquired brain injury in 33 (23.9%). None had a confirmed genetic cause.

MRI brain scans were abnormal in 95(68.9%) patients and 90(65.2%) had abnormal EEGs. Only 52 (37.7%) DRE patients had metabolic testing, 50 (36.2%) were negative and 2(1.4%) positive. The ketogenic diet was used in 6(4.3%) patients. 17 (12.3%) patients reported side effects to ASMs.

Seizure freedom was achieved in 40(29.0%) patients, seizure control in 52(37.7%), partial seizure control in 35(25.4%) and no control in 11(8.0%). Fourteen (10.1%) patients had no comorbidities and 72(52.2%) had comorbid global impairment.

The outcome of 59(42.8%) patients was remaining under paediatric neurology care, 34(24.6%) transitioned to adult neurology care and 37(26.8%) were lost to follow up.

Conclusions: In our study in a LMIC, 25.6 % of children with epilepsy had DRE. The factors associated with DRE were male gender, young age of 1-2years old, mixed seizures, an unknown aetiology and an abnormal MRI and EEG.

Keywords:
Drug resistant epilepsy

EPNS23-2513 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Cephalosporin-induced Nonconvulsive Status Epilepticus in a Pediatric Patient with Chronic Renal Disease

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Case study: Objective: The neurotoxic side effects of cephalosporins can cause both convulsive and nonconvulsive status epilepticus. Myoclonus, dystonic movements, tremor, asterixis, seizure, status epilepticus, encephalopathy, and occasionally coma are some of these neurotoxic adverse effects. Status epilepticus, and more specifically nonconvulsive status epilepticus (NCSE), is a well-known but uncommon side effect of intravenous cephalosporin therapy in pediatric patients with impaired renal function. Methods: we describe an 11-year-old boy who had chronic renal failure and who also had followed with the diagnosis of NCSE after taking cephalosporins, retrospectively.

Case: An 11-year-old kid was admitted to the hospital for peritoneal dialysis-related peritonitis while he was being followed-up for chronic renal failure caused by a posterior urethral valve. Ceftazidime and cefazolin renal dose were started, when peritonitis was diagnosed after his clinical evaluation. After using ceftazidime and cefazolin for four days, the patient became stuporous. His EEG revealed contionus 3 Hz generalized spike-wave activity , he was diagnosed with non-convulsive status epilepticus and benzodiazepine and valproate treatment was started alternately.After stopping ceftazidime and cefazole, clinical symptoms got better after two days. He was then identified as having non-convulsive status epilepticus caused by ceftazidime and cefazole. In the subsequent three months of follow-up, anti-epileptic medications were successfully stopped and the EEG findings were resolved.

Conclusion: To ensure appropriate and timely medical treatment with the awareness of the NCSE related with cephalosporins in pediatric patients with renal failure.

Keywords:

Nonconvulsive status epilepticus, cephalosporins, ceftazidime, chronic renal disease

EPNS23-2596 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

Neurological features associated with AKT2 mutations. A case report.

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Objective: AKT2 is a serine/threonine kinase involved in the mTOR pathway that plays a key role in regulating insulin's control of glucose metabolism. The pathogenic variant c.49G>A: p.(Glu17Lys) in AKT2 gene is a gain of function variant that has been reported in a few patients with hypoinsulinemic hypoketotic hypoglycemia. Dysmorphic features, abnormal fat distribution and variable neurological manifestations are inconsistently mentioned but precise clinical descriptions are lacking.

Methods: We describe a patient harbouring this mutation with special attention to his clinical features.

Results: The patient is a 13 years old boy born to non-consanguineous Colombian parents. He was recently evaluated at our clinic for cognitive impairment and suspected epilepsy. He was born prematurely at 34 weeks with a prenatal overgrowth (Weight: 3400 g, +4.01 SD, Lenght: 50 cm,+ 2.86 SD). Past medical history was consistent with mild global developmental delay. His parents reported frequent fits of uncertain nature since infancy, including episodes of arrested activity and cyanosis, bilateral tonic clonic seizures (BTCS) and nocturnal apneas. Previous CT scan and EEGs were reported as normal. On first examination at our clinic at age 12y, he showed remarkable dysmorphic features including hypertelorism, prominent bilateral exophthalmos with puffy eyelids and gynecomastia and an abnormal fat distribution consistent with lipodystrophy. EEG showed bitemporal epileptiform activity. Brain MRI showed fatty infiltration of ocular muscles but was otherwise normal. WES revealed the abovementioned de novo mutation in AKT2 gene. Endocrinological evaluation, including prolonged glucose sensor monitoring, demonstrated recurrent episodes of nocturnal hypoinsulinemic hypoketotic hypoglycemia associated with pallor, sweating and tremor which had not been previously noticed by the family. Prolonged videoEEG monitoring registered one of the longstanding reported episodes of 'nocturnal apnea', which proved to correspond to a left temporal epileptic seizures evolving to BTCS not associated with hypoglycemia.

Conclusions: Developmental delay/intellectual disability, lipodystrophy and characteristic dysmorphic features in children with hypoinsulinemic hypoketotic hypoglycemia should prompt AKT2 genetic testing. Seizures are also common and might be due to hypoglycemia or epilepsy. Early diagnosis may allow a better glycemic control and eventually improve the cognitive outcome of these patients.

Keywords:
AKT2, hypoglycemia, epilepsy,

EPNS23-2950 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Acetazolamide - an old but the first precision drug for CHD2-related epilepsy?

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Objective: To report two Georgian patients with variants in the CHD2 gene, displaying the typical features of CHD2-related epilepsy, including photosensitive and predominantly myoclonic seizures. Acetazolamide (ACZ) monotherapy reduced seizures in both patients by more than 95%.

Methods: We evaluated two patients with variants in CHD2 gene. Clinical history with particular emphasis on development, seizure type, frequency, and treatment response were reviewed. Long-term video EEG monitoring was conducted.

Results: Patient 1 is an 13 y.o. girl with moderate developmental delay, autistic features with early onset febrile seizures, followed by photosensitive epilepsy syndrome: with frequent myoclonic seizures, eyelid myoclonia with absences, and rare generalized tonic-clonic seizures refractory to the multiple anti-seizure medications. Genetic testing revealed a c.1934C>A variant in CHD2. Acetazolamide add-on has decreased seizure frequency by more than 95% with subsequent gradual withdrawal of Ethosuximide and Clobazam. The patient has been on ACZ monotherapy for more than 2 years with occasional seizures. Patient 2 is an 8 y.o. boy with normal development and with frequent myoclonic seizures and photosensitivity recorded on EEG. The c.236T>C variant was detected in the CHD2 gene by the epilepsy gene panel. Clonazepam and ethosuximide had transient efficacy, Levetiracetam was ineffective. Following ACZ success in patient 1, ACZ was added to the ETX with a dramatic reduction in seizure frequency. Patient 2 has been on ACZ monotherapy for 6 months.

Conclusions: Most Individuals with CHD2-related epilepsy remain refractory to treatment and require multiple anti-seizure medications. ACZ, a carbonic anhydrase inhibitor, reduces the excitability of cortical neurons and suppresses neural discharges in the Maximal Electroshock model. It has been approved for the treatment of epilepsy since 1953, but has been inadequately studied by current standards and its use has been limited. Apart its capacity to increase CO2 levels in the brain, ACZ has shown promise in the field of AQP4 regulation. Despite a small number of patients and the lack of functional studies, the promising results of our study warrants setting up the multicenter studies along with testing ACZ with different CHD2 epilepsy models. Animal studies using a zebrafish model of CHD2 deficiency are ongoing and are expected to yield additional insights into the anti-seizure efficacy and mechanism of action of ACZ with respect to CHD2-related epilepsy.

Keywords:

CHD2, Eyelid myoclonia with absences, Photosensitive epilepsy, Acetazolamide

EPNS23-2445 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

Optimal duration for recording pediatric EEG: an observational study

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Objective: To evaluate optimal duration for recording pediatric EEG in outpatient settings for children and adolescents aged 1month-18years

Methods: Setting: Outpatient EEG Laboratory at Department of Pediatrics at a tertiary care teaching centre in north India.
Exclusion criteria: Epileptic encephalopathy, non-epileptic indications, seizures within last 24 hours and critical sickness
Two categories of protocols
- Category A (awake record with activation procedures followed by sleep, total duration of 60 minutes)
- Category B (55 minutes sleep followed by 5 minutes awake for younger children and those with impaired cognition who cannot undergo detailed awake study, total duration 60 minutes)

Prospective EEG reporting at 20, 30, 40, 50 and 60minute time-points with no retrospective changes allowed at previous time-points.

Results: Population: 225 cases (category A, n=163, 140.6+/-38.7 months and B, n=62, 90.1+/-48.5 months) with 65% males.
Indications: Tapering antiseizure medications (ASMs) (54.2%), Diagnosis of new onset seizures (35.1%) and breakthrough seizures (10.7%)
Proportion with Diagnosis within 20 minutes
- Indication-wise (diagnosis within 20 minutes)

For tapering ASMs: Category A- 85.3%, Category B- 77.8%
Diagnosis of new onset seizures: Category A: 68.4%, Category B: 95.5% (p=0.04)
Breakthrough seizures: Category A: 72.7%, Category B: 76.9%
- Diagnosis-wise (diagnosis within 20 minutes)

Generalised non-structural: Category A- 90.9%, Category B: 100%
Generalised structural: 100% in both category A and B
Focal non-structural: Category A- 71%, Category B- 85.7% (p=0.05)
Focal structural: Category A- 77.5%, Category B: 66.7% (p=0.06)
- Abnormal awake records with and without sleep in category A

55% with and 81% without sleep achieved final diagnosis within 20 minutes (p=0.03)
- Abnormal records in category A with sleep achieved

77% generalised and 52% focal epilepsy achieved final diagnosis within 20 minutes (p=0.1)
- Abnormal records with sleep potentiation

54% generalised and 35% focal epilepsy with abnormal records showed sleep potentiation (p=0.2)

Conclusions: Conclusions: Considerable number of EEGs can achieve correct diagnosis within 20 minutes in both categories (A and B) of protocols. Recording beyond 20 minutes with sleep is particularly beneficial in newly diagnosed epilepsies, more so for focal epilepsies. If awake recording is extended beyond 20 minutes, inclusion of sleep improves yield of the EEG record.

Keywords:
EEG duration

EPNS23-2877 Oral
Epilepsy: Diagnosis and Investigations

Interictal epileptic activity and developmental outcome in KCNQ2-related epilepsy

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Case study: Background: We aim to describe a cohort of patients with KCNQ2-related epilepsy and evaluate the relationship between epileptic activity and developmental outcome. This
topic is relevant for the correct selection of clinical endpoints in future clinical trials, since cessation of seizures may or may not be the most important outcome.
Methods: This retrospective cohort study of children with S(F)NE and DEE due to pathogenic variants in KCNQ2 was conducted between 2019 and 2021. We collected clinical, therapeutic, and genetic information. All available EEG recordings were reviewed by a neurophysiologist. Gross motor function was determined using the Gross Motor Function Classification System (GMFCS). Adaptive functioning was assessed using the Vineland Adaptive Behavior Scales (main value: Adaptive Behavior Composite standard score (ABC SS)).
Results: Among 44 children (mean age 8.1±4.0 years, 45.5% were male), 15/44 had S(F)NE and 29/44 had DEE. Delayed seizure freedom was more frequent in DEE than in S(F)NE (P=0.025), but no correlation was observed between age at seizure freedom and developmental outcome in patients with DEE. Multifocal interictal epileptiform abnormalities at epilepsy onset were more frequent in DEE than in S(F)NE (P=0.014), and were associated with higher GMFCS levels (P=0.027) and lower ABC SS (P=0.048)in patients with DEE. Abnormal background activity at follow-up was more frequent in DEE than in S(F)NE (P=0.001), and was associated with higher GMFCS levels (P=0.009) and lower ABC SS (P=0.005) in patients with DEE.
Conclusions: This study shows a partial correlation between epileptic activity and developmental outcome in KCNQ2-related epilepsy.

Keywords:
KCNQ2-DEE, interictal activity, genetic epilepsy, neonatal seizures

EPNS23-2920 Oral
Epilepsy: Diagnosis and Investigations

Expanding Phenotype of Poirier-Bienvenu Syndrome: New Evidence from an Italian Multicentrical Cohort of Patients

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Case study: Poirier-Bienvenu syndrome (POBINDS) is a rare neurodevelopmental disorder caused by mutations in the CSKN2B gene, encoding a subunit of the CK2 casein kinase, involved in numerous mechanisms of neuronal growth and synaptic transmission. Most of the patients described in the literature manifest epilepsy as the main feature, associated with intellectual disability of variable degree. The phenotypic description of POBINDS is constantly increasing, but the wide spectrum of clinical variability makes diagnosis and follow-up extremely difficult for the clinician. We conducted a multicenter retrospective national observational study recruiting 13 patients with POBINDS, detected using next-generation sequencing panels or whole-exome sequencing. We reported 13 unrelated patients with heterozygous de novo mutations of the CSNK2B gene. All cases presented epilepsy, and ten patients were associated with a different degree of intellectual disability. Other features detected included endocrinological and vascular abnormalities and dysmorphisms. Clinical, laboratory,neurophisiology and neuroimaging data were reported for each patient in order to assess the severity of phenotype, and eventually, a correlation with the type of CSNK2B mutationAlthough it was not possible to assess a genotype-phenotype correlation in our patients, our research further expands the phenotype spectrum of POBINDS patients, identifying new mutations occurring in the CSNK2B gene.
The prevalence of POBINDS is underestimated and the extension of the WES with a larger number of genes would allow us a better diagnosis and a more accurate follow-up of the patients

Keywords:
CSNK2B, Epilepsy

EPNS23-2964 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Evaluation of Etiology, Diagnosis, Treatment and Follow-up Results of Patients With Epilepsy Under the Age of Two

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Objective: Although many etiological causes (genetic, structural, metabolic) have been identified for epilepsies starting underage of two years, a clear etiology cannot be determined in significant part of patients. Imaging and genetic-based studies in the early stages of life have a very important role in the etiology of epilepsy

Methods: Patients diagnosed with epilepsy under age of two between 2011-2016 and 2016-2021 in the Department of Child Neurology at Dokuz Eylül University were evaluated. Etiologies, seizure types, follow-up, treatment and prognosis of the patients were determined retrospectively from archive files. Patients with febrile, symptomatic and single afebrile seizures were not included in the study.

Results: The number of patients in Group1 was 328 and the number of patients in Group2 was 327. When evaluated in terms of the etiology of epilepsy, structural abnormalities were significantly higher in Group1 (Group1 n=113, Group2 n=98 $p<0.05$). In terms of the initial seizure type , the rate of focal seizures was higher in Group1, and generalized seizures were higher in Group2 (Group1: focal seizure n= 109, generalized seizure n=188; Group2: focal seizure n=71, generalized seizure n=256 $p<0.05$). Control of seizures with a single antiseizure drug was higher in Group2 (Group2 n=127, Group1 n=117, $p<0.05$). Neuromotor developmental retardation at the time of diagnosis (Group1 n=194, Group2 n=161, $p<0.05$) and mortality rates were significantly higher in Group1. The most common choice of antiseizure drug was phenobarbital between 2011 and 2016 and levetiracetam between 2016-2021. In Group 1, 7.3% (n=24) of the patients had a genetic diagnosis before 2016. In Group 2, the percent of patients with a specific genetic diagnosis was 10.7% (n=35).

Conclusions: The results of our study showed that the etiology, seizure classification and antiseizure drug choice changed over time. We suggest that this may be due to medical and treatment advances in medicine.

Keywords:
childhood, epilepsy, anti-seizure medication, prognosis

EPNS23-2002 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Effect of anti-seizure medications on thyroid function in children with seizure disorder in the age group of 6 months to 12 years - a cross sectional study

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Objective: To study the effect of antiepileptic drug (AED) on thyroid function in children with seizure disorder

Methods: A Prospective observational study was conducted from January 2019 to December 2021 among children aged 6 months to 12 years with new-onset seizure disorder on AED.Thyroid functions test,factors associated with thyroid dysfunction were analzed after 3 months of follow up.

Results: Among 126 children enrolled, thyroid dysfunction as subclinical hypothyroidism was found in 7 (5.6%) [95% CI 4.3-7.1%]. Median value of TSH in microIU/ml was 2.08 (IQR 1.41-3.31) at enrollment and 2.56 (IQR,1.65-4.14) at follow up with stastically significant p value of < 0.001.

Among children with thyroid dysfunction following results were observed

1.On comparing AED monotherapy with polytherapy group thyroid dysfunction was observed in 4 (3.2%) and 3 (2.4%) respectively.

2.Based on individual AED sodium valproate was observed in 3 (75%) followed by phenytoin in 1 (25%) of monotherapy group and sodium valproate and levetiracetam combination in 3 (100%) of polytherapy group.

3.Mean dose of phenytoin and sodium valproate noticed were 5mg/kg/day and 28.6mg/kg/day respectively.

4. Median months noted was 6 months with an IQR of 4-8 months after AED was started.

5.Median age observed was 10 years with an IQR of 7-12 years with statistically significant p value of 0.011.

Conclusions: AED significantly associated with thyroid dysfunction as subclinical hypothyroidism and was more common among children aged 7-12 years, taking AED for more than 6 months and with sodium valproate.

Keywords:

antiepileptic drug, seizure disorder, thyroid dysfunction

EPNS23-2061 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

A novel mutation in the GNAO1 gene causes a distinct phenotype of borderline-mild intellectual disability and rolandic epilepsy with EEG pattern of ESES

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Objective: GNAO1 mutations are traditionally considered one of the many genetic causes of early onset epileptic encephalopathy. De novo heterozygous mutations in GANO1 are reported to cause severe neurodevelopmental disorder, profound cognitive dysfunction and occasionally, movement disorder.

Methods: We report here on seven individuals from two related families (the mother of family A and father of family B are siblings), who harbour a new heterozygous GNAO1 variant (p.Met1Val; c.1A>G) with much milder and distinct clinical phenotype. This sequence change affects the initiator methionine of the GNAO1 mRNA

Results: Three siblings to non-consanguineous parents in family A, presented with rolandic epilepsy between 4-6 years of age, EEG pattern consistent with electrical status epilepticus in sleep (ESES) and borderline-mild intellectual disability. It is noteworthy that early development was reported as normal and they feature normal tone on neurologic examination with no movement disorders. The three affected siblings and the affected mother harbour the p.Met1Val variant identified through research-based exome sequencing. Segregation of this variant was consistent with the phenotype.

Three siblings to non-consanguineous parents in family B, presented with a phenotype similar to family A along with speech dyspraxia. The three affected siblings and the healthy father harbour the p.Met1Val variant identified through epilepsy panel.

Conclusions: In summary, we report a new GNAO1 variant with milder unique phenotype and incomplete penetrance pattern of inheritance which has not been reported yet in relation to GNAO1 mutations. Additionally, this variant may broaden the genetic landscape of ESES

Keywords:

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EPNS23-2069 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

A case of hyperthermic remissions in drug-resistant epilepsy

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Case study: There are only few reports in the literature when hyperthermia contributes to the reduction and even relief of epileptic seizures for the entire period of fever or for a longer time.

We report a case of 3 year- old girl that presented with recurrent epileptic seizures lasting up to 20 seconds with a change in consciousness, shuddering in the upper limbs with bringing the head to the chest and bowing in the lower limbs, loss of balance with falls. Sometimes seizures developed in the form of clusters (3-7 seizures in each series) with incomplete recovery of consciousness between seizures. Also were noted paroxysms with oromandibular and carpal automatisms and altered consciousness lasting up to 3 minutes with the frequency from 2-3 to 7-8 times a day.

The child was born at 8 months from second twin pregnancy with C section. Birth weight was 1800 gr. (the second child is a practically healthy boy). The child development up to 3 years corresponded to the age. Family history for genetic diseases was negative. Neurological examination reveals no pathological signs. The child has increased anxiety, irritability, aggressiveness, ignoring the appeals of others around her, unwillingness to enter into verbal contact. Routine EEG revealed generalized spike-slow wave complexes. MRI of the brain showed hyperintense on in the T2-T2 Flair in the right mesial temporal region that did not accumulate contrast.

Patient was diagnosed with symptomatic focal (temporal) epilepsy with complex partial and generalized (myoclonic-astatic) seizures.Levotiracetam , valproic acid and clonazepam had only short-term positive effect - for 5-7 days. At 4 years she had acute respiratory virus infection with fever. Parents noted a decrease, and then a complete relief of seizures for 1.5 months, the child's psycho-emotional status, behavior and speech improved significantly, so the parents stopped taking anticonvulsant therapy. After 1.5 months seizures resumed with the same frequency, which was accompanied by a pronounced progression of psycho-emotional, behavioral and speech disorders. Urinary and fecal incontinence appeared.

Thus,hyperthermia has a multidirectional effect on the brain and in some cases can have a positive effect on the course of epilepsy. The study of the pathogenesis of "hyperthermic" remissions in epilepsy in children opens up new directions in the understanding of epilepsy, and can serve as the basis for the research and application of new effective management methods.

Keywords:

epilepsy, hyperthermia, drug-resistant epilepsy

EPNS23-2457 Oral
Epilepsy: Diagnosis and Investigations

Morphometric magnetic resonance postprocessing analysis in pediatric epilepsy surgery

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Objective: Computationally aided Magnetic Resonance Imaging (MRI) analyses has gradually shown exceptional promise in epilepsy surgery. Among them, Morphometric Analysis Program (MAP) has demonstrated to increase the diagnostic yield of MRI. However, there is a lack of studies that have systematically explored its performance in a pediatric population. Aim of the study was to evaluate the potential role of morphometric MRI analysis in the diagnostic presurgical management of a cohort of pediatric patients, in order to improve selection for surgery.

Methods: We enrolled the patients aged 0-18 years with structural epilepsy admitted to our Epilepsy Unit from January 2021 to October 2022. Each case was reviewed in a clinical-radiological session and MAP was performed only if requested after the discussion. All patients underwent a 3 Tesla brain MRI with a dedicated epilepsy protocol. For MAP analysis, we used the volumetric 3D T1 TFE sequences. Morphometric analysis generated 4 volumetric maps: extension, junction, thickness and probFCD. The brain structures that deviated from a normal database appeared as areas of brightness. Descriptive analysis was used to evaluate MAP performance. Sensitivity and specificity were assessed for each morphometric map. Finally, we evaluated the percentage of accuracy of each morphometric map by dividing the patients for age (0-6 years and 7-18 years) to better understand the conflicting data between MAP and MRI.

Results: MAP evaluation was required for a total of 50 candidates for epilepsy surgery. 9 patients (18%) were classified as MRI-. 23 patients (46%) of 50 candidates underwent focal resections, with the majority of the patients with a FCD type II histology (13 patients, 56%). Sensitivity ranged from 44.74% to 60.53%, with the highest value for junction (60.53%), while specificity ranged from 75% to 100%, with the highest value for thickness (100%). We also compared the accuracy of the morphometric features between the age groups, highlighting how the concordance between MRI and MAP increased with age.

Conclusions: MAP showed a good sensitivity slightly inferior to what has previously highlighted in adults. Specificity was high. MRI and MAP data concordance increased with age. MAP could be a potential useful supervised tool in pediatric epilepsy surgery giving physicians major confidence in the presurgical evaluation. The algorithm could represent a noninvasive instrument supporting the electroclinical-radiological assessment.

Keywords:
Magnetic Resonance Imaging, Morphometric Analysis Program, pediatric epilepsy surgery

EPNS23-2697 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Genotype-Phenotype Correlation and Variability in MEF2C Gene Mutations

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Objective: The MEF2C gene is a member of the myocyte enhancer factor 2 (MEF2) subfamily of the MADS (MCM1-agamous-deficiens-serum response factor) gene family of transcription factors. MEF2C is particularly crucial during embryogenesis as it plays a role in multiple organ formation - myogenesis, neural crest formation, anterior heart field development, lymphoid development, neurogenesis, and synaptic formation, among other functions. These are rare mutations, associating a wide phenotype spectrum. This study aims to enrich the phenotypic spectrum , and to better asses the correlation between clinical picture and MEF2C variants.

Methods: A retrospective analysis of the cases with MEF2C variants diagnosed in the last 2 years was performed. The personal and family history, onset, type of seizures, associated signs and symptoms, EEG, laboratory and imaging findings of these cases were reviewed.

Results: 4 cases of MEF2C gene mutation were identified: 1 - whole gene deletion; 2- exons 2 and 3 deletion; 3 - nonsense mutation; 4 - microduplication of 5q14.3 region, including MEF2C gene. All children presented seizures with onset in the first year of life (2 - myoclonic seizures, 1 - tonic-clonic generalized seizures, 1- focal motor seizures). Seizures were controlled in 2 cases with valproate, in one case with levetiracetam, while the fourth case continues to present seizure under lamotrigine and phenobarbital. Global developmental and expressive language delay were observed in all cases. 3 children presented behavior particularities, with stereotype movements. 3 of the children associated cardiac malformation, cleft palate, respectively multiple respiratory infections. MRI showed white matter abnormalities in 3 cases, corpus callosum hypoplasia in one case, and intraventricular cyst in one case. On EEG were observed multifocal spike-wave discharges in 3 cases, while the fourth showed slow-wave generalized discharges. The most severe clinical picture was noted in the microduplication variant, while the pharmacorezistant epilepsy was noted in the exons 2 and 3 deletion variant.

Conclusions: This study brings additional data on the phenotype of MEF2C-related disorders and documents the severity of this condition, which can aid healthcare providers in diagnosing patients and delivering the best care possible to children and their families. The small number of cases introduces a bias in the interpretation of clinical-genetic correlation.

Keywords:

MEF2C, global developmental delay , epilepsy

EPNS23-2678 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

Developmental And Epileptic Encephalopathies: Phenotypic Spectrum and Genetics, Treatment Options, And Outcomes

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Objective: ILAE describes epileptic syndrome as "a characteristic cluster of clinical and EEG features, often supported by specific etiological findings." Epileptic encephalopathy (EE) is described as a severe type of epilepsy in which the epileptic activity itself impacts cognitive and behavioural impairments exceeding what is anticipated from the underlying pathology. The term of "Developmental and epileptic encephalopathy (DEE)" is used when the underlying genetic aetiology and frequent epileptic activity are both associated with regression or slowing of development. A genetic aetiology should be sought, there are more than 100 genes associated with DEEs and counting.

Methods: In this study, we aim to describe clinical features, EEG and MRI investigations, seizure types and discuss treatment options for DEEs. A retrospective chart review of 52 DEE patients, who are followed up in outpatient clinic of Antalya Research and Training Hospital Paediatric Neurology Department was performed. Patients who had a mutation in one of the genes that listed in OMIM, responsible for DEE were identified and presented.

Results: A total of 36 patients found to have at least one mutation in DEE responsible genes, 14 were female, with a median age of 8,5 years. 22 patients had their first seizure within the first year of life, 6 of them had first seizure in neonatal period. Most frequent presenting seizure types were epileptic spasms, myoclonic and focal/generalized tonic. DEE responsible variants were detected in SCN1A (6), MECP2 (4), CACNA1E (4), GRIN2D (4), CACNA1A (1), GRIN2A (3), CUX2 (1), SCN8A (1), TREX1 (1), SCN3A (1), CAD (1), STXBP1 (1), UBA5 (1), AP3B2 (1), GABRB3 (1), SLC13A5 (1), GRIN2B (1), PP3CA (1), SMC1A (1), SLC19A3 (1) genes. Most reported interictal EEG patterns were hypsarrhythmia, diffuse slow spike-wave pattern and multifocal discharges. Most preferred AED was levetiracetam for every age group, followed by valproic acid. Memantine used as a gene specific AED for GRIN2D patients, resulted with favourable outcome. VNS therapy was successfully used in 2 patients for AED resistant seizures. 5 patients had status epilepticus and required PICU admission. One patient died due to complications of intractable seizures.

Conclusions: Disclosing a specific genetic aetiology in these syndromes is highly important for patients, families, and researchers. Current disease specific therapies remain limited, yet a genetic diagnosis could lead to early therapeutic intervention using new or repurposed therapies.

Keywords:
autistic features, developmental epileptic encephalopathy, memantine, status epilepticus, VNS therapy

EPNS23-2929 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Clinical and genetic phenotypes in pediatric patients with double cortex syndrome

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Objective: Double cortex syndrome or subcortical band heterotopia is a rare neurological condition, caused by a neuronal migration disorder associated with the mutation of the DCX gene (doublecortin gene), located on the X chromosome. The clinical presentation includes treatment-resistant epileptic seizures and varying cognitive and motor impairment.

Methods: This is a retrospective, descriptive study, in which we analyzed 9 patients with double cortex syndrome followed in the Pediatric Neurology Clinic of the "Prof. Dr. Alexandru Obregia" Hospital between 2011-2022. Data collected from the digital database and patient medical records include sex, personal and family history, clinical and neurological features, genetic testing, age of onset and epileptic seizure semiology, response to antiepileptic drugs, psychological assessment, imaging (brain MRI) and functional investigations (EEG).

Results: The DCX gene mutation was detected in all patients who were genetically tested. Regarding cognitive impairment, 4 patients (44%) presented profound intellectual disability while 3 of them (33%) present borderline intellectual functioning and are well integrated in the community. All patients presented epileptic seizures, with onset between the ages of 2 months and 12 years, with varied semiology, from epileptic spasms to focal and generalized seizures, and variable response to antiepileptic medication, 88% being treatment-resistant.

Conclusions: Clinical phenotypes in patients with double cortex syndrome can vary significantly, both in terms of epileptic seizure semiology and response to antiepileptic medication, as well as neurological features and degree of cognitive disability. Genetic testing is useful for establishing genotype-phenotype correlations.

Keywords:

double cortex, DCX, epilepsy, brain MRI

EPNS23-2756 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

Phenotypic variability in a recurrent QARS1 variant

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Case study: Background: Aminoacyl-tRNA synthetases are a family of enzymes responsible for the precise attachment of amino acids to their cognate tRNA, ensuring correct protein translation. Biallelic variants in QARS1 are typically associated with severe, early-onset developmental delay, microcephaly and epilepsy. A milder epileptic phenotype has been linked with homozygosity compared with compound heterozygosity. We present two cases with the same homozygous missense variant, but presenting with different phenotypes, illustrating the complex phenotype-genotype association.
Cases: The first child was referred at the age of 8 years with a convulsive status epilepticus. He had a first focal seizure around 1 year of age, and had repeated similar seizures from then on. His development declined after the first year of life, and at referral he could only speak a few words, but walked independently. Head circumference was consistently between percentile 3 and 10. Brain MRI was normal but EEG showed sporadic multifocal epileptic activity.
The second child is a 13-month-old girl who presented with a cluster of focal to bilateral tonic clonic seizures during a febrile illness. After cessation of seizures consciousness remained altered and developmental regression was seen. Head circumference followed the 10th percentile since birth. Brain MRI showed diffuse white matter abnormalities, EEG showed a diffuse slow background without epileptic abnormalities, and metabolic work-up was normal. Currently, at the age of 18 months, she is crawling but has no verbal speech.
In both children, whole exome sequencing showed a homozygous NM_005051.3: c.1133G>A p.(Arg378His) missense variant in QARS1. The same variant was already described in homozygous state in a boy without epilepsy but with important motor delay, absent speech and white matter abnormalities on MRI (Johannesen et al., 2019).
Conclusion: Biallelic missense variants in QARS1 are mainly associated with a typical triad of progressive microcephaly, developmental delay and early-onset epilepsy. A milder or absent epileptic phenotype is described in individuals with homozygous variants in literature. The recurrent homozygous p.(Arg378His) variant indeed lacks an early-onset epilepsy, but is associated with both acute encephalopathy and developmental regression as well as with a developmental and epileptic encephalopathy, illustrating the complex phenotyping in QARS1-related neurodevelopmental disorders.

Keywords:
QARS1; DEE; TRNA-synthetases; progressive microcephaly

EPNS23-2413 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

A girl with CNKSR2-associated Epilepsy imitating Dravet Syndrome

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Case study: Introduction

Fever-associated seizures, especially in the presence of prolonged duration and/ or unilateral occurrence, are a typical presentation in patients with Dravet syndrome. Most of these patients exhibit a pathological mutation in distinct genes, especially SCN1A and PCDH19, the latter being identified especially in girls with clinical onset beyond the first year of life. Mutations and deletions involving the CNSRK2 gene have been recently found in patients with syndromic x-linked intellectual disability, poor language skills and epilepsy. An association with fever-induced seizures has been observed, although most of previously reported cases experienced well controlled course of their epilepsy. The electroencephalograms displayed mainly focal anomalies, partly with a specific pattern of continuous spike-and-waves in slow-wave sleep (CSWS). None of the reported patients showed clinical course resembling Dravet syndrome, as in our patient. Until this report only 3 symptomatic female children with CNSRK2 gene changes had been reported in the current literature, all of them having none or mild, age-limited epilepsy.

Case presentation

Here we report an illustrative case of a 2-year-old girl presenting with a heterozygous Xp22.12 deletion encompassing CNKSR2-gene, performed because of a high index of suspicion for a Dravet syndrome. Her seizures were initially triggered by fever, observed in the form of febrile status epilepticus as well, and became afebrile over time. She presented with psychomotor developmental delay, poor language skills for her age and active epilepsy with focal motor and non-motor seizures. Her EEGs showed characteristic bilateral regional spikes-and-waves, resembling centro-temporal spikes but none CSWS. The MRI was uneventful.

Conclusion

According to the current literature this is the first report on a girl with developmental delay and challenging course of a CNKSR2-related epilepsy. This case broads the knowledge about this genetically determined developmental disorder, and therewith enhance the phenotypical spectrum of this quite rare mutation. Furthermore, it contributes to the candidate genes causing Dravet syndrome since many patients show fever-sensitive seizures on the onset of epilepsy.

Keywords:

epilepsy, developmental delay, CNSRK2, Dravet syndrome

EPNS23-2109 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Interim results from a European real-world study in patients with Lennox-Gastaut Syndrome

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Objective: Lennox-Gastaut syndrome (LGS) is a rare, severe childhood-onset, developmental and epileptic encephalopathy characterized by high morbidity and mortality and presents with various etiologies making management complex, as seizure and non-seizure symptoms evolve over time.
Routine clinical data focusing on characteristics of LGS and its associated disease burden is lacking. We aimed to describe these in the LGS population in Europe, delineated by age groups.

Methods: Data were drawn from the Adelphi LGS Disease Specific Programme, a real-world, cross-sectional survey also comprising retrospective data, conducted in France, Germany, Italy, Spain, and the UK commencing July 2022. Neurologists (child and adult) completed record forms for consecutively consulting patients with LGS, providing data on demographics, clinical characteristics, and antiseizure medications (ASMs) use. Data was delineated into age groups: < 6, 6-18 and >18 years. Outcomes presented are based on an interim cutoff date of 24/11/22.

Results: Overall, 40 neurologists completed records for 139 patients with a physician confirmed LGS diagnosis. By age group: < 6y (n=18), 6-18y (n=63) and >18y (n=58), with a mean [SD] age of 19.1y [11.8]. 55% were male and mean [SD] age at first seizure was 4.2y [4.1]. Mean [SD] age at diagnosis of LGS was 5.9y [5.4] and prior to LGS diagnoses, 29% had a history of West syndrome (infantile spasms). Most reported seizures were atonic 70% (< 6y: 39%; 6-18y: 81%; >18y: 67%), bilateral tonic-clonic 62% (< 6y: 56%; 6-18y: 59%; >18y: 67%), and tonic 60% (< 6y: 50%; 6-18y: 68%; >18y: 55%).
Overall, severe/very severe mental impairment was reported in 29% of patients (< 6y: 11%; 6-18y: 30%; >18y: 34%). Severe/very severe physical impairment was reported in 22% (< 6y: 6%; 6-18y: 17%; >18y: 31%). The use of aids (i.e. wheelchair, feeding tube) was reported in 42% (< 6y: 35%; 6-18y: 36%; >18y: 51%). Overall quality of life was reported as good/very good in 6% of patients (< 6y: 6%; 6-18y: 5%; >18y: 9%). The mean [SD] number of ASMs administered for LGS was 3.5 (< 6y: 1.9 [1.1]; 6-18y: 3.6 [1.8]; >18y: 3.7 [1.9]).

Conclusions: Despite the number of ASMs available for the treatment of LGS, a substantial proportion of patients have diagnosed seizure and non-seizure impairments, increasing with age. Altogether, these data suggest an unmet need for therapies to target both drug-resistant seizures and non-seizure outcomes, to mitigate the long-term poor prognosis of LGS. Funded by UCB Pharma.

Keywords:

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EPNS23-2839 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Development of the Dravet Disease scale with Associated Neuropsychiatric Disorder (D-DAND) interview.

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Objective: Dravet Syndrome (DS) is a developmental and epileptic encephalopathy (DEE) characterized by the seizures' onset before 15 months old with the appearance of global neurodevelopmental disorder encompassing intellectual, psychiatric disability.These main comorbidities make the administration of standardized psychological evaluations difficult and for now, no suitable tests are available to evaluate properly the patients with DS' development. We developed an ecological, holistic, multiaxial tool D-DAND with an outlook of a lifespan assessment based on caregivers' interview and aiming to detect changes in patients with DS considering seizures and comorbidities.

Methods: This study is the joint work of two family associations of DS and two expert centers in rare and complex epilepsies. The team includes four child-neurologists, one child-psychiatrist, and three neuropsychologists. We drew on the known comorbidities to elaborate the D-DAND score. The interview is organized in 9 neuropsychiatric domains (global motor function, dexterity, alimentation, social interaction, communication/language, personal autonomy, primary functions, memory and academic learning, behavioral/emotional difficulty) and 1 medical domain including clinical and electrophysiological data. For the tool's validation, 6 standardized tests (VABS-II, CBCL, CARS-T, BRIEF/-P, SDSC) were administered concomitantly. A follow-up session is planned to assess the reliability of D-DAND interview. The inclusion criterion was the DS diagnosis with SCN1A mutation with a minimal age of 3.

Results: We included 69 patients from January 2021 to January 2023. The average age of the cohort is 12.8 years (y)(median:12.5 y; min-max:[3-34]. The DAND interview lasts 35 minutes(min) on average (median:30 min; min-max:[15-60]). Seventy-three percent of interviews occurred in one session whereas the others in 2. They were conducted at the hospital (68%), videoconferencing (26%), or both (6%). The interview with the neuropsychologist was administered to mothers (79%), fathers (6%), or both (13%). All interviews were fully answered as well as the concomitant tests.

Conclusions: We developed D-DAND interview for comprehensive neuropsychiatric assessment for DS patients adapted to their cognitive and behavioral profile. It has been already tested on a substantial number of patients in parallel with validated scores and interviews. Future steps will aim to explore its reliability to detect individuals' changes and expand it to other infancy onset DEEs.

Keywords:

epilepsy, cognition, evaluation, behavior, neuropsychology, psychiatry

EPNS23-2180 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Clinico-electrographic characteristics and classification of genetic generalized epilepsy in paediatric patients

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Objective: The objective is to study clinico-electrographic characteristics and classification of genetic generalized epilepsy (GGE) in pediatric patients at our center.

Methods: This is a single-center prospective observational study done across 5 years (August,2017 to August,2022). A total of 412 patients under 18 years of age attending pediatric neurology OPD at our tertiary care center were diagnosed with epilepsy out of which 75 (18.2%) were classified as having GGE. Sociodemographic features, clinical profile and EEG findings were evaluated.

Results: Electro-clinical data of 75 patients were analyzed out of which 42 were females and 35 were males (M:F ratio - 1:1.3). Mean age of seizure onset was 8.5 years. Most common seizure type was absence seizure (n=47,65.3%) followed by generalized tonic-clonic seizure (n=32,42.6%). Childhood absence epilepsy (CAE) (n=35,46.6%) was the most common epilepsy syndrome seen (n=35,46.6%) followed by juvenile absence epilepsy (JAE) (n=17,22.6%) and generalized tonic-clonic seizure alone (GTCA) (n=8,10.6%). Development delay was seen in 4%. Prior history of febrile seizures was present in 5.3%. Family history was present in 6.6%. Sleep seizures were seen in 4%. Generalized epileptiform discharges were seen in 93.3% while focal along with generalized discharges were seen in 6.7% patients. Generalized discharges were induced on hyperventilation and photic stimulation in 74.6% and 6.6% of patients respectively. Eye closure sensitivity was seen in 6.6%. Most common drug used was ethosuximide (50.6%) followed by valproate (38.6%). 92% (n=68) responded to treatment [74.6% with monotherapy and 16.1% with combination therapy) while 9.3% (n=7) had drug resistant epilepsy (DRE) (2-JAE, 2-Epilepsy with myoclonic-atonic seizures (EMAtS),2-Epilepsy with eyelid myoclonia and 1-CAE who responded to amantadine]. Neuroimaging was carried out in all the patients with DRE and was abnormal in 1 of them. Genetic testing was done in 2 patients with EMAtS and CAE which showed GRIN2A and CPA6 mutation respectively.

Conclusions: GGE is an umbrella term for a number of distinct and overlapping epileptic syndromes. Correct classification of GGE syndrome often depends on patient history, seizure semiology and EEG characteristics. A detailed history of seizures, in addition to EEG results, is critical in the classification of GGE.

Keywords:

absence seizure, childhood absence epilepsy, generalized tonic-clonic seizures, generalized tonic-clonic seizures alone, genetic generalized epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy

EPNS23-2710 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

The Effects of Antiepileptic Drugs on heart rate, QT interval, TpE interval and Tpe-QTc ratio in children with epilepsy

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Objective: The aim of this study is to evaluate the effects of antiepileptic drugs on the autonomic nervous system in terms of the electrical activity of the heart and cardiac arrhythmia tendency by calculating the QTd (QT dispersion) and Tp-e (Tpeak-Tend) interval in electrocardiography, which are considered markers of susceptibility to ventricular arrhythmia in children with epilepsy.

Methods: 145 patients diagnosed with epilepsy using carbamazepine, valproic acid, levetiracetam and 54 healthy children as the control group were included in the study. Electrocardiograms (ECG) of the patient and control groups were evaluated retrospectively, the effects of the drugs on heart rate, QT interval, Tp-e interval and Tp-e/QTc ratio, the possible differences between the drug groups compared to the control group and the differences in between the drug groups themselves has been examined statistically.

Results: A statistically significant difference was found between the drug groups and the control group in terms of QT interval (p=0.031). It was determined that the QT interval of the patients using carbamazepine (343,82±33,33) was statistically significantly higher than the patients using valproic acid (321,81±37,27) (p=0.020).

Conclusions: Although many studies are conducted on the ECG changes and underlying cardiac electrophysiological changes observed in pediatric epilepsy, their clinical significance is still not fully known. Our study will be important in terms of clinical use of these markers in the evaluation of arrhytmia tendency in childhood, and also in terms of raising awareness about cardiovascular system (CVS) comorbidities in the follow-up of pediatric patients with epilepsy.

Keywords:

Epilepsy, Carbamazepine, Valproic Acid, Levetiracetam, Ecg, QT Interval

EPNS23-2040 Oral
Epilepsy: Diagnosis and Investigations

The Cost Analysis of a 7-Year Cross-Section of Patients with Epilepsy in a Single-Center Child Neurology Outpatient Clinic: A Descriptive Retrospective Analysis

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Objective: The cost analysis of the 7-year cross-section of the patients in pediatric neurology outpatient clinic including patients with foreign nationality was investigated retrospectively.

Methods: In the cross-section of 7-year period between January 10, 2013 and January 10, 2020, the total number of admissions, the nationalities of the patients, and the cost of the hospital were analyzed retrospectively. SPSS 17.0 program (SPSS Statistics for Windows, version 17.0.; Chicago: SPSS Inc.; 2008) was used in the analysis.

Results: Between January 10, 2013 and January 10, 2020, the total number of applicants, the nationalities of the patients, and the hospital cost were analyzed. Of 3,338 patients, aged between 0 and 20 years with mean age of 8.7 years at admission to the child neurology had received 17,476 clinical examinations. The total cost of cases with epilepsy was 1,312,427.73 Turkish Lira (TRY) and 6.2% account belonged to foreign nationals, mostly from Iraq (3.6%, n ¼ 119) and Syria (2.4%, n ¼ 80). The highest proportion of foreigner admissions due to epilepsy was in 2018 (11.1%). Mean average of health expenditures for foreign nationals diagnosed with epilepsy was 6.2% with the highest expenditure in 2019 (27.750,06 TRY). The proportion of admissions for epilepsy was 27.6% (17,476/63,173) among all neurolog ical admissions. The proportion of Turkish patients was 25.6% (6,181/63,173), and 3.8% (1,295/3,398) accounted for foreigners' admissions. The proportion of total epilepsy costs compared with the total neurological admissions was 30% (1.312.427,73 TRY/ 4.347.592,80 TRY) and among them, the expenditure proportion for epilepsy inTurkish patients compared with that of total foreigner admissions was 3.9% (80.416,44 TRY/ 201.490,515 TRY).

Conclusions: Expenditures for evaluating of epileptic children with foreign nationality cover an average of 6.5% of the entire section of the health expenditures made for patients with the diagnosis of epilepsy in the pediatric neurology outpatient clinic over the 7-year period. Epilepsy accounts for 30% admissions among all neurological admissions with 3.9% belonging to foreign national admissions.

Keywords:
health services , child , adolescents , foreign nationality , refugees

EPNS23-2619 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Extreme photosensitivity and self-induced seizures with dramatic response to Lorazepam: expanding phenotype of WDR45 encephalopathy

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Objective: Introduction: Pathogenic variants in the WDR45 gene cause a broad range of neurodevelopment and neurodegenerative disorders. Epilepsy occurs in a substantial portion of patients ranging from 66-75% in adults to 91% in children. In addition to developmental delay, the main feature in adults is dystonia. At the same time, the major phenotype of paediatric patients is epilepsy, varying from infantile spasms, febrile seizures, focal seizures, and drop attacks to myoclonic seizures.Purpose: to delineate the new and previously unreported features of WDR45 epileptic encephalopathy.

Methods: We evaluated a 10 y.o. female with mild developmental delay and epilepsy. Clinical history with particular emphasis on development, seizure type, frequency, and treatments was reviewed. Long-term video EEG monitoring and MRI were conducted. The epilepsy gene panel was performed.

Results: Here we report female patients with de novo missense variant (c.183C>A) in the WDR45 gene. The Epilepsy course started with febrile status epilepticus onset at the age of 3y, followed by polymorphic seizures, resulting in predominantly myoclonic seizures and extreme photosensitivity. MRI showed bilateral hypointense signals in the substantia nigra and globus pallidus - the characteristic sign of WDR45 encephalopathy. On EEG focal and generalized interictal spike/polyspike wave complexes and focal slowing at the left temporal area were seen.Frequent spontaneous as well as triggered by intermittent photic stimulation absences with eyelid myoclonia were recorded. Interestingly, self-induced myoclonic absence provoked by voluntary eyelids blinking were recorded. A similar epileptic phenotype is described in a number of patients with SCN1A encephalopathy/Dravet syndrome as well as variants in PCDH19, SCN2A, SCN8A, SCN1B, GABRA1, GABRG2, GABRB3, STXBP1, HCN1, CHD2, and KCNA2 related epilepsies, but not in WDR45 epilepsy. In our case adding oral Lorazepam to Ethosuximide, the photosensitivity fully disappeared and the total frequency of seizures was dramatically reduced. Such a course of epilepsy and the response to oral Lorazepam have not been described previously in WDR45 encephalopathy.

Conclusions: Epileptic encephalopathy accounts for 90% of children with WDR45 variants. Prominent photosensitivity and self-induced seizures in WDR45 epilepsy have not been reported so far. Oral Lorazepam is likely to be a useful add-on treatment to control seizures in WDR45-related epilepsy.

Keywords:

WDR45 epileptic encephalopathy, Self-induced seizures, Photosensitive seizures, Lorazepam

EPNS23-2823 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Optimization of clinical approaches in patients with epileptic encephalopathy and continued spike-wave activity during sleep.

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Case study: Objective: To determine neurophysiological and genetic diagnostic changes in children with epileptic encephalopathy and continued spike-wave activity during sleep (ESES) and assess targeted treatment effectiveness.

Methods: We have used medical records of 110 children from 1-17 years old with epileptic seizures and continues spike-wave activity during sleep (CWS). In this study, ESES is defined as CWS in non-rapid eye movement (non-REM) sleep of more 65% children. All appropriate candidates then passed next generation sequencing of exome test (NGS).

Results: Complete data were available in 10 children. Age at ESES diagnosis ranged from 30 to 188 months, average result was 68 months. 42 % of the patient were on one or more antiepileptic drugs (AED) at the time of ESES diagnosis. Antiepileptic drugs were used as first treatment for ESES in 73%. Electrical and neurophysiologic changes according to medical record were next, in 45% of all patient had CWS ($p < 0.05$). 3 patients passed NGS test, 66% had GRIN2D variant. To one of them was administrated targeted treatment.

Conclusion: Results of our research demonstrates the clear link between CWS on electroencephalogram, clinical presentation of ESES and genetic changes (like GRIN2D mutation). We found high failure rate of first-line AEDs in preventing ESES. Standardization of ESES management and diagnosis should become important question and needs more clinical researches.

Keywords:

ESES; Epileptic encephalopathy; Continuous pike-wave activity during sleep.

EPNS23-2474 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Diagnosis, management and follow-up of pediatric epilepsy in resource-limited countries: an observational study in Tanzania

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Objective: The main objectives of our study were to classify epilepsy in a newly established epilepsy clinic for children and adolescents in Tanzania as well as to provide suggestions on how to deal with the lack of diagnostic tools in Low-and-Middle-Income Countries. We also aimed to improve the diagnostic work-up and the management of pediatric epilepsy in a resource-limited country.

Methods: We conducted an observational study between April 2022 and October 2022. 120 patients were admitted to our clinic according to the following inclusion criteria: (1) age between 0 to 18 years; (2) known or suspected diagnosis of epilepsy. All patients underwent a medical consultation including anamnesis and neurological examination. Diagnosis was made according to ILAE criteria and management was decided according to medical experience, drugs availability and affordability. For 47 patients the EEG was recorded. Data were collected by using Kobo Toolbox and analyzed through RStudio software.

Results: 64 patients out of 120 (53.33%) were already under treatment and the largely used antiepileptic drug was Phenobarbital (42.5%) followed by Carbamazepine (17.5%), Sodium Valproate (13.33%), Phenytoin (3.33%) and Lamotrigine (0.83%). The diagnosis of epilepsy was reached in 78 patients (65%). 52 of the confirmed cases (66.67%) were diagnosed with Focal epilepsy, 20 (25.64%) with Generalized epilepsy and 6 (7.69%) with Unknown epilepsy. 2.56% of all the epileptic cases was found to have Childhood absence epilepsy. As regard etiology, 35.89% was considered to have epilepsy due to hypoxic ischemic encephalopathy, 3.85% the etiology of the epilepsy was considered as post-meningeal; 2.56% of all cases was considered to have a genetic etiology. EEG was recorded in 47 patients (60.25% of the patients with epilepsy) and was reported as abnormal in 80.85%.

Conclusions: The most common type of epilepsy was found to be focal epilepsy with motor onset and impaired awareness. This is an interesting aspect as in resource-limited countries generalized epilepsy was the mostly reported type of epilepsy. Key facts about epilepsy from the World Health Organization (WHO) claim that up to 70% of people living with epilepsy could live seizure-free. The condition trend of our patients shows that 60% of the patients were seizure-free at the third follow-up, an outcome approaching the prognosis advocated by WHO in a country where epilepsy diagnosis, management and treatment are still a challenge.

Keywords:

pediatric epilepsy, resource-limited countries

EPNS23-2824 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Novel GRIN2D Variation in a baby with Epileptic Encephalopathy and Response to NMDA Receptor Channel Blocker-a Case Report

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Case study: Objective

N-Methyl-D-aspartate receptors (NMDARs) are a subset of ligand-gated ionotropic glutamate receptors that mediate excitatory synaptic transmission in the central nervous system. GRIN2D gene encodes the GluN2D subunit protein of the NMDAR. Genetic variation of GRIN2D is associated with developmental and epileptic encephalopathy (DEE) and these patients are usually refractory to conventional anti-epileptic medications. We report a novel GRIN2D variant in 4-month-old baby with refractory seizures who displayed an improvement in seizure control with NMDA receptor antagonist.

Method

The patient presented at 8 weeks of age with multi-focal seizures and subsequently developed prolonged bilateral clonic seizures and epileptic spasms. Examination revealed a baby with developmental delay and no obvious dysmorphic features. EEG displayed a disorganised background with high amplitude, fairly continuous, bilateral epileptiform abnormalities, in keeping with hypsarrthymia. Brain imaging was normal.

Results

Epilepsy gene panel identified novel GRIN2D variant (NM_000836.4): c.2041A>C p.Met681Leu; (likely pathogenic). Preliminary agonist potency and proton/Mg sensitivity recordings showed 5-10 fold enhancement (more potent, pointing to gain of function) for glutamate and glycine potency. She was started on sodium valproate, clobazam, phenobarbitone, lamotrigione and levetiracetam sequentially which failed to achieve seizure control.
On the basis of literature review, memantine was added. Memantine is a NMDA receptor antagonist which is commonly used in dementia. She initially developed dyskinetic movements including peri-oral dyskinesia, likely due to NMDA receptor blockage which settled with dose reduction. She was also started on prednisolone after two weeks as per UKISS protocol in view of epileptic spasms. Adjunctive therapy with memantine and prednisolone showed marked clinical improvement. Although the repeat EEG remained hypsarrhythmic, overall, there was improvement in the number of clinical events.

Conclusions

Seizures caused by GRIN2D mutations are predominantly refractory to conventional anti-epileptic therapies. Our experience suggests that NMDAR antagonists can be useful along with antiepileptic drug polytherapy in individuals with GRIN2D gain-of-function. It demonstrates the importance of early genetic testing and functional evaluation of mutations. It also highlights the potential for individualized treatment guided by molecular genetics.

Keywords:

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EPNS23-2675 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Ocular phenotype and electroretinogram abnormalities in Lafora disease and correlation with disease stage

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Case study: Objectives: Lafora disease (LD) is a neurodegenerative disorder featuring action and stimulus-sensitive myoclonus, epilepsy, and cognitive deterioration. Mutations in the EPM2A/EPM2B genes classically prove causative for the disease in most cases. Since full-field electroretinogram (ERG) may reveal early-stage changes in a wide spectrum of diseases, we aimed to evaluate retinal cones and rods dysfunction in a cohort of Italian LD patients.

Methods: Patients with genetically confirmed LD were recruited and subjected to ERG analysis following the International Society for Clinical Electrophysiology of Vision (ISCEV) standard protocol aiming at evaluating the rods and cones electrophysiological responses in order to investigate the relationship between Lafora disease stage and rods and cones dysfunction.

Results: Six patients aged between 13 and 26 years (mean 19.5 years) were included. The mean age at disease onset was 12.5 years with a mean disease duration of 7 years.

The ERG analysis revealed a global mild to severe generalized cones dysfunction in all patients. Linear correlation was identified between disease stage and the degree of cones and rods dysfunction, as well as between the type of mutation and the cones and rods dysfunction.

Conclusions: This study brings further evidence of early retinal alterations in LD patients. The cones and rods dysfunction grade is related to disease duration. The ERG is an important tool to determine the disease stage, allowing to evaluate either natural or treatment-related disease progression in a minimally invasive way.

Keywords:

Lafora disease, Electroretinogram, Retinal alterations, progressive myoclonus

EPNS23-2581 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

Infantile Epileptic Spasms Syndrome - Experience from a Tertiary Center

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Objective: Introduction:
Infantile Epileptic Spasms Syndrome (IESS) is one of the most recognized types of epileptic encephalopathy. The diagnosis, evaluation, and management of IESS continues to be challenging.

Objective:
To characterize patients with IESS regarding etiology, clinical, electroclinical and treatment response, progression to another type of epilepsy, neurological outcome, or death.

Methods: Descriptive retrospective study of patients diagnosed with IESS followed at a Neuropediatrics Unit at Centro Materno Infantil do Norte - CHUPorto, from January 2011 to December 2022.

Results: A total of 54 patients, boys were affected more often than girls (34 vs 20). The age of onset of symptoms ranged from 6 weeks to 22 months with a median of 7 months.
Twenty-one (39%) patients were considered idiopathic IESS and thirty-three (61%) symptomatic IESS, of the latter 15 had a genetic etiology (2 of them with tuberous sclerosis).
Overall, twenty-nine (53%) children were seizure-free at 4 months (median). There was a primary electroclinical response on the 14th day in 4 patients. In 17 patients the EEG normalized with a median of 12 months, in this group 76% were idiopathic IESS.
Regarding the treatment, with the first drug 33% of idiopathic IESS patients became seizure free versus 21% in the symptomatic group (p=0,322).
In 37 patients there was a need for a second drug, with a median of 3 weeks, 43% (N=16) of these became controlled.
The two patients with TS responded to the first therapeutic option VGB.
In the total of patients with IESS 17 (31%) progressed to refractory epilepsy.
In the symptomatic IESS 14 (42%) developed refractory epilepsy while in the group of Idiopathic only 3 (14%) had this outcome (p<0,05).
Seventeen patients (31%) of all the cohort met criteria for West Syndrome (WS), 7 of the idiopathic and 10 of the symptomatic groups. From these, only 3 (17%) responded to the first drug, and 8 (47%) did not respond to the second drug either. Nine (53%) are currently with a refractory epilepsy.
Normal cognitive development was documented in 5 patients all of them with idiopathic IESS. Mean follow-up time of 5.2 years and 6 patients died. Only 1 patient evolved to Lennox-Gastaut Syndrome, an idiopathic WS.

Conclusions: Overall, 31% of patients with IESS evolved to refractory epilepsy. All children with normal development had the idiopathic form.
Etiology appears to be the most important outcome predictor, in accordance with other clinical series.

Keywords:
Infantile Epileptic Spasms Syndrome (IESS); West Syndrome (WS); refractory epilepsy; tuberous sclerosis

EPNS23-2875 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Genotype-phenotype correlations in Polish children with SCN8A-related disorders- a multicentre observational study

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Objective: Excitability of neuronal membrane is maintained by a range of membrane proteins controlling the physiological balance of ions between the intracellular space and extracellular matrix. These proteins among others include voltage-gated sodium channels (VGSCs), encoded by 9 genes of the SCN group, whose mutations were found in multiple types of genetic epilepsy. An alpha-subunit of Nav1.6 channel, localized in the axon initial segment and nodes of Ranvier, is encoded by SCN8A (12q13.13; MIM #600702) gene and plays an important role in initial depolarisation.
Disease-causing variants in SCN8A produce a wide spectrum of clinical manifestation, depending on the type of alteration - though loss-of-function (LOF) variants, which are more often reported in patients with intellectual disability without seizures, whereas gain-of-function (GOF) variants may lead to generation of epileptogenic potentials and are seen in patients with epilepsy and epileptic encephalopathy.

Methods: The authors summarizes the clinical and genetic findings in 17 Polish pediatric patients with SCN8A-related disorders. The group was recruited from 7 Pediatric Neurology Departments in Poland. Pathogenic and likely pathogenic SCN8A variants were indentified by next-generation sequencing methods.

Results: Results of genetic examination discovered de novo pathogenic variants in SCN8A gene in 15 patients, whereas in two cases the pathogenic variants were inherited from the parents. The pathogenic variants repeated in a single pair of patients (c.3946G>A, p.Val1316Met in two patients). Consanguinity was not reported in any of the families. New and recently described pathogenic variants (c.802A>C, p.Ile268Leu, c.1582G>C, p.Ala528Pro, c.1582G>C, p.Arg1872Trp, c.2191T>C, p.Ser731Pro, c.2528T>C, p. Leu843Pro, c.2540G>C, p.Arg847Pro, c.2543T>G, p.Leu848Trp, c.3946G>A, p.Val1316Met, c.4312A>G, p.Ile1438Val, c.4889T>C, p.Leu1630Pro, c.5585T>C, p.Leu1862Ser) were found in the studied group.

Conclusions: The neurodevelopmental burden of SCN8A pathogenic variants were recognized relatively recently, which poses a significant risk of patients remaining undiagnosed. It underlines the importance of precise and thorough reports of genotype-phenotype correlations, in order to adequately describe and recognize the spectrum of SCN8A-related phenotypes.

Keywords:

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EPNS23-2915 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Machine learning approach for the outcome prediction of drug resistant epilepsy in children presenting infancy

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Objective: There are many studies investigating the factors that predict drug resistance in both childhood and adulthood. We aim to identify whether the resistance to drugs in infants via machine learning (ML) algorithms.

Methods: We analyzed data from a retrospective study of 229 patients who presented to seizures when they were between 1 and 24 months of age and diagnosed as epilepsy. We implemented and compared 8 ML algorithms for DRE prediction: decision trees, bagging, K-nearest neigbour, linear discriminant analysis, logistic regression, neural networks, deep neural networks and support vector machine. First, the dataset divided 70% train and 30% test set.146 observations from each variable were randomly taken for training. 63 observations from each variable were randomly taken for testing. Then, while the training set was trained, 5-fold cross-validation was performed to avoid overfitting.

Results: In our previous study, multivariate logistic regression analysis showed that developmental delay at onset, multifocal epileptiform discharges, and history of status epilepticus were strong predictive factors for DRE. During model development, bagging obtained the highest performance metrics in this study. This algorithm got an accuracy of 98.63%, a sensitivity of 98.11%, a specificity of 98.93%, a precision of 98.11%, an F1-score of 98.11%, a G-Mean of 98.52%, and AUC value of 0.99. This value is nearest to 1 and this also means the algorithm is the best one. Furthermore, decision trees were the second successful algorithm with an accuracy of 97.26%.

Conclusions: Significants: In this study, we identified important features and validated an ML classification algorithms for predicting the probability of DRE in infancy. Future research should be directed toward conducting larger studies with prospective evaluation of the ML model in patient outcomes.

Keywords:

machine learning; chidren; infancy; epilepsy; prognosis;

EPNS23-2628 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

Pyridoxine-dependent epilepsy in a patient with GEFS+

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Objective: To describe a patient with an atypical mild presentation of pyridoxine-dependent epilepsy carrying two novel variants in heterozygous compound in ALDH7A1 gene.

Methods: We performed neuropsychological evaluation, EEG and neuroradiological investigation in a patient with early onset epilepsy. To identify the possible pathogenic variants related to the patient phenotype, a NGS probe-based target panel for 228 genes involved in rare and complex epilepsy was performed using the Agilent SureSelect Target Enrichement. According to the results of NGS panel, specific biomarker was tested in urinary analysis.

Results: The proband is a male that was referred to our institution at the age of 3 years for recurrent febrile and afebrile convulsive seizures, with a positive family history for febrile convulsions.
At the age of 2 months -after feeding- the patient presented sudden skin paleness, generalized hypotonia and hyporeactivity, spontaneously resolved in few minutes; this event was interpreted as a gastroesophageal reflux syndrome. At 6 months, he presented tonic-clonic generalized seizure. VideoEEG and MRI were negative.
During the 2nd year of life the patient presented several convulsive seizures, in one case configuring a convulsive status epilepticus: all were triggered by infections, not always febrile.
At the age of 3 years neurological evaluation was normal so as psychomotor development, tested by Griffiths Scale.
The clinical picture and positive family history suggested the diagnosis of generalized epilepsy and febrile seizure plus(GEFS+).
Genetic analysis was performed and Valproic Acid (VPA) was introduced with transitory effectiveness. Target gene panel revealed two novel variants in ALDH7A1 gene, inherited independently from parents.
Oral pyridoxine was added with efficacy. Then VPA was stopped and the patient assumed only pyridoxine with a stable clinical picture. After a seizure free period of more than 2 years pyridoxine was gradually suspended to verify the real necessity of this treatment but the child presented a febrile epileptic status.
The diagnosis was confirmed by the increase of pipecolic acid in urine and pyridoxine was reestablished with total remission of seizures.

Conclusions: We describe a patient with GEFS+ associated with novel ALDH7A1 variants, contributing to the characterization of phenotypic spectrum of a treatable early onset epilepsy. Pyridoxine treatment led to seizure control, underlining the crucial role of NGS gene studies for a precision medicine approach.

Keywords:
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EPNS23-2512 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

Prevalence of non-epileptic paroxysmal events among medical students

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Objective: The aim of this study was to determine prevalence of non-epileptic paroxysmal events among medical students and compare the results with literature.

Methods: 162 6th-year medical students (72% (n=116) were female and 28% (n=46) were male), answered an anonymous survey in 2018-2020. The mean age of the students was 24.08±1.10 years.

Results: 49% of students (n=79) have experienced vasovagal syncope (56% between females and 30% between mails). Gender difference was statistically significant (p=0.03). Literature have shown prevalence of vasovagal syncope from 15% to 39%, and it is more common in females.
90% of students (n=146) have experienced hypnic myoclonus (93% between females, 83% between males, p=0.075). According to the literature, 70% of people experience hypnic myoclonus.
72% of students (n=117) have had déjà vu (75% between females, 65% of males, p=0.21). The prevalence of déjà vu in the literature varies between 30% and 96%.
32% of students (n=52) have had ticks (34% between females, 28% between males, p=0.51). Other studies report a prevalence of 4-19%, with boys being affected more often than girls.
48 students (30%) have sleepwalked (30% between females, 28% between males, p=0.81). According to the literature, 30% of 2.5 to 13-year-old children has had sleep walking.
44 students (27%) have experienced a migraine (29% between females, 22% between males, p=0.33). The prevalence of migraine among children is 10-25%.
26% of students (n=42) reported having a panic attack (27% between females, 24% between males, p=0.71). According to literature, the frequency of panic attacks is 14.4%.
18% of students (n=29) have had sleep paralysis (19% between females, 15% between males, p=0.57), whereas the literature suggests a prevalence between 2% and 60%.
10 students (9%) reported having jactatio corporis nocturna (10% between females, 7% between males, p=0.73), while the literature data suggests the prevalence being around 1%.
Febrile seizures were experienced by 2 female students - 1.23% of the respondents. The prevalence of febrile seizures is 2-5%.

Conclusions: Vasovagal syncope, hypnic myoclonus, jactatio corporis nocturna, ticks, and panic attacks were more common in our sample of students than in the literature, while the prevalence of déjà vu, sleep paralysis, sleep walking, febrile seizures, and migraine were similar. Vasovagal syncope was statistically significantly more common between females than males.

Keywords:
non-epileptic paroxysmal events, prevalence, vasovagal syncope, hypnic myoclonus, jactatio corporis nocturna, ticks, panic attacks, déjà vu, sleep paralysis, sleep walking, febrile seizures, migraine

EPNS23-2749 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

Clinical Profile and Outcomes in Children with Drug-resistant Epilepsy

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Objective: To study the clinical profile and outcomes of children with drug-resistant epilepsy (DRE).

Methods: We retrospectively reviewed medical records of children who were diagnosed with drug-resistant epilepsy according to the International League Against Epilepsy (ILAE) definition between January 2006 to November 2022 at a tertiary care referral hospital. All had been followed up at our hospital for at least one year.

Results: One hundred and eighteen patients were identified: 62 girls; 56 boys. The mean age of seizure onset was 2 years (range 1 month - 11 years). Most had generalized tonic-clonic seizures as a first seizure type (55), and the remaining had focal impaired awareness seizures (33), epileptic spasms (18), myoclonic seizures (4), and others (8). The most common etiologies of seizures were structural brain anomalies (52), genetic mutation (17), and central nervous system infection (6). Whole exome sequencing was done on 20 children. SCN1A mutation was the most common mutation (7). The median (range) number of antiseizure medications (ASMs) that had been tried in these children was 4 (2-6). Other treatments were the ketogenic diet (3); vagal nerve stimulation (2) and epilepsy surgery (10). The mean duration of follow-up was 7.9 years (range 1.3 - 17 years). At the last follow-up, all children were on two or more ASMs. One-third (31) of the children had daily seizures. Half of them were non-ambulation and unable to do self-help daily routines. There was no significant correlation between the age of seizure onset or etiologies and seizure outcome ($p=0.697$ and $p=0.083$). Early seizure onset was associated with genetic etiologies ($p=0.011$) and these patients tend to diagnose DRE at an early age compared to structural brain anomalies ($p=0.06$).

Conclusions: Structural brain anomalies are the most common etiology of DRE at our hospital. One-third of these children remain to have daily seizures despite numerous trials of anti-seizure medication. There was no significant correlation between the age of seizure onset or etiologies and seizure outcome. Genetic etiologies are associated with earlier age of seizure onset.

Keywords:
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EPNS23-2684 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

Etiological approach to Lennox-Gastaut syndrome and its impact on prognosis: A single-center experience

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Objective: Lennox-Gastaut syndrome (LGS) is a rare but severe intractable seizure disorder of childhood-onset with a wide range of etiologies. The study aims to evaluate the etiologies of patients followed up as LGS and their reflection on the phenotype and prognosis.

Methods: The study was conducted on 37 children diagnosed with LGS, retrospectively. The diagnostic criteria for LGS were multiple types of intractable seizures (one of which must include tonic), cognitive impairment and the electroencephalographic changes showing generalized slow spike-wave discharges (≤ 2.5 Hz) or generalized paroxysmal fast activity. Prenatal, natal and postnatal risk factors, etiologic causes, seizure types and frequency, neurodevelopmental status, treatment and prognostic features were evaluated.

Results: Of the 37 patients, 51.4% were male and 48.6% were female. Considering the etiology of the patients, 62.2% patients had a defined etiology, while 37.8% patients had an unknown. In the defined group, the most common etiology was hypoxic-ischemic encephalopathy.The genetic mutation (Xp22.33 duplication, 1p36 duplication, PURA missense mutation, 22q11.2 deletion) was detected as the etiology of LGS in 4 patients. The genetic results of 11 patients have not yet been concluded. The history of infantile spasm was present in 13.8% patients. Tonic-clonic, myoclonic seizures and atonic drop attacks were the most common seizure types after tonic seizures. Of the 86.5% patients received polytherapy. Valproate, levetiracetam, clobazam and rufinamide were commonly used anti-seizure drugs. Four patients had vagus nerve stimulation therapy. One patient used ketogenic diet and one patient used cannabidiol. Although 54.1% of the patients continued to have more than one seizure per day, the seizures of 5 patients whose etiologies were hypoxic-ischemic encephalopathy, trauma, metabolic and unknown cause were under controlled and 4 patients had autism spectrum disorder. According to current results, there was no statistically significant difference in prognosis between the groups with defined etiology and unknown etiology.

Conclusions: Lennox-Gastaut syndrome is a devastating epileptic encephalopathy. In the literature, the etiology of 25-35% of the patients is unknown and it is thought that there is probably a genetic cause and/or predisposition in these patients. Therefore, studies about on pathogenesis and genetic origin of LGS are needed to improve the treatment.

Keywords:
Lennox-Gastaut syndrome, LGS, rufinamide, epilepsy, genetic

EPNS23-2819 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Assessment of genetic aetiology in children with pharmacoresistant epilepsy in a tertiary centre over a two-year period

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Objective: Approximately 30-40 % of epilepsies are resistant to treatment (pharmacoresistant) and require numerous modifications of therapy and a more intensive diagnostic approach to determine aetiology. The aim of this retrospective observational study was to search for a genetic aetiology of pharmacoresistant epilepsies in paediatric patients.

Methods: We identified all patients with pharmacoresistant epilepsy treated in our department at a tertiary centre in 2020 and 2021 from our electronic health record system using ICD-10 codes related to epilepsy. Patients who underwent genetic testing were selected and data from their medical records was collected. For each patient, demographic information, information about their epilepsy, current therapy, any medications or other interventions used to date, and genetic testing data were collected.

Results: Of 428 patients with pharmacoresistant epilepsy, we enrolled 237 (55 %) patients who underwent genetic testing. Our cohort consisted of 103 (44 %) males and 134 (56 %) females, with a mean age of 11.7 (SD 5.9) years. Cytogenetic analysis was performed in 30 patients (13 %), Sanger analysis of specific genes, next-generation sequencing (NGS) epilepsy panels or whole exome sequencing (WES) in 82 patients (35 %), and both genetic analyses in 123 patients (52 %). Cytogenetic analysis detected pathogenic alterations in 28 cases (12 % of all patients with genetic testing), variants of unknown significance (VUS) were found in 5 cases (2 %) and clinically irrelevant alterations were reported in 2 cases (1 %). With Sanger analysis, NGS epilepsy panels or WES we found pathogenic variants in 76 patients (32 % of all patients with genetic testing) and VUS in 57 cases (24 %). Pathogenic variants in the SCN1A (n = 20), TSC2 (n = 7), MECP2 (n = 5) and CDKL5 (n = 3) genes were found most frequently. In order to manage the epilepsy in this cohort, we found that patients have been prescribed a median of 7 (range 2-22) different therapeutic interventions to date. Currently, their epilepsy is treated with a median of 3 (range 0-6) medications.

Conclusions: An analysis of the genetic aetiology of patients with pharmacoresistant epilepsy in our tertiary centre was performed. We found that chromosomal and pathogenic monogenic variants together explain the aetiology of approximately 40 % in our cohort. A relatively high percentage of VUS demonstrates the importance of further advancement in the field to improve our understanding and thus the care of our patients.

Keywords:

pharmacoresistant epilepsy, genetic aetiology, genetic testing, micro-arrays, whole exome sequencing, next-generation sequencing

EPNS23-2694 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Trauma-induced hippocampal infarction and onset of CACNA1A developmental epileptic encephalopathy

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Case study: Objective: CACNA1A-related disorders could present with persistent progressive or non-progressive cerebellar ataxia, paroxysmal events, and developmental epileptic encephalopathy (DEE). We aimed to emphasize that CACNA1A DEE should be considered in seizures that started after trauma with hippocampal infarction in the infantile period.

Methods and Results:

A previously healthy six-month-old female patient was admitted to the pediatric emergency room with a focal seizure after falling 30 cm. No pathology was detected in the computerized tomography of the brain. But there were recurrent vomiting attacks, restlessness, and unstoppable crying in the follow-up. On magnetic resonance imaging, diffusion restriction was observed in the left hippocampus. No pathology was detected in the examinations for the etiology of the infarction, and the patient was followed up without medication. A status epilepticus attack was observed one month after the first seizure. Anti-seizure medication and Vitamin B6 were started, and the etiology workup was done. While the investigations were ongoing, two more episodes of status epilepticus attacks were observed. By the time the patient showed truncal ataxia and mild hypotonia. It was observed that she had a global developmental delay. The epilepsy gene panel showed heterozygote c.4186G>A (p.Val1396Met) mutation. In the literature, a case was reported with similar clinical findings with CACNA1A DEE. It was emphasized that the first seizures could be triggered by trauma, and similar MRI findings were present with CACNA1A DEE. Since the cases presented have benefited from acetazolamide treatment in preventing recurrent status attacks, we treated our patient with acetazolamide. There was no status epilepticus attack in the follow-up.

Conclusion:

It should be kept in mind that the seizure observed after trauma may be symptomatic, as may the first seizure of resistant epilepsy such as DEE.

Keywords:

Developmental epileptic encephalopathy, hippocampal infarction

EPNS23-2637 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

EVALUATION OF A COHORT OF PATIENTS WITH EPILEPSY SURGERY FOR TYPE II FOCAL CORTICAL DYSPLASIA ACCORDING TO THE NEW INTEGRATED CLASSIFICATION OF THE ILAE 2022

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Objective: In February 2022, the International League Against Epilepsy (ILAE) published a new classification consensus of focal cortical dyplasia (FCD), proposed by the Task Force of the ILAE diagnostic methods commission. Our objectives were to analyze a cohort of patients undergoing epilepsy surgery for drug-refractory seizures, with a pathological diagnosis of type II FCD and to assess the applicability of the new comprehensive and integrative approach proposed by the ILAE.

Methods: Our epilepsy surgery database was reviewed from 2016 to 2022 and the 49 patients with FCD type II were selected for this retrospective study. Inclusion and exclusion criteria were applied, and 18 patients were selected. To meet our objectives, we completed the level 1 of the integrative approach, corresponding to the histopathological assessment looking for immunohistochemical biomarkers for the mTOR pathway, and the level 2 of molecular genetics, looking for germinal and somatic variants known to be associated with FCD. 8 patients were randomly selected for initial genetic testing of paired blood and tissue. A panel of 24 genes, associated with mTORpathies, was designed.

Results: N=8 patients (5/8 boys). Age, at the surgery time, was between 1.2 years to 20.3 years (mean age=8.6 years). Neurodevelopment was abnormal in 7/8. 2/8 patients had a direct family with epilepsy. No patient had consanguineous parents. The patients had debuted with epilepsy between 10 days of life and 12 years of age. 4/8 had sEEG implantation in the preoperative evaluation. Genetics variants in blood and CNS tissue were found in 5/8 patients. The variants were VUS in all cases, but two genes NPRL3 and TSC1 have AD inheritance and are candidates for validation with other genetic tests. 2/8 had variants in mTOR-related DEE-linked SZT2, but there were heterozygous for an AR inheritance. 1/8 had a TSC2 deletion. We have a percentage of potential genetic findings of 50%.

Conclusions: These types of studies that seek to prove the biological bases and pathophysiological mechanisms of frequent pathologies are useful because they propose new scenarios, that allow the search for new targeted, disease-modifying treatments. The new ILAE 2022 classification seems to be very useful for clinics because integrates phenotype-genotype. However, we see limitations, at the present time, because this type of neuropathological and genetics work up, in the postsurgical brain tissue, are not yet in routine clinical practice.

Keywords:

mTOR pathway; FCD; mosaicism

EPNS23-2630 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

Comparing long and short-term assessment of heart rate variability in Dravet Syndrome and the effect of sleep

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Objective: Heart rate variability (HRV) is a promising prognostic biomarker in drug-resistant epilepsy and Dravet Syndrome (DS), but different studies are not always comparable, limiting its clinical application. In fact, multiple HRV parameters, analyzed over different timescales and in different states (i.e. wake/sleep) are reported. The aim of this study was to assess which HRV parameter is more reproducible and has a stronger connection with clinical features. Moreover, for short-term parameters, differences between wake and sleep are examined.

Methods: 56 patients with DS with available 24h-ECG Holter-derived HRV were screened to evaluate if they had EEG-derived ECG traces available within 1 month before/after the Holter recording date. A 5-minute period in the awake and sleep state were analyzed and correlated with the 24h-HRV. Subsequently, the correlation of HRV parameters with relevant clinical features such as age, a recent history of status epilepticus (SE), and frequent generalized tonic-clonic seizures (GTCS) was studied with multiple linear regression models.

Results: 31 awake recordings and 22 sleep recordings were included. HF was the parameter with the highest correlation awake (Rho 0,745, p<0,001) while in sleep HF and LF were those with the highest correlation (respectively Rho 0,727 and 0,729, p<0,001). Age was a significant factor in simple models for most parameters except RMSSD. A recent history of SE was associated with a significant reduction of HRV both in simple and multiple regressions for all parameters except for awake LF and for sleep RMSSD and PNN50. Frequent GTCS were associated with a significant decrease in sleep RMSSD, HF, and LF, also when correcting for the effect of age and history of SE. When compared pairwise, a significant increase in sleep was seen for HF (median +24,45 ms2, IQR -7,51/+172,18 ms2, p=0,036; increase in 15/22 patients) with a consequent decrease of LF/HF ratio (median -0,13, IQR -5,22/+0,90, p=0,028; decrease in 14/22 patients). No significant differences were seen for RMSSD, PNN50, and LF, which showed high inter-subject variability.

Conclusions: A moderate degree of correlation between long- and short-term HRV was seen for all parameters, both in sleep and awake, and a strong correlation for awake HF. HF, both in wake and sleep, was significantly associated with high seizure burden, including SE and frequent GTCS. Frequent GTCS seem to have a greater effect on sleep compared to wake HRV metrics.

Keywords:
HRV, Dravet syndrome, sleep, short, long;

EPNS23-2687 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Electroencephalographic abnormalities in children presenting with language development delay

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Objective: Electroencephalographic (EEG) abnormalities may be expected in children with language developmental abnormalities, especially in cerebral areas where language centers are located. However, very limited and controversial data are available. We aimed to search the frequency and localization of epileptiform discharges in children presenting with language development delay and the frequency of epilepsy development in these children during a one-year follow-up period.

Methods: Hospital charts of children aged between 24-70 months and presented with the sole complaint of language delay were retrospectively reviewed. Patients with known or newly diagnosed epilepsy or any other neurological and/or psychiatric disorders, including autistic spectrum disorders and cognitive and hearing impairment, were excluded. EEG abnormalities at baseline, including the location and the duration containing epileptiform discharges, and frequency of epilepsy development at the 12th month of follow-up, were recorded. Variables were compared between groups using Mann-Whitney and chi-square tests.

Results: A total of 132 children presented with language development delay were enrolled. Ten of them were diagnosed with autism and excluded from the analysis. The mean age at the first admission was 39.6 months, and 73.8% were boys. Epileptiform discharges were detected in 14 (11.5%) of 122 children at admission, mainly in the temporoparietal region (83.3%) and on the right side or bilaterally, and surprisingly not on the left side unilaterally in any of the patients. This finding may be explained by the theory suggesting right-sided or bi-hemispheric localization of language function during early childhood. An epilepsy diagnosis was made in six children during 12 month follow-up period, and all of them had epileptiform discharges on initial EEG. While a family history of neurological disorder was more frequent in children with epileptiform discharges, age, sex, parental consanguinity, family history of language delay, epilepsy, or febrile convulsions were not significantly different between children with or without epileptiform discharges. However, duration of epileptiform discharges was not different between children with and without epilepsy development.

Conclusions: EEG abnormalities and epilepsy development are not rare in children presenting with language development delay. Language-delayed children with epileptiform discharges on EEG should be followed up for the development of epilepsy.

Keywords:

epilepsy, language delay, speech center

EPNS23-2958 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

CHECC (Child and young person Epilepsy Concerns Checklist) to identify wider needs of epilepsy patients

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Objective: CHECC was sent to certain families and education providers for children and young people with epilepsy. These were seen in a DGH epilepsy clinic supported by a neurodisability epilepsy paediatrician and epilepsy nurse.
CHECC aims to facilitate information sharing between education and epilepsy services to identify concerns relating to epilepsy, neurodevelopment and mental health. It also allows professionals to confirm support that is in place such as special educational needs provision. CHECC also serves to highlight areas that require further evaluation such as intellectual (learning) disability (LD), autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and developmental coordination disorder (DCD).

Methods: CHECC was developed with input from parents, epilepsy charities and professionals including paediatric neurologist, neuropsychiatrist, psychologist, epilepsy nurse, general and neurodisability paediatrician . Three different versions of the checklist were created (parent/carer, education and young person version). Different questions were included in each version. All checklists had a specific space to set their top three goals. Checklists were received from education professionals for 41 patients.

Results: The main areas of difficulty identified by CHECC related to the following: mood and behaviour 20 individuals; attention and concentration 32; communication and social interaction 25; learning and intellectual development 29. 16 Individuals had additional SEN (special educational needs) support. In 22 cases there were clear areas for evaluation, support and goal setting stated. Following or accompanying the CHECC, more focussed information gathering and evaluations were completed. These were associated with the following outcomes: 5 formal cognitive assessments confirming LD and 2 awaiting outcome; 5 ASD, confirmed, 2 in progress. 6 individuals diagnosed ADHD/ADD and 2 individuals diagnosed with DCD

Conclusions: This pilot study indicates that CHECC is an efficient and effective way of enabling education providers to highlight any broader concerns to the epilepsy team, without the need for multiple screening tools. We aim to develop the project further with online versions of each checklist.

Keywords:
Epilepsy, neurodevelopment concerns, ASD, ADHD, DCD, Learning disability,

EPNS23-2520 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Clinical description of patients with PCDH19 mutation. A multicentre retrospective study

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Objective: To describe the prevalence rate, clinical and MRI data of our patients with PCDH19 epilepsy.

Methods: Retrospective and multicentre study was planned, all 0-18 years old children with genetically confirmed PCDH19 epilepsy were enrolled from our country.

Results: 9 children were collected from 7 tertiary epilepsy centres, all of them were female. All were born at term and had negative perinatal history. Mean age at seizure onset was 15 (range 5-22) months. 7/9 patients presented with a cluster of focal/generalized seizures and 7/9 children had status epilepticus. 5 children had febrile seizures. Second seizure / cluster occurred in 2.1 (range 0-10) months. Only 1 patient has normal intellectual development, 6 children have autistic features. All children underwent brain MRI, 6/9 had abnormal -but mostly aspecific- brain MRI findings (1 cavum vergae+septum pellucidum cyst, 1 ventricular asymmetry, 1 right hippocampal sclerosis, 1 left hippocampal sclerosis and focal cortical dysplasia, 1 widened extracerebral liquor space).
Positive family history was found in 5/9 cases. Two of our patients with PCDH19 epilepsy are first degree cousins (their fathers are brothers). One patient's mother has also genetically confirmed PCDH19 epilepsy. Another patient has cousin with non-specified childhood epilepsy and with mother who had febrile seizures during childhood. One patient's sister had febrile convulsion.
2/8 of children are seizure free for more than 1 year, they are on levetiracetam+carbamazepine or valproate bitherapy. 4 children have not had seizure for 4-12 months. 3 has frequent focal seizures/clusters. Only one patient is on monotherapy.

Conclusions: Comparing to the published data we found 1/higher prevalence of PCDH19 epilepsy (approx. 52/100.000); 2/ higher proportion of positive familial epileptic history; 3/high proportion of status epilepticus, 4/ higher proportion of brain anomalies on MRI. Molecular genetic testing for PCDH 19 mutation is necessary especially in girls with early onset childhood epilepsies.

Keywords:

epilepsy, genetic, children, autistic features

EPNS23-2276 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

SCN1A DISEASE-CAUSING VARIANTS: EXPANDING PHENOTYPIC SPECTRUM AND FUNCTIONAL STUDIES GUIDING THE CHOICE OF EFFECTIVE ANTISEIZURE MEDICATION

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Objective: Genetic epilepsies related to pathogenic SCN1A variants manifest with a broad spectrum of phenotypes. We refine the spectrum of SCN1A-epileptic disorders by evaluating 16 novel individuals enrolled in this study. We expand phenotype-genotype correlations, adding information on the functional consequences of three SCN1A variants and assessing the response to antiseizure medications (ASMs). We performed a literature review including individuals with SCN1A variants causing non-Dravet syndrome (DS) and non-generalized genetic epilepsy plus (GEFS+); data from the two cohorts were compared.

Methods: In this multicentre study, we enrolled probands carrying SCN1A disease-causing variants with a non-DS and non-GEFS+ phenotype. A functional study of three variants representative of the phenotypic spectrum was performed. Sodium currents of mutant channels were recorded in transfected cells using the whole-cell configuration of the patch-clamp technique and compared to those of the wild-type. Previously published patients were identified through a PubMed search.

Results: We analysed the 16 subjects included in the study according to whether their SCN1A variant was de novo or inherited. Eleven probands with de novo pathogenic variants presented developmental and epileptic encephalopathy (DEE) with seizure onset at a median age of 2 months and severe global disability. Five subjects with inherited variants manifested focal epilepsies (FE) with mild or no intellectual disability. Sodium-channel-blockers ASMs never worsened seizures, and 50% of patients experienced long periods of seizure freedom. There were 13 SCN1A missense variants, of whom eight were novel and never reported. Functional studies showed that the three variants tested led to a gain of channel function. The literature review identified 44 individuals with SCN1A variants non-DS, non-GEFS+ phenotypes, all manifesting DEE.

Conclusions: The boundaries of SCN1A disorders are wide and still expanding. The increasing number of reports of 'non-DS and non-GEFS+' phenotypes suggests that such patients are not so rare. Our study shows that, unlike DS, these phenotypes might be associated with gain of channel function, and sodium-channel-blockers could control seizures by counteracting excessive sodium channel function. Functional analysis to evaluate the consequences of pathogenetic sodium channel genes variants is thus relevant to tailor the appropriate ASM.

Keywords:

SCN1A gene, Gain of Function, Focal Epilepsy, Sodium channel Blockers

EPNS23-2726 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Variable yield of genetic testing in familiar epilepsies according to epilepsy syndromes

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Objective: The goal of this retrospective study was to evaluate the benefit of genetic testing in families with febrile seizures and/or epilepsy with multiple affected individuals.

Methods: We evaluated retrospectively the results of 611 individuals tested at our Neurogenetics laboratory in between 2015 and 2022. Molecular genetic testing (WES or gene panel testing including up to 277 epilepsy related genes) was performed on the request of paediatric neurologists or clinical geneticists. Most of the cases were individuals with severe childhood epilepsy/epileptic encephalopathy, but cases with less severe but familial cases were also included.

Results: Out of the 611 investigated probands, 525 were sporadic and 86 familial cases (14%) with more than one family member affected, but always only the proband underwent genetic testing.
Pathogenic, causal variants were detected in 22 families.
We detected pathogenic variants in SCN2A (3x), KCNQ2 (3x)and GABRG2 (1x) genes in 7 families with self-limited familial epilepsies starting in the neonatal age or infancy in 2 to 4 generations. A pathogenic variant in SLC2A1 was detected in a boy with absence seizures and his mother and maternal aunt with epilepsy. A 16p11.2 microdeletion encompassing the PRRT2 gene explained infantile onset epilepsy in three generations of one family. Further pathogenic variants were detected in ALDH7A1, GABRB3, SCN2A, PIGA, TSC2, SCN8A, SLC9A1, SMC1A, HUWE1, MECP3, PCDH19 genes in 13 familial cases of epilepsy or epileptic encephalopathy.
For the remaining eight families the analyses are still ongoing, as segregation studies have not been finished yet or more detailed analysis of variants of uncertain significance is needed.
No likely causal variant has been found in 56 families. From these, 35 cases with familial febrile seizures and GEFS+ (genetic epilepsy febrile seizures+) and 21 cases of severe epilepsy with mental retardation.
Pathogenic mutation was found in 25% of familial cases of epilepsy and/or febrile seizures.

Conclusions: High yield of genetic testing can be expected in familial self-limited neonatal and infantile epilepsies and epileptic encephalopathies. On the other hand, genetic generalized epilepsies and febrile seizures are genetically solved only rarely even though they are familial. Correct epilepsy syndrome classification is essential for selection and evaluation of the genetic testing.

Keywords:

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EPNS23-2273 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Stiripentol: update on its mechanisms of action and biological properties

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Objective: In 2007, stiripentol (STP) was granted its first marketing authorization as Diacomit® in Europe. At this time, STP was known as a positive modulator of GABA-A receptor (GABAA-R) mediated neurotransmission. Since then, several studies investigated and characterized STP biological properties.

Methods: This work summarizes additional pharmacological activity of STP.

Results: STP is a positive allosteric modulator of GABAA-R with most efficient effect on GABAA-R containing α3 subunit. This selectivity may explain the clinical efficacy of STP in childhood-onset epilepsies, including Dravet syndrome (DS), as these subunits are highly expressed in immature brain.

STP activity is potentiated by benzodiazepines. Pharmacodynamic interaction studies suggest STP and benzodiazepines act independently on GABAA-R and polytherapy could increase the maximum effect beyond their respective activity used alone.

STP has also been found to inhibit lactate dehydrogenase thereby decreasing ATP production, limiting the inhibition of KATP channels which in turn diminishes neuronal excitability.

In neuronal glial cells exposed to oxygen-glucose deprivation, STP was neuroprotective when used prior the insult. In cells exposed to high glutamate levels, STP at high concentrations was also neuroprotective. A significantly decreased cell injury after lithium pilocarpine-induced status epilepticus was also observed in hippocampus of young and adult rats.

Finally, recent data suggest STP could also interact with voltage-dependent calcium channels involved in abnormal thalamo-cortical oscillations underlying absence seizures. In particular, in vitro manual studies showed that STP inhibits T-type calcium and P/Q type channels.

Conclusions: STP is an antiepileptic drug harbouring multiple mechanisms of action. Its therapeutic efficacy observed in epilepsy derives from the sum of its biological properties and pharmacological actions rather than a single action. Further research is needed to better understand the relation between the different biological properties and beneficial effects observed as well as characterize additional utility for other rare forms of epilepsy.

Keywords:

dravet ; syndrome ; stiripentol ; epilepsy ; seizure ; mechanism ; of ; action ; treatment ; tonic ; clonic ; rare disease ; neuropediatry ; neurology ; pediatry ; drug resistent ; gaba ; gabaa ; receptor ; allosteric ; benzodiazepine

EPNS23-2305 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Efficacy and safety of dexmedetomidine vs. melatonin for sleep induction in children before EEG recording

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Objective: It is not always possible to achieve spontaneous sleep of children for EEG recording, utilisation of pharmacological sleep inducing agents is sometimes required. Most commonly used agent in our department in recent years is oral melatonin, that sometimes fails to induce or sustain sleep, particularly in patients with complex behavioural issues (developmental delay, autism spectrum, mental retardation). Dexmedetomidine is commonly used for sedation in intensive care units and for procedural sedation in children. It is able to achieve sedation without causing respiratory depression and with minimal effects on cardiovascular system, has minimal effect on EEG peak frequency and amplitude, does not affect seizures and does not alter spike wave activity. Due to these characteristics, we started utilizing it for sleep induction for EEG recording in patients in whom melatonin failed to achieve this effect in our department. There are scarce reports in scientific literature on the use of dexmedetomidine for this purpose, its efficacy was however never, to our knowledge, directly compared to melatonin's.

Methods: 156 consecutive patients between 1 and 19 years that were hospitalised in our department for sleep EEG recording were enrolled and randomized by draw into melatonin group - M (n=54; dose: 0,1mg/kg), dexmedetomidine sublingual group - DS (n=51, dose: 3mcg/kg) and dexmedetomidine intranasal group - DI (n=51, dose: 3mcg/kg). We compared the groups in several parameters regarding difficulty of application, efficacy and safety, separately for group of patients with complex behavioural issues.

Results: Sleep was obtained in 99,4% of participants, in 93,6% after first application of the drug. D was efficient in 99% as a first drug and M in 81,8%, however in group of patients with complex developmental issues D was efficient in 100% and M in 73,4%. Patients fell asleep fastest after intranasal application of D and reached deeper stages of sleep during recording. None of the patients had respiratory depression, bradycardia, or desaturation during study period.

Conclusions: Melatonin and dexmedetomidine are both safe to use for sleep induction prior to EEG recording in children. Dexmedetomidine is more effective at inducing sleep than melatonin, particularly in children with complex behavioural issues.

Keywords:

Dexmedetomidine, melatonin, eeg, sleep induction, behavioural issues, children

EPNS23-2924 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

The role of genetic testing in paediatric epilepsy - our experience

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Objective: Genetic testing is an important component in the diagnosis and treatment of many forms of epilepsy. Most utilized tests include chromosomal microarray (CMA), epilepsy gene panels (EGP) and Next Generation Sequencing (NGS). This study documents the results of performed CMA, EGP and NGS in paediatric epilepsy, mostly pharmacoresistant epilepsy, with or without neurodevelopment disorder (i.e. developmental delay, autism spectrum disorders and/or multiple congenital anomalies).

Methods: The research was conducted retrospectively at the Department of Paediatrics, University Hospital Rijeka, Croatia, from June 2016 to December 2022. The blood samples of 150 children with epilepsy were analyzed at different laboratories (Functional Genomic Department of University Hospital Zagreb (Croatia), Children's Hospital Zagreb (Croatia), CeGaT Tübingen (Germany), Blueprint Genetics (Finland) and Invitae (USA)).

Results: The diagnostic yield of CMA in our study was 18% and EGP 40,6%, while the diagnostic yield of the NGS was 71,4% (5/7 patients).

Conclusions: CMA, EGP and NGS techniques represent a valuable diagnostic tool in contribution to etiological diagnosis of epilepsy. Nowadays, these methods should be the first-choice diagnostic option for patients with undefined and/or pharmacoresistant epilepsy with or without additional neurodevelopmental disorder. The obtained results allow the use of more specific and personalized treatment, which significantly contributes to the patient's wellbeing. Furthermore, this data expands our general knowledge regarding the etiology of epilepsy and reveals the phenotype-genotype correlation in children with epilepsy.

Keywords:

epilepsy, genetic testing, diagnostic yield

EPNS23-2540 Oral
Epilepsy: Diagnosis and Investigations

Myoclonic epilepsy in adults with Down syndrome: Case series of 8 patients

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Objective: To describe the clinical and electroencephalographic features, neuroimages and treatment of patients with myoclonic epilepsy in adults with Down syndrome.

Methods: Retrospective review of 592 medical histories of consecutive patients with epilepsy treated from 2017 to 2022.
The diagnosis of epilepsy was made according to the definition of the International League Against Epilepsy (ILAE) and the diagnosis of Down syndrome (DS) was made with genetic testing.
The seizures were classified according to the Operational Classification of Seizure Types by the ILAE (2017).

Results: 8 patients (5 male and 3 female) with myoclonic epilepsy and Down syndrome were found. The average age was 32,36 years old (age range of 18-55 years old) and the average age of onset of seizures was 20,48 years old.
Type of seizures: all patients had generalized myoclonic seizures.
Electroencephalography (EEG): all patients showed diffuse slowing of background activity. 6 had generalized spike-and-wave and 2 had generalized polyspikes.
Neuroimages: 6 showed generalized atrophy, 1 presented an arachnoid cyst and right subcortical sequelae
vascular lesion and 1 had a right occipital sequelae lesion.
Treatment: 3 were receiving monotherapy with valproic acid, 4 were receiving polytherapy due to pharmacoresistance and 1 was treated with Vagus nerve stimulation.
These clinical and EEG findings were similar to those described in Late-onset myoclonic epilepsy in Down syndrome (LOMEDS).

Conclusions: Despite that patients with Down syndrome have a higher risk of epilepsy throughout their lifetime, especially after 40 years old, in our patients we found clinical and electroencephalographic features compatible with LOMEDS at a younger age than described in other studies.

Keywords:
Down syndrome, myoclonic epilepsy, Late-onset myoclonic epilepsy in Down syndrome, LOMEDS

EPNS23-2579 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Long term follow up and patient outcomes, following the diagnosis of Febrile induced refractory epilepsy syndrome (FIRES), at a Tertiary Neurology centre.

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Objective: Febrile infection-related epilepsy syndrome is defined as refractory status epilepticus with a history of fever starting 24 hours to 2 weeks prior to onset. It can affect children of all ages. It has a high morbidity including life-long epilepsy, cognitive and psychological issues. Mortality is reported as 12%.

Methods: A retrospective case review of six children who were diagnosed with FIRES at a tertiary neurology centre.

Results: Six children diagnosed during 8-year period. Age at presentation ranged from 12 to 15 years. All fit and well prior to presentation. 5/6 required intubation and ventilation during acute presentation. 5/6 received treatment with IV methylprednisolone and Anakinra, alongside multiple antiepileptic drugs. 4/6 were started on ketogenic diet acutely.
One patient died due to tonsillar herniation, post mortem results demonstrated evidence of acute encephalitis with seizures leading to cerebral oedema. No definite causative organism found. 5/6 patients were cryptogenic. One patient was found to have a Complement factor I deficiency, treated with eculizimab.
The length of time to cessation of refractory seizures ranged between 9 and 38 days. There was no obvious correlation between length of refractory seizures to long term seizure burden.
The 5 surviving patients continue to have drug resistant epilepsy requiring between 2-5 antiepileptic drugs. 3 patients have no motor deficit, one has a generalised weakness and increased tone through lower limbs, 1 patient has left lower limb neuropathy.
3/5 have had formal neuropsychology assessments which found difficulties with inattention and memory. Using the "Children's memory scale" two children scored extremely low in all domains (0.2-1 percentile) and the third child was scored as average (90th percentile). In the "Strengths and difficulties questionnaire", all three children self-reported a high level of concern with hyperactivity and 2/3 with emotional difficulties.
All 3 children were found to have cognitive difficulties and were not achieving their age-related targets.
3 out of all 5 surviving patients now have an Educational Health and Care plan (EHCP).

Conclusions: FIRES is a devastating condition that in the long term leads to refractory epilepsy with cognitive and memory difficulties. Awareness of the neuropsychological impacts is vital to help counsel the family at diagnosis about long term outcomes, but also to ensure the right educational support is given to the child.

Keywords:

FIRES, NORSE, Outcomes

EPNS23-2833 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Temporal encephalocele associated epilepsy in a patient with tectal glioma: a case report

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Case study: Objective: To bring awareness of temporal encephalocele as a potential etiology for epilepsy in the setting of tectal glioma.

Method: Case report with literature review.

Result: A 17-year-old boy presented with a generalized tonic-clonic seizure. Initial brain MRI revealed a nonenhancing mass lesion arising from tectal region and involving cerebral aqueduct, compatible with a low-grade glioma, with associated mild triventricular enlargement. EEG demonstrated rare generalized 2-4 hertz atypical spike and wave discharges. Levetiracetam started after second generalized tonic-clonic seizure. Endoscopic third ventriculostomy for obstructive hydrocephalus resulted in decompressed ventricular caliber on subsequent brain MRIs.

Seizures continued, with focal onset becoming apparent characterized by blank stare, altered communication, and head and body rotation to the right before evolving to bilateral tonic-clonic seizures, and postictal expressive language difficulty. Repeat EEG showed focal spikes over the left frontotemporal region and a moderate degree of nonspecific left temporal slowing.

Re-review of MRIs demonstrated a left temporal encephalocele with herniation of left anteromedial temporal parenchyma into the skull base. This finding was present on the earliest available MRI without substantial progression. Subsequent head CT confirmed a well-marginated focal defect along the anterior and anteromedial aspects of the left middle cranial fossa associated with the greater wing of the sphenoid; this corresponded with the encephalocele. There was associated thinning of the adjacent left foramen rotundum and narrowing of the left pterygopalatine fossa. Herniated tissue was mildly hyperintense on T2-weighted imaging though without frank gliosis.

Conclusion: Tectal glioma survival is excellent and most often requires only CSF diversion for hydrocephalus management. Seizures are infrequent with tectal glioma, with 12% incidence reported in a series of 66 pediatric patients (Epilepsia, 56(9):e139-e142, 2015). No temporal encephalocele was reported amongst these or in any other reported patients with tectal glioma. We report a case of temporal encephalocele found in association with tectal glioma. Emergence of focal semiology and EEG finding led to re-examination of the MRI, with discovery of left anterior temporal lobe encephalocele. Recognition of temporal encephalocele brings the possibility of surgical management of epilepsy.

Keywords:

brain tumor, tectal glioma, epilepsy, temporal encephalocele

EPNS23-2812 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Elevated TNF-α Levels in Plasma of Children with Tuberous Sclerosis Complex (TSC)-related refractory Epilepsy

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Objective: Tuberous Sclerosis Complex (TSC) is a rare multi-system genetic disease associated with overactivation of the mammalian target of rapamycin (mTOR) pathway caused by loss-of-function mutations in either TSC1 or TSC2. TSC-related neurological disorders such as epilepsy, neurodevelopmental delay, and TSC-associated neuropsychiatric disorders (TAND) greatly affect the quality of life, and roughly 80% of the children present with refractory epilepsy. Efficient seizure management seems to be crucial for the course of cognitive development and TAND. This study evaluated inflammatory cytokines as possible robust and accessible plasma biomarkers of disease activity to improve diagnostic and prognostic precision of TSC-related epilepsy.

Methods: This observational, monocenter, prospective study included children < 18 years of age with TSC-associated focal epilepsy compared to an age-matched group of patients with focal epilepsy of other etiology (controls). Participants were assessed in terms of clinical, EEG and MRI findings, intellectual ability, seizure type and frequency, and ASM. Plasma levels of TNF-α and IL-10 were quantified (ELISA).

Results: 15 pts with TSC-related epilepsy (mean age 6.9y; mutation TSC1 26.7%, TSC2 73.3%) and 20 controls (8.6y) were enrolled. Neurocognitive phenotypes in TSC-pts compared to controls varied from normal cognition (13.3 % vs. 45.0 %) to profound mental retardation (40.0 % vs. 10.0 %). 7/15 (46.7%) TSC pts and 9/20 (45.0%) pts of the control group were seizure-free for at least 12 months. Mean seizure-free period was similar in both groups (TSC: 2.4y vs controls: 2.3y), but ASM varied significantly (TSC: 2.5 ± 1.3, controls: 1.7 ± 0.7, p=0.04). Refractory epilepsy was observed in 8/15 (53.3 %, TSC) and 11/20 (55.0%, controls) pts, whereby 50.0% of TSC and 9.1% of control pts suffered from at least 1 seizure per day. Compared to controls with refractory epilepsy, significantly elevated plasma levels of TNF-α (5-fold, p=0.03) and IL-10 (3-fold, p=0.03) were observed in children with TSC-related refractory epilepsy

Conclusions: Our data suggest, that TNF-α plasma level are related to high seizure frequency in TSC-related epilepsy. However, further studies are required to determine the role of cytokines as biomarkers of a refractory course of TSC-related epilepsy.

Keywords:

Tuberous Sclerosis Complex, TSC, Epilepsy, refractory Epilepsy, TNF-alpha, IL-10

EPNS23-2331 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

A case of two sisters with DEPDC5-related epileptic encephalopathy successfully treated with lacosamide add-on therapy

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Case study: Introduction

Lacosamide (LCM) is a recently developed sodium channel blocker (SCB) effective for focal-onset and generalized drug-resistant seizures. It has been increasingly used for epileptic encephalopathy. However, the evidence regarding the efficacy of lacosamide for Lennox-Gastaut syndrome (LGS) is controversial, and no study in infantile spasms has been reported.

Method

We conducted a record review for the patients.

Case report

Case 1: A four-year and 10-month-old normally developing girl presented with focal tonic seizures from the unilateral upper arm and drop attacks. Electroencephalography (EEG) showed a diffuse slow spike-wave complex and a fast rhythm at sleep. She was diagnosed with LGS. Zonisamide and levetiracetam were ineffective, and Valproate (VPA) was partially effective. Add-on therapy with LCM completely stopped seizures in two weeks. At the age of 4 years and six months, her EEG showed no epileptic discharge.

Case 2: The younger sister of case 1 developed spasms in clusters and showed less smiling from four-month-old. She presented to our hospital at six-month-old with regression and showed hypsarrhythmia on EEG. We diagnosed her with infantile spasms. VPA controlled clinical seizures but not EEG, and ACTH also failed to normalize EEG. Based on LCM's effectiveness on her sister's seizures, LCM was added on and resulted in the normalization of EEG. Both sisters presented with epileptic encephalopathy that responded to LCM. We suspected them of carrying a common genetic lesion, performed whole exome sequencing-based gene panel tests, and found both and their mother carry a novel variant in DEPDC5 NM_001242896:exon37:c.3751delT:p.F1251fs. At 12 months, her development improved, and her Developmental Quotient score was 90.

Discussion

DEPDC5-related epilepsy includes familial focal epilepsies, nonspecific focal epilepsies, infantile spasms, and others. It has a higher rate of drug resistance. Although, there is currently no evidence that seizures respond better to one particular anti-seizure medication, one case series reported some positive effects from SCB anti-seizure drugs, with 5 out of 8 patients seizure free on monotherapy. While DEPDC5 is not a commonly associated gene with infantile spasms, 10% of probands were reported to have infantile spasms, and DEPDC5-related infantile spasms may have favorable responses to LCM.

Keywords:

DEPDC-5, Lacosamide, Infantile spasm, Lennox-Gastaut syndrome

EPNS23-2486 Oral

Epilepsy: Diagnosis and Investigations

AUDITORY STEADY-STATE RESPONSES TO CHIRP IN DRAVET SYNDROME ARE INFLUENCED BY AGE AND BY ANTISEIZURE MEDICATION

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Objective: Dravet Syndrome (DS) is a developmental and epileptic encephalopathy, caused by haploinsufficiency of NAv1.1 sodium channels due to alterations in the SCN1A gene. NAv1.1 is mainly located in GABAergic interneurons, which are involved in cortical oscillatory activity and neuronal synchronization. Loss of function of SCN1A could result in alteration of both processes. A way to study oscillatory activity is auditory steady-state responses to chirp (ASSR to chirp). Chirp is a tone, modulated on amplitude by a time-dependent signal consisting of a linearly increasing frequency sinusoid from 1-120 Hz. It allows to study brain responses along those frequencies and it is possible to analyse three components of the responses: induced activity, evoked activity (EA) and intertrial coherence (ITC). The last two reflect the energy changes along time and the synchronization between phases, respectively. They are represented, on a 3D graph, as a crescent diagonal in which it is possible to identify a maximum peak of power (MPP) and its correspondent frequency (FMPP). Our aim is to describe ASSR to chirp in DS.

Methods: We recruited 42 subjects with DS and registered ASSR to chirp. We collected information as age, gender, age at onset, number of seizures in the 1st year of life, mutation type, antiseizure medication (ASM) and doses. We performed all statistical analysis using R studio programme, with U Mann Whitney test ($p < 0,05$). All participants signed an informed consent and the hospital Ethics Committee approved the study.

Results: We observed ASSR to chirp as a diagonal band in 12/42 subjects. MPP mean was 11,304 uV in EA and 2,847 uV in ITC. FMPP was seen in the low gamma band. When comparing subjects with (n=12) and without (n=30) response, we found significant differences between groups in age (p 0,0464) and in valproate dose (p 8,075e-07).

Conclusions: ASSR to chirp is visible only in 28% subjects with DS. The absence of responses to ASSR in DS can be related to the lack of functional Nav1.1, but other factors, such as age at recording and ASM doses, need to be taken into account to interpret the responses. Age is already known as a modifying factor of amplitude in EEG, and could explain the differences we found between both groups. It had been described that medications could influence cortex oscillatory activity; subjects with ASSR to chirp had lower VPA dose, indicating it is also an influential factor.

Keywords:

chirp, ASSR, dravet syndrome, cortical oscillatory activity

EPNS23-3020 Oral
Epilepsy: Diagnosis and Investigations

WHAT HELPS WITH THE UNKNOWN: THE ROLE OF NEXT GENERATION SEQUENCING IN INFANTILE SPASMS SYNDROME.

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Objective: To investigate the spectrum of genetic etiology in infantile spasm syndrome in relation to genetic testing with an emphasis on next generation sequencing.

Methods: A consecutive cohort of patients with infantile spasm syndrome (ISs) were prospectively enrolled in a ISs registry and examined with standard of care procedures since 2008. Patients with unknown etiology underwent next (generation sequencing clinical whole exome sequencing) for further analysis. Seizure and developmental outcomes at last follow-up were reported.

Results: Genetic etiology was present in 28% (68/240). In 10.4% (25/240) of patients with genetic etiology, only further analysis identified genetic diagnosis. Pathogenic variants included ABAT in n= 1, ALG13 in n= 1, AP3B2 in n= 1, ATP1A3 in n= 1, CEP170B in n= 1, CSNK2B in n=1, COL4A1 in n=1, GABBR2 in n=2, KAT8 in n= 1, KCND2 in n=1, KCNH1 in n=1, KCNT1 in n=2, KCNQ2 in n= 2, POGZ in n=1, PPP3CA in n= 1, SCN2A in n=2, SLC9A6 in n= 1, SLIT3 in n=1, SRPX2 in n=1, TSC1 in n=1, and UFC1 in n= 1- by WGS).
Wes trio sequencing showed no pathogenic variants in further 10% tested.

Conclusions: Genetic etiology is present in 28% all patients, in 10% only next generation sequencing revealed a rare genetic etiology, which is important for further and early treatment plans. Still in 10%, next generation sequencing of unknown etiologies did not identify any pathogenic variant. Accurate and timely next generation sequencing genetic testing is therefore most relevant for early and individually targeted treatment. Further studies and international registries are needed as single cohorts do identify only single patients with rare diseases in infantile spasm syndrome.

Keywords:
infantile spasms, genetics, whole exome sequencing

EPNS23-2135 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Clinical added value of interictal automated electrical source imaging in the presurgical evaluation of MRI-negative epileptic patients: a real-life experience in two paediatric cases

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Case study: Objectives

To show the clinical utility of interictal automated electrical source imaging (ESI) in difficult-to-manage epileptic children undergoing pre-surgical evaluation.

Content

Two girls (16 and 9 years) underwent a pre-surgical evaluation for refractory focal epilepsy in St-Luc University Hospital (Brussels, Belgium), including long-term 25-channel EEG monitoring, 3-Tesla brain MRI, FDG-PET scan and neuropsychological assessment. EEG and seizure semiology were compatible with left frontal epilepsy. No lesion was found on MRI, despite the use of a dedicated epilepsy protocol, a second reading by an expert neuro-radiologist and a voxel-based morphometry analysis. PET-scan revealed lateralizing (on left side for both patients) but no localizing results (hypometabolism found in more than one lobe: fronto-parietal for the first patient and fronto-temporal for the second). The multidisciplinary team formulated its hypotheses about epileptogenic zone (EZ) location and planned stereo-electroencephalography (SEEG), according to the aforementioned results. In a second step, ESI analysis derived from interictal EEG and patient's own MRI (Epilog PreOp, Epilog NV, Ghent, Belgium) was revealed and clinically interpreted. For the first patient, clusters of epileptic abnormalities pointed in the left middle/posterior cingulate cortex; for the second patient, ESI localized the EZ in the left orbito-frontal region. These results changed the management for the two patients, leading to modifications in the SEEG plan to cover the brain regions pointed out by ESI. The changes proved to be crucial: i) the seizure onset zone identified by SEEG coincided with the sublobar location provided by ESI; ii) the resection site included the ESI sublobar location and both patients are seizure-free after 2-year postoperative follow-up (ILAE 1); iii) histopathology revealed focal cortical dysplasia type 1 in one patient and gliotic changes in the other.

Conclusion

These two cases illustrate the additional value of ESI when integrating in the phase I pre-surgical assessment for refractory epilepsy and interpreted in the context of the multimodal evaluation. The major contribution provided by ESI concerns the SEEG plan which represents a crucial step in the clinical management to optimize adequate coverage of the suspected EZ, using a limited number of depth electrodes to reduce perioperative complications.

Keywords:

Electrical source imaging, MRI-negative epilepsy

EPNS23-2691 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Gelastic and dacrystic seizures associated with atypical hypothalamic lesion: case report

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Case study: Objectives: Gelastic and dacrystic seizures are extremely rare types of focal emotional seizures. Their combination particularly point to hypothalamic hamartoma, which is intrinsically epileptogenic. The new ILAE classification of epilepsy syndromes (2021) recognizes gelastic seizures with hypothalamic hamartoma as a unique entity.
Methods: We present the case report of a previously healthy girl has suffered from gelastic seizures not constantly in combination with dacrystic features and abdominal pain since 18 months of age.
Results: The patient's family history was insignificant and there were none perinatal risk factors or potential initial insults. Brain magnetic resonance imaging revealed a hypothalamic lesion and because of clinical expression the hypothalamic hamartoma was highly suspected. There were no biochemical and physical sings of a central precocious puberty. It was decided to perform a transcallosal disconnection and partial resection of the mass. It was not feasible to remove the entire mass of the lesion by this limited approach. Histopathology examination of the resected tissue very unexpectelly revealed the presence of a mature hyaline cartilage. Pathologists considered chondroma or also teratoma in differential diagnosis. The postoperative outcome has been satisfactory, the patient has had about 4 subtle seizures per year, and the second-step surgery has not been required.
Conclusions: It is an unusual case of drug-resistant focal epilepsy with combination of gelastic and dacrystic seizures associated with atypical hypothalamic lesion containing hyaline cartilage. The role of the hypothalamic lesion other than hypothalamic hamartoma in the epileptogenesis remains debatable.

Keywords:

gelastic seizures, hypothalamic hamartoma, atypical

EPNS23-2943 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Analysis of predictors of response to hormonal therapy in children with treatment naïve West syndrome with EEG, fMRI, qEEG and serum Biomarkers: An observational study

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Objective: The gold standard of treatment for West Syndrome has long been hormonal therapy, but only 50-70% of children respond to it, and 30-40% relapse, especially in children with structural etiology. In this study, our objective was to predict response to hormonal therapy (ACTH/oral steroids) in children with treatment naïve West syndrome with clinical features, EEG features, Functional connectivity on fMRI, Serum IL-1b and IL-1RA levels

Methods: This was an observational study conducted between July'20-June'22 with total period of observation and follow up over 12 weeks with conventional EEG, fMRI and quantitative EEG. Children up to 2 years with Electro-clinical diagnosis of West syndrome and who had Clinical spasms in the last 48 hours were included. Children who had received prior hormonal therapy for more than a week in the last 1 month or had Tuberous sclerosis or had Vitamin responsiveness were excluded. Burden of AmplitudeS and Epileptiform Discharges(BASED) score was done on most severely abnormal 5 minutes sleep epoch which would provide the highest score.

Results: Fifty-five children who were scheduled for hormonal therapy during the study period were included. Complete electroclinical resolution was predicted by the baseline BASED score of 3(p value-0.018). Area under the BASED score(cut-off >3) ROC curve was 0.67, (95% CI: 0.53-0.8) with sensitivity of 81.5% (95% CI: 61.9-93.7) and specificity of 55.6% (46.5-80.3). There was no significant difference in spectral power density for the five-frequency band which was analyzed among responders and non-responders. On fMRI, there was significantly increased functional connectivity among the group that was resistant to treatment. There was no significant difference in baseline mean values of IL1-B and IL-1RA among responders compared to non-responders

Conclusions: Baseline EEG based score has both diagnostic and prognostic value in management of West syndrome. Compared to grouped multifocal spikes with paroxysmal voltage attenuation, multifocal epilepsy hypsarrhythmia pattern exhibited significantly higher relapse rates. Increased functional connectivity among the group that was resistant to treatment, supports the hypothesis of ineffective functional connectivity causing an increase in interhemispheric synchronization of epileptiform activity that was resistant to conventional treatment methods. Increased delta power could be a potential prognostic marker of non-responsiveness to hormonal therapy.

Keywords:

Quantitative EEG, Functional-MRI, BASED Score

EPNS23-2649 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Voltage-gated sodium channel gene variants experience in tertiary care center: genotype-phenotype correlation

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Objective: SCN gene mutations are highly associated with epilepsy phenotypes. Our aim is to evaluate the genetic variants and phenotype features of all patients with sodium channel mutations seen in tertiary care center.

Methods: Retrospective review of demographics, seizure types, mutation variants, age of seizure onset, EEG and MRI findings, family history, responses to anti seizure drugs, entellectuel impariment, motor and psychiatric comorbidities of all patients with sodium channel gene mutations seen at paediatric neurology clinic from 2018-2022. Results were presented as median (min-max), and percentage (%). Statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, N.Y., USA).

Results: 16 SCN mutations and 16 different variants has been determined. 14/16 (%87.5) patient's mutations were heterozygous, 2/16 (%12.5) were homozygous (both 2 patients were SCN1A). 12 of them were SCN1A, 3 were SCN2A and 1 was SCN3A. 15/16 patients were diagnosed as developmental epileptic encephalopathy and 1/16 was generalized febrile seizure plus syndrome. The mean age of seizure onset was 5.89 (min:0,25 max:18) months. 4/16 (%25) patients were from consanguineous parents. 11/16 patients had febrile seizure history. 3/16 (%18.8) EEG were normal, 6/16 (%37.5) had generalized epileptic activity, 5/16 (%31.3) had multifocal activity and 2/16 (onewas SCN1A and other one was SCN2A) had hypsarrhytmia. 7/16 (%43.8) patient's seizures were generalized, 6/16 (%37.5) were myoclonic and 3/16 (%18.8) were focal. 12/16 (%75) patients had history of status epilepticus. Just one patient whom has SCN3A mutation reported to have abnormal MRI findings which were corpus callosum agenesis and cortical dysplasia. Motor impariment degrees were; 1/16 (%6.3) was unaffected, 4/16 (%25) had mild gait imbalance, 4/16 (%25) had crouch gait, 4/16 (%25) were ataxic and 3/16 (%18.8) patients were non-ambulatory. All patients had entellectuel impairment. 3/16 (%18.8) were mildly affected, 7/17 (%43.8) had moderate, 3/16 (%18.8) had severe and 3/16 (%18.8) had profound impairment. 14/16 (%87.5) patients had pyschiatric comorbidities. Most efficient anti seizure drugs for SCN1A were valproic acid and clobazam. Carbamazepine was effective for patients with SCN2A and SCN3A mutations.

Conclusions: Early identification of a pathogenic SCN variant clearly influences the choice of anti-seizure therapy and is predictive for prognosis.

Keywords:

SCN, epilepsy, developmental and epileptic encephalopathy

EPNS23-2965 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

ABCB1 gene polymorphisms associated with susceptibility to West Syndrome and steroid-responsiveness in Indian children

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Objective: Genetic polymorphisms of ABCB1 (ATP-binding cassette B1) gene encoding P-glycoprotein have been proposed to be associated with pharmaco-resistant epilepsy. P-glycoprotein, a transmembrane transporter, works as an efflux pump; limiting antiepileptic drugs across the blood brain barrier and subsequently reducing drug concentrations in epileptogenic loci. Limited data exists on genetic associations of West syndrome; none investigating ABCB1 polymorphisms in children. We aimed to assess the association of ABCB1 gene polymorphism with west syndrome in Indian children and with steroid-responsiveness in these children.

Methods: A prospective observational and case-control study was conducted over one year (January-December 2021). Children aged 2 - 36 months diagnosed with west syndrome were enrolled as cases. Children previously treated with steroids and those with tuberous sclerosis and contraindications to steroids (infection, hypertension, immunocompromised) were excluded. DNA was extracted from whole blood and genotypes (CC, CT, TT) of 3435 locus of ABCB1 gene were assayed in 80 cases and 80 age- and sex-matched normal children using polymerase chain reaction (PCR)-restriction fragment length polymorphism technique. Response to steroid therapy (40 mg/day or max 8mg/kg/day) was noted on day 14 (complete, partial or none). The genotypic and allelic frequencies of ABCB1 polymorphisms were compared between children with west syndrome and controls and between responders and non-responders to steroids using Chi-square test.

Results: A significant association was found between 3435CT [p = 0.008] polymorphism, T allele [p = 0.023] and west syndrome in children. 3435CT polymorphism was commonly noted in children with complete to partial steroid response than non-responders (47.5% vs 25%). The risk of non-response was higher in patients with 3435 CC (50% vs 25%) than in those with CT or TT genotype. Non-responders had higher C-allelic frequency than responders (75% vs 25%). However, the association between genetic, allelic polymorphisms and response to steroids was non-significant.

Conclusions: Our results indicate that C3435T polymorphisms in ABCB1 gene increased the susceptibility to west syndrome in Indian children. The above three polymorphisms in the ABCB1 gene were not found to be significantly associated with steroid-responsiveness in the cohort.

Keywords:

west syndrome, ABCB1 gene, polymorphism, steroid response, children

EPNS23-2497 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

First report of Tunisian patients with CDKL5-related encephalopathy

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Objective: Early-onset epileptic encephalopathy (EOEE) (1) is the most recognized phenotype of cyclin-dependent kinase-like 5 (CDKL5) gene mutation. Here we describe phenotypic features in 7 Tunisian patients with CDKL5-related encephalopathy.

Methods: We included all cases with clinical features consistent with CDKL5-related EOEE: epileptic spasm, acquired microcephaly, autism spectrum disorders, movement disorders and visual impairment. We collected data about seizure types, electroencephalogram (EEG), magnetic resonance imaging (MRI), and metabolic analysis. The diagnosis of CDKL5 mutation was made thanks to Sanger sequencing using ABI PRISM 3100-Avant automated DNA sequencer and a Big Dye Terminator Cycle Sequencing Reaction Kit v1.

Results: We collected4 boys and 3 girls aged meanly 10-years-old with DEE and confirmed CDKL5 mutation. Overall, we identified 4 de novo CDKL5 mutations including three Frameshift and one missense mutation at a mosaic state in 3 boys and a heterozygote state in 1 girl. Four patients exhibited two stages epileptic course while epilepsy in the 3 remaining patients progressed on three stages. The mean age at first seizure onset was 3,6 months. The first seizure type was infantile spasm (3/7) with hypsarrythmia on EEG followed by tonic (2/7) and myoclonic seizures (2/7). Regarding development, most cases (5/7) had psychomotor retardation from the start whilst the two others showed psychomotor regression with the onset of seizures. Later, only 2 out of our 7 cases acquired global motor milestones with less improvement in communication skills. Additional clinical features included acquired microcephaly (5/7), dysmorphism (4/7), visual impairment (7/7), hearing loss (2/7), tone abnormalities (6/7), stereotypies (6/7), and movement disorders (3/7). Brain MRI was more often normal (4/7) and showed frontotemporal atrophy in 3 cases and thin corpus callosum in 2 cases.

Conclusions: Our present report delineates an unusual phenotype of CDKL5-related EOEE mutation with male gender predominance and delayed onset epilepsy. It interestingly described new phenotypic features in boys carrying CDKL5 mutation, different patterns of CDKL5-epilepsy, neuroimaging findings and CDKL5 mutational spectrum. Although some patients showed common clinical features, they seemed to have heterogeneous seizure types, epilepsy and developmental course. These findings are in agreement with literature data where no phenotype-genotype correlation was found.

Keywords:

Developmental and epileptic encephalopathy, early-onset, CDKL5

EPNS23-2380 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

EEG parameters related to epilepsy etiology detected by machine learning methods in epilepsies presenting with rolandic spikes

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Objective: It is still not clear if there are interictal electroencephalogram (EEG) parameters that may be related to epilepsy etiology in epilepsies presenting with benign focal epileptiform discharges (rolandic spikes). The aim of the study was to find the differences in rolandic spike morphology in two epilepsy groups, different by etiology, but presenting with visually identical spikes.

Methods: We manually analyzed the Clinic of Children's Diseases EEG database over a 2010-2017 period to identify children with rolandic spikes. Two patient groups were included in the data set: Group I - 62 patients with benign focal childhood epilepsy (self-limiting, with no causal lesion in the brain), Group II - 32 patients with structural focal epilepsy. Inclusion criteria were: 1) hard-to-distinguish (visually identical) rolandic spikes in benign focal childhood epilepsy and rolandic-like discharges in structural focal epilepsy, 2) exact diagnosis known from clinical records, 3) artifact-free EEG recording of at least 2-13 min. containing 50 or more spikes without artifacts.
A novel algorithm for the automatic classification of EEG rolandic spikes according to the epilepsy type was used. The algorithm consisted of three stages: 1) EEG spike detection, 2) determination of EEG spike parameters, 3) classification of EEG by epilepsy type based on estimated spike parameters. The algorithm analyzed the main metrics of the spike: upslope, downslope, baseline level, width at half maximum, durations of sharp and slow components of the spike, and total spike duration.

Results: The estimation of upslopes and downslopes of spike were the most important parameters for classification. The proposed methodology lets us achieve up to 75% the accuracy in classification of EEG.

Conclusions: Even visually similar rolandic spikes are not really identical, possibly because of the different etiology. Statistical differences between Group I and Group II spike parameters can be detected by machine learning type methods.

Keywords:

EEG, Epilepsy, Epileptiform discharge, Spike, Machine learning

EPNS23-2534 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

Clinical spectrum associated with PRRT2 gene mutations in neuropediatric patients

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Objective: The PRRT2 gene encodes a protein highly expressed in the central nervous system that takes part in the process of neurotransmitter release. Mutations in this gene interfere with signaling in the brain and can cause different types of epilepsy and movement disorders. The goal of our study was to improve the knowledge on this gene and its variants by describing the different clinical presentations and the treatment responses encountered in our cohort.

Methods: We retrospectively reviewed clinical and genetic data from our clinic and identified 14 patients with PRRT2 gene variants diagnosed using either epilepsy panels or whole exome sequencing. Personal and family history, epilepsy or movement disorder history, EEG, MRI and genetic testing results were comprised in a database and analyzed.

Results: Out of the 14 patients identified with PRRT2 mutations, 12 had early onset epilepsy with seizures starting before the age of 7 months in 9 cases. While focal motor seizures were the most prevalent type we encountered (8/12), we also had patients with only generalized tonic-clonic seizures or both and even 1 patient with epileptic spasms. 8 of them had favorable response to carbamazepine. 2 of our patients had paroxysmal kinesigenic dyskinesia with good response to carbamazepine. 6 patients also had mild global developmental delay-5 of them with speech difficulties and 3 of the patients had autistic features. 7 patients had positive family history for seizures or dyskinesia. 13 patients had negative MRI while only one had periventricular heterotopia. 13 patients had normal interictal EEG while the patient with epileptic spasms had bilateral generalized spike-wave discharges at onset which later turned normal while under treatment with carbamazepine and valproic acid. The prognosis under treatment was favorable in all 14 patients.

Conclusions: These data add to the current understanding of the PRRT2 related synaptopathies and provide additional tools for early diagnosis while also underlining the importance of genetic testing in being able to orientate targeted treatment options for our patients.

Keywords:

epilepsy, dyskinesia, PRRT2, synaptopathy, carbamazepine

EPNS23-2647 Oral or e-Poster

Epilepsy: Diagnosis and Investigations

2q24.3 DELETION ASSOCIATED WITH DEVELOPMENTAL DELAY AND EPILEPSY

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Case study: Introduction: The extensive use of the array Comparative Genomic Hybridization (aCGH) technique, which precisely detects structural rearrangements, has led to an increasing number of studies describing the epilepsy phenotype of chromosome 2q24.3 deletion. In this particular case, the deletion occurred de novo and the following genes are included in the affected chromosomal fragment: GALNT3, TTC21B, SCN1A, SCN9A. According to literature, the deletion of 2q24.3 chromosomal fragment may result with developmental delay or regression and intellectual disability, epilepsy,autistic spectrum disorders.[1,2]

Purpose: Presenting the importance of array Comparative Genomic Hybridization (aCGH) technique in the assessment of underlying etiology in formerly considered cryptogenic epileptic syndromes.

Material and Methods: Patient's and parents' blood samples were collected for genetic analysis, using array Comparative Genomic Hybridization (aCGH) technique. Clinical features within the physical examination, MRim of the brain, EEG, as well as laboratory analysis were also performed and taken in consideration.

Results: We present a case of a 10 y/o male patient with refractory, early onset epilepsy and developmental regression and mild dysmorphic features. MRI brain scan was performed in a few occasions, showing incomplete myelination in the fronto-temporal lobes and other normal findings. EEG recordings were characterized by right-sided epileptiform discharges prone to generalisation. Genetic analysis revealed de novo 1.4 MB deletion in 2q24.3 chromosomal fragment that encodes the cluster of sodium channel genes, which are important in epilepsy phenotypes.

Conclusion: Deletions in this region are highly likely to contribute to epileptogenicity, developmental delay and dysmorphic features. Due to the genetic analyses, the diagnose can be precisely established that allows further research for the most adequate treatment.

Keywords:epilepsy,2q24.3 deletion,SCN1A,SCN9A

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Keywords:

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EPNS23-2022 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

Interictal Cardiac Changes in Children with Pharmaco-Resistant Epilepsy

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Objective: Background: Childhood epilepsy is one of the most prevalent and serious neurological disorders. Nearly one-third of the children are resistant to anti-epileptic drug treatment. Patients with drug-resistant epilepsy are at increased risk of comorbidities, which may result in sudden unexpected death of epilepsy (SUDEP), which is a multifactorial process, but it seems related to cardiac autonomic imbalance and left ventricular dysfunction.
Objective: To study the prevalence of left ventricular dysfunction and cardio-autonomic imbalance among children with drug-resistant epilepsy.

Methods: Patients and methods: A comparative cross-sectional study that included 40 children with drug-resistant epilepsy (cases group), and 40 healthy age- and sex-matched children (control group). left ventricular function was evaluated by M-mode, two-dimensional, pulse-wave Doppler, and tissue Doppler (TDI) echocardiography while cardiac autonomic function was assessed through heart rate variability measurement (using 24-hours Holter electrocardiographic study).

Results: Results: All time domain measures were found significantly lower in the patient group compared with control group, in the values of SDNN (P=0.003), SDANN (P=0.002) and RMSSD (P=0.006). As for frequency domain measures, mean HF parameters were significantly lower (P=0.035); while mean LF parameters and LF/HF ratio were significantly higher (P=<0.001) in the patient group when compared with the control group. As regard left ventricular function, there was no significant difference between cases and controls regarding all standard echocardiographic parameters. Using standard Doppler and tissue Doppler, there was evidence of subclinical left ventricular dysfunction among epileptic children as evidenced by elevated myocardial performance index (MPI) (P=0.001). Finally, there was no significant correlation between duration of treatment or frequency of seizures with any of cardiac abnormalities.

Conclusions: Conclusions: children with drug-resistant epilepsy showed significant cardio-autonomic and subclinical left ventricular dysfunctions. These abnormalities were independent from duration of epilepsy, frequency, and type of seizures.

Keywords:
Epilepsy, Drug-resistant, Autonomic, Left ventricle, Echocardiography.

EPNS23-2869 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Cannabidiol in the acute phase of Febrile Infection-Related Epilepsy Syndrome (FIRES): report of 2 cases and review of potential etiological mechanisms

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Objective: Febrile infection-related epilepsy syndrome (FIRES) is a catastrophic epileptic encephalopathy affecting previously healthy individuals after a febrile infection. Its treatment is challenging due to its poor response to anti-seizure medications (ASMs) and anaesthetic drugs. High mortality rates in the FIRES acute phase are described and delays in finding adequate treatment may contribute to poor prognosis, with frequent evolution into chronic, drug-resistant epilepsy and severe cognitive and behavioural impairment. Besides the early administration of traditional ASMs and immune modulatory drugs, cannabidiol (CBD) as an adjunctive treatment has been suggested, albeit data about its role in the acute phase of the disease is lacking.

Methods: Here we report the use, efficacy, and tolerability of highly purified CBD in the acute phase of two paediatric cases of FIRES and their long-term outcome.

Results: Two children aged 4 and 6 presented with FIRES and were referred to two different third-level hospitals. A cytokine-mediated inflammation pathway was demonstrated in both, either by interferon signature or cytokine assay in cerebrospinal fluid.
After using several ASMs, immunomodulators, anaesthetics, and non-pharmacological treatment, CBD was administered through nasogastric tube about 30 days after onset. The dosage was gradually increased, and SE resolved within a few days of reaching the target dose in both children. They were seizure-free for one year after, continuing CBD therapy with no evidence of side effects and excellent cognitive recovery.

Conclusions: CBD targets several key molecules involved in FIRES pathogenesis. Its modulatory effect on neural excitability may have helped to counteract pro-epileptogenic, cytokine-mediated neuroinflammatory mechanisms involved in the acute phase of the syndrome, leading to its resolution. Although it is difficult to define the extent to which each previous therapy contributed to healing, in both cases CBD therapy was a turning point, corroborating its potential effectiveness as add-on therapy in FIRES.

Keywords:
CBD; FIRES; Status Epilepticus; Cytokine Storm

EPNS23-2511 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

The incidence and evolution of movement disorder in children with epilepsy treated with vigabatrin

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Objective: To investigate the prevalence and evolution of movement disorder in children with epilepsy treated with vigabatrin (VGB) and to explore relationships with underlying diagnosis & radiological findings.

Methods: We retrospectively reviewed electronic medical records of children and adolescents 0-18 years treated with VGB between Jan 2000 and August 2020 in a tertiary centre. They were classified as per underlying diagnosis as patients with tuberous sclerosis (TS), infantile spasms (IS) and other neurological diagnosis. The indication for VGB use in TS and other diagnosis groups was treatment of drug-resistant focal seizures. We collected data about seizures/epilepsy, movement disorder, dates of commencement and discontinuation of VGB, duration of treatment with VGB, MR imaging.

Results: In total, 240 patients were included (84 TS, 108 IS & 48 other cause, including genetic epilepsies, structural brain abnormalities, stroke, hypoxic-ischemic encephalopathy). Median maximum VGB dose was 117 mg/kg/d(80-150) for TS group, 100 mg/kg/d(50-150) for IS group, 100 mg/kg/d(35-200) for the other causes group. Movement disorder was noticed in 2/84(2.4%) of patients with TS, 31/108(28.7%) of those with IS (pre-existing in 7/31, 22.5%) and 31/48(64.5%) of those with other cause (pre-existing in 16/31, 51.6%). Symptoms mainly included dystonia, chorea, and hyperkinetic movements. Movement disorder eventually resolved in 50% of patients with TS, 22.5% with IS and 19.3% of other cause. An MRI after VGB onset was done in 40 patients with IS and 22 patients with other cause. VGB-related changes were found in 14/40 (35%, 13/14 had movement disorder) and 3/22 (13.6%, 3/3 had movement disorder), respectively.

Conclusions: The prevalence of movement disorder among patients with epilepsy treated with VGB is low for patients with TS, but considerable for those with IS or other neurological cause. In a significant number it is pre-existing and not caused by VGB, which reflects the need for accurate baseline neurodevelopmental assessment. Movement disorder was transient and resolved in a considerable number of patients. A repeat MRI was not frequently done after VGB commencement and therefore the incidence of VGB-related changes among those with movement disorder may be underestimated. More studies are needed to explore causal relationship between treatment with VGB and evolution of movement disorder.

Keywords:

vigabatrin, epilepsy, movement disorder

EPNS23-2799 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Rufinamide efficacy in children with intractable epilepsy: A retrospective single center study

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Objective: Rufinamide is one of the new generation antiseizure medications, which provides seizure control via sodium channels. In 2009, rufinamide was approved by the United States Food and Drug Administration for the treatment of children aged four years and older with Lennox-Gastaut syndrome and was subsequently used as an add-on therapy in patients with focal epilepsy. The aim of this study was to investigate the efficacy of rufinamide treatment in children with intractable epilepsy.

Methods: This is a retrospective study conducted at a tertiary center. Pediatric patients with intractable epilepsy who had been treated with rufinamide between 1/4/2009 and 1/10/2022 were included in the study.

Results: Forty-three patients (M/F: 27/16) were evaluated. Age at seizure onset was median nine months (first day of life -15 years). Rufinamide was started at median 8.4 years (4-16.5 years). Twenty-seven patients had generalized motor, eight patients had focal motor, and eight patients presented with multiple seizure types.
Eleven patients had 1-5 seizures/day, five patients had 5-10 seizures/day, 20 patients had more than 10 seizures per a day, four patients had weekly, and three patients had monthly seizures and they were on 1-6 (median 3) antiseizure medications.
Etiological profile of patients was as follows: structural (n= 20), genetic (n= 16), unknown (n= 5), metabolic (n= 1), and infectious (n= 1). More than 50% seizure reduction occurred in 16 (37.2%) patients, 11 (25.6%) patients had seizure reduction lower than 50%, 15 patients (34.8%) had no change in seizure frequency, in one patient (2.3%) seizures got worse. The median follow-up duration was 12 months (1.5 -36 months), and 37 patients (86%) were still on rufinamide therapy at final visit. Adverse effects with rufinamide occurred in three patients (6.9%), including rash in two patients, and drowsiness in one patient.

Conclusions: Our findings revealed that rufinamide could be an option for adjunctive treatment in children with intractable epilepsy. Side effects are rare; however, close monitoring is required as one patient had increased seizures.

Keywords:
epilepsy, children, rufinamide

EPNS23-2463 Oral
Epilepsy: Medical & Surgical Treatment

Outcome prediction after pediatric epilepsy surgery: a Brain Machine Learning approach

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Objective: Epilepsy surgery is a widely accepted treatment for pharmacoresistant epilepsies. The rate of postsurgical seizure freedom patients (SF) does not exceed 70%. In order to increase the number of patients operated and the SF rate we studied the feasibility of applying a Brain Machine Learning (BML) model using quantitative neurophysiological data. Nonlinear quantitative analysis has demonstrated a good seizure prediction rate (85-92%) and average results in post-surgical outcome prediction (50-65%). Our hypothesis is that SF and NSF patients present different level of epileptogenicity.

Methods: In order to quantify the level of epileptogenicity we extracted 5 nonlinear EEG features (Lyapunove, Entropy, Hurst, Hjorth and PSD) from 60 seconds of awake and sleep interictal VEEG segment without artefacts and epileptiform abnormalities. This nonlinear quantitative analysis was carried out on a cohort of 123 pediatric patients. We used a Logistic Regression (LR) statistical test (p-value < 0.05) to retrospectively study the positive or negative correlation between nonlinear EEG properties and surgery outcome. The statistically significant EEG features create a specific linear combination of inputs of our BML model in order to estimate the probability of seizure freedom. For this purpose, we implemented 9 different Artificial Neural Network (ANN) architectures and 2 topologies for each one, iterated 50 times. In total we obtained 18 ANNs.

Results: LR test evidence a negative correlation between Hurst mean value in awake phase (OR=0.281) and seizure freedom and a positive correlation between Hurst, PSD_alpha_band, and Mobility mean values in sleep phase and seizure freedom (OR=2.681, 1.004 and 2.783). Considering all four features the ANNs provided a mean level of accuracy between 57-65%. The best model that interpolate the interictal EEG properties and surgery outcome was the II architecture of ANN with 9 neurons and 2 hidden layers (64.8%).

Conclusions: The results demonstrate that there is a correlation between nonlinear EEG features and surgery outcome. No single patient outcome prediction was possible at the moment.

Keywords:
Quantitative EEG analysis; Machine Learning; Predictive model; Artificial Neural Networks

EPNS23-2673 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Alterations of Plasma Pro-Inflammatory Cytokine Levels in Children with Refractory Epilepsies

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Objective: Paediatric epilepsy is a multifaceted neurological disorder with various aeti-ologies. Up to 30% of patients are considered drug-resistant. The background impact of interfering inflammatory and neuronal pathways was closely linked to paediatric epi-lepsy. The characteristics of the inflamed state have been described not only in epilep-sies, considered prototypes of having inflammatory pathophysiology, but also in pa-tients with drug-resistant epilepsy, especially in epileptic encephalopathies. The im-balance of different cytokine levels was confirmed in several epileptic models. New targets for exploring neuroimmune communication in epileptogenesis are chemokines, which control leukocyte migration and have a possible role in neuromodulation. Also, prostaglandin E2 (PGE2) is an important effector molecule for central neural inflam-matory responses and may be influencing drug responsiveness.

Methods: We measured serum interictal quantitative levels of chemokines (CCL2, CCL4, CCL11) and PGE2 in corre-lation with seizure frequency and severity in controlled and intractable childhood epi-lepsies.

Results: Our refractory seizure group demonstrated significantly increased concentra-tions of eotaxin (CCL11) compared to the controlled epilepsy group. The higher level of CCL11 was correlated with increased seizure frequency, PGE2 levels was associated with severity of seizure and epilepsy.

Conclusions: These are supporting the findings that proinflammatory cytokines may contribute to epileptogenesis and possibly have a role in developing seizure resistance.

Keywords:
: paediatric epilepsy, refractory seizures, cytokines, chemokines, neuroinflammation

EPNS23-2889 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Effectiveness and tolerability cannabidiol (Epidiolex) in pediatric intractable epilepsy; The UAE experience

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Objective: Cannabidiol (Epidiolex) oral solution is approved for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome and Tuberous sclerosis, in patients two years of age and older.
Epidiolex's effectiveness has not been studied in children with refractory epilepsy under 2 years of age which may not have the classical Lennox-Gastaut syndrome or Dravet syndrome.

Our aim was to study the effectiveness Cannabidiol in children with refractory epilepsy of varied etiology who have failed multiple anti-seizure medication, VNS and ketogenic diet and were started on cannabidiol as addon medication for seizure control.

Methods: We prospectively and retrospectively followed children (0-18 years) with refractory epilepsy following in the pediatric neurology clinic in Sheikh Khalifa Medical City, UAE between January to December 2022.

Results: 17 children (mean age of 4 years) were identified. 4 children were under 2 years of age. The aetiology varied from HIE, malformation of cortical development, tuberous sclerosis, Dravet syndrome (SCN1A), genetic developmental and epileptic encephalopathies and autoimmune encephalitis (FIRES / NORSE).
Mean anti-seizure medications prior to starting Epidiolex was 5.
9 children already had VNS and tried on ketogenic diet.
Epidiolex dose varied from 12 to 25 mg / kg / day. In 9 children 50 % and in 5 children 75 % seizure reduction was observed with in 2 to 4 weeks of starting Epidiolex. 3 children became seizure free with rare breakthrough seizure during illness. Seizure control in 4 children was short lived (under 6 months). 13 children are currently on Epidiolex for more than 6 - 12 months.
In children who had refractory epilepsy for more than 5 years, autoimmune encephalitis, and lissencephaly showed less than 50 % seizure reduction. Adverse events were minimal and not dose related. One child had irritability at the start of cannabidiol and two children had deranged LFT which improved with valproate reduction.

Conclusions: Epidiolex is an effective adjunctive therapy for refractory seizure control in children under 2 and with epileptic encephalopathies / syndromes outside Lennox-Gastaut syndrome or Dravet syndrome. Further studies are needed to study its effectiveness in under 2 years age and acquired etiology like HIE, autoimmune encephalitis.

Keywords:
Cannabidiol, refractory epilepsy

EPNS23-2117 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

12-Month Effectiveness and Tolerability of Brivaracetam in Paediatric Patients in the Real-World: Subgroup Data from the EXPERIENCE Analysis

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Objective: To evaluate effectiveness and tolerability of brivaracetam (BRV) in paediatric patients (<16 years of age) in routine clinical practice.

Methods: Subgroup analysis from EXPERIENCE/EPD332, a pooled analysis of retrospective cohorts that included patients with epilepsy initiating BRV in clinical practice. ≥50% seizure reduction from baseline, seizure freedom (SF; no seizures within 3 months prior to timepoint), continuous SF after baseline (CSF; no seizures reported for any timepoint after baseline), and treatment-emergent adverse events (TEAEs) since prior visit were assessed at 3, 6, and 12 months. Patients with <6 months of follow-up were excluded. Patients with missing data after BRV discontinuation were considered non-responders and not seizure free.

Results: This analysis included 66 paediatric patients; 65.2% were male, 18.2% were aged 0-5 years, 45.5% aged 6-11 years, and 36.4% aged 12-15 years. Median time since epilepsy diagnosis was 6 years; 63.6% and 37.9% of patients had focal-onset and generalized-onset seizures, respectively. At baseline, patients had a mean of 7.2 prior antiseizure medications (ASMs; any ASM used and stopped before BRV initiation); 2 (3.0%), 6 (9.1%), 21 (31.8%), and 37 (56.1%) patients had 0-1, 2-3, 4-6, and ≥7 prior ASMs, respectively. The mean number of concomitant maintenance ASMs at index was 2.1. The median BRV dose at index was 1 mg/kg/day (Q1-Q3, 0.9-1.70 mg/kg/day; n=58). Patients were exposed to BRV for a median of 375.0 days (Q1-Q3, 200.0-730.0 days; n=66). ≥50% seizure reduction from baseline (n=64) was 32.8% at 3 months, and 31.3% at 6 and 12 months. 15.2% of patients were seizure-free at 3, 6, and 12 months (n=66). CSF was experienced by 15.2% of patients at 3 and 6 months, and 12.1% of patients at 12 months (n=66). TEAEs (since prior visit) were reported in 12/66 (18.2%) patients at 3 months, 10/66 (15.2%) patients at 6 months, and 3/62 (4.8%) patients at 12 months. TEAEs at 3 months (n=66) were somnolence (5 [7.6%]), irritability (5 [7.6%]), insomnia (3 [4.5%]) and dizziness (1 [1.5%]). No patients discontinued BRV at or before 6 months, 27/66 (40.9%) discontinued at 12 months, and 16/66 (24.2%) discontinued after 12 months.

Conclusions: In this analysis in a real-world setting, BRV appears both effective and well tolerated in a highly drug-resistant paediatric patient cohort.

Keywords:

Brivaracetam; Effectiveness; Tolerability; Paediatric; Real-World

EPNS23-2016 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

"Efficacy of repetitive transcranial magnetic stimulation (rTMS) therapy in Electrical status epilepticus in sleep syndrome (ESES) in children: A single arm intervention study"

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Objective: We analyzed the effect of rTMS on sleep EEG and neurobehavioral profile of children with ESES at 16±2 weeks of therapy. Baseline and change in regional glucose metabolism of the brain on PET scan and functional connectivity on resting-state functional MR imaging(fMRI)were compared between treatment responders and non-responders.

Methods: Twenty children(5-12 years) with ESES (SWI in sleep EEG >50) were recruited. Seizure focus was identified using interictal/ictal video EEG, brain MRI, and PET CT scan. Cognition and behavior were assessed via valid psychometric tools. Three cycles of rTMS were offered (1st cycle of 10 daily sessions at baseline, 2nd cycle and 3rd cycles of five days each at week 8 and week-12 from baseline. Each session comprised of low frequency (0.5Hz), high intensity (110% of resting motor threshold),and 1200 pulses (2 trains of 600 pulses) using figure-of-8 coil targeted over seizure focus; duration 40 minutes. Clinical responders were defined as having a change in adaptive behavior composite standard(ABCS) score on Vineland adaptive behavioral scale (VABS-II) >15 with improvement (change in domain score >2) documented in at least two domains.

Results: The mean age of the study cohort was 8.98 + 2.94 years. The Etiology of ESES was structural in 55%; presumed genetic in 45%. All children tolerated the therapy cycles well. No attrition occurred,no major side effect was noted in study participants. The mean ABCS score improved in the study group (base line:204.25 ± 55.54; post-therapy: 213.7 ± 51.99 (p= 0.0432). The mean change in SWI was 18.9 %(8.06 - 29.73, 95% CI) (p=0.0008). Ten children (50%) qualified as clinical responders. Receptive language showed a maximum response (baseline v-score 9.4±3.7; post therapy 13± 3.7, p 0.0048). The ROI to ROI connectome analysis revealed that clinical responders had an increase in functional network connectivity in language, default mode network (angular gyrus, precuneus, and cuneus), and primary and secondary visual, motor, and auditory network (p <0.001FDR). Responders showed a significant change in glucose metabolism post-therapy in regions associated with the default mode and salience networks.

Conclusions: Targeted rTMS improves the neurobehavioral profile and EEG of a subset of children with ESES. A head-to-head comparison with steroids should be considered in future studies (CTRI/2021/03/031976).

Keywords:

Electrical status epilepticus in sleep, Spike wave index, Repetitive transcranial magnetic stimulation, Neurobehavioural Profile , Vineland Adaptive Behavior Scales -II

EPNS23-2814 Oral or e-Poster
Epilepsy: Diagnosis and Investigations

Types of focal cortical dysplasias and drug-resistant epilepsy

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Case study: Introduction. Focal cortical dysplasias are a frequent cause of pharmacoresistant epilepsy with childhood onset. The proposed new classification in 2022 points to the importance of studying structural changes and genetic causes of extinction. Genotype-phenotype features can indicate specific manifestations and prognosis of the disease.

Objectives: To present the types of focal cortical dysplasias, localization, clinical manifestations and results after surgery.

Methods. ILAE classification of epilepsy, video electroencephalography, magnetic resonance imaging, histological, immunohistochemical study of the brain, Engels classification.

The results. Clinical cases among girls with drug-resistant epilepsy and FCD of the frontal lobe: 6 years, 7 years, and 14 years. The girls started with focal seizures followed by bilateral synchronous tonic-clonic seizures. Ictal recordings of VEEG and MRI of the brain showed changes in the frontal lobe. Selection of anticonvulsant therapy was not very effective. A significant reduction in the frequency of attacks was noted when Sultiam was used in girls with typical "fencer's pose" attacks (reduction from 120 to 5 per day). According to histological examination, she was diagnosed with PCD IIb. A patient with FCD IIa and a vagus nerve stimulator installed failed to achieve complete seizure control (Engels II)

Conclusions. Among the presented clinical cases for 2022, it was frontal localization in girls (FKD Ia, IIb, IIc). As a result, the best control of attacks was noted with FCD IIb and FCD IIc - Engels IA.

Keywords:
Focal cortical dysplasias, pharmacoresistant epilepsy

EPNS23-2700 Oral
Epilepsy: Medical & Surgical Treatment

Analyses of cytokine-chemokine profiles in mesial temporal lobe epilepsy with hippocampal sclerosis.

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Objective: Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is the most common drug-resistant epilepsy. Approximately 30% of patients with MTLE-HS do not respond to currently available antiepileptic drugs. For the development of new treatment strategies for pharmaco-resistant MTLE, it is critical to understand the molecular mechanisms of development of pharmacoresistance and epileptogenesis in MTLE-HS. The altered neuroimmune response is one of the pathomechanisms linked to progressive epileptogenesis in MTLE-HS, and understanding its role may help design future cures for pharmaco-resistant MTLE-HS. Here, the neuroimmune function was evaluated by the assessment of cytokine-chemokine profiles in brain samples from the hippocampus of patients with MTLE-HS.

Methods: Brain samples from patients with MTLE-HS collected during epileptosurgical resection (n = 21) were compared to those obtained from autopsy controls (n = 13). The typing of HS was performed according to ILAE consensus classification, and patients were additionally sorted into subgroups based on the severity of neuronal depletion (Wyler grading system). Differences between patients with MTLE-HS with and without a history of febrile seizures were also assessed. RNA was isolated from native samples, and real-time gene expression analysis
of cytokine-chemokine profiles, especially levels of IL-1beta, IL-6, IL-10, IL-18, CCL2, CCL3, CCL4, and STAT3, was carried out by qRT-PCR methodology.

Results: Upregulation of IL-1beta ($p = 0.001$), IL-18 ($p = 0.0018$), CCL2 ($p = 0,0377$), CCL3 ($p < 0.001$), and CCL4 ($p < 0.001$) in MTLE-HS patients was detected when compared to the post-mortem hippocampal samples collected from autopsy controls. The STAT3 expression was higher in more severe neuronal loss and glial scaring determined by different Wyler grades in HS patients. Additionally, cytokine-chemokine profiles were not
different in MTLE-HS patients with or without febrile seizures.

Conclusions: The upregulation of specific cytokines and chemokines in MTLE-HS confirm the theory that the neuroinflammatory process contributes to MTLE epileptogenesis. History of febrile seizures did not alter the immune profiles. Understanding of the complex role of specific immune mediators and related immune pathways represent potential therapeutic targets for seizure control and pharmacoresistancy prevention in MTLE associated with hippocampal sclerosis.

Keywords:
Hippocampal sclerosis; pharmacoresistance; cytokine; chemokine; epileptogenesis

EPNS23-2975 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Cannabinoids in the treatment of epileptic encephalopathies - experience from a tertiary epilepsy center in Croatia

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Case study: Objectives: Epileptic encephalopathies (EEs) are a large group of treatment-resistant epilepsy syndromes with onset in childhood characterized by frequent seizures and poor cognitive, behavioral, and social outcomes as well as developmental stagnation or regression. They are usually a genetic etiology. Conventional antiseizure medications (ASMs) are usually used for the treatment of EEs with discouraging results. Drug resistance is frequent, and the persistence of seizures and electroencephalographic (EEG) epileptiform abnormalities contribute to the catastrophic consequences on cerebral functions in the developing brain. As EEs are usually refractory to standard ASMs, alternative options are looked for.
Since ancient times, cannabis has been used for recreational and medical purposes, including epilepsy, pain, and anorexia. Cannabis has more than 80 phytocannabinoids, of which delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most represented. Currently, CBD is the molecule most extensively studied for its therapeutic potential in the treatment of epilepsy. Numerous randomized control trials confirmed efficiency of CBD as add-on treatment in patients with Dravet syndrome, Lennox-Gastaut syndrome and tuberous sclerosis. CBD has favorable safety profile, and the most common adverse effects and drowsiness, loss of appetite and weight loss.
The aim of our study is to present experience with CBD preparations for treatment of EE in a single, third-level epilepsy center in Croatia.
Methods: The study was conducted retrospectively at the tertiary epilepsy center of the Department of Pediatrics, University Hospital Rijeka, Croatia. The cohort included 22 patients with EE, treated with CBD from December 2017 to December 2022. The CBD dose ranged from 8-20 mg/kg/d.
Seizure frequency was assessed by parental report during clinical visits.
Results: Nineteen patients were included in analysis. Ten (53%) patients had a more than 50% improvement regarding seizure burden, 2 of whom (10,5%) became seizure-free. In one patient worsening of seizures was reported, and CBD had no effect in 5 (26,3%) patients. Adverse effects were reported in one patient.
Conclusion: In our study, CBD as adjunctive treatment for patients with EE showed to be safe, well tolerated, and effective in reducing seizure burden. Obtained results gives opportunities for advanced approach in treatment of patients with EE, and possibilities for future prospective studies regarding use of CBD.

Keywords:
cannabinoids, CBD, epilepsy, epileptic encephalopathies

EPNS23-2813 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Long-term effect of early ketogenic diet on PNKP mutation-associated epileptic encephalopathy

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Case study: 4-year-old male diagnosed with microcephaly, seizures, and developmental delay syndrome (OMIM #613402) -described by Shen *et al* in 2010 and since then less than 20 cases have been reported worldwide- due to a homozygous mutation in the PNKP gene (c.1299-2A>T, c.793A>G), causing progressive microcephaly of up to -4SD with radiological signs of brain atrophy -generalized decrease in white matter and diffuse thinning of the corpus callosum-, delayed psychomotor development -autonomous gait at 18 months and first referential disyllables at 24 months- and drug-resistant epilepsy with onset at 3 months with focal to generalized seizures in the form of up to 6 afebrile seizure status up to 10 months, despite treatment with various antiepileptic drugs in various combinations, as well as dozens of focal to generalized seizures daily.
Given the refractoriness of epilepsy to drug treatment, a 2:1 ratio ketogenic diet (KD) was introduced early at 10 months of age, being well tolerated, with a striking reduction in the frequency and intensity of seizures, no new convulsive statuses and improvement in interaction with the environment, showing more reagent. This beneficial effect of the KD was maintained during the time it was received and also in the long term after its withdrawal according to the protocol 24 months after the start. 18 months after the withdrawal of KD, reduction of frequency and intensity of seizures is maintained -two episodes per month of focal seizures less than a minute- with levetiracetam, lacosamide and clobazam.
The good response to the ketogenic diet marked a before and after in the clinical evolution of this patient.
Probably, the early establishment of the ketogenic diet in this and other genetic syndromes that occur with refractory epilepsy can help to better control seizures, even partially improve their psychomotor development.

Keywords:
PNKP, ketogenic diet, epileptic encephalopathy, microcephaly, developmental delay

EPNS23-3001 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Evaluation of medical treatment and brain magnetic resonance imaging (MRI) in children with electrical status epilepticus in sleep (ESES): A single-center experience

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Objective: The aim of this study was to evaluate electroclinical spectrum, brain magnetic resonance imaging (MRI), treatment response and the efficacy of different therapeutic agents in children with electrical status epilepticus in sleep (ESES).

Methods: Clinical data of 63 patients with ESES who were treated, and followed between 2008 and 2022 were retrospectively analyzed. The diagnosis of ESES defined as spikes and waves enclosing more than 50% of the non-REM sleep EEG tracing.

Results: The median age at first afebrile seizure was 3.3 years (range 24-150 months) and the median age at the onset of ESES was 6.4 years (range 11-186 months). Neurological examination was abnormal in 29 patients (46%), and before ESES period, 34 patients (53.9%) had neurocognitive retardation. 37 patients (%58.7) had pathological brain MRI findings. Abnormal findings were predominant grey matter injury in 17 patients , predominant white matter injury in 16 patients, and thalamus lesion in 3 patients. No significant correlation was found between MRI findings and treatment response. Levetiracetam, valproic acid, clobazam and sulthiame were used most frequently. Clobazam was found to be the most effective treatment (%71 complete seizure control) and sulthiame was found to be the most effective treatment on EEG abnormalities, reduction in the spike-wave index (SWI) more than 50% (%58). There was a significant correlation with patient who had normal neurocognitive state before ESES period and seizure control ($p < 0.04$). In addition, complete seizure control was significantly higher in patiens who had Less than monthly seizure frequency ($p=0.02$).

Conclusions: These results indicated that MRI findings have no significant correlation with seizure control and reduction of the SWI on the EEG in children with ESES. On the other hand, seizure control correlated significantly with neurocognitive state and seizure frequency and clobazam was found to be very effective in complete seizure control.

Keywords:
Epilepsy; electrical status epilepticus in sleep (ESES); magnetic resonance imaging (MRI); antiseizure treatment.

EPNS23-2119 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

Long-term Safety and Efficacy of Adjunctive Brivaracetam in Pediatric Patients with Epilepsy: An Open-label, Follow-up Trial

List of authors:

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Objective: To evaluate long-term safety, tolerability, and efficacy of brivaracetam (BRV) as adjunctive treatment in pediatric patients with epilepsy.

Methods: N01266 (NCT01364597) was a phase 3, open-label trial that enrolled patients aged ≥1 month to <17 years with epilepsy who completed other BRV trials, and directly enrolled patients aged ≥4 to <17 years with focal seizures (FS). Patients received adjunctive BRV as tablets/oral solution (≥5 mg/kg/day, not to exceed 200 mg/day). Planned trial participation ≥3 years (until pediatric approval of BRV for patient's age group, establishment of managed access program, transition to another BRV trial, or trial termination). Primary tolerability outcomes: treatment-emergent adverse events (TEAEs); serious TEAEs. Efficacy outcomes based on daily record card data: percent change in 28-day adjusted FS frequency (patients with FS only) and 50% responder rate (RR) for all seizure types, assessed from baseline to end of evaluation period (final evaluation/early discontinuation visit; duration of evaluation period varied). Seizure assessments were performed for subgroups of patients aged ≥2 and <2 years with evaluable data. Kaplan-Meier estimated retention on BRV was assessed.

Results: 257 patients had ≥1 BRV dose (141 [54.9%] male; mean age: 8.0 years; age group: <2 years, 36 [14.0%]; ≥2-<4 years, 15 [5.8%]; ≥4-<12 years, 141 [54.9%]; ≥12-17 years, 65 [25.3%]). 185 (72.0%) patients had history of FS. Mean BRV exposure: 3.2 patient-years; 1 patient was exposed for 114.3 months. 124 (48.2%) patients completed, and 133 (51.8%) discontinued the trial. Most common reasons for discontinuation (≥10% of patients): lack of efficacy (39 [15.2%]); adverse event (32 [12.5%]); withdrawn consent (29 [11.3%]). 240 (93.4%) patients had ≥1 TEAE. 83 (32.3%) had serious TEAEs. 7 patients died (no deaths considered treatment-related). Patients aged ≥2 years had median decrease in 28-day adjusted FS frequency of 62.9% (n=105; range -693.7, 100.0); 50% RR (all seizures) was 50.9% (81/159). Patients aged <2 years had median decrease in 28-day adjusted FS frequency of 96.9% (n=10; range 45.4, 100.0); 50% RR (all seizures) was 68.2% (15/22). Kaplan-Meier estimated retention on BRV at 12/24/36/48/60/72 months was 72.7%/64.5%/57.8%/53.3%/50.1%/44.8%.

Conclusions: Long-term data showed adjunctive BRV was generally well tolerated and efficacious in reducing seizure frequency in patients ≥1 month to <17 years of age.

Keywords:

Brivaracetam, Effectiveness, Tolerability, Paediatric, Long term

EPNS23-2440 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

High-dose perampanel as two divided doses : The effective way to control epilepsy and reduce side effects

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Objective: In epilepsy patients treated with high-dose perampanel (6-8 mg or more once a day), the effect of controlling epilepsy is excellent, but side effects often occur, which limit its use.
We hypothesized dividing high-dose perampanel into two doses could reduce side effects maintaing its efficacy, and aimed to assess the efficacy and side effects of high-dose perampanel in two divided doses versus once-daily dosing.

Methods: We conducted a study from January 2019 to December 2022, among 32 epilepsy patients treated with perampanel at the Department of Pediatrics at Bucheon St. Mary's Hospital, South Korea. The dose of perampanel was increased for patients who could not be controlled with a low dose. The control group was administered perampanel once a day as the conventional method, and the experimental group was administered perampanel in two divided doses.

Results: Of the 32 patients with epilepsy, 26 patients received high-dose perampanel. Among them, 14 patients were administered as a single dose and 12 patients as two divided doses.
Among 14 patients who took perampanel as a single dose, 4 patients showed an effect of controlling epilepsy and had no side effects. 10 patients discontinued high-dose perampanel, of which 8 discontinued due to side effects and 2 discontinued due to ineffectiveness.
Among 12 patients who took perampanel as two divided doses, 10 patients showed an effect of controlling epilepsy and had few or no side effects. 2 patients discontinued high-dose perampanel, of which one discontinued due to side effects and the other discontinued due to ineffectiveness.

Conclusions: Although perampanel is an excellent antiepileptic drug, its use has been limited due to side effects at high doses. However, with high-dose perampanel as two divided doses, patients may not only achieve seizure control but also reduce side effects.

Keywords:
perampanel, dose, efficacy, side effect

EPNS23-2556 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

Etiologic heterogenicity of pyridoxine responsive seizures and long-term outcome in cohort of 15 infants

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Objective: Evaluation of etiology, clinical course and long-term outcome in children with pyridoxine responsive seizures (PRS).

Methods: The study included all children with PRS treated in Institute from 2001-2022. Pyridoxine was initially given as intravenous infusion (100 mg/day in two consecutive days) followed by 20 - 30 mg/kg/day per os. Serial video EEG, brain MR, metabolic and genetic analyses were done in all cases. The patients were divided in two groups: patients with mutation in ALDH7A1 or PNPO genes (I group) and patients with other etiology (II group). Outcome at the end of follow-up included neurologic development and seizure control. The impact to outcome of further parameters to outcome was analyzed: the age of seizure onset; period from seizure onset to pyridoxine introduction; brain MR, type of seizure, etiology, and necessity for additional ASM. For statistical analyses Mann Whitney test and Spearman's rang correlation were used.

Results: Fifteen children were included, nine in I group (7 with ALDH7A1 and 2 with PNPO mutation) and six in II group (microcephaly (1), cerebrovascular insult (1), HIE (1), SLC13A5 gene mutation (1) and cryptogenic (2)). There is no significant defference between two groups in mean age of seizure onset (5.5 days vs. 4.7 days), mean period from seizure onset to pyridoxine introduction, and seizure types. Brain MR showed abnormalities in 4/9 pts in I group and 2/6 in II group. Mean duration of follow-up period was 6.7 years. At the end of follow-up period, normal development had 6/9 patients in I group and 3/6 patients in II, while good seizure control had 6/9 patients in I group and 5/6 patients in II. Pesence of MR abnormalities correlated statisticaly significant (p =0.024) with necessity for additional ASM and developmental delay in patients from I group.

Conclusions: The etiology of PRS includs related genetic mutations (ALDH7A1 and PNPO), structural brain disorders and mutations in other genes. Etiologic heterogenicity suggests introduction of pyridoxine in all infants if two ASM were failed. We found normal development and good seizure control in 66.7% children with ALDH7A1 and PNPO mutations. Half of the patients with other etiology had normal development and better seizure control (83.3%). In children with pyridoxine dependent seizure, association of MR abnormalities were in colerration with poor outcome in term of developmental delay and necessity for additional ASM to achive seizure control.

Keywords:

epilepsy, pyridoxine responsive, ALDH7A1

EPNS23-2857 Oral
Epilepsy: Medical & Surgical Treatment

Baseline characteristics and determinants of treatment effect in epileptic encephalopathy with spike wave activation in sleep (RESCUE ESES Trial)

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Objective: Epileptic encephalopathy with spike wave activation in sleep (EE-SWAS) is a devastating childhood epilepsy syndrome. The goal of treatment is to improve neurodevelopment. This international European multicentre randomised controlled trial was performed between 2013 and 2022 and aimed to compare the effects of starting treatment with either corticosteroids or clobazam. Here, we present baseline characteristics and clinical predictors of treatment effect. Trial results are described separately.

Methods: Patients were eligible when 2-12 years of age, diagnosed with EE-SWAS within 6 months prior to study inclusion and not previously treated with either clobazam or corticosteroids. Linear regression analysis was used to compare demographic and disease-related factors with treatment effect, defined as the difference in total intelligence quotient (delta IQ) after 6 months of treatment that started with either corticosteroids or clobazam. Predictors assessed were: age at diagnosis, time interval from EE-SWAS diagnosis to inclusion, IQ and cognitive sum scores (Z-score based on tests covering 6 cognitive domains) at inclusion, number of anti-seizure medications (ASM) before inclusion, and etiology, dichotomized as unknown versus structural or genetic.

Results: The trial was prematurely terminated for feasibility reasons. Of the 45 patients enrolled 23 were randomly assigned to clobazam and 22 to corticosteroids. The majority of patients were male (66.7%), had a structural/genetic etiology (57.8%) and had tried at least one ASM (73.3%). At baseline, mean total IQ was 75.4 (± 20.7), mean cognitive sum score was -1.7 (± 1.4) and median spike wave index (SWI) was 8.0 (IQR 13.0). Mean age at seizure onset was 4.2 years (± 2.7) and mean age at EE-SWAS diagnosis 6.5 years (± 2.2). In univariate regression analysis, starting treatment with corticosteroids (β = 5.6 CI 0.3 - 10.8, p = 0.039) and having an unknown etiology (β = 7.5 CI 2.6 - 12.5, p = 0.004) were significantly predictive of a higher delta IQ. This effect sustained in a multivariate analysis with a backward selection procedure (adjusted R2 0.265, p = 0.002).

Conclusions: In this selected cohort, effect of treatment in EE-SWAS was not only predicted by type of treatment initiation. Having an unknown etiology also related to a better treatment effect. These findings guide counselling and caring for patients with EE-SWAS.

Keywords:
CSWS, ESES, EE-SWAS, clobazam, corticosteroids, cognition, epilepsy, neuropsychology, sleep

EPNS23-2362 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Report of life threatening ictal apnoeas responsive to Ketogenic Diet

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Case study: Objectives:
To report a case of prolonged ictal apnoeas responsive to ketogenic diet
Methods:
Clinical data, laboratory findings, neuroimaging and ictal/interictal video EEG recordings of the patient were revised
Results:
The patient had a complex background with macrocephaly, developmental delay and low tone. Initial investigations (including neuroimaging, repeated EEGs, metabolic and genetic tests) were normal. Her seizures started on the first year of life, they were stereotyped, tended to happen during sleep and consisted on grunting noises and hypersalivation while the patient was unaware with eyes opened. She was started on Levetiracetam as they were suspected to be epileptic. Around the age of 20 months the episodes started associating a complete cessation of the respiratory effort and profound desaturation lasting up to 11 minutes. She was assessed on an Epilepsy Tertiary Unit where she had a repeated MRI which showed bilateral areas of polymycrogyria and heterotopies suggesting m-TOR macrocephaly spectrum. Trio exome didn't find patogenic variants. A typical event was captured during a sleep study there and the recording showed generalised abnormalities, Valproate was started then. Lacosamide, Topiramate, Oxcarbazepine and Zonisamide were also tried with little benefit as life threatening seizures occur several times a week and were prolonged. Parents received basic life support training and during the periods when she was discharged home they were provided with oxygen saturation monitor, oxygen and an airway bag mask unit to use in case of seizures. Given the drug ressitancy it was decided to initiate ketogenic diet and during the induction of it her epilepsy settled remaining seizure free for the first time for weeks. Seizures re-occured on the diet but they are infrequent, mainly related to intercurrent illness and don't associate prolonged apnoea. The patient's quality of life has improved dramatically with the diet on which she remains with good tolerance.
Conclusions:
Prolonged ictal apnoeas are unusual in children. Ketogenic diet was effective in this patient and despite she does not remain seizure free, the features of the seizures have changed being now safe for the patient being out of hospital. The ketogenic diet should be considered earlier as treatment in patients with these type of seizures.

Keywords:
Ictal apnoeas, ketogenic diet

EPNS23-2264 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

Efficacy of stiripentol in the management of status epilepticus

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Objective: Stiripentol (STP) is indicated for use as add-on therapy to clobazam (CLB) and valproate (VPA) of seizures associated with Dravet syndrome (DS). We collected evidence of the efficacy of STP in preventing or terminating status epilepticus (SE) both in DS and non-DS patients.

Methods: An electronic literature search not restricted either by year of publication nor by language was conducted with Boolean operators, i.e. "(stiripentol) AND (status epilepticus)". Backward citation searching was also conducted manually. Databases used were Cochrane [Wiley] and PubMed [NLM].

Results: 26/60 references identified included data on SE efficacy and safety after STP treatment. Reports in rodents demonstrated the age-dependent anticonvulsant efficacy of STP during prolonged SE, with greater potency in juvenile animals. Accordingly in humans, STP initiation lead to: (i) SE disappearance (10/46) or less numerous (20/46) in DS patients on STP+VPA+CLB, with better decrease in young patients; (ii) Decreased seizure duration in 10/23 patients, disappearance of SE or seizure clustering in 1/23 patient and decrease in frequency in 5/23 patients treated with add-on STP; (iii) ≥50% decrease in SE frequency in 11/26 DS patients (9 with at least 90% reduction in SE events, 7 without SE); (iv) No records of SE in 8/11 of patients in a retrospective study; (v) Reduced prolonged seizure frequency and frequency of use of rescue medication and emergency room (ER)/hospital visits in most of 82 children receiving STP; (vi) Non-observed prolonged seizures or SE or ER visits in 3 patients with drug-resistant SLC13A5-related epileptic encephalopathy after STP in combination with topiramate and carbamazepine; (vii) Cessation of super-refractory SE (SRSE) in 3/5 patients (median age 78 years, interquartile range 11 years) within 2-4 days after first STP administration; (viii) SE cessation (mean time to cessation 30.8 days, range 18-46) without additional adverse effects in 10 adult patients with SRSE after add-on STP. Moreover, STP + ketogenic diet seemed useful in SRSE.

Conclusions: STP is an effective and well-tolerated therapy that should be introduced as early as possible in DS patients in order to suppress SE. In addition, STP is useful to treat SE in patients with drug-resistant SLC13A5-related epilepsy and SRSE.

This study was supported by Biocodex.

Keywords:

dravet;syndrome;stiripentol;status;epilepticus;prolonged;seizure;disappearence;epilepsy;seizure;review;randomized;clinical;trial;early;treatment;tonic;clonic;rare disease;neuropediatry;neurology;pediatry;clobazam;valproate;drug resistent

EPNS23-2403 Oral
Epilepsy: Medical & Surgical Treatment

Hand Postures' Lateralization and Localization Values in Epileptic Patients at Video EEG Monitorization

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Objective: One third of pediatric patients with epilepsy are drug-resistant. Epilepsy surgery can be applied to appropriate patients when antiepileptic therapy is insufficient in resistant epilepsy. Long-term video EEG monitoring is performed to evaluate suitability for epilepsy surgery. The hand postures of patients with intractable epilepsy who underwent in our video EEG monitoring (VEM) unit during ictal activity and the relationship of these postures with the epileptogenic zone were evaluated.

Methods: The ictal activities of patients hospitalized in the video EEG monitoring unit between 2013-2021 were examined. Hand postures of patients during ictal activity were classified into six subgroups. These hand postures are defined as fist, politician fist, cup, pincer, extended hand and pointing. Epileptogenic foci of the patients were classified as generalized and focal. Also we noted the lateralization of hand during the seizure.

Results: Six hundred and seventy-four patients who were monitored in VEM unit were screened, and sixty-one patients were evaluated. The most common epileptic hand postures were "fist" and "politician fist";twenty-two and fifteen. Extended hand, cup, pointing and pincer postures were seen with decreasing frequency. The epileptogenic zone of 16 patients out of 61 was found to be generalized. It was observed that 12 patients originated from the temporal, 15 patients from the frontocentral, 12 patients from the frontotemporal, 4 patients from the temporoparietal, two patients from parietooccipital region. Also twenty-six patients had a contralateral hand posture, twenty-two patients had an ipsilateral.

Conclusions: Fist, politician's fist and extended hand posture were evaluated as contralateral lateralized sign, and pincer, pointing hand and cup postures were evaluated as ipsilateral lateralized signs. Hand postures can be used as lateralizing and localizing findings.

Keywords:
video EEG; intractable epilepsy, epilepsy surgery, localization; lateralization

EPNS23-2165 Oral
Epilepsy: Medical & Surgical Treatment

The Effect Of Long Term Use of Levetiracetam Therapy On Electrocardiography Parameters in Children

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Objective: The purpose of this study was to compare the electrocardiographic parameters before and at the two year of treatment of patients diagnosed with epilepsy and who were started on levetiracetam therapy.

Methods: The files of 20 patients diagnosed with epilepsy based on ILAE criteria at the Balikesir University Medical Faculty pediatric neurology clinic. Patients with additional chronic disease (such as hypertension, diabetes mellitus, congenital or acquired heart disease, or chronic lung disease), with different drug use histories (macrolides, antipsychotics, antidepressants, antihistaminics, or anti-arrhythmic drugs), or receiving polytherapy were excluded. Cases' clinical findings, electroencephalography (EEG), cranial magnetic resonance imaging (MRI) and electrocardiography data before and at the twenty four month of treatment were recorded.

Results: Twenty patients diagnosed with epilepsy and started on levetiracetam therapy were included in the study. The patients' mean age was 12,65±3.50 years. Nine (45%) patients were boys and 11 (55%) were girls. Four (20%) were found to experience focal seizures, and 16 (80%) generalized epilepsy-type seizures. EEG was normal in five cases (25%), focal epileptiform in 8 (40%) cases, and generalized epileptiform in character in 7 (35%). Cranial MRI was normal in 16 (80%) cases, but was interpreted as abnormal in three (15 %). When ECG parameters (PR interval, QTc, QRS and QT) were compared; at the 24th month of the treatment, the QT duration was prolonged compared to the pre-treatment values, and a statistically significant difference was found (p=0.009). Although there was a statistically significant difference among the gender between the PR interval before treatment and the QTc duration at the 24th month after treatment, these values were within the normal range (p=0.031, p=0.020).

Conclusions: Studies in the literature show that the dosage and duration of use of levetiracetam can also cause changes on ECG, that patients using the drug should be closely followed-up in terms of arrhythmia. The monitoring of patients' ECGs is particularly important from that perspective. Our study is important because there is no study in the literature examining the effects of long-term use (24 months) of levetiracetam treatment on ECG in children.

Keywords:
Epilepsy; Levetiracetam; Electrocardiography; Two year

EPNS23-2118 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Cognitive and Behavioral Effects of Adjunctive Brivaracetam in Children and Adolescents with Focal Seizures: Final Data From an Open-label Follow-up Trial

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Objective: To evaluate cognitive and behavioral effects of long-term adjunctive brivaracetam (BRV) in children and adolescents with focal seizures.

Methods: Post hoc analysis of final data from a phase 3, open-label, follow-up trial (N01266; NCT01364597; patients <16 years of age at entry into core trial; max 5 mg/kg/day BRV tablet or oral solution, not to exceed 200 mg/day). Planned trial duration was ≥ 3 years. Cognitive and behavioral outcomes were assessed with Achenbach Child Behavior Checklist (CBCL, patients aged ≥ 1.5-<6 and ≥6-16 years) and Behavior Rating Inventory of Executive Function (BRIEF; patients aged ≥2-<5 [BRIEF-P] and ≥5-16 years).

Results: 140 patients were analyzed (mean age: 9.5 years; 80 [57.1%] male). 32 [22.9%] patients were aged ≥1.5-<6 years [median exposure: 3.6 years], and 108 [77.1%] were aged ≥6-16 years [median exposure: 3.5 years]). Mean changes (baseline to last evaluation) for all Achenbach CBCL and BRIEF-P/BRIEF subscale scores were negative, reflecting stability/slight improvement. The largest decreases in CBCL were for aggressive behavior and anxious/depressed (both age groups) and other problems (≥1.5-<6 years). The largest decreases in BRIEF-P/BRIEF scores were for inhibit, working memory, and plan/organize (both age groups) and emotional control (≥2-<5 years). Most patients had no shift in T-score category (baseline to last evaluation) for each CBCL subscale (between normal and borderline or clinical range [BCR]) and BRIEF-P/BRIEF subscale (between normal and potential clinical significance [PCS]). For all CBCL subscales, higher proportion of patients changed from BCR to normal than from normal to BCR. Changes for BRIEF-P were mostly PCS to normal; for BRIEF, similar proportions of patients changed in either direction. Treatment-emergent adverse events (TEAEs) were reported in 100% and 95.4% of patients aged ≥1.5-<6 and ≥6-16 years (drug-related TEAEs: 31.3%, 30.6%; serious TEAEs: 21.9%, 27.8%; discontinuations due to TEAEs: 6.3%, 9.3%; deaths [not considered drug-related]: 3.1% [n=1], 1.9% [n=2]).

Conclusions: In this analysis, cognitive and behavioral functioning scores in children and adolescents with focal seizures during long-term adjunctive BRV therapy were generally stable or slightly improved. BRV was generally well tolerated.

Keywords:
Brivaracetam, Cognition, Behaviour, Paediatric, Long term

EPNS23-2844 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Repeated use of adrenocorticotropic hormone (ACTH) in treatment of epilepsy in childhood

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Objective: To analyze effectiveness and tolerability of repeated use of ACTH in epilepsy treatment in childhood.

Methods: Retrospectively we analyzed 24 children who received ACTH twice in epilepsy treatment. We assessed age at seizure onset, type of seizures, time lapse between ACTH administrations, effectiveness and tolerability of second ACTH treatment. We also compared responders (patients with a reduction of seizures >50%) and non-responders.

Results: Median age at seizure onset was 5,1 mts. (range 0,1 - 45,0 mts.), at first ACTH administration 12,0 mts. (range 3,23 - 54,5) and at second ACTH use 24,9 mts. (range 7,6 - 61,0). Median of time lapse between ACTH administrations was 5,52 mts. (range 2,6 - 33,2). 14 children (58,3%) had epileptic spasms, 8 children (33,3%) had generalized seizures other than tonic-clonic and 2 patients had focal seizures (8,3%). The most common etiology was genetic (9 cases, 37,5%), followed by structural (7 children, 29,2%) and unknown cause (5 children, 20,8%). 20 children (83,3%) were responders to first ACTH administration and 14 (58,3%) to the second one. Adverse events were present in 12 cases (50%) during first ACTH use, and in 8 children (33,3%) at its second use. Adverse events led to termination of treatment in 3 cases (12,5%) at first use and in 2 cases (8,3%) at second treatment. Comparing responders to non-responders after repeated use of ACTH, there was no significant differences in terms of age at seizure onset, age at ACTH administrations, time lapse between ACTH treatments, proportion of responders after first ACTH use, etiology and seizure type.

Conclusions: In our cohort there was a lower effectiveness of repeated use of ACTH in comparison to its first administration. No significant predictive factors of positive responsiveness to repeated use of ACTH were found. Since there is a lack of data in the literature about the repeated use of ACTH in epilepsy, more studies are necessary to clarify this issue.

Keywords:
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EPNS23-2467 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

Response to Low Glycemic Index Diet Therapy (LGIT) in children aged 2-18 years with drug-resistant epilepsy

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Objective: In spite of the majority of children with epilepsy respond well to antiepileptic drugs and remain well-controlled, 25 %-30 % remain resistant to these drugs. Low glycemic index therapy (LGIT) is one of the alternative diet types to the ketogenic diet (KD) designed to facilitate KD administration. In this study, we aimed to report the efficacy, safety and tolerability of LGIT in our pediatric refractory epilepsy patients.

Methods: A retrospective review was performed on patients initiating the LGIT at the Pediatric Neurology Department , aged 2-18 years , between the years of 2020 and 2022. Demographic and clinical information including seizure type, baseline seizure frequency, medications, side effects, and anthropometrics were collected. Initiation of the LGIT was done in an out/inpatient setting. Patients were educated by a dietitian to restrict foods with high glycemic index and to limit total daily carbohydrates to 40-60 g. Changes in seizure frequency were evaluated first 3 months follow-up. Efficacy was graded using the following categories: (1) Complete response (100% seizure remission); (2) Good response (more than 50% reduction in seizure frequency); (3) Partial response (less than 50% reduction in seizure frequency); (4) No response (seizure frequency unchanged).

Results: Twenty patients (10 male and 10 female) with drug-resistant epilepsy were included in our study. While full response was detected in seizure frequency in 6/20 patients who underwent LGIT, good response was found in 10/20 patients, partial response was found in 2/20 patients, and there was no change in seizure frequency in 1/20 patients. Hypoglycemia was observed in 1/20 patient while applying LGIT, and 1/20 patient discontinued the diet because they could not comply with LGIT.

Conclusions: Our preliminary results such as that the LGIT was associated with reduced seizure frequency in most patients, with limited side effects.

Keywords:

Low glycemic index treatment, Drug-resistant epilepsy, Children

EPNS23-2781 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Lamotrigine effectiveness for eyelid myoclonia.

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Objective: Epilepsy with eyelid myoclonia is frequently misclassified as another genetic generalized epilepsy. Here we report a 3-year-old patient with eyelid myoclonia, and family history of absence seizures, responsive to lamotrigine.

Methods: Clinical history was obtained from the family and EEG was recorded. Brain MRI was performed. Epilepsy gene panel was done.

Results: Our patient is a 3-year-old girl with normal development. The patient had first febrile seizure in the first year of life, at this time EEG was normal. At the age of 3 years she developed eyed myoclonia and had one generalized tonic-clonic seizure. EEG was performed, which revealed 1-2 sec long bilateral spike/poly spike-slow waveactivitycorresponding to myoclonus. The patient was also photosensitive. Family history revealed that the father of the patient had absence seizures since childhood and was taking valproic acid till now. Brain MRI showed atrophic areas in frontal lobes, bilaterally and Arnold-Chiarimalformation. Epilepsy gene panel identified variant of uncertain significance in PRRT2 gene. Treatment with levetiracetam was initited, but wasn't effective. Levetiracetam was replaced with lamotrigine with significant reduction in seizures.

Conclusions: Lamotrigine is an effective drug option in cases of eyelid myoclonia.

Keywords:
Lamotrigine/eyelid myoclonia

EPNS23-2993 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

Evaluation of preoperative and postoperative EEG findings and seizure outcomes in pediatric epilepsy surgery: A single center experience

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Objective: Epilepsy surgery is effective method for treatment in appropriate cases in children with drug-resistant epilepsy and/or epileptogenic lesions.This study aimed to compare the demographic information,preoperative-postoperative EEGs and seizure outcomes of pediatric patients in different etiologies who underwent surgery for resistant-epilepsy in our clinic.

Methods: In this retrospective evaluation,46 pediatric patients underwent surgery for different etiologies in our clinic between 2016-2022 were included.Age,gender,seizure onset age,seizure frequency,time between seizure onset and surgery,type of surgery,preoperative-postoperative EEGs,and postoperative seizure outcomes were evaluated.

Results: The median age of seizure onset was 14 months(3 days-15 years)and median age at operation was 7 years(10months-17years).22(48%)patients were male and 24(52%)were female. Cortical developmental malformations were detected in 71.7% of patients,tumoral masses in 28.3%,and secondary causes in 2%.Two patients performed pre-surgical invasive work-up. Lobectomy(45.6%),lesionectomy(37%), hemispherotomy/hemispherectomy(4 patients),disconnection/collosotomy(5 patients)and combinations were performed.Temporal lobectomy and amygdalohippocampectomy were preferred in 32.6% of patients.Preoperative-postoperative EEGs were performed at a rate of 91.3%(42).Ictal activities were detected in 72.7% of patients in preoperative EEG(44)evaluation.Lateralization was obtained in 88.6%and localization in 68.1% of EEGs.Contralateral EEG findings were detected in 18% of patients.In first EEGs(37 patients) taken within 6 months postoperatively,59.4% interictal and 13.5% ictal activities were observed.In follow-up EEGs(33),63.6% interictal and 18.1% ictal abnormalities were detected 6 months after operation.Becoming seizure-free or more than half reduction in seizure frequency was achieved in 78% of the patients.A reduction in number of antiepileptic drugs was possible in 10 patients and discontinuation of drugs was possible in 3 patients at latest follow-up.Reoperation was required in 5 patients,because seizure control could not be achieved.

Conclusions: Epilepsy surgery is one of safe and effective treatment that can be applied under supervision of appropriate candidates determined by EEG in patients with resistant epilepsy due to different etiologies in childhood.In conclusion,our study determined that although surgical application was late in some patients,many patients had benefit clinically after surgery.

Keywords:

video-EEG monitoring,pediatric epilepsy surgery, resistant epilepsy

EPNS23-2275 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

EPILEPTIC PHENOTYPE & GENOTYPE CORRELATION IN PATIENTS WITH NEURODEVELOPMENTAL DISORDER WITH HEARING LOSS, SEIZURES, AND BRAIN ABNORMALITIES (SPATA5-related encephalopathy). IS KETOGENIC DIET A PRECISION TREATMENT? IN VITRO AND CLINICAL EFFECT

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Objective: Describe the epileptic phenotype and genotype correlation in patients with SPATA5-related encephalopathy (SPATA5-RE). SPATA5 deficiency led to abnormal mitochondrial dynamics. Analyze in vitro mitochondrial effects of ketogenic diet (KD), and clinical response in patients with refractory epilepsy.

Methods: Retrospective and prospective multicentric international study. Bibliographic review and patient's registry. Clinical, EEG and genetic data were assessed. Descriptive study and odds ratio (OR) calculation. KD treatment response (% seizure reduction). Patient fibroblasts grown in a KD-mimicking medium.

Results: 47 SPATA5-RE patients were included (38 previously published, and 9 new patients), 26 males, mean age 8.33 years. Clinical symptoms were: intellectual disability(97.73%), hearing loss(95.35%), microcephaly(86.96%), visual impairment(80.56%), hypotonia(74.42%), epilepsy(72.34%), spasticity(62.79%) and movement disorders(32.56%). Epilepsy features: generalized onset(90%): infantile spasms (IS)(70%), tonic(35%), myoclonic(25%); tonic-clonic(15%) and clonic(15%). All patients, except 1, had interictal epileptiform activity: multifocal 68.42% vs generalized 31.58%. Most patients presented refractory epilepsy (84.62%). 40 patients exhibited compound heterozygous variants. The most frequent variants were: c.2081G>A(14.89%), c.989_991del(12.77%), c.251G>A(9.57%) and c.1714+1G>A(7.45%). Association between some genetic variants and epilepsy was found: c.2081G<A (OR=0.0063; 95%CI=0.0004-0.1124;P=0.0006), c.989_991del (OR=5,7391;95%CI=1.2435-26.4878;P=0,0251), frameshift (OR=6.5455;95%CI=1.4232-30.1031,P=0,0158). 4 patients with refractory epilepsy received KD. Seizure reduction was 0, 30, 70, and 100%. Motor social interaction and awareness improved in 1 patient. Awareness in another patient. In vitro mitochondrial dynamics studies in patient's fibroblasts revealed an aberrant mitochondrial network with fusion-fission ratio alteration which recovered when incubated with KD-mimicking medium. Moreover, ATP production improved without an increase in oxidative stress in KD-medium.

Conclusions: This is the largest SPATA5-RE cohort focused in epilepsy phenotype. Epilepsy was present in 72.34%. Generalized onset, and IS were the most common seizure types. Deletion and frameshift variants were highly associated with epilepsy. Improvement of mitochondrial dynamics and ATP production by KD could explain the clinical benefits in seizure control.

Keywords:

SPATA-5; SPATA5-related encephalopathy;NEURODEVELOPMENTAL DISORDER WITH HEARING LOSS AND SPASTICITY; NEDHLS; KETOGENIC DIET

EPNS23-2636 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Assessment of the Unmet Medical Needs of Patients With Lennox-Gastaut Syndrome: A Survey in Collaboration With the European Collaboration for Epilepsy Trials Consortium

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Objective: Lennox-Gastaut syndrome (LGS) is a rare, treatment-resistant developmental and epileptic encephalopathy resulting from a large spectrum of aetiologies and characterized by a high burden of multiple seizure types and cognitive impairment. This survey was undertaken to assess the current state of care of LGS patients and identify unmet needs in Europe.

Methods: In September 2021, in collaboration with Zogenix (now a part of UCB), the European Collaboration for Epilepsy Trials (ECET) Consortium (https://epi-care.eu/european-collaboration-for-epilepsy-trials/), formally operating within the framework of the non-profit organization Epilepsy Alliance Europe (EAE), conducted a questionnaire survey. Specialized centres with expertise in rare and complex epilepsies were identified and recruited to participate. The survey requested the estimated number of patients who were adults vs children with LGS, the proportion of these patients previously and concomitantly treated with various antiseizure medications (ASMs), and the general effectiveness of their current ASM regimens. Participating centres also ranked 11 goals of treatment in order of importance.

Results: 61 centres, including European Reference Network EpiCARE reference centres, from 23 countries participated in the survey. 75% of the centres managed >=15 LGS patients; 36% managed only children, and 18% managed only adults. Seizure-related goals of treatment (eg, seizure-freedom, fewer drop seizures) were ranked as being the most important goals of care by 66% of centres, followed by quality-of-life improvements by 18% of centres. Nearly 90% of centres reported more than half of their patients experienced breakthrough seizures each month, and 38% of centres reported >50% of their patients experienced monthly drop seizures. The difficulty in managing LGS patients was illustrated by the fact that 69% of centres trialed 5 to 10 ASMs and 18% of centres trialed >10 ASMs in their search for an effective regimen for each patient. Nearly all centres (98%) indicated an unmet need exists for effective ASMs to treat LGS patients, and 87% of centres voiced support for new ASMs with novel mechanisms of action.

Conclusions: The responses to this survey support the existence of important unmet therapeutic needs for the treatment of LGS.
Funded by UCB Pharma.

Keywords:
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EPNS23-2058 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Successful Use of Pulse IV Methylprednisolone in Epileptic Encephalopathy

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Case study: Introduction:
Steroids have been used in epilepsy management typically for infantile spasms. Its use for epileptic encephalopathy (EE) beyond this is less frequent and limited by side-effects. We present a case of successful management of refractory seizures in a child with early EE using pulse intravenous methylprednisolone.

Case:
A 2 year old previously well boy with normal development presented with new onset of refractory seizures. These were initially generalised tonic-clonic and evolved over a period of weeks to include myoclonic jerks, absences, and drops. Alongside this, there was concern about speech regression. An initial EEG captured polyspike activity during a myoclonic jerk but was otherwise normal. His brain MR and extensive neurometabolic investigations were unremarkable, including CSF studies. A microarray and rapid trio exome did not reveal pathogenic mutations in relation to his refractory epilepsy. He was initially commenced on levetiracetam and sodium valproate, and over time, clobazam and topiramate were added. He had recurrent admissions to hospital with generalised seizures. Subsequent EEGs confirmed ongoing EE in keeping with Lennox-Gastaut syndrome. He was commenced on pulse IV methylprednisolone 30mg/kg once daily for 3 days. This was repeated monthly for a total of 3 months. He achieved complete seizure freedom within a week of commencing this treatment and his repeat EEG in the fourth month was normal with no evidence of encephalopathy. Apart from having no further hospital admissions with seizures, he made dramatic improvement with his speech and is now speaking in sentences.

Discussion:
Due to the side-effects of long-term use of prednisolone, there have been a number of studies recently reviewing the benefit of pulse IV methylprednisolone in EE in children. Rangarajan et al. found significant improvement in seizure control and EEG findings in children with EE without significant side-effects using this regime compared to those who just received anti-seizure medications. In another study by Chatterjee et al., the positive effects of using this regime for 3 months were sustained for over a year in some children.

Conclusions:
Pulse IV methylprednisolone is potentially a good and safe treatment option for children with EE, especially if considered early in their management. Further studies are needed to characterise the exact group of children this will benefit.

Keywords:
Epileptic encephalopathy; pulse intravenous methylprednisolone

EPNS23-2296 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Developmental and/or Epileptic Encephalopathy with Spike-and-Wave Activation in Sleep in Saudi Arabia: Electroclinical, Etiologic, Genetic, and Outcome Multicenter Study

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Objective: To investigate the clinical features of developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep (D/EE-SWAS), its electrographic characteristics, and etiology and to compare the effects of different treatment strategies on the outcomes.

Methods: This multicenter cohort study included children with D/EE-SWAS who were evaluated between 2010 and 2020 at 11 tertiary centers. Data were collected on their baseline clinical features, etiologies, and treatment modalities. Three measures of therapy response (improvement in clinical seizures, improvement in the spike-wave index [SWI], and cognitive state) were analyzed across treatments, controlling for baseline variables.

Results: Ninety-one children were diagnosed with D/EE-SWAS, with a median age of 7 years (interquartile range [IQR]: 3-5) and an almost equal sex distribution. The average age at which epilepsy was diagnosed was 3 years (IQR: 5-2). A genetic/metabolic etiology was found in 35.1% of the patients, and a structural etiology was found in 27.4%. Patients with underlying genetic/metabolic diseases exhibited an earlier seizure onset (P=0.001) than children with other etiologies; 62.3% of the patients showed an initial SWI of >85%. On average, each patient received three treatments. Benzodiazepines (76.6%) were the most common treatment, followed by steroids (51.9%). Sodium valproate (75%) was the most frequently used antiseizure medication, followed by levetiracetam (64.9%). Children with a later seizure onset were more likely to have better clinical responses (P=0.046), electroencephalogram (EEG) responses (P=0.012), and cognitive outcomes (P=0.006) than children with an earlier onset. Focal-onset seizures were found to have better SWI improvement (P=0.039) than other seizure types. Patients who received clobazam were seizure responders (odds ratio [OR] 0.539, 95% confidence interval [CI] 0.116-0.996, P=0.001) and EEG responders (OR 0.306; 95% CI 0.098-0.955; P=0.041). Children had a higher likelihood of both clinical and electrographic improvement with combination therapy of benzodiazepines (OR 1.327; 95% CI, 0.433-2.44; P=0.001) and steroids (OR 2.380; 95% CI, 0.546-3.857; P=0.001) than with other therapies.

Conclusions: This Saudi Arabian study shows a higher prevalence of genetic/metabolic causes and suggests the superior efficacy of combination therapy with steroids and benzodiazepines in D/EE-SWAS. Prospective studies that strictly assess the treatment protocols and outcomes are needed.

Keywords:
DEE-SWAS, ESES, CSWS, LKS, SWI, epilepsy

EPNS23-2536 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

Anakinra as acute and chronic treatment for FIRES patients: better motor and cognitive outcome

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Case study: Objectives: To describe the case of a patient with febrile infection-related epilepsy syndrome (FIRES) with better motor and cognitive outcome, and to propose anakinra as a treatment for both the acute and chronic phases.
Methods: We hereby describe the case of a 5-year old female who presented to the emergency room with an altered mental status 4 days after suffering from a febrile pharyngitis. After her admission at PICU, she started having repeated focal seizures with impaired awareness, prompting the diagnosis of FIRES on day 7.
Results: The acute phase was clinically characterized by frequent focal seizures. Initially, the electroencephalogram (EEG) revealed a moderate encephalopathy, and additionally in following controls, right focal electrical discharges and seizures. Later on, such discharges also involved the contralateral hemisphere, and a complex partial status epilepticus diagnosis was made. Plasma and CSF immune panels indicated an increase in IL-1 and normal IL-6 levels. Therefore, in the first week, a ketogenic diet, anakinra, and high doses of phenobarbital were initiated (the latter, until the effectiveness of the ketogenic diet and anakinra would manifest). Good clinical response to acute phase treatment that allowed withdrawal of sedative hypnotic drugs and extubation at day 25. In the chronic phase, she has been presenting with daily 1-3 focal or complex focal seizures, with seizure-free periods of several weeks. She also experiences a mild gait instability and a moderate language regression. Ensuing EEGs continued showing a moderate encephalopathy, with bilateral focal discharges. Anakinka has been maintained since, with positive results and scarce side effects.
Conclusions: This case emphasizes how an early diagnosis of an IL-1-mediated FIRES and implementation of a ketogenic diet and anakinra contributed to a shorter duration of status epilepticus, and to a more optimal long-term cognitive and motor outcome in contrast to other patients described in the literature. Further, it outlines how the coadministration of phenobarbital at high doses during the acute phase may serve as bridge therapy until the effectiveness of the ketogenic diet and anakinra takes effect. Thus, chronic treatment with anakinra may be recommended for such patients. A plasma and CSF immune panel is suggested to determine whether FIRES is IL-1 or IL-6 mediated; conversely, in cases of increased IL-6 levels, tocilizumab may be more suitable than anakinra.

Keywords:
anakinra, epilepsy, phenobarbital, FIRES

EPNS23-2074 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

Corpus callosotomy in children with drug-resistant epilepsy: A 10 year experience from a single centre

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Objective: Corpus callosotomy is a palliative surgical procedure for patients with generalized or multifocal drug-resistant epilepsy, particularly with drop attacks. We describe the experience of corpus callosotomy at our centre over ten years.

Methods: Records of patients who underwent corpus callosotomy between January 2012 and December 2021 were reviewed. We collected clinical, comorbidity, genetic and imaging data. Seizure outcome (Engel Epilepsy Surgery Outcome Scale), use of anti-seizure medications (ASM), type of corpus callosotomy (partial or complete), and complications were recorded.

Results: Inclusion criteria were met for 41 patients, 25 boys (61%) and 16 girls (39%). 13 patients out of 41 (32%) had a diagnosis of Lennox-Gastaut syndrome. 24 patients out of 41 (59%) had associated developmental delay. Brain MRI revealed abnormalities in 27 cases (66%). Genetic testing identified a pathogenic genetic variant in 21 cases (51%). The mean number of previously used anti-seizure medications at the time of surgery was 5.8 ±2.2SD (range 3 to 12). 34 patients (83%) underwent a total corpus callosotomy. Mean age at surgery was 9.8 ± 4.8 SD years old (range 9 months to 19 years old). Transient complications were experienced by 20 out of 41 patients (49%) including hemiparesis, wound and respiratory infection. Two patients experienced disconnection syndrome.35 out of 41 (85,4%) had seizures within 12 months of surgery, 5 cases were classified as Engel II, 14 cases were Engel III, and 16 cases returned to baseline (Engel IV). Six cases remained seizure free at 12 months (Engel I). The median number of anti-seizure medications significantly reduced (p=0.046) from three to two after corpus callosotomy.

Conclusions: Corpus callosotomy is well tolerated in children and the majority have at least a worthwhile reduction in seizure frequency after 12 months of surgery. The number of anti-seizure medications can be reduced after corpus callosotomy

Keywords:

Epilepsy; Corpus callosotomy; Seizure outcome; Epilepsy surgery

EPNS23-2544 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

ELECTRICAL STATUS EPILEPTICUS IN SLEEP (ESES): Diagnostic and management challenges: Single centre experience

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Case study: ESES is a rare condition of childhood characterised by a spectrum of cognitive, behaviour and motor regression and characteristic sleep EEG changes. In the absence of standardised diagnostic and treatment criteria, management of ESES is challenging.

Objective :To review diagnosis, investigations, management and outcome of children presenting with ESES in our institution over a 12-year period.

Method:Data collected from hospital electronic medical records(2010-2022).

Results:12 children, age-3-13yr (3 female, 9 male) were diagnosed with ESES. 9 children had pre-existing epilepsy with initial presentation of focal seizures.Other clinical features were deterioration in language /speech (54%), new onset/worsening seizures (39%), behavioural/ cognitive decline, learning difficulties (23%) and attention disorder (8%).

ESES diagnosis was made based on EEG criteria-predominantly 70% changes on sleep EEG with cognitive, language & behavioural decline. Landau- Kleffner (LKS)was diagnosed in 4 children.

Neuroimaging was normal in all except 1, showing mild right thalamic volume loss with gliotic changes.5 children had genetic testing, 1 abnormal result of 7q31-7q33 deletion.5 children had neuropsychology assessment.

Clobazam was used as monotherapy in 4 children, 4 with other antiepileptics (AED) including Lamotrigine, Levetiracetam, Ethosuximide & Sulthiame. 1 child had Sodium Valproate monotherapy, 1 had steroids (non- response to Clobazam). 2 children relapsed on weaning off clobazam. In 1 out of 4 LKS cases, long course (upto 24mths) of steroids was required.Positive outcome was improvement in cognition, learning and/or EEG improvement. 9 children had no pre-existing developmental delay but only 1 recovered without any sequelae. 11 out of 12 children had one or more sequelae at follow up (cognition -53%, learning difficulties & language- 38% each, ADHD - 30%, co-ordination, ASD, behaviour issues - 15%, dyslexia- 7%)

Conclusion:In our study, Clobazam was found to be superior to other AED monotherapy as reported in the literature. Response to steroids in the LKS cases was 50% with 25% requiring it for 2 years. 92 % of our cases showed significant morbidity of cognition, learning, behaviour, autism and ADHD.Timely neuropsychology assessments and genetic testing was not done for all children. In the era of whole genome sequencing, genetic testing of ESES will pave way for more targeted therapy. Evidence based guideline may help improve diagnostic and therapeutic pathway.

Keywords:

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EPNS23-2876 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

Ketogenic diet treatment of patients with drug-resistant epileptic seizures.

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Objective: Purpose: To evaluate the effectiveness of ketogenic diet treatment in a population of patients with drug-resistant epileptic seizures.

Methods: Material and method: the results of ketogenic diet treatment in a population of 46 patients aged 1 to 45 years were analyzed . 22 patients with epilepsy of known genetic background and 24 patients with seizures of undetermined etiology. The effectiveness of dietary treatment was compared according to the underlying cause of seizures and the type of epileptic seizures observed. The effectiveness of the treatment was determined by the percentage of reduction in epileptic seizures reported by caregivers at 90 days after inclusion, after 180 days and after 12 months, compared to the 90-day period before inclusion of dietary treatment [< 50%, 51-70%, 71-90% and >91%]. The effectiveness of different types of ketogenic diet (classical, Atkins and low glycemic index) was compared. The research was conducted between 2018 and 2023.

Results: Results: The group of patients with drug-resistant seizures with a known genetic background included patients with mutations in the SCN1A, DEPDC5, CHD2, SCN8A, Angelaman syndrome, SLC2A1, KIF1A, SYNGAP1, PIGN and trisomy 21 genes. Ketogenic diet treatment was effective in about 70% of patients. All types of ketogenic diet used showed similar efficacy. Mild and transient side effects were observed. Treatment with the ketogenic diet was more effective in the group of patients with non-motor seizures.

Conclusions: Conclusions: The ketogenic diet was found to be an effective and safe treatment option among patients with drug-resistant seizures. The observed side effects were mild and transient in nature. The type of diet used did not affect the effectiveness of treatment. For patients with mutations in the SLC2A1 and DEPDC5 genes, ketogenic diet therapy was found to be very effective.

Keywords:

Ketogenic diet, seizures, SCN1A, DEPDC5, CHD2, SCN8A, Angelaman syndrome, SLC2A1, KIF1A, SYNGAP1, PIGN, trisomy 21

EPNS23-3011 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

Febrile infection-related epilepsy syndrome - case report

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Objective: Febrile infection-related epilepsy syndrome (FIRES) is a rare syndrome that manifests as a new-onset refractory status epilepticus (SE) in the course of febrile illnesses. Fever can start from 24 hours to 14 days before SE, but it does not have to be present at the time of its onset. It occurs in children without previous neurological diseases and without proven acute infection of the central nervous system, structural, toxic or metabolic disorder.

Methods: We present a case of a pediatric patient with FIRES.

Results: Previously healthy five-year-old boy was hospitalized due to repeated epileptic seizures and impaired consciousness. The symptoms were preceded by a febrile condition that started three days earlier, and at the time of hospitalization he was afebrile. The patient was hospitalized in the Intensive Care Unit because of the rapid development of refractory SE. The seizures were focal with secondary generalization and were refractory to anticonvulsant drugs. Between seizures patient did not regain consciousness. He was intubated, mechanically ventilated with initiation of continuous infusion of midazolam, and afterwards thiopental for seizure control. An extensive diagnostic work-up was performed, which did not clarify the etiology of SE. Acute CNS infections, structural abnormalities, traumatic brain injuries, hypoxic-ischemic insult, metabolic disorders, intoxications, autoimmune or paraneoplastic encephalomyelitis have been excluded. He was treated with acyclovir, ceftriaxone and immunotherapy (high doses of methylprednisolone, intravenous immunoglobulins, plasmapheresis, anakinra). A ketogenic diet and various antiepileptic drugs (levetiracetam, clobazam, lacosamide, topiramate, phenobarbital) were introduced. Serial MRs of the brain showed bilateral periventricular white matter lesions that progressed and serpiginous signal hyperintensities along the corticomedullary area that regressed during time. Subsequent literature search revealed that these changes may correspond to encephalopathy in FIRES. With the applied treatments, control over epileptic seizures was gradually achieved, but severe psychomotor regression was present. After long-term multidisciplinary treatment, child had almost complete recovery of cognitive functions, speech and social interaction.

Conclusions: FIRES is rare but diagnostically and therapeutically challenging disorder which must be considered in the differential diagnosis of refractory status epilepticus.

Keywords:

FIRES, status epilepticus, febrile state

EPNS23-2198 Oral
Epilepsy: Medical & Surgical Treatment

SWALLOWTAIL: An Open-Label Extension (OLE) Study for Children and Adolescents with Dravet Syndrome (DS) who Previously Participated in a Study of Antisense Oligonucleotide (ASO) STK-001

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Objective: DS is a severe and progressive genetic developmental and epileptic encephalopathy that typically begins in the first year of life. Approximately 85% of cases are caused by heterozygous, loss of function, de novo mutations in the *SCN1A* gene, which encodes the voltage-gated sodium channel type 1 α subunit ($Na_V1.1$) protein. DS is characterized by high seizure frequency (SF) and severity, intellectual disability, motor abnormalities, and a high risk of sudden unexplained death in epilepsy. STK-001 is an investigational ASO treatment designed to upregulate $Na_V1.1$ protein expression in the brain by leveraging the wild-type (non-mutant) copy of *SCN1A* to restore physiological $Na_V1.1$ levels, thereby potentially reducing both SF and non-seizure comorbidities.

Methods: SWALLOWTAIL (NCT04740476) is an US ongoing multi-center OLE study, assessing the long-term safety, tolerability, plasma and CSF exposure and clinical effect of repeat doses of STK-001 administered every 4 months by intrathecal (IT) injection in patients with DS who have completed MONARCH (NCT04442295), a Phase 1/2a study of STK-001. Adverse events (AEs) are monitored continuously, and CSF and plasma samples are collected at each visit. Clinical assessments including SF, neurodevelopmental status, gait, and executive functioning are evaluated during the study.

Results: As of 11Jul2022, 96% patients (24 of 25) who completed MONARCH enrolled in SWALLOWTAIL. Patients received up to 5 doses of STK-001 given every 4 months (10-45mg/dose). All treatment-emergent adverse events related to study drug were non-serious and mild or moderate. Dose-dependent increase in CSF C_{trough} levels was observed from 20-30mg across all cohorts, and slight STK-001 accumulation in CSF was observed for 10-30mg for 3 doses though not significant to C_{max}. In a small group of evaluable patients, reductions in convulsive SF that were observed in MONARCH were maintained with ongoing treatment at 30mg (n=4), and a trend toward improvement in executive functioning as measured by the BRIEF-P was observed (n=5-8) in SWALLOWTAIL.

Conclusions: These data support continued development of STK-001 as the first potential disease-modifying approach to treat DS. This study will inform on the long-term safety and tolerability of repeat administration of STK-001 and will help inform future clinical studies of STK-001.

Keywords:
mRNA, splicing, trial, TANGO, United States,

EPNS23-2424 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

Cannabidiol in drug-resistant paediatric epilepsy: A multicentre service evaluation and observational study

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Objective: To evaluate the use of cannabidiol across paediatric neurology centres in the UK against national standards and characterise its safety and efficacy.

Methods: We retrospectively analysed data from all paediatric patients enrolled on Epidyolex(r) in 2 paediatric neurology centres and compared the service against national guidance. Responders were defined as those with a 30% or more decrease in monthly seizures at 3 months.

Results: 54 patients (mean age 10.5, 57% males) were included in the study. Most patients had either Lennox-Gastaut (65%) or Dravet (15%) syndromes. Prior surgical evaluation and trial of ketogenic diet happened in only 44% and 43% of the population, respectively. Regular and event-based LFT monitoring was observed 97% of the time. The overall median monthly seizure burden at pre-Epidyolex baseline was 140 (IQR 16-280). 33/49 (67%) of our patients were responders, with a median 72% reduction in monthly seizure frequency at 3 months and 3 cases (6%) of seziure freedom. For those non-responders who had their prescription continued (n=15), 3 (20%) converted to responders at 6 months. 7 (14%) of non-responders were continued on Epidyolex(r) beyond 6 months against guidance. Using a binary logistic regression model, we found that Epidyolex(r) dose was the only significant predictor of response (OR 1.49 per mg/kg/d, 95% CI 1.11-2.25, p=0.02) when adjusted for baseline characteristics. We did not find a significant relationship between response rate and baseline seizure burden (p=0.06) or see an improved response in those with Lennox-Gastaut (p=0.06) or Dravet (p=0.83) syndromes compared to other epilepsy phenotypes. 27 (51%) patients experienced side-effects, drowsiness (40%) and deranged LFTs (30%) being the most common.

Conclusions: Cannabidiol appears to be an effective therapy for our patients, albeit with a high rate of mild side effects. NHS guidance to allow for a 3 month trial period to evaluate efficacy may lead to a minority of missed responders. More patients should be assessed for surgical interventions or a ketogenic diet before Epidyolex(r) prescription.

Keywords:

Cannabidiol, Epidyolex(r), Lennox-Gastaut, Dravet, seizure

EPNS23-2318 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

GENOTYPE - PHENOTYPE CORRELATIONS AND IMPLICATION FOR TREATMENT IN A CASE SERIES OF SODIUM CHANNELOPATHIES

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Objective: Dysfunction of ion channels in the neuronal membrane is one of the etiologies of epilepsy. The aim of this study is to highlight the genotype-phenotype correlations in patients with sodium channelopathies and the therapeutic implications depending on the type of mutation.

Methods: Using our clinical register of patients diagnosed with epilepsy, we identified 6 patients with sodium channelopathies, other than SCN1A, diagnosed using NGS: 4 of them were tested using an epilepsy gene panel and the other 2 were tested via Whole Exome Sequencing (WES).

Results: We present 4 patients with mutations in the SCN2A gene, of which 2 siblings with focal seizures in the neonatal period, respectively in infancy, with a good response to Carbamazepine, the 2 other patients with intellectual disability with or without disorder of autistic spectrum and focal seizures started in childhood. We also describe the phenotypes of 2 patients with mutations in the SCN8A gene: one of them with generalized secondary seizures and normal intellect, and the other with profound global developmental delay, epileptic encephalopathy, sensory deficits, osteoporosis and multiple recurrent fractures.
Using our patients phenotypes, response to treatment, literature data and international databases we identified: a Loss-of-Function (LoF), a probable LoF and a probableGain-of-Function (GoF) mutation for SCN2A gene, and a GoF together with a probable LoF mutation for SCN8A gene.

Conclusions: The functional effect of a mutation (GoF, LoF) in the genes coding for the voltage-dependent sodium channel is decisive in choosing the appropriate anti-seizure medication, personalized for each patient.

Keywords:

epilepsy, sodium channel, functional effect, GoF, LoF, personalized treatment

EPNS23-2683 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

Adrenocorticotropic hormone (ACTH) in epilepsy treatment - a retrospective study of 131 children

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Objective: To analyze effectiveness and tolerability of ACTH in treatment of epilepsy in childhood.

Methods: Retrospectively we analyzed clinical characteristics of 131 children treated with ACTH in terms of age at seizure onset, type of seizures, duration of epilepsy up to treatment with ACTH, etiology of epilepsy, responsiveness and tolerability to ACTH. Furthermore, we divided the cohort into responders (with reduction of seizures >50%) and non-responders, and analyzed possible factors which can influence effectiveness of ACTH.

Results: Median age at seizure onset was 5,8 mts. (range 0 - 62,7) and at ACTH treatment 9,3 mts. (range 0,9 - 187,3). The most frequent seizure type was infantile spasms, which were present in 96 cases (73,3%). Etiologically, predominated structural causes (66 children, 50,1%), unknown etiology (42 children, 32,1%) and genetical causes (17 children, 13,0%). Before ACTH treatment, the most common EEG finding was hypsarythmia (29,8%), followed by generalized discharges (27,5%) and focal discharges (15,3%). Adverse events were present in 54 patients (41,2%), which in 12 cases (22,2%) led to termination ACTH treatment. 100 children (76,3%) were classified as clinical responders and 114 had improvement of EEG findings (87,0%). Comparing to non-responders, patients with good response to ACTH had later seizure onset (5,9 mts. range 0,03 - 50,7 vs. 3,0 mts. range 0 - 62,7, p=0,005), shorter duration of epilepsy up to ACTH treatment (2,8 mts. range 0 - 48,8 vs. 4,3 mts. range 0,2 - 124,6, p=0,04), higher incidence of infantile spasms (80,0% vs. 47,1%, p=0,004) and lower incidence of adverse events (34,0% vs. 64,5%, p=0,001).

Conclusions: Early start of ACTH treatment and later seizure onset are associated with good effectiveness of ACTH. Responders to ACTH have lower incidence of adverse events in comparison to non-responders.

Keywords:

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EPNS23-2640 Oral or e-Poster
Epilepsy: Medical & Surgical Treatment

The role of genetic testing in surgical forms of epilepsy.

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Case study: Objectives: Mutation for familial genetic epilepsy with variable focus was identified in structural focal epilepsy.
Methods: Anamnesis: a 16-year-old girl, developing according to her age, has the onset of seizures occurred at the age of 3- jerking of the left hand. Since the age of 9-10 she has left-sided hemiclonic and bilateral tonic-clonic seizures. Auras - indescribable sensations in the left limbs. Since the age of 15, a girl's sister (18 years old) has had focal non-motor seizures with impaired consciousness and with opercular and manual automatisms in her right hand. Auras - "deja-vu" sensations. Both girls underwent high-resolution Magnetic resonance imaging (MRI) of the brain, long-term video-EEG monitoring (VEEG), and full exome sequencing (FES) for the first girl. The found mutation (in the NPRL3 gene) was verified by Sanger (proband, siblings and parents).
Results: Examination of the younger girl: MRI of the brain - focal cortical displasia (FCD) type IIa in the right postcentral gyrus. VEEG: interictal regional epileptiform activity was recorded in the right central region and in the right fronto-central-parietal region. Onset of the ictal pattern is not determined. In the postictal period, continued slow-wave was recorded in the right central region. Semiolology indicate the implementation of seizure by the right hemisphere. Examination of the second girl: MRI of - normal. VEEG: the semiotics of seizures indicate their implementation by the temporal lobes. The ictal pattern is in the right temporal region. FES - a mutation in the NPRL3 gene in the heterozygous state associated with familial epilepsy with type 3 variable focus (OMIM 617118). Sanger sequencing - a mutation in the NPRL3 gene in the girl, her older sister, and their mother. The mother hasn't seizures, according to the laboratory, the identified mutation has a mosaic shape. The first girl underwent surgery - resection of FCD of the right parietal lobe (outcome of surgery is Engel Ia), and her sister continues to receive anticonvulsant therapy.
Conclusions: Structural focal epilepsy due to malformation (FCD) may be associated with a mutation in the NPRL3 gene. In the same family, there may be patients with MRI-positive and MRI-negative genetic epilepsy and possibly with the phenomenon of gonadal mosaicism. Timely detection of this mutation is important for further effective surgical treatment of patients with epilepsy and medical genetic counseling of the family.

Keywords:
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EPNS23-2003 Oral or e-Poster

Epilepsy: Medical & Surgical Treatment

In Children with Lennox-Gastaut Syndrome (LGS), Does Adjuvant Cannabidiol Represent an Efficacious and Tolerable Approach to Reducing Total and Drop Seizure Frequency: A Review of the Most Recent Evidence

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Objective: It is estimated that less than 3% of patients with Lennox-Gastaut syndrome (LGS) have adequate seizure control, even on anti-seizure medicine (ASM) polypharmacy. The NICE guidelines recommend the use of Cannabidiol (CBD) as an add-on therapy with Clobazam to treat drug-resistant LGS. There are scanty reviews providing a comprehensive synthesis of the evidence for short- and long-term safety, and efficacy of CBD in this setting. To this end, this study provides an review of the most recent evidence for the efficacy of CBD for reducing frequency of total and drop seizure frequency (SF), and the tolerability of CBD as an adjuvant therapy in paediatric LGS.

Methods: METHOD: We perform a comprehensive literature search of Embase, Cochrane, MEDLINE, and NHS Evidence databases. Titles, abstracts and full texts were independently screened by three reviewers and disagreements solved by consensus. We included all primary studies or reviews that discussed paediatric LGS cases taking adjuvant CBD. Measures of efficacy included a) percentage reduction in total and drop SF and b) whether CBD resulted in a subjective improvement. Measures of tolerability included adverse events (AEs) and death.

Results: Our literature search yielded 120 articles. 14 papers were selected for inclusion. Add-on CBD leads to a greater median reduction in total SF compared to matched placebo (41.2-56% compared to 13.7-18.5%). Across studies, 36-71% of patients achieved a >50% reduction in drop seizures specifically, and in all studies reported this was significantly greater than the matched placebo group (14-24%). Only one study assessed long-term effects, and they demonstrated that efficacy is maintained even after 2 years with no evidence of developing tolerance to CBD. The main AEs noted include vomiting, diarrhoea, convulsions, pyrexia and somnolence. Elevated liver transaminases were linked to concomitant sodium valproate use in all cases.

Conclusions: In patients with LGS, add-on CBD results in greater reduction of total SF and drop seizure frequency compared to ASM alone. The combined data suggests that this efficacy is maintained in the longer-term (>156 weeks). One of the included primary studies analysed SF in patients treated with EpidyolexTM following implementation by NICE, providing the start of real-world evidence of its efficacy in practice. However, concerns still remain regarding AEs especially at higher doses of CBD, and in patients taking concomitant sodium valproate.

Keywords:

Lennox-Gastaut Syndrome, Epilepsy, Cannabidiol, Epidyolex, Epidiolex, Neuropharmacology

EPNS23-2810 Oral or e-Poster
Fetal and Neonatal Neurology

Prenatal Onset Hydrocephalus Associated with Molar Tooth Sign, a Rare Occurrence or New Syndrome?

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Objective: Joubert Syndrome Related Disorders (JSRD) are rare mostly autosomal recessive diseases that are diagnosed upon recognition of a pathognomonic "molar tooth sign" (MTS) that consists of vermian hypoplasia, thick and horizontally oriented superior cerebellar peduncles, and an abnormally deep interpeduncular fossa.
JBTS can be associated with other CNS (i.e. polymicrogyria, agenesis of corpus callosum, Dandy-Walker Malformation) and systemic anomalies (i.e. polydactyl, oral hamartomas, polycystic kidneys, cleft lip and palate).
Hydrocephalus is not one of the features of JBTS. It is rarely described postnatally usually in association with a Dandy-Walker malformation. Only 2 fetal cases have been described.

Methods: We reviewed the patients' medical records and prenatal MRIs. We reviewed the medical literature for hydrocephalus in Joubert.

Results: We present 5 fetuses from 3 families with prenatal onset hydrocephalus associated with a molar tooth sign.

Conclusions: We suggest that this rare association represents a new genetic syndrome due to a hitherto unknown gene.

Keywords:
Joubert-Boltshauser syndroms; hydrocephalus; ffeus; prenatal diagnosis

EPNS23-2488 Oral or e-Poster
Fetal and Neonatal Neurology

Brain Derived Neurotrophic Factor - marker early diagnosis of perinatal Hypoxic-ischemic brain injury in premature newborns

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Objective: To study the relationship between the level of serum concentration of Brain Derived Neurotrophic Factor (BDNF) and the formation of structural changes in the brain in premature newborns with hypoxic-ischemic brain injury in the acute period.

Methods: Conducted prospectively study of 81 premature newborns was performed - 41 girls (50.61%) and 40 boys (49.38%), which included three cross-sections: I - in the delivery room, II - on the 3rd-5th and III - on the 26th-28th day of life.
The criteria for inclusion in the study were: 1) gestational age 26-36 weeks; 2) hypoxia in history; 3) registration structural changes according to neurosonography (NSG).
According to neurosonographic features, 4 subgroups (IA, IB, IC, ID) were distinguished. Subgroup IA included 15 premature newborns with severe hypoxic-ischemic brain injury - cerebral edema (CED); subgroup of IB consisted of 18 premature newborns with intraventricular hemorrhage (IVH) - of the I-IV degree (classification of Papille); IC subgroup - 19 infants with periventricular hyperechogenicity (PVH); subgroup ID - 21 premature newborns without structural changes of the brain (WSC).

Results: It was established that the quantitative level of BDNF in blood serum and the dynamics of its changes during the acute period indicate Hypoxic-ischemic brain injury in premature children, and depends on the severity of brain damage. This is confirmed reliably ($p<0.01$) by the higher level BDNF in umbilical cord blood (delivery room) and on the 3rd-5th day of life in infants premature children with hypoxic-ischemic brain injury compared with morphofunctionally immature children. In premature newborns with IVH the average value BDNF on the 3rd-5th day of life was the highest. In infants with severe hypoxic-ischemic brain injury (CED), the average value of BDNF on the 26th-28th day of life was the lowest - 5.51±1.37 ng/ml, which is likely ($p<0,05$) distinguished them from other premature children with Hypoxic-ischemic brain injury in the acute period.

Conclusions: At the result of conducted research the connection between the level of serum concentration BDNF and formation of structural damage of cerebrum of premature newborns with perinatal hypoxic-ischemic brain injury in the acute period.

Keywords:
BDNF, hypoxic-ischemic injury, brain, premature newborns

EPNS23-2593 Oral or e-Poster
Fetal and Neonatal Neurology

Long term follow-up of babies at risk. Who? Why? - experience of our clinic

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Objective: Rapid and accurate diagnosis of neonatal conditions, understanding the mechanisms and timing of injury and developing a better management (neonatal and neurological) to influence the outcome of at-risk babies. Trying to implement a specific, national follow-up program (since it does not exist in Romania) to monitor the long-term outcome of these patients with special needs.

Methods: Face-to-face follow-up visit and neurodevelopmental assessment every 3-6 months over a period of 2 years (particularly, term/preterm newborns with hypoxic-ischemic encephalopathy, periventricular leukomalacia, very preterm newborns, SGA baby, FIV); head ultrasound (to screen for brain conditions associated with prematurity, such as bleeding or brain tissue damage) .

Results: Partial results show that mild to moderate brain damage cases result in only a lower number of symptoms, some of which can be managed with proper treatment. Instead, moderate to severe brain damage tends to result in permanent symptoms and irreversible conditions like Cerebral Palsy. The final results will be discussed at the time of the conference because at this moment the study is still ongoing.

Conclusions: Because newborns' brains are in a crucial window of rapid development, the goal of following up preterm infants with brain injury is to identify problems as early as possible and to intervene quickly in order to prevent or minimize neurodevelopmental sequelae as much as possible and improve their quality of life.

Keywords:
preterm baby, hypoxic-ischemic encephalopathy, periventricular leukomalacia, neurological outcome

EPNS23-2370 Oral or e-Poster

Fetal and Neonatal Neurology

Brain Derived Neurotrophic Factor - marker early diagnosis of perinatal Hypoxic-ischemic brain injury in premature newborns

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Objective: To study the relationship between the level of serum concentration of brain Derived Neurotrophic Factor (BDNF) and the formation of structural changes in the brain in premature newborns with hypoxic-ischemic brain injury in the acute period.

Methods: conducted prospectively study of 81 premature newborns was performed - 41 girls (50.61%) and 40 boys (49.38%), which included three cross-sections: I - in the delivery room, II - on the 3rd-5th and III - on the 26th-28th day of life.
The criteria for inclusion in the study were: 1) gestational age 26-36 weeks; 2) hypoxia in history; 3) registration structural changes according to neurosonography (NSG).
According to neurosonographic features, 4 subgroups (IA, IB, IC, ID) were distinguished. Subgroup IA included 15 premature newborns with severe hypoxic-ischemic brain injury - cerebral edema (CED); subgroup of IB consisted of 18 premature newborns with intraventricular hemorrhage (IVH) - of the I-IV degree (according to the classification of L.Papille); IC subgroup - 19 infants with periventricular hyperechogenicity (PVH); subgroup ID - 21 premature newborns without structural changes of the brain (WSC).

Results: It was established that the quantitative level of BDNF in blood serum and the dynamics of its changes during the acute period indicate Hypoxic-ischemic brain injury in premature children, and depends on the severity of brain damage. This is confirmed reliably ($p<0.01$) by the higher level BDNF in umbilical cord blood (delivery room) and on the 3rd-5th day of life in infants premature children with hypoxic-ischemic brain injury compared with morphofunctionally immature children. In premature newborns with IVH the average value BDNF on the 3rd-5th day of life was the highest. In infants with severe hypoxic-ischemic brain injury (CED), the average value of BDNF on the 26th-28th day of life was the lowest - 5.51±1.37 ng/ml, which is likely ($p<0$, 05) distinguished them from other premature children with Hypoxic-ischemic brain injury in the acute period.

Conclusions: at the result of conducted research the connection between the level of serum concentration BDNF and formation of structural damage of cerebrum of premature newborns with perinatal hypoxic ischemic brain injury in the acute period.

Keywords:

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EPNS23-3016 Oral or e-Poster

Fetal and Neonatal Neurology

The Impact of Polymorphisms in Antioxidative and Proinflammatory Genes on sequelae after Neonatal Hypoxic-Ischemic Encephalopathy

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Objective: Background: Neonatal hypoxic-ischemic encephalopathy (HIE) is a common cause of lifelong neurologic sequelae, including cerebral palsy (CP). Oxidative stress and inflammation are important contributors of the new-born's brain injury due to a perinatal hypoxic-ischemic insult. Genetic variability in these pathways could influence the response to HI insult and consequently the neurologic outcome.
Aim of our study was to evaluate the association of the selected single nucleotide polymorphisms (SNPs) in the genes involved in response to oxidative stress and inflammation with development of CP after HIE.

Methods: Methods: We included 90 children with moderate and severe HIE; 55 children received treatment with therapeutic hypothermia (TH) and 35 children were not treated with TH. Clinical data were collected from digital and paper medical records. This part of the study was retrospective. The DNA of all subjects was isolated from buccal swabs. Genotyping using competitive allele-specific PCR was performed for polymorphisms in genes encoding antioxidant enzymes (SOD2 rs4880, CAT rs1001179, GPX1 rs1050450) and proinflammatory factors (NLRP3 rs35829419, CARD8 rs2043211, IL1B rs1143623, IL1B rs16944, IL1B rs1071676, TNF rs1800629) that could contribute to the development of CP after HIE. Standard statistical tests (logistic regression, non-parametric tests) were used to evaluate the association of selected SNPs with the development of CP at follow-up at the age of 2-3 years.

Results: Only polymorphic NLRP3 rs35829419 allele was nominally significantly associated with the development of CP in children who were not treated with TH (p = 0,034). In the neonates who were treated with TH none of the SNPs were associated with the development of CP.

Conclusions: The association between genetic variability in antioxidative and proinflammatory pathway with the development of CP after neonatal HIE was not confirmed. However, in a subgroup of children, not treated with TH, polymorphic NLRP3 rs35829419 allele was nominally significantly associated with the development of CP. We conclude that in patients with polymorphic rs35829419 increased expression of NLRP3 could thus lead to a greater inflammatory response, increased production of IL-1beta and IL-18, resulting in larger tissue damage and consequently later CP.

Keywords:

Polymorphisms; Antioxidative genes; Proinflammatory;Newborns; Hypoxic-Ischemic Encephalopathy; Cerebral palsy;

EPNS23-2985 Oral or e-Poster
Fetal and Neonatal Neurology

Brainstem lesions: when in doubt, try steroids

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Case study: Brainstem lesions include a wide range of differential diagnoses particularly in neo-nates, some with poor prognosis. A correct diagnosis may not be easy, even with modern diagnostic tools. By reporting this case, we aim to raise awareness and incentivize caution when making a diagnosis and managing treatment.

A 9-day-old male newborn was admitted to hospital because of hyperbilirubinemia and weight loss (20%). During the hospital stay intermittent abnormal eye movements were noted, beginning when he was 10 days old, with no apparent trigger. There was no other relevant gestational or neonatal medical history. Physical exam showed intermittent bursts of predominantly horizontal conjugate eye oscillations that lasted a few seconds, interpreted as an ocular flutter. Fundoscopic examination and the remaining neurologic exam were normal. He was submitted to a brain MRI, which revealed an intra-axial ill-defined expansive lesion located in the brainstem (specifically in the medulla oblongata), measuring 26x30x20mm extending from the pons to the spinal cord (C2). Radiologic and spectroscopy findings suggested a brainstem glioma (hypointense in T1, hyperintense in T2, no restricted diffusion, no post-gadolinium emphasis, elevated choline, choline/N-acetylaspartate and choline/creatine ratio, lipids, lactate and myo-inositol). There was no hydrocephalus or sign of meningeal dissemination. No lesions were found in the spinal cord MRI or the abdominal ultrasound. Cerebrospinal fluid sampling was unremarkable. Vanillylmandelic and homovanillic acid were normal. Investigation for autoimmune (including anti-MOG and anti-AQP4) and infectious causes was negative. A biopsy wasn't performed because of location and risk of sequelae. Treatment was started with a 5-day course of methylprednisolone (30mg/kg/day), with a complete remission of symptoms after one week. Brain MRIs were repeated at 1 and 4 months after steroids, showing a complete regression of the lesion, with an area of cavitation in the anterior portion; this radiologic evolution, in addition to the spectroscopy (high myo-inositol, low N-acetylaspartate), was less in favor of glioma and pointed more to an encephalitis-like process. 5 months later, he remains asymptomatic, with a normal neurological development.

Caution is advised when formulating a diagnosis, particularly if it is a rare entity, with poor prognosis. Early interventions like biopsy or chemotherapy with iatrogenic potential should be avoided.

Keywords:
Newborn; Brainstem lesion; Steroids

EPNS23-2909 Oral
Infections and Inflammatory Diseases

Acute cerebellar ataxia, cerebellitis

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Objective: Acute cerebellar ataxia (ACA) is a disturbance in motor coordination of abrupt onset, usually preceded by an infection. A minority of the cases might be due to direct viral effect, while most are likely the results of an autoimmune process. It is a self-limiting disorder with no proven benefit of therapeutic measures. Though possibly the most prevalent neuroimmune disorder in children, it might cause a diagnostic challenge. The authors' aim was to retrospectively analyse their patients' clinical, laboratory, radiological characteristics and outcome.

Methods: The authors used descriptive statistical methods to enlighten the typical clinical course of this rare neuroinflammatory disease.

Results: During a period of 25 years 180 patients (91 boys, 89 girls) were diagnosed with ACA. Their mean age was 4.3 years. 91 patients had chickenpox. In 85 kids other conditions (infections, vaccinations, intoxication, malignancy) preceded ACA, while no trigger was found in 4. In a mean of 2.1 days ataxia progressed to loss of ambulation in 44% of patients. Further prevalent complaints were nausea, vomiting, headache, fever, lethargy and speech problems (dysarthria or mutism). Beyond truncal ataxia numerous patients had dysmetria, muscle hypotonia and pyramidal tract signs. Cerebrospinal fluid (CSF) samples showed mild inflammatory changes in 58% of those patients tested. Magnetic resonance imaging (MRI) showed relevant changes of the cerebellum in only 7 cases. Electroencephalograms proved normal in 73% of the recordings, showed mild or moderate slowing in the rest. 10 patients required intensive care. Motor coordination recovered in a mean of 3 weeks, this being slightly longer in chickenpox patients, shorter in the others. 9 patients had mild residua like ataxia, dysarthria, immature coordination, cognitive impairment. 5 kids experienced transient relapses.

Conclusions: ACA is a relatively prevalent neuroimmune disease in children and mostly affects young kids. Diagnosis is based on clinical grounds, though CSF may show mild pleocytosis. MRI may - seldom - detect inflammatory changes. The overall outcome is good, though a minority of patients may have mild residua or transient relapses.

Keywords:
acute, cerebellar, ataxia, cerebellitis, neuroimmune

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Infections and Inflammatory Diseases

Neurosarcoidosis with prominent inner-ear involvement in a child

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Case study: Objective : To report an unusual presentation of neurosarcoidosis with vestibulocochlear involvement.

Methods : case report

Results : We report the case of a 5-year-old boy presenting with bilateral granulomatous uveitis, bilateral profound cochleovestibular impairment with vestibular ataxia and deafness. He was of Guinean origin and his medical history was unremarkable.
Biological highlights were elevated blood levels of angiotensin-converting enzyme (ACE ; 268 U/L) and a mild CSF pleiocytosis (7 cells/mm3). A biopsy of the accessory salivary gland found non-necrotizing granulomas. CT scan found neck and abdominal lymphadenopathy. Brain MRI was unremarkable except for inner-ear imaging that showed a blood-labyrinth barrier disruption with nodular T2-weighted signals of the vestibular organ suggestive of granulomas.
Based on clinical, biological and radiological findings, the diagnosis of neurosarcoidosis was made. Screening for NOD2 mutations ruled out the diagnosis of Blau syndrome. Other causes of granulomatous diseases were excluded by laboratory tests.
High-dose IV steroids were initiated for five days, followed by an oral steroid tapering at 1mg/kg/d and transtympanic steroid injections. Long-term treatment based on anti-TNFalpha monoclonal antibody (Infliximab) and methotrexate was initiated. He fully recovered from uveitis but neither from vestibular ataxia nor deafness. Bilateral cochlear implantation was performed a few weeks after immunosuppressive treatment initiation and successfully improved speech intelligibility and language skills.
Three months after treatment initiation, he developed anti-Infliximab antibodies followed by development of bilateral uveitis suggesting an inflammatory relapse.

Conclusions: Neurosarcoidosis can be treacherous with an atypical neurological presentation. Vestibulo-cochlear inflammation is less documented in the literature than other neurological involvements but should raise the physician's attention to consider the diagnosis. Urgent diagnosis is critical to initiate treatment, not only to prevent irreversible vestibulocochlear deficiency, but also to enable cochlear implantation before cochlear ossification hinders surgery. Moreover, diagnosis should not be delayed as bilateral vestibular deficiency can lead to serious accidents when proprioception is altered (e.g. swimming).

Keywords:
Sarcoidosis, Neurosarcoidosis, Inflammation, systemic disease, vestibular, ataxia, deafness, corticosteroids

EPNS23-2468 Oral or e-Poster

Infections and Inflammatory Diseases

Psychosocial outcome during long-term follow-up after anti-NMDAR encephalitis in children and adolescents

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Objective: Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARE) is an auto-immune encephalitis characterized by a complex neuropsychiatric syndrome. Recent research has been studying cognitive deficits during the prolonged recovery phase, but the broader psychosocial outcome and impact of persisting deficits on quality of life (QoL) and global functioning have barely been explored, especially in children and adolescents.

Methods: In this exploratory case series we sought to explore psychosocial outcome during long-term follow-up (range 2-6.5y) in children and adolescents with anti-NMDARE. Four female patients (age 7-16y) and their caregivers participated in the study. Clinical variables and information about disease course and follow-up were retrieved from the medical records, with additional information provided by the caregivers via a questionnaire. Current and past psychosocial functioning was assessed by interviewing both the patients and their caregiver with the structured clinical interview for DSM-5 disorders, junior version (SCID-5 junior). CGAS and mRS scores were defined by the investigator on basis of the retrieved information. The Pediatric Quality of Life Inventory (PedsQL) was used to assess quality of life of patients and caregivers.

Results: All patients experienced several persisting symptoms with an impact on daily activities and academic trajectory during the post-acute phase of the disease (range 5-10 months after disease onset). In long-term follow up these symptoms partly resolved, but some persisted. Psychiatric symptoms, fatigue and mild cognitive deficits were present in 3 out of 4 patients at current assessment. Two patients still receive supportive therapies. Two patients had to switch to a less demanding study level in their academic trajectory, while another patient receives extra support at school. An impact on quality of life of both patients and caregivers seems present and global functioning was in the range of "obvious problems" and "some noticeable problems" in two patients.

Conclusions: After the acute phase of the disease patients seem to go through a post-acute phase in which several persisting physical, cognitive and psychiatric symptoms gradually resolve over months to a year. However even years after disease onset the majority of patients still experience some residual symptoms or deficits. Our findings suggest that these can have an impact on quality of life of patients and caregivers and affect global functioning of patients.

Keywords:
Anti-N-methyl-D-aspartate receptor encephalitis, long-term outcome, psychiatric symptoms, quality of life, global functioning

EPNS23-2990 Oral or e-Poster

Infections and Inflammatory Diseases

Neurological, neuropsychological and neuroradiological correlations in a monocentric cohort of patients with paediatric Opsoclonus-Myoclonus-Ataxia Syndrome

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Objective: Opsoclonus-Myoclonus-Ataxia Syndrome (OMAS) is a rare neuroinflammatory disease that can leave multiple neuro-cognitive sequelae. Aim of this study is to describe a monocentric cohort of patients with paediatric OMAS, to outline the cognitive and behavioural profile of the participants, and to evaluate whether volumetric brain abnormalities are detectable years after clinical onset.

Methods: Twelve patients between the ages of 2.9 and 16.6 years, with a mean follow-up length of 7.3 years, were evaluated. All participants had previously received steroids and rituximab. Five (41.7%) had a neuroblastoma diagnosis. Participants underwent a videorecorded neurological examination and a psychological assessment with multiple standardized paediatric Intelligence and Neuropsychological Scales. All participants underwent advanced 3-Tesla brain Magnetic Resonance Imaging (MRI). An imaging analysis was performed using Voxel-Based Morphometry (VBM), and a targeted evaluation of the cerebellum was performed through the ACAPULCO and ENIGMA pipelines.

Results: This study confirms that neurological and neuropsychological sequelae are common in patients with paediatric OMAS. In our sample, 75% of the participants had some degree of abnormality at the neurological examination. The mean Full Scale Intelligence Quotient (FSIQ) in our cohort was 76. Two patients had a borderline FSIQ, and five had an intellectual disability. Visuospatial processing impairments were observed. Parents reported affective and internalizing problems. On MRI visual inspection, 50% of the participants exhibited abnormal findings. Four patients out of 12 (33.3%) had some degree of cerebellar atrophy. We found significative volumetric differences between cases and controls in several cerebellar lobules. Compared with younger patients, those with a longer follow-up, exhibited smaller total and lobular cerebellar volumes. Furthermore, patients with lower cognitive scores, particularly in the Working Memory Index (WMI) and Processing Speed Index (PSI), appeared to have, not only a reduced total cerebellar volume, but also smaller volumes in several different lobules.

Conclusions: OMAS can cause neuro-cognitive sequelae. Patients may present cerebellar atrophy in the long term. Cerebellar atrophy in specific lobules seems to correlate with cognitive abilities confirming not only the role of the cerebellum in the pathogenesis of OMAS, but also the fundamental role of the cerebellum in cognitive, behavioural and affective functioning.

Keywords:

OMAS, neuro-cognitive sequelae, MRI, cerebellar volumes

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Infections and Inflammatory Diseases

Peripheral and autonomic nerve affections in children and adolescents with post-COVID-19 syndrome

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Objective: Children and adolescents may develop persistent symptoms, a post-COVID-19 syndrome, for months after infection with SARS-CoV-2, which significantly affect daily life. Potentially neurological symptoms, such as daily headaches, vertigo, fatigue, muscle pain, paresthesia, or olfactory and gustatory disturbances occur.
The aim of this contribution is to analyze somatosensory and autonomic nervous functions in children and adolescents with post-COVID-19 syndrome with neurological symptoms. Cardiovascular autonomic neuropathies usually cause nonspecific symptoms and are often diagnosed late because of this, especially in childhood and adolescence. Individual case reports show that this phenomenon can also occur in patients with post-COVID-19 syndrome.

Methods: To determine a somatosensory profile, 19 patients (15 female; age 13.3±3.2 years) with post-COVID-19 syndrome (7.4 (3-26.2) months after confirmed SARS-CoV-2 infection) the perceptual thresholds for mechanical tactile (MDT) and vibratory (VDT) stimuli assessing large fiber function, and for cold (CDT), heat (WDT), thermal sensory limen (TSL), and paradoxical heat sensation (PHS), which assess the function of small fibers, based on a validated protocol were examined in both feet.
A noninvasive and nonisotopic method for diagnosing and stratifying autonomic neuropathy was used to examine autonomic nerve function. Various non-stressing maneuvers are performed during ECG recording to assess parasympathetic and sympathetic function (at rest, during deep breathing, shortly after rising from supine - Ewing test - and under Valsalva maneuver). Static measures of heart rate variability are obtained.

Results: All 19 children and adolescents who presented with SARS-CoV-2 because of persistent fatigue and subjectively marked impairment of physical performance had unremarkable organ functions (heart, lungs). Half (47%) of the patients had sensory deficits for at least one test parameter. These showed loss of function for the large (MDT/VDT) and 11% for the small sensitive nerve fibers (TSL/PHS).
Measurement of heart rate variability revealed abnormalities in terms of sympathetic dysfunction in 42% of patients. Only 2 patients had unremarkable examination results, and in 3 cases both methods yielded pathological findings.

Conclusions: Obviously, in patients with more functional post-COVID 19 complaints, loss of function of the sensory nerve fibers or autonomic dysfunction could explain part of the complaints, so screening in this regard seems reasonable.

Keywords:
Post-COVID-19-syndrome, autonomic neuropathy, somatosensory function, neuropathy, heart rate variability

EPNS23-2575 Oral or e-Poster
Infections and Inflammatory Diseases

Shorter versus Longer Duration of Antibiotic Treatment in Children with Meningitis: A Systematic Review and Meta-Analysis

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Objective: We aimed to perform an updated meta-analysis comparing shorter versus longer duration of antibiotic treatment in children with bacterial meningitis.

Methods: PubMed, EMBASE, and Cochrane databases were searched for randomized controlled trials (RCTs) that compared shorter (up to 7 days) versus longer (10 days or double the days of the equivalent short course) duration of antibiotic therapy in children with bacterial meningitis. Risk ratios (RR) with 95% confidence intervals (CI) were used for the binary outcomes of interest, with a p-value <0.05 considered statistically significant. Review Manager 5.4.1 was used for statistical analysis. Quality assessment was performed with the Cochrane Collaboration's risk of bias tool (RoB2). Heterogeneity was evaluated using the Cochran Q test and I^2 statistics. The pre-specified protocol was registered in PROSPERO with the identification CRD42022369843.

Results: We included six RCTs with a cohort of 1,333 children, of whom 660 (49.5%) were in the shorter treatment group. The mean age ranged from 3 weeks to 15.5 years. Follow-up ranged from one month to 190 days after the discharge. Ceftriaxone was the antibiotic of choice for all the studies included, except for one study, which also added vancomycin. No differences were found between groups concerning treatment failure (RR 1.11; 95% CI 0.73-1.70; p=0.62; I^2=0%), relapse (RR 1.47; 95% CI 0.57-3.76; p=0.42; I^2=0%), mortality (RR 1.66; 95% CI 0.63-4.38; p=0.31; I^2=0%), and hearing impairment at discharge (RR 0.99; 95% CI 0.79-1.23; p=0.89; I^2=0%). Similarly, there was no difference in hearing impairment during follow-up (RR 1.00; 95% CI 0.80-1.25; p=0.99; I^2=0%). In contrast, neurological complications at discharge (RR 0.73; 95% CI 0.56-0.95; p=0.02; I^2=0%) and follow-up (RR 0.74; 95% CI 0.56-0.96; p=0.03; I^2=0%) were significantly lower in patients undergoing short-course therapy.

Conclusions: In this meta-analysis of 6 RCTs and 1,333 children with uncomplicated bacterial meningitis, a short course of antibiotics (up to 7 days) was associated with fewer neurological complications as compared with a longer treatment course (10 days or double the days of the equivalent short course), without a significant difference between groups in treatment failure, relapse, mortality, or hearing impairment.

Keywords:
Antibiotic; Bacterial meningitis; Children; Duration of therapy; Pediatric population; Shorter versus longer therapy

EPNS23-2557 Oral or e-Poster
Infections and Inflammatory Diseases

PEDIATRIC LONGITUDINALLY EXTENSIVE TRANSVERSE MYELITIS IN A TERTIARY CARE CENTER

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Objective: Longitudinally extensive transverse myelitis (LETM) refers to inflammation of the spinal cord that extends over three or more vertebral segments, constitutes a rare entity with high morbidity.
The main objectives of the study are to review the epidemiological, etiological and clinical characteristics of longitudinally extensive transverse myelitis (LETM) in pediatric patients and to investigate factors related to the presence of sequelae.

Methods: The study was designed as single-center, longitudinal, retrospective and descriptive study. Children (aged 0 to 15 years) who were admitted to the hospital diagnosed of LETM between 2012 and 2022 were included. The patients' medical records were examined for demographic, clinical, radiological, laboratory, treatment, and follow-up data. A descriptive statistical analyses was performed. Also, Fisher test and T-test were applied. P value <0.05 was considered statistically significant.

Results: A total of 13 patients, 8 boys and 5 girls, between 2 and 14 years were included in the study. The most common presenting symptoms were weakness (61%), drowsiness (38%), back pain (30%) and headache (23%). The most frequently affected level was cervicothoracic (46%) and panmyelitis was diagnosed in 3 cases (23%). The 54% have sequelae: motor (5 patients), sensory (2 patients) and sphincter sequelae (2 patients). In 2 of these patients a vascular etiology was found, the rest were idiopathic. In idiopathic LETM patients with sequelae the median treatment starting delay was 4,6 days since symptom onset; 3 patients had panmyelitis, 1 patient cervicothoracic and 1 patient thoracosacral involvement. No statistically significant difference was observed between age at onset, medullary extension or initiation of treatment delay and sequelae.

Conclusions: The incidence of LETM in this series was 0-3 cases per 97,000 per year. Although no statistically significant differences were obtained, a trend was observed for patients with sequelae to have a greater extension of the spinal cord affected and a longer delay in starting treatment.

Keywords:
Longitudinally Extensive Transverse Myelitis, Childhood, Prognosis

EPNS23-2738 Oral or e-Poster
Infections and Inflammatory Diseases

Characteristics of Febrile Seizures with SARS-CoV-2 infection in the Omicron Era

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Objective: While the pandemic of coronavirus disease 2019 (COVID-19) is ongoing, the omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been circulating dominantly recently. The omicron variant causes more severe infection and seizures in pediatric patients compared with previously circulated variants. This study aimed to investigate the incidence and clinical features of febrile seizure (FS) in pediatric patients with COVID-19 during the omicron era.

Methods: The medical records of pediatric patients (18 years or younger) diagnosed with COVID-19 who presented with FS between February 2020, and June 2022, were reviewed retrospectively to analyze clinical characteristics of FS in seven university-affiliated hospitals of Korea.

Results: During the study period, 664 patients presented with COVID-19 and FS (81 patients, 12.2%) during the omicron era. Most (76.5%) experienced simple FS, and 80.2% and 19.8% experienced FS (patient age 60 months or younger) and late-onset FS (patient age >60 months), respectively. Although underlying neurologic disease ($p = 0.013$) and non-generalized seizure ($p = 0.012$) were more common in patients with late-onset FS than in those with normal FS, overall clinical manifestations and outcomes were similar in the two groups.

Conclusions: As the COVID-19 pandemic persists, the incidence of FS has increased with the emergence of the omicron variant. The omicron variant of SARS-CoV-2 causes more frequent FS in older children than do other respiratory viruses; however, clinical characteristics and outcomes are favorable. More information and long-term prognoses in patients with FS due to COVID-19 should be acquired.

Keywords:
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); omicron; febrile seizure (FS); late-onset febrile seizure

EPNS23-2735 Oral or e-Poster
Infections and Inflammatory Diseases

Steroid resistance in acute hemorrhagic leukoencephalitis (AHLE)

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Case study: A 3,5 year old boy presented with weakness of his right leg after mild upper respiratory infection. Three months ago his parents were Covid-19 positive, the boy himself was not tested. Acute brain MR revealed tumor lesion in the left central region. Bevor surgical biopsy neurological detoriation occured due to progression of the lesion. Histological a demyelinating disease was described and the patient was started on high dose steroids.
When steroids were reduced he detoriated again (vigilance and motor function), brain MR revealed rapidly growing lesion. As anti-MOG titer was 1:156 the boy was started on plasmapheresis. After 6 cycles the patient was stable und since then ivIG were initiated for further immunmodulatory therapy.
The boy was diagnosed acute hemorrhagic leukoencephalitis (AHLE). Pathophysiology of AHLE is still unknown, but most commonly seen as a postinfectious complication of an upper respiratory illness.
Conclusion: AHLE is a rare demyelinating disease of the central nervous system (CNS) marked by rapid progression and acute inflammation of the white matter. It is suspected as postinfectious autoimmune disease and regarded as the most severe form of acute disseminated encephalomyelitis (ADEM). Due to a high mortality rate, aggressive treatment is required. AHLE has also been reported in connection to COVID-19. The small number of cases described so far necessitates greater public awareness. The earlier clinical diagnosis is established by early imaging it may allow more aggressive treatment options, potentially reducing fatal outcomes. With this case study we want to focus on symptoms and causes of AHLE, diagnosis and treatment and its connection to COVID-19.

Keywords:
acute hemorrhagic leukoencephaltis, immunmodulatory therapy

EPNS23-2955 Oral
Infections and Inflammatory Diseases

Infantile Onset Autoimmune Encephalitis Associated With Anti-glutamic Acid Decarboxylase Antibody

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Case study: Antibodies against glutamic acid decarboxylase (GAD) are associated with various neurologic conditions described in patients, including stiff person syndrome, refractory epilepsy, and limbic and extralimbic encephalitis. There have been some case reports regarding anti-GAD65 antibody-associated encephalitis in adults, but pediatric cases are rare.Here we present a 10 month-old-girl, admitted with intractable seizures, sleep disorder, drowsiness, dysautonomia, and vomiting.Neurologic examination showed coma (Glasgow Coma Scale score 8), hyperactive deep tendon reflexes. CSF analysis revealed 3 white blood cells per cubic millimeter, along with normal glucose and elevated protein. CSF cytopathology was unremarkable. Brain MRI showed bifrontoparietal subarachnoid enlargement. Serum GAD65-Abs was positive (93.4 IU/mL (0-5IU/mL)). The patient was treated with methylprednisolone (30 mg/kg.d × 5 d) and IVIG (2 g/kg) and showed significant improvement. Early diagnosis and immunotherapy can improve the symptoms. However, patients with limbic encephalitis often have refractory epilepsy in the chronic phase and have a poor long-term outcome.

Keywords:
anti-glutamic acid decarboxylase 65, pediatric, autoimmune encephalitis

EPNS23-2545 Oral or e-Poster
Infections and Inflammatory Diseases

Bilingual girl with selective loss of native language : a case of neurosarcoidosis!

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Case study: Introduction : Paediatric neurosarcoidosis is a rare clinical entity that can mimic several neuroinflammatory conditions.

Method: We report clinical presentation, diagnostic challenge and management of a 12 year old bilingual girl diagnosed with isolated neurosarcoidosis who developed selective deficit of her second language.

Results/Case Presentation: A 12 year old dirl presented with seizures and reduced GCS initially and subsequently stroke like presentation with facial weakness, slurring of speech, right sided weakness and expressive aphasia with selective loss of her second language (Portuguese).
Her initial neuroimaging showed an inflammatory lesion in left frontotemporal region with T2 signal change in left frontal operculum, leptomeningeal enhancement in central and temporal sulci .
She was initially treated with triple therapy of antimicrobials, followed by pulsed steroid therapy and thereafter with oral steroids along with immunosuppression with MMF(Mycophenolate mofetil). She had extensive infectious, autoimmune, demyelinating, inflammatory, metabolic, mitochondrial and neurovascular work up which was negative. Interval neuroimaging demonstrated disease progression radiologically although she remained clinically stable. She subsequently underwent brain biopsy which demonstrated non-necrotizing granulomatous inflammation, consistent with sarcoidosis. She has been managed on steroids and MMF, with infliximab. She was diagnosed as neurosarcoidosis in the absence of other systemic involvement. Motor and speech recovery has been complete, though she has ongoing cognitive difficulties.

Conclusion: This challenging case also highlights the importance of brain biopsy in the evaluation of neuroinflammatory lesions and a MDT approach with input from national experts.

Keywords:
Paediatric neurosarcoidosis, neuroinflammatory, sarcoidosis, chronic granulomatous disease

EPNS23-2989 Oral or e-Poster
Infections and Inflammatory Diseases

Atypical manifestation of Rasmussen's encephalitis - a case study and literature review

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Case study: Rasmussen's encephalitis (RE) is classically diagnosed by clinical, neuroimaging and electroencephalographic criteria. It is characterized by focal seizures including epilepsia partialis continua, unilateral hemispheric cortical atrophy and EEG focal slowing with or without epileptiform activity. The criteria established for the diagnosis by Bien in 2005 are not being met by several patients with atypical features. The etiology of RE remains elusive, but immunopathogenic mechanism with T-cell mediated immunity is presumed. A number of patients described worldwide presented atypical manifestation including chorea, athetosis, dystonia, non-motor seizures, contralateral and ipsilateral cerebellar atrophy, focal cortical dysplasia and ischemic pathologies. Also, other co-existing autoimmune diseases such as psoriasis and uveitis are reported.
A case of nine-year old boy with atypical Rasmussen's encephalitis with concurrent type 1 diabetes and unilateral hypopigmented patches is presented. The patient's neurological examination findings were non-reactive dilated right pupil, nystagmus, dysmetria and dysdiadochokinesia with left-sided hyperreflexia and Babinski sign. Brain MRI showed unilateral cerebral and cerebellar atrophy and basal ganglia asymmetry. EEG revealed right-sided focal epileptic activity. There were no seizures observed clinically in patient's history. After implementation of immunotherapy slowing in clinical and neuroimaging pathologies was observed, postponing the decision of hemispherectomy, which remains definitive treatment approach in RE.
This case supports the hypothesis of autoimmune etiology of RE and indicate uncommon clinical features in this population. Limited literature due to a scarce number of patients does not permit to establish with certainty pathophysiology and treatment guidelines.

Keywords:
Rasmussen encephalitis, Autoimmunity

EPNS23-2892 Oral or e-Poster
Infections and Inflammatory Diseases

Going further in Sydenham's Chorea: a national multicentre retrospective and prospective study on clinical features, treatment, prognostic factors, and long-term psychopathological outcome

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Objective: Sydenham's chorea (SC) is a post-streptococcal, probably autoimmune, disorder of the central nervous system, and a major manifestation of acute rheumatic fever (ARF). It is usually considered a benign and self-limiting disease, although high-quality data over long-term outcome, optimal therapy and prognostic factors are lacking. With this 2-step national multicentre project, we aimed to study clinical features, treatment, and prognostic factors of SC and to evaluate its long-term psychopathological impact.

Methods: In phase one, we retrospectively included a paediatric population with a clinical diagnosis of SC and at least 6 month follow-up. Clinical, instrumental and laboratory parameters were collected and potential risk factors, abnormal MRI, and associated neuropsychiatric symptoms were assessed with univariate and multivariate sub-analysis. In phase two, patients of any age diagnosed with ARF at least 24 months earlier, with or without SC, were prospectively enrolled and underwent several validated neuropsychiatric tests.

Results: In phase one, 171 children (108 females/63 males; median age 9) with SC were included. Additional neurological symptoms were reported in 60% and neuropsychiatric symptoms at onset in 51% (in 10% persisted after 12 months). 93% reached neurological remission at 6 months, and 9% relapsed. 37% were treated with immunomodulatory therapy (IT) alone, 37% with a combination of IT and symptomatic drugs (SD), 16% with SD alone. Patients treated with SD (with or without concomitant IT) had a higher risk of relapse (p=0.045). IT did not show higher efficacy in the medium term, although associated with a slightly lower risk of relapse compared to SD.
In phase two, 48 patients (23 females/25 males; median age 21.6) were included, 21 in the SC group and 27 in the non-SC group. SC patients reported significantly more work and social functioning difficulties than non-SC patients (p=0.021).

Conclusions: SC presents with multiple clinical manifestations and exerts a strong psychopathological impact even years after its onset. The retrospective collection of the treatments revealed great heterogeneity, and it was not possible to provide conclusive results on their effectiveness. Supranational longitudinal studies are needed to assess specific risk factors and identify the best treatment options, also focusing on effectiveness in reducing medium- and long-term neuropsychiatric manifestations.

Keywords:
Sydenham's Chorea; movement disorder; post-infectious; immunotherapy; neuropsychiatric manifestations.

EPNS23-2578 Oral or e-Poster

Infections and Inflammatory Diseases

Clinical utility of visual evoked potentials in children with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)

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Objective: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an inflammatory demyelinating disease of the central nervous system that often affects optic nerves. Clinical and laboratory findings characterise the severity of this process and define the clinical phenotype and outcome. However, younger children may have difficulties perceiving and describing their symptoms. To objectively determine the damage done by inflammation to the optic pathway, we can measure latencies in visual evoked potentials (VEP). This study aims to ascertain the sensitivity of VEP examination in patients with MOGAD compared with referred visual impairment and magnetic resonance imaging (MRI) findings.

Methods: We enrolled 17 children (F:M = 8:9, age: median 8 years, range 0-15) who were diagnosed with MOGAD at our department. The initial clinical phenotypes were as follows: acute demyelinating encephalomyelopathy (7), optic neuritis (6), myelitis (2), neuromyelitis optica spectrum disorder (1) and multiple sclerosis (1). All patients underwent VEP, MRI, MOG antibodies testing and cerebrospinal fluid (CSF) examinations at the onset of the disease. During the VEP examination, we used the pattern-reversal stimulus (pVEP) in cooperative patients and the flash stimulus (fVEP) in the others. Afterwards, we compared the evidence of optic pathway pathology in objective methods (VEP, MRI) with the presence or absence of referred visual impairment.

Results: Vision impairment reported 8 patients (47,1%), 5 of them bilaterally (62,5%). Optic nerve(s) pathology on MRI was also observed in 8 patients and was bilateral in 5 cases. One of the patients with vision impairment had no corresponding VEP abnormity and one of the patients with MRI optic nerve pathology referred no visual impairment. In contrast, abnormal VEP values had 12 patients (70,5%), bilaterally 10 of them (83%).

Conclusions: VEP was a more sensitive tool for determining the optic nerve involvement in the inflammatory process in patients with MOGAD than MRI or clinical testing alone. The VEP results indicate the possible optic pathway affection even in patients without corresponding symptoms. However, the case of a patient with visual impairment and normal VEP values demonstrates the importance of comprehensive clinical and laboratory evaluation in the diagnostic process.

Keywords:

MOGAD, visual evoked potentials, examination sensitivity, optic neuritis

EPNS23-2885 Oral or e-Poster

Infections and Inflammatory Diseases

Rare presentation sign of Multiple Sclerosis: Hearing loss

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Case study: Acute hearing loss is rare in pediatric and adult multiple sclerosis (MS) patients with a reported prevalence of 0.4% to 5%.Monosymptomatic brainstem presentations of MS have usually been described, however, hearing loss as an initial symptom is uncommon in both children and adults and often occurs during the course of the disease and in association with other neurological deficits rather than as a sole symptom.We report a previously healthy 17-year-old girl with MS who had hearing loss as the only initial symptom of presentation.She presented to the child neurology department due to complaints of acute hearing loss on the left side throughout the month and numbness in feet which developed 1 week prior to admission.Hearing loss was not associated with tinnitus,vertigo,loss of consciousness or focal neurological signs.Physical and neurological examinations were normal.In the first audiometric examination,sensorineural hearing loss (SNHL) of 69-dB avarage at all frequencies on the left ear was detected by audiological testing which was consistent with unilateral SNHL.The laboratory findings included a complete blood cell count,serum biochemical and urine analysis and levels of biotinidase and vitamin B12,thyroid function tests,thyroid autoantibodies which were all normal.25 OH vitamin D level was low (5ng/mL).Serum Aquaporin-4 and MOG antibodies and the laboratory tests for rheumatological diseases and serological studies for viral and bacterial infections were negative.Evaluation of the cerebrospinal fluid (CSF) was normal and CSF sample was negative for oligoclonal bands.Cranial and spinal magnetic resonance imaging (MRI) revealed areas of demyelination.In the axial FLAIR sequence,a hyperintense lesion extending to the internal acoustic canal and the 8th cranial nerve was seen in the left cerebellopontine angle and in addition two more demyelinating lesions were seen.On axial T1 post-contrast image the lesion showed contrast enhancement extending to the 8th cranial nerve.Spinal MRI revealed demyelinating focus at the T5 level with post-gadolinium enhancement.The patient was diagnosed with MS and received pulse intravenous methylprednisolone for 5 days, then tapered orally over a month.Eleven days after the onset of treatment,the audiometric test repeated by the otolaryngology department was found to be completely recovered.In conclusion although rare, we should keep in mind that hearing loss might be the first presenting symptom of demyelinating disorders.

Keywords:

Acute hearing loss ,demyelinating disorders, multiple sclerosis, pediatric

EPNS23-2475 Oral
Infections and Inflammatory Diseases

Acute Flaccid Myelitis in Europe

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Objective: Acute flaccid myelitis (AFM) is a polio-like condition, that mostly affects children and often causes severe and persistent deficits. It may be associated with different viruses, but enterovirus D68 (EV-D68) seems to be the most important cause. Demonstrating this virus in AFM cases may however be difficult. Through collaborative efforts of the European non-polio enterovirus network (ENPEN), more insight has been gained in the epidemiology of EV-D68. However, the incidence of AFM in Europe remains largely unknown. We aim to gain more insight in the incidence of AFM.

Methods: Clinicians (Pediatric neurologists, pediatricians and neurologists) from European countries with a possible or demonstrated interest in AFM were sought through different networks, including ENPEN and the Young EPNS. These clinicians were invited to join an European AFM network, embedded in ENPEN and closely collaborating with virologists and public health officers. The goal of this network is to systematically collect data on new AFM cases in Europe via a registry study, to create awareness by sharing information on these cases and EV-D68 circulation, and to function as forum of expertise for possible AFM cases.

Results: A total of 31 clinicians from 21 countries showed interest in participating in the AFM network. Through an informal inquiry within this group, eleven AFM cases were identified between July and October 2022, during a period of increased EV-D68 circulation. In four cases EV-D68 had been demonstrated. Before the initiation of the network, in October-December 2021, which was again during an upsurge of EV-D68 circulation, twenty AFM cases were reported, 9 of which were EV-D68 positive.

Conclusions: AFM cases have been reported infrequently, but the incidence of AFM in Europe is largely unknown. A collaborative effort was initiated to create a registry for new cases, which will help in estimating the incidence of AFM in Europe. This will serve to determine the priority of AFM and EV-D68 as a potential health care threat, to create awareness of potential new outbreaks, to stimulate adequate diagnostics in suspected cases, and to relate cases of AFM to circulation of enteroviruses.

Keywords:
Acute flaccid myelitis, acute flaccid paralysis, non-polio enteroviruses, enterovirus D68

EPNS23-2399 Oral or e-Poster

Infections and Inflammatory Diseases

MOG-ab-associated disorders: a single center experience

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Objective: Myelin oligodendrocyte glycoprotein (MOG)-antibody-associated disorders (MOGAD) comprise an expanding clinical spectrum. We report on pediatric presentation in a single University Hospital.

Methods: Retrospective chart review of all pediatric patients diagnosed with MOGAD over the last 6 years.

Results: Eleven patients (3girls/8boys) were included, mean age 3y5m (range 10m-13y1m) and mean follow up 12m (range 1-90m). Nine patients present with acute disseminated encephalomyelitis (ADEM). The oldest two (7y6m and 13y1m) present with bilateral optic neuritis (ON) as isolated symptom. All but one had prompt effect of treatment with steroids. In the one patient that needed intensive care, plasma exchange and intravenous immunoglobulins were successfully added. Eight patients recovered fully. Two had cognitive and behavioral sequels both with residual white matter lesions on MRI. The only patient with persistent positive anti-MOG antibodies had residual epilepsy. Three patient relapsed during follow-up. A girl who presented at 28 months with ADEM did one ADEM relapse 9 months later consistent with multiphasic disseminated encephalomyelitis (MDEM). Two others relapsed with 1 and respectively 6 episodes of ON consistent with ADEM-ON (ADEM episode followed by one or more ON episode(s)). The later did show relapses whenever steroids were stopped despite trials with rituximab, mycophenolate mofetil, azathioprine and cyclosporine. Currently, she is relapse free for more than 3 years with low dose alternated day therapy with prednisolone. First relapse of optic neuritis was seen after 9 and respectively 4 months. No relapses were seen when treated with steroids. All 3 patients who did show relapses had proven absent oligoclonal bands in cerebrospinal fluid. Half of the not relapsing patients were tested for oligoclonal bands in cerebrospinal fluid and negative as well. When performed, autoantibodies against aquaporine-4 (5/11) and autoimmune encephalitis panel (5/11) were negative.

Conclusions: Our experience in MOGAD is consistent with literature with ADEM as mean presenting phenotype in young children, good response on steroids, no relapses when on steroid and full or nearly full recovery in most patients. Relapses were seen in nearly half of the patients in follow-up for more than 12 months (3/7). ADEM-ON is more frequent than previously thought.

Keywords:

MOG-ab-associated disorders, MOGAD, ADEM-ON

EPNS23-2357 Oral or e-Poster
Infections and Inflammatory Diseases

Transverse myelitis - diagnostic challenges

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Case study: Introduction: Transverse myelitis is a rare, acquired, immune-mediated focal demyelinating, partial or total, spinal cord injury. Clinical manifestations are variable include limb weakness, sensory deficits, and autonomic dysfunction. Diagnostic criteria are based on clinical presentation, neuroradiological evaluation, laboratory analysis and exclusion of other diseases. Secondary causes in the differential diagnosis can be- vascular disorders, parainfectious and postinfectious/postvaccinal, paraneoplastic, autoimmune, systemic and metabolic (deficient) conditions as well as demyelinating diseases. In a certain number of patients, the etiology remains unexplained, and the recovery is partial.
Case report: A previously healthy young man, age 17, with unilateral weakness and hypotrophy of the musculature of the right upper arm with normoreflexia with a radiological correlate of a demyelinating spinal cord lesion suggestive of transverse myelitis.One month before he had a mild respiratory infection and four months earlier he got second dose of the vaccine against COVID-19. Myography showed loss of motoneurons in the ticeps brachii muscle, and neurography showed regular conduction velocity and distal latency with a lower amplitude motor fibers of the ulnar nerve and n. radialis to the right. Magnetic resonance visualized a minor hyperintense change in the medulla spinalis dorsomedially from C3-C4 to C4-C5 with an increase at more caudal levels up to the upper part of the trunk of C6, in places occupying a large part of the medulla spinalis in the central part. Hemato - biochemical laboratory tests were normal. Optic neuritis was ruled out. Analysis of the cerebrospinal fluid was normal. Wider serological results for infectious factors were uninformative. PCR for enteroviruses was negative. Antiganglioside and aquaporin antibodies, oligoclonal bands and antibodies to myelin oligodendrocyte glycoprotein and myositis were also not found. Screening for malignant, immunorheumatological and systemic diseases was negative.
Corticosteroid pulse therapy was performed with supportive treatment with B vitamins and physical therapy.
Conclusion: We have described a case of idiopathic transverse myelitis, probably as a result of an immune response to an unproven postinfectious factor. The diagnostic-therapeutic approach to a patient with a focal demyelinating lesion of the central nervous system is a challenge. Timely diagnosis and longitudinal monitoring are important.

Keywords:
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EPNS23-2977 Oral or e-Poster

Infections and Inflammatory Diseases

Retrospective analysis of children with autoimmune encephalitis

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Objective: In this study, we aimed to define clinical, laboratory, radiologic and electrophysiological findings of children with autoimmune encephalitis.

Methods: Children diagnosed with autoimmune encephalitis between 2015-2022 from two pediatric clinics are included to study.

Results: Eighteen children were included, 10 (55.6%)of them were boys. Presenting age were 1-15 years. Presenting symptoms were encephalopathy (n=18), seizures (n=16), ataxia (n=2), speech dysfunction (n=2), autonomic disability (n=1). Five patients (27.8%) were seropositive; four of them had anti-NMDA antibodies, one had LGI1/CASPR2 antibodies. Four patients had preceding herpes encephalitis, two of them were NMDA positive. Slowing of background was seen in all patients at presentation. Cranial MRI was normal in 11 (61.1%)patients. Among 4 patients with a history of herpes encephalitis, 2 of them had additional neuroimaging findings at the diagnosis of autoimmune encephalitis. Limbic involvement was present in one patient and cerebellar involvement was seen in one. Thirteen patients (72.2%) received first line immunotherapy including steroids, intravenous immunoglobulin and/or plasma exchange. Five patients received rituximab, two of them had also received cyclophosphamide. Among 15 patients with a diagnosis of epilepsy and at least one-year follow-up, 9 (60%) were seizure free, 4 (26.6%) had drug resistant epilepsy. One patient, whose neurologic findings resolved after intravenous immune globulin therapy, died due to co-morbid autoimmune hepatitis, and hepatic failure. Mild to severe cognitive impairment was seen in 4 children with herpes encephalitis. In 13 patients who were previously healthy and had at least one year follow up, 9 (69.2%) had no cognitive impairment, 4 (30.8%) had mild cognitive impairment.

Conclusions: We presented a small cohort of pediatric autoimmune encephalitis. Most of them were seronegative and had normal brain MRI. Herpes encephalitis remains an important etiology for autoimmune encephalitis. Cognitive impairment and epilepsy, which were seen in half of our cohort, are important disabilities of autoimmune encephalitis despite early immunotherapy.

Keywords:
autoimmune encephalitis, herpes encephalitis, NMDA, LGI1/CASPR2, prognosis

EPNS23-2604 Oral or e-Poster
Infections and Inflammatory Diseases

CASPR positive encephalitis with 2 distinct phenotypes

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Case study: Objective: To review the clinical characteristics of autoimmune encephalitis associated with the contactin-associated protein-2 (CASPR2) antibody by two pediatric patients.
Materials and Methods: Medical records of two pediatric patients diagnosed with CASPR2 antibody-associated encephalitis were retrospectively reviewed. Data regarding demographic features, neurological symptoms and signs, laboratory tests, imaging results, treatments, and prognosis were collected.
Results: Patient 1 (P1) was 7 years 7 months old and Patient 2 (P2) was 4 years 3 month old. P1 was diagnosed with autistic spectrum disorders at the age of 2 with loss of speech and behavioral disturbances, and he developed praying all day for the last 2 months. He was brought to pediatric neurology to be evaluated for childhood psychosis. P2 was brought to pediatric neurology outpatient clinic for behavioral changes, regression on speech and cognitive regression such as not remember numbers for the last three months. They all were evaluated for the childhood etiology of autism and neurologic regression. Epileptic seizure was not observed. The concentration of proteins in the CSF were in normal ranges and white blood cells were not detected in the CSF. All patients were positive for anti-CASPR2 antibody in the serum but not detected in the CSF. Electroencephalogram (EEG) activities included awake and sleep were in normal limits. No abnormality were detected by magnetic resonance imaging (MRI) both of the patients. P1 and P2 did not meet the certain criteria for limbic encephalitis because the patients had no evidence of neuroinflammation. The patients receiving immunotherapy with steroid and intra-venous immunoglobulin (IVIG) experienced varying degrees of improvement in 6 months of follow-up.
Conclusion: The clinical symptoms of CASPR2-antibody-mediated autoimmune encephalitis vary in childhood period. The most prominent conclusion revealed by the follow-up of these two pediatric cases is the involvement of both central nerve systems, and a good response to immunotherapy in short-term period. Besides, additional work is necessary to evaluate the long-term prognosis.

Keywords:
CASPR2, autoimmune encephalitis, clinical features, treatment, prognosis

EPNS23-2713 Oral or e-Poster
Infections and Inflammatory Diseases

Avian Paramyxovirus type I encephalitis: clinical course, and MRI features

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Case study: Objective:
Case description of Avian Paramyxovirus type I (APMV-1) encephalitis presenting with Febrile Infection-Related Epilepsy Syndrome (FIRES) in an immunocompromised patient.

Methods:
Description of case: A 2 -year-old girl with a background of infantile pre-B acute lymphoblastic leukaemia (ALL) on chemotherapy presented with respiratory symptoms, fever, nausea/vomiting and seizures. Super-refractory status epilepticus evolved with a syndrome consistent with FIRES. Investigations including extensive autoimmune and genetic testing did not reveal a cause. MRI was initially reported to be normal, but serial MRI showed increased left frontal T2 / FLAIR signal that extended into contiguous regions with evolving necrosis. Neopterin in cerebrospinal fluid (CSF) was highly elevated at 1752 nmol/L (reference 6-30). Extensive investigations for infection, examining CSF, blood and a brain biopsy did not initially reveal a cause. Despite broad spectrum antimicrobials, anti-seizure medications, a ketogenic diet and immunomodulators, the patient died 27 days after presentation. Autopsy was not performed.

Metagenomic sequencing using pan-viral hybridisation-capture and unbiased metatranscriptomic sequencing methods were undertaken.

Results:
Both sequencing approaches independently identified Avian Paramyxovirus type 1 (APMV-1) as the dominant non-human sequences. Phylogenetic analysis indicated a pigeon-adapted lineage of APMV-1 viruses, confirmed on PCR assays targeting genes encoding fusion, polymerase and matrix proteins. Immunohistochemistry on cerebral tissue detected APMV-1 nucleoprotein in neuron-like cells and in parenchyma.

Conclusion:
APMV-1 is a pathogen of birds causing outbreaks of respiratory and neurological disease in pigeon, poultry and other avian species. APMV-1 rarely infects humans and predominantly causes mild conjunctivitis. There have been four recorded human deaths related to APMV-1 infection, all in immunocompromised hosts. In three of these, disease manifested as pneumonia with patients succumbing to respiratory failure. The fourth case had marked similarities to this case with progressive seizures three months after haematopoietic stem cell transplantation. Shotgun metagenomics on cerebral tissue also identified APMV-1.

This case highlights the usefulness of metagenomic methods in complex clinical cases. Although rare, APMV-1 should be considered in immunocompromised patients presenting with FIRES/encephalitis.

Keywords:
APMV-1, Encephalitis, FIRES, Newcastle disease, epilepsy

EPNS23-2047 Oral or e-Poster
Infections and Inflammatory Diseases

Through the unknown, find the new! -a retrospective study on Febrile infection-related epilepsy syndrome (FIRES)

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Objective: To summarize the clinical features and outcomes in children with FIRES and review current evidence.

Methods: A retrospective cohort of children 1-16 years with a diagnosis of FIRES in a district hospital in south India over 1 year and a literature review following consensus on FIRES in 2018.

Results: We had 12 children (70% male) from 3 to 7 years, presenting with high-grade fever followed by refractory seizures on day 3 or 4. The onset was predominantly generalized tonic-clonic seizures (GTCS) along with focal seizures, encephalopathy, or extrapyramidal symptoms in 25%. Baseline blood and MRI were normal. CSF was negative including the N-methyl D-aspartate (NMDA) screen. Electroencephalogram (EEG) was abnormal in 91%. Benzodiazepine and steroids were used in all children. The ketogenic diet was not tried due to limited resources. Mortality was 25% and the rest have persisting neurological sequelae at 1-year follow-up.

Conclusions: Acute refractory seizures preceded by febrile illness in children between 5 and 13 years define the condition with male preponderance (1). The incidence is reported to be 1: 1,000,000 in Germany (2) whilst we had 12 children in a single center in 1 year. Focal followed by GTCS has been mentioned as the common presentation by Nicola et al. (3) however, 83% of our cohort presented with GTCS. We couldn't ascertain a definite EEG pattern that might be helpful. Ketogenic diet and immunomodulation are tried (1,3) both of which were limited due to resources; similarly, genetic tests might help in the future perspective. Mortality ranges from 12-30% with early management playing a key role in reducing mortality (1,3).

FIRES is a diagnostic dilemma in spite of epileptic advances. Early clinical diagnosis with a structured approach might help in reducing mortality. A multicentric approach with extensive investigations might open a new horizon.

Keywords:
FIRES, NORSE, febrile epilepsy

EPNS23-2197 Oral or e-Poster

Infections and Inflammatory Diseases

Is it all about lupus? Neuropsychiatric manifestations as systemic lupus erythematosus opening diagnosis with fatal outcome

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Case study: Objective: To report a case of systemic lupus erythematosus with neuropsychiatric manifestations as opening diagnosis. Methods: Case report. Results: Female, 14 years old, only child of unrelated healthy parents. Previously diagnosed with type 1 diabetes mellitus, anxiety disorder and alleged diagnosis of bipolar mood disorder treated with Risperidone and discontinued 2 years ago according to family report. She presented with vomiting, generalized malaise, headache and dizziness for 5 days, for which she was medicated, without significant improvement. In this period, she presented psychosis, with later prostration and acute confusional state and was taken to pediatric emergency medical care. The physical examination was unremarkable, with a GLASGOW 14 and no neck stiffness. Laboratory tests showed bicytopenia (9.0 hemoglobin, 73,000 platelets), in addition to an increase in creatinine (1.93). Cranial CT scan without evidence of alterations. Cranial MRI showed extensive areas of T2/FLAIR hypersignal with diffusion restriction affecting the white and gray matter of both brain hemispheres, in vascular border territories, also identified in central brain regions and both cerebellar hemispheres, suggestive of an ischemic event. Besides, areas of spontaneous cortical T1 hypersignal were associated, suggestive of cortical necrosis, and there were some small foci with low T2 signal, suggestive of micro hemorrhagic foci. During hospitalization, the patient was diagnosed with systemic lupus erythematosus (SLE) and evolved with abdominal shock and acute renal failure, requiring hemodialysis and, subsequently, orotracheal intubation with mechanical ventilation. Conclusions: Childhood-onset SLE is a rare but severe autoimmune disease with multisystem involvement and wide heterogeneity of manifestations. In the present case, the participation of SLE, previously undiagnosed, in the child's psychiatric symptoms - chronic mood disorder - is questioned. Furthermore, a possible decompensation of the disease is observed through the acute manifestation of psychosis with a subsequent decrease in the level of consciousness, in addition to alterations in renal and hematological laboratory exams. The delay in the presentation of psychosis and other neuropsychiatric symptoms from SLE diagnosis may compromise the institution of the necessary therapeutic measures and culminate in adverse outcomes, as in that case, in which there was brain necrosis due to the disease.

Keywords:

Autoimmune disease; Lupus Vasculitis, Central Nervous System; Lupus Psychosis.

EPNS23-2342 Oral or e-Poster
Infections and Inflammatory Diseases

Rituximab response in very young boy with aggressive relapsing remitting multiple sclerosis in Thailand

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Case study: Objective: Onset of multiple sclerosis(MS) in very young(<10 years) is uncommon. We describe a boy with 2 year-old onset MS. His clinical course and treatment response were reviewed.
Results: 2 years-old boy presented with subacute left arm and leg weakness on three occasions, several months apart, before presenting to our institution, initially misdiagnosed as acute disseminated encephalomyelitis and treated with intravenous methylprednisolone. Brain MRI during each presentation revealed new areas of periventricular demyelination as well as enhanced juxta cortical lesions pattern met with 2010 and 2017 Macdonald criteria. Initial cerebrospinal ﬂuid(CSF) studies and MRI of the spine were normal. CSF analysis revealed negative oligoclonal band and neuromyelitis optica immunoglobulin(NMOIgG) and also negative for cell based assay anti myelin oligodendrocyte glycoprotein(MOG) antibody (blood and CSF). Therefore, his multiple relapses and new MRI findings validated the diagnosis of MS.His relapses response well to intravenous methylprednisolone. After steroid tapering, Azathioprine was titrated until optimal dose, as well as Mycophenolate mofetil. However, his exacerbations still occurred every 2-3 month. We changed disease modifying therapy to subcutaneous interferon beta when he was 4 years-old, which can control the attack only for several months and then relapse again; right hemiparesis with ataxia, his MRI revealed a new demyelinating lesion (periventricular area and cerebellar peduncle). CSF NMOIgG with anti MOG were repeated all negative. After 8 month initiation, interferon beta induced glomerulonephritis was suspected. Therefore, Rituximab was started, at age 6, two weeks apart and 6 month-maintenance. He was in remission around 9 month after first dose of rituximab. His Expanded Disability Status Scale (EDSS) ambulatory score was 4 and functional system score(FSS) was 2.5. Followed up Brain and spinal MRI revealed no new demyelinating lesion. However, due to poor school performance, working memory and processing speed impairment was mentioned from WISC-IV.
Conclusion: MS can be diagnosed in young children with clinical features and characteristic MRI findings. Our patients 'clinical course was aggressive and frequent relapse, resistance to several disease modifying therapy, but remission after rituximab initiation. However, long term clinical outcome should be followed. Proper disease modifying agents in very young children need more study.

Keywords:
Rituximab, young age, multiple sclerosis,Thailand

EPNS23-2430 Oral or e-Poster
Infections and Inflammatory Diseases

Clinical, etiological and neuro-radiological profile of children with Acute Encephalitis Syndrome (AES): A prospective observational study.

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Objective: 1)To study the various demographic, clinical, etiological and neuroimaging attributes of children admitted with Acute Encephalitis Syndrome (AES).
2)To asses the outcome of these patients at the time of discharge and at 1 month follow up.

Methods: This is a hospital based prospective study done over a period of 2 years (November 2020 to November 2022). 60 patients, between the age group of 3months to 18 years, diagnosed with acute Encephalitis Syndrome (fever with altered sensorium with or without seizures) were included. These patients were enrolled at admission to our tertiary care center and followed up till 1 month after the discharge. Data pertaining to their clinical profile, laboratory investigation (CBC, LFT, Sr. electrolytes etc), CSF studies, neuroimaging and EEG were collected and analysed. Outcome at the time of discharge and at 1 month follow up were assessed using modified rankin scale.

Results: Mean age of the study population was 5.4 years and 55% were males. Clinical features include fever (57%), seizures (72%), altered sensorium (100%), cranial nerve palsies (7.5%), spasticity (10%), dystonia (2.5%), cerebellar signs (22.5%) and meningeal signs (12.5%). Abnormal laboratory findings include hypoglycemia (17.5%), CSF abnormalities (52%), Dengue IGM/NS1 positive (32.5%) and abnormal EEG (40%). Viral infections (Dengue- 21.6 %, COVID- 13.3%, HSV-3.3 %, EBV-1.6 %, rabies- 1.6%, Enterovirus-1.6%) were found to be most common etiology along with bacterial (Tubercular-3.3%, Pneumococcal- 3.3 %), autoimmune (6.2%), demyelination (13.3 %) and unknown (33 %) causes. Neuroimaging revealed involvement of thalamus (12.5%), basal ganglia (7.5%), white matter (15%), leptomeninges (12.5%), brainstem (7.5%), splenium (10%) and their diffusion restriction (17.5%). Average duration of hospital stay was 12 days and complete recovery was seen in 62 % patients at 1 month follow up.

Conclusions: Our study showed varied clinical and neuro-radiological spectrum of Acute Encephalitis Syndrome. Dengue virus was seen as the most common etiological agent. Diffusion restriction of CNS structures
were seen as most common neuroimaging finding. CSF study, neuroimaging and EEG are important tool in early etiological diagnosis and apt treatment of AES patients which is reflected in our study as majority of patients showed complete recovery.

Keywords:
Acute Encephalitis Syndrome, Neuroimaging, Outcome

EPNS23-2367 Oral or e-Poster

Infections and Inflammatory Diseases

Challenges in etiologic diagnosis, treatment modalities and outcome of pediatric NORSE with respect to FIRES and non-FIRES: a single-center experience

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Objective: New onset refractory status epilepticus (NORSE) is defined as the acute onset of refractory status epilepticus in previously healthy individuals. Febrile infection-related epilepsy syndrome (FIRES), a subgroup of NORSE, is characterized by a history of preceding febrile illness and catastrophic epileptic encephalopathy.To present challenges in etiologic diagnosis, treatment modalities, and outcome characteristics of a small cohort (N=9) with pediatric NORSE/FIRES.

Methods: Demographics, clinical findings, treatment modalities, hospitalization periods, discharge status, and follow-up data were recorded. Two subgroups were compared for outcome ;FIRES:five patients, and non-FIRES:four patients.

Results: The mean follow-up was 49.6±27.1 months. There was no significant difference between the two groups for the mean age (FIRES:7.4±2.5, and non-FIRES:7.5±6.4 years). Coma induction periods in FIRES were longer [median: 80 days (min-max: 13-141) vs median: 13,5 days (min-max: 9-29)].
Infectious etiologic agents were identified in three patients with FIRES. Etiology-specific diagnoses were defined in two of non-FIRES group; anti-glutamic acid decarboxylase (GAD) positive autoimmune encephalitis and Sjögren syndrome. The remaining two non-FIRES patients were classified as cryptogenic NORSE.
All patients received pulse steroids and intravenous immunoglobulin (IVIg) therapies at the initial phase of the disease. Ketogenic diet was applied to four of the patients with FIRES. Plasmapheresis was performed in three patients, two of them were with FIRES. Second-line immunotherapy was applied to three patients: rituximab in two and cyclophosphamide in one. Anakinra was administered in two cases with FIRES.
Five patients (FIRES: 4 vs. non-FIRES:1) developed drug-resistant epilepsy with 55.6%. The functional outcome (modified Rankin Scores-mRS) of FIRES vs non-FIRES group was worse than non-FIRES group (median mRS:3 vs 0). Anakinra was initiated in one case with FIRES in the 47th month of follow-up with less hospitalization frequency and good seizure outcome. Gross motor and cognitive outcomes also improved: [Functional independence measure score: 22 (pre-anakinra treatment) vs 58 (6th month of anakinra treatment)]

Conclusions: An adverse outcome was defined in the patients with FIRES. However, the overall outcome of non-FIRES patients was related to specific etiology. Early interventional ketogenic diet and second-line immunotherapies are essential for seizure and cognitive outcomes in long-term follow-up.

Keywords:

NORSE, FIRES, refractory status epilepticus, anakinra

EPNS23-2281 Oral or e-Poster
Infections and Inflammatory Diseases

A rare case of CNS hemophagocytic lymphohistiocytosis secondary to dengue fever

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Case study: Introduction -
Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of life-threatening hyperinflammation associated with high morbidity and mortality. It may occur from genetic defects (Primary HLH) or secondary to infectious, neoplastic, autoinflammatory, autoimmune and immunodeficiency etiologies (secondary HLH). CNS-HLH is defined as abnormal CSF and /or MRI of the brain, with or without distinct neurological signs or symptoms in a patient with systemic HLH.

Case -
An 8-month-old male child, first by birth order and product of a non-consanguineous marriage with an uneventful perinatal history and normal development presented to our hospital with fever, vomiting and multiple episodes of hematemesis and haematochezia. On examination the child had pallor and hepatosplenomegaly. Rest of the systemic examination including central nervous system was unremarkable. Investigations were suggestive of acute liver failure with ALT of 18,000, AST of 7000 and INR of 4.4. CBC showed haemoglobin of 7, total leucocyte count of 22,000 (N-80/L-20) and platelets of 82,000. Dengue IgM antibody was found to be positive. On clinical suspicion of HLH work up was done come out to be positive and the patient was started on IV dexamethasone. After 2 days the child developed left sided hemiparesis for which MRI brain was done which showed features suggestive of CNS HLH. CSF Study revealed hemophagocytes which conformed clinical and radiological diagnosis. The patient was started on Intrathecal methotrexate, hydrocortisone and IV etoposide but despite of all the timely initiation of therapy child succumbed on 13th day of illness.

Conclusion -
CNS HLH is a life-threatening condition for which appropriate clinical, immunological, and radiological workup is necessary. Intrathecal methotrexate and corticosteroids have become standard of care in CNS HLH. However, data on value of intrathecal therapy has been limited.

Keywords:
hemophagocytic lymphohistiocytosis, dengue fever, hemiparesis

EPNS23-2013 Oral or e-Poster
Infections and Inflammatory Diseases

Transient hydrocephalus due to a rare case of adenovirus encephalitis is a newborn.

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Case study: Objectives
Adenovirus typically causes respiratory or gastro-intestinal illness. Neurological manifestations are present in 1-3% of children, ranging from (meningo)encephalitis to complex febrile seizures. We present a rare case of a newborn with clinical and radiological manifestations of adenovirus encephalitis.

Methods
A male child was born at term after uneventful pregnancy and delivery. At age 7 days, he was admitted for recurrent episodes of behavioural arrest with apnea and desaturation. Work-up for sepsis, cardiac anomalies and inborn errors of metabolism was negative. He had mild cerebrospinal fluid (CSF) pleocytosis (7 cells/µl). Amplitude integrated electroencephalogram (aEEG) was abnormal during episodes; EEG showed immature tracing without signs of epilepsy. During admission rhinitis, tachypnea, increased oxygen demand and diarrhea developed. Adenovirus PCR was positive on a nasopharyngeal swab but negative on CSF. At age 14 days he had a bulging fontanel and increased head circumference (+0,5 SD). Cranial ultrasound (CUS) demonstrated bilateral frontal white matter hyperechogenicity. Over a course of two days bulging disappeared and head circumference normalised. Follow-up CUS at age 27 days demonstrated a decrease of white matter hyperechogenicity. We thus conclude our patient suffered from an adenovirus encephalitis with transient impairment of CSF homeostasis.
We compared our findings to previously published data in a PubMed literature review.

Results
Few cases of neonatal adenovirus encephalitis have been reported, mostly as part of a disseminated disease. As in older children, the majority of CSF parameters and PCR were negative. Only one report documented imaging findings with CUS, none with MRI. Prognosis in neonates is worse than in older children (full clinical recovery in 91%), as only two out of seven documented neonates survived (including our patient), both of which did not have disseminated disease. Ours is the first case to demonstrate hydrocephalus as a complication of neonatal adenovirus encephalitis.

Conclusions
Adenovirus encephalitis is a rare cause of neurological disease in neonates, yet an important differential diagnosis of culture-negative sepsis given its unfavourable prognosis. Sensitivity and specificity of PCR for detection of adenovirus in CSF needs further study. Follow-up is advised for all neonates with encephalitis to identify hydrocephalus, easily detectable through head circumference monitoring and/or CUS.

Keywords:
Adenovirus, encephalitis, hydrocephalus, neonatal

EPNS23-2752 Oral
Infections and Inflammatory Diseases

Measurement of optic nerve sheath diameter by trans-orbital ultrasound to detect raised intracranial pressure in children.

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Objective: Raised Intracranial Pressure (ICP), a critical illness in children, can be appropriately managed by timely diagnosis. It contributes towards 20% of the admissions in PICU of a tertiary care institute of North India.(1) Optic nerve sheath diameter(ONSD) measurement by trans-orbital ultrasonogram(USG) is non invasive point of care tool to recognize raised ICP however there are very limited studies globally in paediatric population. Our study aims to identify the difference in ONSD among pediatric patients with normal and raised ICP and to achieve the cut-off value for diagnosing raised ICP.

Methods: A hospital based observational comparative study was conducted in a tertiary care institute of national importance in North India. Patients aged 2 to 14 years admitted in paediatrics department were included using complete enumeration technique. Children with the clinical features of raised ICP (Muir's criteria) were included in the raised ICP group and were compared with the patients without any signs of raised ICP. ONSD was measured in both the groups on Day 1 and Day 2 of admission. Last ONSD measurement was done on any day between day 4th-7th.
On each day, three readings were taken from each eye and average was used for final statistical analysis. Total 2454 ONSD readings were taken throughout our study.
Treating team was unaware of the USG findings throughout.

Results: Out of 137 patients recruited, 34 had raised ICP and 103 had normal ICP. Mean ONSD on day 1 was found to be higher in the patients with raised ICP (Mean= 4.99 mm ± 0.57) as compared to normal ICP group (Mean= 4.06 mm ± 0.40) ($p<0.01$) using Student's t test. Mean ONSD on day 2 also was higher in raised ICP patients (Mean= 4.94 mm ± 0.55) in comparison to normal ICP patients (Mean= 4.04 mm ± 0.40) which was statistically significant ($p<0.01$). Mean ONSD at the time of final reading was higher in raised ICP patients (Mean ONSD = 4.48 mm ± 1.26) in comparison to normal ICP patients (Mean ONSD = 3.99 mm± 0.57) which was statistically significant (p value <0.001).The cut-off ONSD value for detecting raised ICP was estimated to be 4.46 mm on ROC (receiver operating characteristic) curve with area-under-curve 0.906 (95% CI, 0.844-0.968), 85.3% sensitivity and 86.4% specificity.

Conclusions: Measurement of ONSD by trans-orbital ultrasound was able to detect raised ICP with excellent discriminatory performance.

Reference: 1. Singhi SC, Tiwari L. Management of Intracranial Hypertension. Indian Journal of Pediatrics. 2009;76:11.

Keywords:
Intracranial Pressure, Optic nerve sheath diameter, Trans-orbital ultrasound

EPNS23-3007 Oral or e-Poster
Infections and Inflammatory Diseases

Anti-NMDAR encephalitis - report of three cases

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Objective: Anti-NMDR encephalitis is an autoimmune encephalitis caused by IgG antibodies against GluN1 subunit of the NMDA receptor. Anti-NMDR encephalitis usually presents with symptoms of limbic or diffuse encephalitis, and is characterized by a good response to immunomodulation therapy.

Methods: We report three cases of children diagnosed with anti-NMDR encephalitis treated in year 2022.

Results: The first is the case of a nine-year-old boy who was hospitalized due to behavioral disorder, insomnia and difficulty speaking. During the examination, tonic spasms of the extremities, choreoathetotic movements and facial dyskinesia were observed. Pleocytosis, proteinorarchy and positive oligoclonal IgG bands were recorded in the cerebrospinal fluid (CSF). The EEG was dysrhythmic, with fast and low-voltage activity, while the MRI of the brain was without pathomorphological changes.
The second is the case of a five-year-old boy hospitalized for epileptic seizures, irritability and urine incontinence. In the neurological status, facial dyskinesia was observed. CSF analysis showed pleocytosis with positive oligoclonal IgG bands. The EEG showed epileptiform discharges, and the MRI of the brain was without pathomorphological changes.
The third case was seven-year-old boy hospitalized for a psychotic attack. Two months earlier he had a tonic-clonic seizure, and one month prior he had partial status epilepticus. Oligoclonal IgG bands were positive in the cerebrospinal fluid. The EEG showed focal changes. MRI of the brain showed a slightly increased signal intensity of the temporal lobe cortex.
All patients had positive anti-NMDR antibodies in serum and cerebrospinal fluid confirming the diagnosis od NMDR-encephalitis. They were treated with immunomodulatory therapy - high doses of metilprednizolone, intravenous immunoglobulins and plasmapheresis with good clinical response in two patients. Due to poor response the second patient was additionally treated with rituximab with good response.

Conclusions: Autoimmune encephalitis has a variable clinical presentation in children. Early recognition and timely initiation of therapy is associated with a better outcome and reduced risk of relapse, therefore early recognition is extremely important.

Keywords:
Anti-NMDR, encephalitis, autoimmune encephalitis

EPNS23-2922 Oral or e-Poster
Infections and Inflammatory Diseases

Recurrent idiopathic longitudinally extensive transvers myelitis responsive to steroid and intravenous immunoglobulin

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Case study: Longitudinally extensive transvers myelitis (LETM) is inflammation of spinal cord along with three or more vertebra. Clinical presentation is consist of motor and sensorial deficit, bladder and bowel dysfunction. Neuromyelitis optica is important etiology but other autoimmune and inflammatory disease can cause similar involvement. Biotinidase deficiency the another disease for pediatric LETM. Here we present ten-years old male admitted with gait disturbance, back and neck pain, urine retention. Neurological examination showed bilateral hyperactive deep tendon reflexes and Babinski signs in lower extremity, sensory defect under level of nipple. Spinal magnetic resonance images showed T2 signal hyper intensity from servical C1 vertebra to lumbar L1 with contrast enhancement. Cerebrospinal fluid examination revealed slightly increased protein with negative culture. Anti-aquaporine 4, Anti-mog and oligoklonal band was negative .Serum biotinidase level, vasculitis panel, flow cytometry for CD59 was normal. Metylprednizolon (30 mg/kg/d) was started. The patient showed dramatic response to steroid. Steroid tapering was started. Clinical and radiological full recovery occurred. But the patient had three more episode radiologically and clinically similar to first attack in three years. CSF analysis were performed again. Anti-mog, Anti- aquaporine 4 analysis were negative. There is no known etiological factor for this recurrent episodes. Spinal magnetic resonance angiography was normal. After last episode periodic intravenous immunoglobuline treatment was started (1 gr/kg/monthly). There is no new LETM attack for the last nine months. The patient walks independently, there is no sensory deficit, neurologic deficit is limited to slightly increased tonus of left Achilles tendon and pozitive Babinski reflex in left.
Conclusion: In this case idiopathic LETM is probably autoimmune process, because steroid was successful agent for recovery and IVIG was successful for relaps. But the exact cause myelitis has not been revealed so far.

Keywords:
idiopathic transverse myelitis, recurrent

EPNS23-2654 Oral or e-Poster
Infections and Inflammatory Diseases

The problem of subacute sclerosing panencephalitis in Kazakhstan

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Objective: Identifying the features of the clinical picture, diagnosis and treatment of Subacute sclerosing panencephalitis (SSPE) in Kazakhstan.

Methods: Cases of SSPE were retrospectively analyzed in three hospitals in Astana and Almaty from 2020 to 2022. It was found that the number of patients with SSPE is increases . A total of 33 cases were identified, 23 cases of them were in 2022.

Results: All children who had measles before 1 year (about 6 months) - 95% - before the immunization period. 70% of children were vaccinated after getting measles at 1 year. The average age of onset is 3-6 years. The ratio of boys and girls among the cases stands at is 3.2:1.
At the time of admission, all children were in a different condition, from moderate severity - 40% (at the initial stage of the disease) to severe severity- 60% - with regression of skills. The clinical picture developed in everyone approximately the same - hyperkinesis (100%), lack of coordination (100%), then developed seizures (80%), and loss of skills, spasticity (70%) developed at the final stage.
There were focal changes in MRI of the brain, various kinds in 90% of children; in 10% of children changes were detected after 6 months. On EEG monitoring changes were detected from the onset of the disease in the form of a slowdown, rarely in the form of epileptiform activity, after a few weeks in all children (100%) was detected an intermittent flash pattern on the EEG, typical for SSPE.
The diagnosis set on the basis of only 2 criteria. One major criteria is a typical and atypical clinical history and one minor criteria is a characteristic EEG pattern. Unfortunately, it is impossible to analyze measles antibodies in CSF in the Republic of Kazakhstan.
Treatment - all 100% received antiviral therapy - isoprinosine, hormonal pulse-therapy, immunoglobulins, anticonvulsants, clonazepam. The treatment did not bring results.
SSPE have been diagnosed from 2 to 8 weeks after the onset of the disease. The primary diagnosis have been diagnosed as epileptic encephalopathy in 60 %.

Conclusions: All children with SSPE had measles before 1 year old. The diagnosis set on the basis of only 2 criteria. It is difficult to diagnosis in the early stages of the disease. Despite numerous publications about temporary effectiveness of antiviral therapy in SSPE, the treatment did not bring results.

Keywords:
Subacute sclerosing panencephalitis , complication of measles, encephalitis

EPNS23-2590 Oral or e-Poster

Infections and Inflammatory Diseases

Reversible splenial lesion syndrome in children; single center experience

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Objective: Reversible splenial lesion syndrome (RESLES) is a rare clinicoradyological entity characterized by a reversible lesion in corpus callosum splenium. The reversible lesion in the splenium of corpus callosum is caused by various conditions. The common associated conditions are seizures, antiepileptic drug withdrawal, infections, trauma, drug intoxication and metabolic disturbances. Our study aims to describe clinical features, neuroimaging and laboratory findings of reversible splenial lesion syndrome in children

Methods: Nine children aged 0-18 years who were diagnosed RESLES between 2011-2022 years were included in the study. We retrospectively analyzed clinical course, etiology, magnetic resonance imaging (MRI), electroencephalography (EEG) findings and prognosis.

Results: There were two boys and seven girls. The mean age was 10,25 ±5,2 years. The common neurological symptoms were altered consciousness, visual complaints (blurred vision, transient blindness, diplopia), nausea and vomiting. Common associated conditions were infection, seizure and head trauma. Rota virus (%33.3, n=2), Bartonella Hanselea (%16.6, n=1), Mcoplasma Pneumonia (%16.6, n=1), Coronavirus OC43 (%16.6, n=1) were inciting infectious agents. All patients had typical radilolgical features of RESLES. One patient was daignosed as mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) associated with Rota virüs infection. All patients in our study recovered clinically and radyologicaly without any sequelae.

Conclusions: RESLES etiology in children is various and has many clinical manifestations. The diagnosis of RESLES is mostly based on neuroradiological imaging especially diffusion- weighed images. RESLES is an entity with a good prognosis and therefore excessive treatment should be avoided.

Keywords:

RESLES, children, MERS, MRI

EPNS23-2021 Oral
Infections and Inflammatory Diseases

CHILD TB LP CLINICAL DECISION TOOL-TUBERCULAR MENINGITIS

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Objective: Tuberculous meningitis (TBM) is a devastating illness that disproportionately affects young children with death or disability in approximately 50% of cases. The early diagnosis and treatment of TBM is important to ensure optimum outcomes. Since microbiological techniques have a low yield and treatment is often delayed resulting in increased morbidity, so several authors have attempted to create scoring systems for the diagnosis of tuberculosis. Goenka et al. developed a tool named 'CHILD TB LP clinical decision tool', which is a rapid clinical decision tool based on the most commonly recorded and predictive markers of childhood TBM as per their study and evaluated their tool on a different set of patients to find the sensitivity and specificity of the clinical decision tool to be 100% and 90% respectively. Since TBM is a very common illness in the developing countries and early diagnosis has a significant effect on the patient outcome, so we planned this study to further evaluate this clinical score to find out whether it can be used in our setup for early detection of tubercular meningitis and initiation of anti-tubercular treatment.

Methods: An observational cross-sectional study was carried out on admitted patients in a tertiary care teaching hospital. CHILD TB LP scoring was applied. Patients were kept as likely TBM and unlikely TBM, which were further classified as true positive, false positive, true negative, and false negative, keeping microbiologically detected TBM as gold standard.

Results: The sensitivity and specificity of the child TB LP Clinical Decision tool were 100% and 30.6%, respectively. The CSF protein, CSF CBNAAT, chest radiography, mantoux and computed tomography/magnetic resonance imaging of CNS were significantly associated with tubercular meningitis.

Conclusions: CHILD TB LP clinical decision tool can be used as a screening tool for tubercular meningitis and aid in the early initiation of antitubercular drugs and requires further research.

Keywords:
Tubercular meningitis, Pediatric infections, CNS infections, CHILD TB LP, Diagnostic tool

EPNS23-2085 Oral or e-Poster
Infections and Inflammatory Diseases

Epidemiology of MOGAD in Slovenia

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Objective: Myelin oligodendrocyte glycoprotein antibody disease (MOGAD) is a rare disease but it is more common in the pediatric population than in adults. It has a heterogeneous clinical presentation and is relapsing in 50% of patients. Diagnosis is challenging and often delayed.

Methods: We included all pediatric patients with confirmed MOGAD treated at the University Children's Hospital in Ljubljana, Slovenia, between 2013 and 2022. Because our center is the only tertiary center for the treatment of pediatric MOGAD, we assume that we identified all patients with a confirmed MOGAD diagnosis from Slovenia during the specified period. Our source was a database of patients with acquired demyelinating disorders.

Results: We identified 7 patients in 9 years. Thus, the incidence of MOGAD in Slovenia is 0.17 per 100,000 children. Six patients were female and one patient was male. The mean age was 7.1 years, and the range was from 2.7 to 15.6 years. We examined the clinical phenotypes of our patients. Three patients had a relapse, 3 had only one event, and one had a progressive phenotype. Two patients had recurrent ON, 2 patients had ADEM, 1 patient had MDEM, 1 patient had NMOSD-like phenotype, and 1 patient had leukodystrophy-like phenotype. Six patients were treated with methylprednisolone pulses for acute onset or relapse, 4 patients also received steroid tapering, 6 patients received monthly IVIG therapy, 1 patient received rituximab, and 1 patient received cyclophosphamide pulses and azathioprine. The median follow-up time was 3.4 years. At the last follow-up, neurologic functions were impaired in only 3 patients. One patient had mild impairment of visual function, one patient had impairment of motor and autonomic function, and one patient had impairment of cognitive function.

Conclusions: MOGAD is rare, diagnosis is often difficult, and the disease may go undiagnosed, especially if a child is not referred to a tertiary hospital experienced in treating children with various demyelinating diseases.

Keywords:
MOGAD, Myelin oligodendrocyte glycoprotein antibody disease, demyelinating disorders, ADEM

EPNS23-2838 Oral or e-Poster
Infections and Inflammatory Diseases

Clinical cases of subacute sclerosing panencephalitis: general clinical symptoms and preventive interventions.

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Objective: SSPE is a progressive and neurodegenerative disease that occurs after a few years in children who have had measles infection in childhood, that is, a complication of measles infection in immunosuppressive patients ends fatally within weeks or months. The lack of awareness of doctors and the population about the complication of measles and its presence in Kazakhstan led to complications, therefore, the purpose of the abstract description is to compare the frequent clinical symptoms and examination data of our patients with international ones.

Methods: We analyzed 3 patients aged 3.5-4.8 years who, after a measles infection, had a clinical picture: complaints of stumbling, myoclonia, developmental arrest, changes in the level of consciousness, decerebration rigidity. EEG, MRI of the brain, laboratory tests were carried out.

Results: - EEG is a typical pattern of bilateral, symmetrical, high-amplitude slow waves with the inclusion of high-amplitude generalized discharges in the form of OMV complexes, in the frontal-central-temporal leads bilaterally synchronously
- Initially, MRI may be normal. After some time, multifocal changes in the cortex, subcortical white matter, followed by atrophy of deep structures
- CF: without features, Oligoclonal IgG was detected in one patient
- ELISA on VC: positive IgM to measles, IgG, avidity 96%
Treatment:gcs, immunosuppression, plasmapheresis, baclofen, trihexyphenidyl, isoprinosine, anticonvulsant therapy - carbamazepine plays an important role. A few days after carbamazepine, myoclonus improved, patients were able to move independently for 3-4 months, after the transition to a vegetative state

Conclusions: A stable persistent state is the result of a balance between virus replication and the host's immune response:
-Factors related to the host. The reason why VC is not eliminated after acute infection may be temporary immunosuppression caused by VC.
-Factors related to the virus. Mutations in VC make it possible to avoid humoral immunity. VC isolated from patients detect mutations in the matrix (M) genes. Mutations in the M protein disrupt the formation of new viral particles, helping the replicating virus to persist in neuronal cells, spread through synapses.

Treatment:gcs, immunosuppression, plasmapheresis, baclofen, trihexyphenidyl, isoprinosine, anticonvulsant therapy - carbamazepine plays an important role. A few days after carbamazepine, myoclonus improved, patients were able to move independently for 3-4 months, after the transition to a vegetative state

Keywords:
panencephalitis, measles

EPNS23-2363 Oral or e-Poster
Infections and Inflammatory Diseases

Subacute Sclerosing Panencephalitis in Children with Atypical Presentations: Case Series

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Case study: Objectives: Subacute sclerosing panencephalitis (SSPE) is a slowly progressive degenerative disorder of the central nervous system (CNS). It is caused by persistent measles virus (MV) and has a high morbidity and mortality. The diagnosis is a challenge especially in patients with atypical clinical findings. Here we report five cases of SSPE with clinical, electroencephalography (EEG) and magnetic resonance (MRI) findings which mimicking metabolic disorders or autoimmune encephalitis.
Case reports: Four of the 5 patients were male; the median age at diagnosis was 7.5 years. Four patients did not have a history of vaccination against measles. Three patients had a history of measles at a mean age of 1.1 years. Patients presented with slurred speech, mental regression, gait difficulties, ataxia, seizures, myoclonic jerks and drop attacks. Brain magnetic resonance imaging (MRI) was normal in 2 patients. MRI revealed hyperintensities in posterior dominant symmetrical periventricular white matter and corpus callosum, suggestive of metachromatic leukodystrophy in 8-year-old patient. Eleven-year-old patient, who was primarily considered autoimmune encephalitis, had a focal, unilateral lesion in putamen. The brain MRI of the 4-year-old patient revealed signs of cerebral atrophy and ventricular dilatation. EEG revealed a slow background with periodic, generalized, high-voltage sharp and slow wave complexes. All patients had elevated cerebrospinal fluid (CSF) measles IgG index. Three of the patients had the fulminant form of SSPE with progression in 3-4 months that they were in vegetative state with decerebrated posturing and spasticity, also these three patients had the highest IgG index values.
Conclusions: SSPE still remains prevalent in developing countries where history of measles or lack of vaccination against measles is a common problem. Clinical suspicion along with MRI, EEG, and CSF studies are important for diagnosis as it can present with different and atypical clinical findings.

Keywords:
subacute sclerosing panencephalitis, magnetic resonance imaging, measles

EPNS23-2562 Oral or e-Poster
Infections and Inflammatory Diseases

Neurobrucellosis: two cases presenting with optic neuropathy and myelitis

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Case study: Neurobrucellosis defines neurological manifestations of brucellosis and may include meningitis, encephalitis, brain abscess, myelitis, radiculitis, cranial or peripheral neuritis.
Background and aims: Two cases are presented to illustrate the spectrum of neurobrucellosis in children.
Methods: Retrospective clinical summary.
Results:
Case 1. Nine-year old girl with leg pain, fever, weight loss of 5 weeks, headache 10 days was diagnosed by serum Brucella IgG 2,57 NTU, IgM 1,36 NTU and Brucella sp. growth in blood culture. She was started on doxycycline, rifampicin, gentamicin. Headache and fever subsided. Three days later blurred vision, diplopia, right 6th nerve palsy, bilateral papilledema developed. Cranial MRI showed leptomeningeal nodular and linear contrast enhancement. CSF biochemistry was normal, microscopy and culture were negative. Steroid and acetazolamide were added to treatment. Visual symptoms resolved in 2 days. Follow-up examination 6 months later revealed no papilledema, normal vision, slight pallor of right optic disc.
Case 2. Eight-year old boy had fever, nausea, vomiting, diarrhea for 1 day then developed paraparesis, bladder-bowel incontinence, motor and sensory loss below T5. Craniospinal MRI showed hyperintense lesions perpendicular to corpus callosum, spinal T2 hyperintensity from low cervical level to conus medullaris, expansion at C5-C7, cavitation at T8-T9, and dense pial, intramedullary and ventral caudal fiber enhancement. IV steroids and immunoglobulin were ineffective. Plasmapheresis was followed by sensory level descending to T10. Fever and neck stiffness developed in hospital week 3; after lumbar puncture, antibiotics and acyclovir were started. CSF showed rare lymphocytes, normal biochemistry and oligoclonal bands type 3. While fever persisted, PCR Brucella sp. was reported positive; antibiotics were revised. Leptomeningeal biopsy was normal. Immunological investigations were non-diagnostic. The patient was discharged after 2 afebile weeks with partial motor and complete sensory recovery. MRI four months after onset showed marked atrophy below T8-T9; enhancement was reduced.
Conclusion: Brucellosis and neurobrucellosis are often overlooked because manifestations are variable and nonspecific, and risk factors like contact or food consumption may be absent. Several weeks' diagnostic delay in our cases after acute presentation with cranial nerve involvement and severe myelitis emphasizes the importance of awareness.

Keywords:
Brucella, myelitis, neurobrucellosis, optic neuritis

EPNS23-2419 Oral or e-Poster

Infections and Inflammatory Diseases

Safety of SARS-CoV2 vaccination and COVID-19 short-term outcome in pediatric acquired demyelinating disorders of central nervous system: a single center experience.

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Objective: Concern of a correlation between disease relapse in patients with acquired demyelinating disorders of central nervous system (CNS) and SARS-CoV2 vaccines has been raised. In this single center study, we retrospectively evaluated safety of SARS-CoV2 vaccination and COVID-19 short-term outcome in pediatric acquired demyelinating disorders of CNS.

Methods: Patients with multiple sclerosis (MS), myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) and neuromyelitis optica spectrum disorder (NMOSD) with disease onset before 18 years of age were included. Demographic and clinical data, and information regarding previous SARS-CoV-2 infection and vaccination were collected.

Results: We included nine patients with MOGAD. Six patients received SARS-CoV2 vaccination and complained pain at injection site while only one had fever and fatigue. Median follow-up was 28 weeks (range 20-48). Seven patients had COVID-19 occurring with mild flu-like symptoms and median follow-up was 28 weeks (range 24-34). Nobody had disease relapse. Five patients with NMOSD were included. All patients received SARS-CoV2 vaccination (BNT162b2-Pfizer-BioNTech). The median follow-up was 20 weeks (range 14-24) and only two patients complained pain at injection site, fever and fatigue. Three patients had also COVID-19 with mild flu-like symptoms, despite two of them being under immunosuppressive treatment. Lastly, forty-three patients with MS were included. 35 out of 43 received SARS-CoV2 vaccination with a median follow-up of 24 weeks (range 8-36). Fourteen patients had no side effects, while 21 complained mild side effects (mainly pain at injection site) and one experienced a disease relapse with complete recovery after steroid therapy. At vaccination, all but one were under treatment. Sixteen patients had COVID-19 occurring with mild symptoms.

Conclusions: COVID-19 outcome was good although many patients were under immunosuppressive treatment. Vaccine-related side effects were frequent but were mild and self-limited. Only one MS patient had a post-vaccination relapse with complete recovery after steroid therapy. In conclusion, our data support the safety of SARS-CoV-2 vaccines in pediatric MS, MOGAD and NMOSD.

Keywords:

SARS-CoV2; COVID-19 vaccination; safety; multiple sclerosis; MOGAD; NMOSD

EPNS23-2785 Oral or e-Poster

Infections and Inflammatory Diseases

Review of children presenting with Optic Neuritis to a tertiary neurology centre in East of England

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Objective: We reviewed characteristics of children presenting with Optic Neuritis in the East of England with the aim of looking for useful trends and prognostic features.

Methods: Children presenting with optic neuritis between 2015 to 2022 to the Paediatric neuroimmunology service at Addenbrookes Hospital, Cambridge, were identified through the service database and their electronic records reviewed retrospectively. Tertiary referrals received from the East of England; children were monitored by the Paediatric neuroimmunology and ophthalmology services.

Results: Of 22 patients (9M:13F) with optic neuritis, 13 (59%) presented with unilateral findings. Nine children (40.9%) tested positive for Myelin Oligodendrocyte Glycoprotein (MOG) antibodies. Four (18%) showed intrathecal production of Oligoclonal bands and were given a diagnosis of Relapsing Remitting Multiple Sclerosis (RRMS). Unilateral presentation was seen in 75% of RRMS and 55% of MOG patients. An antibody negative child was diagnosed with Neuromyelitis Optica spectrum disorder (NMOSD). Five children were thought to have an infective aetiology; no cause identified. Two children showed concomitant signs of raised ICP; 2 were given a diagnosis of ADEM. The average age at presentation was 6.6 years for MOG cases and 13.2 years for RRMS with no difference in presenting age for males (11.1yrs) and females (11.3yrs). Ten were treated with IV Methylprednisolone followed by weaning course of Prednisolone. Four (18%) received Intravenous immunoglobulin (IVIg), two receiving monthly IVIg for a year. Two received plasma exchange without apparent effect. Twenty (91%) showed initial resolution of symptoms and signs after the first course of steroids. Ten (45.4%) presented with relapses. Higher recurrence rate was noted in MOG cases (55%) compared to those who were antibody negative or RRMS (50% in both). Two children underwent irreversible loss of vision in both eyes; one had MOG antibody; no identifiable aetiology was found in the other.

Conclusions: Female patients had higher representation in the RRMS group with higher age of presentation at 13.2 years compared to 6.6yrs in the MOG cases . Infective aetiology appears to play a role in a proportion of cases; however, difficult to elucidate the causes. ON is often part of other neuroinflammatory conditions (ADEM, transverse myelitis). Our data supports a higher rate of recurrence in patients found to be MOG positive as opposed to those who are antibody negative.

Keywords:

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EPNS23-2266 Oral
Infections and Inflammatory Diseases

Risk Of Seizure In Children During The Omicron SARS-COV-2 Infection

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Objective: Children with Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) usually have a mild form of the disease. The common symptoms in children include fever, dry cough, and fatigue, but the disease can range from asymptomatic to severe, including multisystem inflammatory syndrome in children. The clinical manifestation of the SARS-CoV-2 varies depending on the variant of the virus. The common neurologic symptoms included fatigue (32%), myalgia (20%), taste impairment (21%), smell impairment (19%), and headache (13%). Few case reports of seizures were also reported in pediatrics population. In the present study we are analyzing the prevalence of seizures in the Omicron variant of the SARS-COV-2 Infection

Methods: Aim of the study

To calculate the prevalence of seizures the Omicron variant of SARS (Severe Acute Respiratory Syndrome) COVID 19 infection

Methods

A retrospective cross-sectional record-based review was conducted in a tertiary care referral center in central Kerala in India. The study is conducted in all the children admitted with SARS-COV-19 in the age group between 2 months to 18 years, during the third wave, between 28th December 2021 - 15th March 2022, by the division of Pediatric Neurology, Department of Pediatric Medicine at Malankara Orthodox Syrian Church Medical College Medical College Kolenchery Kerala India. Record-based analysis was done, the data were entered in Google sheet and analyzed by SPSS - 28.

Results: A total of 88 SARS-COV-19 infections were admitted over a period of 2 months and 34(38.6%) had seizures, with an odds ratio of 7.26 [3.67, 14.33]. And of the 49 children admitted with seizures bout 69.3% was SARS-COV-19 positive

Conclusions: Amid the confronting factors, the risk of seizures with Omicron SARS-CoV-2 is extremely high in children, with the prevalence of seizures of 38.6%.

Keywords:
SARS-COV-2, Omicron, Risk, Children, Seizure, Infection

EPNS23-2936 Oral or e-Poster
Infections and Inflammatory Diseases

A Never Ending Story: Two Cases of SSPE presented with Focal Dystonia

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Case study: Subacute sclerosing panencephalitis (SSPE) is a slow progressive degeneration of the central nervous system caused by a persistent defective measles virus infection. The disease has a gradual progressive course leading to death in many cases within one to three years. We report two SSPE patients aged 6 and 8 years who presented with focal dystonia.
Patient 1 had a history of measles. He presented with left arm spasm and loss of strength in the left side. The electroencephalogram (EEG) showed high amplitude generalized periodic epileptiform discharges. Patient 2, who had no measles history and whose vaccinations were completed, applied with the complaints of spasms and tremor in the left arm. The EEG revealed that periodic lateralized discharges consisted of high-voltage slow waves in the right hemisphere. Measles antibodies in cerebrospinal fluid of patients were elevated, confirming the diagnosis of SSPE. Isoprinosine, carbamazepine and valproic acid therapies were started for both. Patient 1 died one year later. Patient 2, after three months of follow up, showed a little improvement.
In conclusion, Although SSPE is an almost forgotten disease in developed countries, it continues to be seen insidiously in developing countries. While patients could be diagnosed earlier with typical clinical presentations such as myoclonic jerks, cognitive impairment, and seizures, diagnosis is difficult in patients presenting with focal isolated findings such as focal dystonia. Since, this situation causes delay in diagnosis and treatment of patients, we wanted to emphasis focal findings of SSPE in this article.

Keywords:
SSPE, Focal, Dystonia

EPNS23-2848 Oral or e-Poster
Infections and Inflammatory Diseases

Hodgkin lymphoma cell lines and tissues express mGluR5: a potential link to Ophelia syndrome and paraneoplastic neurological disease

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Objective: Ophelia syndrome is characterized by the coincidence of severe neuropsychiatric symptoms, classical Hodgkin lymphoma, and the presence of antibodies to the metabotropic glutamate 5 receptor (mGluR5). Little is known about the pathogenetic link between these symptoms and the role that anti-mGluR5-antibodies play.

Methods: We investigated lymphoma tissue from patients with Ophelia syndrome and with isolated classical Hodgkin lymphoma by quantitative immunocytochemistry for mGluR5-expression. Further, we studied the L-1236, L-428, L-540, SUP-HD1, KM-H2, and HDLM-2 classical Hodgkin lymphoma cell lines by FACS and Western blot for mGluR5-expression, and by transcriptome analysis.

Results: mGluR5 surface expression differed significantly in terms of receptor density, distribution pattern, and percentage of positive cells. Highest expression levels were found in the L-1236 line. RNA-sequencing revealed more than 800 genes that were higher expressed in the L-1236 line in comparison to the other classical Hodgkin lymphoma cell lines. High mGluR5-expression was associated with upregulation of PI3K/AKT and MAPK pathways and of downstream targets (e.g. EGR1) known to be involved in classical Hodgkin lymphoma progression. Finally, mGluR5 expression was increased in the classical Hodgkin lymphoma-tissue of our Ophelia syndrome patient in contrast to five classical Hodgkin lymphoma-patients without autoimmune encephalitis.

Conclusions: Given the association of encephalitis and classical Hodgkin lymphoma in Ophelia syndrome, it is possible that mGluR5-expression on classical Hodgkin lymphoma cells not only drives tumor progression but also triggers anti-mGluR5 encephalitis even before classical Hodgkin lymphoma becomes manifest.

Keywords:
metabotropic glutamate 5 receptor, anti-mGluR5 encephalitis, neuroimmunology, pediatric neurology, pediatric oncology, transcriptome analysis, Hodgkin lymphoma, Ophelia syndrome

EPNS23-2586 Oral or e-Poster

Infections and Inflammatory Diseases

CLINICO-RADIOLOGICAL SPECTRUM, TREATMENT AND OUTCOME OF PEDIATRIC DEMYELINATING DISORDERS

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Case study: BACKGROUND: Acquired demyelinating disorders are rare disorders occurring with an annual incidence of 0.5-1.66 per 100,000 children. Our understanding of these disorders is rapidly expanding with availability of antibody testing. The objective is to study the clinical profile, radiological features, treatment and outcome of children with demyelinating disorders.
METHODOLOGY: This is a prospective observational study conducted across 3 years (Jan 2020-dec 2022), enlisting 22 children with demyelinating disorders admitted in a tertiary care hospital in department of pediatrics. Sociodemographic features, clinical profile, investigations, radiological findings, treatment and outcome were collected and results were analyzed.
RESULTS: Among 22 children, mean age was 7.6 years, with male preponderance (male: female-15:7). The most common presentation was encephalopathy (14;63.6%) out of which 12 patients had altered sensorium,8 had seizures, 7 had fever, 4 presented with headache and vomiting each; diminution of vision was noted in 7 patients (31.8%); weakness of limbs in 3 patients (13.6%); 6 patients had history of recent infection. CSF analysis performed in 18 patients, out of which 2 showed lymphocytic predominant pleocytosis and 9 (40%) showed elevated proteins. Amongst 22 patients, 10 were tested for OCB's out of which 3 were positive. The anti MOG antibodies were positive in 8 children (36.3%) and 7(31.8%) patients were tested positive for covid antibodies. The majority were diagnosed as acute disseminated encephalomyelitis (ADEM) (12, 54.5%) followed by isolated optic neuritis (5, 22.7%), optic neuritis with transverse myelitis (2, 9%) and ADEM with TM, multiple sclerosis and tumefactive demyelination one (4.5%) each. All the patients were treated with methyl prednisolone pulse therapy, additional IVIg was given in 6 patients, rituximab was given in multiple sclerosis and plasmapheresis was done in tumefactive demyelination. At discharge complete recovery was noted in 15(68.2%) patients and partial recovery in 6(27.2%) clinically.
CONCLUSION: Although demyelinating disorders are rare in children, there has been an increase in number of cases reported post the covid pandemic. Hence one should have a thorough knowledge regarding these disorders as early diagnosis and treatment is associated with better outcome.

Keywords:

demyelination disorders, ADEM, optic neuritis, transverse myelitis, multiple sclerosis, tumefactive demyelination

EPNS23-2086 Oral or e-Poster
Infections and Inflammatory Diseases

Use of newer disease modifying therapies in paediatric multiple sclerosis in Slovenia

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Objective: Treatment of paediatric multiple sclerosis (MS) remains a challenge due to the lack of guidelines for use of newer disease-modifying therapies (DMTs). Our objective was to characterize the use, safety, and efficacy of newer DMTs compared to injectable DMT in a national cohort of children with MS.

Methods: This is a retrospective cohort study including all children with MS, diagnosed between January 2006 and March 2022, treated at the University Children's Hospital in Ljubljana, Slovenia. The variables analysed were age at symptom onset, first line and overall DMTs use, and side effects of DMT. Newer DMTs were defined as drugs approved for use by European Medicines Agency in year 2006 or later.

Results: Our cohort included 62 patients, 69% were female. The mean age at onset was 15.4 years, range 4.5 - 17.8 years, mean follow up time was 3.8 years. Of all patients, 92% were treated with DMTs. The mean time of therapy initiation after symptom onset was 10,8 months. In 56% of patients, at least one newer DMT was used - dimethyl fumarate in 15, fingolimod in 11, ocrelizumab in 9, natalizumab in 8, rituximab in 1, alemtuzumab in 1 and cladribine in 1 patient. In 39% the initial therapy prescribed was a newer agent. In Slovenia, the use of newer agents as the first line therapy began in 2016. All children, who became symptomatic in year 2019 or later received a newer DMT as a first line treatment. We investigated which therapies were most often discontinued. In the time of follow up, 75% of patients discontinued glatiramer acetate, 53% discontinued dimethyl fumarate, 40% discontinued interferon beta, 33% discontinued natalizumab and 20% of patients discontinued fingolimod. Reasons for discontinuation were progress of disease (12 patients), side effects (10 patients), personal choice (6 patients), unknown (1 patient) and other - one patient discontinued treatment with natalizumab due to treatment of gastric diffuse large B cell lymphoma, one patient discontinued treatment with fingolimod due to treatment of metastatic non-seminomatous germ cell tumour.

Conclusions: Newer DMTs have become predominant in treatment of paediatric MS. They have comparable side effects to injectable DMTs, while other studies suggest that they lead to better disease activity control. Further research is needed to develop optimal guidelines for treatment of paediatric MS. Our findings may help to understand current trends of use of newer DMTs.

Keywords:
paediatric multiple sclerosis, disease modifying therapy, demyelinating disease

EPNS23-2439 Oral or e-Poster
Infections and Inflammatory Diseases

Enterovirus infection of the central nervous system in five neonates

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Objective: Description of five neonates presenting with enterovirus (EV) infection of the central nervous system (CNS).

Methods: This retrospective case series describes symptoms including CNS and cardiac complications, laboratory findings, antibiotic treatment, duration of treatment and hospital stay, and outcome in five neonates with EV infection who were diagnosed using cerebrospinal fluid (CSF) for reverse transcriptase polymerase chain reaction (PCR).

Results: All patients were aged 6-23 days at onset and had signs of sepsis and/or CNS infection (5/5 lethargy and poor feeding, 4/5 fever, 1/5 tachycardia and tachypnoea) at first presentation. One developed seizures and cardiac complications (dilatation of coronary arteries) and recovered after treatment with levetiracetam, immunoglobulins (IVIG), prednisolone, and acetylsalicylic acid. This patient was also the only one to show CSF abnormalities including mononuclear pleocytosis (94 %, 479 cells/µL) and elevated protein (1428 mg/l). All other patients had CSF cell counts < 4 and protein < 1000 mg/l. CSF/blood glucose ratio was between 0.48-0.55 in 3/5 and not measured in 2/5. Slightly elevated c-reactive protein in blood was found in 3/5, while leukocytes and thrombocytes were normal in 5/5. Interleukin-6 was normal at onset and later increased (58.7-310 mg/dl) in all patients. Neutrophil-to-lymphocyte ratio was elevated (1.02-4.83) in 5/5. Bacterial cultures did not show growth in any of the patients. All patients received triple (4/5) or dual (1/5) antibiotic therapy consisting of ampicillin (5/5), cefuroxime/cefotaxime (4/5) and/or gentamicin (4/5) and in one case with pleocytosis also acyclovir as initial treatment. Antibiotics were given for 4-7 days; hospital stay lasted 7-13 days. The patient who presented with seizures now shows motor developmental delay at age 3 months, 2/5 develop normally at age 2 months, 2/5 are very recent cases, so development is yet unknown.

Conclusions: In neonates who appear septic without an apparent focus, EV CNS infection should be considered and can be diagnosed rapidly by CSF PCR testing. Diagnosis leads to earlier discontinuation of antibiotic treatment and shorter hospital stay. Neonates with EV infection should be screened for cardiac complications and in severe cases treated with IVIG. CSF abnormalities might predict a more severe disease course and justify closer monitoring. However, CSF and blood parameters should be investigated in a larger cohort.

Keywords:
enterovirus infection, EV infection, EV, enteroviral, neonatal, neonates, meningitis, encephalitis, infection of the CNS, infection of the central nervous system, enterovirus infection of the central nervous system in neonates

EPNS23-2012 Oral or e-Poster
Infections and Inflammatory Diseases

A Case of Progressive Multifocal Leukoencephalopathy in a Child with Hyper-Immunoglobulin M Syndrome

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Objective: Progressive multifocal leukoencephalopathy (PML) is a subacute demyelinating disease of cerebral white matter caused by the John Cunningham virus (JCV). PML is primarily reported in patients with severe immunosuppression caused by human immunodeficiency virus infection. However, PML has also been reported in primary immunodeficiencies (PID).

Methods: We describe PML in an immunocompromised child with hyper-immunoglobulin M syndrome (HIGM) during the coronavirus disease 2019 (COVID-19) pandemic.

Results: A 6-year-old boy with a history of HIGM was visited because of left-side weakness. He had been treated with monthly intravenous immunoglobulin (IVIG) replacement therapy, which had been discontinued 7 months because the patient's parents thought it would be risky to visit a hospital during the COVID-19 pandemic and underestimated the risk of opportunistic infections. He had been showing fatigue and poor concentration for 3 weeks and decreased left hand and arm movement for 10 days prior to the visit. He was alert but he had central left facial palsy, urinary incontinence, mutism, and cognitive decline. The left upper extremity was rated as motor grade III, and the left lower extremity was rated as grade IV. Serum immunoglobulin (Ig) G and IgA levels were extremely low, with elevated IgM levels. The cerebrospinal fluid (CSF) analysis was unremarkable. Brain magnetic resonance imaging (MRI) with contrast enhancement demonstrated bilateral asymmetric multifocal regions at the subcortical white matter with high signals on the T2-weighted images. IVIG replacement therapy was initiated due to the low levels of IgG. Although PML was suspected based on the MRI findings and the history of his immunodeficiency, intravenous methylprednisolone pulse therapy was initiated because other encephalopathies were not excluded. JCV PCR tests of the CSF and urine were positive, and he was diagnosed with PML. A genetic analysis revealed a 4,858-base pair deletion including exon 5 on the CD40LG gene, which encodes CD40 ligand, in this patient. Despite additional periodic IVIG replacement therapy, the disease worsened. Currently, 11 months after the onset of the disease, he is bedridden with a tracheostomy, home ventilation care, and percutaneous gastrostomy.

Conclusions: PML should be suspected when a patient with PID shows subacute neurologic symptoms with multifocal brain lesions primarily in the white matter.

Keywords:
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EPNS23-2739 Oral or e-Poster

Infections and Inflammatory Diseases

Outcome and brain volume changes over time in children with autoimmune encephalitis and MOG antibodies

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Case study: Abstract

Background: MOG-encephalitis (MOG-E) is a rare clinical phenotype of MOGAD presenting with somnolence in combination with focal seizures, MRI changes restricted to grey matter and elevated serum MOG antibodies.

Objective

To describe outcome and brain volume changes over time in children with MOG- E.

Methods

Children with autoimmune encephalitis (AE) who tested positive for serum MOG abs, characteristic MRI changes and a follow up were included. MRI scans at onset and follow up were analyzed including FSL SIENAX for whole brain volume measurements.

Results

22 children (9 female, 13 male) with MOG-E and a median age at onset with 7,9 years (range: 3-17 years) were included. Children presented with a combination of encephalopathy (21/22), headache (7/22), focal neurological signs (6/22), seizures (14/22) or CSF pleocytosis (19/22). Imaging showed grey matter involvement and MOG abs in all children with a median titer of 1:1280 (range: 1:160-1:10240).

Overall outcome after a median follow up of x months (range: 3-104 months) was good with only 4/22 patients having residual symptoms such as severe cognitive impairment, worsening of preexisting dyslexia or seizures (n=2). x/22 children had up to three additional demyelinating relapses associated with persisting MOG abs. 15/22 patients showed decreasing or absent MOG titers in the following 6 months (range: 0-5120). Preliminary whole brain volume measurements indicate that children with MOG-E do not have an expected brain growth overtime.

Conclusion

The majority of children with MOG-E appears to have a good clinical outcome with resolution of MRI changes overtime and decreasing MOG abs.

Keywords:

autoimmune encephalitis, MOG autoantibodies, MOGAD, grey matter involvement, pleocytosis, brain volumetry, brain growth

EPNS23-2942 Oral or e-Poster
Infections and Inflammatory Diseases

Tumefactive Demyelinating Lesions in Children

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Objective: Tumefactive demyelinating lesions (TDLs) are defined as lesions larger than 2 cm diameter on T2-weighted MR images of the brain. Distinguishing their etiology is important to avoid unnecessary interventions and to plan management. We intended to examine the etiological profile of TDL in our pediatric cases for any markers likely to support particular diagnostic groups.

Methods: Patients with TDLs who had been imaged for first clinical events were identified among pediatric neurology patients 1997-2022. Clinical and laboratory data at initial presentation and during follow-up were collected and updated from hospital records. TDLs were evaluated in two groups: single and multiple. In addition, patients with "TDL only" and those with additional non-tumefactive lesions, "TDL+other" were compared.

Results: Sixteen patients, male/female 7/9, were included. Age at onset was mean 10,7 ± 4,6 (median 11, range 1-17) years, higher in girls. Clinical presentation was acute (symptoms <3 weeks) in 87,5%. Polysymptomatic presentation was common (81,2%), predominantly motor (83,3%) followed by sensory (37,5%), cerebellar (31,2%). TDLs were single in 13 (81,2%) cases. Symptoms did not differ between patients with TDL only and TDL+ other, nor between those with single or multiple TDLs. The final diagnosis was multiple sclerosis in 9/13 (69,2%) patients with a single TDL and 2/3 (66,6%) with multiple TDLs. The other with multiple TDLs was diagnosed with myelin oligodendrocyte glycoprotein antibody-associated disorder (MOGAD).
Clinical relapse was observed in 56,2% of the patients within mean 5,3 months follow-up; all also had newly added demyelinating lesions. One patient developed a new TDL and one, 2 new TDL at various intervals. Therefore, total 19 "TDL episodes" were examined. They were well circumscribed (n=14) or infiltrative (n=5). 13/19 were located in cerebral hemispheres. Their localization did not differ between diagnostic groups.

Conclusions: Multiple sclerosis is the most common diagnosis in children with TDL accompanied by other demyelinating lesions and multiple TDLs while single TDLs may be due to a larger etiological spectrum.

Keywords:
Children, Multiple sclerosis, Tumefactive demyelinating lesions,

EPNS23-2008 Oral or e-Poster
Infections and Inflammatory Diseases

A case of central nervous system vasculitis associated with juvenile idiopathic arthritis

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Case study: Although the vasculopathy or vasculitis with underlying juvenile idiopathic arthritis is known to have a systemic distribution, central nervous system (CNS) involvement has rarely been reported and may be under###recognized in children. We report a girl with a diagnosis of systemic onset juvenile idiopathic arthritis (SoJIA), subsequently developed clinical features of CNS involvement, possibly consistent with secondary CNS vasculitis. A 5-year-old girl presented to our clinic with an 8-days history of medial gaze limitation of her left eye, tremor, and gait disturbance. Her temperature was 37.5 and she had normal blood pressure and heart rates with normal oxygen saturation. She was alert and responsive. Ataxic gait and intention tremor were also detected upon complete physical examination. Routine laboratory studies were within normal. The findings of inflammatory markers showed ESR 25 mm/hr, CRP 12.23 mg/mL and IL-6 16.60 pg/ml. In clinical history, she experienced symptoms of midbrain infarction at the age of 2, and she was treated with left optic neuritis at the age of 4. Since then, she has been diagnosed with SoJIA with symptoms of inflamed multiple joints and persistent fever. She was well controlled with steroid and oral non-steroid anti-inflammatory agents. With newly developed neurological symptoms, brain MRI revealed multiple T2 high SI on the left paramedian midbrain with enhancement and multifocal old hemorrhage in both hemispheres, whose cause was thought to be vasculitis. The additional autoimmune antibodies for AQP4 and MOG were negative. She was treated with of high dose intravenous methylprednisolone over three days, diagnosed with secondary CNS vasculitis associated with SoJIA. Her neurologic symptoms gradually improved without relapse. Three months later, she received a follow-up study of MRI, which showed decreased size and chronic change of previous T2 high SI without enhancement. This is the first case with a diagnosis of SoJIA, subsequently developed secondary CNS vasculitis in Korea. Further studies are needed, as improved understanding of underlying mechanisms will improve preventive strategies of CNS vasculitis.

Keywords:
central nervous system vasculitis, juvenile idiopathic arthritis

EPNS23-2845 Oral
Infections and Inflammatory Diseases

UNUSUAL PEDIATRIC LYME DISEASE MANIFESTATION: GARIN-BUJADEUX-BANNWARTH SYNDROME

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Case study: Objectives: Lyme disease is a tick-borne illness primarily caused by B.Burgdorferi. In Europe, neuroborreliosis occurs in up to 15% of infected patients. Garin-Bujedaux-Bannwarth syndrome is a clinical manifestation of neuroborreliosis with painful radiculopathy, facial nerve palsy and lymphocytic pleocytosis in cerebrospinal fluid (CSF). It is rare among children with only a few described cases published in literature.
Methods: In this case study we report pediatric patient with clinical, laboratory and radiological confirmations of Garin-Bujedaux-Bannwarth syndrome.
Results: A 12 years old, previously healthy, male patient was admitted to the hospital with acute lower back pain with pain radiating to the right groin area. Symptomatic treatment with analgesics was administered for three days, after slight clinical improvement, the patient was discharged from hospital. 12 days after discharge, facial asymmetry appeared and the patient returned back to the hospital.
On examination, the patient had subfebrile body temperature, facial nerve palsy on the right side, weakened deep tendon reflexes in both legs and lower back pain with radiation according to L1-L2 spinal root distrubution. Patient denied possible tick bite.
CSF analysis showed pleocytosis (376 cells/uL) with lymphocytic predominance and protein level of 3,1g/L. Magnetic resonance imaging of head and spine revealed contrast enhancement in the right facial nerve and polyradiculoneuritis at the level of cauda equina. In CSF, elevated levels of B.burgdorferi IgM and IgG antibodies(Ab) were found, while IgG Ab were found in serum. Ab index of CSF:serum was not performed due to lack of CSF sample. B.burgdorferi DNA was detected in CSF.
Treatment with intravenous ceftriaxone was initiated. On the second day of treatment, facial nerve palsy appeared also on the left side. After 21 days of treatment, gradual muscle strength improvement in face was seen, lower back pain was absent and body temperature was normal.
Conclusions: We presented a pediatric patient with a rare form of Lyme disease - Garin-Bujadoux-Bannwarth syndrome. With appropriate treatment a favorable outcome was reached. Case showed difficulties that can emerge with initial diagnostics, due to unspecified onset of symtoms. It is possible that due to this aspect Garin-Bujadoux-Bannwarth syndrome is being underdiagnosed among children.

Keywords:
Lyme disease, Garin-Bujedaux-Bannwarth syndrome

EPNS23-2606 Oral or e-Poster
Movement Disorders

Eight years old girl with acute ataxia due to Epstein - Barr virus infection - case report

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Objective: Acute childhood ataxia is a relatively common clinical entity that we encounter in the emergency settings. The etiology is various. Numerous neurological complications of Epstein - Barr
virus (EBV) infection are well - recognized, an acute cerebellar ataxia is one of them.

Methods: Case report

Results: An eight years old, previously healthy girl, was admitted to neurology department of our clinic due to acute onset of gait disturbance. Two weeks before admission she started to feel
fatigue, after a few days she developed high fever and signs of upper respiratory tract infection. She was gradually feeling better but before admission she developed headache, was vomiting, her gait became unsteady. On examination she had finger nose ataxia, difficulty to stand and managed to
walk only a few steps with a wide base, Romberg was positive, with leaning on the right. She did not have nystagmus or other signs of cranial nerves impairment. Liver enzymes were mildly elevated and serology for EBV was positive (IgG - anti VCA, IgG - anti - ENBA). We performed lumbar puncture, the results of cerebrospinal fluid (CSF) investigations were normal, oligoclonal bands were negative both in serum and in CSF and there was no intrathecal synthesis of immunoglobulins present. Polymerase chain reaction (PCR) for EBV both in blood and in CSF was positive. Magnetic resonance imaging (MRI) of head was unremarkable and electroencephalogram (EEG) was normal. We decided not to initiate any specific treatment. The girls clinical picture gradually improved.

Conclusions: We here report a case of an eight years old girl who presented to our department with an acute onset of ataxia due to EBV infection. Acute ataxia during EBV infection is a rare manifestation of the disease. Based on the literature the efficiency of antiviral therapy or immunotherapy is controversial. The disease usually has a benign course.

Keywords:
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EPNS23-2828 Oral or e-Poster
Movement Disorders

Movement disorder perspectives at MCT8 deficiency: Series of 3 Colombian patients diagnosed with Allan Herndon Dudley Syndrome

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Case study: Introduction

Deficiencies in the thyroid hormone transporter monocarboxylate 8 (MCT8) due to pathogenic variants in the SLC16A2 gene, result in a wide range of symptoms including severe developmental delay, global hypotonia, movement disorders and cognitive disability. This rare disorder, named Allan Herndon Dudley Syndrome (AHDS), is inherited in an X-linked fashion and severely affects males, with an estimated prevalence of 1:70,000. In females, it produces milder manifestations.
Our aim is to present a series of 3 Colombian patients diagnosed with AHDS and provide a detailed description of the movements disorders and paroxysmal events to improve the information in medical literature.

Clinical features

Patient 1 (c.407dupA)
Male, hypotonic since birth who at 4 months of age showed dystonic posturing with onset at upper limbs and then generalized plus developmental delay. At 15 months presented transitory symmetrical myoclonic jerks of both arms and hands, with forced adduction and intrarotation of arms, worsened by emotions and sounds that disrupt sleep.

Patient 2 (c.604G>A)
The patient had hypotonia and notorious dystonia from 10 months, with onset in upper limbs and then generalized, with symmetrical axial and appendicular compromise, steady during the day and disappeared during sleep. No oral dyskinesias. Additionally, axial myoclonic jerks that progressively extended to include muscles of both upper limbs with increased frequency, worsened with stimuli and sleep.

Patient 3 (c.461_463del)
At age of 2, first evaluated due to hypotonia, started with involuntary, repetitive, sustained generalized muscle contractions with no response to L-DOPA treatment, the patient has spasticity ,no myoclonus, no other abnormal movements.

Discussion

We report here the main clinical findings in three patients affected by AHDS, a rare syndrome that leads to intellectual disability and movement disorder. In accordance to previous studies, our patients debuted with hypotonia and severe developmental delay followed by dystonia. We also identified a relationship between early onset of symptoms and clinical severity of disease. All of them have axial hypotonia, limb spasticity and some degree of cognitive dysfunction. Our findings may aid in providing patients with an early and accurate diagnosis.

Keywords:
MCT8 deficiency, dystonia, hypotonia, myclonus

EPNS23-2736 Oral or e-Poster
Movement Disorders

Expanding the clinical spectrum of KCNMA1-related disorder: two twins with a tremor-dominant presentation

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Case study: KCNMA1 gene encodes the alpha subunit of the BK large conductance voltage and Ca2+-dependent K+ channel (KCa1.1), which is widely expressed in the central nervous system.
KCNMA1 mutations are responsible for an emerging channelopathy associated with a broad phenotypic spectrum, usually including epilepsy, movement disorders, cognitive impairment, or a combination thereof. Both paroxysmal and chronic movement disorders are associated with KCNMA1-linked channelopathy, Episodic events feature paroxysmal non-kinesigenic dyskinesia and dystonic cataplexic, whereas chronic movement disorders usually encompass ataxia, myoclonus and/or dystonia.
We describe the phenotype of two 8-years old homozygous twins harboring the KCNMA1 pathogenic variant c.1061G>A p.(Gly354Asp).
Both twins presented with motor and language developmental delay and bilateral action tremor with onset around 3 years of age. On neurological examination, both patients showed postural and intention tremor, with only subtle cerebellar signs (slight difficulties in tandem gait and slightly dysarthric speech), but no overt ataxia.
One twin had borderline cognitive functioning, and both presented with attention deficit-hyperactivity disorder.
The phenotye of KCNMA1-linked channelopathy is rapidly expanding. With a tremor-dominant presentation (in the context of a neurodevelopmental disorder), these two patients further expand the phenotypic spectrum. This family highlights the possible occurrence of mild phenotypes, without epileptic or non-epileptic paroxysmal event and only nuanced cerebellar signs.

Keywords:
KCNMA1, tremor, ataxia, channelopathy, movement disorder

EPNS23-2731 Oral or e-Poster
Movement Disorders

Teletherapy for children with cerebral palsy using body-controlled video games: preliminary results of a randomized controlled trial

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Objective: An interactive therapy system based on video games developed specifically for children with movement disorders was used for the first time in home teletherapy. The aim of the accompanying study was to prove the feasibility and to collect first results on the effect.

Methods: In a university outpatient clinic for children with movement disorders, 36 children aged 6 to 18 years were randomly drawn into 4 groups (TV, tV, Vt, and vt): with (T) and without (t) intensive teletherapeutic supervision during the first 3 weeks, and with(V) and without(v) additional vibration therapy.
All children received at least 35 minutes of therapy 5 times per week for 6 weeks. The children were evaluated at 4 time points: V0: 3 weeks before start; V1: at the start of therapy; V2 3 weeks after start; V3 at the end of therapy after 6 weeks. The time between V0 and V1 served as a control period. In addition, automated feedback was obtained from patients and their parents after each session and there was a final questionnaire a few weeks after the end of therapy. The questions were each evaluated with a subjective score with 100 steps.

Here we would like to present the preliminary results of the first 10 children (6-13 years; GMFCS I-III; 4xTV, 3x tv, 2x Tv, 1xVt).

Results: Patient and parent feedback
Exemplary results of 3 of the 12 questions posed directly after therapy: "Did you enjoy therapy today?" 91 (0-100); "How effective did you find this Gamo session for your child's therapy?" 66 (0-100); "How well did today's Gamo session integrate into everyday life?" 26 (-50 - +50).
Exemplary results of the final questions 3 weeks after the end of therapy: Most parents would repeat therapy: 83 (0-100); Therapeutic tele-supervision via online video support was perceived as "helpful": 83 (0-100).
Parents would recommend the therapy to others: 87 (0-100).

Functional improvements:
Increase in GMFM (Gross Motor Function Measure) part D: +1.8%; Increase in GMFM part E: +3.9%; change in 6 minute walk test +49 meters; improvements in COPM (Canadian Occupational Performance Measure) Performance +1.2; COPM Satisfaction +1.2.

Conclusions: Teletherapy using body-controlled video games has been shown to be mature and effective in this study, according to initial subjective and objective observations. In times of the corona pandemic, but also beyond, this home therapy concept could be a real complement to conventional therapies.

Keywords:
teletherapy, cerebral palsy, serious gaming, virtual reality

EPNS23-2820 Oral or e-Poster
Movement Disorders

Safety and tolerability of full spectrum cannabis oil (CBD:THC 10:1) for treatment of spasticity in children and young adults with cerebral palsy

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Objective: to evaluate the safety and tolerability of full spectrum cannabis oil (FSCO) with CBD: THC ratio 10:1 for the treatment of spasticity in patients of 5-25 years with cerebral palsy (CP) GMFCS grade IV and V.

Methods: a pilot open-label study in 7 CP patients receiving FSCO was followed by a prospective double-blind randomized trial (DBT) with 33 participants, with CP. The double-blind phase (DBP) lasted 6 weeks after which randomization was opened and FSCO was introduced to patients in the placebo arm, whereas patients in the FSCO arm opted to continue treatment for the next six weeks. Patients' demographic characteristics, frequency, and occurrence of adverse effects (AE) were analyzed.

Results: The median age of patients was 15 years. The median FSCO dose, gradually titrated to AE or effect, was 0.29 mg/THC/kg body weight (BW) twice daily (range 0.1-0.48 mg/THC/kg BW). The most common AE was drowsiness (in 50% of all 40 participants), followed by poor contact (30%), agitation (22.5%), nausea, and sleep disturbance (20% each). Seven patients (17%) reported no side effects, while others had some type of AE, a median of 3 with a range of 1-7 AE. In the DBP, the probability of experiencing side effects was significantly higher in the FSCO group (N = 18) (p=0.0028) compared to the placebo group (N = 15), while the probability of discontinuing the study due to AE was not higher (p=0.12). In the DBP, a total of 11 patients, (9 on FSCO and 2 on placebo), discontinued the study due to AE. In the other 22 patients who experienced some type of AE, the dose adjustment alleviated AE.
Of all 38 patients in whom FSCO was initiated, 22 participants (57%) chose to continue treatment with FSCO at the end of the study period (week 12), and 12 (31%) of them continued for the next six months.
Only three serious AE were reported: two patients treated with FSCO had allergic reaction and fever during respiratory infection; one patient on placebo experienced more frequent seizures. In the first two patients, AE stopped after discontinuation of the FSCO, which was reintroduced without AE. The third patient discontinued the study drug (placebo) and seizures stopped.

Conclusions: The reported AE during FSCO therapy were quite frequent, but mild to moderate and most of them could be managed by dose adjustment, while 3 patients needed treatment discontinuation. Our results show that FSCO represents a safe option for the treatment of spasticity in children with CP grade IV and V.

Keywords:
safety, cannabis oil, spasticity, cerebral palsy

EPNS23-2341 Oral or e-Poster
Movement Disorders

BH4 METABOLISM DISORDER ATTENDING WITH TREMOR: A CASE REPORT

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Case study: Introduction:
Hyperphenylalaninemia is an autosomal recessive amino acid metabolic disease and is mainly categorized as phenylalanine hydroxylase (PAH) deficiency and tetrahydrobiopterin (BH4) deficiency. PTPS deficiency is the most common alteration of BH4 metabolism and one of the more frequent causes of autosomal recessive Parkinsonism in childhood. 6-Pyruvoyl-tetrahydropterin synthase (PTPS) deficiency (PTPSd) (MIM# 261640) is an autosomal recessive disorder of tetrahydrobiopterin (BH4) synthesis. Two clinical types have been defined as severe and mild form. We was described in a 19-year-old male patient with mild form of PTPS deficiency

Case report: A 16-year-old male patient with four siblings; It was learned that he had complaints of tremors, gait disturbance, slurred speech, hypersalivation, and dysphagia. His complaints worsened in the evening hours, and he could stop by holding his face with his hand to compensate for this movement disorder. Blood phenylalanine level was 1312 µmol/L, tyrosine and prolactin levels were normal. Neuroimaging showed hyperintensities in periventricular white matter in the T2 weighted series. In the whole exome sequencing analysis, a homozygous c.364C>A p.Leu122I variant was detected in the 6th exon of the PTS gene. The homozygous mutation of the mild form of PTPS deficiency has not been identified so far.
Conclusion: BH4 deficiencies are among the treatable neurometabolic diseases. It is frequently reported that severe forms are followed with the diagnosis of cerebral palsy and receive delayed diagnosis and treatment. We should be aware that there may be cases where newborn screening is not performed or there may be incorrect results in this screening, as in our patient.

Keywords:
Movement disorders, BH4

EPNS23-2669 Oral or e-Poster
Movement Disorders

Early-onset parkinsonism in DHDDS-associated neurodegeneration

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Case study: Objective
De novo variants in DHDDS gene have been very recently related to a neurodevelopmental and neurodegenerative disorder phenotype with global developmental delay, early-onset epilepsy, action myoclonus/tremor and ataxia. Later in the disease course, hyperkinetic and/or hypokinetic MDs emerge together with cognitive decline. We describe the case of an infant with de novo variant in DHDDS that presented with progressive tremor and early-onset parkinsonism.
Case description
At 4 years old, a girl was first checked for tremor that was interfering with daily activities. Physical examination revealed a bilateral distal postural and intention high-amplitude tremor, exacerbated by stress and resembling action myoclonus. She also presented clumsiness and mild speech delay. Parents described an intention tremor evident before 6-month-old. Motor development was otherwise normal but after starting school at 3-year-old, they referred a worsening of tremor, attention difficulties and social anxiety. At 6-year-old, tremor was also evident in head and neck, interfering in speech and writing. At 9-year-old, physical exam revealed bradykinesia, hypomimia and rest tremor, with slowly progression at 11-year-old. Non-verbal IQ has decreased from 95 to 77 in the last 5 years. TETRAS clinical scale was performed at 4, 6 and 9-year-old, showing progression of tremor. No dystonia, ataxia or seizures were observed. Trials with propranolol, gabapentin and levodopa did not change tremor, but methylphenidate improved attention. Serial investigations were normal: neuroimaging, electroencephalogram, electromyogram, and targeted biochemical tests (including transferrin isoforms). Fragile-X and copy number variants were ruled out. At 10-year-old, WES study has revealed a heterozygous de novo pathogenic variant (Arg37His) in DHDSS gene, already described in a male adult with ataxia, myoclonus/tremor, epilepsy, and late-onset parkinsonism.
Conclusion
In DHDDS (MIM#617836), most of the patients presented seizures before 10 years, but only one third of the cases developed parkinsonism from adolescence. Our patient contributes to expand the DHDDS phenotype, as early progressive tremor and parkinsonism were the initial and predominant clinical features during the first decade of life, without epilepsy.

Keywords:
DHDDS; parkinsonism; tremor; movement disorders; neurodegeneration

EPNS23-2517 Oral or e-Poster
Movement Disorders

opsoclonus myoclonus in the era of Covid 19 infection : Clinical profile,treatment and outcome

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Objective: This is a descriptive comparative study of OMAS in children in between the years 2014-1019 and the years 2020-2022

Methods: Retrospective study in the neurology department of Mansoura University Department. Electronic records of patients have been reviewed since 2014 till Dec 2022.
Patients have been grouped into Group A : patients diagnosed between January 2014-December 2019 and Group B: patients diagnosed between January 2019-Dec 2022.
opsoclonus myoclonus Ataxia Syndrome was diagnosed if the patients fulfilled 3 criteria of four : 1) characteristic eye opsoclonus or ocular flutter 2) Ataxia or myoclonus 3) Behavior problems: irritability, and sleep disturbance. 4) Neuroblastoma.
Patients were classified to Para neoplastic if tumor was discovered and Para infectious if no tumor was discovered.

Results: We found total of 17 cases ; 4 cases only in Group A and 13 in group B. The four cases in group A were all paraneoplastic and in group B the cases were 9 cases Para infectious and 4 only paraneoplastic.
The para infectious cases were not Covid 19 positive but 5 had contact to close family member. Results will show the mean duration till presentation , mean severity score before and after treatment.
The 9 cases Para-infectious were all chronic relapsing cases.
Escalating protocol of treatment was used to treat patients with different outcomes.

Conclusions: There is a surge in the number of Para infectious OMAS patients. These patients are chronic and resistant to treatment. Combination therapy is still the best approach.

Keywords:
Ataxia, opsoclonus , myoclonus, children

EPNS23-3022 Oral or e-Poster
Movement Disorders

AADC deficiency and gene therapy: limitations of indications and outcomes. About 2 new patients

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Case study: Objectives
AADC deficiency is a rare neurogenetic disorder responsible for an
dopamine and serotonin synthesis. Severe forms have
movement disorders (hypokinesia, dystonia, oculogyric seizures), behavioural disorders, severe developmental delay, dysautonomia. Drug resistance is common. Clinical studies have validated the safety and efficacy of delivery of a viral vector expressing AADC (AAV2-hAADC) to the putamen in children with AADC deficiency. To date, 5 drug-resistant patients have been treated in France. We present 2 patients with discussed operative indication.

Methods:
The first child (2 ½ years old) is the youngest European patient to be operated. Inspite hie youg age, indication for surgery was validated in view of the severity of the clinical condition.
The second (7 years old) is able to walk and talk but has a very fluctuating impairment, with severe attacks of loss of head and holding, ptosis, dystonia, dyskinesias, oculogyric seizures, dysautonomic disorders. The indication was validated by the severity of the attacks. Surgical indications have been validated by the national multidisciplinary team. Surgical procedure followed the Upstaza protocol.

Results
Both patients had no operative complications (except for the expected transient dyskinesias). FDopa TEPscan confirmed the resumption of dopamine secretion in the putamen. At 3 and 6 months post-op both patients were significantly improved, and have clear reduction in oculogyric seizures. First patient can hold his head and sit with support, is able to move and grasp, has dramatic improvement of respiratory condition. Second patient has no more acute attacks and improve in motor skill. We will present the evolution at 6 and 12 months.

Conclusion
In the literature, this therapy in severe forms allows a clear global improvement with acquisition of walking for some (follow-up at 10 years). A case of moderate form has been published with a clear benefit. We confirm the technical feasibility of the procedure for very young and fragile patients; the evolution of our patient with an intermediate form is is very positive with a significant recovery.

Keywords:
gene therapy, AADC deficiency, dystonia, dyskinesia, oculogyric crisis, dysautonomia

EPNS23-2479 Oral or e-Poster
Movement Disorders

Markers to follow rehabilitation efficacy in children with cerebral palsy (CP)

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Objective: CP is a group of motor disorders due to non-progressive brain lesions. CP alters the immune system in children via increased levels of T- and B-cells. Increased levels of immune cells are associated with increased levels of sera markers. These markers are related to extracellular matrix (ECM) remodeling and consequent fibrosis, suggesting a link to contractures - common complications in children with CP. The major approach to managing contractures is to provide rehabilitation. Rehabilitation exercises were shown to decrease the number of B-cells. Thus, we decided to verify the effect of rehabilitation exercises on altered levels of sera markers in toddlers and school-aged children with CP.

Methods: Proteomic chip generated data on pooled sera samples (15 healthy and 14 children with CP) to select CP-associated markers. Next, markers to follow rehabilitation efficacy were studied in 14 children with CP by comparison of expression levels before rehabilitation with levels after 30 days of rehabilitation approach. We used the proteomic cytokine array kit, adapted according to the manufacturer's instructions to allow semi-quantification with Bio-Rad-Image-Lab-Software-6.0.1-Windows by chemiluminescence detection in Bio Rad machine. The accumulation signal of measure analytes is expressed in pixel density units. The statistical analysis was performed by the effect size calculations between the groups. Markers with huge effect size between arrays were identified as significantly different. Using the DAVID web tool we identified associated biological processes.

Results: CRP, BAFF, TARC, angiogenin, serpin E1, RBP-4, EGF, and PDGF-AA - 8 out of 105 inflammatory markers and growth factors showed elevated levels in children with CP. CRP, EGF, and PDGF-AA decreased by up to 31% after 30-day rehabilitation. These 3 markers are associated with protein binding, extracellular region, disulfide bond, extracellular space, signal, and signal peptide, which are linked to ECM remodeling.

Conclusions: Rehabilitation exercises helped to balance levels of markers in the peripheral blood, i.e. increased levels of markers in children with CP returned to the reference values after rehabilitation, promising the utility of efficacy markers.

Keywords:
CP, ECM, CRP, EGF, PDGF-AA

EPNS23-2372 Oral or e-Poster
Movement Disorders

Response to deep brain stimulation in a patient with a hyperkinetic movement disorder due to glutaric aciduria type 1

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Case study: Objective: Glutaric aciduria type 1 (GA1) is a rare autosomal recessive neurometabolic disorder caused by pathogenic variants in the GCDH gene (19p13). The typical presentation of GA1 is an acute encephalopathic crisis during an intercurrent illness within the first 24 months of life causing acute bilateral striatal injury. This can result in severe dystonic dyskinetic movement disorders. Prominent orofacial involvement is common resulting in speech disorders. There are limited reports of GA1 patients treated with DBS, where minimal improvement was found.

Methods: We present the case of a 10-year-old male with a hyperkinetic movement disorder refractory to standard medical treatment.

Results: A 10-year-old boy born to nonconsanguineus parents after a normal pregnancy and delivery consulted with a hyperkinetic movement disorder characterized by the presence of choreodystonic movements involving trunk and limbs, orofacial dyskinesias and dysarthria, secondary to GA1. Brain MRI showed in supratentorial localization a signal hyperintensity of the posterior region of the putamen in T2 and FLAIR sequences. Treatment with trihexyphenidyl, tetrabenazine and pimozide was not effective.
Bilateral globus pallidus internus deep brain stimulation (Gpi-DBS) surgery was performed successfully. Stimulation was initiated on the third day postoperatively. He was discharged on the tenth day after surgery with no complications.
The patient experienced a significant improvement of choreodystonic movements which was maintained in follow-up assessments (up to 32 months post-surgery) without adverse effects. However, he presented persistent dystonia of the left lower limb despite different adjustments of stimulation that required associating treatment with botulinum toxin. Overstimulation was suspected so a therapeutic attempt was made by decreasing the amplitude of the stimulation of the right Gpi which improved left lower limb dystonia. Stimulation parameters at last visit (32 months post-surgery) were: left GPi 0(+)1(-) 3.2V 90mcs 130Hz. Right GPi 8(-)9(+) 3.8V 90mcs 130Hz.

Conclusions: DBS in children is safe and effective in the treatment of primary dystonia. The results of DBS in movement disorders due to neurometabolic diseases such as GA1 are heterogeneous. We report the case of a patient with a choreodystonic movement disorder due to GA1 who experimented a successful and maintained response to DBS for almost 3 years of follow-up.

Keywords:
glutaric aciduria, hyperkinetic movement disorder, deep brain stimulation.

EPNS23-2732 Oral or e-Poster
Movement Disorders

Flunarizine - responsive episodic ataxia type 2.

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Case study: Background: Episodic ataxia type 2 (EA2) is a rare autosomal dominant channelopathy associated with mutations of the CACNA1A gene. Recurrent vertigo attacks in children frequently cause diagnostic uncertainty. EA2 is often mislabeled; therefore early diagnosis and treatment is important. It has been reported that flunarizine is useful in treating certain CACNA1A-related disorders, such as hemiplegic migraine, but there is limited evidence for its efficacy in EA2. We describe a 12-year-old girl with EA2 who showed a favourable response to flunarizine.
Case presentation: Patient presented at 14 months old with stereotypical episodes where she would become quiet, pale, floppy, and vacant with head moving to the right side. A diagnosis of possible focal seizures was suspected, and she was started on lamotrigine which was discontinued as it made her clumsy. As she grew older, she tended to recognise the episodes and complained that her head was spinning. She was pale, floppy, unsteady on her feet, she had jerky eye movements and occasional vomiting. The episodes lasted from minutes to hours. Neurological examination, development, head MRI, microarray and metabolic screen were normal. She had normal sleep EEG and a normal 24-hour EEG, which captured 2 episodes. She underwent audio vestibular assessment, and it was felt that these episodes may be some form of benign paroxysmal vertigo and she was tried on propranolol without any success. Topiramate was tried for suspected migraine but made her sick. On reduction of topiramate her symptoms recurred and at that time clinical suspicion of EA2 was made and she was started on acetazolamide. CACNA1A gene mutation was sent, confirming the diagnosis. She was also diagnosed with developmental coordination disorder, learning difficulties and anxiety. Initially she had a good response to acetazolamide, but this worn off despite an increased dose. Therefore, carbamazepine was added which was not tolerated. Due to poor response to acetazolamide, she was subsequently trialled on 5 mg of flunarizine with very good response. She improved further on 10mg once a day.
Conclusion: This case report involves a long history before final diagnosis and highlights the diagnostic challenges in a child presenting with paroxysmal vertigo attacks. Our report adds important therapeutic considerations. Further studies are needed to prove the efficacy of flunarizine and possible long-term adverse effects.

Keywords:
episodic ataxia type 2, CACNA1A gene, paroxysmal episodes, acetazolamide, flunarizine

EPNS23-3004 Oral or e-Poster
Movement Disorders

GNAO1 mutation-related involuntary movements and rhabdomyolysis: A case report

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Case study: Objective: Mutations in GNAO1 typically result in neurodevelopmental disorders such as developmental and epileptic encephalopathy-17, and involuntary movements. To date, the association of variants in the GNAO1 gene with rhabdomyolysis has been identified in few patients. We present a 2-year-old girl with a GNAO1 gene mutation who developed rhabdomyolysis.
Case presentation: A 2-year-old girl presented with fever, choreoathetosis and inability to eat for two days. She had a history of hypotonia, global developmental delay, and hyperkinetic involuntary movements, including choreoathetosis. Abnormal involuntary movements were exacerbated by illness and fever. She was born after uneventful pregnancy and delivery, with a non-consanguineous marriage of her parents. She had no family history for neuromuscular disease. Laboratory tests showed high serum creatine kinase level, transaminase and lactate dehydrogenase levels, myoglobinuria and normal renal function tests. Brain MRI showed mild cerebral atrophy. Electroencephalography (EEG) revealed no pathological findings. The whole exome sequencing test showed a novel de novo heterozygous variant of GNAO1 gene [c.736G>A; (p.Glu246Lys)], located on chromosome 16q13. The mutation was confirmed by Sanger sequencing. Based on these clinical and laboratory finding, she was diagnosed rhabdomyolysis related to neurodevelopmental disorder with involuntary movements associated with GNAO1 mutation. Initial creatine kinase (CK) level was 76350 U/L. On the third day of hospitalization, creatine kinase level increased to 107000 U/L. She was treated with excessively intravenous isotonic fluids containing sodium bicarbonate. On the sixth day of hospitalization, serum creatine levels and choreoathetosis improved significantly.
Conclusion: Our case demonstrated that GNAO1 variants can cause severe developmental delay and refractory hyperkinetic involuntary movements caused rhabdomyolysis. We suggest caution in terms of rhabdomyolysis when hyperkinetic movements develop in patients with GNAO1 mutation.

Keywords:
GNAO1 mutation, involuntary movements, rhabdomyolysis

EPNS23-2460 Oral or e-Poster
Movement Disorders

Demographic and clinical features of tremor in children and adolescents: a single centre retrospective analysis

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Objective: Unlike in adults, tremor is underinvestigated in children, and its clinical features are poorly defined.

Methods: Medical charts of patients referred to the MD clinic of a tertiary pediatric hospital over a 3-years period (2020-2022) were retrospectively reviewed. Inclusion criteria were (1) tremor as the main MD (2) onset under 18 years. Exclusion criteria were (1) paroxysmal tremor (2) known benign infantile tremor syndromes (i.e. jitteriness, shuddering).

Results: Body distribution was focal (one upper limb) in 5.3% of the patients, segmental (bibrachial) in 70.6%, multifocal (bibrachial + head and/or voice tremor) in 10.6%, generalized (bilaterally involving upper and lower body) in 9.3%, and hemitremor in 4%. 16.1% of bilateral tremors were asymmetric. Tremor was postural in 22.7% of patients, kinetic in 1.3%, combined postural and kinetic in 66.6%, and combined rest, postural and kinetic in 9.3%.
28% of the patients had other overt or soft additional neurological signs, mostly other MD. 14.6% of patients had borderline cognitive functioning or intellectual disability (ID), and 2.6% specific learning disorder.
41.20% of patients had psychiatric comorbidities, mainly ADHD and anxiety.
73.3% of patients underwent blood tests, 9.3% polygraphic recordings, and 49.30% brain MRI. 39.4% of the scans were normal, and 31.6% showed tremor-unrelated abnormalities.
In 15% of the cases, tremor was secondary to structural brain lesions, mainly of neoplastic or vascular origin. Essential tremor (ET) was diagnosed in 27% of patients, and "possible" ET in 16%. In 11% of cases, tremor was related to a proven or likely genetic disorder, and in 7% to non-syndromic ID. Functional and enhanced physiological tremor were both diagnosed in 9% of patients. In 7% of the cases, tremor was labelled as indeterminate. 21% of the patients required pharmacotherapy. Propranolol was the most chosen drug (10 out of 21 treated patients).
74.7% of patients were re-evaluated (mean follow-up time 1.9±2.6 years), and 87.5% of them had a stable or improving course.

Conclusions: Tremor in children is heterogenous and frequently associated with non-motor features. Isolated action tremor in the context of (possible) ET is the commonest condition. Tremor related to sporadic or genetic neurodevelopmental disability or structural causes is not infrequent. Nosography of childhood-onset tremor syndromes should be revisited in the light of standardized assessment and investigations.

Keywords:
Tremor, Movement disorders, Essential tremor

EPNS23-2317 Oral
Movement Disorders

Deep brain stimulation for different forms of paediatric dystonia: the experience of a Paediatric Neuromodulation Unit in Spain.

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Case study: Objective:
To evaluate efficacy and safety of Deep Brain Stimulation of the Globus Pallidus Internus (GPi-DBS) in children with different forms of dystonia.
Methods:
Longitudinal study of 22 children with dystonia who underwent GPi-DBS at our institution from May 2020 to December. A multidisciplinary team selected children according to current dystonia DBS criteria. Directional electrodes were inserted in the GPi, using a stereotactic frame and multitrack microelectrode recording, and connected to a rechargeable generator. Electrode placement accuracy was determined by CT/MRI fusion using a stereotaxic software. Patients were evaluated pre- and post-DBS by clinical dystonia and myoclonus scales. Scores were compared using non-parametric test for paired data.
Results:
Mean age at surgery was 12 (7-20) years. Dystonia was isolated (n=4), combined with myoclonus (n=6) or with other neurological features (n=12, epilepsy, global developmental delay/mild intellectual disability, hypotonia). Aetiology was genetic (n=15, TOR1A, GLB1, SGCE, GNAO1, ATP8A2, GCDH, ANO3), idiopathic (n=3, negative exome) or acquired (n=4, cerebral palsy). Six patients had MRI basal ganglia lesions. We chose the central and medial trajectories in 84% of implants. Lead placement accuracy was X=-0.3±0.8 and Y=-0.7±1.0 (mm). Current stimulation parameters (n=44 leads) are 2.2±0.6mA, 63.9±10.5ms, 134.9±6.6Hz; monopolar 84%, double monopolar 8%, bipolar 8%; directional 9%. After 13 (1-29) months of follow-up, there was an improvement in dystonia (n=20, BFM-motor 47%; BFM-disability 36%) and myoclonus scores (n=6, UMRS-motor 68%; UMRS-questionnaire 39 %)($p<0.05$)
Different outcomes were observed between isolated/combined dystonia and dystonia with other neurological features (BFM 71.6% vs 17%), and between patients with normal or abnormal MRI (BFM 56.7 vs 13.6%)($p<0.05$).
Patients showed a weight gain of 4.7 (1.1-9.9)kilograms 6 months after surgery ($p<0.001$)
Four patients with surgical complications (atrophic scar [n=2), wound infection, broken wire extension) were surgically solved during the first-year follow-up (23% of the series).
Conclusion:
GPi-DBS was a safe and effective procedure, showing most patients an improvement in dystonia severity and disability. Our rate of re-interventions was lower than published data. Best outcomes were obtained in isolated and combined dystonia. Directional stimulation was satisfactorily used in children with side effects/suboptimal lead location.

Keywords:
Deep brain stimulation, Globus Pallidus Internus, Childhood-onset dystonia

EPNS23-2688 Oral or e-Poster
Movement Disorders

Treatment of chorea in NXK2-1-related disorders: A Systematic Review

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Objective: NKX2-1-related disorder (NKX2-1-RD), also known as benign hereditary chorea, is a rare disorder characterized by early onset choreiform movements in addition to respiratory and endocrinological abnormalities. To conduct a systematic review on the management of chorea in NKX2-1-RD as part of the development of the first clinical practice guideline by The European Reference Network of Rare Neurological Disorders (ERN-RND) in the framework of the European Programme ERNs Guidelines.

Methods: A systematic pairwise review was conducted. The literature search was conducted in MEDLINE (Ovid and PubMed), Embase, Cochrane, CINAHL, and PsycInfo, as well as HTA-specific databases and studies identified by field experts. The criterion for selection were: 1) participants: patients with chorea and NKX2-1-RD genetic diagnosis; 2) intervention: drug treatment; 3) comparator: not determined because this is a rare disease; 4) outcomes: chorea improvement and adverse events. There was an evaluation of the results methodological quality. The research was registered in the PROSPERO database

Results: After screening 1417 studies, 28 case studies or case-control studies were included. 68 patients were reviewed in total. There were 22 reported chorea treatments: L-dopa (30), Tetrabenazine (21), Carbidopa/Levodopa (8), Clonazepam (7), Methylphenidate (7), Carbamazepine (4), Topiramate (4), Trihexyphenidyl (3), Haloperidol (2), Propranolol (2), Risperidone (2), Valproate (2), No clear benefits of L-Dopa, Tetrabenazine, Carbidopa/Levodopa, or Clonazepam treatment were described (improvement: 11/24, 9/17, 4/8, and 4/7, respectively), and variable adverse effects were reported (4/30, 12/21, 1/8, and 2/7, respectively). Six out of seven patients treated with methylphenidate reported improvement, while one out of seven reported a negative effect (loss of appetite). The overall quality of the methodology was poor.

Conclusions: Chorea treatment for NKX2-1-RD patients is heterogeneous and poorly defined. The percentage of patients treated with methylphenidate who experience improvement in chorea is greater than that of patients treated with other medications. However, due to poor methodological quality, additional treatment studies may be required to recommend therapeutic options.

Keywords:
Chorea; NKX2-1-related disorder; benign hereditary chorea; ERN-RND

EPNS23-2974 Oral or e-Poster
Movement Disorders

GNAO1 Mutation-Induced Pediatric Severe Dystonic/Hyperkinetic Movement Disorder

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Case study: Mutations in the GNAO1 gene cause a complex constellation of neurological disorders including epilepsy, developmental delay, and movement disorders. We present a 14-year-old boy whohad global developmental delay, dystonic/hyperkinetic movement disorder attacks. Clobazam efficient when he admitted our oupatient clinic. Genetic dystonia panel (sequencing and NGS-based CNV analyses)with a de novo GNAO1 mutation (c.137A>G (p.Lys46Arg))heterozygouspatogenic variant detected. We present prospectively evaluated changes in dystonia/hyperkinetic symptoms and quality of life for a patient with GNAO1 mutation treated with clobazam.

Keywords:
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EPNS23-2104 Oral or e-Poster
Movement Disorders

Kernicterus: A radiologically underdiagnosed entity?

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Objective: Despite the possibility of preventing kernicterus by sufficient treatment of neonatal hyperbilirubinemia, the clinical picture has not yet disappeared. Characteristic long term sequelae are dyskinetic cerebral palsy (CP), hearing disorders, vertical gaze palsy and dental enamel dysplasia. The MRI pattern (hyperintensity of globus pallidum) is specific but may be missed after the neonatal period.

Methods: According to the clinical criteria, we identified 8 patients in whom we expected chronic kernicterus. Kernicterus was not confirmed in all but two patients by previous investigators. Of these patients, a total of 15 MRIs were available. Previously, 3/15 MRIs from 2 patients had been assigned to kernicterus; in 2/15 MRIs abnormalities were seen, but not attributed to kernicterus; 10/15 MRIs were judged by radiologists as normal. We retrospectively analyzed the MRIs of patients.

Results: We were able to confirm the clinical diagnosis by typical MRI findings in all patients: We found the following abnormalities in our patients: In the neonatal period, bilateral diffuse hyperintensity of the globus pallidus (GP) on T1w images (1 MRI, 2 weeks), in infancy on T2w images (4 MRIs, 9 - 26 months). In children two years of age and older, bilateral hyperintensity on T2w affected only the boarders of the GP (8 MRIs, 20 months - 12 10/12 years). Two children showed no MRI pathology at 2 months of age, which we interpret as a "blind window" in the transition from T1w to T2w hyperintensity. In both patients pathology then appeared at a later time point on T2w. Thus, the kernicterus pathology on MRI, changes over time.

Conclusions: Although all our patients had the typical MRI-pattern, characteristic clinical history and signs, diagnosis of kernicterus was often missed. Hyperintensity in globus pallidum as the characteristic MRI-pattern in patients with kernicterus changes over time. Abnormalities on later MRIs seem to be underrecognized.

Keywords:
kernicterus, bilirubin encephalopathy, dyskinetic cerebral palsy, globus pallidus, MRI, hyperintensity

EPNS23-2274 Oral or e-Poster
Movement Disorders

DIAGNOSIS AND TREATMENT OF NKX2-1-RELATED DISORDERS IN THE EUROPEAN UNION: FINDING FROM THE EUROPEAN REFERENCE NETWORK FOR RARE NEUROLOGICAL DISORDERS (ERN-RND) SURVEY.

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Objective: NKX2-1-related disorder (NKX2-1-RD) is a rare disease characterized by the triad of primary hypothyroidism, neonatal respiratory distress (NRD), and neurological features, including chorea. Describe and highlight discrepancies in the European Union (EU) management of NKX2-1-RD).

Methods: Cross-sectional, multicenter study. The ERN-RND Chorea and Huntington disease group created a survey about the management of NKX2-1-RD, which was answered by EU specialists. A descriptive analysis was performed, and the total responses by group are presented for each item.

Results: 23 experts from 13 EU countries plus Norway and Iceland participate. The respondents were: adult (11) and pediatric (12) neurologists. Their relevant career history experience was 6-10 years(5), 11-14 years(4), and >15 years(13). Annually, they reported to evaluate a total of 20(6), 21-49(1), 50-99(4), or >100(12) hyperkinetic patients. The time between onset of symptoms and first MD expert evaluation was <1 year(11), 1-2 years(10), and 3-4 years(2). The NKX2-1-RD patients followed up by each neurologist was 1(5), 2-5(15), 6-10(2) and 11-20(1). Age at genetic diagnosis of NKX2-1-RD patients was < 3 years(5), 3-5(7), 6-10(5), 11-15(3) and >15(3). The most common initial symptoms described were hypotonia and/or motor developmental delay(11), chorea(8), congenital hypothyroidism(3), and NRD(1). The oldest age for chorea onset of any of the patients followed up on was 3 years(4), 3-5(8), 6-10(7), 11-15(1), and >15 years (3). Chorea was found in the upper limbs (21), trunk (12), face (11), lower limbs (10), neck (7), and tongue (3). Chorea improved (9), stabilized (12), and worsened (2) with age. 14 neurologists reported to misdiagnosed patients in the past. 20 neurologists reported that < 25% of the patients presented the complete clinical triad; 25-50% (2) and no answer (1). Difficulties in recognizing symptoms and ask for non-specific tests were recognized by 8 experts. Endocrinology and pulmonary evaluations were routinely requested by 12 and 7 neurologists, respectively. Time between the initial evaluation and the genetic diagnosis was < 1 year (8), 1-2(10), 3-4(2), 5-10(1) and >10(2). The NKX2-1 mutation was confirmed in >75%(12), 50-75%(4), 25-49%(3) and <25%(4).

Conclusions: A clinical practice guideline for the management of NKX2-1-RD would be helpful for both patients and healthcare practitioners within the EU due to the vast variation in the management of NKX2-1-RD within the EU.

Keywords:
NKX2-1-RELATED DISORDERS; BENIGN HEREDITARY CHOREA;NKX2-1; ERN-RND;

EPNS23-2294 Oral
Movement Disorders

Correlations between magnetic resonance imaging, gait analysis and anamnesis of patients with cerebral palsy

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Objective: Background
Limitation in the ability to walk is one of the most disabling consequences in patients with cerebral palsy. In the perinatal period and up to the age of two years malformations, infections, bleeding or trauma can lead to different kinds and dimensions of brain lesions. Movement, posture and balance of these patients are affected in different severities due to different extends of brain lesions. With growth these children often develop contractures and an abnormal gait. Most patients undergo numerous therapies and interventions to achieve a better mobility in everyday life.
Objective
The aim of this retrospective study is to find correlations between data from magnetic resonance imaging, gait analysis and the anamnesis of patients diagnosed with cerebral palsy to investigate if there are possible reference points for early prediction of the expected gait disturbance in the future.

Methods: Included in this project are patients diagnosed with cerebral palsy who are registered in the Swiss Cerebral Palsy Registry. The brain MR images are uniformly evaluated and classified. Detailed perinatal data is gathered from archive reports and is quantified. The included patients underwent a gait analysis where the joint angles and forces were measured over many gait cycles. Also the general degree of joint mobility was evaluated. It is made sure, that no significant orthopaedic surgery was done prior to the gait analysis. The earliest gait analysis is used for the project to ensure the most original state of gait.

Results: Preliminary data shows that a quantitative gait description and a detailed mri description shows crucial information what to expect in neonatal brain lesions. At the EPNS we will show the complete data analysis of the project.

Conclusions: Modern gait analysis offers no insights into the pathophysiology of cerebral palsy.

Keywords:
cerebral palsy,CP,gait analysis,gait,

EPNS23-2532 Oral or e-Poster
Movement Disorders

Recessive variants in SLC9A1 cause a syndrome of cerebellar ataxia, amelogenesis imperfecta and variable sensorineural hearing loss

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Objective: The SLC9A1 gene encodes the mammalian Na+/H+ exchanger isoform 1 (NHE1), a ubiquitously expressed membrane-bound enzyme involved in intracellular pH regulation. Ultra-rare recessive variants in SLC9A1 have previously been described to cause autosomal recessive spinocerebellar ataxia type 19 (SCAR19) in two families. SCAR19 is characterized by early-onset ataxia and variable hearing loss. Slc9a1 knockout mice exhibit ataxia, seizure and growth retardation. Here, we report 12 patients with recessive SLC9A1 variants and a complex syndrome of cerebellar ataxia, amelogenesis imperfecta, developmental delay and variable sensorineural hearing loss.

Methods: Patient phenotyping was performed through serial clinical assessments, dental examinations, audiograms and brain MRI. Candidate variants in SLC9A1 were first identified by whole-exome sequencing and next characterized in vitro. The expression and enzymatic activity of mutant NHE1 proteins were respectively examined by immunoblotting and transient induction with ammonium chloride of transfected NHE1-deficient cells. Intracellular targeting of mutant proteins was assessed by a combination of immunocytochemistry and cell surface biotinylation studies.

Results: We identified 12 patients belonging to eight consanguineous families with homozygous SLC9A1 variants. Eight novel variants were discovered, including two nonsense, four missense, one frameshift and one splicing variant. Patients presented with moderate to severe cerebellar ataxia from infancy associated with cerebellar atrophy (10/11; 91%) and occasional thinning of the corpus callosum (3/11; 27%) on MRI. In addition to developmental delay, all patients exhibited amelogenesis imperfecta, which had not been previously reported with SLC9A1 mutations. Sensorineural hearing loss of variable severity was present in nine out of 12 subjects (75%). All identified variants caused lower protein expression, reduced NHE1 enzymatic activity and protein mislocalization.

Conclusions: This study expands the mutational and phenotypic spectrum of SCAR19 and provides functional evidence for the pathogenicity of the newly identified variants. Mutations in SLC9A1 should be specifically sought for in the presence of early-onset cerebellar ataxia and amelogenesis imperfecta.

Keywords:
ataxia; spinocerebellar ataxia; SLC9A1

EPNS23-2701 Oral
Neurodevelopmental Disorders

Short Stature and Distinct Growth Characteristics in Angelman Syndrome

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Objective: Angelman syndrome (AS) is a rare, genetic, neurodevelopmental disorder characterized by developmental delay with severe impairments in speech, motor and coordination and unique behaviours, accompanied with distinct facial features and high prevalence of epilepsy and sleep problems. Despite a few reports regarding short stature among AS patients, this feature has not been extensively studied and is not included in the clinical criteria defined in 2005. We investigated growth patterns among AS patients with respect to mutation type, growth periods, family history and endocrine abnormalities.

Methods: Data regarding growth and puberty of patients and their parents were collected from medical files of AS patients in the Israeli national AS clinic. The cohort was divided into two subgroups - deletion and non-deletion. Growth data was divided to four main periods - preschool, childhood, peak height velocity and final height.

Results: The cohort included 88 individuals (46 males), out of which 54 (61.4%) had the deletion subtype. There was a median of 3 observations per individual (range 1-10), which produced 280 data points distributed from birth to final height. Mean final height-SDS of the cohort was significantly lower compared to the general population (-1.23 ±1.26, $p<0.001$), and among the deletion subgroup it was significantly lower compared to the non-deletion subgroup (-1.67±1.3 vs -0.65±0.96, $p=0.03$). Final height-SDS was significantly lower compared to height SDS in preschool period (-1.32 vs -0.47, $p=0.007$). Patient's final-height-SDS was significantly lower than the parents' (Delta final-height-SDS=-0.94±0.99, $p=0.002$). IGF1-SDS was significantly decreased compared to the general population (-0.55±1.61, $p=0.04$), with lower values among the deletion group (-0.70±1.44, $p=0.01$). IGF1 was positively correlated with height-SDS ($r=0.65$, $p=0.007$). No significant changes were seen in timing of puberty.

Conclusions: AS patients demonstrate a unique growth pattern, with deceleration throughout life up to a significantly decrease in final height compared to the normal population, and even lower among the deletion subgroup, which could be attributed to decreased IGF1 levels. We propose to add short stature to the clinical criteria and develop adjusted growth curves for the AS population.

Keywords:
Angelman syndrome, growth curves, short stature, height, weight, deletion, non-deletion, IGF1

EPNS23-2208 Oral or e-Poster
Neurodevelopmental Disorders

Predicting nonresponse to intraglandular botulinum toxin injections: working towards an individualised treatment approach for drooling in children with neurodevelopmental disabilities

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Objective: Botulinum neurotoxin type-A (BoNT-A) injections are commonly used to diminish drooling in children with neurodevelopmental disabilities. Nevertheless, there is no consensus on which salivary glands should be injected to sufficiently diminish drooling. An individualised treatment approach, based on the child's risk of nonresponse, would be preferable. We aimed to develop multivariable prediction models for nonresponse to 1) submandibular BoNT-A injections and 2) concurrent submandibular and parotid (four-gland) BoNT-A injections.

Methods: A retrospective cohort study was conducted, using prospectively collected data from 262 children (aged 4-18 years) treated with submandibular injections and 74 children treated with four-gland injections after initial submandibular injections. Multivariable logistic regression analyses were used to estimate associations between biologically plausible candidate predictors and nonresponse (i.e., <50% reduction in drooling quotient and visual analogue scale for drooling severity) eight weeks post-injection.

Results: Ninety-six children (37%) were classified as nonresponders to submandibular injections, for which developmental age <6 years was the strongest predictor (adjusted odds ratio [aOR] 2.08; 95% CI 1.00-4.31). Other identified predictors were the child's diagnosis, sex, and head position. Nonresponse to four-gland injections occurred in 34 children (46%), for which tongue protrusion (aOR 3.10; 95% CI 1.14-8.43) and a single preceding submandibular injection (aOR 2.94; 95% CI 0.85-10.0) seemed most predictive. Predictors were, however, unstable across different definitions of nonresponse and both models had insufficient discriminative ability.

Conclusions: Significant predictors of nonresponse to BoNT-A injections were identified, but the developed prediction models appeared inadequate for guidance of treatment decisions. Future studies may include more specific (i.e., mediating) variables and aim for consensus on a comprehensive definition of nonresponse.

Keywords:
Botulinum neurotoxin type-A, drooling, prediction model

EPNS23-2765 Oral or e-Poster
Neurodevelopmental Disorders

Gastrointestinal and eating problems in SCN1A-related seizure disorders

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Objective: SCN1A-related Dravet syndrome is characterized by early onset, fever-sensitive, refractory epilepsy, intellectual disability, and behavioral problems. Additional comorbidities have increasingly been reported in literature over the past years, with a high impact on the daily functioning of patients and caregivers. Gastro-intestinal and eating problems are often addressed by caregivers of patients with Dravet syndrome as a burdensome symptom, but have not been well characterized previously. This study aims to describe the prevalence and characteristics of gastrointestinal and eating problems in Dravet syndrome and other SCN1A-related seizure disorders and to test associations with other comorbidities.

Methods: A cohort of 169 patients with an SCN1A-related seizure disorder, consisting of 118 (69.8%) patients with Dravet syndrome (DS) and 51 (30.2%) with GEFS+/FS (non-DS) phenotype, was evaluated. Gastrointestinal and eating problems were quantified using a questionnaire developed by the researchers in consultation with a dietitian and a speech therapist. For participants with Dravet syndrome or minors with non-DS, questionnaires were filled out by their parents/caregivers. Associations between gastrointestinal and eating problems and other comorbidities were tested with an ordinal logistic regression.

Results: Gastrointestinal and eating problems are highly prevalent in patients with Dravet syndrome. A total of 61.9% of patients with DS reported at least three symptoms associated with a gastrointestinal or eating problem; in non-DS patients, this was 5.9%. The most prevalent symptoms were obstipation, choking on food, drooling, distraction during meals, and loss of appetite. In 35.6% of patients with DS, these occurred weekly or more often. Of patients with DS, 17.8% have a feeding tube, either for full intake or partly. In 51.7% of patients who experienced eating problems, parents reported a high impact on daily life. Of all DS patients, only 24.6% are currently treated by a speech therapist for eating problems. DS patients with more severe motor disabilities and who used more ASM had more symptoms associated with gastrointestinal or eating problems.

Conclusions: Gastrointestinal or eating problems are relevant comorbidities in Dravet syndrome and should be given appropriate attention by treating physicians. Repeated evaluations with structured questionnaires aid in early detection and enable a timely referral to a dietitian or speech therapist.

Keywords:
SCN1A, Dravet syndrome, gastrointestinal, eating problems

EPNS23-2976 Oral or e-Poster
Neurodevelopmental Disorders

EVALUATION OF THE PHENOTYPE-GENOTYPE RELATIONSHIP IN AUTISM SPECTRUM DISORDERS WITH ISOLATED AND COMORBID COMPLEX NEURODEVELOPMENTAL PROBLEMS

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Objective: In our study,it is aimed to investigate the genetic analysis results of patients who applied to our center with neurological disorders such as neuromotor developmental delay, cognitive developmental delay, focal or generalized seizures, abnormal electroencephalography/brain magnetic resonans imaging findings as well as autism spectrum disorder symptoms and to examine the correlation of these genetic data with clinical findings.

Methods: Sociodemographic data, current clinical findings, neuroradiological imaging, electroencephalography and whole exome analysis results of patients diagnosed with autism spectrum disorder and accompanying neurological findings,who applied to the Pediatric Neurology Outpatient Clinic of Istanbul Medipol
University Medical Faculty Hospital between 2016 and 2022,were retrospectively analyzed. Statistical analyzes were performed using Statistical Package Program for Social Sciences(SPSS, 21.0).

Results: The mean time between the onset of the symptoms of the cases and the sampling for genetic diagnosis was 65.98 months(±4.8). According to the results of Whole Exome Sequence Analysis(WES),42(42.9%) of the cases were positive for pathogenic gene mutations,and 16(16.3%) of them were genetic changes of Variant of Uncertain Significance(VUS).
It was determined that 18.1%(4 cases) of variants evaluated as VUS in the initial analyzes of the study were classified as pathogenic in the reanalysis performed at the end of the study. Delay in motor development was found to be statistically significantly more common in patients with pathogenic mutations(p:0.01).It was determined that pathological brain magnetic resonans imaging findings(brain atrophy p:0.015) and pathological electroensephalography findings(generalized epilepsy p:0.001) were statistically significantly more common in cases
with genetic pathogenic mutations.

Conclusions: As a result of our study, it has been determined that the clinical significance of variants classified as VUS detected from WES may change over the years. It has been concluded that it is beneficial to perform genetic tests at an earlier period in cases with autism spectrum disease for diagnosis and especially with neurological additional findings and to re-evaluate the clinically inexplicable WES results in the light of the literature at regular intervals.

Keywords:
Autism Spectrum Disorder, Neurodevelopmental Retardation, Genetics

EPNS23-2132 Oral or e-Poster
Neurodevelopmental Disorders

Case report of novel compound heterozygous missense variants of Mitochondrial Aconitase (ACO2) manifesting as Infantile Cerebellar-Retinal Degeneration (ICRD) - the benefits of genome sequencing and re-imaging for the diagnosis of ICRD

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Case study: Objective: We describe the presentation and follow up of an 8-year-old boy with ICRD, secondary to variants of unknown significance in ACO2.

Method: Clinical concerns were from 4 months when poor head control and floppiness were noted then inability to roll from prone at 12 months. Paediatric neurology reviewed at 18 months and central hypotonia was noted with an inability to sit unsupported. He displayed expressive and receptive language delay with limited vocabulary. However, his fine motor and social skills developed appropriately. From 12 months he was noted to have bilateral large angle esotropia. He was also noted to have hypotelorism, plagiocephaly and positional equinovalgus. From 5 he was noted to have bilateral dislocated hips and by 7 years was wheelchair dependent.

Results: A brain MRI at 1 year showed a normal feature of dilated CSF spaces. A quadriceps muscle biopsy when he was 3 years old showed mild, non-specific myopathic features only. Pelvic X-rays at 5 years showed bilateral coxa valga and subluxation of the femoral heads. At 6, he was investigated with visual electrophysiology demonstrating bilateral optic atrophy. Whole genome sequencing via the 100,000 Genomes project, revealed variants of unknown significance in the mitochondrial aconitase, ACO2, gene, located on 22q13.2.

Compound heterozygous variants affecting ACO2 have been described in association with an extremely rare condition, ICRD with fewer than 50 patients reported internationally (per OMIM). There are even fewer reports of optic nerve atrophy. Considering this, a repeat brain MRI scan was performed, aged 7, which demonstrated new findings of bilateral optic nerve and cerebellar atrophy, with hyperintensities within the dentate nuclei. The investigation findings, along with developmental delay, hypotonia and visual impairment, were consistent with a diagnosis of ICRD. In addition to previously reported features, we report bilateral optic nerve atrophy as well as telangiectasias of the face and sclera.

Conclusions: This report describes new phenotypic features of this ultra-rare genetic condition with undescribed allelic variants of the ACO2 gene. The patient's signs, symptoms and neuroimaging findings are consistent with the diagnosis of ICRD in the presence of compound heterozygous ACO2 variants of unknown significance. Of note, while described as 'Infantile', neuroimaging findings became evident six years after infancy.

Keywords:
Infantile Cerebellar-Retinal Degeneration, Optic Atrophy, ACO2, aconitase

EPNS23-2905 Oral or e-Poster
Neurodevelopmental Disorders

VALIDATION OF A NEWBORN FOLLOW-UP PROTOCOL FOR THE EARLY DETECTION OF AUTISM IN VERY PRETERM CHILDREN: PRELIMINARY RESULTS.

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Objective: According to recent studies, there is a strong relationship between extreme prematurity and the risk of suffering from Autism Spectrum Disorder (ASD). The objective of this longitudinal study is to verify the usefulness of a follow-up protocol for very preterm newborns (less than 32 weeks of pregnancy or less than 1500g of birth weight) for an early detection of ASD. In addition, as secondary objectives, it is intended to determine the prevalence of Autism in this sample, to examine the predictive value of a screening questionnaire and to relate risk factors (prenatal, perinatal and postnatal) of ASD.

Methods: We studied a sample of 163 very preterm children who were admitted to the Neonatal ICU of the Hospital Universitari Vall d'Hebron in Barcelona. During admission, prenatal, perinatal and postnatal data were collected. At two years of age, the parents passed the Modified Checklist for Autism in Toddlers (M-CHAT). The ones with a positive screening result have been administered Module T (Toddler Module) of the Autism Diagnosis Observation Schedule, second edition (ADOS-2) and a certain range of concern has been established (little-or-no, mild-to-moderate, or moderate-to-severe).

Results: Up to the date of writing the abstract, 60% of the sample is negative and 40% positive according to the M-CHAT. Of the 57 positive screenings, 52 ADOS-2 have been administered so far, and 17 of those have obtained a score in the moderate/severe range of concern for ASD.

Conclusions: The first results seem to indicate that the follow-up protocol is useful in early detection of Autism. Likewise, they seem to confirm a high prevalence of ASD in very premature children.

Keywords:
Autism spectrum disorder (ASD) - follow-up protocol - early diagnosis - screening questionnaire - Autism diagnostic observation schedule - very preterm-born children - very-low birthweight infants

EPNS23-2408 Oral or e-Poster
Neurodevelopmental Disorders

Clinical and etiological profile of Epileptic Encephalopathy in a Tertiary Hospital experience

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Objective: We aim to provide a detailed description of the etiology and clinical features of Epileptic Encephalopathy (EE) patients in Oman.

Methods: This is a descriptive retrospective cross-sectional study of a consecutive series of patients diagnosed with EE at a tertiary hospital in Oman. A chart review was performed for all patients who fulfilled the diagnostic criteria of EE over a period of 14 years (2008 - 2022).

Results: 282 patients were included in the study, with 52% accounting for males. Out of the 282 patients, 172 were a product of a consanguineous marriage,74 patients had a significant perinatal history such as premature birth (18), Hypoxic ischemic encephalopathy (11) and hyperbilirubinemia (9). Majority of the patients (60%) had their first presenting symptoms during infancy, with 75% having seizures as their first presentation. Speech delay was found in 92% of all patients with EE. The commonest type of seizure seen in this study population was isolated Tonic (29%) followed by isolated generalized Tonic-clonic (28%). A minimum of 2 medications were required to control seizures in 65% of the studied patients. MRI findings were significant in 168 patients (60%), with brain atrophy being the most common finding in 72 patients (26%). In terms of confirmed diagnoses, the most common was genetic (confirmed in 52 patients) followed by metabolic (confirmed in 33 patients).

Conclusions: In this cohort, EE seemed to be associated with inherited genetic causes. This could be explained by the high rate of consanguinity in Oman. Further studies are required to better understand the true nature of EE in the Omani population.

Keywords:
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EPNS23-2904 Oral
Neurodevelopmental Disorders

A METABOLIC BASED FORMULA IMPROVES NEURODEVELOPMENTAL ITEMS IN A GROUP OF NEUROPEDIATRIC DISEASES

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Objective: Neuropediatric diseases affect the developing brain and, usually, lack therapeutic options to significantly improve developmental items. This work reports the effect of a nutraceutical formula in both a mouse model and in a cohort of patients with diverse neurodevelopmental diseases.

Methods: Based on brain metabolism knowledge and to target biochemical pathways that tend to be affected in most neuropediatric disease, we have developed a "neuroprotective formula" comprising over 20 different nutraceuticals as complex lipids, vitamins, energy molecules and amino acids known to have an effect on brain maturation. We first evaluated the effect of the formula on a RTT animal model. We recorded an improvement in motor coordination and cognitive activity, measured by Rotarod and NOR tests. Due to these positive results, we performed a clinical study during 6 months in 35 pediatric patients, including RTT (14), Phelan McDermid (9), GRINpathies (8) and other genetic disorders (SCNA8, CACNA2, RAC1 and AUTS2). Attention, communication, motor abilities and general development through specific scales (Vineland, McArthur, Peabody and KBIT) were evaluated.

Results: The overall response to the treatment was positive and the effects tended to increase over time. Most Vineland subdomains improved in all diseases. The most significant improvements were observed in the Phelan-McDermid cohort, where all Vineland subdomains improved, especially receptive communication, scoring from 16 to 22, and gross motor function, from 50 to 62. GRINopathies improved receptive communication (from 20 to 30), interpersonal relationships (from 18 to 29) and gross motor function (from 30 to 45). RTT patients experienced some improvement mostly in receptive communication (from 18 to 23), interpersonal relationships (from 10 to 28) and fine motor skills (from 10 to 15). In general, patients increased self-confidence and autonomy. Some of them acquired abstract and double meaning thinking, and one patient increased her language capacity from an equivalent age of 5.2 to 6.5 years of age. The formula was well-tolerated and did not cause secondary effects, except for 2 RTT patients who increased the already present epileptic activity and 1 GRIN patient who presented behavior abnormalities.

Conclusions: Our work describes a new treatment for the management of neurodevelopmental diseases. It is a safe-to-use formula that can make a difference on the management of neuropediatric patients.

Keywords:
Treatment; Neurometabolism; Neurodevelopment; Synaptic metabolism

EPNS23-2959 Oral or e-Poster
Neurodevelopmental Disorders

Eating behaviors in children with ASD

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Objective: Comorbid conditions (such as feeding disorders) are more common among people with autism than among the general population.. The purpose of this study was the evaluation of the nutrition and eating behaviors of children with autism in comparison to the group of neurotypically peers.

Methods: Participants included 75 Caucasian children (41 children diagnosed with pure autism, and the control group consisting of 34 children without autistic traits).

Results: The analysis was performed based on a questionnaire of own design Results: Autistic children presented a shortened time of breastfeeding (the children fell asleep at the breast) ($p = 0.04$), a delayed introduction of dairy products ($p = 0.001$), the need of more trials to introduce new foods ($p = 0.006$), a delayed introduction of foods with solid and lumpy structure ($p = 0.004$), a longer duration of bottle feeding ($p = 0.005$), delayed attempts to eating using own hands ($p = 0.006$) and needed a greater support of parents to divert their attention from food during eating ($p = 0.05$).

Conclusions: The feeding food selectivity occurs significantly more frequently among children with ASD and eating problems should be considered on a wider scale. The cooperation of the multidisciplinary and the parents teams should be proposed in the ASD patients care.

Keywords:
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EPNS23-2768 Oral or e-Poster
Neurodevelopmental Disorders

Elementary visuo spatial perception deficit in preterm children with or without neurodevelopmental disorder

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Objective: To investigate the prevalence of elementary visuo-spatial perception (EVSP) deficit in preterm children without cerebral palsy (CP) consulting for suspected neurodevelopmental disorder (NDD) because learning difficulties.

Methods: A screening test designed and validated to measure dorsal EVSP was administered to 70 preterm children aged between 6- and 15-years without CP. EVSP test, sub-tended by the dorsal visual stream, consists in comparing, through vision, the relative position and orientation of objects in the environment (landmark tasks), as well as their magnitude (size, length). NDD diagnosis was based on DSM 5 criteria. The EVSP screening test was analyzed according to prematurity criteria (gestational age and growth development) and NDD diagnosis or not.

Results: The prevalence of EVSP deficit (27%) was significant in the total sample of these preterm children. Deficit of perception of length comparison, angle comparison, midline localisation, and relative position in cluttered environment was reported. Among children diagnosed with NDD, 28% of children with DCD (Developmental Coordination Disorder) scored as outliers at the landmark comparison tasks. Children with DCD and comorbidities (another NDD as Attention Deficit Disorder or Specific Learning Disability) were severely impaired in EVSP with almost half scoring as outliers. Moreover, even children not diagnosed with any NDD exhibited impaired EVSP performance: 23% scored as outliers at total score, and 31% scored as outlier at the magnitude sub-score.

Conclusions: Early EVSP screening test in pre-term children even without NDD diagnosis could allow these children at-risk for developmental and academic difficulties to benefit therapeutic and educational intervention.

Keywords:
Elementary Visuo Spatial Perception, preterm child, test, neurodevelopmental disorder

EPNS23-3005 Oral or e-Poster
Neurodevelopmental Disorders

ADHD children with epilepsy, maintenance on methylphenidate (MPH) treatment, and risk for epileptic seizures (SZ)

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Objective: Children with ADHD tend to have much higher rates of co-occurring epilepsy than children without ADHD. We investigated the maintenance on the MPH treatment in ADHD children with and without epilepsy and risk for SZ.

Methods: 692 children with ADHD (aged between 6 and 17 years) were included in the study. We examined occurrence of epilepsy, positive response to MPH treatment (if significant reduction in ADHD symptoms scores assessed with ADHD IV rating scale was found), and maintenance on MPH. We also examined risk for SZ in children with and without epilepsy. Controls group consistent of age and gender matched ADHD children without epilepsy. All cases had opportunity the use MPH. Outcome measures were: initial positive response to MPH after 4-6 weeks titration, the use of MPH at three-year follow-up and risk for SZ.

Results: 16 (2.3%) had epilepsy. All patients with epilepsy received antiepileptic drugs. 4 patients had pharmacoresistant epilepsy. All children with epilepsy were treated with MPH and positive response to MPH was achieved in 12 of 16 (75%). In control group positive response to MPH was achieved in 81%. Maintenance on MPH at three years follow up was similar (62 % vs. 56%). Of the children with epilepsy, only 4 children with previous difficult to treat epilepsy developed SZs during the 3 year follow-up, but without any change in SZ frequency.

Conclusions: ADHD children with or without epilepsy did not have significant differences in the use of MPH. MPH was safe to use, without increased risk for SZ in ADHD children with and without epilepsy.

Keywords:
ADHD, Epilepsy, Methylphenidate

EPNS23-2531 Oral or e-Poster
Neurodevelopmental Disorders

Congenital cataracts, facial dysmorphism, peripheral neuropathy (CCFDN) syndrome - a regional experience

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Objective: The syndrome associated with congenital cataracts, facial dysmorphism, peripheral neuropathy (CCFDN) is a rare syndrome. The additional features are global developmental delay, growth impairment hypogonadotropic hypogonadism, cerebral or spinal cord atrophy visible on MRI evaluation, postinfectious rhabdomyolysis, osteoporosis.
Although the diagnosis is clinical, the diagnostic confirmation is made by genetic testing, indicating the presence of the c.863 + 389 C T homozygous mutation in the CTDP1 gene in the telomeric region of chromosome 18q, a mutation known as IVS6 + 389 C T.
The aim of this study is to highlight the clinical characteristics of this syndrome and to compare the clinical data with the literature and also with the genotype, drawing attention to a particular form of polyneuropathy with geographical distribution.

Methods: This is a retrospective, descriptive study. We analyzed the medical files of the patients with congenital cataracts and polyneuropathy. We included in this study only the patients with the genetic confirmation of this syndrome, the number of compatible phenotypes being bigger, but the availability of genetic testing was limited. The group was completely characterized - clinically, including also imagistic and functional studies.

Results: Our cohort consists of six cases with the diagnostic age from infancy till adolescence, two of them being siblings. All of them have the same homozygous founder genetic mutation - the c.863 + 389 C T homozygous mutation in the CTDP1 gene described in the literature. The clinical picture is heterogenous. We can notice different degree of intellectual disability, motor impairment and various comorbidities, all the patients having the same genetic mutation. The path to diagnostic was variable, underlining the suboptimal awareness of this form of polyneuropathy.

Conclusions: The CCFDN syndrome is a rare disease, which should be on the list of differential diagnosis for all the patients with congenital cataract and global developmental delay, movement disorder and polyneuropathy. Our cohort highlights the importance of an early clinical recognition and also the importance of the genetic testing in the specific ethnic population it seems confined to. There is also a need for a networking prospective study in order to identify the real incidence in this part of Europe and allow implementing targeted management strategies for a better quality of life of affected population.

Keywords:
Congenital cataract, facial dysmorphism, polyneuropathy, CCFDN

EPNS23-2306 Oral or e-Poster
Neurodevelopmental Disorders

Allergic disease in a cohort of ASD patients from Romania: prevalence and description

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Objective: Autism spectrum disorder (ASD) is a developmental disorder, characterized by impairment in social interaction and communication, and stereotypical behavior. Allergic disorders are often a predominant co-morbidity in ASD, with a prevalence of up to 19%. Both conditions are thought to be widely influenced by events of either the mother or the fetus, during pregnancy and birth. Previous studies showed that C-section delivery may cause disruptions in the newborns' microbiome, putting them at risk for both autistic behavior and allergic diseases.
In this paper we present our data regarding the association between ASD and allergy in relationship with pregnancy, birth type, and sex.

Methods: We evaluated 327 children diagnosed with ASD according to ICD-10 criteria and using specific ASD tests (ADOS, ADI-R). Allergic disease was defined in the presence of one (or more) of the ICD-10 code for allergic diseases. The statistical analysis was done using the JASP 0.16.2.0 program by applying the Chi square test for the association of the research variables and the descriptive analysis of the data.

Results: 36 out of 327 children had allergies, 28 boys and 8 girls, aged between 23 months and 17 years. The most common types of allergies in boys are: skin allergies (10), and in girls, drug and food allergies (4). 27 children were born by C-section, skin allergy being the most common (9), and 9 children were born through vaginal delivery, food and drugs allergy being the most common type (5) in this group. 10 patients were born from pathological pregnancies, the most common type of allergy being skin allergy (4 children). One child was born through IVF had combined allergies. There were no statistically significant relationships between the types of allergies and the evolution of pregnancy, the type of pregnancy or type of birth ($p>0.05$).

Conclusions: In our cohort of ASD patients allergy was present in 11% of cases, especially in males; skin, food and drugs allergy were the most common types of allergies. Most allergic children were born by C-section. Considering that the immune and nervous system are in a tight synergy further research are needed to establish whether there is a cause-effect correlation in ASD.

Acknowledgment: The research leading to these results has received funding from the EEA RO NO Grant 2014-2021, under the project contract No 6/2019.

Keywords:
autism, ASD, allergy, pathological pregnancy, c-section, allergic disease

EPNS23-2438 Oral or e-Poster
Neurodevelopmental Disorders

Is transient hypertonia in the lower extremities in infancy an early sign of autism spectrum disorder? An on-going prospective study.

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Objective: Early diagnosis of autism spectrum disorder (ASD) before the language acquisition is difficult. Social cognitive findings such as the poor eye contact in infancy are well-established early signs of ASD. However, early motor signs including transient hypertonia in lower extremities have not been recognized as early signs of ASD. Here, we are prospectively examining if the delay in motor development due to hypertonia in the lower extremities and ankle stiffness at the 4-month checkup is associated with ASD and thus can serve as the first symptom of ASD, by parallel examination of facial cognitive function in early infancy.

Methods: This study is conducted under the IRB approval at San-iku university. Infants at the regular check-up at 4 months after birth who had no obvious abnormalities in pregnancy and delivery have been recruited. At the enrolment, they are divided into three groups; hypertonia (n=20) showing hypertonia in the lower extremities and ankle stiffness, ASD-at-risk (n=15) having siblings with symptoms of ASD, and the normal controls (n=15). At the 10, 16, and 24 months check-ups, the development of fine and gross motor skills and the sociality and cognition were examined and scored semi-quantitatively. Frequency of eye contact was counted by video-taped monitoring. Psycho-social development was evaluated by an adaptive behavior questionnaires, Vineland-II. Visual cognitive function was examined using an automatic eye-tracking system, Gazefinder (JVC Kenwood) by selective gaze tasks on human faces and geometric patterns.

Results: Currently at 10 months evaluations, hypertonia was mitigated in 77% of cases. Both hypertonia and ASD-at-risk groups revealed abnormalities by psychosocial and developmental evaluation. Vineland-II revealed that the hypertonia group showed significantly lower overall adaptive behavior scores, and a tendency for delayed social and motor skills compared to the control group, while no significant difference was seen in communication. The number of eye contacts showed no difference among three groups. The visual cognitive examination showed that the control group tended to focus on eyes and mouths on face, whereas both the hypertonia group and the ASD at risk group had a low rate of gazing at faces.

Conclusions: The hypertonia group showed a subsequent delay in motor development as well as a decline in social skills and adaptive behaviors, suggestive of ASD. Further follow-up will delineate if transient hypertonia is an early sign of ASD.

Keywords:
autism spectrum disorder, transient hypertonia, early diagnosis, visual cognitive function

EPNS23-3023 Oral or e-Poster
Neurodevelopmental Disorders

Development of reaching and grasping in infancy: position does matter

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Objective: The aim of the current study is to investigate effect of position on reaching performance and to examine whether this effect is different for typically developing (TD) infants and infants at-risk (AR) for developmental disorders. Young TD infants show better reaching performance during secured sitting in an infant chair than in supine. Reaching performance is closely linked to postural control, which is frequently impaired in AR infants. We therefore hypothesize that reaching performance of AR infants is not better in sitting position, in which postural control is essential, than in supine.

Methods: The study population was part of the IMPSINDA project in which norm data were gathered for two infant assessments: the Infant Motor Profile (IMP) and the Standardized Infant NeuroDevelopmental Assessment (SINDA). The infants were assessed with the IMP and the SINDA and perinatal data were collected with parental questionnaires. For the current study the IMP performance items on reaching and grasping in supine and supported sitting on the lap of the parent were used. Neurological condition was assessed with SINDA's neurological scale, with a score of 21 or lower indicating increased risk for developmental disorders. Differences between groups were assessed with McNemar test (paired proportions).

Results: 600 infants aged 3 to 8 months were included, of which 480 were assessed both in supine and sitting position. Mean birth weight was 3402g (SD 580) and mean gestational age was 39.3 weeks (range 27.3-42.1). Fourty-three infants (9%) had an at-risk SINDA neurological score.
TD infants showed better reaching and grasping performance in supine than in sitting position at ages 4 and 5 months: at 4 months 61 of 91 infants were able to grasp an object in supine vs. 39 of 91 in supported sitting, at 5 months this were 83 of 90 vs. 73 of 90 (4 and 5 months pooled: $p<0.001$). In older infants grasping success was similar in both positions. In the AR-group 50% was able to grasp an object in supine and 56% in sitting ($p=1.000$).

Conclusions: In young TD infants reaching performance was better in supine than in sitting position, a finding at variance with literature. Conceivably the difference is brought about by the difference in postural support, which is less during lap than during chair sitting. The limited data on AR-infants suggest the absence of a similar position effect.

Keywords:
reaching and grasping, position, infancy, at-risk

EPNS23-2881 Oral or e-Poster
Neurodevelopmental Disorders

Comparison of periodic & aperiodic neural activities between preschool children born preterm and full-term - an electroencephalogram (EEG) study

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Objective: This study aimed to compare quantitative EEG (qEEG) profiles and cognitive function between preterm and full-term children aged 4 to 6 years.

Methods: Children's cognitive ability was assessed using the Griffiths Development Scales-Chinese (GDS-C). Resting-state EEG was recorded using single-electrode EEG. In addition to conventional band power analysis, aperiodic components (exponent and offset) and peak frequency of the dominant oscillation were calculated by fitting oscillations and one-over-f (FOOOF).

Results: The study recruited 28 preterm children (15 girls, mean age = 62.14 months, SD = 7.31) and17 age-matched full-term children (7 girls, mean age = 59.8 months, SD = 8.49 The qEEG profile of preterm children showed significantly elevated aperiodic offset ($p = 0.047$) and exponent ($p = 0.033$), and significantly slower peak frequency of the dominant oscillation ($p = 0.005$), and delta ($p = 0.029$) and theta band power ($p = 0.003$) compared to full-term children.

Conclusions: Preterm children demonstrated elevated aperiodic offset and exponent and slower peak frequency of the dominant oscillation compared to full-term children, at preschool age. These findings may indicate that preschool children born preterm have less efficient functional neural connections and brain immaturity.

Keywords:
Quantitative Electroencephalogram, preterm children, development, cognitive function

EPNS23-2496 Oral or e-Poster
Neurodevelopmental Disorders

Characteristics of visual cognition in preterm infants and children with neurodevelopmental disorders

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Objective: Preterm infants are known to be at high risk for neurodevelopmental disorders, especially autism spectrum disorders, and have various problems during their development. However, there are many unclear points about the social development of premature infants. We investigated the characteristics of visual cognition in preterm infants and children with neurodevelopmental disorders using a gaze tracking device Gazefinder (JVC Kenwood).

Methods: The subjects were 20 preterm children and 30 typically developing children aged 2 to 12 years. Gazefinder was used to measure the line of sight, and the gaze transition, fixation time, and region of interest were measured in the three areas of "human face," "geometric pattern," and "others" in each content such as "Human and Geometry." In particular, we focused on the gaze rate of geometric patterns, and examined the characteristics of visual cognition in typically developing children, premature autism spectrum disorder(ASD) children, and full-term ASD children. Furthermore, premature ASD infants were divided into three groups according to age, and the differences were observed. He used the Kruskal-Wallis test and the Mann-Whitney U test for the test, and set the significance level to 5%.

Results: In "Human and Geometry", we examined the difference in the rate of gaze, and found that preterm ASD infants had different gaze patterns from those of typically developing infants and full-term ASD infants. Preterm children with ASD showed a significant increase in the rate of attention to geometric patterns with age ($p=0.014$), and the rate of attention to geometric patterns was similar to that of full-term children with ASD during school-age. On the other hand, in full-term ASD children, there was no significant age difference in the rate of attention to geometric patterns from early infancy to school age, and the rate remained relatively high.

Conclusions: It has been reported that children with ASD have a higher rate of gazing at geometric patterns than children with typical development. In this study, it was shown that preterm ASD infants have a high rate of fixation on geometric pattern areas, similar to full-term ASD infants. It was also suggested that the characteristics are difficult to understand in early childhood, but become more pronounced with age. This indicates the usefulness and importance of early diagnosis using Gazefinder and early clinical intervention for preterm infants with ASD characteristics.

Keywords:
preterm infants, visual cognition, autism spectrum disorder, neurodevelopmental disease

EPNS23-2090 Oral or e-Poster
Neurodevelopmental Disorders

High Frequency Oscillations in Autism Spectrum Disorder: Is it related with clinical severity?

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Objective: Autism Spectrum Disorders (ASD) are characterized by impaired social communication and interaction, restrictive and repetitive patterns of interest, behavior, and activities causing developmental delays in children. High-frequency oscillations (HFO) are oscillatory high-frequency (>80Hz) signals that can be recorded by scalp EEG. They can be physiological or pathological. Physiological HFOs related to sleep spindles (SS) had been reported. In addition, some reports indicate HFOs as a marker in the prediction of seizures. An association between non-epileptic scalp HFOs and brain development had also been documented. The present study aimed to explore the presence of HFOs in children with ADS and its relation to clinical symptomatology.

Methods: Fifty-two children with ASD and 49 healthy children enrolled in the study. N2 sleep records of at least 10 minutes were evaluated retrospectively. EEG records were evaluated by the open-source Python library MNE-HFO for the detection of scalp HFOs. The sleep spindles were detected using the open-source YASA. Sleep spindles and HFOs evaluated by artificial intelligence.

Results: The mean ages were 63.8 ± 23.9 and 64.6 ± 25.3 respectively for ASD and healthy subjects. The duration of SS was shorter and the frequency was higher significantly in children with ASD when compared to the healthy group. HFOs unrelated to SS were documented to be higher in children with ASD ($p<0,01$). Younger children with ASD had particularly higher HFOs unrelated to SS ($p<0,01$). Within the ASD group of patients, HFOs unrelated to SS were significantly higher in sub-groups who had moderate-severe social interaction problems (<0,01), moderate-severe restricted interest (0,018), and severe linguistic delays (0,006). However, no relation with stereotypes had been found.

Conclusions: The HFOs unrelated to SS were found to be significantly higher in children with ASD, particularly in subgroups with moderate-severe communication problems, moderate-severe restricted interest, and severe linguistic delays. HFOs seem to be a reliable marker for ASD that can be used in clinical settings. However, the exact mechanism is not clear; the HFOs may be the underlying pathology affecting clinical symptomatology or other etiological factors might cause emerging of HFOs in children with ASD that needs to be clarified with future studies.

Keywords:
autism spectrum disorders, high-frequency oscillations, HFO, sleep spindles

EPNS23-2076 Oral or e-Poster
Neurodevelopmental Disorders

Predictors of the development of autism spectrum disorder in genetic epilepsy

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Objective: to establish predictors of the development of ASD in patients with genetic epilepsy (GE).

Methods: 95 patients with GE were analyzed: 60(63.2%) females and 35(36.8%) males, mean age 6.0 [IQR 4.0; 10.0] years. 76(80.0%) children had monogenic, 19(20.0%) - chromosomal pathology. The autosomal type of inheritance was established in 80(84.2%) cases, linked to the X chromosome - in 15(15.8%). Mean age of epilepsy onset was 1.0 [IQR: 0.58; 3.0] year. Focal epileptic seizures were in 36(37.9%) patients, tonic-clonic - in 35(36.8%), myoclonic - in 26(27.4%), epileptic spasms - in 7(7.4%), behavior arrest - in 22(23.2%), tonic - in 16(16.8%), atonic - in 22(23.2%), febrile provoked seizures - in 36(37.9%) and status epilepticus - in 28(29.5%). Infantile epileptic spasms syndrome was in 9(9.5%) children, Lennox-Gastaut syndrome - in 1(1.1%). Daily seizures were in 51(53.7%) cases, weekly - in 13(13.7%), monthly - in 14(14.7%), several times a year - in 8(8.4%) and single - in 6(6.3%). Pharmacoresistant epilepsy was observed in 51(53.7%) patients. Interictal epileptiform activity was present in 72(75.8%) children, slowing down of the main background activity - in 32(34.8%), CSWS - in 8(13.6%). MRI revealed ventriculomegaly in 34(38.2%), enlargement of the anterior subarachnoid space in 19(21.3%), and other cerebral anomalies in 12(13.5%) cases. 81(85.3%) patients had cognitive impairments: mild - 22(23.2%), moderate - 17(17.9%), severe - 18(18.9%) and profound - 24(25.3%). Impaired motor development was in 38(40.0%) patients: GMFCS II was in 18(18.9%), GMFCS III in 4(4.2%), GMFCS IV in 12(12.6%) and GMFCS V in 4(4.2%). The binary logistic regression method and the ROC-curve were used to predict ASD.

Results: ASD was detected in 55(57.9%) patients. A prognostic model for the development of ASD in GE was developed and the following independent risk factors were established: 1)linked to the X chromosome inheritance (p=0.017, OR=20.5, 95% CI [1.72-243.6]), 2) ventriculomegaly (p=0.006 , OR=7.47, 95% CI [1.8-30.9]), 3) slowdown in the background activity on the EEG (p=0.013, OR=5.54, 95% CI [1.44-21.2]) and 4) concomitant cognitive impairment (p= 0.022, OR=25.7, 95% CI [1.61-413.0]). The sensitivity and specificity of the model were 87.2% and 74.4%, respectively.

Conclusions: The risk of developing ASD in GE does not depend on the characteristics of the course of epilepsy, but is determined by impaired functioning of neurons resulting from mutation.

Keywords:
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EPNS23-2863 Oral or e-Poster
Neurodevelopmental Disorders

Ataxia rating scales reveal increased scores in very preterm born 5-6 year old preschool children and young adults

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Case study: Objective: To investigate whether scores in ataxia rating scales (ARS) are different in very preterm (VP, less/ equal 32 weeks of gestation) preschool and adult participants compared to term controls.
Methods: Case-control study. 60 VP children (years: 5.5 - 6.5; gestational age: 23.9-31.7 weeks) and 56 VP adults (years: 17.8-27.9; gestational age: 23.3-32.0 weeks) without major cerebral lesions (less/ equal intraventricular hemorrhage grade II, IVH) and norm intelligence. 60 age and sex-matched term children and 64 term adults for comparison. Assessment with International Cooperative Ataxia Rating Scale (ICARS) and Scale for Assessment and Rating of Ataxia (SARA). Primary outcome: Total ICARS and SARA scores in preterm (VP) participants versus controls.
Results: VP children showed significantly higher total ICARS (M 15.98, SD 6.29, range 4.0-32.0; $p < .001$) and SARA scores (M 6.5, SD 2.53, range 1.0-15.0; $p < .001$) than controls (ICARS: M 9.17, SD 3.88, range 2.0-20.0; SARA: M 3.51, SD 1.54, range 1.0-8.0). VP adults also showed significantly higher total ICARS (M 1.0, SD 1.99, range 0.0-11.0; $p < .001$) and SARA scores (M 0.54, SD 1.08, range 0.0-6.0; $p < .001$) than controls (ICARS: M 0.11, SD 0.44, range 0.0-2.0; SARA: M 0.04, SD 0.18, range 0.0-1.0).
Conclusions: VP children showed significantly higher scores in ARS than controls. These differences were also present in VP adults, suggesting that deficits likely prevail until adulthood. ARS are a time and cost-effective method to screen for difficulties in coordination and balance in a patient group at risk. Data suggest that ARS may be useful screening tools to decide which patients should be tested with more extended motor scales such as the M-ABC-2.

Keywords:
very preterm children, very preterm adults, ataxia rating scales, difficulties in coordination and balance.

EPNS23-2409 Oral or e-Poster
Neurodevelopmental Disorders

Clinical Characteristics and Possible Risk Factors of Epilepsy in Children with Cerebral Palsy

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Objective: The aim of this study was to evaluate the clinical characteristics of children with cerebral palsy (CP) and to investigate possible risk factors and prognosis of epilepsy in children with cerebral palsy (CP) with a special emphasis on drug-resistant epilepsy (DRE).

Methods: A total of 145 pediatric patients who were followed up with a diagnosis of CP between 2019 and 2022 were evaluated. Demographic features, prenatal/perinatal history, etiology and type of CP, degree of impairment in motor and cognitive functions, seizure type, neuroimaging, and electroencephalography (EEG) findings were obtained retrospectively from hospital records. The patients were divided into two groups: CP patients with epilepsy and patients without epilepsy. Study variables were compared between these two groups and also between DRE and controlled epilepsy groups.

Results: There were 91 (63%) boys and 54 (37%) girls with a mean age of 11.1 ± 4.2 years (3-18 years). Epilepsy was present in 107 (73.7%) cases and 40.1% of them had refractory epilepsy. Epilepsy was most common in the tetraplegic form of CP (p=0.028). Term gestation, birth weight of >2500 g, and history of neonatal seizures were significantly higher in patients with epilepsy (p=0.03, 0.01, and 0.03, respectively). Children with DRE were more likely to have tetraplegic CP (50%) and severe intellectual disability (56%).

Conclusions: Determination of potential risk factors is important in predicting the development of epilepsy in patients with CP, as it may provide closer follow-up of patients at high risk. Particular attention should be paid to the early identification and treatment of comorbid epilepsy in children with CP.

Keywords:
cerebral palsy, epilepsy, pediatric, risk factors, refractory epilepsy

EPNS23-2470 Oral or e-Poster
Neurodevelopmental Disorders

Developmental diagnostics for neurofibromatosis type 1 in early childhood

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Objective: Neurofibromatosis type 1 is a common autosomal dominant inherited disease often accompanied by a developmental delay. So far mostly targeted development tests for preschool children are described in the literature [1]. We analyzed the development of toddlers.

Methods: In a cross-sectional study 27 children (mean age=37.9months [14-53]; male=59%) with NF-1 (n=26) and NF-like disease (n=1) were examined with the newly standarized-Munich functional development diagnostics 1.-4. year of life (MFED 1-4). Nearly 400 individual items- cognitive development, receptive and expressive language, gross and fine motor skills, social development and independence- were tested in an age-dependent manner.

Results: All children showed a striking development profile compared to the norm group, especially in the area of expressive language and fine motor skills. With regard to the individual items, tasks involving spatial imagination were solved significantly less often than in the norm group. Despite a general language delay, results in the color-related items of expressive and receptive language were comparable to healthy children. The social development and independence were developed equal to the norm group.

Conclusions: The significant developmental delay in school age children with NF1 concerning motor skills, language and cognition can be illustrated by the MFED 1-4 in early childhood. Despite the association of NF1 with ADHD, our toddlers show no significant differences in social development and independence. Thus, in the case of NF1 the lack of attention in preschool and school age could rather lead to the diagnosis of ADHD. Limitations result from the cross-sectional study and the conspicuous profile in all children examined. Further investigations in a larger collective as well as the targeted further investigation of the conspicuous individual items are necessary to derive a personal development profile and specific support.
[1] Walsh et al,2016:Neuroconitive outcomes in neurofibromatosis clinical trials.AAN,87,21-30.
[2] Mall et al, in prep.

Keywords:
neurofibromatosis type 1; early childhood development; developmental delay; MFED 1-4; developmental neurological testing

EPNS23-2703 Oral or e-Poster
Neurodevelopmental Disorders

What do we know about the outcomes of individuals with cerebral palsy who have a tracheostomy? An observational study from South-West England

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Objective: In a recent review of life expectancy for those with cerebral palsy (CP) with severe impairment, Rosenthal's conclusions stated, "tracheostomies deserve further debate and data acquisition". We sourced clinical information using healthcare coding data (used for funding within the National Health Service) from one regional hospital.

Methods: The authors collaborated with business intelligence data analysts to identify two deceased CP datasets; with and without a history of tracheostomy. ICD10 codes were used for CP and tracheostomy in addition to OPCS4 (procedural codes) for tracheostomy. The need for ethical approval was checked but was not required.

Medical records of deceased patients with CP were reviewed. The data collected included: demographic data, age at death, cause of death, aetiology, age of tracheostomy and co-morbidity data of: tube feeding, non-invasive ventilation, epilepsy, movement disorder, severe learning difficulties and unassisted ambulation.

Results: Six records were identified with cerebral palsy and a history of tracheostomy. 132 records were identified for CP without a history of tracheostomy. Patients with tracheostomy were cross-checked with an in-department record; no records had been omitted. Missing data was represented in the analysis of co-morbidity data. Among the non-tracheostomy group, the median age of death was 19 (range 1-92).

In those with CP and tracheostomy the median age of death was 19 (range 8-38). Survival from the date of tracheostomy ranged from 6 to 12 years (median 8 years). The ages of insertion varied from neonatal period to age 28. 100% had Grade 5 GMFCS, 100% tube fed, 67% receiving NIV, 50% with epilepsy, 67% with a movement disorder, 100% with severe learning difficulties and 50% ambulant. Indications were upper airway obstruction in 50%, secretion management in 33% and prevention of recurrent pneumonia in 16%.

Conclusions: We prove that coding data can support clinical research on rare and complex conditions. We have proven that this method does not omit patients with a history of tracheostomy. We provide the first observational data on the outcomes of individuals with CP and a history of tracheostomy, and the differing prevalence of co-morbidities compared to the CP population without tracheostomy.

This study would benefit from a greater cohort size via analysis of national, Hospital Episode Statistics, data and the use of additional codes to assess for comorbidities e.g. epilepsy, in place of author review of medical notes.

Keywords:
cerebral palsy, tracheostomy, survival, life expectancy, ICD10, OPCS4

EPNS23-2911 Oral or e-Poster
Neurodevelopmental Disorders

A case of Brain-Thyroid syndrome caused by NKX2-1 mutation

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Case study: An 8-year-old boy was initially diagnosed as congenital hypothyroidism at the age of 16 days. Neonatal thyroid screening test performed outside revealed persistently elevated TSH levels (18.2 mIU/L and 23.11 mIU/L). He was referred to our Clinic and TSH level was elevated to 36.28 mIU/L. Thyroid sonography showed normal thyroid gland with normal echogenicity. Medication with L-thyroxine started immediately. After 2 months of treatment, he moved to other place and then came back to our clinic at the age of 26 months, when he showed global developmental delay. During follow-up with thyroid hormone replacement, mild facial tic and dystonia were noted. His mother also showed facial tic and dysarthria. Under the impression of the Brain-Thyroid syndrome, whole exome sequencing was performed. It revealed likely pathogenic variant in the gene NKX2-1. His mother also showed same mutation. There was no structural abnormality in basal ganglia on brain MRI, however bilateral optic nerve thickness was found. Ophthalmologic consultation did not show any visual abnormalities. During follow-up with annual brain MRI, optic nerve thickness was stationary over 3 years with no specific visual discomfort. Facial tic and dystonia was modestly responsive to the medication with tetrabenazine.
Here we report a case of Brain-Thyroid syndrome caused by NKX2-1 mutation in an 8-year-old boy with developmental delay, facial tic and dystonia, and optic nerve thickness.

Keywords:
Brain Thyroid NKX2-1

EPNS23-2283 Oral or e-Poster
Neurodevelopmental Disorders

Visual cognition in patients with Kabuki syndrome; Comparison with Williams syndrome

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Case study: Objectives:
Patients with Kabuki syndrome (KS) have been noted to have visuo-spatial difficulty as in patients with Williams syndrome (WS). We have reported that patients with KS were worse at simultaneous than sequential processing tasks.
In this study, we investigate the functions of the dorsal and ventral pathways of the visual system in KS and checked if the interventions for WS patients are also effective.
Methods:
Four patients with KS participated in the following tests. Benton's 3D block construction test (test 1), tests of copying line drawings of 2D and 3D objects (test 2), the line drawing test modified from the Developmental Test of Visual Perception (test 3: Participants were asked to copy a pattern of lines connecting black dots) to investigate the dorsal visual function and Benton's facial recognition test (test 4) to investigate the ventral visual function. Remodeling the test 3, the intervention used for WS patients (dots in the test 3 are presented with colors) was performed.
Results:
All four patients showed visuo-spatial difficulty in the test 1,2,3 to some extent. However, the function of facial recognition (test 4) was not preserved as well as in WS. The intervention using colors was not as effective as in WS.
Conclusion:
The difference between the degree of dysfunction of the dorsal pathway and that of the ventral pathway in KS is not as remarkable as that in WS. It is probably the reason why the similar intervention as in WS is not necessarily helpful in KS.

Keywords:
Kabuki syndrome, Williams syndrome

EPNS23-2937 Oral or e-Poster
Neurodevelopmental Disorders

Movement skills in children with autism spectrum disorder

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Objective: Various neurodevelopmental disorders can occur in children with autism. Among other issues, balance and motor skills may be impaired.

Methods: The aim of work was evaluation of fine and gross motor skills and balance among children suffering from autism and in comparison to healthy children. Study group consisted of 71 children both genders with ASD, aged 5-12. Control group comprised 91 children at the same age, both genders, without autistism. Exclusion criteria were the presence of cooccurring genetic and neurological diseases, especially mental disabilities, epilepsy and cerebral palsy.
Motor skill evaluation was carried out using the Motor Assessment Battery for Children MABC-2. The evaluation included 8 motor tasks such as manual dexterity, aiming and catching, and balance.

Results: Children in the study group were scored significantly lower ($p<0.0001$) in all three assessed categories.

Conclusions: Complex evaluation of the motor skills among patients suffering from autistic spectrum disorder without genetic or neurological commorbidities will serve for a better wholistic characterization of this population.

Keywords:
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EPNS23-2270 Oral or e-Poster
Neurodevelopmental Disorders

The implication of developmental history of independent walking age in a patient with autism spectrum disorder and global developmental delay

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Objective: It is sometimes difficult to differentiate clinically between global developmental disorder (GDD) and autism spectrum disorder (ASD) in infancy and early childhood, and it is known that patients with ASD have a lower rate of delay in independent walking than patients with GDD.
This study aimed to investigate the usefulness of independent walking age as a clinical marker for differential diagnosis of ASD and GDD.

Methods: Among 622 patients with developmental delay who visited Dongtan Sacred Heart Hospital from 2013 October to 2021 December, 148 patients with ASD and 129 patients with GDD who were tentatively diagnosed according to the DSM-5 diagnostic criteria after a developmental evaluation were retrospectively analyzed.
Fifty-four patients with ASD and 31 patients with a GDD with independent walking records were included

Results: The mean age at diagnosis was 35.0±10.8 for ASD and 34.1±10.9 for GDD, and the male to female ratio was 3.5:1 for ASD and 2.9:1 for GDD. There was a statistically significant difference in independent walking time with an average of 13.0±2.3 for ASD and 15.0±3.0 for GDD. In GDD patients, except for one patient, who did not walk independently before 12 months, but in ASD patients, 12 out of 54 (22%) patients walked independently before 12 months

Conclusions: Patients with ASD showed a faster independent walking age than patients with GDD, and it is implicated that it can be used as a clinical marker for the differential diagnosis of the two diseases.

Keywords:
autism spectrum disorder, walking, global developmental disorder

EPNS23-2240 Oral or e-Poster
Neurodevelopmental Disorders

STXBP1 ENGAGE: Families' lived experiences with STXBP1-related disorders

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Objective: STXBP1-related disorders (STXBP1) are a severe developmental and epileptic encephalopathy with significant unmet need and no currently approved targeted treatments. Limited data exist describing the full range of symptoms and disease impact on children living with STXBP1 and their families. We initiated STXBP1 ENGAGE to shape our understanding of the lived experience and journey from caregivers and inform the design of clinical studies of disease-modifying therapies.

Methods: In-depth interviews were conducted with caregivers of children living with STXBP1 (Castle IRB Exemption, STX ENGAGE-123). While prompts and open-ended questions were used to semi-guide the discussion, caregivers described experiences in their own words and preferred sequence. Interviews explored various topics: diagnosis, type and timing of symptoms, medical specialties visited, therapies tried and disease impact on the whole family. A narrative thematic analysis was conducted based on interview transcripts.

Results: As of 31Dec2022, caregivers of 20 children from 5 countries (US, UK, ES, CA, AU) were interviewed. Children were aged 1-8 years, 8 male and 12 female. All caregivers reported emergence of symptoms in the first year of life and half (10/20) "felt something was wrong" within the first weeks from birth. Initial signs observed were commonly described as "spasms", "muscle contractions" or "tremors." Despite early onset of symptoms, the average reported time to diagnosis was 19 months (range 5wk-5yr), with the largest obstacle being access to genetic testing.

Although most (18/20) children had seizures at some point (9/18 were seizure free at the time of interview), seizures were not considered to have the greatest impact on most families. All caregivers reported that their child had cognitive development issues and most described the limited ability to communicate as most impactful on daily life. While varied, other symptoms commonly reported as affecting activities of daily living included mobility, behavior, eating and sleep issues.

Conclusions: Children living with STXBP1 experience numerous symptoms beyond seizures. Despite substantial phenotypic heterogeneity, STXBP1 has a significant negative impact on the daily lives of children, caregivers and family members, highlighting the need for therapies that address the full spectrum of seizure, cognitive, behavioral and motor symptoms.

Keywords:
STXBP1, developmental and epileptic encephalopathy, DEE, ENGAGE, caregiver, lived experiences, journey, disease-modifying therapies

EPNS23-2963 Oral or e-Poster
Neurodevelopmental Disorders

Visual function in children with GNAO1 related encephalopathy

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Objective: GNAO1 related encephalopathies include a broad spectrum of developmental disorders caused by de novo heterozygous mutations in the GNAO1 gene, encoding the G subunit alpha of G-proteins.
These conditions are characterized by epilepsy, movement disorders and developmental impairment in combination or as isolated features.
This study aims to describe the profile of neurovisual competences in children with GNAO1 deficiency in order to better characterize the phenotype of the disease spectrum.

Methods: Four male and 3 female patients with confirmed genetic diagnosis, underwent neurological examination, visual function assessment, including neurovisual and ophthamological evaluation. Present clinical history of epilepsy and movement disorders together with neuroimaging findings were also evaluated.

Results: there are two different trends of visual development, according to the aspects assessed. Some aspects of visual function such as discrimination and perception of distance, depth and volume, appeared to be impaired at all ages with no sign of improvement.
Other aspects , more related to object-face exploration, recognition and environmental control, reliant on temporal lobe competences (ventral stream), appeared to be preserved and improved with age.

Conclusions: Our data suggest that in children with GNAO1 mutation several visual aspects are impaired. The early recognition of these difficulties is important as it may lead to early rehabilitation specifi-cally targeting visual function.
Visual impairment did not appear to be grossly related to the presence of others clinical signs such as epilepsy or movement disorders. Further studies using a more global assessment will help to establish whether this mild but specific impairment of distinct aspects of visual function have an effect on neurodevelopmental ad cognitive abilities.

Keywords:
neurovisual competences; GNAO1 mutation; visual function.

EPNS23-2398 Oral or e-Poster
Neurodevelopmental Disorders

NEURODEVELOPMENTAL DELAY - CORNEAL CLOUDING - HYPOMYELINATING LEUKOENCEPHALOPATHY - THINK MUCOLIPIDOSIS IV

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Case study: Mucolipidosis type IV (MLIV) is an ultra-rare autosomal recessive lysosomal disorder characterized by typical neurological (early onset developmental delay, spasticity), ocular (corneal clouding, retinopathy), and characteristic MRI findings (hypomyelinating leukoencephalopathy, thin corpus callosum, cerebellar atrophy). Although MLIV was predominantly reported in patients in the Ashkenazi Jewish community, it is a pan-ethnic disorder.
We report on two siblings of Armenian origin with global neurodevelopmental delay, ophthalmological abnormalities and characteristic MRI suggesting MLIV. Whole Exome Sequencing confirmed two pathogenic variants in the MCOLN1 gene.
We confirm that this constellation of clinical and neuroimaging findings provides the basis for the diagnosis of MLIV, and we suggest that a targeted diagnostic work-up should be considered in unexplained neurodevelopmental disorders.

Keywords:
Mucolipidosis IV, MCOLN1, corneal clouding, hypomyelination, cerebral palsy

EPNS23-2326 Oral or e-Poster
Neurodevelopmental Disorders

Effectiveness of genetic studies in neurodevelopmental disorders after applying a clinical prediction scale.

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Objective: In patients with neurodevelopmental disorders (ASD, intellectual disability, epilepsy) the clinician has to decide whether to request a genetic study in a cost-effective manner. In these patients we have developed a clinical prediction scale based on 5 items (macrocephaly, low birth weight, ASD, presence of 1 dysmorphia, presence of 2 or more dysmorphia) to which different scores are assigned with adequate sensitivity and specificity. (Amado et al, PMID: 30939599), establishing a score of 1.5 as the cut-off point to request a genetic study. Our objective is to validate this scale in patients seen in an outpatient clinic for neurodevelopmental disorders and to analyze the data obtained.

Methods: Retrospective study in a neuropediatric outpatient clinic focused on neurodevelopmental disorders. The following variables were collected from 100 consecutive patients in whom genetic studies were performed: age, ICD-10 diagnosis, checklist score, type of study performed, and results of the genetic study. We excluded patients with clear clinical suspicion and those with that an etiological study was carried out aimed at clinical suspicion or patients with malfomative symptoms without associated neurodevelopmental pathology. As limitations of our study, we should highlight the heterogeneity of the techniques, since they were not always sent to the same laboratory.

Results: We have collected the data of 100 patients seen consecutively in a consultation for neurodevelopmental disorders who underwent a genetic study. The age range was between one year and 14 years, with a mean of 4 years at the time of the study. The main diagnoses were ASD (F84) and macrocephaly (Q753). The average score of the checklist was 1.8, with a range between 0 and 6 points. The score of 1.5 was seen in 33% of the patients. The most requested test was array-CGH (73% of patients), followed by exome (22%). A normal result was found in 56% of patients, VUS in 26% of patients, pathogenic variants in 11% of patients, probably benign in 4%, and probably pathogenic in 2%. If we add the studies in which some significant finding was found, these would represent 40% of the sample.

Conclusions: All individuals with a score of 1.5 or higher should be genetically screened with a aCGH and/or clinical exome. This approach can improve clinical indications for genetic analysis in patients with neurodevelopmental disorders but this scoring system needs to be validated in a larger population.

Keywords:
Neurodevelopment, genetics, Array-CGH, Autism Spectrum Disorders, scale, checklist.

EPNS23-2171 Oral or e-Poster
Neurodevelopmental Disorders

Comparative study of recreational screen time in neurodevelopmental disorders

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Objective: Digital screen time has been largely studied in children's population, but few have focused on children with neurodevelopmental disorders.
Our main objective was to study the characteristics of use of recreational screens (television (TV) and video games), in children with neurodevelopmental disorders.

Methods: We conducted a case-control study in which children with neurodevelopmental disorders under the age of 6 were compared with controls of the same age range. We analyzed TV and video game exposure through a designed questionnaire for parents (K index >0.7) that included daily time exposure, sociodemographic characteristics, home media environment, sociocultural habits, attitudes and beliefs about TV.

Results: Sixty-one individuals with neurodevelopmental disorders and 153 controls were enrolled. To analyze the differences between groups, we use Student's t-test for continuous variables
and the Chi square test for categorical variables.
Children with neurodevelopmental disorders spend more time watching TV than controls (124.4 +-83.4 vs 71,5 +-47,4 min/day $p<0.0001$), while video game was similar in both groups (37.6 +- 39.,6 vs 31.7 +-32,6 min/day $p=0.138$). Children with neurodevelopmental disorders began earlier to watch TV than controls. There were no relevant differences between groups in demographics, sociocultural, environmental and attitudinal and belief variables.

Conclusions: Children with neurodevelopmental disorders start watching TV at an earlier age and consume more screen time than healthy children. Our findings indicate that children with neurodevelopmental disorders are more vulnerable to screen abuse. To avoid potential negative impact on neurodevelopment, we consider relevant to offer advance guidance to their parents.

Keywords:
Digital screens; Screen time;Neurodevelopmental disorders; TV; Video game

EPNS23-2251 Oral or e-Poster
Neurodevelopmental Disorders

Kynurenine Pathway in Autism Spectrum Disorders in Children

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Objective: There is increasing evidence that altered immune responses play a role in the pathogenesis of autism spectrum disorders (ASD), together with dysfunction of the serotonergic and glutamatergic systems. Since the kynurenine (KYN) pathway that degrades tryptophan (TRP) is activated in various neuroinflammatory states, we aimed to determine whether this pathway is activated in ASD.

Methods: Sixty-five pediatric ASD patients (including 52 boys) were enrolled from an epidemiological survey covering 2 counties in Norway; 30 (46.5%) of these patients were diagnosed with childhood autism, 16 (24.6%) with Asperger syndrome, 12 (18.5%) with atypical autism, 1 (1.5%) with Rett syndrome, and 6 (9.2%) with other ASD. The serum levels of the following markers were measured in the children with ASD and compared to those in 30 healthy children: TRP, KYN, kynurenic acid (KA), 3-hydroxykynurenine, and quinolinic acid.

Results: The mean serum level of KA was significantly lower in the ASD group than in the healthy controls (28.97 vs. 34.44 nM, $p = 0.040$), while the KYN/KA ratio was significantly higher in the ASD group (61.12 vs. 50.39, $p = 0.006$). The same relative values were found when comparing the childhood autism subgroup with the controls. Also, the mean serum level of TRP was significantly lower in children with a subdiagnosis of childhood autism than in those with Asperger syndrome (67.26 vs. 77.79 μ m, $p = 0.020$).

Conclusions: The results for TRP metabolism (TRP, KYN, KA, 3-OH-KYN, and QA levels, and the KYN/TRP, KYN/KA, and QA/KA ratios) have shown abnormalities in KP in ASD. Our finding of the serum KA level being significantly lower in ASD children than in healthy controls thus suggests that the level of neuroprotection is lower in ASD children. The KYN/KA ratio was significantly higher in the serum of ASD children than in healthy controls, which together suggest that the level of neurotoxicity is higher and the KAT activity is lower in ASD children. The same relative values were also found when comparing the childhood autism subgroup with controls. Although the QA/KA ratio did not differ between patients and controls, the lower KA level may be influential in autism. Our study indicates that there is an increased neurotoxic potential and also a possible lower KYN aminotransferase activity in ASD.

Keywords:
Autism spectrum disorders · Kynurenine pathway · Kynurenic acid · Tryptophan

EPNS23-2093 Oral or e-Poster
Neurodevelopmental Disorders

Validation test of a new approach for screening and treatment of neurodevelopmental disorders

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Objective: We developed a screening test (https://www.encajamosdiferente.com/en/) in order to enable early and equitable care to families with suspected neurodevelopmental disorders, especially Autism Spectrum Disorder (ASD). "Encajamos diferente" means "we fit different". The objective is to facilitate the detection of problems in communication, social interaction, and behavior difficulties such as repetitive, restricted and stereotyped behaviors as soon as possible, as well as eating and sleeping difficulties, which are usually presented in patients with ASD. The screening test is based on previous screening methods (M-CHAT / ADI-R) updated to get 3 degrees of concern (low-medium-high) so that parents clear up their doubts and get the necessary tools to start working immediately from home.

Methods: We carried a retrospective study analyzing data from January to June 2022. We have analyzed the data on traffic to the web, number of tests carried out, test scores, tests completed, patients age, and willingness of families to start a remote therapeutic intervention.

Results: 8027 people have visited the website during the first semester. 33% completed the test (2,593 tests). 80% have a child between 1-5 years of age. Actions on the web regarding the tests: subscribe to the newsletter 58.5%, browsed to the web La Ruta Azul (neurodevelopmental center) 35.4%, requested a call 3.5%, called directly 2.6%. The results of the screening test were: low concern 683 (26%), medium concern 1,108 (43%), high concern 802 (31%). 63% of the families were willing to do an online treatment, with an opening rate of the email to initiate the remote treatment of 34.88%

Conclusions: There is a lot of interest in families to identify possible neurodevelopmental disorders in their children. The fact of carrying out a remote screening test reduces the friction of families to request medical help. In children with neurodevelopmental problems, especially ASD, early detection and early initiation of treatment implies a better prognosis. Families are prone to this type of approach under the supervision of neurodevelopmental specialists.

Keywords:
autism, screening test, neurodevelopmental disorders, digital therapeutics

EPNS23-2253 Oral or e-Poster
Neurodevelopmental Disorders

A prospective study for early detection of neurodevelopmental disorders in preterm infants in the follow-up outpatient clinic

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Objective: Neurodevelopmental disorders are long-term neuropsychiatric complication of preterm infants. Because of psychosocial problems they face after school age, "early diagnosis and rehabilitation" are essential. We report an ongoing prospective study aiming for early diagnosis of autistic spectrum disorder (ASD) in preterm infants by combining neurological, psychological, and visual-cognitive assessments in preterm infant follow-up outpatient clinics.

Methods: Preterm infants born earlier than 33 weeks of gestation were included in the study and compared with term, typically developing infants. Fine and gross motor development and social skills (e.g., weakness in novel situations, facial expressions, irritability, and eye contacts) were evaluated semiquantitatively after videotaping at the modified 9 to 11-month checkups. The Vineland-II was used to assess adaptive behavior, and the Gazefinder (JVC Kenwood), a gaze measurement device, was used to assess visual cognitive function. This study was approved by the Ethical Review Committee and the informed consent of the parents were obtained. Ten preterm infants and 10 typically developing infants have been currently recruited.

Results: Preterm infants showed equivalently good eye contact, but had poorer facial expressions, increased muscle tone in the lower extremities and stiff ankle joints. Preterm infants showed significantly lower social skills on the Vineland-II (95.8 ±9.8 vs. 84.1 ±9.26 in the typical infants, $p<0.05$). And they also showed relatively lower motor skills as well as social skills (95.7 ±7.0 vs. 86.8 ±12.1 for typical vs. preterm infants, $p=0.061$), although the differences were not significant. In the evaluation of visual cognitive function, the preterm infants gazed at human faces less frequently.

Conclusions: In the developmental assessment of preterm infants at the corrected 9-11 month age group, eye contact, which is generally recognized as an early sign of ASD, was retained, while other ASD characteristics such as poor facial expression, poor social skills, and delayed motor development were observed. We suspect that these signs are often overlooked in the routine follow-up outpatient clinic. We will continue to recruit cases and conduct longitudinal developmental assessments to identify indicators that can specifically capture ASD characteristics in preterm infants.

Keywords:
Preterm infants, Autistic spectrum disorder

EPNS23-2849 Oral or e-Poster

Neurodevelopmental Disorders

INFLUENCE OF THE SARS-CoV-2 PANDEMIC ON THE PRESENTATION PATTERNS OF PATIENTS WITH ASD. DIFFERENCES BY GENDER.

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Objective: Due to the effects that the pandemic has had on neurological diseases and neurodevelopmental disorders (Lugo-Marín, J. et al. 2021), we considered reviewing the frequency and age of presentation at the first visit of patients with ASD in a reference population with epidemiological significance in the five-year period 2018-22.

Methods: Cross-sectional study from closed reference population of 32,909 children under 15 years of age, the information from the first visits referred to our multidisciplinary unit from primary care is studied. We recorded the date and place of birth, gender, referral centre, and specialist. The data obtained from the electronic registration system of the Valencian health agency, obtained with the corresponding permits, conveniently anonymized, are tabulated and analysed for descriptive statistics in the corresponding Excel 2010 modules and EpiInfo 7.2.5.0 for association studies.

Results: In **2018**, of 5,341 visits, 144 were diagnosed with ASD (boys=123; girls=21). In **2019**, of 4,841 visits, 94 were diagnosed with ASD (boys=68; girls=26). In **2020**, out of 3,346 visits, 68 were diagnosed with ASD (Boys=48; Girls=20). In **2021**, out of 4,006 visits, 71 received a diagnosis of ASD (Boys=55; Girls=16). In **2022**, out of 4,333 visits, 104 were diagnosed with ASD (boys=75; girls=28). (X^2 for trend=3.97; p=0.046). **The age at diagnosis of ASD among Boys** in the years 2018-19 was mean=5.54 ±3.75 SD, and in 2021-22 it was mean=4.46 ± 3.38 SD (t=2.72; p=0.009). **The age at diagnosis of ASD among girls** in 2018-19 was mean=5.27 ± 5.38 SD, and in 2021-22 it was mean= 4.68 ± 3.72 SD (NS). None of the other factors studied presented significant differences.

Conclusions: 1) The pattern of presentation of children diagnosed with ASD before, during, and after the pandemic differed significantly between boys and girls, with boys presenting a higher frequency of ASD diagnoses at the beginning and end of this series, while the diagnoses girls remained more stable throughout the pandemic.

2) The mean age of diagnosis of ASD at the first visit in Boys, before the pandemic, was significantly higher by almost one year than the age of diagnosis after the pandemic. These differences did not occur significantly among girls.

3) Although socioeconomic factors have been described as influencing the ASD presentation phenotype, for longer series such as this one, independent variables of a more biological nature should continue to be assigned weight in the interpretation of the evolution of these patients.

Keywords:

ASD, epidemiology, pandemic, SARS-CoV-2, diagnosis, social

EPNS23-2073 Oral or e-Poster
Neurodevelopmental Disorders

Docosahexaenoic Acid Plus Piracetam Versus Piracetam Alone for Treatment of Breath-Holding Spells in Children: A Randomized Clinical Trial

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Objective: Piracetam is the most widely used drug in breath-holding spells (BHS), however its efficacy might not be satisfying to parents. Docosahexaenoic acid (DHA) can be promising in the treatment of BHS as an add-on drug to piracetam leading to reaching a complete cure in a shorter period. This study aimed to compare the efficacy of DHA plus piracetam compared to piracetam alone in reducing the frequency of BHS in infants and preschool children.

Methods: This randomized controlled study included two groups diagnosed with BHS. Anemic children or who received iron supplementation or children with underlying organic brain disease were excluded from the study. Group I included 50 patients who received Docosahexaenoic acid dose plus piracetam. Group II (control group): included 50 children who were managed with piracetam plus placebo. All patients were subjected to detailed history taking, full clinical and neurological examination before treatment and after treatment by 1,3, and 6 months. Occurrences of side effects and mortality were also recorded. The primary outcome was to evaluate the effect of combined treatment of piracetam and DHA on the severity of spells.

Results: Breath holding spells were reported in only 16% of children after treatment with piracetam and DHA and in 50% of those treated with piracetam only (P-value= 0.001).

Conclusions: Conclusion: Docosahexanoic acid plus piracetam is more effective than piracetam alone in preventing BHS in children.

Keywords:
Breath-holding spells, Seizures, Cyanosis, Pediatrics, Piracetam and Docosahexaenoic acid.

EPNS23-2039 Oral or e-Poster
Neurodevelopmental Disorders

Growth in a large international cohort of children and adults with CDKL5 Deficiency Disorder

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Objective: Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare and X-linked genetic disorder caused by a variant in the CDKL5 gene. CDD displays some common features of developmental epileptic encephalopathy, namely refractory seizures. In the absence of available published data on this topic we aimed to compare growth in individuals with CDD with the unaffected population and to investigate the effect of gastrostomy on growth.

Methods: The study included individuals from the International CDD Database with pathogenic or likely pathogenic variants in CDKL5, and whose families have provided any anthropometric measurement in the baseline and/or follow-up questionnaires. The British 1990 growth reference was used to determine the age and gender standardised Z-score. Longitudinal data were fitted using a generalised linear regression model with Gaussian distribution and identity link, and the generalised estimating equations method was used to account for clustering within individuals.

Results: Data on the 353 individuals with CDD revealed that height, weight, and head circumference were below the general population's norm (Z-score: height -0.67, weight -0.93, head circumference -2.04). The disparity was particularly pronounced after 4 years of age. Moreover, individuals with gastrostomy placement were shown to have a larger decrease than those without. The annual change in weight-for-age Z-score using measurements before and after gastrostomy placement was -0.17 in a subset of 20 individuals whose gastrostomy placement occurred between the baseline and follow-up questionnaire.

Conclusions: This is the first study to investigate the effect of CDD on growth parameters such as height, weight, and head circumference. We found that not only weight and height but also head circumference were compromised in this disorder. This is the first and largest study to show that CDD, much like Rett's syndrome, causes microcephaly.

Keywords:
CDKL5, CDD, developmental epileptic encephalopathy

EPNS23-2902 Oral or e-Poster
Neurodevelopmental Disorders

Phenotypic Spectrum of MECP2 gene mutations - a single center retrospective study

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Objective: Methyl-CpG-binding protein 2 is a multi-functional protein, highly expressed in neurons, required for proper brain development and maintenance of normal brain function encoded by the MECP2 gene which is located on the X chromosome. Its pathogenic variants are associated with Rett syndrome and one of the most common causes of intellectual disability in females. Our aim with this study was to get a better insight into the clinical spectrum of MECP2 gene mutations.

Methods: We performed a retrospective observational study in which we included 30 patients with MECP2 gene mutations and reviewed their personal history, neuropsychological development, symptoms progression, complications and overall management.

Results: We identified 30 patients with MECP2 gene mutations, 27 with classical Rett syndrome and 3 with atypical Rett Syndrome. Developmental delay with psychomotor regression was the most frequent onset symptom, followed by seizures. All patients had significant motor dysfunction, only 11 of them without gait loss. Other common symptoms were language delay or absence of speech, midline stereotypies, severe intellectual disability, feeding impairment, progressive microcephaly, scoliosis and breathing disturbances. 25 patients also had epilepsy, most of them with generalized seizures, fewer with focal motor seizures or polymorphic seizures. EEG recordings showed slowing of the background rhythms in most patients and a variety of epileptiform abnormalities with intermittent fast frontal activity being the most frequent.15 patients required more than 2 antiseizure medication while just 7 patients were treated only with one, such as Valproate or Topiramate, which provided its efficiency. Out of the patients with atypical Rett Syndrome, one was male, with unfavorable progression. The others were 2 girls who had milder symptoms. The evolution of most patients was unfavorable. 17 patients benefited from at least one adjuvant therapy.

Conclusions: Rett syndrome should always be considered in females with developmental regression following apparently normal initial development, progressive microcephaly, seizures, breathing abnormalities and autistic features, especially midline hand stereotypies. We are adding our statistical analysis to the current understanding of the phenotypic spectrum associated with MECP2 gene variants in order to highlight the importance of clinical pattern recognition in early diagnosis of this type of disorders.

Keywords:
MECP2, Rett syndrome, epilepsy, psychomotor regression, midline stereotypies, microcephaly

EPNS23-2209 Oral or e-Poster
Neurodevelopmental Disorders

Comparison of two approaches for botulinum toxin injections to treat paediatric drooling secondary to neurodevelopmental disability: a scoping review

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Objective: Thist study aimed summarize available evidence on the effectiveness of submandibular botulinum neurotoxin type-A (BoNT-A) injections and concurrent submandibular and parotid (i.e. four-gland) injections, respectively, and assess whether outcomes could be compared across studies to improve decision making regarding the optimal BoNT-A treatment approach for paediatric drooling.

Methods: A scoping review was performed. Three databases (PubMed, Embase, and Web of Science) were searched to identify studies on submandibular or four-gland BoNT-A injections for the treatment of anterior drooling in children with neurodevelopmental disabilities. Similarities and differences in participant, treatment and outcome characteristics between these studies were assessed.

Results: Twenty-seven studies were identified, of which 7 studied submandibular injections and 20 studied four-gland injections. No major differences in treatment characteristics (e.g. BoNT-A formulation and dose, use of ultrasound guidance and anaesthesia) were found between studies. However, patient characteristics were generally poorly reported, especially with regard to cerebral palsy subtype (27%), comorbidities (38%), feeding method (35%), speech ability (19%), cognition (23%), and posture (8%). Additionally, there was great variety in outcome measurement across the included studies. A total of 25 unique scales and questionnaires were applied to assess the severity, frequency or impact of drooling. Moreover, a great variety in the definition of treatment response was identified.

Conclusions: This review shows heterogeneity in outcome measures and insufficient reporting of patient characteristics among studies on paediatric BoNT-A injections, limiting the ability to compare treatment effectiveness between submandibular and four-gland injections. These findings highlight the need for more extensive and uniform reporting of patient characteristics and the introduction of a core outcome measurement set, to eventually allow for comparison of results between studies.

Keywords:
Botulinum neurotoxin type-A, drooling, scoping review

EPNS23-2110 Oral
Neurodevelopmental Disorders

Digitalized support in the care of children and adolescents with fetal alcohol spectrum disorder

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Objective: Fetal alcohol spectrum disorder (FASD) is a highly prevalent, often undiagnosed, neuropaediatric disorder in Europe. Even though the diagnosis of FASD is facilitated by the German S3-guideline, there are still significant unmet needs in area-wide, easy accessible care structures and therapeutic tools for children with FASD. The aim of our project "German FASD COMPETENCE CENTER Bavaria" is to improve the knowledge of professionals and the care for children with FASD.

Methods: Existing digital tools for families and professionals caring for children with FASD in Germany were evaluated. Content correct tools for the support of children with FASD - at home and in clinical settings - were developed in an interdisciplinary team. Furthermore, structured educational modules for various, FASD relevant disciplines were established. The tools were evaluated by the users via online questionnaires (Lime Survey), and then further analyzed by Stata (Version 16). Other tools were assessed by the Institute for Information Systems (iisys) at Hof University via anonymous user statistics.

Results: Except for videos about FASD and non-interactive websites of different institutions, no specific digital tools for FASD existed in Germany. The interdisciplinary team at LMU University Munich in cooperation with the iisys Hof developed an interactive website with discipline-specific information for professionals and support for parents of children with FASD, a web app for the diagnosis of FASD, a "FASD Complexity Signature", an app for parents with children with FASD including an everyday rating of the behavior of the child and the quality of life of the family, and other digital tools. The overall satisfaction with the digital tools was good to very good. The dissemination of the tools is proving difficult. The best distribution was via congresses and professional societies.

Conclusions: The "German FASD COMPETENCE CENTER Bavaria" with its scientifically evaluated, interdisciplinary character is a pilot project in Munich that provides digital education for professionals, as well as digital support for families with children with FASD. Further amelioration of care for children with FASD and their families is urgently needed - in Germany as well as in the rest of Europe.

Keywords:
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EPNS23-2834 Oral or e-Poster
Neurogenetic Disorders

Rapid exome sequencing for children with severe acute encephalopathy - a case series

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Objective: The utility of next generation sequencing NGS and whole exome sequencing WES in the diagnosis of chronic neurological disorders such as epilepsy and intellectual disability is clear. Increasingly, NGS is becoming an invaluable tool in the diagnosis of acute neurological disorders where a monogenic etiology is not often suspected such as acute encephalopathy\encephalitis
Here, we describe a brief series of pediatric patients hospitalized with acute encephalopathy initially suspected to be of infectious or inflammatory origin but subsequently diagnosed with a monogenic disorder. Rapid and timely diagnosis informed clinical decisions in these cases.

Methods: WES was performed during initial hospitalization for three unrelated patients with severe acute encephalopathy referred by the pediatric intensive care unit (PICU) team at Rambam. All patients were of Muslim Arab descent with a history of consanguinity. The age range was 18 months - 3 years. All were previously healthy with reportedly normal development. One patient presenting with acute necrotizing encephalopathy (ANEC) had a sister who presented with ANEC one year prior.

Results: WES was diagnostic in all three cases. One patient had a homozygous pathogenic variant in MOCS2, c.3G>A p.(Met1Ile) associated with late onset Molybdenum cofactor deficiency B. A second patient harbored a homozygous likely pathogenic variant in NDUFS8 c.441G>C p.(Met147Ile). Surprisingly, the initial work-up including serum and CSF lactate levels were normal and MRI\MRS should nonspecific mid brain lesions with no lactate peak. . Brain imaging supportive of Leigh disease was evident only at a later stage. Finally, a likely pathogenic homozygous missense variant c.359T>C p.(Ile120Thr) in the DBR1 gene was identified in the patient presenting with ANEC which segregated as expected in the family. Interestingly, bi-allelic variants in this gene have been reported in 3 families with post viral brain stem encephalitis

Conclusions: While the cause of acute encephalopathy\encephalitis is often an acquired insult clearly a wide range of metabolic and genetic disorders can also present in this manner. Timely and urgent use of NGS can provide rapid diagnosis preventing extensive and expensive work up while directing initial treatment as well as informing decisions regarding long term care. As this case series demonstrates use of WES is shifting the paradigm of diagnostics even in critical care situations and should be considered early on in acute encephalopathy.

Keywords:
acute encephalopathy, whole exome sequencing. intensive care

EPNS23-2873 Oral or e-Poster
Neurogenetic Disorders

Phenotypic spectrum of FINCA disease associated with NHLRC2 variants

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Case study: Objectives: FINCA disease is a novel early-onset neurological and multiorgan disease named by its clinical and histopathological findings (Fibrosis, Neurodegeneration and Cerebral Angiomatosis, OMIM 618278). In the initial report in 2018, it was shown that FINCA disease is caused by pathogenic variants in the NHLRC2 gene encoding a protein with undefined function. We studied further the genotype-phenotype spectrum of FINCA disease in novel patients and NHLRC2 expression in human brain autopsy samples.

Methods: All the available clinical, laboratory and radiological data on novel FINCA patients from three centres was collected by this retrospective and prospective study. The patients were initially identified by whole exome sequencing revealing biallelic NHLRC2 variants and clinical features suggestive of FINCA disease. Studies on neuropathology and NHLRC2 expression in the brain were performed on the available autopsy samples of deceased FINCA patients and control samples.

Results: All the patients presented with developmental delay, hypotonia, recurrent infections, respiratory symptoms, and macrocytic anaemia associated with homozygous or compound heterozygous pathogenic NHLRC2 variants. Intellectual disability together with epilepsy was diagnosed in all alive patients, while liver or kidney dysfunction and decreased immunoglobulin levels were seen in individual patients. The eldest patient (61 years) also presents with neuromuscular phenotype and ataxia. Two patients died due to multiorgan failure in infancy. In autopsy samples the NHLRC2 expression was stronger in neuronal and glial cells in control brain, whereas interestingly, a higher expression was detected in the Purkinje cells of FINCA patients.

Conclusions: FINCA disease presents typically in infancy, and although patients can live to late adulthood, interstitial lung disease, recurrent infections and chronic anaemia can lead to early death. The characteristics of NHLRC2-related diseases, namely Fibrosis, Infection susceptibility/Immunodeficiency/Intellectual disability, Neurodevelopmental disorder/Neurodegeneration, and Chronic Anaemia/Cerebral Angiomatosis are summarised by the acronym FINCA. We suggest that the heterogenous spectrum of FINCA disease could depend on the loci of the rare damaging variants within the NHLRC2 gene and additional genetic and environmental factors, including exposure to infections. NHLRC2 has an essential role in the maintenance of multiorgan homeostasis in humans.

Keywords:
NHLRC2, FINCA disease, neurogenetic disorder, neurodevelopmental disorder, macrocytic anaemia

EPNS23-2994 Oral or e-Poster
Neurogenetic Disorders

CD59 deficiency: a very rare, potentially curable form of infection induced neuromotor regression

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Case study: Whole exome (WES) based gene panels caused a revolution in the diagnosis of rare genetic diseases. However, for the correct evaluation of found variants multidisciplinary interaction between geneticists, biochemists and clinicians remains of uttermost importance.
A 2,5-year-old girl presented to the outpatient clinic because of progressive walking problems. She was born as the first child of healthy consanguineous parents. The pregnancy was uneventful. Her early motor development was normal until the age of 15 months when she developed a viral upper airway infection with fever. When she recovered from the infection the parents noted that she lost the ability to stand without support. On clinical examination in a peripheral hospital ataxia was noted and the diagnosis of post viral cerebellar ataxia was made. She was treated with corticoids and intensive physiotherapy. However, this only brought minor improvements.
On first presentation at the pediatric neurology, we saw an active and reactive toddler with a wobbly gait and slow movements of the arms. She could only walk a few steps without support. Rossolimo's and Babinsky's signs were present but Achilles and patellar reflexes were rather weak. MRI of the brain and the spine were normal as well as a routine metabolic screening. Genetic testing with an inhouse Ataxia Spasticity gene panel returned normal. Yet, on reanalysis of the WES data a homozygous frameshift variant was found in CD59 (c.200_203del). CD59 can prevent C9 from polymerizing and forming the complement membrane attack complex. CD59 deficiency is known to cause the very rare hemolytic anemia with immune-mediated polyneuropathy, with neuromotor regression typically occurring during infections. The patient never suffered from hemolytic crises, but increased reticulocyte count and decreased haptoglobin were present on routine blood examination. Additionally, cytoflow demonstrated a complete absence of CD59 on the surface of red blood cells and thus conforming the pathogenetic nature of the mutations.
Eculizumab is a humanized antibody that inhibits the terminal pathway of complement by blocking the activation of C5. Several case reports suggested that eculizumab could ameliorate neuromotor function in patients with CD59 deficiency. Currently one year after start eculizumab the patient did not suffer from neuromotor regression anymore. Moreover, her muscle force and mobility ameliorated.

Keywords:
CD59 regression complement infection eculizumab

EPNS23-2890 Oral or e-Poster
Neurogenetic Disorders

Characterization of *CLTC*-associated seizures according to the location of genomic variants in functional domains of CLTC protein

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Case study: Background: Intellectual developmental disorder type 56 (MIM#617854) is a rare autosomal dominant condition with variable presentation of seizures. Twenty-eight patients have been described to carry a point mutation in *CLTC* gene.

Objectives and methods: We present 3 children with previously unreported variants in *CLTC* gene and seizures. We also reviewed the correlation between epileptic presentation and functional domains of CLTC protein in our patients as well as of those described in previously published studies.

Results: All our patients carried previously unreported heterozygotic likely pathogenic variants: P1: *CLTC* c.307dup (p.Thr103AsnfsTer4) - frame-shift duplication, P2: *CLTC* c.1947+1G>A (p.?) *de novo* - non-coding splicing variant, P3: *CLTC* c.2919G>C (p.Gln973His) *de novo* - missense variant. Our patients P1-P2 with 6 previously published patients with identified *CLTC* variants were classified to the group 1 with seizures meeting the diagnostic criteria for epilepsy (25.8% of all patients). Our patient P3 with 5 previously described patients were located in the group 2 with possible epilepsy (not meeting all diagnostic criteria for epilepsy) (19.4% of all patients). The group 3 without seizures consisted of 17 previously identified patients (54.8% of all patients). Most cases with clinical seizures (group 1-2) were associated with *CLTC* variants located in the CHCR5 and CHCR7 domains (7 patients), especially in CLC binding region (5 patients). Clinical presentation as absence seizures was typical for CHCR5 domain and as intractable seizures with West syndrome for CHCR7 domain. The *CLTC* variants in CHCR4 domain were related to early-onset focal seizures with good response to LEV and VPA treatment. Patients with transient neonatal seizures were carriers of the *CLTC* variants located in CHCR3 domain. Our patient P2 with West syndrome was the second identified patient with *CLTC* variant in CHCR2 domain. Among non-epileptic patients, none with the *CLTC* variant located in CHCR2 domain were identified. In non-epileptic patients, variants related to the CHCR3 domain dominated (38.5%). Our patient P1 with early-onset focal seizures was the first reported patient with *CLTC*-associated epilepsy to carry a variant located outside the heavy chain arm of CLTC protein.

Conclusion: Localization of CLTC variants in protein domains may be a good functional marker for predicting the risk of seizures and their further clinical course and response to antiepileptic treatment.

Keywords:
seizures, CLTC gene, CLTC protein, CHCR domains

EPNS23-2160 Oral
Neurogenetic Disorders

Immunotherapy - responsive childhood neurodegeneration with systemic and central nervous system inflammation - a 4th case?

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Case study: In 2018, Sa et al. described 3 infants with normal developmental milestones presenting subsequently with hemiparesis. MRI was notable only for contralateral hemispheric atrophy. There was a continuing downhill course up to complete paresis, dystonia, drooling, spasticity, and regression of speech. Repeat MRI showed atrophy of the 2nd hemisphere. Exhaustive workup was notable only for elevated neopterins in CSF and elevated expression of Interferon Signature Genes. Marked improvement was noted after immunomodulatory treatment was begun.
We present an additional case of an infant who developed normally up to 1.5 years. Then appeared Lt. hemiparesis with Rt. Hemispheric atrophy. Subsequently she was quadriplegic, spastic, with drooling and loss of speech. 2ND MRI showed Lt. brain atophy as well. Neopterin level was 330. ISGs were expressed 4 times above norm indicating an interferonopathy. Immunomodulatory treatment was begun.
We believe this is the 4th case of a new neuroinflammatory disease.

Keywords:
developmental regression,elevated neopterins,Interferon Signature

EPNS23-2900 Oral or e-Poster
Neurogenetic Disorders

KIF1A- related spastic paraparesis mimicking cerebral palsy- a case report

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Case study: Objective: Mutations in the KIF1A (kinesin family member 1A) gene are connected with a wide phenotypic spectrum of central and peripheral nervous system involvement (progressive encephalopathy, congenital contractures, spasticity, dystonia, dysautonomia, polyneuropathy, optic atrophy, learning/behavioural difficulties). We report a paediatric case with pure spastic paraparesis which was described mostly in adults.
Patient and results: A 21- year-old male with an unremarkable family history, positive perinatal history (caesarean section - risk of fetal hypoxia, but no asphyxia after delivery), normal psychomotor development was observed from the age of 3 years for gait disorder (clumsiness, frequent falls). Neurological examination showed mild central paraparesis of lower limbs with dystonic features. A detailed investigation was performed at the age of 3 and 7 years with normal results - blood tests, EEG, EMG, brain and spinal MRI, psychological examination, examination of inherited metabolic disorders, DNA analysis of genes associated with hereditary spastic paraplegia (SPG3, SPG4) and TOR1A gene. No progression was apparent and a diagnosis of cerebral palsy, diparetic form was established. From the age of 13 years he experienced gradual worsening of gait - slow speed, toe walking. The whole genome sequencing was performed at the age of 16 years and a heterozygous pathogenic de novo mutation c.452G>A (p.Cys151Tyr) in exon 6 of KIF1A gene was detected.
Conclusion: KIF1A-related spastic paraplegia is another hereditary disorder which can be misdiagnosed as cerebral palsy.

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Keywords:
KIF1A-related disorders, spastic paraplegia, cerebral palsy

EPNS23-2235 Oral or e-Poster
Neurogenetic Disorders

A patient with an HK1 gene variant leading to developmental and early epileptic encephalopathy, recurrent aspiration (feeding difficulties), absent corpus callosum and early death.

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Case study: The search for a diagnosis can be challenging for patients and families alike. The journey they go on is referred to as the diagnostic odyssey. For our patient -Q -, that search revealed a diagnosis after he died at eight months of age.
While an earlier diagnosis may not have altered the long term outcome for Q, it could have provided prognostic indicators, helped parents understand the condition and avoided more extensive investigations. Genomics is revolutionising how medicine is practiced. Sharing phenotypic information relating to genetic diagnoses helps expand knowledge around conditions. We share Q's story for this reason.

Q was diagnosed antenatally with an absent corpus callosum. He was born in poor condition requiring intubation and ventilation followed by ten days of CPAP. His neurological status was noted to be abnormal soon after birth. . Q was noted to be dysmorphic with slightly wide mouth and high arched palate, he had overlapping toes, and low central tone.
Around 3 days of life, Q had seizures and developed an early epileptic encephalopathy that was drug resistant. EEG confirmed a burst suppression pattern. MRI brain showed multiple periventricular germinolytic cysts in the frontal and parietal lobes with underdevelopment of the corpus callosum. Despite multiple anitseizure medications he continued to suffer multiple daily seizures and despite efforts to manage these and improve quality of life, Q continued to deteriorate and was transferred to a hospice where he died at eight months of age.

Q had significant gastrointestinal issues. He was noted to have an abnormal suck and no gag reflex after birth and was initially fed nasogastrically. He suffered recurrent aspiration, had extended periods dependent on parenteral nutrition and required a Roux-en-Y jejunostomy to allow enteral feeding.
Initial testing with microarray and epilepsy gene panels did not reveal any abnormality. The 100,000 genome project detected a heterozygous de novo mutation on Chromosome 10 - c.1370C>T p. (Thr457Met).
This specific mutation has been described previously in two siblings with anatomical brain abnormalities(atrophy, neuromigration) , seizures (infantile spasms and early myoclonic epileptic encepahlaopathy), marked feeding difficulties Both of these siblings however had optic atrophy, no evidence of dysmorphism and an unremarkable antenatal history

Keywords:
Genomics; HK1; Absent corpus callosum; seizures; diagnostic oddysey; c.1370C>T p.(Thr457Met)

EPNS23-2709 Oral or e-Poster
Neurogenetic Disorders

Deep phenotyping and genotyping in childhood-onset Hereditary Spastic Paraplegia

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Objective: To analyse the phenotype and genotype in a cohort of childhood-onset Hereditary Spastic Paraplegia (HSP) patients

Methods: We conducted a descriptive retrospective study of childhood-onset HSP cases actively followed-up in a tertiary Hospital from 2004 to 2022.
Family history, clinical presentation, neurological signs and symptoms, neurophysiologic data, neuroimaging, genetic test results and treatment were recorded and analysed. All patients underwent whole exome sequencing (WES), and 4 chromosomal microarray or multiplex ligation-dependent probe amplification (MLPA).

Results: 43 patients were included. The age of onset was 2.1y [0-11], being global and isolated motor developmental delay the most common presentations. 59% of patients had a pure form and 41% a complex one, being epilepsy and intellectual disability the most common comorbidities. More than 50% of patients had an abnormal brain MRI, most commonly involving the corpus callosum. Half of the patients received treatment for spasticity, most often botulinum toxin.
26/43 patients had a definitive genetic diagnosis. 24 were diagnosed through WES (2 of them after reanalysis) and 2 by MLPA. 13 patients had AD forms and 13 AR forms. Genes involved were: SPAST (n=4) , KIF1A (n=3); EPRS (n=2), ALDH3A2, DDHD2, ATP1A3, SARS1, SLC16A2, DLG4, POLR3A, KIF11, AMPD2, CYPU2, APZ51, RNASEH2B, TMEM106B, ALDH18A1, KIF5A, CTNNB1 and GJC2.

Conclusions: We describe a large cohort of childhood-onset HSP patients with emphasise in the high proportion of complicated forms in this age group.
The diagnostic yield of whole exome analysis was close to 60%. In comparison with adolescent and adult-onset HSP, the genetic aetiologies appear to be more heterogeneous and more often follow a recessive inheritance pattern.

Keywords:
HSP, spastic parapareis, WES, exome

EPNS23-2176 Oral or e-Poster
Neurogenetic Disorders

Primary coenzyme Q10 deficiency: a treatable cause of metabolic ataxia

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Objective: To report the biochemical, neuroimaging and molecular genetic findings relating to two patients with primary coenzyme Q10 deficiency.

Methods: Individuals with genetically confirmed primary coenzyme Q10 deficiency who harbored homozygous variant in COQ8A and COQ4A were recruited.

Results: We report two patients with ataxia, multisystem involvement (1 patient) and mitochondrial respiratory chain deficiency who were shown to have primary CoQ10 deficiency. MRI showed cerebellar atrophy in both patients. Treatment with coenzyme Q10 led to marked improvement in the symptoms in one patient and stabilization in the second patient.

Conclusions: This report expands the molecular genetic spectrum associated with primary coenzyme Q10 deficiency and highlights the importance of thorough investigation of candidate pathogenic variants to establish phase. Rapid diagnosis is of the utmost importance as patients may benefit from therapeutic CoQ10 supplementation.

Keywords:
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EPNS23-2642 Oral or e-Poster
Neurogenetic Disorders

Whole genome sequencing and variant discovery in 112 children with autism spectrum disorder

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Objective: Autism spectrum disorder (ASD) is a very heterogeneous genetic disorder. In whole genome sequencing (WGS) studies, only few genes presented strong evidence of ASD-association. Our objective was to perform a trio-WGS study in a cohort of patients with ASD to ascertain a molecular diagnosis and to discover new candidate genes.

Methods: We recruited 112 children with ASD (range 2.5-15-year-old) and their parents from outpatient clinics of a single centre for 18 months period. Eighty percent presented comorbidity with developmental delay (DD), intellectual disability (ID), or epilepsy. A specialized paediatric clinical team assessed their eligibility, and each family received a detailed genetic counselling consultation before recruitment. Fragile-X syndrome and copy number variants were ruled out in all patients before entering the study. Trio-WGS was performed on germline DNA, and variants were filtered and reported by extensive bioinformatic analysis. We validated candidate variants by Sanger sequencing or MLPA.

Results: We identified candidate variants in 15 patients (13.4%). Of those, 13 pathogenic or likely-pathogenic variants were associated to 12 phenotypes described with ASD features and comorbid DD/ID: ADNP, GNB1, POGZ, NF1, RORB, MECP2, ASXL3, PAH, ZNF292, KMT2E, SZT2 (2) and AGO1. Of those, six variants were novel, 10 were heterozygous de novo and two were inherited as autosomal recessive trait (PAH and SZT2). A recently immigrated 10-yo girl with severe ASD, ID and atonic seizures carried a homozygous frameshift variant in PAH. Untreated phenylketonuria was confirmed in this patient, since biochemical studies were performed in parallel. In three children (3/15), we found novel likely damaging variants in new candidate genes: ASTN1, STXBP5 and DSCAM. Remarkably, a girl with a homozygous variant in a splice site of ASTN1 presented with global developmental delay evolving to severe autistic traits, hypotonia, stereotyped hand movements and atypical absences; she died at 8-yo due to severe intracranial hemorrhage of unknown origin. The two children with STXBP5 or DSCAM heterozygous de novo stop codon variants both presented with autism features and language delay.

Conclusions: In our selected cohort with ASD, the diagnostic yield was low but comparable with recent studies using a similar methodology in single families (10-14%). Our results contribute to the documentation of new potential ASD-associated rare damaging variants and their related phenotypes in children with ASD.

Keywords:
autism spectrum disorder; whole genome sequencing; candidate variants

EPNS23-2932 Oral or e-Poster
Neurogenetic Disorders

AN INFANT WITH DUAL PHENOTYPE, COCKAYNE AND LEIGH SYNDROMES, REVEALED BY WHOLE GENOME SEQUENCING

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Case study: Objective: To describe a patient with a prompt diagnosis of Cockayne and Leigh syndromes, before the onset of typical symptoms, by whole genome sequencing (WGS).
Methods: A 3-month-old female infant with congenital bilateral cataract, borderline microcephaly, and mild hypotonia but without any syndromic features was referred for WGS (PCR-free, 30x). It was the third child of nonconsanguineous parents, with two older healthy children and an unremarkable family history.
Results: WGS identified a homozygous deletion 223kb on the 5q12.1 region encompassing the entire ERCC8 gene and exon 1 of the NDUFAF2 gene. Subsequent chromosome microarray analysis (CMA) confirmed the ERCC8 deletion but failed to detect the NDUDFA2-exon 1 loss. PCR designed to amplify NDUDFAF2-exon 1 indicated a homozygous loss in the child. Biallelic pathogenic variants on the ERCC8 gene are causative of Cockayne syndrome, characterized mainly by slow growth and development, cutaneous photosensitivity, a progeroid appearance, ophthalmologic disorders, sensorineural hearing loss, and severe progressive neurologic degeneration. Biallelic pathogenic variants on NDUFAF2 are associated with mitochondrial complex I deficiency leading to progressive encephalopathy, ataxia, hypotonia, optic atrophy, episodic respiratory insufficiency and neuroimaging consistent with Leigh syndrome.
Based on the WGS result, regular monitoring was scheduled. At three months of age, the MRI showed mild lateral ventricle asymmetry. Sensorineural hearing loss was also noticed and failure to thrive. The phenotype was attributed to Cockayne syndrome based on clinical and molecular characteristics. However, a workup was initiated towards Leigh phenotype due to increased serum lactate and molecular finding of NDUDFA2-exon 1 loss. A new MRI at the age of 10 months revealed extensive lesions in mesencephalic structures and the medulla oblongata, consistent with Leigh syndrome. The baby deceased at the age of 10 months due to cardiorespiratory arrest.
Conclusions: WGS led to a rapid and accurate diagnosis of Cockayne and Leigh syndromes revealing a homozygous deletion encompassing ERCC8 and part of the NDUFAF2 gene, altering the medical follow-up of the infant. If CMA (HD) had been applied alone, the genetic diagnosis of Leigh syndrome would have been missed. This case supports the favorable role of WGS in diagnosing rare neurological diseases; thus, it may be considered a first-tier test for rare neurological diseases.

Keywords:
whole genome sequencing, cockayne syndrome, Leigh syndrome

EPNS23-2882 Oral or e-Poster
Neurogenetic Disorders

Familial hypocalciuric hypercalcemia with seizure

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Case study: Familial hypocalciuric hypercalcemia(FHH) is known as a benign endocrine condition affecting parathyroid hormone and calcium levels. FHH is caused by mutations in the calcium sensing receptor gene. Here,we present a 5-month-old girl who was referred to the hospital with seizures and diagnosed with FHH. She was referred to hospital due to recurrent seizure. According to the anamnesis taken from the mother, she had a tonic seizure lasting 1-2 minutes accompanied by deviation in the eyes. Similar seizure had repeated 5 times in the last 2 days. There was no history of fever. There was no history of drug use. She was born by cesarean section at 37 weeks. Prenatal, natal and postnatal history was unremarkable. There is a first degree consanguinity between the parents.There is no family history of epilepsy or febril convulsion. She was breastfed. The child was admitted to the hospital for observation. In the observation, she had a short-term clonic seizure in the right arm once, midazolam was administered. Her neurological examination was normal. Her head circumference was normal. No features were found on physical examination. In laboratory tests blood glucose, sodium and magnesium levels were found to be normal. There was mild hypercalcemia. Metabolic tests were normal. The patient underwent a lumbar puncture and no cells or infection were detected. Cranial MRI and brain CT were reported normal. There was no epileptic discharge in sleep-activated EEG. Parathyroid tests and vitamin D levels were observed due to the relapse of the patient's seizures and the mild persistence of hyperclaemia. There was no finding other than hypercalcemia as the cause of the seizure. Upon detection of hypercalcemia in the examinations taken from the mother, genetic tests were sent. Mutations of the calcium-sensing receptor gene(CaSR) was found.

Keywords:
CASR gene, Hypercalcaemia; Hypocalcemia; Hypocalciuria; Seizure

EPNS23-2493 Oral or e-Poster
Neurogenetic Disorders

Expanding the phenotypic spectrum of NUS1-related disorder

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Objective: Heterozygous variants in the NUS1 gene have been related to epilepsy, ataxia, myoclonus, and developmental delay. By describing two patients with a non-classical presentation, we aim to expand the phenotypic spectrum of NUS1-related disorder (MIM#617831).

Methods: We describe the clinical features of twin brothers in whom a pathogenic variant in NUS1 was identified.

Results: The twins were born prematurely (33 weeks) after an uncomplicated pregnancy. There were no complications of prematurity. At the age of 10 months, both boys presented with prolonged febrile seizures. These recurred frequently, evolving to a status epilepticus requiring admission to the intensive care unit once for the eldest boy (patient 1). Development was within the normal range at the age of 1 year. Family history was negative for neurologic disorders. The initial EEG in patient 1 (age: 14 months) showed no abnormalities Initial genetic test results (whole-exome-sequencing (WES) gene panel fever-provoked seizures (incl 21 genes) and multiplex ligation-dependent probe amplification of SCN1A) were normal.
At the age of 21 months, the youngest boy (patient 2) developed brief generalized seizures and myoclonus. An EEG showed a normal background pattern with multifocal spike waves. WES gene panel epilepsy (incl ~450 genes) revealed a novel de novo pathogenic variant (c.15C>G p.(Tyr5*)) in the NUS1 gene in both brothers.
After the genetic test result, both boys were re-examined and videos were made of the movement pattern. On initial assessment, we were uncertain if they had a subtle ataxic gait or an age-compatible waddling gait. In a multidisciplinary assessment of the videos, involving movement disorder specialists, there was a consensus of slight gait ataxia and subtle myoclonus in the face and limbs.

Conclusions: These cases illustrate that NUS1 variants may present with atypical febrile seizures in the spectrum of generalized epilepsy with febrile seizures plus (GEFS+). Furthermore, they demonstrate the importance of follow-up, expanded genetic testing when new clinical features develop the value of multidisciplinary assessment of (videos of) movement disorders.

Keywords:
NUS1, febrile seizures, GEFS+, ataxia, myoclonus, movement disorders

EPNS23-2791 Oral or e-Poster
Neurogenetic Disorders

To test or not to test: the importance of genetics in the diagnostic workup of cerebral palsy

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Objective: Cerebral palsy (CP) is the most frequent cause of motor impairment in children. Perinatal asphyxia was long thought to be the leading cause of CP. However, studies have illustrated its causation in only about 10% of patients. Hence, the role of genetic factors has gained interest in the aetiology of CP. In this research project, we systematically performed genetic investigations in a paediatric CP cohort. By using this strategy, we aim to expand the knowledge regarding the contribution of genetic variants in the development of this disorder.

Methods: Medical files of 716 patients with CP were analysed for exclusion criteria: (1) extreme prematurity (<30 weeks postmentrual age); (2) history of perinatal asphyxia; (3) other aetiology (e.g. perinatal infection, trauma, etc.); (4) parental refusal of genetic test; (5) absence of parental blood samples for trio analysis. This led to the exclusion of 310 patients. In 337 out of the remaining 406 patients, both single nucleotide polymorphism array and exome sequencing were performed. In patients with a recognizable phenotype, targeted analyses were conducted. In the remaining 69 patients, analysis is still ongoing.

Results: A genetic disorder was diagnosed in 129/337 patients, resulting in an overall genetic diagnostic yield of 38.3%. A large proportion of these patients had 1 or more of the following comorbidities: intellectual disability/developmental delay, epilepsy, autism spectrum disorder. In this subgroup the diagnostic yield was even higher, namely 49.6%.
Overall, the most frequently affected genes were KIF1A (8/129, 6.2%) and COL4A1 (4/129, 3.1%). Other genes with variants in >1 patient were FRRS1L, MECP2, BRAF, TSEN54, DYRK1A, RNASEH2B and RNU7-1.

Conclusions: Genetic investigations in our CP cohort led to a diagnostic yield of 38.3%. This highlights the importance of genetic testing in CP. Diagnosing these disorders is crucial for the patient's prognosis and clinical follow-up, as well as genetic counselling.

Keywords:
Cerebral palsy, Exome sequencing

EPNS23-2887 Oral or e-Poster
Neurogenetic Disorders

Bi-allelic Pathogenic Variants in CASP2 Are Associated with Lissencephaly and Mild Intellectual Disability

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Case study: Objectives: Intellectual disability (ID) is clinically and genetically heterogenous and associated with different groups of neurodevelopmental disorders. Lissencephaly (LIS) is one of the malformations of cortical development (MCDs) occurred due to deficient neuronal migration and abnormal formation of cerebral convolutions or gyri matter. Thin pachygyria or thin lissencephaly (TLIS) is a subgroup of LIS. Up to date a total of 31 LIS-associated genes were reported. In this report we described a case who has mild ID, diffuse lissencephaly and pachygyria associated with CASP2 mutation.
Method and Case: 7 years 10 months female- patient was firstly admitted to child neurology outpatient clinic with complaints of delayed speech, hyperactivity and attention disorder and inability of some motor activities. There was a first-degree consanguinity between her parents. Physical and neurological examination was normal except for hyperactivity and minimal motor disability. EEG showed two different epileptiform activity which originated from right fronto-central region and fronto-temporal area. Brain MRI revealed diffuse lissencephaly and pachygyria on fronto-temporo-parietal region. Whole exome sequence analysis (WES) for proband and sanger sequencing for segregation of the variant in proband's family were performed. She is now 10 years old; she can fluently speak and can consecutively say sentences. There is improvement in hyperactivity. Also, Na-valproate therapy has been decreased.
Result: A homozygous frameshift mutation c.1156delT in exon 13 of CASP2 (NM_032982.4) predicting a premature stop codon p.Tyr386Thrfs*25 was found at WES analysis of proband. Sanger sequencing confirmed that none of the other healthy family members had the mutation at homozygous state.
Conclusions
The CRADD gene encodes a protein which is essential for activation of caspase-2-mediated programmed cell death. Loss of CRADD function causes mild or moderate ID or global developmental delay, megalencephaly, frontal predominant pachygyria and seizures. In 2016 , Di Donato et al reported six cases of TLIS variant with megalencephaly and ID due to loss of CRADD function and then the phenotypic variability associated with CRADD variant was reported in 22 Finish patients. To our knowledge this is the first report of association of CASP2 gene with ID and pachygyria in a patient.

Keywords:
CASP2; pachygyria; lissencephaly; Intellectual disability; speech delay

EPNS23-2175 Oral or e-Poster
Neurogenetic Disorders

Pontocerebellar hypoplasia type 9: tissue loss and gliosis in both thalami as predominant radiological finding

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Case study: Objectives: Pontocerebellar hypoplasia (PCH) type 9 is a rare neurogenetic disorder caused by a homozygous pathogenic variant in AMPD2, with around 20 to 30 reported cases worldwide. This subtype of PCH is usually characterised by a severe delay in psychomotor development, progressive microcephaly, spasticity and seizures. Typical findings on central imaging are a hypoplastic pons and cerebellum, hypoplasia or absence of the corpus callosum and a characteristic 'figure 8' shape of the midbrain on axial imaging. Here, we describe a case with thalamic lesions as predominant finding on brain MRI, hereby expanding the phenotypic spectrum of PCH type 9.

Methods: Our case is a boy presenting at the age of four months old with developmental delay, uncoordinated eye movements, feeding difficulties and microcephaly (Z-score -3.09). His first brain MRI showed partial agenesis of the corpus callosum and mild atrophy of the mesencephalic region. Over the years, his condition deteriorated and he developed peripheral hypertonia and pronounced epilepsy. Repeated central imaging confirmed the partial agenesis of the corpus callosum, showed generalised tissue loss of the cerebral white matter and aberrations in the periventricular white matter, but also revealed a striking T2 hyperintense signal in both thalami due to tissue loss and gliosis. Because of the complexity of his condition, a genetic disorder was highly suspected. Genetic investigations were performed using microarray, a panel for malformations of cortical development and an exome sequencing based gene panel for intellectual disability and cerebral palsy.

Results: All genetic investigations initially returned normal. However, at the age of 5 years, a reanalysis of the exome data was performed, which revealed a previously reported homozygous pathogenic variant in the AMPD2 gene c.1132C>T (p.Arg378Trp) (NM_004037.7).

Conclusions: This case expands the phenotype of PCH type 9 with striking T2 hyperintensities in the thalamus, due to tissue loss and gliosis, as predominant finding on central imaging. A mitochondrial disorder was initially suspected, however this was ruled out by additional metabolic testing. The diagnosis of PCH was quite unexpected, since the underdevelopment of the cerebellum was not very apparent and the typical 'figure 8' configuration of the midbrain could not be seen. Furthermore, this case illustrates the importance of reanalysing genetic data in children with a suspected genetic disorder.

Keywords:
Pontocerebellar hypoplasia, AMPD2

EPNS23-2267 Oral or e-Poster
Neurogenetic Disorders

CAN SEVERE MICROCEPHALY (< 6 SD) BE A GOOD CLINICAL INDICATOR OF DISEASE SEVERITY AND FUNCTIONALITY OF SEQUENTIAL VARIANTS IN PATIENTS WITH *KIF-11*-RELATED CONGENITAL MICROCEPHALY?

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Case study: Background: Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation syndrome (MCLMR) is a rare autosomal dominant neurodevelopmental disorder with variable expressivity. Ninety-six patients have been described to carry a point mutation in *KIF11* gene.

Objectives and methods: We present 2 MCLMR patients with previously unreported variants in *KIF11* gene. We also reviewed the correlation between clinical phenotypes and functional domains of KIF11 protein according to degree of microcephaly (group 1 - microcephaly < SD 6.0; group 2 - microcephaly ≥ SD 6.0) in our patients as well as of those described in previously published studies.

Results: In our patients we identified two previously unreported heterozygotic variants *de novo*: P1: *KIF11* c.1294_1296del (p.Glu432del) - VUS in-frame deletion in highly conservated region with prediction to be pathogenic and P2: *KIF11* c.1009dup (p.Ser337PhefsTer8) - likely pathogenic frame-shift duplication in highly conservated region. Our 2 patients with 22 previously published patients with identified *KIF11* variants were classified to the group 1 with the severest degree of microcephaly (24.5% of all patients). Seventy-four previously published *KIF11*-related MCLMR patients were located in the group 2 with milder degree of microcephaly (75.5% of all patients). In the group 1 dominated frame-shift and stop-codon *KIF11* variants (29% and 25% respectively). Only 2 missense *KIF11* variants (8.3%) were identified in this group. Fifty-nine percentage of all variants in the group 1 were located in main functional domain of the *KIF11* protein - the kinesin domain. There was a slightly advantage of frame-shift *KIF11* variants in the group 2 with quite equal amount of other types of *KIF11* variants (41% - frame-shift; 21.6% splice/donor site; 20% stop-codon; 16.6% missense). Forty-five percentage of all variants in the group 2 were located in the kinesin domain. There was a higher incidence of coexistence of clinical symptoms triad in patients in the group 1 (group 1: ID 87.5%, retinal changes 79.2%, lymphoedema 58.3% vs. group 2: ID 74.3%, retinal changes 58.1%, lymphoedema 51.3%).

Conclusion: Severe microcephaly (< 6.0 SD) in *KIF11*-related MCLMR patients may be a good clinical marker to predict the location of variants in functional protein domains, as well as to assess the risk of developing intellectual disability and retinal changes in the further clinical course of the disease.

Keywords:
congenital microcephaly, intellectual disability, KIF-11 gene

EPNS23-2981 Oral or e-Poster
Neurogenetic Disorders

Identification of *LAMA1* mutation in a patient with presumed Joubert syndrome

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Case study: OBJECTIVES

Poretti-Boltshauser syndrome (PTBHS) (OMIM #615960) caused by mutations in *LAMA1* is a rare neuro-ophthalmological disease mostly labeled as Joubert syndrome with phenotype featuring delayed motor and language development, non-progressive cerebellar ataxia, intellectual disability and eye involvement without molar tooth sign as a neuroimaging distinctive feature. We reviewed the data of a patient with clinical diagnosis of Joubert syndrome but negative genetic analysis.

METHODS

We present a 19 year-old- boy of healthy non consanguineous caucasian parents, who was diagnosed as Joubert syndrome during the first years of life. He started with abnormal eye movements followed by global developmental delay and non-progressive cerebellar ataxia. No kidney, liver and heart abnormalities. Brain MRI performed at 2 years of age showed cerebellar dysplasia with vermis hypoplasia. Neurocognitive evaluation showed borderline intellectual functioning. Initial symptoms have been improving over time so he didn't have medical supervision. After a few years the family restarted the follow-up. MRI was repeated with evidence of the same findings. We appreciate compatible initial clinical symptoms but atypical radiological features and clinical evolution for Joubert syndrome.

RESULTS

A genetic analysis using a next-generation sequencing 35 genes panel associated with Joubert syndrome was negative. Filtering of variants was adjusted to examine all rare variants within the exome dataset and this identified two likely pathogenic deletions in *LAMA1*, comprising exons 52 to 63 and exons 2 to 3 and confirmed by parent's segregation study.

CONCLUSION

PTBHS syndrome could overlap clinical but not radiologically with Joubert syndrome. *LAMA1* needs to be considered within the spectrum of atypical evolution of Joubert syndrome.

Keywords:
Poretti-Boltshauser syndrome, LAMA1

EPNS23-2982 Oral or e-Poster
Neurogenetic Disorders

Strategy for Diagnosis of Neuronal Ceroid Lipofuscinoses

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Objective: The Neuronal Ceroid Lipofuscinoses (NCLs) are a group of inherited neurodegenerative disorders that affect children and adults. They are grouped together by similar clinical features and the accumulation of auto-fluorescent storage material. Enzyme deficiency NCLs are caused by genetic mutations resulting in enzyme deficiency leading to lipopigment accumulation and / or protein dysfunction necessary for cell mechanisms in nerve and other tissues. More than a dozen genes containing over 430 mutations have been identified to cause at least 13 known types of NCLs. The clinical differential diagnosis of the NCL types is based on age of onset, clinical phenotype, ultra-structural characterization of the storage material and enzyme levels. Symptoms associated with these disorders can vary widely. Although protein dysfunction or lipopigment accumulation influences many cells, brain cells are typically affected first. Clinical presentations include vision loss, epilepsy and myoclonic epilepsy, dementia, speech loss, movement disorder, behavior problems and learning disabilities and problems.

Methods: Our medical laboratory has developed, validated and accredited novel diagnostic panel for differential diagnosis of NCLs utilizing single Dried Blood Spot (DBS). Our assay includes testing for NCL1 and NCL2.

Results: Here we are presenting data from high-risk population screening of over 580 cases suspicious of NCL1 and NCL2 from over 20 countries where we measured enzyme activity for palmitoyl protein thioesterase 1 (PPT1) and tripeptidyl-peptidase 1 (TPP1), followed by confirmatory genetic testing for over 60 cases. 27 cases were submitted for PPT1 genetic confirmation, and 6 patients were diagnosed. 37 cases were submitted for TPP1 genetic confirmation with final diagnosis for 25 patients.

Conclusions: The presented data underlines the benefit of a fast and reliable diagnostic work-flow for NCLs suspected individuals.

Keywords:
Neuronal Ceroid Lipofuscinoses (NCLs), enzyme deficiency, DBS

EPNS23-2841 Oral or e-Poster
Neurogenetic Disorders

Expanded clinical spectrum of CSTB mutations: severe encephalopathy with acquired microcephaly, progressive volume loss and white matter degeneration

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Objective: CSTB mutations cause Unverricht-Lundborg disease or progressive myoclonic epilepsy-1A (EPM1A). Our aim is to report two patients with a severe neurodegenerative phenotype carrying homozygous null mutations in CSTB.

Methods: Descriptive study of two pediatric patients followed at the Metabolic Unit of a tertiary hospital. Clinical features, neuroimaging and genetic data were analyzed.

Results: We report two unrelated Caucasian patients borned to healthy parents residing in an island territory. Patient 1: 10 year-old female with unremarkable perinatal history. At 6 months of age, she developed seizures. V-EEG showed bilateral multifocal spikes with background slowing. Acquired microcephaly (-3 SD) is noted at 2.5 years of age. Physical examination showed axial hypotonia and appendicular spasticity, language abilities were not achieved. Comprehensive metabolic assessment was normal. Serial brain MRI showed, cortico-subcortical cerebral atrophy with hypomyelination, dysgenesis-atrophy of the corpus callosum and widening of the cerebellar folia. Patient 2: 21-month-old female with perinatal history of intrauterine growth retardation and preterm birth. Developmental delay was observed since the first months, associated with microcephaly, dysmorphic features, dysphagia and neurosensory hypoacusis. Examination revealed poor eye contact, axial hypotonia, spasticity, and dystonic movements of the limbs and mouth. No clinical seizures have been registered to-date, although EEGs revealed epileptiform abnormalities. Brain MRI at 5-months of age showed cortical atrophy. On subsequent imaging, white matter volume loss and diffuse thinning of the corpus callosum was present.
Exome sequencing reported a homozygous variant in CSTB gene affecting splicing (c.67-1G>C) in both patients. Parents were heterozygous carriers.
The variant has been previously described in compound heterozygosis with the unstable expansion allele, in EPM1A and a milder phenotype. Functional analysis of the c.67-1G>C variant have suggested null mRNA and protein expression.

Conclusions: Severe early-onset encephalopathy related to CSTB mutations expand the clinical spectrum beyond EPM1A. Isolated cases have been previously reported associated to null mutations in CSTB, supporting a genotype-phenotype correlation. CSTB variants should be considered in infants presenting with unexplained severe neurodevelopmental delay, dyskinesias, and acquired microcephaly with grey and white matter degeneration.

Keywords:
EPM1A, CSTB, microcephaly, white matter degeneration, encephalopathy, severe neurodevelopmental delay

EPNS23-2804 Oral or e-Poster
Neurogenetic Disorders

An escalating continuum of learning and attention difficulties from premutation to full mutation in female carriers of FMR1 expansion

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Objective: Carriers of Fragile X premutation may have associated medical comorbidities, such as Fragile X Associated Tremor and Ataxia (FXTAS) and Fragile X Associated Premature Ovarian Insufficiency (FXPOI). We examined the Fragile-X premutation effect on cognition and we assumed that there is a direct correlation between the continuous spectrum of specific learning and attention deficits to the number of CGI repeats on FMR1 gene.

Methods: 98 women were referred to our center due to a related Fragile X Syndrome (FXS) patient, 79 women carried a premutation of 56-199 repeats and 19 women carried a full mutation of more than 200 CGG repeats on the FMR1 gene. Genetic results of CGG repeats, demographic information, structured questionnaires for ADHD, learning disabilities of language and mathematics, and independence level were analyzed in females carrying FMR1 premutation and compared to the group carrying the full mutation. Females with fully symptomatic FXS were excluded.

Results: When analyzed as a continuum there was a significant increase in the following complaints which are correlated with higher number of repeats: labor difficulties and C-Section, FXPOI, not being able to drive a car, ADHD severity, learning disabilities and specifically language difficulties, dyscalculia, inattentiveness, spelling difficulties, executive dysfunction. When observed within the premutation group as compared to the full mutation group, a linear correlation was found between FXPOI, ADHD, spelling and organization skills to number of CGG repeats. Distractibility correlated inversely with CGG repeats.

Conclusions: ADHD and learning difficulties correlate with increased number of CGG repeats and are common features of premutation and of full mutation in carrier females.

Keywords:
Fragile X, permutation, females

EPNS23-2174 Oral or e-Poster
Neurogenetic Disorders

Further characterization of SERAC1-related neurophenotype

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Objective: Background. MEGDEL syndrome is an autosomal recessive disorder caused by SERAC1 variant, clinically characterized by psychomotor delay or regression, hypotonia, sensorineural deafness, 3-methylglutaconic aciduria, and Leigh-like lesions on brain MRI.

Objective. To report three new patients with MEGDEL syndrome, their clinical phenotype, and genotype-phenotype correlation.

Methods: Individuals with genetically confirmed MEGDEL syndrome who harbored homozygous variant in SERAC1 gene were recruited.

Results: Three patients were analyzed, whose multisystem dysfunctions, including an elevated 3-MGA concentration in early age, transient liver impairment and Leigh-like syndrome as determined by MRI, were consistent with MEGDEL syndrome. Two novel mutations in the SERAC1 gene were identified.

Conclusions: The individuals presented here expands the clinical spectrum with early detectable basal ganglia lesions and extends the genetic spectrum.

Keywords:
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EPNS23-2169 Oral or e-Poster
Neurogenetic Disorders

Two Siblings with Spinocerebellar Ataxia Autosomal Recessive Type 14; Case report

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Case study: Introduction: Spinocerebellar ataxia (SCA) is a neurodegenerative genetic disease group that can involve brain stem-related regions and cause ataxia resulting from progressive degeneration of the cerebellum. Its prevalence is estimated 3/100000. Homozygous loss of function mutations in SPTBN2 gene have been associated with early-onset cerebellar ataxia and developmental delay (Spinocerebellar ataxia autosomal recessive type 14 / SCAR 14).

Case: A 17-year-old male was admitted to the outpatient clinic due to slurred speech since 14. His prenatal and natal history was unremarkable. But his healthy parents were first-degree cousins. He had said his first word at age two and started making sentences and walking at age three. When he was four years old, it was noticed that he was walking with a broad base. On physical examination, dysarthric speech, titubation, hyperactive deep tendon reflexes in the lower extremities and broad-based ataxic gait were detected. He had dysdiadokinesia and intentional tremors. Complete blood count and biochemistry were within normal limits. Cranial magnetic resonance imaging (MRI) showed marked atrophy of the cerebellar hemispheres. It was observed that her 33-year-old sister, who was followed up with the diagnosis of cerebral palsy, had similar complaints and similar cranial MRI findings. Whole-exome sequencing of two siblings were homozygous for a novel variant in the SPTBN2 gene (c.682-683 del p. Leu228Glufs chr11:66481191), and their parents were carriers for this mutation. The diagnosis of SCAR14 was genetically confirmed.

Conclusion: In a patient with a family history of cerebellar ataxia, genetic testing is the most effective and definitive way to identify the ataxia subtype. In recent years, with the widespread clinical use of next-generation sequencing, genes and mutants underlying SCA, as well as affected phenotypes, have been identified.

Keywords:
Ataxia, Genetic, Childhood

EPNS23-2808 Oral or e-Poster
Neurogenetic Disorders

Electroclinical features of epilepsy in Kleefstra syndrome

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Case study: Background: Kleefstra syndrome or 9q34.3 microdeletion syndrome is a rare genetic disorder caused by a microdeletion in 9q34.3 or pathogenic variants in the euchromatin histone methyltransferase 1 gene (EHMT1, *607001). The syndrome is characterized by intellectual disability, hypotonia, and dysmorphic facial features. Autism spectrum disorder, severe language impairment, and sleep disorders have also been described. To note, although epilepsy has been documented in about 20-30% of subjects, a detailed description of epileptic features and underlying etiology is still lacking.
Methods: We conducted a retrospective multicenter study to investigate eight patients with genetically confirmed Kleefstra syndrome and epilepsy.
We examined available data concerning clinical and genetic features, type of epilepsy, EEG characteristics, pharmacological treatments, and the severity of the developmental delay. We compared patients with early-onset epilepsy with those with later onset evaluating the probability of suffering from frequent seizures, developing drug resistance, and showing a severe developmental delay. The association between the developmental delay and, respectively, the seizure frequency and drug resistance have been tested. Then, our results were compared with the literature data.
Results: We included eight patients with 9q or 9q34.33 deletions, a complex translocation involving EHMT1, and pathogenic EHMT1 variants. All patients had moderate to severe developmental delay, language impairment, microcephaly, and infantile hypotonia. Regarding epilepsy, most patients experienced focal seizures. The seizure frequency differs according to the age of epilepsy onset, with patients with early-onset epilepsy presenting more frequent seizures. An overtime reduction in seizure frequency, as well as in anti-seizure drug number, was observed in all patients.
Conclusion: epilepsy is a frequent finding in Kleefstra syndrome. Patients show clinical improvement during life with reduced seizure frequency and required medications.

Keywords:
Kleefstra syndrome, epilepsy, neurodevelopmental disorder, EHMT1

EPNS23-2136 Oral or e-Poster
Neurogenetic Disorders

PERSEUS STUDY: Clinical trial in children with Down Syndrome of the Tolerance and Preliminary Efficacy of EGCG on their cognitive and adaptive performance.

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Objective: Epigallocatechin gallate (EGCG) is a green tea extract, inhibitor of the DYRK1A gene overexpressed in Down Syndrome (DS) and involved in cognitive difficulties. A study in young adults with DS showed that the administration of EGCG slightly improves some cognitive functions. Early administration of EGCG, especially in children, allows us to hope for a more significant improvement in cognition. The toxicity of high dose EGCG on hepatic and cardiac functions led us to conduct a study on tolerance and safety associated with the study of cognitive and adaptive performance in children with DS.

Methods: Prospective, double-blind, phase Ib, placebo-controlled study. 73 children with DS aged 6 to 12 years were randomized. Participants received EGCG 0.5% (daily dose of 10 mg/kg in 2 doses) or placebo for 6 months, with a follow-up 3 months after treatment discontinuation. Tolerance and safety were measured using blood markers, cardiac assessments, electroencephalograms and hetero-questionnaires. Cognitive and adaptive functions were measured by neuropsychological assessments and hetero-questionnaires.

Results: A total of 72 children were treated and 66 completed the study.
38 participants were included in the EGCG group and 35 in the placebo group. In the EGCG group, there were no serious adverse events (AEs) or increased incidence of AEs.
No statistically significant and consistent differences were observed at 6 and 9 months for cognitive and functional assessments in favor of EGCG.

Conclusions: The use of EGCG is safe and well tolerated in children with DS, but efficacy results do not support its use in this population.
The easy-to-administer FontUp 'placebo' product behaved like an active placebo because it contains omega-3 fatty acids and trace minerals
Cognition measurement tools, the significant placebo effect, and the search for biomarkers are the challenges for future studies on cognition in children with Intellectual disability.

Keywords:
clinical trial-Children with Down Syndrome-EGCG

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Neurogenetic Disorders

Cerebral creatine deficiency syndrome with a novel missense variant in SLC6A8 gene

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Case study: Cerebral creatine deficiency syndromes are three metabolic diseases characterized by loss of function in three proteins (GATM, GAMT, SLC6A8) that required in creatine synthesis pathway and transport. A 12-year-old male patient was referred with the diagnosis of cerebral creatine deficiency syndrome guided by intellectual disability, epilepsy, expressive dysphasia, autistic features, urinary metabolite measurements and MRI-Spectroscopy findings. A new de-novo hemizygous likely pathogenic missense (NM_005629.4 : c.1400T>G, p.Met467Arg) variant in the SLC6A8 gene was identified in the patient. The variant was not found in ClinVar and population databases, it alters the physicochemical properties of the amino acid, the region is moderately conserved across species and in-silico prediction tools consistently emphasize pathogenicity. Molecular analysis is recommended as it confirms clinical diagnosis, guides treatment, allows appropriate genetic counselling.

Keywords:
creatine, SLC6A8, intellectual disability, epilepsy

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Neurogenetic Disorders

Clinical and laboratory findings in the first published Czech patient with autosomal recessive spastic ataxia Charlevoix-Saguenay (ARSACS)

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Case study: Objectives: ARSACS is a neurodegenerative disease caused by mutations in the SACS gene for sacsin. The main clinical symptoms are slowly progressive spasticity, cerebellar ataxia and polyneuropathy. Specific retinal optic nerve hypermyelinization can be detected by optical coherence tomography (OCT). Sacsin is probably involved in controlling microtubule balance and mitochondrial connectivity in neurons. The contribution provides detailed information about the first patient with ARSACS in the Czech Republic.
Methods: Comprehensive clinical data, including results of brain MRI, electromyography (EMG), and OCT, were collected. Results of exome analysis were confirmed by Sanger sequencing in the DNA of the patient and both parents. Enzyme assay of respiratory chain and coenzyme Q10 concentration assessment were performed in isolated lymphocytes.
Results: After uncomplicated delivery patient's motoric development was borderline with independent walking at 16 months. Physiotherapy and neurologic follow-up were started at 2 years for clumsiness. Despite complex care, patient's dyscoordination proceeded, and mild spasticity and dystonia appeared during school age with attacks of paroxysmal kinesiogenic dyskinesia during adolescence. The patient's intelligence is above average. Brain MRI revealed nonprogressive frontal and temporal arachnoidal cysts in the left hemisphere and mild thinning of the corpus callosum. Results of karyotype, DNA analysis of Friedreich ataxia, examination of inherited metabolic disorders, and DNA analysis of genes associated with dystonias were normal. Exome sequencing detected variants in the SACS gene: a pathogenic variant c.922C>T (p.Leu308Phe) inherited from mother and two variants of unknown significance (VUS) c.11485C>A (p.Pro3829Thr) and c.7487T>C (p.Leu2496Pro) inherited from father. EMG confirmed chronic demyelinizating polyneuropathy, OCT retinal optic nerve hypermyelinization with normal vision. Normal enzyme activities of complexes I-IV of respiratory chain with decreased COX/CS ratio and coenzyme Q10 deficiency in the isolated peripheral lymphocytes were detected.
Conclusion: Comprehensive evaluation of all data suggests a diagnosis of ARSACS in the patient. The causality of paternal VUS is supported by the fact that the most of the SACS gene mutations are private and especially by specific OCT findings. In agreement with literary sources, signs of mitochondrial dysfunction were found.

RVO VFN64165, Cooperatio

Keywords:
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Neurogenetic Disorders

A novel pathogenic WDR45 variant in male patient and male/female different phenotype spectrum

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Objective: The WDR45 gene is localized on the X-chromosome and variants in this gene are associated with different neurodegenerative disorders - beta-propeller protein associated neurodegeneration, Rett-like syndrome, intellectual disability, epileptic encephalopathies, and also malignancies. The phenotypic spectrum ranges between males and females, very likely because WDR45 is X-chromosome linked. The exact cellular function of WDR45 still remains unknown, but its variants can lead to macroautophagy/autophagy defects, malfunctioning mitochondria, endoplasmic reticulum stress and unbalanced iron homeostasis.

Methods: We present two new cases of de novo WDR45 variants.

Results: Patient 1 is an 11-year-old boy with profound developmental delay, spastic quadriparesis, and intractable epilepsy. The patient was first noted to have a developmental delay at 4 months. At the age of 9 months he developed seizures (atypical absence and spasms). Brain MRI showed delayed myelinization, but no iron accumulation. EEG revealed features of epileptic encephalopathy with frequent epileptic discharges and brief tonic seizures. Despite various antiseizure medication (ASM) and implantation of vagus nerve stimulation, frequent seizures persisted until the age of 9 years. The patient was investigated extensively, but only whole-exome sequencing demonstrated novel de novo pathogenic variant c.973+1G>A in the WDR45 gene. At present, seizures occur sporadically, the main clinical presentation includes spasticity and severe developmental delay.

Patient 2 is a 5-year-old-girl who initially presented at the age of 6 months with developmental delay and hypotonia. Subsequently, dysmorphic, Rett-like features and also gait disturbances were observed. At 2 years of age tonic and clonic seizures started. She was treated with ASM although no obvious abnormality was found on EEG. She also developed non-epileptic seizures with kicking and smiling. Brain MRI showed mild hypersignal T2 changes around IV. ventricle and temporal horns of lateral ventricles. Only at the age of 4 her EEG revealed encephalopathic graph with multifocal discharges. Next-generation sequencing confirmed variant c.436+5G>A in the WDR45 gene.

Conclusions: This report decribes two patients with de novo variants in the WDR45, one of them being novel and one being previously reported. Our results expand the variant spectrum of WDR45 and the phenotypic characteristics of this X-linked dominant neurodegenerative disease.

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Keywords:
WDR45, epilepsy, developmental delay

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Neurogenetic Disorders

Phenotypic and genetic landscape in MECP2-point mutations in males

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Objective: Methyl CpG binding protein 2 (MECP2) is a multifunctional gene with variable expression located at Xq28. Hemizygous MECP2-mutations in boys may cause a broad clinical range in a low incidence, so the clinical diagnosis is challenging. We aim to study the male?s phenotype of MECP2-mutations and its relationship with males and mother's? genotype and protein quantification

Methods: We performed a retrospective study reviewing medical records of males with MECP2-point mutations detected by clinical exome sequencing (CES), excluding MECP2 duplication syndrome. We conducted functional studies of MeCP2 protein quantification in patients and mother's fibroblasts. We compared our results to those described in the scientific literature.

Results: Ten male subjects were included, aged between 2 to 23 years old. The phenotypes identified were X-linked intellectual deficiency (XLMR13) (n=4), severe neonatal encephalopathy (n=3) and pyramidal signs, parkinsonism, and macroorchidism (PPM-X) (n=2). We described one case with an aberrant expression of MeCP2 and an atypical presentation: early-onset West syndrome. In our study, the XLMR13 mean age of onset was 1.7 years-old with a global neurodevelopmental delay, while the mean age of the MECP2 variant diagnosis was at 12.2 years old (from 12 months to 21 years old). Two of the four XLMR13 patients had epilepsy, and three of the four XLMR13 cases had a significant familiar history. Our severe neonatal encephalopathy cases were similar as the literature, highlighting one of them that suffered from severe Ondine syndrome. We described two PPM-X cases with different guide signs: extrapyramidal signs and psychiatric manifestations; the onset of one of them was a psychotic episode during adolescence. The most common MECP2 variants were missense with low ranges of MeCP2 quantification, and we detected punctual deletions and duplications that result in truncated proteins. Maternal inheritance was identified for missense variants and de novo for nonsense.

Conclusions: We have identified in the cohort three phenotypes previously described, corresponding to: XLMR13, severe neonatal encephalopathy, and PPM-X. We identified a wide clinical spectrum within our cohort, showing overlapping phenotypes. MeCP2 expression studies are needed to evaluate the pathogenicity of new MECP2 variants. We highlight the significance to be aware of the MECP2 phenotypes to establish an early clinical diagnosis and may benefit from a personalized treatment.

Keywords:
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Neurogenetic Disorders

Fatal neonatal Hepathopathy with severe Hypoglycaemia, Hyperammonaemia and Lactic Acidosis: A novel phenotype of COASY deficiency

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Case study: Objectives: Coenzyme A (CoA) is a central cofactor of cellular metabolism. The final two steps of CoA *de-novo* synthesis are catalysed by the bifunctional CoA synthase (COASY). Pathogenic biallelic variants in COASY have been reported in 5 families with COASY protein-associated neurodegeneration (CoPAN): three presenting with early onset neurodegeneration with brain iron accumulation (NBIA) and two with lethal pontocerebellar hypoplasia, microcephaly, and arthrogryposis. Herein, we present a male patient with fulminant and early-onset hepatopathy with hypoglycaemia, hyperammonaemia and lactic acidosis (HHHLA) who died at the age of 6 days due to progressive multiorgan dysfunction.
Methods: Autoptic material was analysed in standard and immunohistochemical stains. Candidate *COASY* variants were identified by whole exome sequencing (WES) and verified by Sanger sequencing. Content and activity of COASY were measured in fibroblasts by SDS-PAGE, immunoblotting, and reversed-phase high performance liquid chromatography. Mitochondrial functions were assessed in isolated mitochondria by spectrophotometry and respirometry using Agilent Seahorse XF24 Analyzer according to standardized procedures.
Results: Autopsy findings were nonspecific. Brain edema and reduction of white matter with periventricular leukomalacia dominated the pathology of central nervous system. Liver histopathology showed diffuse loss of hepatocytes and cholestasis. Two novel pathogenic *COASY* variants were identified by WES. While c.612C>G (p.His204Gln) variant compromised the predicted active site of the COASY 4'-phosphopantetheine adenylyltransferase domain, c.1485+1G>T (p.Lys464Cysfs*12) resulted in skipping of exon 7 and nonsense-mediated decay of the *COASY* transcript. No enzymatic COASY activity was detected in the patient's fibroblasts which corresponded to minimal amounts of residual mutated protein by Western blotting. Parallel negative impacts of COASY deficiency on the mitochondrial function were hallmarked by overall reduction of amount and activity of OXPHOS complex IV and decreased mitochondrial respiration and ATP production.
Conclusions: We document a novel neonatal HHHLA syndrome - a fatal condition allelic to CoPAN. Our data support the lethality of biallelic loss-of-function COASY variants.

Keywords:
COASY deficiency, coenzyme A synthase deficiency, CoPAN, COASY protein-associated neurodegeneration, neonatal hepatopathy, neonatal hypoglycaemia, neonatal hyperammonaemia, neonatal lactic acidosis, mitochondrial dysfunction

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Neurogenetic Disorders

AN INFANT WITH DEVELOPMENTAL DELAY, HYPOTONIA AND DYSMORPHIC FEATURES, DIAGNOSED AS CHROMOSOME 2q37 DELETION SYNDROME CARRYING TWO ADDITIONAL 3q21 AND 6q27 DUPLICATIONS.

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Case study: Objectives: To report a unique case of 2q37 Deletion Syndrome combined with two additional duplications; to understand the impact of additional duplications in a case report of 2q37 Deletion Syndrome.

Methods: We reviewed the literature and data bases of 2q37 Deletion Syndrome and the reported duplications and have these compared with the clinical phenotype of our case and with the results of her CGH Array technique.

Results: The proband showed a severe clinical picture in relation to a large deletion of 65 genes that comprehend all the ones described in 2q37 Deletion Syndrome (also known as ALBRIGHT HEREDITARY OSTEODYSTROPHY-LIKE SYNDROME and as BRACHYDACTYLY-MENTAL RETARDATION SYNDROME). The presence of two additional 3q29 and 6q27 duplications of 10 and 40 genes respectively is also another possible cause of the impairment severity.

Conclusions: The unique clinical and molecular genetics features of this case make it difficult to understand the contribution of each genetic anomaly to the phenotype. We hypothesize that the 3q29 duplication played a major role in the severity of this 2q37 Deletion Syndrome case. Family genetic testing and further similar case reports would be needed in order to support the pathogenicity of these duplications.

Keywords:
2q37 deletion syndrome, hypotonia, developmental delay, dysmorphic features

EPNS23-2705 Oral
Neurogenetic Disorders

BRAT1 - clinical challenges as well as difficulties with genomic interpretation

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Case study: OBJECTIVES:
We aim to show that extremely severe drug-resistant seizures with myoclonus/movement disorder in the early neonatal period are characteristic and relatively specific for BRAT1 variants. We report the challenges in variant interpretation noting they can also cause a non-progressive ataxia without seizures or life limitation.
METHODS:
We report the results of whole genome sequencing in the only two infants presenting within the first days of life with severe, intractable seizures characteristic of rigidity and multifocal seizure syndrome, lethal neonatal (RMFSL) to our regional service covering a population of 5 million over the last 10 years. To highlight the pitfalls in genomic interpretation, we report a child with a non-progressive ataxia, with disease-causing variants in the same gene.
RESULTS:
Patient A was delivered at term hypotonic and tachypnoeic, presenting at Day 3 with multifocal epileptic seizures and non-epileptic myoclonus evolving to status epilepticus by 3 weeks of life, despite therapy with pyridoxal phosphate, folinic acid, 5 anti-epileptic drugs (AEDs) and ketogenic diet. Rigidity was also noted. EEG was discontinuous with multifocal epileptiform discharges. WGS analysis on Day 23 after the first seizure identified a bi-parentally inherited homozygous 11.5kb deletion in the BRAT1 gene. Patient B presented with multifocal status epilepticus (confirmed on EEG at first assessment) and more severe rigidity, myoclonus and distress. WGS identified biallelic variants (c.529C>T and c.1083_1095del) at 4 weeks of age. Patient C exhibited a distinct phenotype, initially presenting with developmental delay at 4 years of age. Ataxia, dysmetria, dysarthria and intention tremor were noted. Trio Agnostic WGS revealed bi-allelic variants in BRAT1.
CONCLUSIONS:
Literature review and our experience suggests unexplained, severe seizures with rigidity/myoclonus presenting in the first week of life, resistant to multiple AED and vitamin trials, is strongly suggestive of BRAT1 variants, and warrant urgent trio genomic sequencing within 3 weeks. Early and repeated video EEG is helpful to characterise the syndrome and differentiate from other myoclonic syndromes. Although biallelic variants presenting with RMFSL are likely to be life-limiting, care should be taken with genomic interpretation considering the milder BRAT1 disorder associated with non-progressive ataxia, intellectual disability and long life expectancy.

Keywords:
RMFSL, seizure, seizures, myoclonus, myoclonic, BRAT1, genomic, EEG, epileptiform, multifocal seizure, ataxia, rigidity, neonate, neonatal, neurology, variant

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Neurogenetic Disorders

Unusually Early-onset case of Spinocerebellar ataxia type 40: A first case report

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Case study: Objective: Spinocerebellar ataxia type 40 (SCA40; OMIM # 616053) is a very rare subtype and adult-onset form of autosomal dominant cerebellar ataxia, characterized by progressive gait abnormalities, dysarthria, intention tremor, and hyporeflexia. The disease is caused by mutations in the *CCDC88C* gene (14q32.11-q32.12). Based on two reports of *SCA40*, the age onset of patients is above 30. The aim of this case study is to report a childhood onset first case of *SCA40*, gene mutation, and phenotype characteristics.

Methods: Whole exome sequencing (WES) from peripheral blood was performed for the case.

Results: 23-month-old female patient of a nonconsanguineous marriage presented with ataxia, walking on tiptoes, and spastic gait starting at 19 months. Her family history is noncontributory to neurological disorders. Her laboratory results were significant for a slightly increased CK level (202 U/L). Her EEG and EMG were unremarkable. MRI demonstrated unmyelinated T2 hyperintense areas in the periantral region, otherwise normal. The Denver Developmental Screening Test showed gross motor delay otherwise normal. WES revealed the heterozygous missense likely pathogenic variant in the *CCDC88C* gene (NM_001080414.4:c.1391G>A (p.Arg464His)). The segregation analysis was planned for the parents.

Conclusions: *CCDC88C* c.1391G>A (p.Arg464His) variant was reported previously in adult-onset SCA40. Functional studies associated with this variant identified the role of c-Jun N-terminal kinase (JNK) and caspase-mediated apoptotic pathways in *SCA40* pathogenesis. Unlike previous reports, our case is the first to demonstrate that mutations in the *CCDC88C* gene may cause pediatric-onset ataxia. Further studies are required to understand different presentations of the same variant, including symptoms and age onset of the disease.

Keywords:
SCA40, CCDC88C, pediatric-onset ataxia, neurogenetic disorders, movement disorders

EPNS23-2676 Oral or e-Poster
Neurogenetic Disorders

CACNA1A gene-variants: Our experience with the ''Chameleon'' gene

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Case study: Objective: To analyze the cases with CACNA1A variants in our care with respect to the wide clinical spectrum, genotype-phenotype-correlations and therapeutic implications.
Results: We report altogether 6 children with CANA1A Variants, 4 of them boys and 2 girls. There were two pairs of siblings and the mother of one pair also carried the mutation in CACNA1A gene. The clinical presentations consisted of hemiplegic migraine in 1, episodic ataxia in 5, non-progredient cerebellar ataxia 2 , nystagmus in 2 , torticollis in 1, epilepsy in 1 , epileptiform EEG-abnormalities without epilepsy in 1, behavioral disorders in 1 and intellectual disability in all but one of the patients who experienced school difficulties and concentration problems. The patients showed considerable overlap in symptoms. Both familial and non-familial forms were seen. There was a considerable intrafamilial phenotypic variability. Brain MRI revealed normal or non-specific findings. No clear genotype-phenotype correlations were observed.
Of the 3 cases who received therapy with acetazolamide 2 showed significant response and one a poor response.
Conclusion: CACNA1 variants lead to dysfunction of a voltage-gated calcium channel and can present with a wide spectrum of paroxysmal and non-paroxysmal clinical phenomena ranging from hemiplegic migraine, episodes of cerebral oedema and coma following trivial head trauma , episodic ataxia and paroxysmal non-epileptic movement disorders like paroxysmal upward tonic gaze deviation and benign paroxysmal torticollis as well as epilepsy, intellectual disability and chronic cerebellar ataxia in adults. It is important for clinicians to consider this disorder early as differential diagnosis when confronted with children with several types of unexplained neurological manifestations. This can help avoid unnecessary lengthy and expensive investigations. Also clinical research should be directed towards delineating genotype-phenotype correlations and to explore the possibilities of precision therapy with the ultimate aim of optimizing the therapy of the debilitating manifestations.

Keywords:
episodic, ataxia, migraine, CACNA1A gene

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Neurogenetic Disorders

A genetic diagnosis of King Denborough Syndrome - RYR1 congenital myopathy

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Case study: Ryanodine receptor type 1 (RYR1)-related myopathies are the most common class of congenital myopathies (CM), and recently with next-generation sequencing methods new phenotype has emergence. The authors present a 4 years old girl, with prenatal history of irregular and late pregnancy surveillance, but normal blood tests and fetal ultrasounds. She was born at term, needed neonatal resuscitation in the first ten minutes of life, maintaining global hypotonia. Multiple dysmorphias were noted described below and left clubfoot. She was discharged home with multidisciplinary follow-up. At 2 months old, was submitted to correction of left clubfoot under general anesthesia, with no complication. On physical examination, she has facial appearance with downslating palpebral fissures, ptosis, low set ears, micrognathia, malar hypoplasia, and a high-arched palate. She also presented a barrel chest with pectus excavatum, lumbar lordosis, short stature, congenital hypotonia, proximal weakness and hyporeflexia. The hypothesis of myopathy led to several workup tests, with normal creatine kinase, thyroid function levels and electromyography. The cerebral MRI requested showed no abnormal findings. Finally, the NGS panels for hereditary myopathy, was performed and detected a heterozygotic mutation in the RYR1 gene, compatible with King Denborough Syndrome (KDS). At 4 years old, she has a mild motor delayed development, myopathic gait, a positive Gowers maneuver, mild scoliosis, short Achilles tendon resulting in tiptoes walk. She has no comorbidities on ophthalmologic and cardiac consultations. Unfortunately, in the past 2 years, she started with irregular rehabilitation attendance due to low family support and COVID-related cessation therapies. Later the genetic family testing of her mother with similar characteristic, but less motor skills impairment and an 11 years old brother, with a normal workup, including muscular biopsy revealed the same heterozygotic mutation. No FDA-Therapeutic for the RYR1-myopathy is approved, but children with this diagnosis benefit from early and regular rehabilitation, orthopedical surgery in order to improve motor function and help correct the skeletal abnormalities. KDS is a rare myopathy with characteristic skeletal and craniofacial abnormalities and a susceptibility to malignant hyperthermia (MH). The authors highlight the importance of genetic testing on undiagnosed and probable CM diagnose, as KDS children are predisposed to develop MH.

Keywords:
Congenital Myopathy; RYR1; King Denborough syndrome; Malignant hyperthermia

EPNS23-2518 Oral or e-Poster
Neurogenetic Disorders

The physical and psychological burden of essential interventions in paediatric NF2

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Objective: The care of individuals with Neurofibromatosis Type 2 (NF2) is complex. In 2009 NHS England set up 4 specialised services in the UK to centralise expertise and improve long-term survival.
We explore the impact of invasive interventions on children with NF2, cared for by the Manchester NF2 service.

Methods: 56 patients (0-25 years) were identified; male to female ratio (M:F) 32:24, median age 16.5 years. 30 patients had a family history, M:F 17:13, median age 17 years. 26 patients were sporadic M:F 15:11, median age 14 years. Patient's genetic severity scores and outcomes of interventions received were recorded.

Results: Children with grade 3 severe phenotype were most likely to have had interventions. 10 children had severe NF2 phenotype grade 3 and 2 children had moderate 2b. The negative impacts of these interventions are listed below:

- Severe needle/hospital phobia (3)
- Loss of vision due to resection of optic nerve meningioma (1)
- Severe Hemiparesis secondary to brain stem arterial stroke (1)
- Young age (<10 years) at first major CNS surgery (5)
- Rapid regrowth of resected meningiomas (1)
- Kidney impairment secondary to Avastin (2)
- Raised haematocrit secondary to Avastin (1).
- Cervical vertebral fusion after three surgeries (1).
- Severe oppositional behaviour and problematic interaction with professionals (2)
- Multiple brain interventions, resulting in significant behavioural problems including ADHD/disinhibition.(1)
- Severe low mood needing antidepressants-(2)

Conclusions: Improved therapeutic options for children and young adults with NF2 come with their own cost. Children with severe phenotypes (3 and 2b) are more likely to be at risk of complications, sporadic cases are more likely to be at the severe end of the spectrum. Targeted support for these children is essential.

Keywords:
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EPNS23-2102 Oral or e-Poster
Neurogenetic Disorders

A novel case of ARFGEF1-related developmental disorder and epilepsy identified in revision of genetic analysis.

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Objective: There is emerging evidence associating haploinsufficiency of ARFGEF1 with a broad spectrum of neurodevelopmental disorders. We present a male patient with drug-resistant epilepsy, distinctive facial features, learning disability and challenging behaviour. Initial whole exome sequencing (100,000 genome project) did not identify a genetic cause. High suspicion led to further analysis of his genomic data, revealing a pathogenic ARFGEF1 variant, c.3002_3006del, p.(Gln1001Profs*15). Our case contributes to an expanding phenotypic and genotypic spectrum of ARFGEF1-related neurodevelopmental disorders and highlights the importance of revisiting genomic data when the phenotype is strongly suggestive of a genetic disorder.

Methods: Previous whole exome sequencing data were reanalysed. The initial whole exome sequencing did not identify the pathogenic variant in our patient, as ARFGEF1 variants had not been well-characterized in human disease.

Results: Our patient is an 11-year-old male with distinctive facial features and polymorphic epilepsy. He had a difficult treatment course with numerous anti-seizure medications, Vagus Nerve Stimulator(VNS) insertion and Carpus Callosotomy. He also has outbursts of anger and a severe aversion to medical procedures (even those that are not painful), which has not been widely reported in previous cohorts. The initial whole exome sequencing did not identify any pathogenic variants. His clinical features, however, were strongly indicative of a genetic cause, which was eventually identified on re-examination of his genomic sequence. The pathogenic ARFGEF1 was also identified in his father, who is reported to have marked outburst of anger but does not have a neurodevelopmental disorder or epilepsy.

Conclusions: Until recently, there had been no substantial evidence of an association between ARFGEF1 and neurodevelopmental disorders. The evolution of genetic sequencing played a key role in identifying pathogenic ARFGEF1 variants causing sporadic and familial cases of developmental delay with or without epilepsy. There is variable penetrance and consistently a male dominance in affected individuals, which are still to be explained. Finally, our case further expands the phenotypic and genotypic spectrum of ARFGEF1 related epilepsy and neurodevelopmental disorders. We highlight the need to revisit genetic analysis when there is a high suspicion of genetic disorder, as it often has significant implications for genetic counselling and treatment strategies.

Keywords:
ARFGEF1, neurodevelopmental disorder, epilepsy

EPNS23-2566 Oral or e-Poster
Neurogenetic Disorders

GENERATING NEW EVIDENCE ON 7Q11.23 DUPLICATION SYNDROME BY ANALYSING A SPANISH COHORT

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Case study: INTRODUCTION: Chromosome 7q11.23 duplication (dup7q11.23) syndrome is a rare autosomal dominant disorder that comprises the same chromosomal region as Williams-Beuren syndrome. This duplication encompasses a heterogeneous clinical profile and has been associated with frequent neurological features that include mild cognitive impairment, autism spectrum disorder and language deficits.

OBJECTIVES: To describe the clinical spectrum of patients with dup7q11.23 syndrome.

METHODS: A retrospective and descriptive study of individuals with dup7q11.23 syndrome was conducted by performing a systematical review of their medical records taken from different hospitals across Spain. Data about genetics, extraneurological manifestations, brain MRI, neurological development, and dysmorphic features were collected.

RESULTS: A total of eleven patients formed the cohort, seven of them were boys and four were girls. All participants were genetically identified by array-CGH with typical duplication in 7q11.23 and about 90% had a "de novo" mutation. The global mean age at diagnosis was 8 years old. Ventriculomegaly was the most common feature before birth, accounting for 10% of patients. Complex congenital heart disease consisting of pulmonary atresia with intact ventricular septum and hypoplasic right ventricle was detected in one patient and ascending aorta dilatation was registered in another patient. Nearly half of them had refractive errors with astigmatism being the most frequent, affecting up to 36% of patients. Cryptorchidism was present in almost 30% of patients and two cases required a surgical intervention. In 45% of individuals, brain MRI revealed abnormalities such as hydrocephalus, myelination delay and cerebellar vermix hypoplasia. Epilepsy was only found in one patient who had focal epilepsy that was difficult to manage with antiepileptic drugs. Global developmental delay with evolution to mild intellectual disability and autistic features were widely recorded. Dysmorphic features were found in more than 50% of patients and included macrocephaly, broad forehead and nasal tip, short philtrum and minor ear defects. Other recognizable anomalies were hyperlaxity, foot deformity and kyphosis.

CONCLUSIONS: Although epilepsy is not a common condition, a case of refractory focal epilepsy was found.Through the clinical information obtained in this study, it is hoped that this new knowledge will enable easier recognition of this phenotype in future patients.

Keywords:
dup7q11.23, intellectual disability, dysmorphic features

EPNS23-2101 Oral or e-Poster
Neurogenetic Disorders

The story of neurology in the language of genetics- Ponto Cerebellar Hypoplasia (PCH) with EXOSC3 mutation in first Asian child

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Case study: Pontocerebellar hypoplasia type 1 (PCH1) is a major differential for spinomuscular atrophy (SMA). The spectrum ranges from neonatal to adolescence with mild to severe disability and death. Genetic advances have created a milestone in the diagnosis. We present the first Asian child with PCH1 and EXOSC3 mutation.

An 8-year-old boy presented with profound developmental delay, walking with a bent knee and exaggerated lumbar lordosis. He was born to consanguineous parents at term with an uneventful perinatal period. His elder sister had a similar developmental delay and died at the age of ten. Examination showed microcephaly, exaggerated reflexes, increased tone, and extensor plantar. MRI was normal and did not show any pontine hypoplasia. He did not have any nystagmus, and the fundus was normal. Genetics showed homozygous missense variation in exon 2 of the EXOSC3 gene resulting in the substitution of Alanine for Aspartic acid at codon 132 (p.D132A). This variant has been associated with PCH1B.

PCH is a heterogeneous group of disorders characterized by abnormally small cerebellum and brainstem. Eight subtypes have been described thus far (PCH1-8) based on clinical and genetic features. Common characteristics include hypoplasia and atrophy of the cerebellum, variable pontine atrophy, and severe mental and motor impairments (1). Although PCH1 has been thought to lead to death in infancy, the spectrum of this disease has been extended to include less severe variants, with genetic advances some of which are associated with minimal atrophy of the brainstem (2).

Recently, mutations in the exosome component 3 gene (EXOSC3) have been identified in 60% of the patients with PCH1. Limited data including some case series are available in the literature. Patients with p.D132A mutation were shown to have prolonged disease course and normal pons (1). Our child had a homozygous mutation with normal pons and cerebellum in MRI in keeping with the findings. Milder form of PCH1 has been reported but EXOSC3 mutation was not identified at that point (3). The overall incidence of PCH1 remains unknown but the identification of a newer mutation has been a breakthrough.

Given the higher carrier status of spinomuscular atrophy (4), clinical dilemma, and limited resources for genetic testing in the Indian population, a keen eye for clinical examination and a structured approach with resources for genetics would open a new horizon in the field of neuro-genetics.

Keywords:
neuro-genetics, Pontocerebellar hypoplasia, EXOSC3 mutation

EPNS23-2987 Oral or e-Poster
Neurogenetic Disorders

BIALLELIC PI4KA MUTATION: A WIDE SPECTRUM OF SYNDROMES

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Objective: Phosphoinositide lipids play roles in cell signalling, controlling cell shape and motility and the interaction of cells with their environment. Pujol et al (2021) identified 10 patients carrying biallelic variants in PI4KA that presented a spectrum of conditions ranging from severe global neurodevelopmental delay with hypomyelinating leukodystrophy to pure spastic paraplegia. We described two patients with PI4KA mutations: one affected by neurodevelopmental syndrome with hypomyelination and the second affected by perisylvian polymicrogyria, cerebellar hypoplasia and arthrogryposis (only reported in fetus, Kini et al 2015).

Methods: Review clinical data of 2 patients: family history, perinatal data, neonatal examination, metabolic, imaging and genetic test.

Results: Patient 1) First child of a non-consanguineous couple. Pregnancy was uneventful. Born by cesarean (fetal taquicardia) at 38 weeks. Normal Apgar. She developed tonic seizures the first day of life that only responded to oxcarbazepine. Neonatal central hypotonia was observed in the first examination. Metabolic test (blood, urine and cerebrospinal fluid) and first genetic test (neonatal onset epilepsy panel) were normal. Neonatal MRI showed mild delay of myelination. At 12 months (first visit in our hospital) she presented global developmental delay, central hypotonia, hypertonia in extremities, horizontal nystagmus and tremor. New MRI: showed supratentorial hypomyelination and thin corpus callosum. Clinical exome sequence showed: biallelic mutation in PI4KA (c5773G>C / c5462-6G>A).
Patient 2) Second pregnancy of a non-consanguineous couple. Induced labor at 40 weeks (severe ureterohydronephrosis). Normal Apgar. First neonatal examination showed dismorphic facial features, arthorgryposis, hypocinesia and hypotonia. Metabolic tests (blood and urine) were normal. Neonatal MRI showed: cerebellar hypoplasia, thin and dismorphic corpus callosum and bilateral perisylvian polymicrogyria. Clinical exome sequence showed biallelic mutation in PI4KA (c.5764C>T/. c2665 A>G).

Conclusions: PI4KA biallelic mutations cause a wide spectrum of syndromes, from severe neurodevelopmental syndrome with hypomyelinating leukodystrophy to mild syndrome of spastic paraparesia. Most importantly, we describe a third phenotype previously only reported in three fetuses who showed bilateral polymicrogyria with cerebellar hypoplasia and joint contractures. The phenotypes presented by these fetuses may represent the most severe extreme of the spectrum.

Keywords:
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EPNS23-2550 Oral or e-Poster
Neurogenetic Disorders

TREATMENT OF LABRUNE SYNDROME WITH BEVACIZUMAB

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Case study: OBJECTIVES
Labrune syndrome (LS) is caused by SNORD118 gene mutations with a particular neuroimaging of white matter disease, intracranial calcification, and cysts. LS is a rare disorder characterized by progressive cerebral degeneration, seizures, and mixture of extrapyramidal, pyramidal and cerebel-lar signs. There has been no effective treatment until now. Recently the use of the vascular endo-thelial growth factor (VEGF)-blocker bevacizumab has been used to treat LS in three published cases, one of which was followed by our team. Besides, we report an additional unpublished case.

The main objective of the study is to review the clinical and radiological response in patients treated with bevacizumab with LS until now.

METHODS
The study is retrospective and descriptive. All patients with LS secondary to a mutation in the SNORD118 gene who have been treated with bevacizumab were included. Our two patients were treated using biweekly infusions of the VEGF inhibitor bevacizumab for more than one year and performed clinical examinations and brain imaging at six months intervals. Patient records were reviewed for demographic, clinical, radiological, laboratory, treatment, and follow-up data. The clin-ical-radiological improvement after treatment was qualitatively evaluated.

RESULTS
A total of 4 patients, all of them male, between 2 and 18 years were included in the study. After treatment for more than one year, our two patients showed no improved bradykinesia and range of motion, but the brain magnetic resonance imaging showed a marked reduction in cyst volume and white matter lesions. The two other published cases presented clinical improvement in movement disorder and seizures.

CONCLUSIONS

Bevacizumab might be clinically beneficial in late-onset LS and produced a variable reduction in brain lesions. However, optimal dosage and treatment length duration are still unknown. More case studies and longer follow-up are needed.

CONFLICT OF INTEREST DISCLOSURE
The authors declare no potential conflicts of interest with respect to the research, authorship, and/or submission of this study.

Keywords:
Labrune syndrome, SNORD118 gene, bevacizumab

EPNS23-2551 Oral or e-Poster
Neurogenetic Disorders

Mitochondrial disease mimicking Charcot-Marie-Tooth disease

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Case study: Objectives: To draw attention to the mimics of Charcot-Marie-Tooth (CMT) disease and neurodegenerative disorders that are associated with peripheral neuropathy.
Methods: A case report with clinical, neuroimaging, and genetic data.
Results: We present a 15 years old Armenian male who was diagnosed with CMT at the age of 9 years. Family history for neurologic disorders was negative. Abdominal pain episodes prompted medical investigations at the age of 9 years. Familial Mediterranean fever was genetically confirmed. The patient's pes cavus was noticed, and nerve conduction studies revealed predominantly demyelinating polyneuropathy with axonal involvement. Based on clinical features and electrophysiological findings diagnosis of CMT was made. Genetic evaluation was not done due to financial constraints. 3 years later the boy had additional symptoms: right-sided divergent strabismus and right upper eyelid ptosis. These features were attributed to the cranial 3rd nerve involvement in the context of CMT disease. At the age of 15 years, the patient started having muscle pain in the lower extremities, nausea, and difficulties in weight gain. Bilateral external ophthalmoplegia, bilateral ptosis, and slight right-sided divergent strabismus were revealed. Brain MRI showed confluent brain white matter hyperintensity on FLAIR and T2-weighted images with relative sparing of the U-fibers and no diffusion restriction. Mitochondrial Neurogastrointestinal Encephalopathy Syndrome (MNGIE) was suspected. Whole exome sequencing revealed compound heterozygous variants in the TYMP gene: c.647-2A>T (p.?) and c.1282G>C (p.Gly428Arg). Both variants are classified as likely pathogenic according to ACMG criteria.
Conclusions: We conclude that MNGIE can mimic CMT at an early stage. The diagnosis of CMT should be questioned over time if atypical clinical features appear.

Keywords:
mitochondrial disorder, Charcot-Marie-Tooth disease, ophthalmoplegia

EPNS23-2740 Oral or e-Poster
Neurogenetic Disorders

The genotype-phenotype correlations to DYNC1H1 de novo mutation.

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Case study: Introduction
DYNC1H1 encodes for a protein that plays an essential role in retrograde axonal transport and other intracellular functions. DYNC1H1 is related to a broad-spectrum disorder: Spinal muscular atrophy with lower extremity predominance 1 (SMALED1), neurodevelopmental disorders (NDD) or malformations of cortical development (MCD) between others. It is been suggested the clinical picture could be related to the specific DYNC1H1 domain affected (beginning tail, dimerization, linker or motor domain).
METHODS
We present two cases with pathological del novo mutation in DYNC1H1. Both presented an unremarkable pregnancy and perinatal period and no family history of neurological disorders.
Case 1
Male with the variant c.4868G>A (p.R1623Q), localized in liker region domain. First seizure started at 4 months old, microcephaly, global developmental delay, facial diplegia and hypotonia with preserved reflexes were evident at that moment. Metabolic study and EMG were normal. Brain MRI showed bilateral perisylvian polymicrogyria, hypoplasia of corpus callosum and the cerebellum, EEG exhibited epileptic discharges in temporal areas. At 13 years old he presented severe intellectual disability without verbal language, epilepsy with generalized tonic-clonic seizures and aggressive behaviour but an independent gait, EMG was performed again without axonal impairment.
Case 2
Female with the variant c.1834 G>A (p.V612M) localized in dimerization domain. She initiated neuropediatric follow up at 2 years old due to speech delay, not delay in motor skills had been previously detected. Neurological examination evidenced a developmental expressive language disorder, some autistic traits and mild proximal lower-limb muscle weakness (she could not walk upstairs or jump) with preserved reflexes. Blood test, EEG and brain and spinal MRI were normal, in EMG revealed axonal neuropathy in lower limbs according to SMALED1.
CONCLUSION
According to literature, case 2 with a mutation in dimerization domain present SMALED1. Although, literature specifically associates alterations in the motor domain with MCD, but it can also see when linker region is affected as our case 1. In patients with DYNC1H1 mutations it is mandatory to perform a thorough physical examination and in order to discard associated disorders to the mean feature. We consider an EMG should be performed even if reflexes are preserved. Further investigations are necessary for a better understanding of DYNC1H1 related disorders.

Keywords:
DYNC1H1, spinal muscular atrophy, cortical malformation, neurodevelopmental disorders, epilepsy

EPNS23-2107 Oral or e-Poster
Neurogenetic Disorders

TRAPPC4-related neurodevelopmental disorder: a recent TRAPPopathy

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Objective: In 2020 Van Bergen et al described a neurodevelopmental disorder with epilepsy, spasticity and brain atrophy (NEDESBA; 618741), in 7 children from 3 unrelated families, associated with a recurrent homozygous splice site variant (c.454+3A>G) in TRAPPC4 gene. TRAPPC4 is one of the core proteins of TRAPP complex, essential for cell survival. We report two sisters with a TRAPPC4-related neurodevelopmental disorder, diagnosed by whole-exome sequencing (WES) after extensive investigation.

Methods: Case report

Results: A family of consanguineous parents, with no known family history of neurological diseases, has two daughters, a 7-year-old and 2-year-old child. The older sister, after an uncomplicated pregnancy and neonatal course, demonstrated acquired microcephaly (-3SD) and developmental delay at 6 months. Bilateral frontotemporal cerebral atrophy and white matter abnormality was reported on brain MRI. Metabolic workup and ophthalmological evaluation had no changes. Array CGH was normal. At 2 years-old with severe developmental delay, with no communicative interaction, microcephaly and spastic quadriparesis, trio-WES revealed no changes. Mitochondrial genome was also requested, with no alterations. At 5 years-old, she had clonic seizures in the left body, with spikes in the right fronto-centro-temporal region on electroencephalogram (EEG), starting antiepileptic treatment with levetiracetam (LVT). Severe and progressive atrophy, white matter abnormality and hypointense thalami/basal ganglia was reported on brain MRI, repeated at age 6. Meanwhile her mother became pregnant and a girl was born, after an uneventful pregnancy. The younger sister started oculogyric crises at 4 months, associated with microcephaly (-4SD), developmental delay, dystonia and psychomotor agitation. EEG reveled centrotemporal and temporal spikes arising independently in the right and left hemispheres. She was put on LVT treatment, but it was necessary to add valproate and clonazepam due to persistent crises. Brain MRI reported moderate cerebral atrophy and marked hypointense thalami/basal ganglia. Re-analysis of WES was performed and showed a pathogenic homozygous variant (c.454+3A>G) in TRAPPC4 gene.

Conclusions: TRAPPC4-related neurodevelopmental disorder is a recent TRAPPopathy that should be considered in children with microcephaly associated with neurodegenerative disease. With this report we intend to draw attention to the emergence of new diagnoses of neurogenetic diseases and the importance of genome re-analysis.

Keywords:
TRAPPC4, NEDESBA, TRAPPopathy

EPNS23-2969 Oral or e-Poster
Neurogenetic Disorders

Episodic ataxia associated with SCN2A mutation: A case report

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Case study: Introduction
The term episodic ataxia (EA) encompasses cerebellar ataxia manifestations of varying duration and frequency due to various gene mutations. Up to 2010, eight types of EA were known, but Liao et al. described the ninth type of EA due to sodium voltage-gated channel, alpha subunit 2 (SCN2A) mutation. We report an 8-year-old girl with SCN2A mutation presenting only with recurrent cerebellar ataxia.

Case Presentation
An 8-year-old girl was admitted to our pediatric emergency outpatient clinic with inability to stand, unsteady gait, and vomit. She was born after uneventful pregnancy and delivery, with a non-consanguineous marriage of her parents. Her developmental milestones are consistent with age and gender group. She was first hospitalized at the age of 3 with unsteadiness and ataxic gait after lower respiratory tract infection. Brain MRI and cerebrospinal fluid (CSF) findings were normal. She was diagnosed with post-infectious cerebellar ataxia and completely recovered within 7 days without any treatment. On admission to the hospital, on neurological examination, cerebellar tests showed dysdiadochokinesia, dysmetria, and ataxia. She had no signs of meningeal irritation or nystagmus. Brain MRI was normal. On laboratory tests, the complete blood cell count and biochemical parameters were normal. Viral serology tests and metabolic workup were normal. Thoracic, abdominal, and pelvic MRI for accompanying paraneoplastic diseases were normal. Based on these findings, she was diagnosed with episodic ataxia. On the third day of admission, acetazolamide (10 mg/kg/d) was started. On the sixth day of admission, persistent vomiting stopped and she was discharged. Ataxia completely recovered after 14 days after admission to the hospital. The gene test detected a pathogenic heterozygous mutation of c.2300T>C (p.I1e767Thr) in the SCN2A gene.

Conclusion
Pathogenic mutations in SCN2A are reported in a spectrum of neurological disorders including epileptic encephalopathy, developmental delay, intellectual disability, episodic ataxia, autism spectrum disorder, and schizophrenia. SCN2A-related EA is a rare neurological disorder that may benefit from acetazolamide therapy.

Keywords:
Episodic ataxia, SCN2A, acetazolamide

EPNS23-2954 Oral
Neurogenetic Disorders

RARE-ID: An Eastern European project for the identification of genetic causes of pediatric autism and Undiagnosed Neurologic Disorders via WGS; preliminary results. European Structural and Investment Funds 2014-2020

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Objective: The project aims to develop a. a comprehensive diagnostic tool with integrated whole genome sequencing (WGS) and metabolomics data for autism and Undiagnosed Neurologic Disorders (UND) and b. the first Eastern European database of genotype-phenotype associations of the above disorders.

Methods: There are two primary cohorts: a. pediatric cases with a clinical indication for syndromic or non-syndromic autism or UNDs, b. neonates with severe clinical courses from the neonatal intensive care unit. The pediatric cohort is subdivided into three groups: 1. non-syndromic autism, 2. syndromic autism 3. Undiagnosed Neurologic Disorders (UND) cases with negative whole exome sequencing (WES) and negative chromosomal microarray analysis results. These participants were subjected to a. WGS followed by a thorough analysis of raw data via a bioinformatic pipeline (NsPatient, Neogenetics) which integrates tools for point variants detection and filtering as well as for the identification of copy number variations and repeat expansions in the nuclear DNA and detection of small variants in the mitochondrial DNA. b. metabolomic profiling, c. behavioral assessment. Rapid WES analysis is applied to critically ill neonates.

Results: Till 31/10/2022, 92 pediatric cases have been recruited, of which 33 belong to group 1, 13 to group 2, and 46 to group 3. Group 3 consists of cases with muscular dystrophy, myopathy, peripheral neuropathy, early cerebellar ataxia, epilepsy, severe psychomotor delay, epileptic encephalopathy, spasticity, and suspected mitochondrial disease. Data analysis has been completed for this group and yielded genetic diagnoses for 5 of the 46 cases. Regarding groups 1 and 2, statistical analysis is underway to develop a polygenic risk score algorithm. Recruitment of neonates began in November of 2022. Four cases were referred till December 2022, of which two have been fully processed. A pathogenic/likely pathogenic variant (c.92G>C) in the EXOSC3 gene was detected in both cases with similar clinical manifestations.

Conclusions: Based on the preliminary data of group 3, WGS increases diagnostic yield in undiagnosed rare disease cases by approximately 10%. Rapid WES integration is an emerging efficient and cost-effective diagnostic tool for the second cohort of critically ill infants, but further evidence will be acquired by the end of the project, which will investigate 20 such cases.

Keywords:
RARE-ID, whole genome sequencing, whole exome sequencing, autism, undiagnosed neurologic disorders, neonates

EPNS23-2428 Oral or e-Poster
Neurogenetic Disorders

The role of WGS re-analysis in a rare neurodegenerative condition - a case report

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Objective: It can be a diagnostic challenge to find the cause of developmental delay and seizures in many children who have syndromes, and the routine genetic panels, neuroimaging and other ancillary test does not aid with the etiology. We report on a case of a rare severe infantile-onset neurodegenerative condition caused by a pathogenic variant of the Negative Regulator of Reactive Oxygen Species (NRROS) microglial-associated protein diagnosed by re-analysis of the initial whole genomic sequencing (WGS) a few years after the initial presentation.

Methods: The patient electronic medical records were reviewed and summarized into a case report.

Results: Case Report
In 2018, a 2-year-old female presented with status epilepticus after a febrile illness. She was born to consanguineous parents after an unremarkable pregnancy and delivery but began to show developmental regression at one year of age.

After her initial presentation, she was extensively investigated, but no abnormalities were identified, except for bilateral intracranial calcifications and ventriculomegaly without hydrocephalus detected on CT and MRI scans. Her chromosomal microarray was normal. She was referred to the clinical geneticist and she was then enrolled on the DDD and 100K Genome projects, which gave negative results.

Over the years, she continues to show progressive loss of skills and microcephaly. In addition, she developed drug-resistant seizures, feeding problems, and recurrent chest infections requiring ICU admissions.

In 2020, her genomic sequencing was re-analyzed, and a pathogenic variant of the homozygous mutation NRROS.c.[232C>T]p.[(Gln78Ter)];[(Gln78Ter)] was identified. The inheritance was autosomal recessive with both parents being carriers of the gene.

Conclusions: Microgliopathies are rare and can lead to neurodegenerative disorder in childhood. NROSS is characterised by developmental delay and regression, drug-resistant seizures and intracranial calcifications. This very rare condition is life-limiting, and cases usually do not survive the first decade of life. However, early diagnosis may help with prognosis and family counselling.

WGS is now commonly used in clinical practice, but the rapid advances in sequencing and analysis techniques entail that subsequent re-analysis of previous genomic data may be able to identify pathogenic variants previously unknown and provide a diagnosis for otherwise unexplained diseases.

Keywords:
WGS, NROSS

EPNS23-2952 Oral or e-Poster
Neurogenetic Disorders

Relapse neurological deficits (facilitated by viral infections): when a pseudo-inflammatory presentation reveals a genetic disease.

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Objective: We report two patients presenting iterative neurological deficits mostly occurring during a febrile episode, and characterized in time by cerebellar, visual, auditory, sensorimotor impairment. Genetic analysis revealed a biallelic mutation of the FDXR gene, expanding the spectrum of reported phenotypes.

Methods: Patient 1 with history of hypotonia and psychomotor retardation, experienced a first episode of sudden decrease in visual acuity at 4 years, resolute spontaneously, then a second episode at 7 years, evolving towards blindness. Pain in the feet became insomniant around 5-6 years, then resolved to reappeared at 14 years. At 15 years he presented a cerebellar syndrome, pyramidal signs, areflexia of the lower limbs, a proprioceptive disorder, a global slowdown, movements of visual wandering. At 17 years, he lost walking ability during influenza, recovered after few months but lost autonomy using a wheelchair. At the same time, the family noted hearing loss, social withdrawal and language loss.
Patient 2 was a girl aged 3 years 11 months when she presented during influenza an acute episode with loss of walking and language, sphincter disorders, leading to the diagnosis of cerebellitis. Recovery was gradual but partial. Three months later, she had a sudden and severe decrease in visual acuity during a new febrile episode, with no noticeable response after 3 infusions of methylprednisolone. She maintained a severe visual impairment associated with pyramidal signs. At the age of 7, she was diagnosed for a mixed deafness. At 10 years, a new episode of aggravation occurred during acute gastroenteritis with sensory-motor symptomatology. She received corticosteroids infusions, with partial effects. A treatment of multiple sclerosis was introduced for a few months, then stopped considering the hypothesis of a mitochondrial disease.

Results: Additional tests showed in both patients, optic atrophy, deafness, axonal peripheral neuropathy, posterior cordonal involvement, spinal and cerebellar atrophy, signal abnormalities of the dentate nuclei. In this context, biological, and genetic markers of primitive mitochondrial disorders, mutations in OPA1, OPA3, MFN2, wolframine were ruled out. Access to the exome/genome finally identified recessive mutations in FDXR, coding for a mitochondrial "ferrodoxin reductase".

Conclusions: This report expands the phenotypic spectrum of FDXR mutations to a progressive neurological disorder marked by acute neurological deteriorations facilitated by viral infections.

Keywords:
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EPNS23-2702 Oral or e-Poster
Neurogenetic Disorders

Exome sequencing in a child with neurodevelopmental disorder and epilepsy: Variant analysis of the PPP2R1A and IQSEC1 gene

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Case study: Introduction:
For some patients with severe phenotypes complicated with epilepsy the diagnostic oddysey is rather long. Here we present a girl with pathogenic variant in the PPP2R1A gene and likely pathogenic variants in the IQSEC1 gene. She was first examined in 2009 but the diagnosis has been obtained only in 2022.
Patient and Methods:
The patient presented with first seizure at the age of 9 months. At last examination at the age of 15 years, she presented with a developmental delay, severe intellectual disability, microcephaly, short stature and epilepsy. Previously used targed gene panel did not identifed cause of her disease. Exome sequencing was finally used to obtain genetic diagnosis.
Results:
Previously published pathogenic variant in the PPP2R1A gene (NM_014225.6): c.658G>A, p.(Val220Met) was detected in heterozygous state. This rare variant affecs a highly conserved amino acid, was not found in parents and is presumed to occur de novo. De novo heterozygous variants in this gene cause developmental delay with or without epilepsy with broader clinical presentation. However, our patient has no joint hypermobility and no hearing loss. In addition, we also found two heterozygous variants with low gnomAD frequency in the IQSEC1 gene, variants are in trans. Both variants are novel, not described previously as pathogenic. Bi-allelic variants in the IQSEC1 gene were described in several patients with intellectual disability, developmental delay and a short stature.
Conclusion:
These data suggest that both variants in PPP2R1A and IQSEC1 genes might contribute to the neurodevelopmental disorder in our patient. Nevertheless, variants in IQSEC1 gene could present rare polymorphism or might have a synergistic effect to already described pathogenic variant in PPP2R1A gene probably causing patient's phenotype.

Supported by: AZV NU20-04-00279

Keywords:
epilepsy, neurodevelopmental disorder, exome sequencing

EPNS23-2254 Oral or e-Poster
Neurogenetic Disorders

MCT 8 DEFICIENCY: POINT OF A NEUROLOGICAL VIEW

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Objective: The SLC16A2 gene encodes an integral membrane protein responsible for the transport of thyroid hormone and is also called monocarboxylate transporter 8 (MCT 8). This gene is expressed in many tissues and plays an important role in the development of the central nervous system. Mutations in the SLC16A2 gene have been associated with Allan-Herndon-Dudley syndrome, which is characterized by motor-mental retardation, hypotonia, spastic paraplegia, and hypothyroidism.

Methods: In this report, 11 patients were examined with the participation of 6 centers from different regions of Turkey and their clinical findings were documented.

Results: The earliest diagnosed patient was 6 months old. No consanguinity was found in eight patients (72%). Delayed head control was the first prominent finding in 55% of patients. Nutritional difficulties were reported in 71% of the patients. Anti-seizure medication was used in 5 patients due to epilepsy. Spasticity (especially in the lower extremities) was present in all patients except one patient using Triac. Movement disorders were detected in 4 patients (dystonia, paroxysmal kinesigenic dyskinesia, opsoclonus myoclonus). Skeletal deformities was found in 73% of the patients. As cranial MRI findings, delayed myelination was observed in 5 patients, cerebral atrophy and increased perivascular space were observed in 3 of these patients. A history of surgery was found for cryptorchidism in 2 patients and inguinal hernia in 1 patient. All 11 patients had global growth retardation and their head circumference percentiles were <-2 SD.

Conclusions: Mutations in the SLC16A2 gene cause a deficiency of the MCT 8 protein, resulting in clinical manifestations such as microcephaly, severe growth retardation, thyroid hormone disorders, spasticity. When a patient with these major findings is encountered, MCT 8 Deficiency should be kept in mind and the patient should be evaluated in terms of genetic diagnosis.

Keywords:
Microcephaly, spasticity, hypotonia, hypothyrodism, global growth retardation, Allan-Herndon-Dudley Sendrom

EPNS23-2912 Oral or e-Poster
Neurogenetic Disorders

Evaluation of clinical, laboratory, and imaging findings of patients with the diagnosis of Pontocerebellar Hypoplasia: A multicenter national study

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Objective: Pontocerebellar hypoplasia (PCH) describes a rare, heterogeneous group of neurodegenerative/neurodevelopmental disorders mainly with severe hypoplasia or atrophy of cerebellum and pons, and also variable involvement of supratentorial structures. This study aimed to discuss the clinical, laboratory, genetic and neuroimaging findings with the diagnosis of PCH.

Methods: We retrospectively collected patients who were diagnosed with PCH by national and multicenter participation. Age of diagnosis, gender, consanguinity, pregnancy duration, occipital frontal circumference at the examination, psychomotor development, seizure, neurological findings, neuroimaging features, other system findings, biochemistry tests, metabolic investigations, dysmorphic findings, and, genetic analysis were evaluated.

Results: A total of 65 patients with PCH were included in the study from seven geographical regions in Turkey, 28 were female (43%) and 37 (59%) were male. We identified 16 distinct PCH-related genes: CLP1 (17), EXOSC3 (7), AMPD2 (7), TSEN54 (6), RARS2 (5), VLDLRL (5), HEATR5B (3), CASK (3), MINPP1 (2), TOE1 (2), EXOSC8 (2), TBC1D23 (2), PLCO (1), TSEN2 (1), SEPSECS (1), and CHMP1A (1). Among these genes, 89.2% (58/65) of the patients exhibited homozygous mutation. Consanguinity was 80%(52/65) and pregnancy at term was 85.5% (53/62). Microcephaly was found in 91.5% (43/47). Psychomotor retardation with 98.5% (64/65), abnormal neurological findings with 100% (65/65), seizure with 62.7%(37/59), normal biochemistry and metabolic investigations with 92.2% (47/51), and dysmorphic findings with 50%(22/44) were determined. CLP1 gene mutations (PCH 10) found is the most common genetic mutation. Moreover, All CLP1 gene mutations exhibited a homozygous pathogenic variant c.419G>A.

Conclusions: This multicenter study has the feature of being the most comprehensive study conducted in Turkey on PCH. Unlike other studies, we found the most common CLP1 gene mutations.

Keywords:
Pontocerebellar hypoplasia, psychomotor retardation, microcephaly.

EPNS23-2826 Oral or e-Poster
Neurogenetic Disorders

A severe phenotype of developmental and epileptic encephalopathy associated with mutation in *AP3B2*

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Case study: OBJECTIVES

AP3B2 encodes for a neuron-specific subunit of the adaptor protein complex 3 (AP-3), which is involved in signal-mediated trafficking of vesicle membrane proteins between the neuronal cell body and the nerve terminus. *AP3B2* mutations have only been described in eight consanguineous families with developmental and epileptic encephalopathy featuring severe global developmental delay, poor eye contact with optic atrophy, and postnatal microcephaly (DEE 48, OMIM 616276). The aim of this case is to contribute to clarify the phenotypic spectrum of *AP3B2* variant carriers.

METHODS

We present a female of healthy consanguineous parents from Senegal, referred for the study of abnormal developmental delay. Pregnancy and birth at week 42 were uneventful and birth measurements were normal. The first clinical sign of the disease appeared when she was 3 months old with developmental delay and shortly after seizures started. She presented with infantile spasms and generalized seizures that were pharmacoresistant to multiple treatments and after two years of follow-up she has no acquisition whatsoever of developmental milestones (no eye-contact nor head support or purposeful movements). Physical exam reveals axial hypotonia, dyskinesia and postnatal microcephaly. The EEG shows a severely abnormal background with multifocal interictal epileptiform anomalies and normal MRI. Ophthalmological examination reveals mild optic disc pallor with normal visual-evoked potentials.

RESULTS

Whole Exome Sequencing analysis identified a novo homozygous predicted loss-of-function variant in AP3B2 gene which causes a deletion from exon 8 to 26. This results in a non-functional protein and an impairment of neuronal protein trafficking and neurotransmitter release.

CONCLUSION

Our observation confirms the association of *AP3B2* mutations with a very severe phenotype including developmental arrest, refractory epilepsy and possible eye involvement, which is highly consistent with the expression pattern of this gene.

Keywords:
Developmental and epileptic encephalopathy, AP3B2

EPNS23-2168 Oral or e-Poster
Neurogenetic Disorders

DHX30-Associated Neurodevelopmental Disorder with Severe Motor Impairment and Absent Language: First Korean Case in Two Siblings and a Literature Review

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Objective: DHX30 variants have recently been reported in patients with neurodevelopmental disorders with severe motor impairment and absent language (NEDMIAL). Despite the fact that there is currently no effective curative treatment for NEDMIAL, its early diagnosis enables more informed management, including genetic counseling for the affected children and their families where applicable. To the best of our knowledge, there are no previous reports of genetically confirmed NEDMIAL in the Korean population. Here we describe the clinical and molecular analyses of two siblings with a de novo DHX30 missense variant.

Methods: The proband was a 10-year-old boy presenting with intellectual disability with severe motor impairment, absent language, facial dysmorphism, strabismus, sleep disturbances, and feeding difficulties. A physical examination showed dysmorphic facial features, including thick eyebrows, long eyelashes, strabismus, freckles on the cheeks, decreased muscle tone, and talipes valgus. Karyotype, chromosomal microarray, metabolic screening test, and brain magnetic resonance imaging were conducted. Whole-exome sequencing (WES) was performed using genomic deoxyribonucleic acid (DNA) isolated from the patient's buccal swab.

Results: Karyotype, chromosomal microarray, and metabolic screening test results were normal. Brain magnetic resonance imaging revealed diffuse atrophy of the bilateral corpus callosum and periventricular white matter with no significant focal parenchymal lesions. We performed whole-exome sequencing using genomic deoxyribonucleic acid isolated from buccal swabs, which revealed a heterozygous missense variant of DHX30: (c.2344C>T, p.Arg782Trp). Sanger sequencing was conducted for the proband, the affected sister, and each parent. The same variant was confirmed in two siblings but not in their parents, suggesting the possibility of de novo germline mosaicism.

Conclusions: We reported here the first Korean cases of two siblings who presented with NEDMIAL and previously unreported clinical features harboring a rare de novo missense variant in DHX30. With a detailed clinical analysis of other cases, this paper further delineates and expands the spectrum of clinical phenotypes associated with DHX30 variants and highlights the importance of careful scrutiny of clinical findings in the early recognition of rare conditions such as NEDMIAL.

Keywords:
DHX30, whole-exome sequencing, developmental delay, intellectual disability, NEDMIAL

EPNS23-2758 Oral or e-Poster
Neurogenetic Disorders

Xq triplication including PCDH19 gene associated to PCDH19-like clustering epilepsy phenotype: a potential novel disease mechanism?

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Objective: PCDH19 clustering epilepsy is an early-onset seizure and neurodevelopmental disorder affecting heterozygous females and males with postzygotic somatic mutations. There are hundreds of different deleterious variants in PCDH19 reported in the literature all of which are speculated to lead to a loss of PCDH19 protein function. To date phenotypes associated with gain-of-function or gain-of-dosage have not been described. Hypothesis: Gain-of-dosage in PCDH19 results in a similar phenotype to the one found in patients with loss-of-function variants.

Methods: Description of a single case. Examination of the patient's medical record for clinical, radiological, laboratory, treatment, and follow-up data. Genetic studies included genomic array (Affymetrix CytoScan 750 array), karyotype, X-chromosome inactivation study.

Results: Our female patient, with no remarkable pre/perinatal history, had the first seizure at three months of age. Her epilepsy displays various seizure types, including focal and generalized seizures. Associated features include fever and sleep as triggering factors, cluster presentation and drug resistance. Comorbidities include global developmental delay with autistic traits, language delay and difficulties in gross motor skills. Metabolic screening and cerebral magnetic resonance showed no pathological findings. In the genomic array study a de novo triplication (two extra copies) of 12.2 megabases of the chromosomal region Xq21.3-q22.1 (chrX:89355579-101615553; Hg19) was found. The triplicated segment included 41 genes, of which one (PCDH19 gene) has been associated with a compatible clinical phenotype. This implies an unbalanced dose gain in the PCDH19 gene (1 and 3 copies on each chromosome). The pattern of inactivation of the X chromosome in blood cells showed a preferential, but not complete, inactivation of the maternal X chromosome (98:2), demonstrating the existence of functional mosaicism. This is compatible with the "cellular interference" theory proposed as molecular basis of PCDH19 related disease. A similar pathogenicity mechanism has been described in a case of familiar hypertelorism, in which a dose gain due to a complete duplication of EFNB1 gene caused imbalance in Ephrin-B1 expression. The abnormal phenotype was confirmed in animal model (mice).

Conclusions: The dose gain in the PCDH19 gene may be a potential novel disease mechanism, which causes a clinical phenotype consistent to the one described in the PCDH19-related clustering epilepsy.

Keywords:
PCDH19 clustering epilepsy, early-onset epilepsy, gain-of-dose genetic variant

EPNS23-2396 Oral or e-Poster
Neurogenetic Disorders

Expanding the clinical, molecular, and imaging spectrum of DYNC1H1-associated disorders

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Objective: Neurons require dynamic intracellular trafficking networks for development and survival during cellular stress. The dynein complex is essential for the retrograde transport of cellular components, Golgi maintenance, and autophagolysosomal processing. Genetic disorders in this complex ('dyneinopathies') are largely associated with ciliopathies, while pathogenic heterozygous variants in its core component, cytoplasmic dynein heavy chain (DYNC1H1), are associated with neurological diseases: spinal muscular atrophy with lower extremity dominance (SMALED), Charcot-Marie-Tooth disease type 2O, and mental retardation type 13 (MRD13). In our previous works, we defined a clinical and molecular spectrum ranging from neuromuscular disorders with peripheral nervous phenotypes to neurodevelopmental disorders (NDD) with central nervous involvement. The pathomechanisms in the spectrum of DYNC1H1-related disorders remain elusive to this date.

Methods: We have recruited patients with expanding phenotypes via international collaborations and patient networks. We present clinical, molecular, and imaging data and a detailed classification of novel phenotypes both within and outside of the spectrum of dyneinopathies.

Results: We identified over 30 unreported cases (ages 0-58 years) with pathogenic heterozygous variants in DYNC1H1, presenting novel neurological and non-neurological phenotypes that led to significant delay in genetic testing and disease detection. Non-neurological phenotypes include primary immunodeficiency, organ anomalies, and skeletal manifestations that resemble the phenotypic spectrum of other dyneinopathies. Of note, we observed several cases with NDD that showed distinct neurodegenerative courses after bouts of systemic infections with double-stranded DNA viruses (Herpesviridae) or single-stranded RNA viruses (Ross-River fever, SARS-CoV-2). We discuss the implication of the dynein complex in neuronal health in light of recent findings in anti-viral immunity, and identify how presentation of viral triggers in our cases altered disease courses regardless of NDD severity or age at viral infection.

Conclusions: Our findings expand the clinical, imaging, and molecular spectrum of pathogenic DYNC1H1 variants beyond neurological disorders and suggest a link between neuronal immunity and cellular survival due to deficient intracellular trafficking. This will facilitate early diagnosis and improve counselling and anticipatory guidance of affected families.

Keywords:
DYNC1H1, neurodevelopmental disorder, neuronal immunity, genotype-phenotype correlation

EPNS23-2219 Oral or e-Poster
Neurogenetic Disorders

Update on the CINDI project; an integrated approach towards a diagnosis in patients with unsolved likely neurogenetic disorders

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Objective: The overall aim of this research project is to develop a pathway for children with probable neurogenetic conditions but who have not had a diagnosis made using current clinical standard of care testing (up to and including exome analysis).
We will give an update on the progress of the CINDI project.

Methods: This framework includes setting up a research clinic (UNSOlved Neurology clinic; UNiSON) which integrates deep phenotyping of the patient and allows the paediatric neurologist and clinical scientist to reanalyse commercially available exome data in the clinical setting. A diagnostic prescription is formulated.

The diagnostic prescription is used to direct investigations. Investigations may include genetic re-analysis, transcriptomic analysis and functional work. A multidisciplinary team meeting is carried out to discuss outputs from the multi-omic pipeline. Research findings are confirmed using accredited laboratory testing and delivered back to the patient in the clinic.

CINDI (Collaboration In geNomic Disorders in Ireland) is a cloud based register to record patients with/and without a diagnosis so that patients and their families can be contacted should a research study, clinical trial or precision medicine become available in future.

CHI REC approval GEN 739-19.

Results: This research project started in November 2022 and recruitment is ongoing. The CINDI register is in user acceptance testing phase. We will report an update on the progress of the CINDI project.

Conclusions: A large number of children presenting with neurological syndromes do not have a genetic diagnosis despite detailed investigation. We are developing a research platform to aid in diagnosis. The CINDI register will allow for diagnosed patients to be recruited to future research studies, clinical trials or for precision medicines.

Keywords:
Diagnostics

EPNS23-2832 Oral or e-Poster
Neurological Emergencies in Children

characteristics of seizures in febrile children after easing of COVID-19-related social restrictions

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Objective: To investigate clinical characteristics of seizures in febrile children after easing of COVID-19-related social restrictions.

Methods: This study is based on a retrospective study using electronic medical record review of 96 children who visited emergency department with febrile seizure in Seoul Medical Center between December 2021 and December 2022. We reviewed demographics, developmental status, laboratory data, characteristics of seizures, need to critical care, neuroimaging and electroencephalogram, critical care, and medications. Differences in the clinical characteristics between COVID-19 positive and negative were evaluated.

Results: Of the 96 patients included in our study, the male to female ratio was 1.6:1. The mean age was 2.9 months and 15 patients (15.6%) were 5 years of age and older. Eighteen patients(18.8%) had complex febrile seizures, 14(14.6%) had multiple seizure and 4 (4.2%) had febrile status epilepticus that lasts for 30 minutes or longer. Epileptiform abnormalities on EEG were seen in one patient with prolonged seizure. There were no abnormalities in brain MRI and spinal fluid. No patients died and all patients had no neurological deficit on discharge. The identified etiologies of fever were listed as follows; COVID-19 in 32 patients (33.3%), Parainfluenza in 8 (8.3%), Influenza in 3 (3.2%). There is no statistical differences between COVID-19 patients and other patients with regard to the male preference, age, peak fever, complex febrile seizure, laboratory findings, and critical care.

Conclusions: Our findings suggest that extensive diagnostic evaluations may not be necessary for febrile children with seizure regardless of COVID-19 positivity. Further studies with a larger cohort are warranted to clarify long term outcome and risk factors of epilepsy in these patients.

Keywords:
COVID-19, children, seizure, febrile seizure

EPNS23-2696 Oral or e-Poster

Neurological Emergencies in Children

Acute unilateral motor deficit in childhood - exemplification through clinical cases

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Objective: The acute unilateral motor deficit in childhood carries some diagnostic and treatment problems. For a correct diagnosis the clinician has to pay attention to the key aspects of history and physical examination, to establish the precise anatomical level, whether the deficit is transitory or persistent, and the etiology. Only by answering correctly to "where" and "why" questions, the clinician will be able to provide the proper treatment. Thus, our study goal is to exemplify through representative and also some particular cases, an algorithm of diagnosis in acute unilateral motor deficit.

Methods: We reviewed retrospectively all the cases of unilateral motor deficit that presented at the ER in our clinic in the last 5 years (December 2017 - December 2022), using "monoplegia" and "hemiplegia" as search keywords. We selected the cases with acute onset and we analyzed 10 cases, one for each etiology of acute unilateral deficit encountered in this period. The history (type of onset, signs and symptoms associated), the clinical exam and the most important investigations (including imaging studies) are illustrated following an algorithm which leads to the final diagnosis.

Results: The 10 cases selected exemplify the main etiologies for acute unilateral motor deficit: complicated migraine, trauma, stroke, tumour, alternating hemiplegia of childhood, demyelinating disease, postictal deficit, hemiconvulsion-hemiplegia-epilepsy syndrome. Each of these children presented at the ER with acute unilateral motor deficit as the main complaint. We highlighted both the classical pictures and particularities of the cases.

Conclusions: A careful assessment of the history and a thorough clinical exam, proper investigations, following an algorithm based on what, where and why questions are essential for a correct diagnosis. The prompt diagnosis allows an urgent therapeutic decision with significant implication on patient's outcome.

Keywords:

acute unilateral motor deficit, stroke, hemiplegia, migraine.

EPNS23-2962 Oral or e-Poster
Neurological Emergencies in Children

Three cases of cytotoxic lesions of the corpus callosum with different etiologies

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Objective: The cytotoxic lesions of the corpus callosum (CLOCCs) was named also as mild encephalitis/encephalopathy with a reversible splenial lesion (MERS), is characterized by transient cytotoxic ovoid lesions at the splenium of the corpus callosum in patients without epilepsy or viral infections. Neurological manifestations include altered consciousness, seizures, behavioral changes, and delirium. Various clinical conditions are associated with CLOCCs.
We aim to report three cases of CLOCCs with different etiologies.

Methods: .....

Results: Case 1
A 13-year-old girl was referred to our pediatric intensive care unit because of altered consciousness and fever. On the physical examination, no abnormality was detected except for hyperpigmented spots in the folds of the hands and feet and on the gingiva. Laboratory tests detected hyponatremia. Brain MRI showed diffusion restriction in the splenium of the corpus callosum. The serum level of adrenocorticotropic hormone, which was checked for hyperpigmentation, was found to be very high. Based on these findings, she was diagnosed with CLOCCs associated with primary adrenal insufficiency. Oral hydrocortisone therapy was administered. She completely recovered.
Case 2
A previously healthy 17-year-old girl was admitted to our pediatric emergency outpatient clinic with a fever, vomiting, and headache. Physical examination revealed signs of meningeal irritation. Brain MRI showed a cytotoxic ovoid lesion in the splenium of the corpus callosum. Lumbar puncture was performed and no pathological finding was found except for mild protein elevation. Based on these findings, she was diagnosed with CLOCCs associated with aseptic meningitis.
Case 3
A 14-year-old girl was admitted to our pediatric emergency outpatient clinic with a fever, altered consciousness, and syncope. The systemic and neurological examination were normal. Brain MRI was compatible with CLOCCs. The level of troponin T was very high and electrocardiography showed ST elevation. Echocardiography revealed effusion in the pericardium. She was diagnosed with acute perimyocarditis, but no viral agent was found.

Conclusions: CLOCCs may present with acute encephalopathy and therefore may often be confused with meningoencephalitis clinically. However, diffusion restriction in the splenium of the corpus callosum, indicative of transient cytotoxic edema, is typical. CLOCCs should be kept in mind in patients who had acute neurological symptoms with typical MRI findings, even if the symptoms were mild.

Keywords:
CLOCCs, MERS, transient cytotoxic edema

EPNS23-2983 Oral or e-Poster
Neurological Emergencies in Children

2 B in Motion - Balance after mild traumatic brain injury - feasibility and first results

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Case study: Objectives:Pediatric mild traumatic brain injury (mTBI) represents a major health issue worldwide. Impairment in balance and postural control are often reported after mTBI and may set the patient at risk of sustaining a re-mTBI in the short term and of persistent post-concussion symptoms. A balance assessment may inform the clinician about pacing or clearance for return to physical activity after pediatric mTBI. However, no standard investigation in the point of care setting has been established so far and there is a high variability in the management of pediatric TBI. In our interdisciplinary pediatric concussion clinic, we set up a clinical study to explore differences in postural control between children recovering from mTBI and healthy controls.

Methods:In an explorative prospective controlled longitudinal cohort study we examine balance after mTBI in 50 children and adolescents (6-18 years) within 72 h, 2 weeks and 3 months after the injury. In addition, 50 age-matched healthy controls will undergo the investigations. Postural control is assessed by instrumented BESS (balance error scoring system) on a Leonardo Mechanograph®GRFP LT force plate (Novotec) and simultaneous innovative 3D markerless posturography using ReFit Gamo®of ReFit Systems GmbH with the Microsoft KinectTM as motion capture camera. All inquired outcome parameters of postural control derive from the participant's centre of pressure and 3D velocity of center of mass displacement.

Results:By time of abstract submission we included 36 patients. Analyses of the dataset are currently ongoing. First, all results of mTBI cases will be interpreted in the light of the results of recently published normative control data by Pilz et al, Mechanography in children: pediatric references in postural control [J Musculosk. Neuron. Interact.2022 Dec 1;22(4):431-454] and Heidth et al Simplified digital balance assessment in typically developing school children [Gait Posture.2021 Feb;84:389-394]. COVID-related restrictions did not allow control testing during the last months.

Conclusion:In our running study we provide data on feasibility and limitations of innovative 3D balance assessment in combination with clinical BESS and 2D force plate data. A standardized balance assessment is of importance for clinicians in day-to-day care of pediatric patients with mTBI to give personalized, appropriate advice for return-to-protocols in order to prevent re-trauma, minimize long-term effects and have best outcome.

Keywords:
pediatric mild traumatic brain injury, mTBI, balance, postural control, posturography, BESS

EPNS23-2310 Oral
Neurological Emergencies in Children

Prediction of "severe outcome" after near-drowning and other hypoxic events using early MRI - a pilot study

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Objective: The diagnosis of severe brain injury in children and adolescents after acute hypoxic events often trigger discussions about the continuation versus withdrawal of life-supporting therapies (like mechanical ventilation). To date, these decisions about life or death must be made despite a dramatic scarcity of supporting scientific data. In this pilot study, we attempted to clarify whether it is possible to identify predictors of severe outcome in children and adolescents with acute hypoxic brain damage, using MRI acquired within two weeks after the hypoxic event.

Methods: Retrospective analysis of 42 MRIs acquired within 14 days after an acute hypoxic event in 34 children and adolescents (age at hypoxia: 8 months- 17 years). Outcome was classified as "severe" when no voluntary motor activity and no social interaction was observed for at least 5 months after the hypoxic event, using our own RemiPro instrument which was designed to monitor the recovery of activity and participation in children with severe brain damage during early-phase neurorehabilitation.

Results: In our sample, the most reliable prediction of severe outcome was possible using diffusion-weighted MRI obtained on the 4th or 5th day after the hypoxic event (12 patients):
Only patients with severe outcome (n = 8) showed diffusion restrictions in the globus pallidus (7/8), the striatum (4/7) and the substantia nigra (4/8), while none of the patients with less severe outcome (n = 4) showed diffusion restrictions in any of these structures.

Conclusions: Prediction of "severe outcome" (the way we defined it in this retrospective analysis) after childhood hypoxia seems possible with early MRI, ideally performed on the 4th or 5th day after the hypoxic event. These findings should, however, not yet be transferred into discussions about withdrawal of life-supporting therapies (like discontinuation of mechanical ventilation), although there is urgent need for a data basis for such existential decisions. Future and prospective studies will first have to clarify the adequate outcome criterion for such decisions. In other words, we should be able to describe which of the potential consequences of hypoxic brain damage are worse than death, and then to predict these consequences, thereby justifying the withdrawal of life-supporting therapies.

Keywords:
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EPNS23-2671 Oral or e-Poster
Neurometabolic Disorders

Peroxisomal disorders spectrum - a case series.

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Case study: Peroxisomal disorders are a group of metabolic diseases in which peroxisome structure or function is altered - disorders of peroxisome biogenesis or deficiency of a single enzyme in peroxisome. There is a variable clinical presentation - the age of onset of symptoms, type of symptoms, evolution and severity of disease. Most often there is a clinical and biologic disease pattern, but there are also atypical cases that doctors should be aware of.
Objectives: The purpose of this study is to compare the clinical features of patients with peroxisomal disorders and to emphasize the existence of atypical clinical presentations, thus expanding further the spectrum of these disorders.
Methods: This is a retrospective study, and we report a series of five cases of patients with peroxisomal diseases: one with Zellweger syndrome (ZS), three with D-bifunctional protein (DBP) deficiency and one with peroxisome biogenesis disorder-4B (PBD4B). The clinical features, biological results and brain imaging findings were analysed, and the diagnosis was confirmed with genetic testing.
Results: Three out of five patients had typical presentations - early onset epilepsy, severe hypotonia, craniofacial dysmorphism, visual or hearing impairment, elevated very long chain fatty acids (VLCFA) levels, subependymal cysts and early death. The patient with the most severe form had Zellweger syndrome, the other two had DBP deficiency. Two out of five patients did not fit the pattern - one with DBP deficiency had later clinical onset and a milder course of disease (cognitive delay and autistic features, progressive gait abnormalities with demyelinating polyneuropathy, normal VLCFA, growth hormone deficiency with delayed puberty, malformations of cortical development), reaching adulthood. The other one, with PBD4B, also had an atypical onset, with nodular subcutaneous hemorrhagic lesions and cerebral hemorrhage at the age of 2 months, with focal seizures afterwards and psychomotor regression, hypotonia, hearing and visual impairment, elevated VLCFA; she is now 3 years old. All patients were confirmed with genetic testing.
Conclusions: Peroxisomal disorders are metabolic diseases difficult to diagnose because of the clinical heterogeneity, being also a rare entity in pediatric neurology. There is a necessity for a structured algorithm in diagnosing that can prevent the diagnostic delay and allow prompt tailored intervention.

Keywords:
peroxisomal disorders, Zellweger syndrome, D-bifunctional protein deficiency, peroxisome biogenesis disorder-4B, VLCFA

EPNS23-2843 Oral or e-Poster
Neurometabolic Disorders

Analysis of occurrence and treatment of device related adverse events under longterm ICV-ERT in CLN2 patients

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Objective: Biweekly intraventricular (ICV) application of Cerliponase alfa (ICV-ERT) is the only approved treatment for CLN2 disease. We have treated 61 patients with 6607 ICV device punctures at our centre. Long infusion time of 4 hours and recurrent ICV-ERT increase the risk for device related adverse events. In this study we analysed occurrence and treatment of any device related adverse event in our patient cohort.

Methods: This is a single center retrospective observational study.

Results: The following device related adverse events were encountered in 25 patients: Mechanical tube blockage (n=3), device leakage (n=15), device infections (n=15), and bacterial colonization of the device (n=12) without clinical signs of infection. All mechanical tube blocking events as well as 3 events of device leakage were treated with exchange of the respective devices. Device infections were defined as a combination of positive bacterial evidence in CSF culture, any clinical symptom such as headache, fever, nausea, and CSF pleocytosis (>30 cells/ul). All device infections were treated with device removal and intravenous antibiotic treatment, followed by placement of a new device after completion of antibiotic therapy. The combination of CSF pleocytosis and bacterial detection without clinical symptoms has not yet occurred. Device colonizations were defined as two consecutive positive CSF culture results with C. acnes without any clinical symptoms nor CSF pleocytosis. These 12 cases were treated with an antibiotic lock therapy by applying 10 mg of vancomycin, dissolved in 2 ml NaCl 0,9%, into the device after each ERT. Follow-up of these patients showed that this treatment was able to prevent infection of device with C. acnes in all patients to date with follow-up periods ranging from 24 weeks up to 224 weeks. As we prophylactically exchange the device in all patients after around 200 weeks per standard of care, the latter is the maximum follow-up time.

Conclusions: Bacterial device infections remain a significant risk under this treatment. Antibiotic lock treatment of device colonisations with C. acnes using vancomycin has been successful in preventing subsequent C. acnes device infections and avoiding necessity for device replacement. Therefore, distinction between device infection and colonisation is important in order to provide optimal treatment for these patients.

Keywords:
CLN2 disease, Biweekly intraventricular (ICV) application, Device infections, Cutinbacterium Acnes

EPNS23-2481 Oral or e-Poster
Neurometabolic Disorders

Adolescent-onset rapidly progressive encephalopathy associated with NAXE gene mutation

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Case study: Background. Biallelic mutations in NAXE (NAD(P)HX epimerase) gene leads to accumulation of NADHX and NADPHX toxic metabolites and mitochondrial dysfunction. Clinical manifestations include fluctuating encephalopathy, gait disturbance, speech impairment, ataxia, dystonia, psychiatric problems, spasticity, and coma.

Objective. To draw attention to this rare syndrome, which is difficult to distinguish clinically from many other neurometabolic disorders, and to emphasize its treatment alternatives which may improve the outcome.

Case presentation. A 16-year-old girl presented with parkinsonism, gait disturbance, speech disorder, dysphagia, ataxia, dystonia, and spasticity noted in the previous six months. Her past history was unremarkable except third degree parental consanguinity. The initial brain MRI (magnetic resonance imaging), cerebrospinal fluid analysis, autoimmune work-up, metabolic panels, and toxic screening were all negative. As the initial diagnosis was hereditary spastic paraparesis or juvenile parkinsonism, symptomatic treatment with baclofen and L-Dopa were initiated. The case was discharged with partial improvement. One month later, she presented with severe encephalopathy and loss of motor skills. The repeated MRI revealed symmetrical diffusional restriction of bilateral caudate nuclei and putamen with mild T2 hyperintensity. The patient had slightly low ceruloplasmin levels, but no Kayser-Fleischer rings, and low urinary copper excretion, which did not confirm Wilson disease. Negative Dopamine-2 receptor antibodies ruled out autoimmune basal ganglia encephalitis. With a preliminary diagnosis of thiamine-biotin-responsive basal ganglia disease, high doses of biotin, thiamine and mitochondrial coctail were initiated.

Whole exome sequencing (WES) analysis revealed a homozygous c.757G>A (p.Gly253Ser) variant in NAXE gene. The variant has been predicted as likely pathogenic in accordance with the ACMG recommendations. The patient had moderate improvement with niacin and coenzyme Q10.

Conclusion remarks. The clinical phenotype of NAXE gene mutations is diverse, depending on the genetic variants. Although the disease is more common in infancy and early childhood, it may also appear in adolescence and early adulthood. Since early initiation of niacin and coenzyme Q10 may provide clinical improvement and prevent further attacks, NAXE gene mutations should be kept in mind in cases with intermittent encephalopathy, gait disturbance, dystonia, or spasticity.

Keywords:
NAXE gene, progressive encephalopathy

EPNS23-2521 Oral or e-Poster
Neurometabolic Disorders

Thiamine (B1) Deficiency In Children Following Bariatric Surgery

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Case study: Introduction:
The prevalence of obesity among children is rising and poses a major health concern. Bariatric surgery is well established in adults and is becoming an option for adolescents. B1 deficiency is common following bariatric surgery. It may present as Beri-Beri, Wernicke's encephalopathy, or Korsakoff's psychosis.
Objective:
The aim of this report is to increase the awareness of neurological sequel of B1 deficiency due to bariatric surgery and the importance of prompt diagnosis and treatment to prevent neurological deficits. .
Methods:
The data of 3 children presenting with symptomatic B1 deficiency following bariatric surgery was collected retrospectively from the electronic database.
Results:
Three adolescents with morbid obesity (2 boys, 1 girl, ages 15.5 to- 17-year-old), presented with progressive lower limb pain and weakness 2-2.5 month following a bariatric procedure (sleeve gastrectomy or narrowing of a bariatric band). The girl also had upper limb involvement and dysarthria.
They've lost 25-50 kg and were non-compliant with their vitamins. On examination the two boys had lower limb weakness, hypo/areflexia. The girl had quadriparesis, areflexia, loss of vibration, position, fine touch, and cerebellar signs. Nerve conduction studies showed axonal sensory-motor polyneuropathy. The girl also had high signal intensities in T2/Flair in the cerebellum and mamillary bodies on brain MRI.
One boy was treated with intravenous (IV) immunoglobulins for suspected Guillain Barre syndrome. He then received IV thiamine and per os (PO) multivitamin supplements. The others received IV thiamine and PO multivitamins on admission. Thiamine deficiency was later confirmed in two of the cases, for the third case confirmation was lacking due to technical problems. The girl also had vitamin C, D, and folate deficiencies.
On follow up one recovered completely; the other remained with foot drop; the girl's cerebellar signs resolved, except for mild dysmetria, weakness resolved in upper limbs and improved in proximal lower limbs, and sensation improved greatly.
Conclusions:
Vitamin supplementation following bariatric surgery is crucial to prevent deficiencies. In children, assessment of compliance before surgery, and its assurance after surgery are essential.
Thiamine deficiency may cause polyneuropathy among other symptoms. Treatment prevents permanent damages. In young children even subclinical deficiency may impair neurodevelopment.

Keywords:
thiamine deficiency, B1 deficiency, bariatric surgery, sensory-motor polyneuropathy, adolescents

EPNS23-2878 Oral or e-Poster
Neurometabolic Disorders

2 siblings with vanishing white matter disease

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Case study: Vanishing white matter disease; is one of the most common inherited leukoencephalopathies. It affects individuals of all ages, from prenatal to advanced age, but is most common in young children.It is caused by mutations in any of the five genes that encode subunits of eukaryotic translation initiating factor 2B (eIF2B). In this article, 2 siblings with the same genetype are presented. First case: A five-month-old girl was brought with the complaint of seizures. It was learned that the patient had a seizure for the first time, and the seizure was generalized tonic-clonic, lasting for 1-2 minutes during the fever-free period. From the history of the case, it was learned that a 28-year-old father and a 26-year-old mother, who were first-degree consanguineous (children of uncles), She was breastfed in the first three months, head and neck control began, her head circumference measurements were normal, object tracking began, she was related to the environment, but after the third month she started not taking the breast, refusing to feed, recurrent vomiting and diarrhea attacks that lasted for one or two days. In physical examination is no dysmorphic sign or organomegaly.There is spontaneous movement in all four extremities, hypotonic and deep tendon reflexes were increased. On Cranial MRI, it is observed that white matter areas that appear hyperintense on T2 sections are hypointense on FLAIR sections. These findings are more clearly distinguished in Cranial MRI taken at 16 months of age. While cerebral white matter disappears, CSF intensity is seen in T1 and FLAIR sections .Homozygous mutation found inEIF2B4 gene. The patient uses multiple antiepileptic drugs due to his seizures.She is 2.5 years old now.Seizures are under control with triple antiepileptic.She is tetraparesis The mother conceived spontaneously despite genetic counseling. He was born as a term boy by cesarean section. Genetic analysis was sent due to sibling history and the same genetic mutation was detected. The patient achieved head and neck control at the age of 2-3 months. He started sitting at 7 months old. At 8 months of age, motor retardation started after fever. His seizures started when he was 9 months old.Although neuromotor developmental retardation started later than her sibling, MRI findings started to be detected early.

Keywords:
EIF2B gene; Vanishing white matter; Epilepsy

EPNS23-2563 Oral or e-Poster
Neurometabolic Disorders

Riboflavin transporter deficiency as a cause of progressive encephalopathy

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Case study: Riboflavin transporter deficiency (RTD), previously known as Brown-Vialetto-Van Laere syndrome and Fazio-Londe syndrome, is a rare neurodegenerative disease caused by mutations in the SLC52A2 (RFVt-2) or SLC52A3 (RFVT-3) gene. Patients have predominant symptoms of progressive encephalopathy in the form of peripheral neuropathy and neuropathy involving the cranial nerves, consequently causing muscle weakness, decreased muscle tone, vision loss, sensorineural hearing loss, plexiform syndrome, sensory ataxia, and respiratory failure associated with diaphragmatic paralysis.
Riboflavin at the cellular level is converted into activated flavin cofactors: FMN via riboflavin kinase mediating riboflavin phosphorylation, and then FAD via flavin dinucleotide synthetase 1 mediating FMN adenylation. FMN and FAD are incorporated into 90 different proteins, collectively referred to as the "flavoproteome," most of which are oxidoreductases located in mitochondria that catalyze electron transfer during various redox metabolic reactions, including: oxidative decarboxylation of amino acids and glucose, and ?-oxidation of fatty acids. Of particular note are flavoproteins, which are key to the function of mitochondrial oxidative phosphorylation .
The description concerns siblings diagnosed with riboflavin transporter deficiency caused by a mutation in the SLC52A2 gene. The first symptoms appeared in the older 5-year-old sister, in whom the progressive course of the disease (during 6 months: complete regression of motor and speech development, ataxia, horizontal nystagmus, lack of fixation, hearing loss)was arrested after the implementation of high doses of vitamin B2. Gait abnormalities, which then occurred in her younger sister at age 3, prompted the beginning of molecular diagnostics and confirmation of RTD.

Keywords:
riboflavin transporter deficiency, progressive encephalopathy

EPNS23-2190 Oral or e-Poster
Neurometabolic Disorders

Prevalence of Aromatic L-Aminoacid Decarboxylase Deficiency and Selected Inborn Errors of Metabolism Mimic Cerebral Palsy in South Eastern Turkey

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Objective: Cerebral palsy (CP) is a clinical diagnosis used to describe a group of disorders of movement and posture that attributed to the disturbances in developing brain. Genetic, metabolic, ischemic, and infectious causes are defined in the etiology of CP. Out of metabolic causes Aromatic L-Aminoacid decarboxylase (AADC) deficiency is one of the ultra-rare and treatable inborn error of metabolism that mimics CP. When the etiology of CP can be identified, there will be a chance for specific treatment and prenatal diagnosis. Although, Southeastern of Turkey is a region with the highest prevalence of parental consanguinity and birth rate, up to now there have been no study performed for the etiological evaluation of CP-like conditions.

Methods: The prevalence of neurotransmitter disorders and AADC deficiency in the etiology of CP-like conditions and the important clinical signs and symptoms that indicate these disorders were aimed to document in 750 patients with the coordination of Çukurova University, Department of Pediatric Metabolism and the participation of 11 other centers. A case report form consists of the symptoms of hypotonia, dystonia, delayed developmental and motor functions, oculogyric crisis, and other movement disorders together with metabolic investigation results, electroencephalography and cerebral magnetic resonance imaging findings was prepared. Patients who had overt hypoxic-ischemic encephalopathy, resistant epileptic seizures, and encephalitis history, organic brain lesions and lack of deep tendon reflexes on physical examination were excluded. A dystonia panel including 88 genes was performed.

Results: Out of 364 samples, two patients had AADC deficiency (0.55 %) and 15 (4.12 %) had other neurometabolic or neurological diseases. Two late-diagnosed AADC deficiency cases who had phenotypic heterogeneity also shared some clinical features with the other neurometabolic disorders.

Conclusions: This project may be a small step for detection of some treatable neurometabolic diseases including AADC deficiency considered in differential diagnosis of CP. But to prevent future brain damages, counselling with the parents for family screening and prenatal diagnosis, behind putting forward the most frequent clues in thinking a neurotransmitter disorder in CP-like conditions will be great options. The epidemiological data obtained from this study will also give an idea about some candidate diseases for newborn screening in Southeastern Turkey.

Keywords:
Cerebral Palsy, Aromatic L-Aminoacid Decarboxylase Deficiency, Inborn Errors of Metabolism

EPNS23-2480 Oral or e-Poster
Neurometabolic Disorders

Title. Cognitive profile and its relation to MRI findings in pediatric patients with Glutaric Aciduria Type-1

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Objective: Objectives. Glutaric acidemia type 1 (GA-1) is an autosomal recessive disorder of lysine, hydroxylysine, and tryptophan metabolism associated with an increased risk of neurodevelopmental alterations. Here we aim to describe the cognitive phenotype and the MRI findings that might be related.

Methods: Methods. A total of 41 patients underwent a neuropsychological testing consisting of the Bayley Scales of Infant and Toddler Development (Bayley-III) in case of patients < 4 years old and a battery of cognitive tests considering abstract reasoning, information processing speed (IPS), language, visuocognitive skills, executive functions (EF), psychomotor speed for > 4 years old. 21 of these patients also underwent an MRI scan.

Results: Results. In terms of the Bayley-III results, the mean cognition score was within the average range (0.44±1.27) showing the lowest results in the gross motor subscale (-0.35± 1.29). Mean intellectual indexes were on the average. Mild specific cognitive deficits were shown in attention (-0.93±0.96) and visuocognitive skills (-0.71±0.65) more severe in executive functions (-1.47±0.71). Regarding MRI, IPS, language, EF and abstract reasoning were related to MRI alterations. Specifically, IPS was related to opercular dysplasia, WM restriction and lesions in WM. Striatal lesions were related to abstract reasoning and language.

Conclusions: Conclusions. Our results show patients with AG-1 are in risk of specific cognitive deficits being more evident when an MRI alteration is presented. Still, cognitive outcomes vary between patients and are important for targeting the most adequate neurorehabilitation program.

Keywords:
Glutaric acidemia, cognition, MRI

EPNS23-2465 Oral
Neurometabolic Disorders

GENERALIZED CHOREODYSTONIA SUCCESFULLY TREATED WITH INTERNAL GLOBUS PALLIDUS DEEP BRAIN STIMULATION IN A PATIENT WITH AIFM1-RELATED DISORDER.

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Case study: Objectives. Apoptosis-inducing factor mitochondria associated 1, a mitochondrial flavoprotein, is encoded by AIFM1. Variants in this gene have been associated with several phenotypes but have not previously been associated with generalized choreodystonia. To describe the case of a 6-year-old boy with generalized choreodystonia and a AIFM1 variant who underwent internal Globus Pallidus deep brain stimulation with good results.
Methods. Exome sequencing was performed with confirmation by Sanger sequencing. Muscle biopsy, OXPHOS activity, spectral and redox properties of the S57P AIF in E. coli, and apoptotic functional analysis in fibroblasts were completed to assess the pathogenicity of the variant. Deep brain stimulation was performed on the patient.
Results. Exome sequencing of the proband identified a X-linked missense AIFM1 variant (c.169T>C/S57P), classified as a variant of unknown significance. Mitochondrial cocktail and tetrabenazine have been started since the diagnosis, with only minor improvement. Plasma lactate, amino acids, and urinary organic acids were normal, but the activities of mitochondrial complex III and citrate synthase in the muscle biopsy were decreased. Brain MRI showed agenesis of the knee and rostrum of the corpus callosum, agenesis of both olfactory bulbs, hypomyelination, and dysmorphic basal ganglia. Spectral and redox properties of human wild type (WT) and S57P AIF in E. coli did not show any significant difference. A functional apoptosis examination with staurosporine revealed significant apoptosis impairment when compared to control, confirming the pathogenicity. Deep brain stimulation of the internal Globus Pallidus improves choreodystonia.
Conclusion. This case of a patient with generalized choreodystonia and an AIFM1 variant highlights the benefits of appropriate patient selection for deep brain stimulation and the need for functional studies to confirm the pathogenicity of variants, particularly in this gene, for which there may be no other clinical or laboratory evidence to support the diagnosis of a mitochondrial disease. It also suggests a link between deep brain stimulation and the treatment of choreodystonia in patients with mitochondrial diseases.

Keywords:
AIFM1, mitochondrial disorders, deep brain stimulation, apoptosis

EPNS23-2416 Oral or e-Poster
Neurometabolic Disorders

Ketogenic diet treatment for children with mitochondrial diseases

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Objective: The ketogenic diet (KD) is the treatment of choice in patients with pyruvate dehydrogenase deficiency (PDHD), but its efficacy is still unproven in patients with mitochondrial diseases (MD) of different pathogenesis than PDHD.

Methods: This study retrospectively analyzed the efficacy and adverse effects (AEs) of ketogenic diet treatment in patients with PDHD and MD. Clinical symptoms (in particular: psychomotor development, severity of movement disorders, muscle tone, exercise tolerance, occurrence and severity of epileptic seizures were evaluated) and additional tests: ALT, ASPT, cholesterol triglycerides, blood gas, glucose, creatine kinase, abdominal ultrasonography, ECG were taken into account.

Results: 12 PDHD and 14 MD patients treated with DK were analyzed. The median age of DK treatment initiation in these patients was, respectively: 33.5 (4-70) and 40.5 (3-181) months, and median duration of treatment: 38.5 (5-134) and 10 (0.5-147) months. In the PDHD group, only 1 patient had no improvement/benefit from treatment vs 4 in the MD group. DK had to be discontinued due to AE in 5 with MD but in no patient with PDHD. Mild hypertriglyceridemia (TGA>150 mg/dl, max 249) was more frequent in patients with MD vs PDHD, but other AEs occurred with comparable frequency in both groups: nausea, vomiting, mild hypercholesterolemia, metabolic acidosis, mild hypertransaminasaemia, hyperuricemia, kidney stones.
Significantly greater improvement in psychomotor development, improvement in muscle tone or in movement disorders (ataxia, tremor) was observed in PDHD patients than in MD, and a reduction in epileptic seizures was obtained in both groups. In patients with PDHD, complete seizure control was achieved in 4 of 5 patients, whereas in patients with MD such control was achieved in only 1 of 9 epileptic patients.

Conclusions: DK in patients with MD should be managed with caution, occurrence of AEs is more frequent than in PDHD patients and may be a reason to discontinue the treatment. The benefits of DK treatment in patients with MD are less than in patients with PDHD, but are noticeable. DK treatment can be cautiously considered in patients with MD.

Keywords:
ketogenic diet, PDHD, mitochondrial diseases

EPNS23-2648 Oral or e-Poster
Neurometabolic Disorders

Case report of a patient with Menkes disease

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Case study: Introduction: Menkes disease is a rare condition which is caused by mutations in the ATP7A, which is related to copper-transporting1. It is characterized as lethal multisystemic disorder of copper metabolism, including connective tissue abnormalities, neurodegeneration and peculiar "kinky hair". Non-febrile seizures are the main symptom that appears early in life, within the neurodevelopmental regression2. The disease is X-linked inherited.3 The incidence is about 1 in 35000 live male births.
Aim: To describe a case of a male infant with Menkes disease and discuss the challenges regarding the treatment and prognosis.
Materials: Patient's blood was taken for genetic analysis for ATP7A, as well as blood for copper analysis.
Methods: Automatic DNA extraction, using sequence analysis and deletion/duplication testing of 320 genes. Also, brain CT, brain MRI and electroencephalogram were used as diagnostic tools.
Results: We present a male infant on the age of 3 months, who firstly visited the neurology department because of non-febrile seizures and trunkal hypotonia. The genetic analysis showed one pathogenic variant identified in ATP7A, which is associated with X-linked Menkes disease, occipital horn syndrome and distal hereditary motor neuropathy.
Conclusion: Although this condition is quite rare, the typical clinical picture of the patient is noteworthy and has the main role in the diagnostic procedure. Once the suspicion for Menkes disease is present, further laboratory, imaging and genetic testing is necessary. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risksupport a clinical diagnosis and assist with the development of a personalized treatment and management strategy.

Keywords: ATP7A gene, Menkes disease, X-linked, seizure

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Keywords:
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EPNS23-2616 Oral or e-Poster
Neurometabolic Disorders

Effects of sodium lactate infusion in two teenagers with Glucose Transporter 1 Deficiency Syndrome.

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Objective: Glucose is the principal fuel for the brain. The passive transport of glucose across the blood-brainbarrier is limited in glucose transporter type 1 deficiency syndrome (GLUT1DS). Most induviduals with GLUT1DS present with developmental problems, epilepsy, and (paroxysmal) movement disorders. The ketogenic diet is the standard treatment for GLUT1DS, but is not effective in all individuals. Similar to ketones, lactate can be an alternative energy source for the brain. The aim of this study is to investigate whether intravenous lactate infusion can therapeutically be applied in children with GLUT1DS.

Methods: We performed a prospective, proof of principle study with two subjects with GLUT1DS, not following a ketogenic diet. After the start of EEG recording, sodium lactate (600 mmol/l) was infused, starting with a rate of 0,1 mmol/kg/min for 15 minutes, followed by 0,06 mmol/kg/min for 105 minutes. Serial blood samples were taken to monitor serum lactate, glucose, electrolytes and pH.

Results: Baseline EEGs of both subjects showed frequent bilateral, frontocentral poly-spike-and-wave complexes. In one subject no more epileptic discharges were seen 40 minutes after the start of lactate infusion, corresponding with no clinically observable seizures. The EEG of the other subject did not change during or after lactate infusion. Lactate and sodium concentrations is serum increased during infusion and decreased at the end of the study.

Conclusions: This study suggests that lactate infusion might have the potential to offer a safe, alternative energy source for the brain in individuals with GLUT1DS, without adverse effects. Additional cellular abnormalities, beyond neuronal energy failure, may contribute to the underlying disease mechanisms of GLUT1DS and explain why not all individuals respond to the supplementation of alternative energy sources like ketones or lactate.

Keywords:
Glucose Transporter 1 Deficiency Syndrome; Lactate; Sodium lactate infusion; EEG; Neurometabolic Disorders; Movement Disorders;

EPNS23-2157 Oral or e-Poster
Neurometabolic Disorders

Aromatic L-amino acid deficiency in 16 patient cases from countries in the Middle East

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Objective: Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare, life-threatening, neurometabolic disorder resulting from mutations in the dopa decarboxylase (*DDC*) gene. Diagnosis of AADC deficiency is frequently delayed owing to non-specific symptoms and lack of disease awareness. Improving diagnosis is crucial to ensure patients achieve early access to treatment.

Methods: To examine the clinical presentation and diagnostic workup for 16 patients with confirmed AADC deficiency from the Gulf Cooperation Council countries in the Middle East.

Results: Sixteen patients (six females and ten males) from the Middle East, all born to consanguineous parents, were diagnosed with AADC deficiency (AADC-d). The age at diagnosis ranged from 10 months to 18 years, despite the majority of patients (n=15/16) presenting with symptoms of AADC-d before 12 months of age. The most commonly reported symptoms were developmental delay (81%), hypotonia (75%), insomnia/disturbed sleep and oculogyric crises (both 56%). Most patients (n=14) were misdiagnosed prior to receiving a diagnosis of AADC deficiency, cerebral palsy and seizures were common misdiagnoses. AADC-d diagnosis was confirmed by genetic testing (16/16, 100%), with 10 patients confirming diagnosis through use of a second diagnostic test, including cerebrospinal fluid metabolite analysis, AADC enzyme activity analysis or measurement of 3-O-methyldopa levels in dried blood spots. Eight separate variants in the DDC gene were identified; one patient carried a previously undescribed variant: an intronic mutation between exons 13 and 14 (c.1243-10A>G). The recommended first-line pharmacological treatments were used to treat many of the patients, i.e. dopamine agonists (n=9), vitamin B6 (n=13), and MAO inhibitors (n=3); however, many patients were judged to have had no response (n=6) or a mild-to-moderate response (n=5) to treatment. To date, the majority of patients have failed to reach motor or developmental milestones with only two patients achieving the ability to walk. Five patients (31.3%) were deceased at the time of data collection.

Conclusions: There is an urgent need for earlier diagnosis, particularly given the potential for gene therapy as a transformative treatment for AADC deficiency when provided at the earliest age possible.

Keywords:
AADC deficiency, delayed diagnosis, developmental delay, whole exome sequencing, case report

EPNS23-2847 Oral or e-Poster
Neurometabolic Disorders

FASTKD2 gene mutation presenting with status epilepticus evolving to super-refractory status in dizygotic twins

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Case study: Objectives:Status epilepticus is less frequently the initial manifestation of mitochondrial disorders in pediatric cohorts.FASTKD2 gene encodes a mitochondrial protein associated to human COX deficiency,and seems to have a role in the maturation of different mitochondrial transcripts.Methods:Our aim is to present dizygotic twins with status epilepticus evolving to super-refractory status, metabolic stroke and homozygous frameshift mutation in the FASTKD2 gene.Results: A 10-month-old boy(corrected age 8.5 months) and his dizygotic twin,a girl,were admitted due to fever and focal motor seizures.Parents were second cousins.Developmental milestones were age-appropriate.Twin girl had a prodromal right-sided weakness before admission.Physical examinations were otherwise normal.Blood tests revealed mild lymphopenia and increased lactate levels.Cranial MRI showed symmetric diffusion restriction in bilateral subthalamic nuclei.Initial CSF studies were negative.Ceftriaxone,acyclovir,thiamine,biotin and mitochondrial cocktail were introduced.EEG showed periodic high amplitude spike-wave discharges alternating with periods of suppression in the right hemisphere.The boy developed left-sided hemiparesis at day 3;follow-up MRI showed diffusion restriction in the right basal ganglia and hippocampus which was considered as a metabolic stroke.First tier metabolic screening was negative.First and second line treatments were ineffective.Midazolam, bolus steroid therapy,magnesium,IVIg,lorazepam,ketamine and thiopental infusions were used.Levetiracetam,clobazam,phenytoin,oxcarbazepine,topiramate were introduced gradually,and finally seizures responded to lacosamide.CSF lactate was 17.8 mg/dL in the repeat study. Limbic and viral encephalitis panels were negative.MRI at two-weeks showed newly emerged diffusion restriction in the contralateral putamen and hippocampus.Both twins were ventilated through tracheostomy by the 1st month,feeding was through gastrostomy by the 2nd month of admission.Despite seizure control with polytherapy,prognosis was poor with severe developmental regression,loss of visual contact and pyramidal tract signs.WES revealed a homozygous frameshift mutation in FASTKD2 gene.Conclusions: Mitochondrial status epilepticus is reported rarely and challenging in terms of management and prognosis.Other than a lateralization difference, this dizygotic twins had identical clinical and radiological findings which further expands the phenotype of FASTKD2 gene mutation.

Keywords:
status epilepticus, child, COX deficiency, FASTKD2 gene

EPNS23-2526 Oral or e-Poster
Neurometabolic Disorders

Impact of novel or rare AIFM1 pathogenic variants on mitochondrial metabolism and clinical manifestation in eight patients, including three girls

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Objective: Apoptosis-Inducing Factor 1, mitochondrial (AIFM1) protein interacts with coiled-coil-helix-coiled-coil-helix 4 (CHCHD4) protein, the main protein of the CHCHD4/Mia40 mitochondrial import pathway. Both proteins are indispensable in the transport, assembly, and maturation of small, nuclear-encoded proteins with CXnC motifs, which include several structural subunits of complex I (CI), complex III (CIII), and complex IV (IV) of the respiratory chain (RC) and their assembly factors. AIFM1 gene mutations lead to an X-linked combined oxidative phosphorylation deficiency (MIM*300169).

Methods: Patient 1 (P1), suffering from encephalomyopathy due to rare variant c.506C>T (p.Pro169Leu) in the AIFM1 gene, died at 3 months (M) of age. His heterozygous sister is 3.5 years old with microcephaly, delayed development, hypotonia, and paleocerebellar syndrome. Patient 2 (P2) and his brother (P3), both died at age of 3 M suffering from hypertrophic cardiomyopathy (HCMP) and Leigh syndrome (LS), are hemizygotes for the same variant as P1. Their two heterozygous sisters (33 and 6M) manifest HCMP and epilepsy. Patient 4 is a 7-year-old boy with myoclonic epilepsy and psychomotor retardation due to a novel variant c.1267G>A (p.Val423Ile). Patient 5 (P5) with optic atrophy and LS died at 18M due to a novel variant c.1391T>C (p.Leu464Trp). We characterized the effect of the AIFM1 variants on mitochondrial metabolism using SDS-PAGE/WB, BN-PAGE/WB, and spectrophotometry in available tissues.

Results: The levels of AIFM1 and CHCHD4 proteins were decreased significantly, and a correlation between the remaining level of both proteins was found. The analysis of RC subunits from P1-P5 showed a significantly reduced level of all analyzed CI and CIV proteins. The most affected were P1 and P2 with p.Pro169Leu. Almost complete absence of CI and respirasome, decreased CIV, and increased III2+IV in P2 were found. Mitochondria of the P2 sister P2 showed a reduced level of CI and respirasome by approx. half compared to controls and significantly decreased levels of AIFM1 protein and CI subunits.

Conclusions: We confirmed and characterized the negative impact of three distinct AIFM1 gene variants on RC. The most profound effect p.Pro169Leu variant is consistent with the severity of the disease. In two families, girls heterozygous for a pathogenic AIFM1 variant manifest severe phenotype, which should be considered in genetic counseling.

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Keywords:
AIFM1, mitochondria, X-linked, respiratory chain, metabolism

EPNS23-2931 Oral or e-Poster
Neurometabolic Disorders

Mucopolysaccharidosis type 1- neuroradiological presentation in children based on single centre experience

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Objective: Mucopolysaccharidoses (MPS) are group of inherited lysosomal storage disorders resulting from mutations of genes encoding various lysosomal hydrolases involved in degradation of glycosaminoglycans (GAGs, previously named mucopolysaccharides). These enzyme deficiencies lead to undegraded GAGs accumulation within the lysosomes, resulting in progressive cellular dysfunction and multisystemic disease. The MPS disorders are classified based on genes affected, lack or defect of specific lysosomal enzymes, age of presentation and typical clinical features. Presented analysis of neuroimaging manifestations is based on 5 children with MPS 1.

Methods: Brain and spine MRI were performed using Optima 1.5T or Artist 1.5T GEM (General Electric, GE Healthcare, Milwaukee, WI, USA). Imaging protocol of brain MRI includes standard sequences: T1, T2, T2 Flair, DWI (diffusion weighted imaging) and SWI (susceptibility weighted imaging) and T1 3D post contrast. Imaging protocol of spine MRI includes standard sequences: sagittal T1, T2, STIR, DWI, 3D CUBE T2, when scoliosis is present - coronal 3D STIR. For assessment of cranio-cervical junction focused 3D T1 or T2 sequence is additionally performed.

Results: The most consistent findings among our patients were observed at the border of head MRI. All five of them presented with sella turcica distortions and fluid effusion in temporal bone. Within the brain, either delayed myelination or white matter (WM) signal abnormalities were observed. Although two of the examined children did not present perivascular spaces (PVS) enlargement, one of the remaining three cases had typical corpus callosum PVS enlargement. Other neuroradiological symptoms covered: narrow corpus callosum, prominent ventricular system, arachnoid cyst, optic nerve sheath enlargement, posterior fossa horns, closed sagittal suture, vertebral bodies deformity, intervertebral disc anomalies.

Conclusions: Neuroimaging - mainly magnetic resonance (MRI) plays a crucial role in disease diagnosis and monitoring. Early diagnosis is of utmost importance due to the necessity of an early therapy implementation. New imaging tools like MR spectroscopy (MRS), semiquantitative MRI analysis and applying scoring systems help substantially in MPS 1 surveillance. The vigilance of radiologist based on knowledge of neuroradiological patterns is highlighted.

Keywords:
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EPNS23-2947 Oral or e-Poster
Neurometabolic Disorders

Clinical and imaging features of mitochondrial disorders

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Objective: Mitochondrial disorders are a group of genetic diseases where the function, the number or the dynamics of mitochondrial replication are affected. The goal of our study is to raise awareness of these rare diseases and provide some diagnosis clues by describing clinical and imaging features which are evocative and highly compatible with these conditions.

Methods: From the cohort of patients with mitochondrial disorders evaluated in our clinic from January 2019 to December 2022, we selected 9 patients, 5 boys and 4 girls, with genetically confirmed syndromic mitochondrial disorders. Targeted next-generation sequencing (NGS) methods were used for the genetic diagnosis. We took in consideration the pathogenic variants, as well as the variants of uncertain significance (VUS) where the phenotype was highly compatible.

Results: In our cohort, there are 6 children with chronic progressive course of the disease and 3 with acute episodes of decompensation. Regarding the genetic etiology, 4 of them had a variant in the mitochondrial genome, while the rest had a variant in the nuclear genes involved in the synthesis of mitochondrial proteins. The onset of the disease was in the first year of life for most of our patients, while in a third of cases the first symptoms appeared between the age of 1-3 years and in other 2 cases after the first decade of life. Almost all of them presented failure to thrive. Most common the neurological examination revealed global developmental delay, while epilepsy was a common feature in almost a half of our cohort. Four children presented ataxia, 3 of them severe motor impairment, and 1 dystonic movements. Multisystem involvement was also found in 2 cases with cardiac dysfunction, 2 with progressive visual impairment and one case with respiratory insufficiency. The serum lactate was elevated just in 3 cases, of which had periodic acute metabolic decompensations. Brain MRI showed cerebral and cerebellar atrophy in 2 cases and corpus callosum anomalies in other 2. Leukodystrophy, basal ganglia and brain stem anomalies were also described.

Conclusions: The 9 cases we present are representative for 6 mitochondrial disorders. The suspicion of mitochondrial disorders is made by correlating the clinical features with neuroimaging, then genetic testing gives the diagnosis certainty. A better understanding of the mitochondrial genetics can lead to an early diagnosis and appropriate management of these conditions.

Keywords:
mitochondrial disorders, neuroimaging, genetics

EPNS23-2057 Oral or e-Poster
Neurometabolic Disorders

Baseline Demographics in MIT-E: Efficacy and Safety Study of Vatiquinone for the Treatment of Mitochondrial Disease Subjects with Refractory Seizure

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Objective: In mitochondrial disease, pathogenic variants in mitochondrial or nuclear genes result in energy dysregulation and cellular dysfunction. This leads to oxidative stress and accumulation of lipid peroxides, promoting regulated cell death (ferroptosis), pro-inflammatory signaling, and depletion of reduced glutathione. It is hypothesized that this creates an excitatory/inhibitory imbalance resulting in seizures. Vatiquinone, a novel inhibitor of 15-lipoxygenase, can prevent lipid peroxidation and subsequent oxidative stress and has been reported to slow disease progression in clinical studies of patients with mitochondrial disease. MIT-E is a phase 2/3 randomized, placebo-controlled study of vatiquinone for the treatment of mitochondrial disease associated seizures.

Methods: Target enrollment was 60 subjects with mitochondrial disease and associated refractory seizures (unsatisfactorily treated with ≥ 2 anti-seizure medications). In this double-blind study, subjects were randomized 1:1 to receive vatiquinone at a dose of 15 mg/kg if body weight < 13 kg, and 200 mg if body weight ≥ 13 kg, three times daily (TID), or placebo TID for 24 weeks. The primary endpoint is percent change from baseline in frequency of observable motor seizures per 28 days. Key secondary endpoints include the number of disease-related hospitalization days, occurrence or recurrence of status epilepticus, number and percent of patients with disease-related inpatient hospitalization/emergency room visits, and health-related quality of life. Following the 24-week blinded phase, subjects are eligible for a 48-week open-label treatment phase.

Key inclusion criteria are genetic confirmation of mitochondrial disease with associated seizures, stable dose of anti-seizure medications 30 days prior to screening, and electroencephalogram for diagnosis of seizures. Key exclusion criteria are alanine transaminase or aspartate transaminase ≥ 3 × upper level of normal (ULN) at screening, coagulation function measured by international normalized ratio (prothrombin time and partial thromboplastin time) >ULN at screening, and serum creatinine ≥ 1.5 × ULN at screening.

Results: The MIT-E study enrolled 68 patients (50% female) with a mean age of 7.6 years. Their mean body mass index was 17.28 kg/m^2 and mean baseline seizures was 440.4 per 28 days.

Conclusions: The MIT-E study will provide data on the effect of vatiquinone on reduction in observable motor seizure frequency in subjects with genetically confirmed mitochondrial disease.

Keywords:
Vatiquinone, mitochondrial disease, seizure

EPNS23-2018 Oral or e-Poster
Neurometabolic Disorders

Acute Intermittent Porphyria as a Rare Challenging Neuro-Metabolic Disease; a Case Report

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Case study: Introduction:Porphyrias are a group of rare metabolic disorders representing a wide range of clinical manifestations.Clinical presentation of acute intermittent porphyria (AIP) is rare before puberty and the diagnosis is suggested by a triad of symptoms; severe abdominal pain, quadriparesis due to peripheral nerve involvement, delirium, and depression as the most common neuropsychiatric manifestation which dominates the clinical picture.
Case presentation:
A 9-year-old girl with no history of medical or familial diseases presented to the emergency department of Al-Araby international Hospital, Monufia, Egypt with severe abdominal pain, constipation, and headache which had started 10 days ago. Within the next few days following admission, the patient developed an attack of generalized tonic-clonic seizure associated with low-grade fever. On examination, the patient was confused in post ictal state. Otherwise the neurological and general examination was unremarkable. Patient was hemodynamically stable. Urgent brain computed tomography scan showed brain edema.The initial results of laboratory investigation revealed marked electrolyte disturbances.Our thinking about the case was changed after we considered multiple diagnosis and we had a rising concern about genetic disease. At that time, the whole-exome sequencing was sent abroad to CENTOGENE GmbH for genetic analysis.Electrophysiological studies were done which revealed evidence of purely motor axonal polyneuropathy affecting upper and lower limbs with bilateral facial axonal neuropathy.The CSF examination showed cytoalbuminous dissociation, and this made the diagnosis more challenging for Guiliane-Baree Syndrome. The patient received intravenous immunoglobulin with partial improvement.Genetic sequencing results showed a heterozygous pathogenic variant in the hydroxymethylbilane synthase gene which confirmed the diagnosis of autosomal dominant AIP. The patient received dextrose 25% and 2 doses of hemin 250 mg divided on four days, 2 weeks apart followed by another dose after 2 months. There was a marked improvement as regards the weakness, and abdominal pain, and we managed for weaning her from mechanical ventilation.
Conclusion:A diagnosis of porphyria should be considered particularly in those patients with abdominal complaints associated with electrolyte disturbances, seizures, and severe progressive neuropathy. Moreover, early diagnosis may considerably improve patient prognosis through proper management.

Keywords:
Electrolyte disturbance; acute intermittent porphyria; polyneuropathy; acute inflammatory demyelinating polyneuropathy

EPNS23-2583 Oral or e-Poster
Neurometabolic Disorders

Phenotypic spectrum related to biallelic variants in ALDH18A1 gene: insights into new therapeutic strategies involving the ornithine synthesis pathway

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Objective: ALDH18A1 encodes delta-1-pyrroline-5-carboxylate synthase (P5CS), an enzyme that catalyzes the first and common step of proline and ornithine biosynthesis from glutamate. ALDH18A1 mutations have been described in autosomal recessive neurocutaneous syndrome as well as in recessive and dominant hereditary spastic paraplegia. The aim of this work is to report two new cases and a therapeutic approach targeting P5CS deficiency.

Methods: Descriptive study of patients evaluated at the Metabolic Unit of a tertiary hospital. Clinical, biochemical, and genetic data of two patients were collected.

Results: Patient 1: 6-year-old male patient with personal history of feeding difficulties since neonatal period, failure to thrive, gastroesophageal reflux, and global neurodevelopmental delay with autistic features. Clinical examination showed microcephaly, hypotonia and ataxic gait with normal tendon reflexes. No ocular or skin abnormalities were found. Clinical exome sequencing revealed compound heterozygous variants in ALDH18A1 gene. Amino acid profile showed low CSF citrulline and low plasmatic ornithine and proline levels, consistent with P5CS deficiency. L-Citrulline supplementation was started. Plasmatic amino acid profile was normalized after 5-month treatment. There was a marked improvement in gastrointestinal symptoms and behavior. On follow-up, gait evolved to a spastic-ataxic pattern. Patient 2: 3-year-old female patient born to consanguineous parents, with personal history of feeding difficulties, failure to thrive and global neurodevelopmental delay. Physical examination showed microcephaly, dysmorphic features, hypotonia with unstable sitting posture and hyperreflexia. Brain MRI showed hypomyelinization and supratentorial. Fundus oculi revealed mild optic atrophy. A homozygous variant in ALDH18A1 gene was identified. Amino acid profile showed low CSF citrulline and low plasmatic arginine levels. L-Arginine, L-Citrulline and L-Proline supplementation was started. Amino acid monitoring is pending.

Conclusions: Predominant early-onset ataxia without cutaneous/ophthalmological signs expands the clinical presentation spectrum of biallelic ALDH18A1-related diseases. Spastic paraparesis might not be the presenting sign. Plasma amino acids are useful biomarkers to assess the ornithine synthesis pathway and ALDH18A1-related diseases. Long-term supplementation with citrulline, arginine and proline should be considered, although further evidence is needed to assess its therapeutic benefit.

Keywords:
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EPNS23-2953 Oral or e-Poster
Neurometabolic Disorders

A rare cause of cerebellar ataxia: Primary coenzyme Q10 deficiency-4, the first pediatric case from Turkey

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Case study: Background
Primary coenzyme Q10 deficiency-4(COQ10D4), also known as autosomal recessive spinocerebellar ataxia-9 is a rarely seen autosomal recessive disorder characterized by childhood onset of cerebellar ataxia and exercise intolerance. Primary coenzyme Q10 deficiency-4 is caused by homozygous or compound heterozygous mutation in the COQ8A gene. The number of cases reported in the literature is quite low, and to the best of our knowledge, no case has been reported from Turkey so far. Rarely, It is reported that high-dosage coenzyme Q10 supplementation in patients with COQ10D4 may help a positive clinical response. Herein, we report a pediatric patient who was diagnosed with COQ10D4 and showed good clinical outcomes in cerebellar symptoms with coenzyme Q10 supplementation as the first report from Turkey.
Case
An 8-year-old boy was admitted to our pediatric neurology department with speech and gait disturbances. He was born in term from a non-consanguineous Turkish family. He had a moderate neurodevelopmental delay, especially in language and motor functions, and an afebrile seizure history at four years old. He had a slight intellectual disability, minimal dysmorphic features, oculomotor apraxia, dysarthric speech, dysmetria, Achilles spasticity, and wide-based ataxic gai His metabolic screening was normal. Brain MRI showed cerebellar atrophy and vermian hypoplasia. Whole exome sequencing revealed compound heterozygous mutations in the COQ8A gene (c.1651G>A (p.Glu551Lys), pathogenic, and c.910_922del (p.Ala304fs), likely pathogenic). Each of his asymptomatic parents had one of the mutations heterozygously. After treatment with COQ10 for 3 months, his symptoms showed improvement, especially speech and walking skills.
Conclusion
COQ8A-ataxia is a rarely seen early-onset cerebellar ataxia, with complicating features ranging from epilepsy and cognitive impairment to exercise intolerance and hyperkinetic movement disorders. In the literature, it is reported that most of the patients who have been diagnosed with COQ10D4 could not have a remarkable improvement, especially in cerebellar symptoms with coenzyme Q10 supplementation. Our patient showed good clinical recovery especially speech and gait skills with coenzyme Q10 supplementation. To emphasize the COQ8A mutation at ataxia etiology, the present child with COQ10D4 who showed good clinical outcomes with coenzyme Q10 supplementation reported as the first pediatric patient from Turkey.

Keywords:
Primary coenzyme Q10 deficiency-4, cerebellar ataxia, coenzyme Q10, child

EPNS23-2695 Oral or e-Poster
Neurometabolic Disorders

Clues in the diagnosis of gangliosidoses

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Objective: The gangliosidoses comprise a family of autosomal recessive lysosomal storage disorders characterized by the accumulation of complex glycolipids in different tissues, including the brain. They are classified in GM1 (infantile, juvenile and chronic forms) and GM2 gangliosidosis (Tay-Sachs disease, Sandhoff disease, and the AB variant). Seldom the diagnosis is delayed because these are rare diseases, with overlapping phenotypes and various clinical and imaging findings. Thus, considering the severity of these disorders and the new therapies emerging, including gene therapy, an early diagnosis is imperative. The aim of our study is to identify clinical and paraclinical clues for an early diagnosis, emphasizing the importance of considering this diagnostic in the differential diagnosis of a neurodegenerative picture with onset in infancy.

Methods: This is a retrospective analysis of the medical data recorded between January 2010 and December 2022 of the patients diagnosed with gangliosidosis (search keywords: gangliosidosis, GM1, GM2). The history, clinical, laboratory and imaging findings of these cases were reviewed. The following data was assessed: demographic data, age of onset, early and late symptoms, evolution, clinical picture, global developement, laboratory and MRI findings. The definite diagnosis was made by molecular testing and/or enzyme assay.

Results: There were 6 cases of gangliosidosis, 5 of them diagnosed with GM1 gangliosidosis and 1 with GM2. In all cases children presented in the first 2 years of life. 4 children had normal development in the first 3-5 months of life. All 6 cases presented motor and cognitive regression, important axial hypotonia. 2 patients had hearing impairment, 5 children had progressive dysmorphism with coarse facial features, 3 developed limb spasticity, 3 had pharmacoresistant epilepsy and 2 had involuntary movements. In 3 of the cases red cherry spots and abnormal urinary oligosaccharides pattern were observed. 4 of the children had white matter lesions on MRI, 3 of them associating bilateral basal ganglia abnormalities.

Conclusions: Although the group of patients analyzed is not very large, there were observed important clues of diagnosis such as hypotonia, with a neurodegenerative clinical picture, progressive dysmorphism, and MRI white matter and basal ganglia abnormalities. Therefore this clues would increase the possibility of an early diagnosis confirmed by molecular testing.

Keywords:
GM1 Gangliosidosis, GM2 Gangliosidosis, neurodegenerative

EPNS23-2986 Oral or e-Poster
Neurometabolic Disorders

SLC35A2-CDG related early onset epileptic encephalopathy: Clinical features and treatment of epilepsy

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Case study: SLC35A2 encodes a Uridine diphosphate (UDP)-galactose transporter at Xp11.23. Its deficiency leads to inadequate galactosylation of N-glycosylated proteins in the Golgi apparatus and endoplasmic reticulum. Neurological symptoms are generally remarkable and epileptic encephalopathy can be devastating in SLC35A2-CDG patients. We describe a 12 month old female presenting with intractable epileptic spams and burst suppression electroencephalography pattern. Hypotonia, global developmental delay, skeletal deformities and retinal abnormalities were prominent features in the infantile period. Epileptic seizures were refractory to anti-seizure drugs (phenobarbital, topiramate, levetiracetam, valproate, vigabatrin, pyridoxine, tetracosactide, prednisolone). Ketogenic diet reduced epileptic seizure duration and frequency more than 50%. Brain magnetic resonance imaging revealed thinning of the corpus callosum at 12 months of age. Sanger sequencing analysis revealed c.747_757dup (p.Ala253Glyfs*100) in SLC35A2 gene. When the genetic diagnosis was confirmed, she was supplemented oral D-galactose 1.5 g/kg/day for 6 months. It was reported that galactose supplementation results in clinical and biochemical improvement in SLC35A2-CDG patients but she had no benefit from galactose. Moreover, increased frequency of epileptic seizures was observed probably due to reduction in serum ketone levels. Although seizure control was partially achieved (>50%) with the ketogenic diet, she did not benefit from oral galactose supplementation, which can be considered as a precision medicine for SLC35A2-CDG in the literature.

Keywords:
SLC35A2, CDG, ketogenic diet, galactose

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Neurometabolic Disorders

Clinical phenotypes associated to GLUT1-DS

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Objective: GLUT1 Deficiency Syndrome is a neurometabolic disease represented by the poor transport of glucose to the brain. GLUT 1 protein is synthesized at a molecular level by SLC2A1 gene. Chronic neuroglycopenia in the brain causes a various clinical picture such as: seizures, paroxysmal eye-head movements, movement disorders, cognitive and/or motor delay, microcephaly. Description of the phenotypic spectre of GLUT1 deficiency syndrome through a case series from our department.

Methods: Descriptive study-case series. I retrospectively reviewed clinical data, laboratory tests and genetic data for 10 cases from our clinic starting from 2014 to the present. All the results were comprised in a database and analyzed.

Results: All the patients had their first symptoms under the age of 2. Seizures and movement disorders dominated the clinical picture. Only 3 patients had microcephaly. There were some specific triggers for movement disorders such as: infections, fever, exercise, fasting. More than half of the patients suffered from cognitive and/or motor delay

Conclusions: GLUT 1-DS is a rare genetic disease with a various clinical picture which may represent a challenge for physicians to diagnose. The main laboratory tests for a certain diagnosis remain the lumbar puncture resulting in hypoglycorrhachia and genetic testing. Ketogenic diet is the treatment of choice for this syndrome.
Particularities: Presence of paroxysmal eye-head movements, recognized as a clinical sign highly specific for the diagnosis of this syndrome was present in just one patient.

Keywords:
GLUT-1, SLC2A1, hypoglycorrhachia

EPNS23-2214 Oral or e-Poster
Neurometabolic Disorders

Opportunities to improve screening programmes identifying patients with aromatic L-amino acid decarboxylase deficiency (AADCd) in the UK

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Objective: Aromatic L-amino acid decarboxylase deficiency (AADCd) is a rare neurometabolic disorder resulting from variants in the dopa decarboxylase (*DDC*) gene. AADCd diagnosis is often delayed because of variable clinical presentation. Patients are frequently misdiagnosed with more common conditions, such as cerebral palsy (CP), due to a lack of AADCd awareness. REVEAL-CP is a prospective, multicentre, multinational, interventional, non-registrational study designed to investigate AADCd prevalence in patients presenting with symptoms of CP and characterise genotypes associated with high 3-O-methyldopa (3-OMD) levels in dried blood spot samples. Following the study, UK paediatric neurologist investigators completed a survey on learning opportunities to improve AADCd early identification in patients who may be eligible for treatment.

Methods: In REVEAL-CP, patient records were first screened to exclude patients with genetic and/or CSF neurotransmitter analysis; 49 UK patients were then identified as suitable for 3-OMD testing. Following the study, UK investigators completed a survey developed in collaboration with PharmaGenesis, a third-party agency, including questions requiring yes/no, Likert scale and/or qualitative responses. Consensus was reached if most investigator respondents somewhat/strongly agreed to individual questions.

Results: Six investigators reached consensus on recommendations to improve UK AADCd patient identification: adoption of a more centralised record system between NHS trusts (e.g., between community and secondary paediatric practices); implementing genetic testing as the primary diagnostic tool for patients with CP-like symptoms of unknown aetiology; increasing clinicians' awareness of the differential diagnosis of neurotransmitter disorders in patients with CP-like symptoms; and earlier use of 3-OMD testing in the diagnostic workup of patients presenting with unexplained movement disorders or CP-like symptoms through the establishment of a nationally accredited 3-OMD service.

Conclusions: A greater number of patients with CP-like symptoms of unknown aetiology could be screened for AADCd if the investigators' suggestions are considered. The provision of additional resources will be key for targeted patient screening. Given the recent EMA and MHRA marketing authorisation approvals for the first licensed gene therapy for AADCd, these improved efforts for early diagnosis could prove critical to the timely and effective management of patients with AADCd.

Keywords:
AADCd, cerebral palsy, 3-OMD, REVEAL-CP

EPNS23-2612 Oral
Neurometabolic Disorders

The clinical and genetic spectrum of NCL in Children

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Objective: To describe the clinical spectrum, neuroimaging changes in children with genetic diagnosis of Neuronal ceroid lipofuscinosis (NCL)

Methods: Ambispective study of children with progressive myoclonic epilepsy undergoing genetic confirmation at the Pediatric Neurology clinic of a tertiary care center between 2014 and 2021. Clinical presentation and neuroimaging data were recorded in the case record proforma.

Results: 34 patients of NCL were included in the study and were divided into four clinical subgroups based on the age of onset (INCL n=7, LINCL n=20 & JNCL n=7). The common initial presentations were regression of milestones (88%), seizures (82%), visual impairment (41%), microcephaly (32%), movement disorder (30%) and developmental delay (12%). Fundoscopy showed bilateral optic atrophy (27%), pigmentary changes (18%) and bilateral cherry red spot (9%), maculopathy (4.5%) and normal (50%). On neuroimaging, diffuse cerebral (61%) and cerebellar atrophy (61%) were the commonest findings, while periventricular white matter hyperintensities were found in 25% children,
Among 35 cases, 31 were genetically confirmed and four were enzymatically proven. Sequencing showed pathogenic variations in TPP1 (35%), CLN6 (19%), CLN8 (16%), CLN5 (13%), PPT1 (10%), and MFSD8 (6%). All had worsening cognition with progressive myoclonic jerks and severe neuromotor impairment in the follow-up.

Conclusions: NCL is an important cause of childhood dementia. The most type of NCL in North Indian children is NCL-2 and NCL-6. Common clinical presentation is developmental regression and severe epilepsy with diffuse cerebral and cerebellar atrophy. Next generation sequencing is an efficient tool in its molecular diagnosis.

Keywords:
Neuronal ceroid lipofuscinosis, progressive myoclonic epilepsy, TPP1, CLN6, CLN8, CLN5, PPT1, MFSD8

EPNS23-2908 Oral or e-Poster
Neurometabolic Disorders

Cerebral Creatine Deficiency Syndrome; Long Term Follow-Up Outcomes

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Case study: Creatine (Cr) has an essential role for storage and transmission of energy through the regeneration of ATP. Arginine:glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT) are enzymatic pathways required for endogenous synthesis of Cr. Specific sodium and chloride-dependent creatine transporter (SLC6A8) is required for cellular uptake of Cr. Cerebral creatine deficiency syndromes (CDSs) are characterized by severe intellectual disability, seizures, development and speech delay, autistic features, movement disorders, and motor dysfunction. CDSs are potentially treatable inherited metabolic disorders and early diagnosis is essential for improved outcomes. We report, clinical and molecular characteristics and long-term follow-up outcome of five patients from four unrelated families with GAMT and SLC6A8 deficiency.
Two of five patients had GAMT deficiency while three had SLC6A8 deficiency. All of patients had symptom onset in the first year of life. Mean age of CDSs diagnosis was 8 years (range 3-13 years). Mean age at last follow up was 16.6 years (range 10-24 years). The mean time from symptom onset to diagnosis was 7 years (range 2-11 years).All of patients had autistic features, speech delay, developmental delay and intellectual disability while four had seizure and one had movement disorder. None of patient had drug resistance seizure. One patient had delayed white matter myelination, one had cerebral atrophy and one had slightly thin corpus callosum while two had no abnormality on brain MRI. Proton magnetic resonance spectroscopic imaging was performed for three patients and revealed severe decrease of creatine peak. Creatine monohydrate and ornithine supplementation was started with arginine restriction for two patients with GAMT deficiency, and their symptoms improved. Three patients with SLC6A8 deficiency had no improvement with creatine supplementation.
We suspected for CDSs in patients who had nonverbal autism with developmental delay or seizure. Creatine monohydrate and ornithine supplementation results in improvement of seizures, movement disorders, cognition and behavior problems for patients with GAMT and AGAT deficiency especially when started early.
There were few patients in our cohort to suggest an inclusive conclusion. However, in patients who had nonverbal autism with developmental delay or seizure we suggest to evaluate these patients for CDSs.

Keywords:
cerebral creatine deficiency, autism, speech delay, seizure

EPNS23-2222 Oral or e-Poster
Neurometabolic Disorders

Results of functional and sonographic examination in children with insulin-dependent diabetes mellitus

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Objective: The aim of the study was to identify changes in the functional and sonographic state of the peripheral nerves (n.) of the legs in children with insulin-dependent diabetes mellitus (IDDM).
Objects of the study: 52 children were divided into 2 groups: the study group, which included 69.2% children with IDDM, and the control group - 30.8% children without IDDM. Girls-48.1%, boys-51.9%. The average age 14.53±0.17 y.
Study group: the average age-14.92±0.24 y., the HbA1c level-9.08±0.43%, the average duration of IDDM-6.42±0.52 y.
Control group: the average age-4.13±0.38 y, the HbA1c level-4.55±0.28%.

Methods: Electroneuromyography (ENMG) and sonographic examination (SE) of peripheral n. of legs.
During ENMG motor (peroneal and tibial) and sensory n. (sural and superficial branch of the peroneal) were studied; amplitude of the M-response and neural potential, distal latency, and the conduction velocity (CV) of sensory and motor n. were analyzed.
During SE the cross-sectional area (CSA) of sensory and motor n. was analyzed.

Results: There was no statistically significant difference in the amplitude of the M-response and neural potential, as well as distal latency in healthy children and children with IDDM.
CV along the motor fibers of the peroneal n.: study group 43.5±0.78, control group 48.63±0.62 ($P<0.05$);
CV along the tibial n.: study group 42.32±0.85, control group 47.38±1.07 ($P<0.05$);
CV along the sensory fibers of the sural n.: study group 43.29±1.05, control group 47.25±0.76 ($P<0.05$);
CV along the sensory fibers of the superficial branch of peroneal n.: study group 41.81±1.46, control group 50.63±1.53 ($P<0.05$);
SE of peripheral n. revealed: CSA of motor fibers of the peroneal n. in study group 2.61±0.17, in control group 1.88±0.15 ($P< 0.05$); CSA of motor fibers of the tibial n. in study group 12.69±0.67, in control group 11.75±0.67 ($P >0.05$);
The CSA for sensory fibers of the superficial branch of the peroneal n. in study group 2.5±0.19, in control group 2.75±0.11 ($P>0.05$); sural n. in study group 2.12±0.17, in control group 2.88±0.15 ($P<0.05$).

Conclusions: In children with IDDM there were: a decrease in CV for sensory and motor fibers; an increase in CSA in motor fibers of the peroneal nerves and sensory fibers of the sural n. in comparison with healthy children.

Keywords:
children, IDDM, electroneuromyography, sonographic examination

EPNS23-2248 Oral or e-Poster
Neurometabolic Disorders

A RARE LYSOSOMAL STORAGE DISEASE: MUCOLIPIDOSIS TYPE IV

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Case study: Introduction: Mucolipidosis type IV is a rare autosomal recessive lysosomal storage disorder with psychomotor developmental delay, visual impairment, and achlorhydria. A mutation in the MCOLN1 gene causes an alteration of the protein mucolipin-1. Its true prevalence is unknown, but it is considered to be very rare, with 100 cases described so far.
Case report: A 19 months old boy; born third from a cousin's marriage, admitted with the complaint of inability to walk and speak. He had a slightly rough face appearance and syndactyly in the toe. He was walking with support ataxic. Muscle tone and deep tendon reflexes were normal. In the ophthalmological examination; the right was -3 / the left was -2.5 degrees myopic. Hb was 10.5 g/dl, MCV was 75 fl, and lactate was 1.5 mmol/l. Creatine phosphokinase, thyroid function tests, vitamin B12, and Tandem mass test levels were within normal limits. Brain magnetic resonance imaging showed diffuse hyperintensities in the periventricular white matter and corpus callosum hypoplasia in the T2-weighted/FLAIR sequences. Whole exome sequencing revealed a c.877G>A homozygous mutation in the MCOLN1 gene (MLIV, OMIM#252650). Segregation analysis of the family determined that the parents were carriers his variant and two sisters were healthy.
Conclusion: The most common ophthalmic findings reported corneal clouding, strabismus, optic nerve pallor, retinal dystrophy/pigmentary changes, and retinal vascular attenuation in Mucolipidosis type IV, but our case had only myopic abnormalities. Diagnosis may be delayed due to the absence of dysmorphic features, skeletal dysplasia, organomegaly, and ophthalmological findings. Early diagnosis of ML4 is important in forming a multidisciplinary management plan and genetic counseling strategy.

Keywords:
Mucolipidosis, Lysosomal storage disease, Neurometabolic

EPNS23-2879 Oral
Neurometabolic Disorders

Seizures in CLN2 patients receiving enzyme replacement therapy

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Objective: Classical Late Infantile Neuronal Ceroid Lipofuscinosis (CLN2) due to deficiency of TPP1 is caused by mutations in CLN2. Key features are motor and language skills deterioration, seizures, myoclonus and vision loss from the age of 3 years. Intra-cerebro-ventricular enzyme replacement therapy (ERT) was shown to slow down disease progression. We reviewed seizure management, EEG changes and score progression on CLN2 rating scale over three years after ERT start for 10 patients with CLN2 in a single centre.

Methods: Retrospective electronic medical records review of 10 patients (4M+6F) with a mean age of starting ERT: 4y6m (3y7m-5y11m), mean age at diagnosis: 3y9m (2y-4y6m). 6/10 patients were homozygous or heterozygous for the two common mutations (c.509-1G>C and c.622T>C); 2 patients were heterozygous for 1 common and 1 rare mutations; 2 patients had rare mutations only.

Results: Median (range) loss of motor (M) and language (L) scores on CLN2 scale over 3 years: M: 0.5 (0-1) and L: 0.5 (0-1). The number of patients experiencing at least one generalised tonic-clonic seizure (GTCS) per 6 months (m) was as follows: 1-6m: 3;7-12m: 3; 13-18m: 4; 19-24m: 3; 25-30m:1; 31-36m:1.
8/10 patients experienced myoclonus prior to ERT and 10/10 in the follow up, 7/10 requiring medication change. 3/10 had vacant spells prior to ERT and 10/10 during the follow up, 3/10 required medication change. 12 different antiepileptic drugs (AED) were used. Sodium valproate (VPA) and clobazam (CLB) were most commonly used AEDs (in 7/10). Other AEDs included levetiracetam, clonazepam, rufinamide, topiramate, perampanel, zonisamide, lamotrigine, piracetam and ketogenic diet. All AEDs were used in combination.
Serial EEGs showed persisting abnormal delta>theta activities, multifocal spikes, fluctuating in amount in 1/10 and deteriorating in 1/10. Posterior dominant rhythm persisted in 1, was lost in 1 and absent in 8/10. Photoparoxysmal spiking persisted in 3, was lost in 1. Clinical events were captured in 3; 1 had an epileptiform correlate.

Conclusions: In our cohort the number of patients with at least one GTCS per 6 months decreased from year 1 to 3. Most patients were treated with 2 AEDs, most common being VPA with CLB. EEG deterioration was found in two patients. Median CLN2 score loss was 0.5 for L and M scores. All patients experienced myoclonus or vacant spells but usually did not require medication changes. Whilst patients experienced seizures and myoclonus, in most the symptoms remained stable.

Keywords:
Batten disease, CLN2, Enzyme replacement therapy, epilepsy,

EPNS23-2229 Oral
Neurometabolic Disorders

Treatable inherited metabolic epilepsies: Middle east experience on 146 patients

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Objective: To identify and provide a detailed description of treatable metabolic disorders causing epileptic encephalopathy in patients presenting to different tertiary center in Saudi Arabia.

Methods: We conducted a retrospective cohort study of children presenting with genetically confirmed cases of inherited treatable metabolic disorders presenting as epileptic encephalopathy to a tertiary care centers in Saudi Arabia from January 2014 till December 2021. The international league against epilepsy definition was used.

Results: A total of 146 patients were analyzed. To our knowledge, This is the largest study of treatable metabolic epilepsy conducted in Middle east. Consanguinity rate was 77%. Biotine-thiamine basal ganglia disease was the most common encountered treatable metabolic epilepsy (46 patients, 32%), followed by pyridoxine- dependent epilepsies (32 patients, 22%). This study highlights the clinical and genetic data of Saudi Arabian patients with treatable inherited metabolic epilepsies and, identifies several differences among patients with inherited metabolic epilepsies in Saudi Arabia and Western countries. The development of a national registry will help both clinicians and families to ascertain the prevalence of this condition and facilitate further research in this field.

Conclusions: Treatable Metabolic diseases are common cause of epileptic encephalopathies in Saudi Arabia. Knowledge about these amenably treatable pediatric epilepsies allows early identification, testing and treatment.

Keywords:
inherited treatable metabolic disorders, epileptic encephalopathy

EPNS23-2192 Oral or e-Poster
Neurometabolic Disorders

Pediatric case series of Pompe disease- is ERT efficient?

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Objective: Pompe disease(PD) is a rare autosomal recessive disorder of glycogen metabolism caused by the deficiency of function of lysosomal hydrolase acid alfa-glucosidase; it is also known as glycogen storage disease type II(GSDII). There are about 500 mutations known within the coding region of GAA gene. Two clinical types of PD are distinguished: infantile-onset Pompe disease(IOPD) with the symptoms of generalized muscle hypotonia, weakness and cardiomyopathy present before the age of 12 months, and late- onset (LOPD) with proximal muscle weakness and respiratory insufficiency of different stage with potential onste at childhood too. The prognosis of survival, especially for the patients affected with IOPD, was very poor before the era of treatment, with high mortality in early childhood. The predictors of poorer outcome in IOPD patients are : male gender, degree of muscle weakness, time of disease duration and CRIM-negative(cross-reactive immunological material) status. Since 2006 ERT(enzyme replacing therapy) is available.
The authors -presents the case series of six patients: two with IOPD and four, two are the siblings, with LOPD.The diagnosis confirmation in all of the patients was made on both enzyme activity and genetic tests. Control evaluation consists in carrying out biochemical tests (CK activity) and gait evaluation in the 6-minute walk test; all children have a cardiological evaluation performed every 6-12 months, taking into account the degree of cardiomyopathy in the case of IOPD.

Methods: The diagnosis in two PD infants, a girl and a boy, (IOPD) was established during neonatal period for muscle weakness, feeding difficulties and cardiomyopathy. The ERT treatment started during the second month of life, still- one of the children died in his fifth month of life for cardiac arrest, while the other ,now at the age of 4 yrs, makes progress of psychomotor development.

Results: The children with LOPD were diagnosed at the age range of 5-12 years (3 boys and 1 girl), all for hypertransaminazemia. The ERT was administered within few weeks after the diagnosis and the course of the therapy in all children is uneventful. All the children are under multidisciplinary care, according to current standard of care for patients with neuromuscular disorder. The parents of the oldest patient refused to consent to the treatment of the child.

Conclusions: ERT is an efficient and safe method of tretment of children diagnosed of Pompe disease, both IOPD and LOPD.

Keywords:
Pompe disease- ERT treatment, case series presentation

EPNS23-2587 Oral or e-Poster
Neurometabolic Disorders

Susceptibility of muscle shear wave elastography to the physical pressure exerted by ultrasound probe in the paediatric population

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Objective: The diagnosis of neuromuscular diseases in children often proves to be difficult as the standard but often necessary electrophysiological tests are painful, and as a result, their results may be ambiguous due to the lack of cooperation with the child. Shear wave elastography (SWE) is a new ultrasonographic tool used to measure tissue stiffness that may be helpful in diagnosing and monitoring neuromuscular diseases. Our team decided to investigate in paediatric population whether physical pressure exerted on the examined muscle significantly changes the obtained results; thus, it should be taken into account while performing the examination.

Methods: 2D SWE of the medial head of the gastrocnemius muscle of the dominant leg was performed in a group of 24 children (13 girls, 11 boys) aged 8,99±2,74 years hospitalized because of headaches, learning difficulties, were otherwise healthy during the examination, and had no history of muscle-related nor motor deficits. A custom-made ultrasound probe cover with strain gauge pressure sensors was used to assess the physical pressure of the ultrasound probe on the examined limb. During the examination, a result of the obtained stiffness measurements with gradually increasing probe pressure was noted, as well as the age, sex, and maximum calf limb circumference. A statistical analysis of the results was performed.

Results: The muscle's stiffness gradually changed with the applied force. The application of 2 newtons resulted in a significant change in all of the subjects. The observed effect was more pronounced in superficial tissue, with less force needed to affect the results. The impact of probe pressure was less apparent in older children; however, the low group count does not allow for a reliable analysis of this aspect at a given time. No differences between boys and girls were observed.

Conclusions: While 2D SWE might prove to be very useful in paediatric neuromuscular diseases due to its painless nature, safety, repeatability, and availability our results indicate that the examination protocol should consider the pressure applied on examined tissue, especially in young children.

Keywords:
elastography, muscle ultrasonography, neuromuscular disorders

EPNS23-2193 Oral or e-Poster
Neurometabolic Disorders

Mitochondrial Depletion Syndrome- case report in first Asian child

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Case study: Mitochondrial DNA depletion syndrome (MDS) is a rare inherited autosomal recessive disorder with a few cases in the literature. RR2MB mutation has been reported in about 15 infants with early onset encephalopathy and multi-organ presentation. We highlight the importance of genetics in neurometabolic disorders by reporting the first Asian child with RR2MB mutation.

A 4-month-old girl child was presented with clinical indications of poor feeding and lethargy. She was born at term to non-consanguineous parents through normal delivery and previous sibling death at 3 months of age. Examination showed reduced tone with intermittent extensor posturing and no organomegaly. Blood gas showed metabolic acidosis. Genetics showed homozygous missense variation in exon 4 of the RRM2B gene that results in the aminoacid substitution of Histidine for Arginine at codon 121.

MDS is due to defects in mitochondrial DNA (mtDNA) functions caused by mutations in nuclear genes. They can be responsible for either mitochondrial nucleotide synthesis (RRM2B) or replication. Phenotypically, MDS can be classified into myopathic, encephalomyopathic, hepatocerebral, or neurogastrointestinal. MDS 8A and 8B are caused by mutation in the RR2MB gene. MDS 8A is characterized by neonatal hypotonia, lactic acidosis, and neurological deterioration similar to our child. MDS 8B is characterised by ophthalmoplegia, ptosis, gastrointestinal dysmotility, cachexia, peripheral neuropathy, and brain MRI changes. The combination of hypotonia with upper motor signs and lactic acidosis prompted neurometabolic disorders as a differential. Genetic testing was prioritised before MRI due to the combination of the presentation which indeed helped in the early diagnosis of the condition.
No efficacious therapy is for any of these disorders to date. Treatment is directed mainly toward providing symptomatic management. Nutritional modulation and cofactor supplementation are debatable. Stem cell transplantation is under research.

MDS is a severe disorder with a poor prognosis in the majority of affected individuals. A combination of neurological signs with lactic acidosis should raise suspicion of the condition. Affected individuals should have a comprehensive evaluation with genetic testing to assess the degree of involvement of different systems. Global case reports with genotyping will help in understanding the condition and formulating effective management plans in the future.

Keywords:
mitochondrial, neurometabolic, hypotonia

EPNS23-3015 Oral or e-Poster
Neurometabolic Disorders

A case of NDUFV1 gene mutation associated with mild developmental delay and cystic leukoencephalopathy

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Case study: Objectives: Mitochondrial energy metabolism disorders are a clinically and genetically heterogeneous group of diseases that result from dysfunction of oxidative phosphorylation caused by mutations in mitochondrial and/or nuclear DNA. Mutations in the NDUFV1 gene, which encodes a structural subunit of Complex I involved in mitochondrial oxidative phosphorylation, are disorders clinically associated with early-onset psychomotor decline, hypotonia, spasticity, dystonia, and epilepsy. We aimed to present a case who presented with mild developmental delay and was found to a homozygous mutation of NDUFV1 gene.
Case Presentation: A 32-month-old girl was admitted to our pediatric neurology outpatient clinic with mild motor developmental delay. She was born after uneventful pregnancy and delivery, with a second-degree consanguineous marriage of her parents. She had a history of birth with mild intrauterine growth retardation. Physical examination at admission was normal except for strabismus and mild hypotonia. Laboratory tests did not reveal any pathological findings for neurometabolic disorders. Brain MRI showed diffuse and cystic leukoencephalopathy. The whole exome sequencing analysis revealed a pathogenic homozygous mutation of NDUFV1 gene.
Conclusion: Mitochondrial energy metabolism disorders are a heterogeneous group of diseases with a wide clinical spectrum. The mutations of NDUFV1 should be kept in mind in patients who had mild developmental delay with diffuse and cystic leukoencephalopathy on MRI, even if the symptoms were mild.

Keywords:
NDUFV1, mutation, mild, cystic leukoencephalopathy

EPNS23-2006 Oral or e-Poster
Neurometabolic Disorders

Allan-Herndon-Dudley syndrome: devastating neurometabolic disease in a child with novel frameshift hemizygous mutation

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Case study: Introduction
SLC16A2 gene encodes thyroid hormone transporter monocarboxylate 8 (MCT8).Located on Xq13.2, its deficiency results in a wide range of symptoms including motor and cognitive disability, caused by decreased thyroid hormone signalling in the brain and elevated T3 serum concentrations, producing a chronic thyrotoxic state in peripheral tissues. This rare disorder (OMIM #300523) inherited in an X-linked fashion severely affects males, with an estimated prevalence of 1:70,000. In females it produces milder manifestations associated with thyroid hormone deficits.
Our aim is to present a 24 month old boy with Allan Herndon Dudley syndrome carrying a mutation not previously described in medical literature and explore possible novel treatment options currently being studied in clinical trials.

Patient and methods
A 24-month-old male patient, only child of healthy non-consanguineous parents, adequate weight and height at birth, debuted with neonatal hypoglycemia due to feeding difficulties. By 4 months had no head control pointing to congenital hypotonia.He had a particular phenotype, neurodevelopmental delay with severe axial hypotonia and upper limbs hypertonia, brisk reflexes, high-pitched cry and poor visual tracking.At 5 months dystonic postures began elicited by stimuli, increasing over time with no response to Ldopa-carbidopa. Studies for genetic and metabolic diseases were performed with unremarkable serum amino acids, urine organic acids, acyl carnitines, neurotransmitter metabolites in plasma including AADC. Brain MRI was normal.VEEG showed generalized background slowing and non-epileptiform abnormalities with subcortical myoclonus; patient had no history of clinical epileptic seizures.Due to progressive worsening of abnormal movements and dystonic posturing we initiated clonazepam with good response and exome sequencing was performed reporting gene mutation SLC16A2 variant c.407dupa p. asn136lysfs*31 pathogenic homozygosity confirming Alan Herndon Dudley Syndrome.To support this finding, peripheral hyperthyroidism was confirmed with a full thyroid profile showing normal T4 with elevated T3 values.

Conclusion
Alan Herndon Dudley syndrome is a rare neurometabolic disease with high mortality rates, with heterogeneous clinical manifestations that may mislead diagnosis. Early detection is key since ongoing clinical trials offer promising outcomes in patients treated from a young age, reducing peripheral symptoms and improving neurocognitive phenotype.

Keywords:
Alan-Herndon-Dudley Syndrome, psychomotor disorder, dystonia, SLC16A2 protein

EPNS23-2060 Oral or e-Poster
Neurometabolic Disorders

GAMT deficiency: A Treatable Cause of Epilepsy Not to be Forgotten

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Case study: Introduction: Guanidinoacetate methyltransferase (GAMT) deficiency is an exceedingly rare but treatable cause of childhood epilepsy and developmental impairment with unique neuroradiological findings. We present a case of early diagnosis of this disorder with favourable outcomes.

Case: A 2 year old previously well boy presented with myoclonic jerks and tonic-clonic seizures just before his second birthday, responding to sodium valproate. Previously, he had episodes of eye rolling from 10 months of age which gradually settled over time. He had gross motor and speech and language impairment alongside this. Given the nature of his epilepsy and concerns about early speech regression, he underwent extensive investigations. An MR brain showed symmetrical T2 high signal with restricted diffusion in the globi pallidi and tegmental tracts bilaterally. MR spectroscopy (MRS) was not undertaken as this is not included in our epilepsy protocol at present. His plasma creatinine was undetectable and his R14 exome revealed compound heterozygous variants in the GAMT gene. Biochemical serum studies showed a low creatine level and elevated guanidinoacetate (GAA) level. He has been commenced on ornithine and creatine supplements and remains seizure free and is making good developmental progress at the age of 3.

Discussion: GAMT deficiency is the commonest creatine synthesis disorder with very few reports of early diagnosis in literature. This autosomal recessive disorder results in low creatine levels and toxic accumulation of GAA. Early onset epilepsy in association with developmental difficulties, particularly expressive speech delay is a common presentation. The pathognomonic MR brain findings are bilateral signal abnormality in the globi pallidi and central tegmental tracts with absent creatine peak on MRS. Creatine and ornithine supplementation improve seizure control and developmental profile in affected children, especially if started early. In cases where the diagnosis is delayed, this improvement is limited. Although our patient did not undergo MRS, other clues in the history and biochemical findings aided a rapid diagnosis.

Conclusions: Although rare, GAMT deficiency has to be considered in a child with early onset epilepsy and developmental impairment given its treatment implications. We would strongly recommend that all children with early onset epilepsy have MRS as part of their radiological protocol to aid prompt diagnosis and management.

Keywords:
Guanidinoacetate methyltransferase (GAMT) deficiency; cerebral creatine synthesis disorder

EPNS23-2835 Oral or e-Poster
Neurometabolic Disorders

AD GTP-Cyclohydrolase-1 Deficiency (Segawa Syndrome; DYT5a) - Case Report

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Case study: Objective: Autosomal dominant GTP-cyclohydrolase-1 deficiency (Segawa syndrome) is a rare inherited neurometabolic disease with an estimated incidence of 1:300 000. Segawa syndrome is caused by a pathological variant of gene *GCH1* leading to insufficient production of tetrahydrobiopterin, which results in a lack of dopamine in the central nervous system. The disease manifests as a motoric developmental delay, early parkinsonism, and dystonia without significant cognitive impairment. The first clinical signs typically appear before six years of age. Patients show a dramatic and sustained improvement when treated with low-dose L-DOPA/carbidopa (DOPA-responsive dystonia). This report depicts a case of a recently diagnosed Segawa syndrome in a female pediatric patient who shows promising treatment results. The authors tend to familiarize health professionals with crucial aspects of Segawa syndrome.

Methods: The authors describe a case of a female pediatric patient presenting with motoric development impairment, an early manifestation of extrapyramidal symptoms, without significant mental disability. The diagnosis remained unclear after a standard neurological and pediatric clinical and paraclinical examination. The authors considered DOPA-responsive dystonia and began an L-DOPA/carbidopa test (1 mg/kg/d) and genetic testing.

Result: The L-DOPA/carbidopa test improved the patient's symptoms significantly and rapidly. Genetic testing revealed an autosomal dominant pathological variant in the *GCH1* gene. The patient was diagnosed with Segawa syndrome. The girl remains in the authors' medical care and shows sustained improvement.

Conclusions:
Segawa syndrome is a rare neurometabolic disorder with an early manifestation and usually favorable prognosis. The authors suggest considering this disease in all children with motoric development impairment, early parkinsonism, and dystonia without significant cognitive impairment.

Keywords:
Segawa Syndrome, Dopa Responsive Dystonia, DYT5a, L-DOPA, Tetrahydrobiopterin, GTP-Cyclohydrolase-1

EPNS23-2755 Oral or e-Poster
Neurometabolic Disorders

Treatment of metachromatic leukodystrophy with atidarsagene autotemcel - autologous lentiviral hematopoietic stem-cell gene therapy - in the EU: A case report

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Case study: Atidarsagene autotemcel ("arsa-cel") is a hematopoietic stem cell gene therapy (GT) consisting of autologous CD34+ cells transduced ex vivo with a lentiviral vector encoding for the human ARSA gene, administered intravenously following myeloablative busulfan conditioning. So far, there are 38 reported cases of children with MLD treated with arsa-cel; which resulted in sustained, clinically relevant benefits in children with early-onset MLD by preserving motor function and motor development in most patients and slowing demyelination and brain atrophy. In the European Union (EU) and United Kingdom (UK), arsa-cel is approved for the treatment of metachromatic leukodystrophy (MLD) in children with the late infantile or early juvenile forms of MLD without clinical manifestations or in children with an early juvenile form with early clinical manifestations. Since December 2020, arsa-cel has been approved for use in selected qualified treatment centers (QTCs) in the EU and UK.
We present a case of a 6 months old child identified with early juvenile MLD in a pre-symptomatic state. The diagnosis of MLD was based on low ARSA enzyme activity and biallelic mutations of the ARSA gene (c.911delA [p.Lys304Argfs*25]; c.1283C>T [p.Pro428Leu]) and family history (older sibling with symptom onset at 3 years of age and further deterioration at 6 years of age.) Considering the pre-symptomatic status and fatal course of MLD if untreated, the patient was considered for treatment with arsa-cel as the only therapeutic option. Consent from parents was obtained and eligibility was discussed with the QTC.Cost of treatment was reviewed and approved by health insurance as per European Social Security Regulation (Form S2).
After confirmation of eligibility, treatment was initiated at the QTC at 9 months of age, and arsa-cel was administered to the child at 11 months of age. After haematological recovery (neutrophil and platelet engraftment on day +31 and + 28 post-GT, respectively), the child is continuing follow up at the QTC as an out-patient with clinical and laboratory examinations twice a week until approximately 90 days post-GT.This is the first case of an MLD patient treated in Europe with arsa-cel according to the European cross-border healthcare legislation, and made possible by the support of an external team facilitating the approval process and its implementation, especially in communication with the Company, the local center, the QTC, and the state health authorities.

Keywords:
metachromatic leukodystrophy (MLD), gene therapy, ARSA gene, cross-border treatment, qualified treatment centers, hematopoietic stem cell gene therapy (GT), Atidarsagene autotemcel ("arsa-cel")

EPNS23-2663 Oral or e-Poster
Neuromuscular Disorders

Duchenne muscular dystrophy - medical, psychological and financial aspects of the disease. Results of the survey

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Objective: Duchenne muscular dystrophy (DMD) is with its incidence 1:5000 newborn males the most frequent muscle disease in childhood. The aim of the study was to explore medical, psychosocial and financial aspects of DMD and care given to them in CZ and to describe how the disease influences their quality of life, family budget and work productivity.

Methods: The results of the survey were collected from 63 patients from January 2018 to April 2019. The survey itself was divided into four sections: 1) state of the disease and available care, 2) quality of life measured by EQ-5D and PedsQL questionnaires, 3) financial burden from patient's perspective, 4) work productivity.

Results: The mean age was 13.7 years with mean age at diagnosis of 3.4 years and loss of ambulation at 9.4 years. The first symptoms were problems with movement in 67.2%, abnormal blood tests in 65.6% but also speech development delay in 23.4%. 48.4% of respondents were using corticosteroids in time of the survey and 21.9% of respondents were using them in the past. 61 respondents were at least annually examined by a neuromuscular specialist, 81% of respondents were satisfied with the care provided and 69.8% felt they had been offered sufficient help at diagnosis.

The EQ-5D Utility Index decreased from 0.712 in children under 5 years to 0.026 in 18+years group. In PedsQL, the worst rated ability of DMD patient by both respondents and their parents was communication in general, arm strength and change of weight when needed.

Regarding financial burden of DMD, caregivers stated that on average 20% of family's income is spent on the care of DMD patient, monthly 54Euros on vitamins or other dietary supplements, 42 Euros on medical devices, 41 Euros on travel costs, 21Euros on medication.

Family caregiver dedicates on average 16.3 hours/day to taking care of a DMD patient. Moreover, 64.5% caregivers are not employed. Usual activities are impaired by 47.8% in all caregivers

Conclusions: The survey provides an insight into overall burden of DMD patients and their caregivers in Czech Republic. It showed actual status of quality of care given to DMD patients as well as the effect of the diagnosis on the quality of life of the patients and its impact on caregiver's daily activities and their ability to work. This was one of the biggest DMD patient and caregivers study in Czech Republic and we hope results will help improving care for DMD patients in CZ.

Keywords:
Duchenne muscular dystrophy (DMD), survey

EPNS23-2543 Oral or e-Poster
Neuromuscular Disorders

Gastrointestinal and urological problems in children with myotonic dystrophy type 1

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Objective: Gastrointestinal and urological problems impact on daily life of patients with myotonic dystrophy type 1 (DM1) but have remained understudied. This study aims to assess the frequency, nature and impact of gastrointestinal and urological problems in children with DM1.

Methods: In a cross-sectional study, children aged 4-18 years with a clinical and genetically confirmed diagnosis of DM1 were recruited from the Myotonic Dystrophy expertise centers in the Netherlands. A combination of the Childhood bladder and bowel dysfunction questionnaire/CBBDQ, the supplementary BBD questionnaire used in Duchenne muscular dystrophy and the Clinical Rating Scale for Gastrointestinal symptoms/GSRS) was used to collect the following items: constipation, diarrhea, urinary incontinence, encopresis, enuresis nocturna, nausea, acid reflux, abdominal pain, oropharyngeal dysphagia and esophageal dysphagia. Parents were asked to rate the influence of urological and gastrointestinal problems on daily life, both from the patient's as well as family perspective.

Results: 58 children with DM1 were included; 30 males and 28 females with a mean age of 13 years. 74.1% of these children reported at least one gastrointestinal problem. Abdominal pain was the most frequently reported problem (51.7%), followed by diarrhoea (36.2%), encopresis (36.0%) and constipation (32.7%). Oropharyngeal dysphagia and oesophageal dysphagia were reported with a frequency 38.1% and 19.2%. The most frequently reported urological problem was urinary incontinence (22.0%). Enuresis nocturna was found in 10.3%. Voiding symptoms were also frequent, as 23.5% reported hesitancy, 4.8% intermittency and 13.8% dysuria. The process of toilet training was described as difficult by 59.3% of the parents and 13.8% of the children was not successfully toilet-trained at enrolment. The majority considered urological and gastrointestinal symptoms to have a negative influence on their daily life, for 22.4% this was reported as a severe influence (feelings of shame, social restrictions, school absence for children and concerns for their children's future from parents perspective).

Conclusions: Considering the high prevalence of urological and gastrointestinal problems in children with DM1 and their influence on daily life it seems key to correctly recognize, diagnose and treat these problems. We recommend standard screening for gastrointestinal and urological complaints in children with DM1.

Keywords:
Myotonic dystrophy type 1, DM1, Steinert disease, Gastrointestinal, Urological, Neuromuscular diseases

EPNS23-2179 Oral or e-Poster
Neuromuscular Disorders

Lower limb Muscle MRI patterns in early onset recessive TTN myopathy: A diagnostic "fingerprint" and potential biomarker of disease progression.

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Objective: Define the muscle MRI involvement pattern in recessive TTN congenital myopathy (TTN-CM).

Methods: Patients were included if they had symptom onset ≤ 10 years of age. Lower limb T1 MRI of TTN-CM patients seen at Great Ormond Street Hospital or collaborating UK and European centres were identified. Modified Mercuri scoring (MMS) of 20 thigh (including gluteal) and lower leg muscles was performed. Relative involvement of each muscle was calculated as the difference in the MMS compared to the median MMS in the other 19 muscles. Significance was assessed using the sign test. Spearmans rank correlation was applied to assess correlations between age and muscle involvement.

Results: Forty-nine patients (mean age at symptom onset 1.7 years) with available MRI (mean age at MRI 15.7 years) were analysed. In the thigh, semitendinosus (ST), semimembranosus (SM), vastus lateralis, vastus intermedius and short head of biceps femoris showed comparative involvement (p=<0.02). The sartorius (Sar), gracilis (Gra) and adductor longus (AL) showed comparative sparing (p=<0.001). All patients showed average (12/49) or above average (37/49) involvement of the ST compared to other muscles. In the lower leg, the peroneal (Per) and soleus muscles were comparatively involved (p=<0.001), whilst the tibialis posterior and extensor digitorum longus were comparatively spared (p=<0.001). There was asymmetric gastrocnemii involvement with preferential involvement of the medial head (p=<0.001). There was a correlation (Cor) between advancing age and higher MMS in the gluteal (GM) (Cor 0.41 p=0.004), SM (Cor 0.31 p=0.032), Gra (Cor 0.032 p=0.026), AL (Cor 0.34 p=0.017), Per (Cor 0.29 p=0.049) and tibialis anterior (TA) (Cor 0.37 p=0.012) muscles.

Conclusions: We present the largest dataset of TTN-CM muscle MRI described to date and highlight a muscle involvement pattern that expands upon previously reported findings from smaller cohorts. The observed pattern may serve as an imaging "fingerprint" for TTN-CM that may assist in the integrated clinical-genomic evaluation of patients and the interpretation of TTN variants. Higher MMS in the GM, SM, Gra, AL, Per and TA correlated with increasing age, suggesting a possible role as a biomarker of disease progression. Further evaluation of this finding through serial clinical and MRI assessments, using more sensitive measures of fat infiltration (Dixon MRI) is warranted and may serve as a potential outcome measure for future clinical trials.

Keywords:
TTN, Titin, Myopathy, Muscle MRI, Biomarker

EPNS23-2984 Oral or e-Poster
Neuromuscular Disorders

Rapid identification of IOPD and early-onset Pompe disease by biochemical enzymatic testing followed by genetic confirmation

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Objective: Glycogen storage disease type II, also called Pompe disease, is an autosomal recessive metabolic disorder which damages muscle and nerve cells throughout the body. It is caused by an accumulation of glycogen in the lysosome due to deficiency of the lysosomal enzyme, acid alpha-glucosidase (GAA). It is the only glycogen storage disease with a defect in lysosomal metabolism and the build-up of glycogen causes progressive muscle weakness (myopathy) throughout the body and affects various body tissues, particularly the heart, skeletal muscles, liver and nervous system.

Methods: In this study our medical laboratory screened over 30,000 samples suspicious for Pompe disease from over 57 countries by a 2-step approach utilizing dried blood spots: (I) biochemical testing of alpha-glucosidase activity followed by (II) complementary genetic sequencing of GAA in biochemically conspicuous cases. We were able to identify more than 700 PD patients at a very early stage.

Results: The results have shown that infantile cases with undetectable GAA enzyme activity (0 umol/L/hr) were confirmed with at least two GAA genetic variants. Samples with GAA enzyme activities between 0-0.5 umol/L/hr were genetically confirmed for early-onset Pompe disease. At the same time, symptomatic LOPD cases were analyzed successfully as well.

Conclusions: Based on our data, we can confirm that the combined testing at our single center can reliably identify infantile Pompe disease which can significantly accelerate diagnosis in critical cases of small babies within a few days. Furthermore, we identified new genetic variants that contribute to the pathogenic variant's spectrum of the GAA gene. In addition, a genotype-phenotype correlation for several GAA variants could be drawn from the data obtained.

Keywords:
DBS, IOPD and early-onset Pompe disease

EPNS23-2473 Oral or e-Poster
Neuromuscular Disorders

Glycogen storage disease type VII as a rare cause of rhabdomyolysis

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Case study: Objectives: Glykogen storage disease (GSD) type VII is a rare autosomal recessive metabolic myopathy due to muscle phosphofructokinase deficiency caused by mutations in the PFKM gene. Patients with GSD VII usually present with exercise intolerance and/or rhabdomyolysis. Mild compensated haemolytic anemia is commonly found.
Methods: A 17-year-old girl presented with two episodes of exercise-induced rhabdomyolysis with myoglobinuria and kidney failure. Post-episodic duration of increased serum creatine kinase (CK) and hyperuricemia led to the special metabolic investigations.
Results: The blood acylcarnitine profiles showed abnormalities similar to the carnitine palmitoyltransferase (CPT II) or carnitine-acylcarnitine translocase (CACT) deficiency, but next generation sequencing (NGS) including the CPT2 gene and the SLC25A20 gene did not identified disease causing mutations. Abnormal acylcarnitine profiles thus indicated overload of mitochondrial fatty acid oxidation and muscle cell damage. Blood lactate levels did not rise during exercise and led to the suspicion of muscle glycogenosis. NGS and Sanger sequencing of the PFKM gene showed the c.194T>C (p.I65T) variant in the homozygous state, which had not been described before and indicated the diagnosis of GSD VII. We recommended to avoid both the consumption of carbohydrate before exercise and to exclude heavy intensive exercise. Four years later the young woman benefits from diet and lifestyle recommendation. She is doing sport regularly. CK a uricemia are in normal range. Mild compensated hemolytic anaemia is permanent.
Conclusions: GSD VII should be considered in the differential diagnosis in patients with exercise-induced rhabdomyolysis or exerciese intolerance with muscle cramps and hyper-

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Keywords:
glycogen storage disease type VII, metabolic myopathy, rhabdomyolysis

EPNS23-2837 Oral or e-Poster
Neuromuscular Disorders

CLINICAL CHARACTERIZATION OF PATIENTS WITH CONGENITAL MYOTONIC

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Objective: The aim of this review of patients is to Clinically characterize, electrophysiological study and genetic features in patients with Myotononia Congenita with variants in the genes CLCN1 and SCN4A, in order to more specifically define this condition, with diagnostic and prognosis consequences.

Methods: We studied the Clinical, Genetic and electrophysiological characteristics of 6 pediatric patients; 4 with diagnosed Myotonic congenital Becker and 2 with Myotonic congenital Thomsen, with variants in the genes CLCN1 and SCN4A, respectively Medical reports were reviewed and personal examination of the cohort was performed.

Results: Congenital myotonia can be inherited as an autosomal dominant (Thomsen's disease) or autosomal recessive (Becker's disease) trait. Becker's congenital myotonia presents late from ages 4-7 years. The main symptom is difficulty in walking after being at rest; 1 patient walked on tiptoes.The exome shows a pathogenic variant in CLCN1, carrier parents.

Thomsen's congenital myotonia presents early from 11 months -3 years, 1 patient course with intermittent convergent strabismus and the other difficulty in muscle relaxation. The exome shows a pathogenic variant in SCN4A, carrier parents and a de novo variant.

All presented signs of myotonia, warming phenomenon, and 2 with a herculean phenotype. The electrophysiological study was abnormal, with myotonic discharges.

Treatment: mexiletine was used as first line therapy, and sodium channel blockers as second line.

Conclusions: Congenital myotonias are a heterogeneous group of skeletal muscle ion channelopathies; knowledge of the pathogenic mechanisms and detailed phenotyping may offer the possibility of developing more specific therapies with greater efficacy and safety in the future.

Keywords:
ion channels, myotonia, SCN4A, CLCN1

EPNS23-2401 Oral or e-Poster
Neuromuscular Disorders

Diagnostics and clinical and genetic characteristics of Duchenne muscular dystrophy in Kazakhstan

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Objective: Phenotypic and genotypic description of a cohort of DMD patients from the southern regions of Kazakhstan.

Methods: 103 boys with muscular dystrophy symptoms, retrospective analysis, clinical and genetic studies.

Results: 103 male patients in the age from 1 to 18 living in 6 southern regions of Kazakhstan. The patients' mean age was 9 years at the time of the examination. As part of the study, the dystrophinopathy diagnosis was confirmed in 64 (62.1%) patients with a referral diagnosis of Duchenne/Becker MD and was first established in 39 patients (37.9%) with other diagnoses. The average age of the disease onset was 4.3 years, clinical diagnostics was made at 6.8 years, genetic diagnostics - 8.7 years. The disease ranking by stages: 1 (1%) patient is at the preclinical stage, 77 patients (75.1%) are at the early and late ambulant stages, 35 patients (34%) are at the non-ambulant stage. The average age values when the ability to move independently was lost - 9.8 years; duration of the walking period - 8.1 years; the duration of the ambulant period - 5.4 years were determined in the subgroup of non-ambulatory patients (n=35). Exon deletions were found in 52 patients (50.4%), exon duplications in 7 patients (6.7%) by MLPA method. Deletion mutations potentially correctable by 45, 51, 53 exon skipping were found in 17 children (32%). Small and point mutations were found in 45 children (43.6%) by gene sequencing method. Nonsense mutations (n=15) accounted for 14.5% in the overall structure, and 33% among small and point mutations. 1 boy had a combined mutation: exon deletion and intron mutation.

Conclusions: The frequencies of the detected large and small mutations correspond to world data. Systemic approaches are needed to increase the early detection of the disease and timely genetic testing, access to targeted therapy.

Keywords:
Duchenne muscular dystrophy, nonsense mutation, exon skipping therapy

EPNS23-2189 Oral or e-Poster
Neuromuscular Disorders

Respiratory outcomes associated with the natural history of patients with Types 1-3 SMA

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Objective: The goal of this systematic literature review (SLR) was to describe the respiratory outcomes associated with spinal muscular atrophy (SMA) natural history.

Methods: The SLR identified natural history studies of untreated patients with Types 1-3 SMA based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Electronic databases (Embase, MEDLINE and Evidence-Based Medicine Reviews) were searched from database inception-27th June 2022. Observational/registry studies, case-control studies, cross-sectional studies and case series reporting respiratory outcomes were included, although the initial search was broader. Eligible studies included respiratory function data, need for ventilatory support or tracheostomy, forced vital capacity (FVC), peak cough flow (PCF), sniff nasal inspiratory pressure (SNIP) and polysomnography (PSG). Risk of bias was assessed using the Joanna Briggs Institute checklist.

Results: Sixteen studies that reported respiratory outcomes were included. All 16 studies reported FVC data; few studies reported on PCF (n=3), SNIP (n=3) and PSG (n=1). Studies showed that the most pronounced declines in FVC occurred at younger ages, with a slower decline in adults with Types 1-3 SMA. Lower PCF values and SNIP scores were associated with more severe forms of SMA. PSG data showed higher median total and median rapid eye movement apnoea-hypopnea indices in individuals with Type 1 SMA. Three studies reported Kaplan-Meier data: one reported a significantly shorter median time to respiratory support (tracheostomy positive pressure ventilation) in patients with Type 1a SMA (6 months; n=38 patients) compared with Type 1b SMA (122 months; n=9 patients; P<0.0001). Another study reported that patients with Type 2b SMA needed respiratory support less often at night compared with those with Type 2a SMA (P=0.01). The third reported that the probability of being alive and not requiring ≥16 hours/day of non-invasive ventilation for ≥2 weeks decreased with age (n=23 patients) in children with Type 1 SMA. Notably, the studies included in the SLR reported heterogeneous populations, differences in definitions of respiratory support and varying follow-up times.

Conclusions: These findings indicate that untreated patients with Types 1-3 SMA remain at risk of respiratory decline, particularly patients with more severe forms of disease, and support the importance of respiratory stabilisation in individuals with SMA.

Keywords:
Spinal muscular atrophy, natural history, rare disease, systematic review

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Neuromuscular Disorders

Newborn screening programs for spinal muscular atrophy worldwide: second edition

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Objective: 5q Spinal muscular atrophy (SMA) is an autosomal recessive inherited disease caused by a deficiency of functional survival motor neuron (SMN) protein. In recent years, much attention has been paid to the introduction of newborn screening (NBS) for SMA in order to avoid delays in treatment and thus irreversible consequences. The aim of our work was to provide a global overview of the progress of SMA NBS two years after our first global screening article at SMA NBS.

Methods: Experts in the fields of SMA and NBS were contacted worldwide to obtain a global overview of the current status of SMA NBS in their respective countries. The experts were asked to answer a questionnaire on the availability of SMA disease-modifying medicines, implementation of SMA NBS, difficulties and barriers encountered, support and prediction of future developments of SMA NBS.

Results: For the purpose of the study, 133 experts from 123 countries were contacted and we received 35 responses by this stage. Ten (29%) countries reported that they have SMA NBS throughout the country, 6 (17%) only in part of the country, and 19 (54%) reported that they do not have SMA NBS, although 9 of these are planning to introduce SMA NBS in the future. The biggest barriers are lack of funding, no treatment for SMA and that it is not a government priority. Four (57%) of those who introduced SMA NBS during the Covid 19 pandemic felt that it had no impact on implementation.

Conclusions: Our work shows the current situation at SMA NBS worldwide. Despite the clear benefits of SMA NBS in countries where disease-modifying drugs are available for SMA, there are still many obstacles to overcome in organising and implementing future NBS programmes.

Keywords:
spinal muscular atrophy, newborn screening, neuromuscular disorder, treatment

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Neuromuscular Disorders

Bulbar Function in Children with Two or Three *SMN2* Copies Who Received Onasemnogene Abeparvovec Presymptomatically for Spinal Muscular Atrophy

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Objective: A goal of disease-modifying treatment for spinal muscular atrophy (SMA) is the improvement and maintenance of bulbar function, but there are no standardized and validated measures, and no widely accepted definition of bulbar function in SMA exists. We conducted a *post-hoc* analysis on bulbar function from a Phase III study (SPR1NT) of presymptomatic children with SMA with two (n=14) or three copies (n=15) of the *SMN2* gene who received onasemnogene abeparvovec.

Methods: A group of experts on deglutition, respiratory function, physical therapy, nutrition, and neurology, and Novartis Gene Therapies staff defined bulbar function as the ability to establish verbal communication skills and to swallow to orally meet nutritional needs and maintain airway protection. Four endpoints were selected to represent key components of bulbar function: (1) achievement of item #6 or above on the Bayley Expressive Communication subtest, (2) receiving full oral nutrition, (3) absence of clinician-identified (clinical/fluoroscopic) markers of physiologic swallowing impairment, and (4) absence of adverse events relating to respiratory health (aspiration/aspiration pneumonia). Because communication skills were not assessed during SPR1NT, numbers/percentages of children who achieved each of the three available endpoints and all three endpoints (composite endpoint) were descriptively assessed. Last follow-up was at 18 and 24 months of age for children with two and three *SMN2* copies, respectively.

Results: Twenty-nine children were included in the analyses of three outcomes pertaining to bulbar function. At end of study, 100% (29/29) received full oral nutrition, 100% (29/29) had evidence of a normal swallow, and 100% (29/29) had no respiratory adverse events related to aspiration; 100% (29/29) met the composite endpoint.

Conclusions: Presymptomatic children with SMA treated with onasemnogene abeparvovec could swallow, meet oral nutritional needs, and maintain airway protection, indicating they achieved good bulbar function and achieved motor milestones consistent with typically developing children.

Keywords:
bulbar function, disease-modifying treatment, onasemnogene abeparvovec, spinal muscular atrophy

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Neuromuscular Disorders

The clinical, histological and genetic spectrum of RYR1 mutations - a multi-center Israeli cohort study

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Objective: To review a cohort of sporadic and familial cases with RYR1 mutations, in order to characterize the clinical, histologic, and genetic heterogeneity associated with such mutations in the Israeli population, and to assess the genotype-phenotype correlation in order to predict the trajectory of the disease caused by RYR1 mutations.

Methods: A cohort of 33 patients with RYR1 mutation ascertained by genetic testing, was assembled by national collaboration of multiple pediatric and adult Israeli neuromuscular clinics. Clinical features, molecular, laboratory, electromyographic tests and muscle histology were retrospectively reviewed. Each mutation was defined according to its domain location in the RYR1 gene.

Results: Twenty-eight individuals from 11 (85.7%) unrelated familial and 5 (14.2%) sporadic patients carrying RYR1 mutations, either affected (25 /71%)or unaffected (10/28%) were included. Most of affected patients presented with perinatal weakness accompanied by respiratory impairment in only one family, or rarely by arthrogryposis. Muscle involvement was mainly proximal, though distal weakness was also prominent. The disease course was diverse; most patients showed deterioration, while improvement or stabilization were observed among some. Other clinical presentations included: malignant hyperthermia, periodic paralysis and 2wo familial cases of King-Denborough syndrome were detected The RYR1 pathogenic mutation included: 2 highly inbred families with homozygous autosomal mutations, 7 families with compound heterozygous mutations, 2 families with autosomal dominant mutation and 5 sporadic cases , harboring either de novo heterozygous mutation, compound heterozygous or homozygous mutation.

Conclusions: This series confirms and expands the clinical and histologic variability associated with RYR1- mutations including related myopathy, periodic paralysis and syndromic myopathy. Dominant and recessive mutations of the RYR1 gene vary and include mild clinical features, severe neonatal-onset phenotype, progressive, periodic, stable or even, improving course. There is an impression that there is a tendency to a positive correlation between mutations located in the Bslo domain and severity of the disease. There was a great clinical variability even in the same family with the identical heterozygous mutation or compound heterozygous mutations. This work adds to the genotype-phenotype correlation of RYR1-related confirming the complexity of the RYR1 related disorders.

Keywords:
RYR1 mutation, myopathy, Israeli cohort

EPNS23-2693 Oral or e-Poster
Neuromuscular Disorders

Longitudinal multicentric study to assess the reliability and sensitivity of digital outcomes issued from wearable magneto-inertial devices in DMD

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Objective: A key issue in Duchenne muscular dystrophy (DMD) research is identifying objective, reliable and sensitive outcome measures to assess drug effects. Wearable devices present an excellent opportunity to provide new outcomes for clinical development, as demonstrated by the 95th centile stride velocity (SV95C), which represents the most rapid 5% of strides during real-life assessment with such a device, has been qualified by the European Medical Agency as a secondary endpoint in 2019. The ActiLiège study is a multicentre clinical study aiming to gather data issued from a magneto-inertial wearable device to validate new outcomes in DMD. The device is designed specifically for clinical trials to identify and measure the spontaneous limb movements of ambulant and non-ambulant patients with neuromuscular diseases in daily life.

Methods: Ambulant and non-ambulant patients with DMD and healthy controls are included and will be followed up for three years. The patients will wear the ActiMyo magneto-inertial device (Sysnav, France) every day during the first 3 months after the inclusion and afterwards for one month every 3 months; placed on the ankles for the ambulant patients and controls, and on the ankle and the wrist for the non-ambulant. Controls will wear the device for a period of one month every 12 months. Data from the wearable sensors, including SV95C, walking perimeter, stair-climbing velocity, and upper limb activity will be compared to standardised assessments (6-minute walk test, 4-stairs climbing test, 10-meter walk test, time to rise from the floor, North Star Ambulatory Assessment and strength tests). In addition, all participants will complete a Patient Reported Outcome (PGI-C) every 6 months after inclusion.

Results: We enrolled 82 ambulant patients with DMD, 17 non-ambulant patients and 40 age-matched controls across 8 sites in Belgium, Poland, Hungary, Romania, Czech Republic, Slovenia and Egypt. All ambulant patients are either on a 6-month stable course of steroids or are initiating steroids. In June 2023 we will present the baseline data of the patients and controls, and the available 1-year data of 37 (26 ambulant) patients and 11 controls.

Conclusions: This large international study will provide data on patients' compliance and the reliability and clinical consistency of a panel of digital outcomes obtained from a wearable magneto-inertial sensor. We will also present longitudinal data that may indicate sensitivity to change compared with other classically performed outcomes.

Keywords:
Duchenne muscular atrophy, DMD, assessment, stride velocity

EPNS23-2070 Oral or e-Poster
Neuromuscular Disorders

Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis

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Objective: Strategic Targeting of Registries and International Database of Excellence (STRIDE; NCT02369731) is an ongoing, multicenter, observational registry providing data on ataluren use in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients in routine clinical practice.

We investigated if nmDMD patients receiving ataluren plus standard of care (SoC) in the STRIDE Registry experienced a lesser decline in pulmonary function versus DMD patients receiving SoC alone in the Cooperative International Neuromuscular Research Group (CINRG) Natural History Study (NCT00468832).

Methods: Data were extracted on January 31, 2022. Propensity score matching identified STRIDE and CINRG patient cohorts (N=260) comparable in established predictors of disease progression: age at first symptoms; age at initiation of corticosteroid use; duration of deflazacort use; and duration of other corticosteroid use. Patients from CINRG who had received investigational drugs for DMD were excluded from this analysis. Kaplan-Meier analyses were used to estimate ages at %-predicted forced vital capacity (FVC) <60% and <30%.

Results: The mean (standard deviation) ages at onset of first symptoms (STRIDE vs CINRG; N=260 per cohort) were 2.8 (1.7) and 2.8 (1.5) years, respectively. Most patients (STRIDE vs CINRG) received corticosteroids for greater than or equal to 12 months (85.0% vs 83.8%), with a similar proportion receiving deflazacort (47.7% vs 44.2%) or other corticosteroids (41.9% vs 43.5%). Median (95% confidence interval [CI]) ages at %-predicted FVC <60% (STRIDE vs CINRG) were 17.7 (16.8, not estimable) and 15.3 (14.9, 16.5) years, respectively (p=0.0053). Median (95% CI) ages at %-predicted FVC <30% (STRIDE vs CINRG) were not estimable and 22.5 (20.3, 25.4) years, respectively (p=0.0008).

Conclusions: These interim registry data suggest that treatment with ataluren and SoC in routine clinical practice slows disease progression in pulmonary function in nmDMD patients.

Keywords:
Rare disease, Duchenne muscular dystrophy (DMD), patient registry

EPNS23-2634 Oral or e-Poster
Neuromuscular Disorders

Neurofilaments as a biomarker of progression and effect of therapy in spinal muscular atrophy

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Objective: Spinal muscular atrophy (SMA) is a rare, autosomal recessive neurodegenerative disease of peripheral motor neurons. Clinically, the disease manifests as progressive muscle weakness. In recent years, opportunities for innovative treatment of this disease have emerged thanks to new insights into the pathogenesis and the availability of new technologies. Treatment with nusinersen (Spinraza®) was the first available for Czech (CZ) and Slovenian (SI) patients. The drug modulates RNA splicing of the SMN2 gene, thereby increasing SMN protein production. In addition to this treatment, risdiplam (Evrysdi®) and onasemnogene abeparvovec (Zolgensma®) are also approved and reimbursed for CZ and SI patients. As more causal therapy options become available and more patients switch from one therapy to another, there is a need for biomarkers that could help select the optimal therapy and monitor patient response. Currently, the treatment effectiveness is evaluated only by physio tests using standardised motor scales, which, however, face many limitations.

Methods: In pediatric SMA patients treated with an intrathecal application of nusinersen, we collected serum and cerebrospinal fluid (CSF) samples at intervals before treatment initiation and subsequently after 1, 3, 6 and 12 months of treatment. Samples were processed in the Cerebrospinal fluid laboratory. The levels of neurofilament phosphorylated heavy chains (pNF-H) were determined in the CSF and serum of all patients using commercially available ELISA kits (Normal and High Sensitivity) and then correlated. In addition, we assessed the clinical status of the patient by standard motor scales (CHOP INTEND, HFMSE) and correlated the results with the pNF-H levels.

Results: In a cohort of 55 CZ and SI pediatric SMA patients treated with nusinersen for at least 1 year, there was a statistically significant decrease in pNFH levels in both serum and CSF during the nusinersen therapy. We also demonstrated a correlation between pNFH levels in CSF and serum at all time periods. We found a negative correlation between neurofilament levels and motor scales.

Conclusions: Our data suggest that serum pNFH levels are a useful biomarker for the efficacy of causal SMA therapy. Moreover, pNFH serum levels correlate with CSF levels, so the biomarker could be used in patients in whom CSF samples are not available.

Keywords:
spinal muscular atrophy, SMA, nusinersen, neurofilaments

EPNS23-2437 Oral or e-Poster
Neuromuscular Disorders

NUSINERSEN ADMINISTRATION IN PATIENTS WITH COMPLEX SPINAL ANATOMY

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Objective: Nusinersen was the first drug approved for spinal muscular atrophy (SMA), which is a genetic disease caused by homozygous disruption of survival motor neuron 1 (SMN1) gene and deficient functional SMN protein. Standard nusinersen administration is via posterior interlaminar injection delivered every 4 months after a 4-dose loading. However, many patients with late onset SMA develop spine deformity, such as scoliosis, that needs surgery with spinal instrumentation hardware. Such patients require an alternative drug delivery with imaging-guided injection via transforaminal posterior pathway. We compared a group of complex-spinal anatomy SMA patients treated with CT-guided transforaminal delivery with a control group treated using the interlaminar injection.

Methods: Between 2020 and 2022 we collected retrospective and prospective data on SMA patients receiving nusinersen via CT-guided transforaminal injection (study group) and via standard interlaminar approach (control group). Demographic and clinical data including motor evaluation scores on Hammersmith Functional Motor Scale-Expanded, Revised Upper Limb Module, Revised Hammersmith Scale and Functional Rating Scale were compared and statistically analyzed.

Results: The study included 53 SMA patients (27 males): 15 patients who received nusinersen via CT-guided transforaminal injection (11 type II, 4 type III) and 38 patients in control group (15 type II, 23 type III). The age at first nusinersen was significantly higher in the study group (median interquartile range (IQR) 19.73 years [17.38-32.04] versus controls median (IQR) 17.2 [10.58-29.32]). No patient in the study group was able to walk, while 19 were able to walk among controls. No difference was found in mean number of injections and treatment duration (range 16-58 vs. 10-56 months) between study and control groups. There were no significant intergroup differences in motor progress and ventilation status. Adverse effects were reported in 3/15 (20%) in the study group and 2/38 (5.3%) in controls (p=0.131), all were procedure-related such as post lumbar puncture syndrome and back pain. CT-guided injections were discontinued in one patient due to ovarian tumor.

Conclusions: There were no differences in motor or respiratory outcomes of SMA patients between the two drug delivery pathways (transforaminal versus standard interlaminar). CT-guided transforaminal injection is a good alternative solution for nusinersen delivery in patients with complex spinal anatomy.

Keywords:
Spinal muscular atrophy, SMN1, SMN2, motor function, nusinersen, antisense oligonucleotide, CT navigation

EPNS23-2320 Oral or e-Poster
Neuromuscular Disorders

Gene therapy in spinal muscular atrophy: the Portuguese experience in real-world practice

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Objective: Spinal muscular atrophy (SMA) is a neurodegenerative disorder associated with high morbidity and mortality, being SMA type 1 its most severe form. Recently, the natural history of the disease has been modified by novel genetic therapies. This study aimed to describe the portuguese experience with onasemnogene abeparvovec treatment of infants with SMA, regarding the clinical outcome, tolerability and safety profile.

Methods: We conducted a multi-center, prospective observational study of children with SMA treated with onasemnogene abeparvovec, from August 2019 to December 2022. Clinical assessment included evaluation of motor milestones, Children's Hospital of Philadelphia Infant Teste of Neuromuscular Disorders (CHOP Intend) progression, respiratory support, and oral ability. Possible adverse effects were monitored.

Results: A total of 25 children were treated from six portuguese centers, currently with 27.8 months (age range 4-54 months). The majority was SMA type 1 (n=24) and only one patient was SMA type 2. Eight patients had been previously treated with nusinersen. The most frequent treatment related side-effects were nausea and vomiting (16%) and fever (8%). Moderate to severe transient elevation of transaminases was common (38%) and none showed signs of hepatic insufficiency. Thrombocytopenia and leukopenia were observed in 2 patients. SMA phenotype at dosing was predominantly non-sitters (79%, n=19). All patients showed continuous motor improvement. At 12 months of follow-up, 15 patients have gained at least one motor milestone, with Chop-Intend improvement of 18,1 points. Five patients have a follow-up period of 24 months, with a Chop-intend increase of 28,4 points. Seven patients can stand with assistance. There was a reduction of 3,2 hours per day of ventilatory support from baseline. Stabilization or improvement of oral function was observed in all patients; however one gastrostomy was still performed after treatment.

Conclusions: Our study represents real-world experience of onasemnogene abeparvovec treatment. As described by previous case-series, this therapy is associated with markedly improvement of motor, bulbar and respiratory functions. Attentive multidisciplinary care and long-term surveillance is crucial to understand full clinical impact of this therapy and defining new phenotypes.

Keywords:
spinal muscular atrophy, gene therapy, onasemnogene abeparvovec,

EPNS23-2017 Oral
Neuromuscular Disorders

Five patients with Spinal muscular atrophy-progressive myoclonic epilepsy (SMA-PME): a novel pathogenic variant, treatment and review of the literature

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Case study: Spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME) is a rare inherited autosomal recessive disease due to bi-allelic mutations in the ASAH1 gene. SMA-PME is characterized by progressive muscle weakness from three to seven years of age, accompanied by epilepsy, an intractable seizure, and sometimes sensorineural hearing loss. To the best of our knowledge, 47 cases have been reported. The present study reported five patients from four different families affected by SMA-PME characterized by progressive myoclonic epilepsy, proximal weakness, and lower motor neuron disease, as proven by electrodiagnostic studies. Genetic analysis identified two different mutations in the ASAH1 (NM_177924.4) gene, a previously reported pathogenic variant, c.125C>T (p.Thr42Met), and a novel likely pathogenic variant c.109C>A (p.Pro37Thr). In addition to reporting a novel pathogenic variant in the ASAH1 gene causing SMA-PME disease, this study compares the signs, phenotypic, and genetic findings of the case series with previous reports and discusses some symptomatic treatments

Keywords:
SMA-PME, Children,Seizure

EPNS23-2371 Oral or e-Poster
Neuromuscular Disorders

The Safety and Efficacy of Light Aerobic Training in Children with Dystrophinopathy

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Objective: To evaluate the safety and efficacy of a light aerobic training program in children with dystrophinopathy.

Methods: Twelve week light aerobic training study in children with Duchenne and Becker muscular dystrophy (DMD/BMD) and healthy controls in a tertiary medical center in Israel. Functional tests; six-minute walk test (6MWT), North Star Ambulatory Assessment (NSAA), Handheld dynamometer (HHD), and Plasma Biomarkers; as well as CPK and microRNAs were tested. The training program included low-intensity walking training, up to 3 sessions/week, and up to 70% of maximal heart rate (HR). The duration was progressively increased up to 30 min/per session in DMD and 60 min/per session in BMD and controls. Training sessions were monitored with an m430 Polar activity watch. Statistical analysis was done using One-way ANOVA, Paired t-test, or Wilcoxon matched-pairs test.

Results: Thirty children were enrolled; DMD (n=10, 10.7 ± 2.3 yr.), BMD (n=10, 12.9 ± 2.2 yr.) and healthy control (n=10, 11.2 ± 1.5 yr.) The 6MWT mildly increased in BMD and controls, and did not change in DMD. NSAA scores remained unchanged in all three groups after 12-week training. Significant increase in Hamstrings muscle peak force was recorded in children with DMD/BMD ($p<0.05$). No significant differences were found in resting as well as post-6MWT CPK values in all study groups. Sixteen plasma miRs in children with DMD and Forty-three plasma miRs in children with BMD were significantly different compared with Healthy control in the pre-intervention period. Muscular dystrophy and muscle damage associated miRs (hsa-miR-133a-3p; hsa-miR-206, hsa-miR-208b-3p) were not increased following the aerobic training intervention. In addition, significantly decreased adipocytes and inflammation biomarkers were observed (hsa-miR-378a-5p and hsa-miR-4508). In children with BMD, seventeen of 26 miRs which changed after training, suggesting muscle regeneration and myogenesis, mitochondrial biogenesis, anti-inflammatory response, and reduced fatigue.

Conclusions: In the short term, light aerobic training was safe in children with BMD and DMD. Plasma miRs evaluation did not show increased muscle damage after training and suggested myogenesis, mitochondrial biogenesis, and anti-inflammatory response in children with BMD, with similar trends in children with DMD. These positive results support personalized tailored light aerobic training prescriptions for children with dystrophinopathy.

Keywords:
Dystrophinopathy, Muscle damage, Plasma biomarkers, Aerobic training

EPNS23-2300 Oral or e-Poster
Neuromuscular Disorders

Quantifying Variability in Duchenne Muscular Dystrophy: Centiles by Age for the NorthStar Ambulatory Assessment in Glucocorticoid-steroid Treated Boys

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Objective: We describe for the first time centiles of the North Star Ambulatory Assessment (NSAA) in Glucocorticoid-steroid (GC) treated boys with Duchenne Muscular Dystrophy (DMD) between the ages of 5 and 16 years. This includes NSAA-for-age trajectories and tables to calculate the centile and Z-score for a given age and total score.

Methods: Participants with a confirmed diagnosis of DMD came from a national, observational DMD registry, excluding those enrolled in any trial. All participants were on GC, primarily deflazacorts or prednisolone, intermittent or daily, but regime and type varied over time. We analysed assessments where all 17 items of the NSAA were completed. In addition, where the assessment was not performed but the participant was recorded as non-ambulant, the total NSAA was set to 0 to avoid informative drop-out. The centiles were fitted using a GAMLSS model with the 0-1 inflated logit Normal family, a basis spline with age for the mean model, and quadratic models with age for the variance and ceiling/floor models.

Results: We analysed 4,704 complete observations of the NSAA in 863 DMD boys aged between 5 and 16 years, of which 1,123 (24%) were zero scores. We present the 10th, 25th, 50th, 75th and 90th centiles to visualise NSAA progression. The 25th centile shows peak motor function at a NSAA total score of 19 at 6.2 years, and median loss of ambulation at 10.9 years. The 50th centile shows peak motor function at a NSAA total score of 26 at age 6.4 years, and average loss of ambulation at 12.5 years. The 75th centile shows peak motor function at a NSAA total score of 29 at 6.7 years, and average loss of ambulation at 14.8 years.

Conclusions: The NSAA centiles, combined with additional analysis, could provide valuable information for clinical monitoring of boys with DMD, particularly to differentiate typical rates of decline from unusual rates of decline in boys in the late ambulatory disease stage. The NSAA centiles could be used for modelling changes in the NSAA score according to baseline NSAA centile, which could help to clarify the effect of treatments on NSAA trajectory. Additional work will be performed to validate the centiles in external datasets, including observational natural history, trial placebo arms and prospectively collected data.

Keywords:
Duchenne Muscular Dystrophy, Glucocorticoid, North Star Ambulatory Assessment

EPNS23-2141 Oral or e-Poster
Neuromuscular Disorders

Ataluren preserves muscle burst activity in nmDMD patients from Study 041, a phase 3, randomized, double-blind, placebo-controlled trial

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Objective: Study 041 (NCT03179631) is an international, phase 3, randomized, double-blind, placebo-controlled 72-week ataluren trial in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) followed by a 72-week open-label period. Here, we describe the effects of ataluren on muscle burst activity, as assessed by timed function tests (TFTs).

Methods: Boys with nmDMD aged ≥5 years, on corticosteroids, and with a 6-minute walk distance (6MWD) ≥150m were eligible and randomized 1:1 to ataluren:placebo. The intention-to-treat (ITT) population comprised randomized boys who received ≥1 dose of study treatment; a key subgroup included boys with baseline 300-400m 6MWD. Change from baseline to week 72 in TFT (10-metre walk/run, 4-stair ascent, 4-stair descent) results were secondary endpoints. A mixed model for repeated measures was employed to analyse the efficacy endpoints.

Results: The ITT population comprised a total of 359 patients with nmDMD randomized to receive ataluren (n=183) or placebo (n=176); groups were balanced according to enrolment age, baseline 6MWD, corticosteroid use and supine-to-stand time. Treatment with ataluren significantly reduced the mean change from baseline in time to perform the 10-metre walk/run vs placebo in the ITT population by 20% (-0.78s, p=0.0422) and the 300-400m 6MWD subgroup by 30% (-1.29s, p=0.0429). Significant differences in the mean change from baseline in time to perform the 4-stair ascent favoured ataluren in the ITT population (-1.06s, p=0.0293) and 300-400m 6MWD subgroup (-2.29s, p=0.0050), representing a relative change to placebo of 18% and 30%, respectively. The mean change from baseline in time to perform the 4-stair descent was numerically reduced in patients who received ataluren vs placebo (ITT population: -0.29s, p=0.5749; 300-400m 6MWD subgroup: -0.97s, p=0.2714).

Conclusions: These results from Study 041 demonstrate that ataluren preserves performance in TFTs, and therefore muscle burst activity, in patients with nmDMD.

Keywords:
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EPNS23-2770 Oral or e-Poster
Neuromuscular Disorders

MLIP-associated myalgia and rhabdomyolysis: clinical and genetic data of five additional cases

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Case study: Objectives: Recently, a novel genetic condition caused by biallelic variants in the MLIP (Muscular A-type lamin-interacting protein) gene was identified in patients with mild muscular dystrophy with episodic rhabdomyolysis. MLIP is mainly expressed in the heart and skeletal muscles. Until now only fourteen cases have been described worldwide. Here we report a cohort of five individuals from three unrelated families with mild muscle weakness, exercise-related muscle pain and rhabdomyolysis.

Methods: Re-analysis of previously generated exome data was performed using a panel for known myopathy genes combined with exome-wide HPO-based variant analysis (Moon software, Diploid/ Invitae).

Results: Re-analysis of exome data of myopathy patients in 2022 revealed novel and known truncating pathogenic variants in the MLIP gene (NM_001281747.2). Family 1. Sister and brother born to consanguineous parents presented at our clinic with myalgia, increased serum creatine kinase (CK) up to 15657U/l at rest and episodic rhabdomyolysis at the age of 10 and 12 years, respectively. Exome sequencing revealed a previously described homozygous frameshift variant in exon 4 of the MLIP gene, c.715A>G r.646_715del p.(Thr217Ilefs*17). Family 2. This boy, also of consanguineous parents, experienced the same symptoms since the age of 14 months. Additionally, clinical examination revealed mild proximal muscle weakness. He showed the same pathogenic variant as described in family 1 in homozygous state. Family 3. Two brothers of non-consanguineous parents presented with muscle stiffness and exercise-induced muscle pain in early childhood. The oldest one experienced proximal muscle weakness. Laboratory analysis showed serum CK up to 3451U/l. On exome sequencing, two novel compound heterozygous MLIP variants were identified, a maternally inherited likely pathogenic c.2213C>A p.(Ser738*) nonsense variant in exon 4 and a paternally inherited likely pathogenic c.2319del p.(Ser773Argfs*8) frameshift variant in exon 6. No evident cardiac abnormalities were detected in any of our patients.

Conclusions: Our cases confirm that pathogenic loss-of-function variants in the MLIP gene are characterized by myalgia and hyperCKemia with or without episodic rhabdomyolysis. The identification of this genetic cause allows us to better understand the clinical picture and counsel patients appropriately. Finally, these results demonstrate the importance of regular reanalysis of previously generated exome data.

Keywords:
MLIP, rhabdomyolysis, myalgia, creatine kinase

EPNS23-2237 Oral or e-Poster
Neuromuscular Disorders

Assessment of a comprehensive digital health solution to improve the independence of people living with spinal muscular atrophy (SMA)

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Objective: People with SMA face everyday risks including assistive-equipment failures or being stuck outside on a wheelchair. They often need help to retain their independence as long as possible. Falls and respiratory complications require prompt reaction, in particular, as they can quickly degenerate into life-threatening situations. We present an ongoing study to assess the potential of digital health to support the independence of people with SMA. A primary focus is nocturnal respiratory function including cough efficiency, as it is impaired by muscle weakness, and can lead to pulmonary infections and emergency visits.

Methods: Our main objectives are to evaluate safety tools within a comprehensive digital health solution, and to assess their benefit for people with SMA and caregivers. The ultimate goal is to assess whether digital health technologies that interfere as little as possible with the independence of people with SMA (non-invasive ambient sensors, wearable devices, and mobile apps) can be leveraged to better manage or even prevent emergency situations.

Results: The data collected in this study will be used to improve existing solutions including GPS immobility detection and alarm buttons, so that people with SMA can get the help they need when they need it.
This study also aims to evaluate the usefulness of sleep and nocturnal respiratory measures for patients as well as their caregivers and physicians, and to explore whether new measures and potentially new digital biomarkers derived from non-invasive passive monitoring devices can be developed. Customized visualizations of collected measures will be created so that: 1) people with SMA can see more objectively where they stand in terms of respiratory function, and how this changes over time, and 2) caregivers can detect early signs of degradation and initiate prevention efforts as quickly as possible. We will try to develop algorithms to automatically detect acute respiratory complications when in bed, including rapid degradations in respiratory patterns and increased difficulty in airway clearance.

Conclusions: We present the methodology that we developed with patients and clinicians for this study, detailing the digital health solution to be assessed and the data modalities to be collected. We also outline our analysis plan and envisioned outcomes.

Keywords:
SMA, digital health, digital platform, spinal muscular atrophy, neuromuscular

EPNS23-2088 Oral or e-Poster
Neuromuscular Disorders

Heart medications and heart-related causes of death in patients with Duchenne muscular dystrophy

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Objective: Cardiomyopathy in patients with Duchenne muscular dystrophy (DMD) develops progressively over time. In the adult population of patients with DMD, more than 90% have developed heart dysfunction. This in-depth study is based on a nation-wide, population-based study which explored the life expectancy, leading causes of death and co-morbidity in patients with Duchenne muscular dystrophy. The results showed that 42% of patients with DMD died from heart-related complications. This in-depth study aims to identify prognostic factors, including risk factors and protective factors, impacting the patient's cardio-vascular condition from the onset of symptoms to death.

Methods: A retrospective nation-wide study was performed. Patients with DMD, born since 1 January 1970 who died by 31 December 2019, were identified via the National Quality Registry for Neuromuscular Diseases, the National Registry for Respiratory Failure, pathology laboratories, medical clinics, as well as the network for neuromuscular diseases. Information regarding the age and cause of death was retrieved from the Cause of Death Registry and was cross-checked with the medical records, along with co-morbidity.

Results: 129 patients with DMD had deceased during the study period. We found that patients who died from heart-related complications died at a median of 25,8 years. This was 2,8 years later than those patients who died from other causes. Median survival after loss of ambulation was 3,6 years longer for patients who died from heart-related complications, compared to other causes of death. 54 patients received both heart medications and corticosteroid treatment while 26 patients received heart medications but no corticosteroids. Patients receiving heart medications survived to a median of 29,9 years compared to 22,5 years for patients receiving both heart medications and corticosteroids. More analyses are to be performed during the first quarter of 2023.

Conclusions: Our preliminary results show that cardiologic complications lead to death at later stages of the disease. Treatment for heart disease, both prophylactic and disease-specific, seems to be important for increased survival.

Keywords:
Duchenne muscular dystrophy, Epidemiology, Survival, Neuromuscular, Cause of death

EPNS23-2666 Oral
Neuromuscular Disorders

SHEAR WAVE ELASTOGRAPHY IN PATIENTS WITH SPINAL MUSCULAR ATROPHY TYPE 2-3

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Objective: This study aimed to investigate selective muscle involvement by shear wave elastography (SWE) in patients with spinal muscular atrophy (SMA) types 2-3 and to compare SWE values with magnetic resonance imaging (MRI) in demonstrating muscle involvement.

Methods: Seventeen patients with SMA types 2-3 were included in the study. SWE was used to evaluate stiffness of the upper, lower extremities and paraspinal muscles. Involvement of the paraspinal muscles was evaluated using 1.5-Tesla MRI.

Results: Among the upper extremity muscles, SWE values were the highest for the triceps brachii; however, no significant difference was noted (p=0.23). In post-hoc analysis, a significant difference was observed between triceps brachii and biceps brachii (p:0.003). Patients with a longer disease duration have the highest SWE values for the triceps brachii (r=0.67,p=0.003). Among the lower extremity muscles, SWE values for the iliopsoas were significantly higher than the gluteus maximus (p<0.001). A positive correlation was found between SWE values and MRI scores of paraspinal muscles (r = 0.49,p = 0.045;r = 0.67,p = 0.003).

Conclusions: This is the first study to report muscle involvement assessed by SWE in patients with SMA type 2-3. Our findings are similar to the presence of selective muscle involvement demonstrated in previous studies and also SWE and MRI values were similar. SWE is a alternative non-invasive practical method that can be used to demonstrate muscle involvement in patients with SMA, to understand the pathogenesis of segmental involvement and to guide future treatments or to monitor the effectiveness of existing new treatment options.

Keywords:
spinal muscular atrophy, shear wave elastography, magnetic resonance imaging,

EPNS23-2387 Oral or e-Poster
Neuromuscular Disorders

Efficacy of Omaveloxolone in Patients with Friedreich's Ataxia: Update of the Delayed-Start Analysis

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Objective: Friedreich's ataxia (FA) is a rare, degenerative neuromuscular disease with no available therapies. Omaveloxolone (Omav), an investigational drug, is an activator of the transcription factor, Nrf2. MOXIe (NCT02255435) was a 2-part study of the safety and efficacy of Omav in patients with FA that included an open-label extension (OLE). MOXIe Part 2 showed that Omav significantly improved modified FA Rating Scale (mFARS) scores by -2.40 points relative to placebo after 48 weeks of treatment (p=0.014; n=82).

Methods: Patients in both MOXIe study parts were eligible to receive Omav in the OLE; only patients who participated in Part 2 were included in the Delayed-start analysis. In MOXIe Part 2, the full analysis set (FAS) included patients without severe pes cavus. In the FAS, a post-hoc, non-inferiority test was performed to assess if the difference in mFARS change from baseline between the Omav and placebo groups at the end of the 48-week placebo-controlled period (MOXIe Part 2) was sustained in the delayed-start period (defined as Week 72 in the OLE for the primary endpoint) using a single mixed model repeated measures model with all available data from the MOXIe Part 2 and data through Week 144 in the OLE.

Results: Seventy-three patients from MOXIe Part 2 FAS went on to receive Omav in the OLE. This included 34 patients who were originally randomized to Omav (i.e, Early-Start group) and 39 patients who were originally randomized to placebo (i.e., Delayed-Start group).
The noninferiority testing demonstrated that the difference in mFARS scores between the Early-Start and Delayed-Start groups observed at the end of MOXIe Part 2 (-2.17 ± 1.09 points) was preserved at the end of the delayed-start period (-2.91 ± 1.44 points). Additionally, patients in the Delayed-Start group had an annualized mFARS slope (0.76 ± 0.28 points/year) that was not convergent with the slope for the Early-Start group (0.45 ± 0.63 points/year); both slopes were less than the expected 1 to 2 points per year observed in natural history data.

Conclusions: The results of this post-hoc delayed-start analysis showed a persistent effect of early treatment on the disease course that could not be recovered by patients who only received omaveloxolone in the OLE. While treatment benefit was observed in both the Early-Start and Delayed-Start groups, compared with published natural history data, patients who started treatment earlier had a greater benefit over time.

Keywords:
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EPNS23-2292 Oral or e-Poster
Neuromuscular Disorders

The importance of implementing a transition strategy for patients with muscular dystrophy: from child to adult - insights from a tertiary center for rare neurological diseases

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Objective: Muscular dystrophy (MD) is a multisystemic X-linked genetic disease that causes progressive muscle degeneration. Given the recent years' advancement in the understanding of this disease, nowadays we approach it in a multidisciplinary manner accordingly to the international standards of care. As a result, the patient's life expectancy has increased significantly.
While the problem of transition from pediatric to adult healthcare has been raised for more than a decade, it still remains a last-minute concern. There is no consensus on how to implement the transition and no tools to evaluate its effectiveness or how it affects patient's care and quality of life.
Our study aims to identify how well-prepared are patients with MD for the transition to adult healthcare services and determine our patients' needs.

Methods: We carried out a descriptive, cross-sectional study, that included patients aged between 14 and 21, diagnosed with MD, in the care of tertiary center for rare neurological diseases. The patients completed a Transition Readiness Assessment Questionnaire (TRAQ) and a sociodemographic questionnaire. TRAQ quantifies the ability of people between the ages of 14 and 21 to manage their health.

Results: Fifteen patients with MD were included in the study. The diagnostic gap was 3 years. The study's average enrolment age was 17 years. Only 46.7% of the patients had a conversation about transitioning with a medical professional, and in all cases, it was with the child neurologist. Most frequently (57.1%) the discussion was initiated by the doctor.
Most patients (60%) have confidence in their self-care ability. However, the mean TRAQ score of 2.8 shows that they overestimate themselves. This variation may exist because the transition process is not standardized, which leaves patients confused about what it includes. The lowest score was found in the "Managing medication" category, with a mean score of 2.5. The capacity to communicate openly with medical professionals yielded the best results, with a mean score of 3.5.

Conclusions: We emphasize the necessity for a personalized and slow transfer to ensure the continuity of state-of-the-art care from pediatric to adult healthcare services and to achieve the highest quality of life.
To really prepare patients for the transition and to ensure the highest level of independence, it is essential to provide them with clear explanations. The multidisciplinary team must carry out the responsibility of turning the transfer process into a transition.

Keywords:
muscular dystrophy, transition, quality of life, neuromuscular disorder

EPNS23-2464 Oral or e-Poster
Neuromuscular Disorders

Incomplete spinal artery syndrome due to pericardial tamponade

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Case study: Spinal cord infarction is extremely rare (1-2-% of CNS ischemias) due to minimally invasive procedures, cardiac or scoliotic surgeries, sickle cell anemia, and umbilical catheterization.

Incomplete spinal artery syndrome produced by selective ischemia of the medullary anterior horns, produces acute paraplegia without sensory abnormalities or sphincter dysfunction, or in bilateral brachial diplegia if the lesion is cervical (man-in-the-barrel syndrome).
Spinal cord MRI on T2 and diffusion initially normal may rarely show the owl eyes sign, hypersignal on axial slices and absence of enhancement after contrast.

Objetives and methods: We present the case of a 2-year-old boy whith flaccid paralysis from C7 to D1, distal amyotrophy, radioulnar shortening, flexed elbow and absence digital movements.

Personal history; CIR, prematurity, pericardial effusion, cardiac tamponade with 2 pericardiocentesis. Ductus with catheterization and reintervention due to device migration.

Results: Neurophysiologically
2 months. No manual motor responses except musculocutaneous and axillary. EMG contractions of low proximal amplitude, with absence of voluntary activity or denervation in the hands.
6 months. Bilateral distal denervation of C7-C8, preservation of ulnar sensory conduction suggesting a very proximal preganglionar medullar injury.
27 months. Sensory and motor proximal conduction normal. Absence of motor response in median, ulnar and left radial. Electromyography: denervative activity in muscles dependent on C7, C8 and bilateral T1, with fibrillations and positive waves in interosseous, fasciculations. Intermediate effort patterns with submaximal contraction without an evident myopathic or neurogenic tendency. Severe preganglionic neurogenic affectation in segments C7, C8 and bilateral T1 (second motor neuron in anterior spinal cord) asymmetric, especially left.
MRI skull spinal cord at 2 and 34 months normal.
Negative SMA genetic study

Conclusions: It points to a second motor neuron affectation in the spinal anterior horn of a chronic/sequel nature.
He developed abnormal posture of the hands and flexed elbows, with palmar grip, but not digital, he required rehabilitation and trauma treatment to improve the functionality.
Although the MRI did not show abnormalities, the dates point to an incomplete anterior spinal cord syndrome and, although rare, we must think about it, to guide the case and not perform more unnecessary testing.

Keywords:
medullar, stroke, incomplete spinal artery syndrome, pericardial tamponade

EPNS23-2494 Oral or e-Poster
Neuromuscular Disorders

Taldefgrobep Alfa: Preclinical and Clinical Data Supporting the Phase 3 RESILIENT Study in Spinal Muscular Atrophy

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Objective: Spinal muscular atrophy (SMA) is a debilitating, progressive, genetic condition characterized by weakness, muscular atrophy, and motor neuron loss due to deficient survival of motor neuron (SMN) protein. SMN upregulators have been approved to treat SMA, but despite their use, many patients continue to experience weakness that impairs function and quality of life. Pharmacologic inhibitors of myostatin, a natural protein that limits skeletal muscle growth, have been studied in murine models of SMA and show promise for increasing muscle mass and function when used with SMN upregulators. Taldefgrobep alfa (BHV 2000) has a differentiated profile; targeting the myostatin pathway to lower myostatin directly, as well as blocking key downstream receptor signaling by myostatin. Extensive nonclinical studies and a well-established safety profile in patients with neuromuscular disease support the continued development of taldefgrobep. Here, we evaluate preclinical data from murine models of SMA and clinical data to establish support for a phase 3 clinical trial of combined treatment with an approved SMN upregulator and taldefgrobep.

Methods: The combination of taldefgrobep and the SMN upregulator SMN-C1 was evaluated in 2 independent studies of SMA in murine models using SMN delta 7 mice. Changes in muscle structure and function and other outcomes were compared to controls, including wild-type mice, in each study.

Results: The addition of taldefgrobep to high-dose SMN-C1 was associated with improved plantar flexor muscle function ($P < .05$) and demonstrated a trend of higher gastrocnemius muscle weight ($P = .08$), compared to use of SMN-C1 alone. Furthermore, the addition of taldefgrobep to low-dose SMN-C1 was associated with increased body weight, improved gastrocnemius weight, as well as contraction and/or relaxation kinetics and restored type IIa and IIb atrophic muscle fibers, compared to use of SMN-C1 alone ($P < .05$ for each).

Conclusions: Preclinical data suggest a potential benefit from taldefgrobep combined with SMN upregulation in SMA treatment. In addition to robust safety data from clinical studies, these preclinical results support conducting the global, prospective, randomized, double-blind, placebo-controlled phase 3 RESILIENT study (NCT05337553). The study is now enrolling ambulatory and non-ambulatory patients with SMA who are receiving SMN-upregulating therapies, with the aim of evaluating the efficacy and safety of taldefgrobep in this population.

Keywords:
Spinal muscular atrophy, survival of motor neuron protein, myostatin, taldefgrobep, RESILIENT

EPNS23-2992 Oral or e-Poster
Neuromuscular Disorders

Results of a prospective high risk population study for the frequency of alpha-Mannosidosis within MPS like phenotype patients in Europe and the Middle east

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Objective: alfa-Mannosidosis is an inherited ultra-rare disorder in which certain glycoproteins can't be broken down due to alfa-mannosidase deficiency resulting in oligosaccharides building up inthe lysosome damaging organs and tissues. Individuals affected by alpha-Mannosidosis suffer from similar clinical symptoms as patients with mucopolysaccharidoses (MPS), such asrespiratory infections, and skeletal changes. The diagnostic tests are limited due to the lack of patient population.

Methods: Our medical laboratory has accredited the test, alpha-mannosidase activity inDBS by tandem mass spectrometry. As previously revealed by a retrospective analysis of >1000 DBS submitted for MPS diagnostics, the frequency of alpha-Mannosidosis within thissample cohort of symptomatic patients suspected of MPS is high (4 within >1000 cases), even when in an additional second study (only ~400 samples from Germany), no additional casehas been identified. Due to this higher-than-expected frequency, a prospective study was initiated in September 2022 in collaboration with Chiesi.

Results: Our lab receives around 5000 DBSsamples for biochemical and genetic MPS testing from Europe and the Middle East per year. Every DBS sample submitted for MPS diagnostics, which turns out to be negative for MPSI,MPS-II, MPS-IIIb, MPS-IVa, MPS VI, and MPS VII, will be automatically evaluated for alpha-mannosidase activity. All biochemically suspected cases will be submitted to genetic confirmatorytesting. The results of the first 6 months of this prospective pilot study in matters of frequency of the tested and diagnosed MPS and alpha Mannosidosis within this high-risk populationwill be presented.

Conclusions: This easy-to-access diagnostic test will be a valuable tool for diagnosis of the disease allowing patients rapid aces to novel treatment therapy, a better understanding ofthe disease pathogenesis, medical awareness, and therapeutic monitoring.

Keywords:
alpha-mannosidosis ; mucopolysaccharidosis (MPS) ; mass spectrometry

EPNS23-2385 Oral or e-Poster
Neuromuscular Disorders

CuidAME: Spanish longitudinal data collection of SMA patients

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Objective: Spinal muscular atrophy (SMA) is a genetic disorder characterized by loss of motor neurons in the spinal cord, leading to progressive muscle atrophy, weakness, and disability. Natural history of SMA has changed due to improvements in treatment and technological advances. However, the real-world evidence on the impact of new treatments is unknown and registries could be a useful tool for this purpose. The aim of CuidAME Registry is to collect Longitudinal Data of Spanish SMA patients.

Methods: CuidAME Registry uses Smartcare platform to collect retrospective and prospective data of SMA patients, regardless of their treatment regimen. The data is collected during routine clinical visits and updated every eight months. The data collected includes the main characteristics of the onset and evolution of the disease, genetic diagnosis, treatment and motor function assessments. The estimated sample size for this project is 450 patients followed for 5 years.

Results: We analysed the baseline data collected for 338 patients followed at 16 different hospitals. The analysis showed that 22% of patients were SMA type 1, 49% type 2, 26% type 3, 1% type 4 and 1% were presymtomatic. 281 patients (84%) were treated: 68% received nusinersen; 5% received other treatments (gene therapy or risdiplam) and 11% received treatment under clinical trial conditions. Treated patients' distribution were: 97% type 1; 80% and 82% for type 2 and 3 respectively. 49 % of patients were female; 51% were less than 15 years and mean age at baseline. Mean age at baseline visit was 3,7y in type 1; 17y in type 2; 31 y in type 3 and 45,1 in type 4 and range for total population was (0-76y).
These are the baseline results after 3 years follow up. Longitudinal data measuring different outcomes will be presented at the time of the congress.

Conclusions: CuidAME is currently the platform containing the largest harmonized and standardized SMA clinical lead database in Spain. CuidAME is providing crucial data about the current management of SMA patients and the potential impact of new treatments across Spain. It also promotes national and international collaboration between centres and registries expanding the knowledge on SMA

Keywords:
SMA, CUIDAME, results

EPNS23-2626 Oral
Neuromuscular Disorders

Episodic exercise-induced gait disorder in a child

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Objective: Case presentation with videos of a rare neuromuscular disorder

Methods: Clinical examination, laboratory investigations and genetic study.

Results: A 3 years old girl presenting with episodic exercise -induced gait disturbance with stiffness of foot muscles without pain. The neurological examination revealed a mild generalized muscular hypotonia and weak deep tendon reflexes in the lower extremities. Muscle strength and bulk were normal and equal on both sides. No muscular fibrillation, no myotonia and no signs of local inflammation. The cognitive, motor and speech development were normal for age. Parents are non-consanguineous and of German origin. There is no family history of neurological illness.
The CK value was within normal limits and a genetic test for spinal muscular atrophy (SMA) was negative. Further investigations in our hospital including Blood-Gas-Analysis, Serum electrolytes including serum potassium before and after exertion, blood glucose profile , metabolic screening in plasma and urine, antibodies for myasthenia gravis, ECG and Echocardiography delivered normal reports.
A genetic test for Dopa-responsive -dystonia (Segawa-Syndrome) as well as a panel for dystonia was negative. A Trio-Exome-Analysis revealed compound heterozygous variants in the ATP2A1 Gene. The mother was found to be the heterozygous carrier for a possible pathogenic variant and the father the heterozygous carrier for a variant of unclear clinical significance.

Conclusions: The ATP2A1 gene encodes SERCA1, which is a sarcoplasmic/endoplasmic reticulum Ca(2+) ATPase that catalyses the ATP-dependent uptake of calcium from the cytosol to the lumen of sarcoplasmic reticulum in skeletal muscle. Pathogenic mutations in ATP2A1 gene cause Brody disease which is a rare, autosomal recessive myopathy leading to exercise-induced muscle stiffness. that may worsen upon exposure to cold temperatures.There is an increased risk of Rhabdomyolysis and malignant hyperthermia . Verapamil and dantrolene, drugs that limit the Ca2+ release from the sarcoplasmic reticulum, have been prescribed but often stopped because of side effects. In general the disease is not progressive and the prognosis for motor function is good.

Keywords:
Exercise-induced, muscle stiffness, rare

EPNS23-2312 Oral or e-Poster
Neuromuscular Disorders

SMA linked to the SMN1 gene: Multidisciplinary management in developing countries

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Objective: Evaluate the evolutionary profile of children with SMA with multidisciplinary care

Methods: This is a retrospective study of children diagnosed with SMA linked to the SMN1 gene who have followed a motor rehabilitation program in the pediatric neurology department of Sfax (Tunisia). We determined the clinical history, the motor level at the first and last consultation using the MFM scale, respiratory and cardiac involvement, and joint deformities.

Results: 40 patients with SMA linked to the SMN1 gene. The type Ia is predominant (42%) followed by type II (25%). The mean duration of follow-up was 6.3 years (4 months-26 years) and varied according to type: SMA I: 0.53 years; SMA II: 5.4 years; SMA III: 12.9 years.
Nearly 80% of patients were followed in motor physiotherapy and 27% used equipment and technical aids. The mean age at the start of rehabilitation was 3 months (type I) and 19 months (type II). If the rehabilitation program made it possible to limit joint deformities (22%), scoliosis (42%), and respiratory distress (32%) in patients with SMA II and III, it did not significantly prolong the vital prognosis of children with SMA I whom all died at an average age of 7months. 4 patients with SMA type II were able to benefit from a compassionate treatment program in November 2022 with Risdiplam. The evolutionary profile will be reassessed after 6 months

Conclusions: Rehabilitation care improves the functional prognosis and well-being of children but does not prolong the life of children with severe impairment. For these severe forms, early therapeutic management is necessary.

Keywords:
SMA, Rehabilitation, Risdiplam, prognosis

EPNS23-2113 Oral or e-Poster
Neuromuscular Disorders

Long-Term Follow-Up of Onasemnogene Abeparvovec Gene Therapy in Patients with Spinal Muscular Atrophy Type 1

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Objective: In the Phase I trial, START (NCT02122952), spinal muscular atrophy (SMA) type 1 patients who received the proposed therapeutic dose of onasemnogene abeparvovec (n=12) demonstrated substantially improved outcomes versus natural history. We evaluated long-term safety and efficacy of onasemnogene abeparvovec for patients with SMA type 1 (biallelic *SMN1* mutations/deletions and two *SMN2* copies) who enrolled into the LT-001 study (NCT03421977).

Methods: The primary objective was to evaluate long-term safety assessed by medical history and record review, physical examination, laboratory evaluation, and pulmonary assessments. Efficacy was evaluated by assessing developmental milestones.

Results: As of May 23, 2022, 13 patients (low-dose, n=3; therapeutic dose, n=10) were enrolled and followed for a mean of 95.1 (low-dose) and 83.5 (therapeutic dose) months. The oldest patient was 8.5 years old (8.0 years post-dosing). No deaths, serious treatment-emergent adverse events related to treatment, or any late-onset treatment events were reported. Five patients had respiratory events and dehydration that resolved. All patients who received the therapeutic dose survived and were free of permanent ventilation and have maintained achieved developmental milestones (mean [range] age at last data cut, 7.1 [6.6-7.9] years). Three achieved a new developmental milestone of standing with assistance (two without add-on therapy and one with nusinersen add-on). One patient in the low-dose cohort also achieved new developmental milestones (head control, sitting with support). Only three of 10 patients who received the therapeutic dose required respiratory support, a decrease from five of 10 in December 2019. Four of 10 patients required no non-mechanical feeding support; all 10 fed orally. Four patients who received the therapeutic dose had no add-on therapy. Of the six remaining, two started risdiplam, three switched from nusinersen to risdiplam, and one discontinued nusinersen.

Conclusions: Onasemnogene abeparvovec continues to demonstrate a favorable risk-benefit profile and durable efficacy up to 8 years post-dosing.

Keywords:
disease-modifying treatment, long-term follow-up, onasemnogene abeparvovec, spinal muscular atrophy

EPNS23-2956 Oral or e-Poster
Neuromuscular Disorders

DRUG THERAPY IN PEDIATRIC PATIENTS WITH SPINAL MUSCULAR ATROPHY: A SINGLE CENTRE EXPERIENCE

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Objective: Spinal muscular atrophy (SMA) is a rare neuromuscular disorder resulting in progressive muscle weakness and atrophy. Over the past few years, there has been an increasing number of therapeutic approaches for SMA. Nusinersen was the first disease-modifying drug approved to treat children with SMA, followed by onasemnogene abeparovec-xioi and Risdiplam. This study aimed to report our center's experience in the efficacy and safety of SMA therapies in our patients.

Methods: All patients with genetically confirmed SMA type I, II, and III, treated in our department during 2017-2022, were reviewed. Extracted data included SMA type, age at diagnosis and treatment onset, physical examinations and blood test results, and musculoskeletal, gastrointestinal, and respiratory comorbidities. Patients were assessed at baseline and regularly after treatment initiation to evaluate response to therapy, disease progression, and any treatment side effects.

Results: A total of 11 children, six boys and five girls, with a mean age of 8 ± 5,34 years, were reviewed. Three patients were classified as SMA type 1, four as type 2, three as type 3, and one as presymptomatic. The patients' mean age at diagnosis was 20 ± 15 months and at treatment onset, 61,7 ± 66,5 months. Two patients were initially treated with Nusinersen, followed by Risdiplam, and six were exclusively treated with Nusinersen. Onasemnogene abeparovec-xioi was administered in three patients. The mean follow-up time was 43 ± 17,8 months. We found a mean improvement of the HFMSE Score by 7,22 ± 14,7/66 points (10,94%) and the RULM score by 6 ± 3,15/37 points (16,2%). Most patients developed scoliosis (8/11, 72,7%) and joint contractures (8/11, 72,7%). Two older patients with SMA type 2 and 3 underwent spinal fusion at 10 and 14 years, respectively. No patient required nutritional support (nasogastric tube or gastrostomy), and two patients with SMA type 1 required ventilatory support (BiPAP) during sleep at the age of six months and three years. All patients and caregivers reported a subjective improvement in overall clinical status.

Conclusions: All therapies have shown significant clinical efficacy with stabilization or improvement in motor function, prolonged survival after two years, and decreased respiratory and nutritional support, particularly for patients with SMA type 1. Reported side effects were transient and self-limited. Despite therapy, musculoskeletal problems remain an issue and often require intervention.

Keywords:
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EPNS23-2183 Oral or e-Poster
Neuromuscular Disorders

Statistical modelling to estimate patients' weight in Types 1-3 SMA

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Objective: Individuals with spinal muscular atrophy (SMA) may have atypical weight with possible correlation to other disease morbidity, such as feeding difficulties and reduced mobility. The objective of this study was to develop a statistical model that describes weight deviations in patients with SMA compared with the general population.

Methods: Using baseline data from the FIREFISH (Type 1 SMA; NCT02913482), SUNFISH (Types 2 and 3 SMA; NCT02908685), JEWELFISH (Types 1-3 SMA; NCT03032172) and NatHis-SMA (Types 2 and 3 SMA; NCT02391831) studies, percent deviation of patient weight from World Health Organization median references was calculated. Reference weights were based on age, sex and height standards up to age 19 years. Percent weight deviation was linearly regressed on 10 a priori predictors. Four statistical models were developed using 75% of the data, and model fits tested using the remaining 25%. Final model selection was based on goodness-of-fit and statistical parsimony.

Results: This analysis included 526 patients with median age of 10 (range 0-61) years, and 50% were female. Non-sitting motor status (n=145; 28%) and prior exposure to SMA disease-modifying therapies (DMTs; n=160; 30%) were associated with below-reference weights, whereas sitting and more-advanced motor statuses; SMA type; age; sex; region; survival of motor neuron 2 gene copy number; feeding support; history of scoliosis; gastroesophageal reflux disease; and pneumonia were not. An alternative model without prior treatment and a null model had comparable ability to estimate reference weight in the 25% hold-out set. The intercept term was significant in all models, indicating that, on average, non-sitting patients with SMA weigh less than the general population reference weights according to age, sex and height.

Conclusions: This study provided a validated algorithm for estimating the weight of patients with SMA based on few input parameters. Variability in weight is primarily accounted for by age, sex and height. A simple yet accurate prediction of patient weight could be useful in clinical practice or for resource planning, as dose regimens for some DMTs are weight based. Associations implied by our models are not necessarily indicative of causal relationships.

Keywords:
Spinal muscular atrophy, disease-modifying therapies, weight, percent-weight deviation, linear regression

EPNS23-2867 Oral or e-Poster
Neuromuscular Disorders

Transaminases and Traditional Muscular Markers in Duchenne and Becker Muscular Dystrophies: Retrospective Analysis of National Registry of Dystrophinopathies

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Objective: Raised transaminases (ALT and AST) are a common finding in Duchenne (DMD) and Becker (BMD) muscular dystrophies, but distinguishing their muscular from hepatic origin can be challenging. We, therefore, hypothesized that there is a dependence of the levels of transaminases on the levels of creatine kinase (CK), a traditional muscular marker and that a mathematical equation can be defined to predict the upper limit of transaminases based on levels of CK in these patients.

Methods: We analyzed retrospective data of all pediatric patients with DMD (n=165) and BMD (n=47) followed in the three largest neuromuscular centers in our country, that were available in the REaDY database [Strenkova J, Vohanka S, Haberlová J, et al. REaDY - Ceský registr svalových dystrofií (REaDY - Czech Registry of Muscular Dystrophies). Ceská a Slovenská neurologie a neurochirurgie. Praha: Ceská lékarská spolecnost J.E. Purkyne, 2014, 77(2):230-234. ISSN: 1210-7859.], including entry levels of ALT [ukat/l], AST [ukat/l], LD [ukat/l], CK [ukat/l], and myoglobin [ug/l], and age at the time of the blood draw. Continuous variables were described as median with the 5th and 95th percentile, and mean and standard deviation. Mann-Whitney U Test was used to compare the two groups. We performed multiple linear regression to define the best predictors for the levels of transaminases. The model with $p<0.05$ was chosen for each parameter.

Results: All the studied biochemical parameters were above the normal upper limits on average in both BMD and DMD and were all higher in DMD than in BMD (all $p<0.001$). The estimations of normal transaminases from CK levels were:
ALT [ukat/l] = 3.816 + 0.011*CK [ukat/l] for DMD, and
ALT [ukat/l] = 2.079 + 0.011*CK [ukat/l] for BMD.
AST [ukat/l] = 2.796 + 0.012*CK [ukat/l] - 0.106*age [years] for both (all $p < 0,001$).

Conclusions: Both transaminases and traditional muscular markers are significantly raised in dystrophinopathies. There is a strong dependence of the transaminase levels on CK levels, suggesting their muscular origin in these patients. Further tests for hepatopathy should be considered in case of a persisting increase of transaminase levels not corresponding to the rise of creatine kinase.

Keywords:
Kreatin Kinase, Transaminases, Duchenne, Becker, Muscular Dystrophy

EPNS23-2143 Oral or e-Poster
Neuromuscular Disorders

EMBARK, a Phase 3 trial evaluating safety and efficacy of delandistrogene moxeparvovec in DMD: Study design and baseline characteristics

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Objective: Delandistrogene moxeparvovec (SRP-9001) is an investigational gene transfer therapy developed to address the root cause of Duchenne muscular dystrophy (DMD) through targeted skeletal and cardiac muscle expression of SRP-9001 dystrophin protein, which contains key functional domains of dystrophin. We describe the design of EMBARK (Study 301; NCT05096221), a Phase 3, global, randomised, double-blind, two-part, placebo-controlled prospective study assessing the safety and efficacy of intended commercial process delandistrogene moxeparvovec material in ambulatory individuals with a confirmed *DMD* mutation within exons 18-79 (excluding individuals with a mutation fully contained within exon 45), aged ≥4 to <8 years (N=125).

Methods: In Part 1, participants will be stratified by age at randomisation (≥4 to <6 years or ≥6 to <8 years) and North Star Ambulatory Assessment (NSAA) total score (≤22 points or >22 points) at screening and randomised (1:1) to receive a single intravenous dose of intended commercial process delandistrogene moxeparvovec material ($1.33x10^{14}$ vg/kg by linear standard quantitative polymerase chain reaction) or placebo. Participants will be evaluated at Week 52. In Part 2 (52-week follow-up period), participants randomised to placebo in Part 1 will receive delandistrogene moxeparvovec, and participants randomised to delandistrogene moxeparvovec in Part 1 will receive placebo.

The primary endpoint is change from baseline to Week 52 in NSAA total score (Part 1). Secondary endpoints include safety; SRP-9001 dystrophin protein production at Week 12 by western blot (Part 1); and change from baseline to Week 52 (Part 1) in: key timed function tests, stride velocity 95th centile measured by a wearable device, and Patient-Reported Outcomes Measurement Information Score® (mobility and upper extremity function).

Results: We present baseline characteristics of participants enrolled in EMBARK, a Phase 3 study of delandistrogene moxeparvovec.

Conclusions: EMBARK will provide placebo-controlled information on the efficacy and safety of delandistrogene moxeparvovec in a large population of ambulatory patients with DMD aged ≥4 to <8 years.

Keywords:
Duchenne muscular dystrophy, gene therapy, clinical trials, gene transfer

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Neuromuscular Disorders

Gene expression analysis of mtDNA of patients with hereditary myopathies

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Objective: To study the mitochondrial DNA (mtDNA) gene expression for assessment of mitochondrial dysfunction in case of various hereditary myopathies.

Methods: 47 patients were included into the study, 27 of them were male, 20 were female. Age of patients ranging from 2 to 37 years old.
The patients were divided into three groups: 1) Patients with clinical signs of mitochondrial encephalomyopathy (mtEMP); 2) Patients with muscular dystrophies (MD); 3) Patients with congenital myopathies (CM).
Clinical assessment of the of the severity of pathological process was conducted according to the Vignos, MRS scales and Gowers test. All patients underwent a muscle biopsy with a following study of the mitochondrial enzyme activity, taking into account the amount and severity of RRF.
We analyzed the expression of 49 mtDNA and nDNA genes associated with the work of mitochondria in muscles. The nCounter technology from Nanostring Technologies was used to analyze the level of gene expression. Statistical data analysis was carried out using SPSS version 22.

Results: The results of the genetic analysis associated with mitochondria were different between three groups included into the study. Significant changes in genetic expression were found in group 1 (mtEMP), and also, they were correlated with the severity of clinical and morphological signs of mitochondrial changes. In MD group, detected changes in genetic expression were mainly directed in the opposite direction. In the CM group the changes in the expression of most genes corresponded to those in MD, but a small part of them changed their expression similarly to mtEMP. Perhaps it can be associated with the presence of possible mitochondrial changes that can occur in case of core myopathies.

Conclusions: The study of gene expression in case of hereditary myopathies is a reliable marker of mitochondrial disorders and can be used in diagnostics and in refining the tactics of management of these patients.

Keywords:
myopathy, mitochondrial DNA, gene expression

EPNS23-2548 Oral or e-Poster
Neuromuscular Disorders

Ataluren in the treatment of myocardiopathy in a patient with dystrophinopathy

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Case study: Introduction: Ataluren, 3-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl) benzoic acid (also known as PTC124), is a small molecule drug developed for the treatment of Duchenne/Becker muscular dystrophy (DMD/BMD) resulting from a nonsense mutation in the DMD gene. Ataluren allows the readthrough of the premature termination codon, enabling the production of the full-length functional dystrophin protein. In 2018, Ataluren received conditional approval for the treatment of DMD/BMD due to a nonsense mutation in the DMD gene. The criteria for treatment includes ambulatory patients, 2 years and older.

Case presentation: This patient was diagnosed with a dystrophinopathy at the age of 7 years when elevated CPK values (12635U/L) were detected in a routine laboratory test. His neurological exam was normal with no evidence of muscle weakness or pseudohypertrophy. Molecular analysis disclosed a heterozygous nonsense mutation in the DMD gene [(GRCh37): ChrX: 33038278G>A, exon 2, (NM_004006): c.71G>A, p.Trp24*]. Heart magnetic resonance imaging (MRI) showed evidence of myocardial involvement including left and right ventricle dysfunction, subepicardial fibrosis of the inferior lateral wall of the left ventricle and left ventricle microfibrosis. At the age of 8 years he was started on ataluren at 40mg/kgr/day. One year later heart MRI showed normal right ventricle function, mild left ventricle dysfunction, reduction of subepicardial fibrosis and reduction of the diffuse microfibrosis.

Conclusion: This is the first report of the use of ataluren for the treatment of myocardial involvement in a patient without muscle weakness carrying a nonsense mutation in the DMD gene.

Keywords:
ataluren; dystrophinomathy, DMD; BMD; nonsense mutation

EPNS23-2191 Oral
Neuromuscular Disorders

Long-term comparative efficacy and safety of risdiplam versus nusinersen in children with Type 1 spinal muscular atrophy

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Objective: Risdiplam and nusinersen are disease-modifying therapies (DMTs) approved for the treatment of spinal muscular atrophy (SMA). There are no long-term data on relative efficacy and safety of these DMTs. In the absence of head-to-head trials, indirect treatment comparisons adjusted for cross-trial differences can inform treatment decision-making.

The objective of this study is to compare long-term efficacy and safety of risdiplam versus nusinersen in children with Type 1 SMA.

Methods: Patient-level risdiplam data from 58 children in FIREFISH (Parts 1 and 2; NCT02913482) were compared with published nusinersen data from 81 children in SHINE (ENDEAR cohort; NCT02193074).

Matching-adjusted indirect comparisons were used to compare outcomes between risdiplam and nusinersen groups, adjusting for age at first dose, disease duration and Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) total score at baseline. Cox proportional hazards models were used to compare overall survival, event-free survival and the times to Hammersmith Infant Neurological Examination, Module 2 [HINE-2] motor milestone responses, CHOP-INTEND responses, and the occurrence of any serious adverse event (SAE).

Results: After matching, relevant baseline characteristics were identical across groups. The effective sample size for risdiplam was 40.6. Median follow-up was 3 years (range 2.5-4.5). Compared with the nusinersen group, the risdiplam group had 78% lower rate of death (95% CI 53-96%), 81% lower rate of death or permanent ventilation (95% CI 65-93%), 57% lower rate of SAEs (95% CI 42-68%), and higher rates of HINE-2 and CHOP-INTEND responses. While adjustments were made for known prognostic factors, as in any non-randomized comparison, results may be confounded by unobserved baseline differences between groups.

Conclusions: Risdiplam was associated with longer survival, higher rates of motor function responses and lower rates of SAEs than nusinersen in children with Type 1 SMA. This comparative analysis leverages the longest follow-up currently available from two robust clinical trial sources. Additional data sources should be consulted to expand on these findings.

Keywords:
Spinal muscular atrophy, indirect treatment comparison, risdiplam, nusinersen

EPNS23-2995 Oral or e-Poster
Neuromuscular Disorders

Results from two year pilot study for identifying inherited myopathies by combining enzymatical testing with "clinical symptomatic-based Next-Generation Sequencing"

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Objective: Neuromuscular diseases include a large diverse group of more than 400 diseases. Due to a very broad and heterogeneous phenotypic presentation, and their rarity and complexity, neuromuscular diseases are often diagnosed with a very significant delay. Whole exome sequencing approaches covering hundreds of genes are often complex in interpretation and counseling.

Methods: We developed and validated a novel approach in combining a biochemical and targeted-NGS muscle panel for differential diagnosis of inherited myopathies using Dried Blood Spots. Hereby, a working group of experts in pediatrics, neurology, genetics have defined several gene panels with well known and common genes in daily clinical routine. After an initial pre-test for alpha-glucosidase (for Pompe disease) using tandem mass spectrometry as well as gene copy determination of SMN1 (for 5q-SMA), a targeted-NGS panel is performed depending on CK level and clinical symptoms. Six different gene panels with a total of 30 genes were developed specific for children depending on age. For adults, an additional three gene panels were developed including a total of 17 genes.

Results: Physicians can participate by a clinical questionnaire in this study supported by Sanofi Genzyme. 308 blood samples from patients with unknown diagnosis were analyzed so far. Approx. 1/3 were pediatric samples. One adult Pompe and one child with SMA were identified, in addition, 25 cases with mutations in different neuromuscular panels.

Conclusions: We present a more clinical approach of using quick enzymatic testing for Pompe as well as SMA for children, followed by specific targeted gene-panels. The selection of genes were based on the experience of several clinicians. Broader gene panels or whole exome sequencing may identify more mutations but interpretation is often complex, time consuming and counseling is challenging. Even though our gene panels were limited, we could provide diagnosis in approx. 10% of all cases fast and easy (using DBS).

Keywords:
inherited myopathies, Pompe, genetic testing

EPNS23-2552 Oral or e-Poster
Neuromuscular Disorders

Evaluation of gait in ataxia patient through spatio-temporal gait parameters measured with Kinect

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Objective: Ataxic syndromes include several rare, inherited and acquired conditions. Despite high phenotypic variability, ataxia patients can be split into two categories: progressive ataxias (PAs) and chronic ataxias (CAs). One of the main issues, in monitoring subjects' motor ability, is the absence of specific automatic evaluation tools. The level of precision and accuracy of gait analysis (GA) have reached high results but in association with high costs, long preparation and motor fatigue. We aim to test the usability of a Kinect-based system (KS) for assessing ataxia severity, exploring the potentiality of clustering algorithms and validating KS with gold standard that is GA.

Methods: We compared standardized GA (Vicon MX, UK) and KS during the same day. We enrolled 16 CA patients, 19 PA patients and 21 healthy subjects (H). Here, we analyzed the gait Spatio-temporal parameters and we looked at the differences between the two systems through agreement test. We looked at possible correlations between all variables and the SARA. The 1st and 2nd principal components of PCA were used for observing similarity of the following gait classes: low, medium, high and PA, CA, H, respectively.

Results: The presence of biases and linear relationships between all the parameters means that the Spatio-temporal parameters measured by KS cannot be used interchangeably with those acquired with a standard GA in clinical practice but can still provide fundamental information. This conclusion is reinforced by the correlations between SARA and Speed, Stride Length and Step Length. PCA results, highlight that machine learning combined with the Kinect protocol have great potential to automatically assess the gait score gravity and consequently the highly correlated SARA score.

Conclusions: These results bring to the development of a system capable of performing an easy and quick evaluation that characterizes the patient's gait and with the ability discerning automatically pathological gait and impairment level.

Keywords:
ataxia, SARA scale, gait analysis, artificial intelligence

EPNS23-2973 Oral or e-Poster
Neuromuscular Disorders

Ryanodine receptor 1-related disorder presenting with malignant hyperthermia

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Case study: Introduction
Malignant hyperthermia is a hypermetabolic reaction involving fever and muscle rigidity due to continued muscle contraction. It usually occurs with volatile anesthetic exposure in individuals with malignant hyperthermia susceptible. We present a 9-year-old girl with a ryanodine receptor 1 (RYR1) gene mutation who developed malignant hyperthermia due to anesthetic exposure.

Case Report
A previously healthy 9-year-old girl presented with generalized tonic-clonic seizures and fever after receiving anesthetic agents for appendicitis. After she was diagnosed with malignant hyperthermia, 2.5 mg/kg/dose of dantrolene sodium was administered intravenously three times and the symptoms improved. She was born after uneventful pregnancy and delivery, with a non-consanguineous marriage of her parents. She had no family history in terms of neuromuscular disease.
Neurological examination was normal except for mild scoliosis. Serum value of creatine kinase ranged from 800 to 3000 U/L (normal range up to 170 U/L). Transthoracic echocardiography was normal. Electroneuromyography showed the presence of a short-term, low amplitude, polyphasic motor unit action potential (MUAP) consistent with myopathic involvement. The next-generation sequencing test showed a heterozygous mutation of the RYR1 gene [c.7304G>A; (p.R2435H)]. Thus, she was diagnosed with malignant hyperthermia associated with ryanodine receptor 1-related disorder.

Conclusion
RYR1 variants may lead to dysfunctional RYR1-mediated calcium release, resulting in susceptibility to malignant hyperthermia. RYR1-related disorders are characterized by delayed motor milestones, scoliosis, ophthalmoplegia, contractures, and respiratory insufficiency. Familiarity with the wide spectrum of RYR1 is of great importance to all pediatric neurologists and anesthesiologists in recognizing patients at risk for malignant hyperthermia.

Keywords:
Malignant hyperthermia, RYR1, myopathy

EPNS23-2194 Oral
Neuromuscular Disorders

Practical considerations for delandistrogene moxeparvovec gene therapy in patients with Duchenne muscular dystrophy (DMD)

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Objective: Delandistrogene moxeparvovec (SRP-9001) is an investigational gene transfer therapy developed to address the root cause of Duchenne muscular dystrophy (DMD) through targeted skeletal and cardiac muscle expression of SRP-9001 dystrophin protein, which contains key functional domains of dystrophin. We outline several practical considerations for delandistrogene moxeparvovec treatment in patients with DMD.

Methods: Drawing on delandistrogene moxeparvovec clinical trials (Study 101 [NCT03375164], Study 102 [NCT03769116], and ENDEAVOR [Study 103; NCT04626674]), we describe the observed time-course of events, the monitoring for and management of adverse events, and mitigation strategies.

Results: The observed safety profile of delandistrogene moxeparvovec has been largely consistent (regarding types and timing of events), monitorable, and manageable. Recommendations for initiating delandistrogene moxeparvovec treatment in patients with DMD include: (1) screening for the presence of elevated levels of anti-rAAVrh74 total binding antibodies prior to infusion; (2) assessing liver function, platelet count, and troponin I levels before administration; (3) monitoring liver function weekly for the first 3 months following infusion and, if clinically indicated, continuing monitoring until results are unremarkable; (4) postponing administration for patients with acute liver disease until the issue is resolved or controlled; (5) monitoring troponin I levels pre-infusion and weekly for the first month post-infusion, continuing monitoring if clinically indicated; and (6) administering corticosteroids starting 1 day prior to infusion (for patients already on corticosteroids), and maintaining the corticosteroid regimen for a minimum of 60 days post-infusion, unless earlier tapering is clinically indicated.

Conclusions: Though the safety profile of delandistrogene moxeparvovec to date has been relatively consistent, monitorable, and manageable, appropriate mitigation of potential risks can help ensure patient safety. The practical considerations of delandistrogene moxeparvovec treatment provided are based on clinical trial data and aim to aid physicians treating patients with DMD.
Implementation of these practical considerations is recommended.

Keywords:
Duchenne muscular dystrophy, gene therapy, clinical trials, gene transfer

EPNS23-2811 Oral or e-Poster
Neuromuscular Disorders

Col VI Muscular Dystrophy in a Neuromuscular Center in Northern Portugal

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Case study: Introduction
Collagen VI is an extracellular matrix protein, composed by three subunits and found in most tissues. Its absence or aberrant formation results in muscle disease associated with dermatologic changes, join hypermobility and contractures.
Dominant and recessive patterns of inheritance have been observed and genotype-phenotype association is challenging.
Objective
Analise our group of patients with collagen VI-related myopathies.
Results
From our database (1995-2022), we selected patients with both clinical and genetic diagnosis of ColVI muscular dystrophy.
We found 12 patients, pertaining to 10 families. Eight males with a mean age of 14,8 ys (2-36). First symptoms were reported at a mean age of 15 months, most of them with walking abnormalities, developmental delay, frequent falls and difficulty climbing stairs. All patients were able to walk and the median age of acquisition was 22,8 months.
All have weakness, mainly proximal, and 2 lost ambulation. Two are under noninvasive ventilation.
Pathogenic variants were found in the three genes involved: 6 patients in COL6A1, 5 patients in COL6A2 and 1 patient in COL6A3.
In eight patients, four missense and two splice-site variants were found, located in COL6A1 and COL6A2 genes, and compatible with a dominant inheritance pattern. Four recessive splicing variants were detected in three patients.
Notably, three of these variants were not previously described: one missense variant and 2 small deletions affecting splicing, one of them subsequently characterized at the mRNA level. Also, one of the patients presents a deep intronic splicing variant, found to be a recurrent pathogenic variant in another COL6 patient cohort study, and that is only detectable using specific gDNA or cDNA approaches.
Conclusions
Patients had early clinical signs but clinical suspicion was made years later. This can be due to the fact that some of the signs are subtle, the full triad is not present or the clinicians are not familiarised with these disorders. We found that in recent years the diagnosis is made earlier and in two cases based on family history.
The majority of our patients have a better clinical condition, considering the other series, but this can be a bias of our small sample.
The number of different (only one recurrent variant), novel and intronic variants identified in this cohort supports the genetic heterogeneity observed in this type of disorders and the need to apply complementary molecular approaches.

Keywords:
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EPNS23-2970 Oral or e-Poster
Neuromuscular Disorders

Treatment of Patients with Spinal Muscular Atrophy with Spinraza (Nusinersen) - three-years of Experience

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Objective: To present a 3 year-experience in the treatment of SMA with Nusinersen.
The incidence of Spinal muscular atrophy (SMA) is 1 in 6,000 to 1 in 10,000 live births. Spinraza (Nusinersen) is the first registered European SMA therapy that aims reduction of the severity of the disease.

Methods: Fiveteen patients (5 with SMA I, 8 with SMA II, 2 with SMA III), treated with Spinraza from July 2019 to December 2022 in our center were prospectively followed up.
The outcome measures were clinical assessment (respiratory rate, swallowing number of respiratory infections per year and their severity), laboratory (oxygen saturation, spirometry) and scales for motor function - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) for SMA I; Hammersmith Functional Motor Scale - Expanded (HFMSE), Revised Upper Limb Module (RULM) for SMA II and SMA III. They were assessed before treatment and on regular intervals during the treatment.

Results: The average age at the initiation of the therapy was 6.7 years (5 months - 17 years). The average applied doses were 10 per patient (min 4- max 13 doses). Three of SMA I patients had severe clinical manifestation before starting the therapy. They had lethal outcome before completion of loading doses.
The initial phase led to stabilization of the motor skills in 3/4 of the patients.
At baseline in SMA I CHOP intend score was 12/64 (min 4, max - 22); in SMA II and III HFMSE score was 19/66 (min 5, max - 34) and RULM was 31 (min 28, max 34).
At the end of the induction phase the average increase in the CHOP score in SMA I was 4 (min 4 , max 11); in HFMSE score 3/66 (0-12).
At the end of the follow-up (after the 4th or 5th sustained dose) the increase in HFMSE score was 9 (min 8 , max13); in RULM - 4 (min 2 , max 4).
At the end of the induction phase 2 of 5 patients with SMA I kept normal oxygen saturation and respiratory rate and up to 1 respiratory infection per year. In all the patients with SMA II and III the oxygen saturation remained normal. In 4 of 10 there was an improvement in pulmonary function tests, in 2 patients they remained unchanged. Four of 10 could not perform the tests.
No serious adverse reactions were registered.

Conclusions: Nusinersen treatment stabilized the motor and respiratory functions and in one-third of the patients with SMA it led to their improvement.

Keywords:
Spinal muscular atrophy; Spinraza; treatment; child neurology; neuromuscular

EPNS23-2028 Oral or e-Poster
Neuromuscular Disorders

A Global Disease Registry Strategy for Generating Real-world (RW) Evidence in Spinal Muscular Atrophy (SMA): Overview and Recent Progress

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Objective: Biogen supports a rare disease registry approach for SMA with multiple partners to enable collection of high quality RW data to meet key needs of the SMA community, healthcare providers, researchers, regulators, payors, and industry. An overview of partnerships and progress made to date is provided.

Methods: Based on EMA guidance, Biogen established collaborations with multiple SMA registries to gather robust information on outcomes, characterize SMA natural course and evolving phenotypes, and improve understanding of nusinersen and other emerging treatments in a RW setting. Over the past 6 y, work has been undertaken to improve capacity and capability of registries to collect reliable patient-level data, standardize data to an international aligned core data set (TREAT-NMD), and provide financial support to implement data collection and ensure sustainability. This data set includes demographics, clinical characteristics, medical history, functional outcomes, hospitalizations, and treatments.

Results: Biogen has partnered with 25 registries in 29 countries, which have enrolled >8,300 individuals as of November 2021. As both the number of patients and the longitudinal data grow, data are increasingly used to provide insights on SMA natural history and effectiveness/safety of nusinersen. The registries supported by Biogen have led to >86 independent publications (manuscripts, congress presentations) as of November 2022. Findings from registries in Europe (Italy, Spain, Germany, Belgium) have been included in regulatory submissions and as part of reimbursement submissions to inform treatment value in specific populations including adults. In 2021, registry data supported inclusion of RW evidence on nusinersen safety and effectiveness in adults with SMA into the EMA Summary of Product Characteristics. These data, which demonstrated the benefits of nusinersen in adults with SMA, played a role in expanding access and reimbursement for UK SMA Type III patients who lost the ability to walk.

Conclusions: Registry data continue to play a critical role in addressing key questions in SMA management, such as treatment-response predictors, and inform treatment decision making in a multi-treatment era. This will help healthcare professionals optimize outcomes for RW patient populations. Registry data can also help broaden disease understanding and continue to support access and reimbursement decisions, helping more patients gain access to effective treatments.

Keywords:
spinal muscular atrophy, nusinersen, real-world evidence, registries

EPNS23-2926 Oral or e-Poster
Neuromuscular Disorders

Pre-B Cell Leukemia in a patient with distal SMA and TRPV4-pathy: Is it just a coincidence?

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Case study: Objectives: Transient receptor potential (TRP) cation channel, subfamily V, member 4 (TRPV4) is expressed in a variety of tissues, mainly the peripheral nervous system and bone, and it plays a role in a number of physiological processes. TRPV4 is located on chromosome 12q24.11, encodes a calcium-permeable, non-selective cation channel protein. TRPV4 mutations have been implicated in skeletal dysplasias, peripheral neuropathies, scapuloperoneal spinal muscular atrophy (SMA), and congenital distal SMA. Moreover, TRPV4 expression has been reported to be involved in tumor progression in various tumor types mainly endometrial cancers.

Methods: We present a patient with distal SMA who later developed Pre-B cell acute lymphoblastic leukemia (ALL).

Results: A 3-year-old boy with a history of congenital pes equino varus deformity after a correction surgery presented with complaints of delayed walking and frequent falls. His examination revealed weakness and atrophy in the distal lower extremities, mild neck weakness and scapular winging. Phenotype was compatible with dSMA and whole exome sequencing revealed a de novo 806G>A p.(Arg269His) heterozygous mutation in the TRPV4 gene. At the age of 4 years and 3 months, he presented with fever lasting for two weeks. He had cervical lymphadenopathy on examination and had bicytopenia on routine blood count. Bone marrow examination revealed Pre-B cell ALL. After the induction phase of the protocol, he is in remission and currently on maintenance treatment.

Conclusions: Transient receptor potential (TRP) channels are a family of ion channels belonging to voltage-gated superfamilies with a variety of different physiological functions. Expression of TRP channels in hematological malignancies is of great interest and tied to different subtypes. Furthermore, TRPV4 expression in AML is reported to increase chemotherapy efficiency indicating the role of TRP channels as promising candidates for precision medicine. Although the role of TRPV4 in neuromuscular diseases and skeletal dysplasia is known, its role in tumor based on case reports and remains unclear. This coincidence requires further evaluation.

Keywords:
Distal SMA, Leukemia, TRPV4-pathy

EPNS23-2856 Oral or e-Poster
Neuromuscular Disorders

DYNC1H1 mutation: phenotypic spectrum, cases series report.

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Objective: Mutations in DYNC1H1 are related to a wide diversity of pathologies; autosomal dominant lower extremity-predominant spinal muscular atrophy (SMALED), axonal Charcot-Marie-Tooth disease type 20 and neurodevelopmental disorders, malformations of cortical development, epilepsy, autosomal dominant mental retardation, and hereditary spastic paraplegia, etc.

Methods: We report 5 cases of patients from our institution who have different types of mutations involving DYNC1H1 and their clinical manifestations.

Results: Patient 1: Patient presented with congenital vertical talus, weakness predominating on lower extremities, a WISC V test was preformed which resulted in a IQ of 61. A de novo mutation on gene DYNC1H1 (missense c.C751T) (p.R251C, NM_001376) in heterozygosity was found. SMALED was then diagnosed.

Patient 2: Symptoms began at 16 months of age with a waddling gait and difficulty to stand up from a sitting position. EMG showed a distal motor axonal neuronal affectation. A de novo variant on DYNC1H1 was found.

Patient 3: Onset of symptoms between 18-24 months, caregivers reported frequent falls, difficulty getting up off the ground, impressive mild pelvic girdle weakness.. A de novo mutation on gene DYNC1H1 (c.1834G>A, p.V612M) was found. SMALED was then diagnosed.

Patient 4: Patient began showing symptoms during the first year of life, with delay on walking, being able to walk util 4 years old, MRI with Temporal frontoparietal cerebral dysgenesis. Also at age 4, autism spectrum disorder was diagnosed. A de novo mutation on DYNC1H1 (pArg1623Trp) was reported.

Patient 5: Onset of symptoms began an birth with presence of clubfoot. Patient developed a global neurodevelopmental delay. ADHD was diagnose. MRI reported presence of lissencephaly and pachygyria. DYNC1H1 (NM_001376.4) p.Glu2294Lys/c.6880G>A 14-102478673-G-A Heterozygosis

Conclusions: This report demonstrates the broad spectrum of phenotypes of DYNC1H1-related disorder to include neurodevelopmental delay and intellectual disability, malformations of cortical development, SMALED and orthopedic involvement.
In patients with brain developmental malformation associated with axonal neuropathy and SMALED we should think of mutations in DYNC1H1 as the main differential diagnosis, however there are mild phenotypes that only involve the peripheral nervous system without CNS involvement.

Keywords:
DYNC1H1, SMALED, Neurodevelopmental disorders, CMT

EPNS23-2627 Oral or e-Poster
Neuromuscular Disorders

Effect of Risdiplam on Respiratory Support in Patients with Spinal Muscular Atrophy Types I and II

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Objective: Spinal muscular atrophy is one of the most common neuromuscular disorders of childhood that results in global muscle weakness and atrophy. Respiratory muscle function is severely altered frequently with the need for ventilatory support. New treatment options have shown a positive impact on the disease progression, although they primarily focused only on significant improvement in motor function. We aimed to explore the effect of risdiplam on the mechanical ventilatory support requirements in SMA patients.

Methods: This single-centre retrospective study identifies nine patients (four with SMA1 and five with SMA2) treated with risdiplam between March 2021 and December 2022. In March 2021, the compassionate use programme (CUP) started and provided risdiplam for SMA1/2 patients in Slovakia who could not be treated with an approved therapy because they were not eligible for it. Patients were treated with risdiplam orally once daily (dose ranged from 0,2 mg/kg to 5 mg depending on age and weight).

Results: Between March 2021 and March 2022, eight patients enrolled in CUP and one SMA patient enrolled after risdiplam approval in Slovakia. The median patient age at baseline was 12 years (range 6-24 years). The median treatment duration was 19,4 months (range 7,3-19,9 months). Only one patient was treated previously with another disease-modifying therapy (nusinersen). At baseline, five SMA patients required ventilatory support - non-invasive ventilation (n=1; 11,2%) or invasive ventilation via tracheostomy (n=4; 44,5%). After 12 months of risdiplam treatment, 3 of 5 subjects with NIV/IMV required less ventilatory support per 24 h in comparison with the baseline. In one case, there was a possibility of changing invasive ventilation via tracheostomy to NIV.

Conclusions: We present real-world data in SMA patients treated with risdiplam focused on respiratory outcomes. In the literature, there is a limited amount of data describing SMA patients who could be weaned off the ventilator or could reduce NIV needs per 24 h. Our observations showed a positive effect of risdiplam on ventilatory functions.

Keywords:
spinal muscular atrophy, risdiplam

EPNS23-2082 Oral or e-Poster
Neuromuscular Disorders

RESPONSE TO CORTICOSTEROID TREATMENT IN LIMB-GIRDLE MUSCULAR DYSTROPHY R9 FKRP-RELATED: A CASE SERIES

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Case study: Objectives: Limb-girdle muscular dystrophy R9 FKRP-related (LGMD R9) is a hereditary myogenic disorder caused by function affecting variants in the FKRP gene, resulting in progressive muscle wasting and weakness. While corticosteroid (CCS) therapy is the standard of care in Duchenne muscular dystrophy, the evidence regarding the efficacy of CCS treatment in LGMD R9 is lacking. The purpose of this study was to report a case study of LGMD R9 patient treated with CCS and summarise the clinical effect of CCS in previously published LGMD R9 patients.
Methods: Retrospective clinical, radiological and laboratory data of one LGMD R9 patient treated in our clinic was reviewed. Reports of previously published patients with LGMD R9 who received CCS treatment were reviewed and summarized.
Results: We report a 16-year-old female LGMD R9 patient, diagnosed at 10 years of age. She presented with progressive muscle weakness in legs from the age of 14 years. Due to rapid deterioration, she was started on CCS. After CCS initiation with prednisolone 0.4mg/kg/day, progression of muscle weakness stopped. 6 months after CCS initiation functional status was re-evaluated and showed stabilisation of motor function: Brook score 1, Vignos score 2, North Star Ambulatory Assessment scale 27 points. Before CCS treatment creatine kinase (CK) level was 3672 U/L and after 6 months of treatment 710 U/L. MRI of lower extremity muscles before treatment showed dystrophic changes and adipose tissue infiltrates. In addition, we summarized 7 previously published LGMD R9 patients treated with CCS. Reported CCS doses ranged from 0.35-0.75 mg/kg/day. 86% patients (N=6) showed improvement in muscle strength, motor function tests and time tests. In 29% patients (N=2), tapering of CCS lead to worsening of symptoms. In 14% patients (N=1), therapy was discontinued after which muscle weakness increased. CK ranged from less than 1000 U/L to more than 20000 U/L. Muscle biopsies were performed on all patients. 86% (N=6) patients had inflammatory infiltrates in muscle biopsy.
Conclusions: 88% LGMD R9 patients (N=7) showed clinical improvement in motor function after initiation of CCS treatment including our additional case. Although currently no treatment for LGMD R9 is available, the use of CCS might be beneficial in some LGMD R9 patients. However, more studies should be performed to evaluate CCS as a potentially suitable treatment option for LGMD R9 patients.

Keywords:
Limb-girdle muscular dystrophy R9 FKRP-related, corticosteroids, muscle weakness

EPNS23-2918 Oral or e-Poster
Neuromuscular Disorders

Longterm longitudinal assessment and treatment outcome comparision of Croatian spinal muscular atrophy (SMA) patients treated with disease modifying therapy (DMT)- Pediatric SMA Registry data based analysis

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Objective: Objectives: long term longitudinal assessment of SMA patients (pts) on disease modifying therapy (DMT), comparison of treatment course and outcome based on Registry data.

Methods: Registry analysis involved functional motor abilities, motor function measurements, treatment safety and efficiency, breathing and feeding abilities of SMA pts based on TREAT-NMD dataset.

Results: All 43 SMA pts (20 type 1, 16 type 2, 7 type 3 pts) were treated with at least one of DMT, 30 SMA pts were treated with 2 DMTs sequentially. 34 pts initially treated with nusinersen, including 8 SMA 1 pts on permanent invasive mechanical ventilation (PIMV), switched to risdiplam. 1 pt previously treated with nusinersen switched to onasemnogen abeparvovec (OA) at 13 months of age, achieving ability to sit unassisted at the age of 20 months. 2/3 pts treated with OA, age 4-5 months, manifested improvement in at least 1 motor milestone. 9 SMA type 1 pts treated with nusinersen achieved significantly higher CHOP scores at follow up (10-12 vs. 38-53) after 4 years of treatment. 3 pts achieved ability to sit unassisted at age 18-24 months and to stand with support. 1 pt required PIMV after 20 months of treatment and died, age 3,5 years. 8 SMA 1 pts on PIMV improved initial mean CHOP score from 4 to 9, without impact on feeding or breathing abilities.
10 non-ambulant SMA 2b/3 pts 4 y on risdiplam in clinical trial, initial HFMSE was 2-23 at the ages 3-14 years, forced vital capacity (FVC) was 61%, while 3/8 were dependent on non-invasive ventilation; at follow up after 3 years HFMSE was 1-20, with breathing function significantly impaired (FVC 41%) due to scoliosis progression.
No significant difference in efficiency between DMTs was observed. SMA type 2 and 3 patients reported global impression of improvement of strength and endurance, and less fatiguability equally on nusinersen and /or risdiplam.
Adverse effects (AE) are most common in patients on OA at least 3 AE for each 3/3 ,all reversible, 1/3 patient developed respiratory arrest during pneumonia, requiring mechanical ventilation and tracheotomy.

Conclusions: Standardized data in registries present strong basis for clinical data sharing, data on best treatment practice, patient outcomes and their quality of life. DMT revealed no significant impact on breathing abilities. Earlier onset of treatment enables higher motor milestones achievements regardless DMT.

Keywords:
Spinal muscular atrophy, Registry data, disease modifying therapy, coparision

EPNS23-2184 Oral or e-Poster
Neuromuscular Disorders

Motor function outcomes associated with the natural history of patients with Types 1-3 SMA

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Objective: A systematic literature review was conducted to identify studies reporting on the natural history of motor function in untreated patients with Types 1-3 spinal muscular atrophy (SMA) of all ages using time-to-event (TTE) outcomes.

Methods: Electronic databases (Embase, MEDLINE and Evidence-Based Medicine Reviews) were searched from respective database inception to 29th May 2021. Observational/registry studies, case-control studies, cross-sectional studies and case series reporting motor outcomes in untreated patients with Types 1-3 SMA were included. Studies were assessed for their feasibility in generating pooled datasets which included reviewing TTE outcomes/definitions and availability of Kaplan-Meier (KM) curves. KM curves were digitised to create pseudo individual patient data and pooled in a single data set. Sensitivity analyses were conducted to account for heterogeneity in characteristics that could impact results (e.g. definition of time to motor milestone loss).

Results: Eight studies reported motor loss TTE data as KM curves (probability of sitting in Types 2/3 SMA [n=3 studies]; probability of walking/ambulation in Type 3 SMA [n=8 studies]). No KM curves were identified for patients with Type 1 SMA, as these individuals typically do not achieve these motor milestones. KM curves displayed greater homogeneity for Type 2 'sitters' (those whose maximum ability was to sit independently) and Type 3 SMA (those with a disease onset at <2 years [3a] and ≥2 years of age [3b]), and were thus pooled within subgroups. Median time to loss of sitting (95% confidence interval) for Type 2 'sitters' was 14.5 years (14.1-31.5). Median time to ambulation loss was 13.4 years (12.5-14.5) and 44.2 years (43.0-49.4) for patients with Types 3a and 3b SMA, respectively.

Conclusions: These findings indicate that untreated patients with Types 2/3 SMA continue to be at risk of losing motor milestones into late adulthood and support the importance of stabilisation even at older ages.

Keywords:
Spinal muscular atrophy, SMA, systematic literature review, SLR, natural history, motor function

EPNS23-2750 Oral or e-Poster
Neuromuscular Disorders

Evaluation and assessment of Maximal Mouth Opening (MMO) in Children with Spinal Muscular Atrophy (SMA) before and after the Gene Replacement Therapy

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Objective: The primary objective of this study was to evaluate the difference, if any, in the maximal mouth opening (MMO) following gene replacement therapy (Onasemnogene aboparvovec) in patients with Spinal Muscular Atrophy (SMA).

MMO assessments are essential parameters in the clinical evaluation of TMJ and muscles of mastication for oral physicians. It is an important diagnostic criterion for evaluating the stomatognathic system, especially for those with temporomandibular and neurogenic dysfunctions. It also facilitates maintaining good oral hygiene, which is needed to prevent odontogenic and non-odontogenic infections. MMO is also required for the ease of endotracheal intubation, when needed, in children with developmental and neuromuscular disorders.

SMA affects muscles, including the muscles of mastication and the Temporomandibular Joint (TMJ). Hence the MMO is also affected in these patients. Evaluation of MMO is, therefore, should be an essential part of their motor assessment.

Methods: Informed consent was obtained from the respective parents before enrolling the eligible children in this study. All the children receiving Onasemnogene aboparvovec at our hospital had an assessment of the baseline measurement of the MMO, which was measured as the inter-incisal distance keeping the head in a stable position and by using a 12 mm WHO perio probe and a standard ruler. A total of 22 children were enrolled in this study. Intraoral, extraoral and facial exercises were advised as a daily practice for all these children as a regimen.

These 22 children were followed up again after three months of receiving Onasemnogene aboparvovec. Repeat measurement of MMO with the same method and by the same assessor was performed in all these children. The data was used for statistical analysis, and paired t-test was used for interpretation.

Results: The results were significant before and after the gene therapy clinically as well as statistically. The results of paired t-test for n=22 indicated that there was a significant difference in the MMO before (Mean= 18.8, SD = 5.9) and after (Mean= 20.7, SD = 5.002) the gene therapy with $p < 0.0001$ at the 5% significance level and mean difference = 1.886 95%CI [1.110, 2.663].

Conclusions: Onasemnogene aboparvovec is known to provide a positive outcome in the motor function of children with SMA. With this study, we have also noted a significant increase in the maximal mouth opening (MMO) in children with SMA who received Onasemnogene aboparvovec.

Keywords:
Maximal mouth opening, Spinal Muscular Atrophy, Onasemnogene aboparvovec

EPNS23-2112 Oral or e-Poster
Neuromuscular Disorders

Intravenous and Intrathecal Onasemnogene Abeparvovec Gene Therapy in Symptomatic and Presymptomatic Spinal Muscular Atrophy: Long-Term Follow-Up Study

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Objective: Patients who received intravenous (STR1VE-US; STR1VE-EU; STR1VE-AP; SPR1NT) and intrathecal (STRONG) onasemnogene abeparvovec demonstrated improved survival and motor function versus natural history. We examined the long-term safety and durability of intravenous or intrathecal onasemnogene abeparvovec in symptomatic and presymptomatic patients with spinal muscular atrophy (SMA) who enrolled into the LT-002 study (NCT04042025).

Methods: Long-term safety was assessed by medical history/record review, physical examination, laboratory evaluation, and pulmonary/cardiac assessments. Efficacy was assessed by developmental milestones and Hammersmith Functional Motor Scale Expanded (HFMSE).

Results: As of May 23, 2022, 81 patients (intravenous, n=63 [symptomatic, n=38; presymptomatic, n=25]; intrathecal, n=18) were enrolled in LT-002, with a mean (range) follow-up of 3.4 (1.0-4.3) and 3.6 (2.6-4.3) years for the intravenous and intrathecal cohorts, respectively. There were no deaths or treatment-emergent adverse events (TEAEs) resulting in discontinuation. The most frequently reported TEAEs were gastroenteritis, nasopharyngitis, pneumonia, respiratory distress, and viral infection. All patients survived and maintained developmental milestones with a mean (range) age at cutoff of 3.7 (2.4-4.7) and 5.3 (3.4-7.4) years for the intravenous and intrathecal cohorts, respectively. Only one patient required permanent ventilation. Twenty-seven patients achieved new developmental milestones (presymptomatic-intravenous, n=6; symptomatic-intravenous, n=16; intrathecal, n=5); more than half (n=16) did so without add-on therapy. Improvements in HFMSE were clinically significant (≥ 3 points; presymptomatic-intravenous, 81.25%; symptomatic-intravenous, 66.6%; intrathecal, 50%). No patients treated presymptomatically required ventilatory/nutritional support; few symptomatic patients required ventilatory (intravenous-symptomatic, 32%; intrathecal, 5.6%) or feeding (intravenous-symptomatic, 20%; intrathecal, 0%) support at cutoff. Most patients fed orally (intravenous, 95%; intrathecal, 100%). The majority (57/81) never received add-on therapy. Of those receiving add-on therapy, half did not achieve a new developmental milestone after initiation of add-on therapy.

Conclusions: Intravenous/intrathecal onasemnogene abeparvovec demonstrates consistent, substantial, and durable efficacy and no new safety signals in symptomatic and presymptomatic patients with SMA.

Keywords:
clinical trial, disease-modifying treatment, onasemnogene abeparvovec, presymptomatic, spinal muscular atrophy

EPNS23-2181 Oral or e-Poster
Neuromuscular Disorders

JEWELFISH: 24-month safety, pharmacodynamic and exploratory efficacy data in non-treatment-naïve patients with SMA receiving treatment with risdiplam

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Objective: To determine the safety, tolerability, pharmacokinetics and pharmacodynamics (PD) of risdiplam in non-treatment-naïve patients with SMA.

Methods: JEWELFISH (NCT03032172) is a multicentre, open-label study of daily risdiplam in non-treatment-naïve patients with SMA (inclusion criteria aged 6 months-60 years at enrolment) who were previously enrolled in the MOONFISH study (RG7800) or previously treated with nusinersen (SPINRAZA®), olesoxime or onasemnogene abeparvovec (ZOLGENSMA®).

Results: The enrolled population (N=174) included a broad range of ages (1-60 years), SMA types (1-3), *SMN2* copy numbers (1-4) and motor functions (non-sitters/sitters/walkers). Of the 174 patients enrolled, 13 patients were previously enrolled in MOONFISH (three patients were treatment naïve as they had received placebo and never switched to RG7800), 76 received nusinersen, 70 received olesoxime and 14 received onasemnogene abeparvovec. One patient withdrew from the study at baseline. Risdiplam treatment led to a >2-fold increase in SMN protein versus baseline within 4 weeks, irrespective of previous treatment. No drug-related safety findings leading to withdrawal were reported for any patient. The safety profile of risdiplam was consistent with the safety profile in treatment-naïve patients treated with risdiplam in the FIREFISH (NCT02913482) and SUNFISH (NCT02908685) studies. Based on the exploratory efficacy analysis, an overall stabilisation of motor function was observed following 24 months of risdiplam treatment in patients aged 2-60 years as assessed by the 32-item Motor Function Measure and Revised Upper Limb Module scales (data-cut: 31 January 2022).

Conclusions: JEWELFISH is ongoing at sites across Europe and the USA and is providing important data on the safety, PD and exploratory efficacy of risdiplam in a broad population of non-treatment-naïve patients with SMA.

Keywords:
Risdiplam, spinal muscular atrophy, clinical trial

EPNS23-2945 Oral or e-Poster
Neuromuscular Disorders

Onasemnogene aboparvovec in children with SMA: Outcome and experience from a single centre in the United Arab Emirates

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Objective: The objective of this study was to demonstrate the clinical, motor and respiratory outcomes in children with Spinal Muscular Atrophy (SMA) following Onasemnogene abeparvovec at a single centre in the United Arab Emirates (UAE).

Methods: A retrospective analysis of 52 children with SMA treated with Onasemnogene abeparvovec at our centre between November 2020 and December 2022 was conducted. They were given 1 mg/kg (n=27) or 2 mg/kg (n=25) oral prednisolone. Liver function, coagulation profile, and other clinical parameters were monitored. Motor skills were measured with CHOP-Intend and other scales.

Results: These children belonged to Turkey(34), UAE(4), Iran(4), Russia(3), Romania(2), Kazakhstan(2), Kyrgyzstan(1), Ethiopia(1), and Nepal(1). The age group was between 7 and 83 months (mean=30), while they weighed between 5 and 15.6 kg (mean= 10.28 kg).

31(60%) were on assisted (46% on invasive and 14% on non-invasive) ventilation. 36(69%) received Nusinersen before gene therapy. 42(80%) patients received through crowdfunding.

Transaminitis (47/52) and thrombocytopenia (49/52) were noted in the first week after therapy which responded by continuing prednisolone. It was evident in the group receiving 1 mg/kg prednisolone. This difference seen in the first week was statistically significant with $p<0.05$ when analyzed with the Mann-Whitney test (for ALT: U value = 212.5; z-score 2.28019, p 0.0226 and for AST: U value=271; z-score 2.289; p0.0226). There was no second transaminitis peak in the double-dosed group. Other Liver functions, ultrasound, coagulation profile, and clinical examination remained normal. There was no incidence of vomiting, thrombotic microangiopathy, or bleeding. All 52 children had normal Troponin-i levels before and after the therapy.

Among children with invasive ventilation, 60% showed increased time-off ventilation. Ventilator settings could be reduced within three months in 29%. 53% reported reduced airway secretions while nearly half of them (25%) stopped using hyoscine. In 47% paradoxical breathing was resolved.

The improvement in the CHOP-intend score was significant with $p < 0.0001$, Anova f=6.3092 CI [11.18 to 4.74] (Mean scores 37.46 points (SD 11.31) in pre-treatment vs 45.42 points (SD 8.73) in the post-treatment group.

Conclusions: Our experience shows that Onasemnogene abeparvovec is well tolerated, and the transient side effects can be minimized with a higher dose of steroids. Improvements in the motor skills are notable with improved respiratory outcomes.

Keywords:
Onasemnogene aboparvovec, Spinal Muscular Atrophy, CHOP Intend, Transaminitis

EPNS23-2577 Oral or e-Poster
Neuromuscular Disorders

Tertiary single-center experience in treating children with spinal muscular atrophy in Bulgaria.

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Objective: To describe the characteristics of Bulgarian patients with spinal muscular atrophy (SMA) that are being treated with either nusinersen, risdiplam, or onasemnogene abeparvovec and to emphasize the problems that lead to poor results.

Methods: Single-center prospective study including SMA patients treated with disease-modifying medications starting from 2019. The collection of data was based on the medical records of the patients including demographics, disease characteristics, and panel data on standardized assessment tools - The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) and the Hammersmith Functional Motor Scale - Expanded (HFMSE) at baseline and approximately six months after initiation of therapy.

Results: 21 patients were included in the study, of whom 15 were males. The mean age of diagnosis was 29.1 months (range, 2-156). The initial treatment was started at 55.8 ± 55.9 months. The most common subtype was SMA type I (9/21). SMA type II consisted of four patients. Eight patients were diagnosed with SMA type III. Two copies of the SMN2 gene were present in 10/21 patients, the most common genetic variant. Four copies of the SMN2 gene were detected in four patients and only one of them is still ambulant.
Nusinersen was the most utilized drug (15/21) with a mean treatment duration of 21.7 months. The patients on nusinersen were divided into two groups - the HFMSE was used in patients older than 24 months (11/21) and the CHOP-INTEND was used in the other four cases. There was a statistically significant worsening in the HFMSE group (p=0.03). The CHOP-INTEND group discovered no difference in two of the cases at six months follow-up; one case increased by four points and one case showed a regression by four points.
The most common complication was lower respiratory tract infection (LTI) (11/21), four patients died.

Conclusions: Despite the availability of all three contemporary treatment options in Bulgaria - a worsening tendency was discovered in the early follow-up of patients with SMA. Diagnosis delay, poor overall compliance, and lack of adequate follow-up are some determinants that may lead to such results. Additional research is needed in the field.

Keywords:
SMA, treatment, nusinersen, risdiplam, onasemnogene abeparvovec

EPNS23-2927 Oral
Neuromuscular Disorders

Swallowing in Patients with SMA - New findings in DYS-SMA Trial

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Objective: Spinal muscular atrophy (SMA) is a progressive autosomal-recessive neuromuscular disease characterized by premature degeneration of the 2nd motor neuron and a broad phenotype. The clinical hallmarks of SMA are progressive muscle weakness and muscular atrophy. Bulbar muscle weakness including dysphagia represents an important diagnostic and therapeutic challenge. Dysphagia is an important factor of morbidity in SMA, adequate diagnosis and care of this symptom are essential to maintain a good quality of life. Only a few retrospective studies with small numbers of patients or case reports dealing with dysphagia in SMA are on record, and no standardized assessments using validated tests have been applied. No larger study has systematically analyzed which percentages of SMA 1, 2, and 3 patients suffer from dysphagia, and no data are available about severity of dysphagia in the single types.
The aim of the DYS-SMA trial (ClinicalTrials.gov Identifier: NCT04773470) is to implement Flexible Endoscopic Evaluation of Swallowing (FEES) and standardized FEES-scores in the diagnostic work-up of dysphagia in SMA 1, 2, and 3 patients.

Methods: FEES is used for quantification of dysphagia severity displayed via standardized FEES-scores using a severity score FEES algorithm. Total FEES score is correlated with SMA severity, motor function scores as well as with pulmonary function as external factors at the first and second measure time point, in order to determine the association with external measures related with dysphagia. We will determine whether the total FEES score at the first measurement time point is associated with SMA severity, pulmonary function, and occurrence of pneumonia during the follow-up four months after the first visit (i.e. its ability to predict disease progression).

Results: Since we intend to present the preliminary results we assume that scores will correlate at least moderately. As the FEES-scales measure related, but distinct, aspects of swallowing, we assume that there is a significant moderate association (i.e. correlation). For interpretation of re-test reliability, we will take into account that SMA is a progressive disease, and changes in motor and swallowing functions from the first to the second time point are to be expected.

Conclusions: We do not assume a perfect, but rather moderate correlation of scores. Inter-rater reliability, however, is hypothesized to be high because of the standardized nature of the assessment.

Keywords:
SMA, dysphagia, FEES

EPNS23-2185 Oral or e-Poster
Neuromuscular Disorders

Observational study of the natural history of Types 1-3 spinal muscular atrophy (SMA): An exploration of genotype

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Objective: Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disorder leading to progressive muscle weakness and disease-related complications. SMA encompasses a broad range of phenotypes typically classified into Types 0-4 based on age at symptom onset and highest motor milestone achieved. SMA severity generally correlates inversely with the copy number of the survival of motor neuron 2 (*SMN2*) gene. With the advent of early diagnosis relying on genetic characteristics, there is a need to understand the trajectories of natural history to demonstrate the benefits of early treatment.

Here we investigate the natural history of untreated patients with SMA when stratified by *SMN2* copy number.

Methods: This observational retrospective study utilised data from the US-based Pediatric Neuromuscular Clinical Research Network; a consortium of SMA-treating clinics participating in SMA research. Untreated individuals with a genetically confirmed clinical diagnosis of Types 1-3 SMA, for whom milestone achievement and/or loss was reported and *SMN2* copy number was ≥2, were included. Time-to-event (milestone achievement/loss, permanent ventilation, respiratory and feeding support, scoliosis surgery and survival) was stratified by *SMN2* copy number. Time-to-event analyses estimated median survival from Kaplan-Meier curves.

Results: The study cohort included 134 individuals (male/female: 54%/46%); 33 had 2 *SMN2* copies (91% of whom had Type 1, 9% Type 2 SMA), and 101 had ≥3 copies (10% of whom had Type 1, 52% Type 2 and 37% Type 3 SMA). The mean time-to-loss of sitting increased with *SMN2* copy number. The mean time-to-loss of standing was earlier in individuals with 3 *SMN2* copies (3.67 years, standard deviation [SD] 2.5) compared with ≥4 copies (17 years, SD 8.5). Similar results were seen for walking. The time to respiratory and feeding support, and scoliosis surgery, was earlier in those with 2 compared with 3 *SMN2* copies. Survival correlated with increasing *SMN2* copy number; no deaths were reported in those with ≥4 copies.

Conclusions: Results from this cohort confirm that loss of milestones and need for respiratory and feeding support can be stratified by *SMN2* copy number (which can be verified via newborn screening) as an alternative to SMA type. Milestone loss and need for support occurred earliest in individuals with 2 *SMN2* copies yet are still substantial in those with 3 copies. In individuals with ≥4 *SMN2* copies, milestone loss continues gradually over a lifetime.

Keywords:
SMA, SMN2, motor milestones, genotype, natural history

EPNS23-2130 Oral or e-Poster
Neuromuscular Disorders

Treatments and Outcomes for Patients with Spinal Muscular Atrophy Type 2: Findings from RESTORE Registry

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Objective: Real-world data describing treatment patterns and outcomes for patients with SMA type 2 are limited. Patients with untreated SMA type 2 typically have clinically identifiable disease symptoms between 6-18 months of age, and are able to sit independently, but are unable to walk without support. We sought to describe real-world treatment patterns and outcomes for patients with SMA type 2 receiving onasemnogene abeparvovec monotherapy or who switched to onasemnogene abeparvovec from nusinersen.

Methods: RESTORE is an ongoing SMA patient registry that captures patient data from a variety of sources. We analyzed changes in motor milestones and motor function scores and assessed treatment-emergent adverse events (TEAEs) for patients who received onasemnogene abeparvovec monotherapy or switched to onasemnogene abeparvovec from nusinersen.

Results: As of Nov. 23, 2021, 34 patients with SMA type 2 were identified. Six (17.7%), 27 (79.4%), and one (2.9%) had two, three, or four *SMN2* gene copies, respectively. Median age at SMA diagnosis was 13.0 months. Age at first disease-modifying treatment (DMT) administration was 14.0 months. Median interval between diagnosis and first DMT was 1 month. Two-thirds (n=23/34) of patients received onasemnogene abeparvovec monotherapy; 11 patients switched to onasemnogene abeparvovec from nusinersen. Of 23 patients with ≥2 motor milestone assessments (≥1 post-DMT administration), all but three (onasemnogene abeparvovec only [n=3]) maintained or achieved new milestones: 14 (60.9%) received onasemnogene abeparvovec monotherapy and six (26.1%) switched to onasemnogene abeparvovec from nusinersen. Ten of 11 (90.9%) patients evaluable for CHOP INTEND improved/maintained score, with eight (72.7%) achieving a ≥4-point increase. Any-stage TEAEs were recorded for 11/23 (47.8%) patients who received onasemnogene abeparvovec monotherapy and 7/11 (63.6%) who switched to onasemnogene abeparvovec from nusinersen. AEs in RESTORE are consistent with overall onasemnogene abeparvovec experience. No new safety signals were identified.

Conclusions: Real-world data from RESTORE indicate that onasemnogene abeparvovec is effective and has an acceptable safety profile for patients with SMA type 2, regardless of prior treatment with nusinersen.

Keywords:
disease-modifying treatment, onasemnogene abeparvovec, registry, spinal muscular atrophy, survival motor neurons

EPNS23-2896 Oral or e-Poster
Neuromuscular Disorders

Recurrent sensory-motor neuropathy mimicking CIDP as predominant presentation of PDH deficiency

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Case study: Introduction: PDH deficiency (OMIM # 312170) is a relatively common mitochondrial disorder, caused by mutations in the X-linked PDHA1 gene and presenting with a variable phenotypic spectrum, ranging from severe infantile encephalopathy to milder chronic neurological disorders.
Isolated peripheral neuropathy as predominant clinical presentation is uncommon.
Results: We report on a patient, now 21 years old, presenting at the age of 2 years with recurrent symmetric weakness as first symptom of a PDH deficiency. Neurophysiological evaluation proving a sensory-motor polyneuropathy with conduction blocks and presence of elevated CSF proteins, suggested a chronic inflammatory polyneuropathy (CIDP). The evidence of high serum lactate and the alterations in oxidative metabolism in muscle biopsy pointed toward the final diagnosis. After starting nutritional supplements, no further episodes occurred. A hemizygous mutation in PDHA1 (p.Arg88Cys) was identified. This mutation has been previously described in 5 patients with a similar phenotype. A 3D-reconstruction demonstrated that mutations affecting this arginine destabilize the interactions between the subunits of the E1 complex.
Conclusion: We summarize the clinical and genetic characteristics of one patient with PDH deficiency presenting isolated peripheral nervous system involvement. This study highlights that the diagnosis of PDH deficiency should be considered in children with unexplained peripheral neuropathy, even with features suggestive of acquired forms, especially in case of early onset and limited response to treatment. A simple analysis of lactic acid could help to target the diagnosis.
In addition, we suggest that the residue Arg88 is the most frequently involved in this specific phenotype of PDH deficiency.

Keywords:
PDH deficiency, peripheral neuropathy, episodic weakness, mitochondrial disorder

EPNS23-2089 Oral or e-Poster
Neuromuscular Disorders

Ataluren preserves upper limb function in nmDMD patients from Study 041, a phase 3 placebo-controlled trial, and the STRIDE Registry

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Objective: To assess performance of upper limb (PUL) function in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients receiving ataluren+standard of care (SoC) in Study 041 (NCT03179631), a phase 3, double-blind, placebo-controlled 72-week trial, and in the STRIDE Registry (NCT02369731), an ongoing, long-term, real-world evidence study.

Methods: In Study 041, nmDMD boys aged ≥5 years, on a stable corticosteroid regimen, and with a 6-minute walk distance (6MWD) ≥150m were randomized 1:1, ataluren:placebo. The intention-to-treat (ITT) population comprised randomized boys who received at least one dose of study treatment (N=359; mean age 8.1 years); a key subgroup included those with baseline 300-400m 6MWD (n=169). STRIDE patients were propensity-score matched to patients receiving SoC alone in CINRG DNHS (NCT00468832), yielding a comparable population (N=261). Kaplan-Meier analyses estimated age at loss of upper limb function.

Results: Least-squares mean PUL total score change from baseline to week 72 (by a mixed model for repeated measures analysis) numerically favoured ataluren vs placebo (0.44, p=0.1059) in the Study 041 ITT population and was significant in the 300-400m 6MWD subgroup (1.02, p=0.0165).
In matched STRIDE vs CINRG patients (mean last assessment age, 13.1 vs 14.6), ataluren preserved hand-to-mouth function by 3.4 years (p=0.0046) as assessed by entry level items of PUL vs Brooke Scale, respectively. Median age at loss of overhead reach numerically favoured STRIDE, consistent with the overall trend (15.8 vs 12.6; p=0.2872). Median age at loss of distal hand function was non-estimable for STRIDE patients.

Conclusions: Results indicate that ataluren may help preserve upper limb function in advanced nmDMD patients.

Keywords:
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EPNS23-2388 Oral or e-Poster
Neuromuscular Disorders

Inflammatory polyneuropathy associated with onset of Type 1 Diabetes Mellitus.

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Case study: Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia; it can be associated with a number of peripheral nerve disorders, which include some inflammatory neuropathies.

Objetive:
To describe a patient with DM presenting with an acute complication of inflammatory polyneuropathy.

Methods:
Clinical case: 17-year-old female patient with onset of type 1 diabetes mellitus, who presented different acute complications: diabetic ketoacidosis, coma, acute intestinal ischaemia.. After recovery from the complications (6 weeks) the patient presented weakness of four limbs, with absence of gait and areflexia.
Neurography: No motor or sensory potential evoked in the lower extremities. EMG: Abundant fibrillations and positive waves. No voluntary activity. Given the findings of acute denervation, it was decided to start treatment with IV IG 0.4 grams/k/day for 5 days.
Result: After the treatment, the patient progressively recovered strength. Control neurography showed potential and no fibrillations or positive EMG waves were observed.

Conclusions:
Neuromuscular autoimmune complications may present as clinical manifestations at the onset of DM. Early detection and treatment of DM-associated autoimmune polyneuropathy improves the prognosis and thus prevents CIDP.

Keywords:
Inflammatory polyneuropathy Diabetes mellitus

EPNS23-2603 Oral or e-Poster
Neuromuscular Disorders

Spinal Muscular Atrophy type 1 in patients with 4 or more SMN2 gene copies.

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Objective: Spinal muscular atrophy (SMA) is a devastating neuromuscular disorder caused by the mutations in SMN1 gene. SMA1 is the most severe type of the disease, with the premature death before the age of 2 in about 90% of cases, in not treated. The clinical severity of SMA depends on the number of SMN2 gene copies and 4 or more copies are associated with later onset of symptoms and milder course of the disease. Recently, disease-modifying therapies have been introduced in SMA. Newborn screening programmes allow early genetic diagnosis of SMA, before the onset of symptoms in the increasing number of cases. The efficacy of treatment is highest in the presymptomatic patients, but there is still no consensus on the treatment initiation in the presymptomatic patients with 4 or more SMN2 gene copies. The aim of this work was to establish the risk of SMA1 symptoms in patients with 4 or more SMN2 gene copies in the Polish SMA patients treated with nusinersen in the national SMA treatment programme.

Methods: 953 patients with SMA diagnosis treated in Poland were analyzed in order to identify cases with 4 or more SMN2 copies and the onset of symptoms before the age of 6 months.

Results: Four SMN2 gene copies were found in 201 cases, five copies - in 5 patients, and 6 copies in 1 patient.
Six patients with 4 SMN2 copies were diagnosed with SMA type 1, with the onset of symptoms ranging from 1 to 6 months. All these patients received nusinsersen treatment starting from the age of 4 to 35 years. Their baseline CHOP-Intend scores ranged from 11 to 27. One patient died after 5 doses of nusinersen. Five patients responded to therapy; their latest scores ranged from 17 to 46 (mean improvement by 14.5 points) after receiving 11 to 20 doses.
SMA type 1 symptoms were also found at the age of 6 weeks in one patient with 5 SMN2 copies who had been diagnosed in the newborn screening programme at the age of 2 weeks and had no symptoms at that time. The watch-and-wait strategy was used with the neurological check-ups every 4 weeks. At the age of 6 weeks she started nusinersen treatment. Her baseline CHOP-Intend score was 30 and after 4 doses of nusinersen it was 39. The symptoms of the disease were no longer present.
Patient with 6 copies of SMN2 was without symptoms.

Conclusions: Infants with 4 or more SMN2 gene copies are at substantial risk of early development of SMA symptoms and should be subjected to frequent neurological examinations. Early treatment should be considered.

Keywords:
SMA type 1, SMN2 copies

EPNS23-2805 Oral or e-Poster
Neuromuscular Disorders

First lessons of Gene replacement therapy in Kazakhstan

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Objective: Spinal muscular atrophy 5q (SMA5q) is an autosomal recessive neuromuscular condition characterized by progressive, symmetrical muscle weakness eventually leading to muscle atrophy and disability. The overwhelming majority of SMN5q cases are due to homozygous absence of the part of SMN 1 gene. It is a serious condition that gets worse over time, but there are some approaches to help manage the symptoms.

Methods: We have assessed a fist experience to use a gene replacement therapy of SMA in Kazakhstan.
During last two years, we used this treatment for seven children with different types of SMA.

Results: We had two patients with SMA type 2, 3 patients with SMA type 1, 1 patients with preclinical SMA; all of them were under 2 years of age at infusion day. We have one case of death after infusion on day 56. This child developed a liver failure. All other children have a good response for gene replacement therapy with increased points according to CHOPINTEND score.

Conclusions: Gene replacement therapy is an effective option for management of SMA symptoms at children under two years of age. This therapy need to be provided in specialized treating center under supervision of well trained and experienced team of specialists who will do posttreatment monitoring at least 3 months after infusion or till normalization of liver transaminases levels

Keywords:
SMA 5q, gene replacement therapy.

EPNS23-2064 Oral or e-Poster
Neuromuscular Disorders

Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis

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Objective: Strategic Targeting of Registries and International Database of Excellence (STRIDE) Registry (NCT02369731) is an ongoing, multicenter, observational registry providing data on ataluren use in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients in routine clinical practice.

We examined if nmDMD patients receiving ataluren plus standard of care (SoC) in the STRIDE Registry experienced a delay in age at loss of ambulation (LOA) versus DMD patients receiving SoC alone in the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (NCT00468832).

Methods: Data were extracted on January 31, 2022. Propensity score matching identified STRIDE and CINRG patient cohorts (N=260) comparable in established predictors of disease progression: age at first symptoms; age at initiation of corticosteroid use; duration of deflazacort use; and duration of other corticosteroid use. Patients from CINRG who had received investigational drugs for DMD were excluded. Kaplan-Meier analyses were used to estimate age at LOA.

Results: The mean (standard deviation) ages at first symptoms in the STRIDE and CINRG cohorts (N=260 per cohort) were 2.8 (1.7) and 2.8 (1.5) years, respectively. Most patients (STRIDE vs CINRG) received corticosteroids for greater than or equal to 12 months (85.0% vs 83.8%), with a similar proportion receiving deflazacort (47.7% vs 44.2%) or other corticosteroids (41.9% vs 43.5%). In the STRIDE cohort, 26.5% (69/260) of patients lost ambulation compared with 54.6% (142/260) of patients in the CINRG cohort. The median (95% confidence interval) ages at LOA (STRIDE vs CINRG) were 17.9 (14.8, not estimable) and 12.5 (12.0, 13.5) years, respectively. Kaplan-Meier analyses showed that ataluren plus SoC delayed age at LOA compared with SoC alone ($p<0.0001$).

Conclusions: These Kaplan-Meier analyses showed that in routine clinical practice ataluren plus SoC delayed age at LOA by 5.4 years compared with SoC alone in patients with nmDMD.

Keywords:
Rare disease, Duchenne muscular dystrophy (DMD), patient registry

EPNS23-2116 Oral or e-Poster
Neuromuscular Disorders

Ataluren preserves muscle function in nmDMD patients: a pooled analysis of results from three randomized, double-blind, placebo-controlled trials

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Objective: Study 041 (NCT03179631) is an international, phase 3, randomized, double-blind, placebo-controlled 72-week ataluren trial in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) followed by a 72-week open-label period. Here, we describe results of a pooled analysis of ataluren muscle function efficacy results from the placebo-controlled phase of Study 041 and two previous randomized, placebo-controlled 48-week ataluren trials (Study 007 [phase 2b] and Study 020 [phase 3]).

Methods: In all three studies, patients were eligible if they were male, had phenotypic evidence of DMD based on the onset of characteristic clinical signs or symptoms, and had an nmDMD diagnosis confirmed by genetic testing. Patients were randomized 1:1 to ataluren:placebo.
The pooled efficacy results were analysed using an ANCOVA model after missing values were imputed using a multiple imputation method. Pooled efficacy results for 48-week change in 6-minute walk distance (6MWD), North Star Ambulatory Assessment (NSAA) total and linear scores (where available), and timed function tests (TFTs; 10m walk/run, 4-stair ascent and 4-stair descent) are described for the overall pooled study population; and 48-week change in 6MWD for a subgroup with baseline 6MWD 300-400m. This subgroup of patients has been reported to experience a linear rate of decline and is more responsive to ataluren than a broader population over the limited time course of a clinical trial.

Results: The overall pooled study population included 354 patients receiving ataluren and 347 patients receiving placebo. Treatment with ataluren significantly reduced mean change from baseline in all measures vs placebo for the overall population (6MWD: 19.3m, p=0.0002; NSAA total score: 1.07, p=0.0010; NSAA linear score: 2.70, p=0.0031; 10m walk/run time: -1.31s, p=0.0001; 4-stair ascent time: -1.45s (p=0.0003); 4-stair descent time: -1.54s, p=0.0003). The pooled subgroup with baseline 6MWD 300-400m included 155 patients receiving ataluren and 157 patients receiving placebo. Ataluren preserved 32.1m of 6MWD in this subgroup compared to placebo (p=0.0005).

Conclusions: Pooled randomized, placebo-controlled clinical trial data from 701 patients demonstrate that ataluren preserves muscle function, assessed by multiple clinical meaningful endpoints, in patients with nmDMD.

Keywords:
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EPNS23-2978 Oral or e-Poster
Neuromuscular Disorders

Spinal Muscular Atrophy - An odyssey from a tertiary care centre

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Objective: The newer emerging therapies in spinal muscular atrophy(SMA) have shown encouraging short-term outcomes in terms of motor function scores and life expectancy. Nusinersen, Zolgensmaand Risdiplam are the drugs that have been approved by the US-FDA for SMA. Due to their prohibitive exorbitant costs, these are being mostly provided to SMA patients under humanitarian access programs. We present our data of children who have received these medications at our center over the last 3 years.

Methods: Two groups of patients(12 and 35) have been receiving intrathecal Nusinersen and are under follow-up. Change in the Modified Hammersmith functional motor scale extended version(HFMSE) is being evaluated. Nine patients(humanitarian-access:7) received intravenous Zolgensma and are under follow-up. Nine children(humanitarian-access:7) have been receiving Risdiplam, out of which 3 have a follow-up of more than 1-year

Results: Twelve children have been receiving Nusinersen for >2.5 years, out of which 11 have shown improvement in HFMSE scores(non-compliance: 1). 35 children have a follow up of 15 months. Nine children who have received Zolgensma, showed significant improvement in motor function (those with SMA-II can now stand with orthoses and those with SMA-I can sit independently without support). There has been reduction in the incidence of lower respiratory tract infections. Three children who have been receiving Risdiplam for > 1.5 years, have shown significant improvement in HFMSE scores, with gain in motor milestones.

Conclusions: The newer emerging therapies in SMA have shown favourable results in improving the short-term functional outcome. The initial success if replicated in long term, may change the way we view SMA and other genetic neuromuscular disorders.

Keywords:
Nusinersen, Zolgensma, Risdiplam

EPNS23-2187 Oral or e-Poster
Neuromuscular Disorders

Guillain-Barré syndrome with overlapping Bickerstaff brainstem encephalitis: a case report

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Case study: Objective: In this work, an overlapping of Guillain-Barré Syndrome (GBS)/ Miller-Fisher (MF) with possible Bickerstaff brainstem encephalitis (BBE) is presented, emphasizing that, despite the absence of diagnostic confirmation by antibody research, therapeutic and supportive measures should not be delayed. Methods: Case report. Results: Male, 10 years old, previously healthy, is admitted to the pediatric emergency service with weakness in the lower limbs that started 2 days ago, difficulty walking and an episode of falling from standing height. On physical examination, anisocoria, nystagmus to the left, convergent strabismus, reduced strength in lower limbs and in right hemiface. History of flu-like symptoms 7 days before the current condition. Assessed by pediatric neurology, under the hypothesis of GBS/MF. CSF with 11 cells; glucose 74; proteins 65.4; negative culture. Cranial CT unremarkable. Brain MRI showed a flair hypersignal lesion in the posterior and right lateral aspect of the pons and medulla, involving the topography of several cranial nerve nuclei, with an indeterminate aspect. Other nonspecific foci of flair hypersignal were identified in the supratentorial white matter, more evident in the left cingulate gyrus, and these imaging aspects could be compatible with BBE. One day later, the patient had progressive worsening, becoming unable to walk and presenting paralysis of the right hemiface, dysphagia, dyslalia and respiratory distress. He was referred to the ICU and evolved with respiratory failure, opting for orotracheal intubation, which was maintained for 3 days. He was treated with intravenous immunoglobulin and, afterwards, had a gradual resolution of signs and symptoms. The patient returned for an outpatient consultation 1 month after hospital discharge, verifying complete recovery of strength, absence of visual and gait changes. He remains clinically stable. Conclusion: In the present case, it was not possible to confirm the BBE condition, due to the unavailability of the anti-GQ1b antibody. However, given the clinical features and complementary tests characteristic of GBS and suggestive of overlap with BBE, and the sudden worsening of the patient's respiratory condition, treatment with immunoglobulin was promptly instituted. Other therapeutic options include plasmapheresis, in combination or alone, and immunoglobulin itself.

Keywords:
Neuromuscular Diseases; Pediatric Emergency Medicine.

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Onasemnogene abeparvovec in Spinal Muscular Atrophy: the experience in Singapore

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Objective: To provide an overview of the tolerability, safety and clinical outcomes of onasemnogene abeparvovec in a population of children with Spinal Muscular Atrophy (SMA) in Singapore.

Methods: This is a retrospective study of children with SMA who were treated with onasemnogene abeparvovec. Efficacy assessments included The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), Hammersmith Functional Motor Scale (HFMS), feeding abilities, and requirements for respiratory support. Safety outcomes included clinical and laboratory evaluations.

Results: 4 children were treated with onasemnogene abeparvovec (age range 4 months to 23 months old and body weight range 5.5 to 11.2kg). 3 of them had SMA type 2 and 1 had SMA type 1. 2 children had previous treatment with risdiplam. All 4 patients experienced transient treatment-related side effects. These included transaminitis, thrombocytopenia and elevated troponin I. Duration of prednisolone treatment was up to 7 months for one child in view of prolonged transaminitis. All treated children had improvement in their motor milestones. One child was weaned off nasogastric tube to oral feeding. One child required ventilation via tracheostomy prior to treatment with no significant change in ventilatory requirements at the time of writing.

Conclusions: This study provides evidence of the tolerability, safety and clinical outcomes of onasemnogene abeparvovec, which were similar to worldwide published data. However, little data has been published with regards to the use of onasemnogene abeparvovec after risdiplam. Longer term monitoring of this group of patients would provide more experience with single and combination therapy in SMA.

Keywords:
Onasemnogene abeparvovec; Zolgensma; Spinal muscular atrophy; gene therapy

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Real-life outcomes after gene replacement therapy for spinal muscular atrophy: a multicenter experience

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Objective: Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease caused by biallelic deletion or mutation of SMN1 gene located on chromosome 5q13, and characterized by muscle weakness and respiratory symptomsdue to progressive motor neuron loss. Prior to gene therapy, children with the most severe form of SMA did not survive beyond two years. Since 2019, gene therapy with onasemnogene abeparvovec-xioi (OA) has been available for infants under two years of age. We report the real-life clinical outcomes in an Israeli cohort of children, 12-24 months after OA.

Methods: A multicenter retrospective study included all infants with genetically confirmed SMA types I-II, carrying homozygous deletions of SMN1 gene with 2-3 copies of SMN2 gene, who received a single intravenous (IV) dose of OA between November 2019 and April 2021 in four Israeli medical centers. Clinical and laboratory parameters and motor progress including motor function tests data were analysed using descriptive statistics.

Results: Twenty-five infants (16 treatment-naïve) received OA between 11 days-23 months of age, median (IQR) follow-up duration was 18.0 (12.4-18.3) months. Motor measure (CHOP INTEND) scores increased by a median (IQR) of 13 (8-20) points during the follow-up period. At last follow-up, 20 (80%) patients were sitters, 9 (36%) were able to crawl, 9 (36%) were able to stand up and 8 (32%) could walk. Motor function significantly improved among pre-symptomatic children (P=0.001) with shorter disease duration before gene therapy ((up to 8 months; P=0.001), and who did not experience recurrent infections following treatment (P=0.001). All SMA type I patients who achieved walking ability had started first treatment (either nusinersen or OA) before 5 months. Adverse effects included laboratory-documented asymptomatic hepatotoxicity treated with corticosteroid for a median (IQR) of 3.2 (2.2-5.0) months, elevated troponin I with no cardiac decompensation, which resolved, and insignificant thrombocytopenia. One patient died after 6 months due to respiratory complications.

Conclusions: OA in our cohort was a safe and potent genetic transfer therapeutic agent, extending the survival and improving the quality of life of children with SMA, irrespective of the SMN2 copy number, or type. No patient regressed in their motor abilities post-treatment. Ongoing motor function improvement was most remarkable in children treated while pre-symptomatic and/or at an earlier age.

Keywords:
spinal muscular atrophy, gene therapy, onasemnogene abeparvovec-xioi, motor milestones

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Neuromuscular Disorders

The importance of upper limb function in non-ambulant DMD patients in daily life activities

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Objective: In more advanced stages of Duchenne muscular dystrophy (DMD), upper limb (UL) function is crucial for daily life activities. Muscle strength and functional assessments of UL can be used as outcome parameters in clinical trials only if they relate to changes or end points that are relevant to patients and families. Aim of the study was to assess the longitudinal correlation between UL strength and function to the patient reported performances in daily life.

Methods: non-ambulant DMD patients were included in a natural history study with visits at baseline, 12 and 18 months. Assessments included the Performance of Upper Limb (PUL) module 2.0, elbow flexion and shoulder abduction maximal voluntary contraction using Microfet 2, and the Patient Reported Outcome Measure Upper Limb (PROM-UL) questionnaire. Changes in median longitudinal scores were analyzed with Wilcoxon signed rank test. Relationships between clinical assessments and PROM-UL and age were studied using Spearman's rank test.

Results: 22 patients were included (median age 13.39, range 8.59 - 24.08). Follow-up was completed for 17 patients at 12 and 18 months. Median DMD UL PROM score was 46.5 (35-51.75) at baseline and decreased significantly to 43 (34-53; p=0.035) at 12 months and 38 (32-50; p=0.002) at 18 months.
PROM-UL was correlated with shoulder abduction strength in at baseline and 12m (baseline R=0.56; p=0.010, 12 months R=0.56; p=0.025, 18 months R=0.56 p=0.074). The correlation was stronger and statistically significant in every visit for the PUL (baseline R=0.73; p<0.001, 12 months R=0.88; p<0.001, 18 months R=0.83; p<0.001) and elbow flexion strength (baseline R=0.80; p<0.001, 12 months R=0.72; p=0.002, 18 months R=0.84; p<0.001). There was no statistical correlation between PROM-UL and age.

Conclusions: Performance of the upper limb (PUL) and elbow flexion strength tested in a clinical setting correlated well to the patient reported ability to perform daily life activities. This provides an important link between body functioning and activities according to the International Classification of Functioning, Disability and Health.

Keywords:
Duchenne muscular dystrophy, PROM-UL, PUL

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Neuromuscular Disorders

Safety of onasemnogene aberparvovec administration to SMA patients who have received risdiplam

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Objective: 3 disease-modifying therapies are now available for treatment of SMA (spinal muscular atrophy). There is lack of information on patients who switch from risdiplam to onasemnogene aberparvovec (OA). We present a case series of 5 patients who switched to OA after receiving risdiplam and consider the safety aspects of this.

Methods: This was a retrospective study describing our centre's experience with switching from risdiplam to OA in SMA patients.

Results: The children were between 7 to 87 months at time of infusion of OA (mean of 26 months). Age at genetic diagnosis ranged from 1 to 12 months (median 5.8 months). All were SMA type 1. Patients were started on risdiplam between 3 to 79 months old and was on risdiplam for 11 days to 14 months (mean of 5.6 months). One patient was on nusinersen for 46 months prior to switch to risdiplam. All patients continued risdiplam until the day before administration of OA, with a wash out period of between 24-33 hours prior. All patients have had follow up for atleast 12 weeks.
Prior to OA, all patients received NIV support for 6 to 12 hours overnight. 2 children needed sole nasogastric feeding for unsafe swallow, 1 child was mixed fed orally/nasogastric tube, and 2 children did not need support for feeding. 12 weeks following OA, all patients had stable or improved motor score. All patients remained stable or improved in their need for NIV support. 4 children remained stable with regards to their feeding and 1 demonstrated far fewer vomiting episodes.
Adverse events reported following OA switch included tachycardia, fever, nausea, vomiting, raised transaminases, and mild neutropenia. 1 patient had transient neutrophilia which was attributed to PEG site infection and is unlikely to be an adverse effect. Raised transaminases was the most common side effect that was present in all 5 patients but was felt to be aligned with previous experience following OA monotherapy. The patient with mild neutropenia had this prior to risdiplam or OA therapy and this resolved later. All adverse events in these children were known adverse events of OA apart from neutropenia .

Conclusions: All patients demonstrated stable or improving motor scores and feeding support requirement. Most patients had stable ventilatory requirements. No unexpected adverse event was demonstrated post-OA in patients stopping risdiplam a day before OA infusion.

Keywords:
onasemnogene aberparvovec, risdiplam, spinal muscular atrophy type 1,

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Interim Analysis of EVOLVE: A Long-term Observational Study Evaluating Eteplirsen, Golodirsen, or Casimersen in Routine Clinical Practice

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Objective: Eteplirsen, golodirsen, and casimersen are exon-skipping therapies approved for patients with Duchenne muscular dystrophy (DMD) with mutations amenable to 51, 53, and 45 exon skipping, respectively. An ongoing 5-year, phase 4, multicenter, observational study is assessing the safety, usage, and clinical outcomes of their long-term use in routine clinical practice.

Methods: This interim analysis includes data on serious adverse events (SAEs) and adverse events of special interest, as well as loss of ambulation (LOA).

Results: As of December 2021, 144 patients were enrolled with a mean (SD) age (years) of 13.7 (5.5) for eteplirsen (n=123), 13.5 (4.3) for golodirsen (n=17), and 16.3 (11.7) for casimersen (n=4). Mean (SD) duration of treatment (years) was 4.7 (1.88) for eteplirsen, 1.3 (0.45) for golodirsen, and 0.3 (0.22) for casimersen. Mean time (years) from DMD diagnosis to treatment initiation was 6.0 (4.74) for eteplirsen, 8.2 (3.76) for golodirsen, and 13.5 (14.04) for casimersen. At treatment initiation, 82/123 (66.7%) eteplirsen-treated, 7/17 (41.2%) golodirsen-treated, and 2/4 (50%) casimersen-treated patients were ambulatory. To date, favorable safety profiles have been observed for all 3 therapies. During EVOLVE, SAEs occurred in 14 (11.4%) eteplirsen-treated patients, consistent with the known safety profile of eteplirsen; none were reported for golodirsen or casimersen. Median age at LOA for eteplirsen-treated patients is 15.3 years, which is consistent with prior clinical trial post hoc results; the small sample size to date precludes analysis of age at LOA for golodirsen and casimersen.

Conclusions: These real-world data from the interim analysis of EVOLVE support the safety profiles and will continue to describe long-term clinical outcomes of eteplirsen, golodirsen, and casimersen.

Keywords:
eteplirsen, golodirsen, casimersen, exon-skipping, DMD

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A clinical case of late diagnostics of spinal muscular atrophy, type III

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Case study: Aim: Description of clinical case of the SMA in a 9 yo boy.
Results: Early psychomotor development is normal. Self-walking skills are from 11 months. Family history is unknown. The debut of complaints from 3 years: gait disorder, muscle weakness, difficulty in climbing stairs. In dynamics, the muscle weakness worsened: the patient often stumbled and fell, the deformity of feet developed, there was an asymmetry in the legs. The condition worsened after suffering respiratory infection. Serum creatine kinase is moderately elevated. The differential diagnosis was made between muscular dystrophy (gender, age, myopathic symptoms), CMT-syndrome (foot deformity, axonal changes), acquired neuropathy (deterioration after infection), spinal malformation (legs asymmetry, spina bifida on MRI). Genetic studies have not been conducted. The patient is referred for the consultation with diagnosis «congenital myopathy».
Neurological status: Cognitive status-corresponds to age. Focal symptoms are not determined. Fasciculations of the tongue is absent. Diffuse muscle hypotonia, hyporeflexia. Abdominal reflexes are reduced. Hypotrophy of the proximal parts of the arms and legs. Muscle strength in the hands is up to 4.0 points, in the legs is up to 3.5-3.0 points. Myopathic gait. Tremor of the hands. Gover's symptom is positive.
Skeletal deformities: pterygoid scapulae, equinus contracture of the left foot, lumbar hyperlordosis. Pseudohypertrophy of the calf muscles.
Genetic test: a homozygous deletion of 7 and 8 exons in SMN1 gene was identified using the MLPA method of searching for mutations in the SMN1 gene, copies of the SMN2 gene n=3.
Thus, diagnosis of "spinal muscular atrophy, type III" was confirmed by clinical and genetic studies. Currently patient is receiving pathogenetic therapy.
Conclusion: The described clinical case demonstrates complexity of defining the diagnosis of SMA due to heterogeneity of the clinical picture in the debut, the gradual appearance of specific symptoms. The myopathic symptom complex directed primary care specialists towards the diagnosis of "myopathy". The diagnosis of "SMA" was not included during differential diagnostic search. The importance of genetic diagnostics for diagnosis and prognosis is illustrated. Late diagnostics of the described case: debut of complaints from 3 years, a genetically verified diagnosis from 9 years-dictate the need to raise awareness among primary care specialists on neuromuscular diseases.

Keywords:
spinal muscular atrophy, III type, SMN1 7 exon homozygous deletion

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A case of multiple sclerosis presentation in spinal muscular atrophy type 3 patient.

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Case study: SMA type 3, also called Kugelberg-Welander disease is a neuromuscular disorder characterized by motor neuron degeneration, characterized by muscle weakness and atrophy after early childhood. Multiple sclerosis (MS) is considered an autoimmune inflammatory demyelinating disease of the central nervous system. We report a rare case of coexisting SMA and MS. 16 years male patient that was born from normal spontaneous delivery from relative parents. The symptoms initiated with a resting tremor in both hands since the 8 year of age. Also, since the 14th year of age, a progressive limb weakness was gradually started, especially in attempting for stair-up, standing, and hand washing. In physical examination, patient's tongue was obviously atrophic with fasciculation movements. He had waddling gait pattern in walking, and his Gower's sign was positive indicating of proximal weakness. Muscle forces in upper limbs were 4/5, lower limbs, the strength was 2/5 for both hip and knee muscles; and it was higher in distal muscles of legs (3/5), patellar knee jerk was absent. Sensory exam for small and large fibers was not remarkable. On the other hand deep tendon reflexes in in Biceps brachii, Triceps brachii, Brachioradialis, and Achilles were slightly increased, resting tremor was present in both hands, babinski sign was positive on the left side. Also finger nose test was positive and patient had adiadochokinesia.
Laboratory blood tests including complete blood count (CBC), lactate dehydrogenase (LDH), and ammonia, plus thyroid, renal, and liver function tests were all within normal ranges .Creatine phosphokinase (CPK) was slightly increased to 38,6.
Brain MRI scan revealed a multifocal white matter disease - contrast-enhanced areas of increased T2 signal in both cerebral hemispheres periventricular. Spine MRI showed also lesions in cervical and thoracal spine.
Needle-EMG demonstrated a spinal (motoneuron) type of damage. Afterward, the genetic study confirmed SMA type 3. But the presence of other pyramidal signs and MRI scan suggest a presence of concomitant multiply sclerosis. He was treated with intravenous methylprednisolone and plasmapheresis, with partial improvement of pyramidal symptoms.
Kugelberg-Welander disease is a milder form of SMA, manifesting as slowly progressive muscle weakness. But the occurrence of symptoms unusual for this disease with lesions on MRI scan proposes another disease in our case it is a coexisting multiple sclerosis.

Keywords:
SMA, multiple sclerosis

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Neuromuscular Disorders

Functional outcomes in DMD - daily deflazacort vs intermittent prednisone/deflazacort

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Objective: Duchenne muscular dystrophy (DMD) is treated with chronic corticosteroids. Worldwide different regimens are used. Knowledge on differences in long term effects is lacking. Here we report natural history data in patients from national referral centers in Belgium, treated with daily deflazacort (DD), and the Netherlands treated with 10 days on 10 days off (10/10) prednisone or deflazacort.

Methods: All patients were annually assessed at outpatient clinics in the Netherlands and Belgium. Functional assessments were performed by a certified physical therapist and included North Star Ambulatory assessment (NSAA), 10 meter run velocity (10mrv) and performance of upper limb (PUL) 2.0. Age at loss of ambulation (LoA) was obtained from patient history. Height was measured standing in ambulant patients or estimated using ulnar length in non-ambulant patients.

Results: We retrospectively included 102 patients from the Netherlands and 82 patients from Belgium with a total of 1724 visits between 2007 and March 2022. Mean age at first visit and follow up duration were similar between the 2 cohorts (6.2 vs 6.1 years; 9.3 vs 9.4 years). Median age at LoA was 11.2 years on 10/10 and 15.0 years on DD ($p<0.001$). NSAA and 10mrv outcomes peaked at age 6 years in both cohorts (NSAA 27.3 vs 27.9pts; $p=0.675$; 10mrv 2.1 vs 2.4m/s, $p=0.001$). Decline in NSAA scores and 10mrv until age 10 was more rapid on 10/10 (mean 1 year decrease NSAA -3.0 vs -0.7pts, $p=0.079$, 10mrv -0.2 vs -0.1m/s $p=0.001$; mean 4 year decrease NSAA -12.0 vs -3.4pts, $p<0.001$, 10mrv -0.7 vs -0.4m/s, $p=0.002$). PUL scores peaked at age 6 years in both cohorts (38.8 vs 41.9pts, $p=0.03$), decline until age 18 years was more rapid on 10/10 (mean 1 year decrease -0.2 vs -0.6pts; mean 12 year decrease -23.0 vs -17.7pts). Hand-to-mouth function was lost in 32% on 10/10 vs 4% on DD. Height was similar in both cohorts up until age 5 years (110.1 vs 108.6cm, $p=0.180$). Increase in height until final measurement at age 17 years was larger on 10/10 (171.2 vs 145.2cm, $p<0.001$).

Conclusions: DMD patients treated with daily deflazacort had better motor outcomes than those treated with intermittent corticosteroids. Vice versa, height was significantly reduced in the cohort on DD and within normal limits in patients on 10/10. Results may facilitate shared decision making when steroid treatment is initiated in young DMD patients.

Keywords:
Duchenne muscular dystrophy, DMD, treatment, corticosteroids, deflazacort, prednisone, long-term effects

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Neuromuscular Disorders

A clinical case of predisposition to malignant hyperthermia due to a new mutation in the RYR1 gene

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Case study: Background: A rare non-dystrophic, ryr-1 associated myopathy characterized by the triad of congenital myopathy, dysmorphic features and susceptibility to malignant hyperthermia, can match King-Denborough syndrome. A description of this condition in a Kazakh boy aged 10 years is presented.
Results: Complaints of skeletal deformity, short stature, moderate muscle weakness, intolerance to hot weather, high fever in respiratory diseases. In the prenatal period were weak fetal movements, in the neonatal period and an early age bulbar symptom, facial weakness and frequent pneumonia were observed. Delayed psychomotor development: head control from 6 months, sits independently from 14 months, crawls on all fours from 18 months, walks independently from 5 years; simple words and phrases after 2 years. Family history is negative.
Examination: Bulbar symptoms: quiet voice, nasolalia, frequent choking, difficulty swallowing. Myopathic face: 2-sided ptosis, down-slanting palpebral fissures. Facial dysmorphism: eyeballs hypertelorism, wide glabella, thick eyebrows, low-set large ears, high palate, micrognathia. Diffuse muscular hypotonia, hyporeflexia. Muscle weakness in the proximal parts of the arms to and legs up to 3,5-4 points. Physical abnormalities, including short neck, short stature (110 sm), hypotrophy (17 kg), cryptorchidism, chest deformity, lumbar lordosis, thoracic kyphosis, joints stiffness and contractures.
Needle EMG: myogenic changes.
Whole exome sequencing: a previously undescribed heterozygous mutation in exon 106 of the RYR1 gene (chr19:39078020G>A) was detected, leading to an amino acid substitution at position 5026 of the protein (p.Gly5026Asp, NM_000540.2).
Serum creatine kinase is normal.
EchoCG: an open oval window, a small defect of the interventricular septum.
Conclusion: based on the symptoms of slowly progressive myopathy, facial dysmorphism, skeletal deformities, short stature, congenital heart anomalies, cryptorchidism, mutation in the RYR1 gene, one can think of the presence of King-Denborough syndrome. The syndrome was first described in a patient from Kazakhstan. There is a high risk of malignant hyperthermia. Further follow-up required

Keywords:
congenital myopathy, ryr-1, malignant hyperthermia, King-Denborough syndrome, skeletal deformity

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Report of four cases of Ullrich Congenital Muscle Dystrophy (UCMD)

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Case study: Objectives:
Ullrich Congenital Muscle Dystrophy (UCMD) is a rare disease with an incidence of1-9 : 1 000 000 and less than 50 cases described. The genetic underpinning is a recessively inherited variant in the COL6A(1-3) gene. The produced collagen 6 is responsible for forming nests for muscular stem cells in the extracellular matrix, its defect leading to an overlap syndrome of muscular and connective tissue disorder. The goal of this work is to further elucidate phenotypic characteristics and the natural history of this disease.
Methods:
Presentation of four cases affected by UCMD of the Charité outpatient center (SPZ - sozialpädiatrisches Zentrum), department of neuropediatrics, neuromuscular division.
Results:
We present four cases of children affected by UCMD. They were diagnosed at 5 months, at 1 year, and two identical twins at 3 years of age, respectively. Mutations were found within COL6A1 and COL6A2 genes. Symptoms shared by all four patients and typical for the condition are proximal joint contractures, hyperlaxity of distal joints, progressive neuromuscular scoliosis/kyphosis, and generalized muscle weakness leading to gross motor developmental delay. Two of them learned to walk and lost this ability by the onset of puberty, another child is now able to roll and sit with 17 months of age. At birth, arthrogryposis multiplex was described in two patients, while unilateral hip dislocation, bilateral hip dysplasia as well as protruding calcanei were reported in one child each. Associated symptoms present in described cases include torticollis, respiratory function decline requiring invasive or non-invasive night time ventilation, and constipation. Cardiac function has remained normal in all patients.
Medication taken is supportive or aiming at non-associated medical conditions. Spine surgery has been performed on two of four patients. All individuals obtain supportive measures including regular physiotherapy and orthopedic visits. Orthoses and helping devices are implemented.
Conclusions:
UCMD is a spectrum disease with high impact on quality of life of affected individuals. There is no effective targeted treatment to date, such that most affected individuals live until their early adulthood, limited by progressive decline in breathing function. Due to its rarity and thus scarce data, collaborative research is needed in order to fully understand the pathophysiology and allow the development of appropriate treatment options.

Keywords:
UCMD Ullrich Congenital Muscular Dystrophy Arthrogryposis Contractures

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Neuromuscular Disorders

Risdiplam-treated patients in Singapore: A retrospective, observational case series

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Objective: Previously a devastating neurodegenerative disease, Spinal Muscular Atrophy (SMA) now has three disease modifying therapies that have been shown to radically change its natural history and significantly improve function in patients, especially when treatment is started early. Risdiplam, the orally administrated SMN2 pre-mRNA splicing modifier, was initially prescribed in Singapore via the Compassionate Use Program, and subsequently commericially available from October 2021. We aim to describe our experience of patients who have received Risdiplam in Singapore.

Methods: We retrospectively collected data from all paediatric patients who received Risdiplam in two paediatric tertiary institutions in Singapore from February 2021 to August 2022.

Results: Nine symptomatic patients (5 males) with Type 1 (n=3) or 2 (n=6) SMA were prescribed Risdiplam, of which 3 were given in combination with Onasemnogene abeparvovec (2 pre, 1 post). Seven patients had 3 copies of SMN2 gene, two had 2 copies. One was tracheostomised, and 2 required nocturnal ventilation. Three required nasogastric tube feeding. Mean age at drug commencement was 4.2 years (range, 0-7.9 years). Both patients who received Risdiplam prior to gene therapy stopped after 3 months. The remaining 7 patients received a median treatment duration of 19 months (range, 5-23 months). CHOP INTEND and MFM were the two most commonly used scoring tools. Amongst the 6 who received Risdiplam monotherapy, 3 continued to show deterioration in their scores, 2 showed improvement and 1 remained stable. Patient-reported symptoms that improved included increased energy level, skipping of afternoon nap, stronger voice and more fluent upper limb movements. Risdiplam was generally well tolerated by all, with 1 patient reporting mild diarrhoea. One Type 1 patient passed away from pneumonia after 5 months of treatment.

Conclusions: Efficacy outcomes were more varied than those reported in clinical trials, likely secondary to a wider range of patient ages at therapy commencement, disease phenotypes and comorbidities.

Keywords:
Spinal Muscular Atrophy; Risdiplam

EPNS23-2827 Oral or e-Poster
Neuromuscular Disorders

Benign Presentation of Partial Exon 49 deletion in the Dystrophin gene

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Case study: Background: Dystrophinopathies are an X-linked disorders with variable phenotypes ranging from Duchenne muscular dystrophy or to milder forms such as Becker muscular dystrophy, or X-linked dilated cardiomyopathy. Female carriers may have subtle muscular symptoms with an increased risk for cardiac complications. Rhabdomyolysis has been reported in patients with in-frame deletions and to a lesser extent with missense mutations. In-frame exon 49 deletion has been reported with highly variable phenotypes ranging from asymptomatic to Becker or Duchenne dystrophy, adding to growing number of reported DMD deletions and duplications with widely varying clinical phenotypes.
Case Presentation: We report a family with a deletion involving exon 49. The variant was first reported in the family in a 33-year-old pregnant patient who pursued routine carrier screening. The pregnant patient's nephew, an 8-year-old boy with recurrent episodes of rhabdomyolysis triggered by a viral illness over the course of one year, was subsequently found to carry the same DMD variant. He had normal CK between the attacks, suggesting a metabolic myopathy, and had normal muscle strength. Carnitine profile and urine organic acid screen were normal. Next generation sequencing based on a metabolic myopathy panel including LPIN-1, blood mitochondrial genome analysis and whole exome sequencing were unrevealing. The mother of the boy (sister of the original pregnant patient) was found to carry the same DMD variant and thus, testing of the sisters' parents was pursued. The variant was also found in the patient's father, a 73-year-old man who had normal motor developmental milestones and had no limitation of physical activity. He had no history of myalgias or rhabdomyolysis. His past medical history was significant for seronegative rheumatoid arthritis and ischemic heart disease. He had a normal muscle strength and his CK level was 154 U/L (normal 39-308 U/L).
Conclusions: Partial deletion of DMD exon 49 can present as a benign phenotype and may be asymptomatic in some individuals. If the partial deletion is predisposing to increased CK level during intercurrent infections is uncertain. Genetic counseling for this deletion and other DMD variants reported with highly variable phenotypes must include careful discussion regarding uncertainty in potential phenotypic outcomes. This is particularly important in the preimplantation and prenatal setting.

Keywords:
Dystrophin, exon deletion, genetic counseling

EPNS23-2213 Oral or e-Poster
Neuromuscular Disorders

Feeding and Swallowing in Congenital or Early Developing Neuromuscular Diseases

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Objective: The aim of this presentation is to give an overview on how muscle weakness directly or indirectly affect feeding and swallowing in congenital or early developing neuromuscular diseases . A second aim to address the role of the Speech and Language Pathologist as part of the team around individuals with neuromuscular diseases.

Methods: A literature search was performed in PubMed for the 1st of January 1998 to 31st of August 2021. The results were published in an article by Sjögreen and Bengtsson in Journal of Neuromuscular Diseases 2022. This presentation builds on parts of the findings from this review but focuses on and provides a more in-depth presentation of feeding disorders and swallowing in the target population.

Results: Of 67 clinical studies included, 46 (68.7%) focused on feeding and swallowing and (14) (20.9%) on a combination of feeding, swallowing, saliva control and/or speech. The studies confirm that muscle weakness and impaired motility in many neuromuscular diseases have an effect on feeding, swallowing, saliva control and that respiratory function, general health and neurodevelopmental delay also influence these functions.

Conclusions: Paediatric feeding disorders and dysphagia are prevalent in congenital or early development neuromuscular diseases. The survival of individuals with neuromuscular diseases is increasing and it is urgent to follow up the effect of medical treatment on the development feeding and swallowing and to include Speech and Language Pathologists as part of the NMD-team.

Keywords:
neuromuscular disorder, feeding, swallowing, dysphagia

EPNS23-2807 Oral or e-Poster
Neuromuscular Disorders

PREPL associated congenital myasthenia: a rare cause of neonatal hypotonia

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Case study: Introduction:
PREPL deficiency can cause neuromuscular, dysmorphic, endocrine and cognitive features. The most common genetic defect involve recessive contiguous gene deletions comprising PREPL and SLC3A1 genes, causing a hypotonia-cystinuria syndrome In contrast, isolated PREPL deficiency is a rarer condition associated with congenital myasthenic syndrome 22, with less than 15 patients reported to date.

Objectives:
Describe mutational profile, clinical manifestations and treatment response of two girls with isolated PREPL deficiency.

Results:
A 3 ys child presented in neonatal period with severe hypotonia and feeding difficulties. She had axial and proximal limb weakness and ptosis. Nasogastric tube feeding was needed.
NGS panel revealed two compound heterozygous variants in PREPL gene (c.753-2A>C/r.spl?; c.1996G>T/p.Glu666*). She started treatment with pyridostigmine at two months of age. Clinical improvement was observed: able to feed orally by 6 months, walk by 17 months and run by 3 ys. At age of 3 she has a normal language. The height developed in percentile (P) 50 until 8 months, then progressing to under P1 at present.

A 13 ys female born at 37 weeks of gestation. In neonatal period she had severe hypotonia with axial weakness and feeding difficulties. Nasogastric tube feeding was needed from birth to 22 months. Although she persisted with an axial and proximal weakness, she sat by 25 months and walked at 3 ys. At age of 4 she had a normal language with dysfonia. Her height and weight velocity was under P3 and at present her BMI is under normal range. Mitochondrial disorder was suspected due to multiple respiratory chain deficiency, but genetic investigation was negative. At 8 years, a NGS multigene panel performed reveal a homozygous nonsense variant in PREPL gene (c.883C>T/p.Arg295*). She started pyridostigme with clinical benefit objectified in 6MWT.
None of the patients had cystinuria or GH deficiency.

Conclusions:
Etiologic diagnosis of congenital hypotonia can be challenging, specially when systemic manifestations are present. Both cases were solved resorting to an extensive NGS panel, with 154 genes involved in congenital myasthenia and myopathies. In the second child an improvement even without treatment was observed. However, in the first child, early treatment allowed a better motor development and an earlier normal feeding, highlighting the value of a comprehensive and fast diagnostic approach for this disorder.

Keywords:
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EPNS23-2144 Oral
Neuromuscular Disorders

One-year data from ENDEAVOR, a Phase 1b trial of delandistrogene moxeparvovec in patients with DMD

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Objective: Delandistrogene moxeparvovec (SRP-9001) is an investigational gene transfer therapy developed to address the root cause of Duchenne muscular dystrophy (DMD) through targeted skeletal and cardiac muscle expression of SRP-9001 dystrophin protein, which contains key functional domains of dystrophin. This study evaluated the expression and safety of intended commercial process delandistrogene moxeparvovec material in ambulatory and non-ambulatory patients with DMD.

Methods: ENDEAVOR (NCT04626674) is a two-part, open-label, prospective, Phase 1b study of five cohorts of ambulatory and non-ambulatory patients across a broad age range and with varied *DMD* mutations. Cohort 1 (n=20) enrolled ambulatory ≥4 to < 8-year-olds. Participants received a single intravenous $1.33x10^{14}$ vg/kg (linear standard quantitative polymerase chain reaction) dose of intended commercial process delandistrogene moxeparvovec material. The primary endpoint is change in SRP-9001 dystrophin protein expression from baseline to Week 12. Secondary endpoints include safety and change from baseline in SRP-9001 dystrophin expression as measured by immunofluorescence (IF) intensity and IF percent dystrophin-positive fibres. Exploratory endpoints include the North Star Ambulatory Assessment (NSAA) and timed function tests. A propensity-score-weighted external control (EC) cohort was employed to contextualise results.

Results: We present safety, 1-year functional, and 12-week expression data from Cohort 1. SRP-9001 dystrophin expression corresponded with vector genome copies, confirming successful delivery of delandistrogene moxeparvovec to target cells. Safety of intended commercial process material was consistent with clinical process material. No new safety signals were identified. There was a clinically meaningful and statistically significant difference in least-squares mean change from baseline to Year 1 in NSAA total score ($\Delta=3.2$; $P<0.0001$), Time to Rise ($\Delta=-1.2$; $P<0.0001$), and 10-metre Walk/Run ($\Delta=-1.0$; $P=0.0018$) in treated patients relative to EC patients.

Conclusions: Cohort 1 data suggest the safety and efficacy profile of intended commercial process delandistrogene moxeparvovec material is consistent with that of clinical process material, with no new safety signals identified, and robust SRP-9001 dystrophin expression and positive functional benefit observed.

Keywords:
Duchenne muscular dystrophy, gene therapy, clinical trials, gene transfer

EPNS23-2798 Oral or e-Poster
Neurocutaneous Syndromes

Somatic NF1 loss of heterozygosity associated with NF1-related pectus excavatum deformity

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Case study: Objectives. Neurofibromatosis type 1 (NF1) is a neurocutaneous genetic disorder with a broad spectrum of associated signs and symptoms, including skeletal anomalies. The association of NF1 with anterior chest wall deformities has been recently reported, especially the pectus excavatum (PE). Over the years, several authors have suggested loss of heterozygosity (LOH) as the possible pathogenic mechanism underlying the development of the typical NF1 skeletal features.
Methods. Here, we report a NF1 patient with severe chest deformity and harboring the germline heterozygous pathogenic NF1 variant NM_001042492.3: c.4271delC p.(Ala1424Glufs*4). The patient was diagnosed with NF1 at the age of 2 years, when he presented with cafè-au-lait macules and Lisch nodules. At the age of 4 years, the patient was referred to our Center for a rapidly enlarging deformity of the anterior chest wall. Clinical examination revealed a severe PE deformity, consisting of a severe depression of the sternal manubrium associated with marked thoracic asymmetry and marked protrusion of the left costal cartilages. Thoracic CT-scan confirmed the severe bony depression between the manubrium and the body of the sternum, which led to the compression of the right ventricle and supra-aortic vessels. The patient underwent a major elective surgery combining minimal Invasive Repair of PE/MIRPE and open reconstruction of thoracic wall, with good overall outcome.
Results. Through Next Generation Sequencing (NGS), we investigated the affected cartilage from the PE deformity and identified the additional frameshift variant NM_001042492.3: c.2953delC p.(Gln985Lysfs*7), occurring as a somatic NF1 second hit mutation. Western blot analysis showed the absence of wild-type NF1 protein in the cartilage of the patient, consistent with a somatic LOH.
Conclusions. Taken together, our findings support the role of LOH in NF1-related PE, widening the spectrum of the pathophysiological mechanisms involved in NF1-related skeletal features. Our objective is to study this mechanism in the future and search mew somatic mutations in other tissues, including non-skeletal tissues (plexiform neurofibromas, vasculopathy, optic way glioma and many others). The discovery of this possible pathogenetic mechanism helps us in understanding a varied and complex disease and tells us to pay attention to the possible exposure of patients to sources emitting ionizing radiation, trying to spare exams such as CT scans and similar.

Keywords:
NF1; frameshift; somatic; second hit; loss of heterozygosity; pectus excavatum

EPNS23-2574 Oral or e-Poster
Neurocutaneous Syndromes

Neurocutaneous melanosis

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Case study: Congenital melanocytic nevus (CMN) are benign, pigmented skin lesions of various sizes as a result of abnormal melanocytic proliferation with the possible development of cutaneous melanoma or neurocutaneous melanosis (NCM). NCM is rare but characterized by the presence of large or multiple congenital melanocytic nevi and benign or malignant pigmented cell tumors of the leptomeninges. Most patients with neurocutaneous melanosis present in the first 2 years of life with neurologic manifestations of mass lesions, spinal cord compression, or increased intracranial pressure. Here we present 2 female patients who were born at our hospital in a time gap of less than 2 years, one with a large CMN and one with gigantocelular congenital melanocytic nevus (GCMN) with nodule of uncertain malignant potential. The first patient had initial magnetic resonance imaging (MRI) of the brain (1.5 Tesla) performed on the 6th day of life. It showed a lesion posterior to the vermis and caudally to the sinus confluencing, 5 mm thick, as well as linear change along the right cerebellar hemisphere, characterized by hyperintensities on T1W images and low signal on T2W images, suspected to be leptomeningeal melanosis or acute subdural lamellar hemorrhagic collection. Follow-up MRI scans at the age of 3 months and 15 months were normal. The second patient had a normal MRI. Both currently have normal neurodevelopment but considering the course of the disease, dermatological and neurological monitoring is necessary.

Keywords:
ceongenital melanocytic nevus, neurocutenous syndroms, gigantocelular congenital nevus

EPNS23-2343 Oral or e-Poster
Neurocutaneous Syndromes

Expanding the phenotype of tuberous sclerosis: congenital lymphedema, aortic aneurysm, sclerotic bone changes and catastrophic epilepsy in a boy with tuberous sclerosis type 2 (TSC2)

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Objective: Tuberous sclerosis complex (TSC) is a genetic multisystem neurocutaneous disorder caused by pathogenic variants in TSC1 or TSC2 genes, resulting in mTOR pathway overactivation. Here, we present a rare clinical picture of TSC.

Methods: The patient underwent a thorough clinical investigation, neurological and cardiovascular therapy and exome sequencing (ES) to determine the genetic causes of his complex phenotype.

Results: Currently 4 years old son of healthy parents was diagnosed with left side hydrothorax with swollen ipsilateral upper limb by prenatal ultrasound at 34th gestational week. Shortly after delivery, cardiac rhabdomyomas were found on ultrasound and brain MRI revealed cortical tubers and subependymal nodules. TSC was diagnosed clinically. At 6 months of age, the patient developed epileptic spasms; antiseizure medication (vigabatrin and valproate) were only partially effective, therefore adrenocorticotropic hormone was administered with good effect, but only for 9 months of seizure freedom. His epilepsy became drug-resistant. Everolimus was discontinued due to lack of effect on lymphedema and potential interactions with other medications. Before the third year of age he was started on a ketogenic diet despite concerns of negative effect on lymphedema. A small skin telangiectasia was observed on the oedematous limb. At 3 and half years of age, regular chest MRI revealed unexpected aortic enlargement spanning from isthmus to its descending part, verified by CT angiography. Partial replacement of aortic aneurysm by graft (at 3 years and 7 months of his age) was successful.
ES revealed a de novo likely pathogenic variant in TSC2 gene NM_000548.5(TSC2):c.4616C>A, p.(Ser1539*) and a paternally inherited, previously described pathogenic variant in ACVRL1 gene (NM_000020.3(ACVRL1):c.199C>T p.(Arg67Trp)).
Currently, at 4 years of age, the patient remains seizure free on the ketogenic diet (2:1 ratio) and his psychomotor development progresses.

Conclusions: We describe a very rare combination of congenital lymphedema, aortic aneurysm, sclerotic bone changes and drug-resistant epilepsy in a boy with TSC2.
Congenital lymphedema is rarely associated with the TSC, however, it can represent a possible prenatal sign of TSC. The significance of the finding of the ACVRL1 variant is unclear. Our case is the second with described finding of congenital lymphedema with simultaneous occurrence of aortic aneurysm and bone dysplasia, expanding the clinical picture of TSC2.

Keywords:
tuberous sclerosis complex, cardiac rhabdomyoma, congenital lymphedema, sclerotic bone changes, aortic aneurysm, ketogenic diet

EPNS23-2561 Oral or e-Poster
Neurocutaneous Syndromes

CLINICAL FEATURES OF PATIENTS FOLLOWED WITH THE DIAGNOSIS OF TUBEROUS SCLEROSIS COMPLEX: SINGLE CENTER EXPERIENCE

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Objective: Tuberous sclerosis complex (TSC) is an inherited neurocutaneous disease that affects many systems such as the brain, skin, eyes, kidneys, heart and lungs. This study was planned to examine the characteristics and clinical course of patients with TSC and to investigate the factors that may affect the prognosis.

Methods: The files of patients diagnosed with TSC in our Izmir Dr. Behçet Uz Children's Hospital Pediatric Neurology Clinic between January 2012 and January 2022 were retrospectively analyzed in terms of clinical, laboratory, molecular and demographic data.

Results: Twenty-three (53.5%) of the patients were male and 20 (46.5%) were female. The first clinical finding of the patients before diagnosis, it was observed that 29 (67.4%) patients were followed up due to seizures and 9 (20.9%) patients were followed-up due to rhabdomyoma. Five (11.6%) patients had a diagnosis of tuberous sclerosis in their families. Vigabatrin was the first choice of treatment in 48.8% of the patients. The most common physical examination finding was hypopigmentation in 37 (86%) patients. Heterozygous variant in TSC2 gene was detected in 21 (48.8%) patients and heterozygous variant in TSC1 gene in 4 (9.3%) patients. Tsc 2 gene exon 17-27 duplication was detected in one patient. Focal and generalized seizures were detected in 16 (42.1%) of 38 patients who had seizures, focal seizures in 12 (31.5%) and generalized seizures in 10 (26.3%). Fifteen patients (34.8%) had refractory epilepsy. Focal epileptiform disorder was observed in the EEG of 25 patients (58.1%). When we look at the cranial MRI findings, cortical-subcortical tubers were seen in 41 (95.3%) patients, subependymal nodules in 38 (88.3%) patients, and subependymal giant cell astrocytoma in 5 (11.6%) patients. Fourteen (32.5%) patients had mild intellectual disability, 9 (20.9%) had moderate intellectual disability and , 6 (13.9%) patients had severe intellectual disability.

Conclusions: Tuberous sclerosis complex (TSC) is a genetic, multisystemic disease with multiple hamartomas in many systems. In our study, it was observed that the patients were diagnosed with seizures most frequently after they were admitted to the hospital, which was consistent with the literature. We would like to emphasize that skin examination, especially in patients with seizures, is an important clue in the diagnosis of tuberous sclerosis complex.

Keywords:
tuberous sclerosis complex, epilepsy, genetics

EPNS23-2311 Oral or e-Poster
Neurocutaneous Syndromes

Two is better than one: a case report of pediatric patient with Tuberous Sclerosis and Multiple Sclerosis

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Case study: Objective: To present a rare/first pediatric case with Tuberous Sclerosis Complex (TSC) and Multiple Sclerosis (MS).

Methods: Workup of a boy with TSC and SM, including physical examination, blood tests, diagnostic imaging and lumbar puncture. Results: Here we report the first case of co-occurrence of TSC and MS in a young boy. He has been diagnosed with TSC after seizure onset at the age of 4 years. During the routinary neuroradiological follow-up at the age of 10, multiple asymptomatic demyelinating lesions have been detected on MRI, later framed as typical of MS because the new MRI showed two additional lesions in the right frontal white matter and in left cerebral peduncle, the latter showing contrast enhancement. Neurophysiologic assessments (visual evoked responses, brainstem auditory evoked responses and somatosensory evoked potentials) were normal, cerebro-spinal fluid examination showed a type 3 pattern of oligoclonal band, with a link index of 0.75. The search for AQP4-IgG and MOG-IgG was negative. He was then administered intravenous methylprednisolone and later started chronic therapy with interferon beta-1a. The 6-month neuroradiological follow-up showed decreased size of inflammatory demyelinated lesions and resolution of contrast enhancement.

Conclusions: This comorbidity is probably pure coincidence since the two diseases have different pathophysiological mechanisms, but a possible role of the mTOR pathway might be hypothesized as it is associated with the progression of inflammation within the nervous system. There is unique in vitro and ex vivo evidence that the complex mTOR pathway could be implicated in both diseases and be a potential therapeutic link to exert immunomodulation and prevent and limit the progression of MS, in order to slow down the disability progression, particularly in our patient who may benefit from mTOR inhibitory therapy in both TSC and MS.

Keywords:
TSC; tuberous sclerosis; mTOR; Multiple sclerosis; comorbidity

EPNS23-2690 Oral or e-Poster
Neurocutaneous Syndromes

The impact of early sirolimus treatment on the tuberous sclerosis complex clinical outcome - a case report

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Case study: Objectives: mTOR inhibitors demonstrate a great potential in tuberous sclerosis complex (TSC) treatment. However the concerns about their safety and the efficiency in individual patients still hamper their generalized application, particularly in early childhood. Nonetheless, recently published reports suggest that introduction of sirolimus as well as everolimus in infants may be beneficial for patient and does not increase the susceptibility to adverse effects. Here, we present the successful treatment with sirolimus for cardiological and neurological complications of TSC in an infant and follow-up results for 18 months.

Methods: We analyzed follow-up data of full-term boy diagnosed prenatally with TSC due to the presence of multiple heart tumors and tuberous lesions in CNS. The newborn presented with numerous heart tumors causing left ventricular outflow tract obstruction (LVOTO) and polymorphic arrhythmia as well as multiple cortical and subcortical lesions in MRI examination and polycystic kidney lesions. Surgical removal of cardiac lesions was not possible and the treatment with sirolimus was introduced.

Results: Sirolimus was introduced at the age of five days. Additionally patient received propranolol, lisinopril and ivabradine to maintain effective control of arrhythmia. The reduction in heart tumors volume was observed and the LVOTO has been reliably relieved. At the age of 6 months vigabatrin treatment was introduced due to ictal discharges in EEG and resulted in the resolution of EEG abnormalities in 4 months. Besides one febrile seizure at the age of 15 months, the clinical seizures are not observed. In the last MRI performed at the age of 7 months cortical and subcortical tumors were stable and no renal cysts were observed. The patient exhibits normal psychomotor development, attaining the developmental milestones according to the WHO standards. No side effects of the sirolimus therapy have been reported.

Conclusions: Despite of the factors predictive for severe clinical manifestations of TSC (TSC2 mutation, polycystic kidney changes), the successful control of cardiological and neurological TSC-manifestations was obtained in the reported case. Initiation of sirolimus therapy in infancy might have positive impact on the clinical outcome, thus additional studies are needed to establish the optimal treatment of newborns with TSC.

Keywords:
sirolimus, tuberous sclerosis complex, mTOR inhibitors

EPNS23-2572 Oral
Neuropsychiatric Disorders

Tourette Syndrome and Anti-GAD Positivity: More Than a Coincidence?

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Objective: Tourette syndrome (TS) is a neurodevelopmental disorder characterized by multiple motor tics and at least one vocal tic caused by striatal focal disinhibition secondary to block of gamma aminobutyric acid (GABA) A transmission. Anti-glutamic acid decarboxylase antibodies (anti-GAD) similarly disrupt the function of GABA-ergic neurons. We aim to present our anti-GAD experiences in TS.

Methods: Between January 2018 and December 2019 nine behavioral, medical and surgical treatment resistant TS patients who were treated with intravenous immunoglobulin (IVIG), were included. All patients were investigated for TS etiology. Patients evaluated prospectively by demographic datas, physical examination, electroencephalography, brain magnetic resonance images, infectious serology, celiac and anti-thyroid autoantibodies, anti-streptolysin O, anti-GAD antibodies were studied. All patients were administrated IVIG 2gr/kg in every 3 weeks during 4 months and were evaluated by Yale Tic Severity Score (YTSS) at baseline and at 4th months of IVIG treatment.

Results: In the evaluation of TS etiology, anti-GAD was found positive in 4 of 9 patients. (150,25,30,100 U/mL, 0-20 normal). When the course of IVIG treatment was evaluated, anti-GAD positive patients showed a more important but not statistically significant, decrease in motor tic number, frequency and impairment parts of YTSS compared to negative ones. 3 of 4 patients did not have any complex tic, while the other patient, who was anti-GAD positive, also decreased complex tic number. Significant improvement was observed in the vocal tics of these 4 patients. No change was observed in the tic characteristics of patients who were anti-GAD negative. There was correlation was detected between high anti-GAD antibody titer and YTSS changes.

Conclusions: Even without expected manifestations, anti-GAD may present with neuropsychiatric symptoms like tic disorders. These results may suggest that anti-GAD may play a role in TS etiology and TS may be a candidate for being one of the anti-GAD positive neurological syndromes. According to this study, anti-GAD autoantibody should be investigated in patients with treatment resistent TS.

Keywords:
Anti- GAD, Childhood, Intravenous immunoglobulin, Tic, Tourette syndrome

EPNS23-2244 Oral or e-Poster
Neuropsychiatric Disorders

Migraine Abortive treatment in Children and Adolescents in Israel

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Objective: Primary headaches are common in children and adolescents. Migraine headaches, as oppose to TTH, maybe causing a severe headache attack that requires abortive treatment. The aim of our study was to evaluate the incidence and efficacy of the medications used for relieving migraine headache attacks in the pediatric population in Israel.

Methods: Children 6-18 years of age who were assed in the pediatric neurology clinic and were diagnosed as having migraine headaches enrolled into the study. Children and their parents filled questionnaires about abortive treatment, two hours after use, during three acute headache attacks. The questionnaire included; demographic data, baseline headache intensity, migraine-associated symptoms, mediations used, pain assessment.

Results: Fifty children entered the study (30 Females 60%; mean age 12; range 6-18). Forty seven (94%) reported on abortive treatment in the first questionnaire, 43 (86%) filled out the second questionnaire and 26 (52%) children filled out the third questionnaire. Forty one (87.5%) children reported taking only one type of medication for each headache episode; 44 - 53% of the children used Ibuprofen, 23 - 31% Acetaminophen and 11-15% Dipyrone. The improvement rate after two hours was; 65.4%±27 for Ibuprofen, 59.8±35.3 for Acetaminophen and 50.9±27.4 for Dipyrone. Acetaminophen was associated with a better response.

Conclusions: Children with migraine in Israel mainly use a single medication for each headache episode. Ibuprofen is the most commonly used abortive treatment, however, Acetaminophen was associated with a better response.

Keywords:
Headache Treatment Migraine Children

EPNS23-2122 Oral
Neuropsychiatric Disorders

Autism Spectrum Disordes - what are we waiting for? : 7 year follow-up study

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Objective: Rehabilitation of children with Autism is the issue of the day in psychiatry and neurology. It is attributed to constantly increasing quantity of autistic children - autistic sprectrum disorders (ASD) diagnosed in 70 million people throughout the globe. Prevalence of ASD in Ukraine, according to official statistical data, is 2 cases in 10 thousand children. Currently there is more patients with Autism, then ones with diabetes, cancer and AIDS. Tackling a problem of autism is of great importance, cost of supervision for one patient with ASD during lifetime is $3.2 million.

Methods: 120 children aged 5 to 14 were examined from 18 countries. They were diagnosed "ASD" (F84.0-F84.5). For assessment standardized tool was used, namely Autism Treatment Evaluation Checklist (ATEC). Normal range 0 to 30.

Results: Mean score according to ATEC scale in ASD children was 64,75±9,23. It reveals occurrence in examined children of severe communication, speech, socialization and behavioral impairments. If rehab was not applied after ASD was diagnosed mean score after 1 year improved anyway to 62,23±7,12 (-2,52 points) and to 50,11±7,01 (-14,64) in 5 years. If psychocorrectional rehab started at once mean score was 58,52±6,41 (-6,23) and 43,09±7,12 (-21,66) respectively. If intensive physical and psychocorrectional therapy applied score was 53,00±6,19 (-11,75) and 31,98 (-32,77) respectively.

Conclusions: Reduction of autistic symptoms was noted for all treated or not.Those who received intensive physical and psychocorrectional therapy combined improved more, their autistic symptoms were much less manifested

Keywords:
ASD, treatment, rehabilitation

EPNS23-2301 Oral or e-Poster

Quality of Life in Children with Neurological Disorders

Three child with CTNNB1-associated neurodevelopmental disorder improved with levodopa treatment

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Objective: Heterozygous deleterious CTNNB1 variants cause neurodevelopmental disorder with spastic diplegia and visual defects. Its incidence is estimated to be 2.6-3.2 in 100,000 births but probably is an underdiagnosed cerebral palsy mimic. There is no curative treatment but a recent case study reported a child with significant improvement in hypertonia and an acceleration in acquisitions (fine motor and language/cognitive skills) with levodopa treatment.

Methods: case report

Results: we described three girls from three families with CTNNB1-associated neurodevelopmental disorder confirmed by molecular testing. All patients had global development delay, axial hypotonia and limb hypertonia from infancy, resembling cerebral palsy but with no risk factors. Currently aged 22 months, 6 years and 6.5 years, only one patient acquired independent gait (with paretic pattern). All had intellectual disability and behavioral abnormalities including autistic features and aggression, and all had speech impairment. Visual defects were identifiable in two (strabismus and hypermetropia). All have microcephaly, poor growth and mild dysmorphic facial features. None had seizures or hearing loss. Magnetic resonance imaging was unremarkable except for a thin corpus callosum in one.
Additionally to spasticity, all our patients exhibited dystonia and underwent a trial with levodopa with evident improvement of hypertonia, social interaction and language. All parents reported a clear benefit in attention and fluidity of movements. The beneficial effects were reported a few weeks after levodopa introduction and improved with the progressive increase in the dose (max 10mg/Kg/day) with no secondary effects.
Of interest, one of the children lost gait after starting risperidone prescribed by child psychiatry, and regained it after its interruption.

Conclusions: we reinforce the importance of etiological investigation in patients with cerebral palsy but absent history of perinatal risk factor for brain injury or typical neuroimaging findings. In these three girls, identification of deleterious variants in CTNNB1 led to changes in care, including personalized treatment with levodopa. In CTNNB1-associated neurodevelopmental disorder, levodopa may be considered as it can impact motor, cognitive and social function, maximizing acquisitions in critical periods of development. We warn of the potential worsening of symptoms with antagonists of dopamine receptors.

Keywords:

CTNNB1, cerebral palsy mimic, levodopa

EPNS23-2340 Oral

Quality of Life in Children with Neurological Disorders

Feeding failure - a new final frontier in children with severe neurological impairment

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Objective: Breakthroughs in medical care have enabled children with severe neurological impairment (SNI) to live longer, albeit medical complex lives. Life-limiting gastrointestinal dysfunction is now emerging as a new final frontier.
Feeding failure in children with SNI is poorly defined. Gaps in understanding of the diagnostic pathway, natural history, and management are reflected in inconsistent terminology, scant literature and treatment lacking practice guidelines and an evidence base.

We sought to describe the healthcare experience of children with SNI and severe gastrointestinal dysfunction known to pediatric palliative care, who died from resultant feeding failure.

Methods: A retrospective chart review was conducted of patients of a statewide Australian pediatric palliative care service seen between 2015-2020. To be included children needed to have SNI and severe GI dysfunction and feeding failure contributing to their death.

Nine patients were identified.

Data were collected from electronic medical records. Data were analyzed and summarized using descriptive statistics. Institutional ethics was obtained.

Results: Mean age at death was 10 years (range: 5 - 15). Location of death was hospital (n=5) including one child who died in the intensive care unit, home (n=3), pediatric hospice (n=1).

In the records of seven children, the terms gastrointestinal "failure" or "dysfunction" were documented (median time between documentation and death was almost 4 months (range: 0.1-13).

All nine children received nutrition via a gastrostomy tube (median age of insertion 2.5 years (range: 1.2 - 6.8 years). For seven children, this was advanced to the jejunal route (median age 9.2 years (range 2.4-14.7 years)).

Time from palliative care referral to death was 3 months. Children lived a median of nine percent of their lives after jejunal tube feeding was commenced. No child received home-based parenteral nutrition. Multiple medications were required for symptom management.

Conclusions: Feeding difficulties are present in many children with SNI. Feeding failure is an important phase of disease progression or a marker of severity in these children. This is usually difficult to manage and may contribute to death. It is important for clinicians to recognize these critical issues and provide opportunity to discuss goals and priorities of care with families/carers. Recognition, better reporting in a common language and discussion around feeding failure is vital to improve the care of children with SNI.

Keywords:
severe neurological impairment; palliative care; intestinal failure

EPNS23-2131 Oral or e-Poster

Quality of Life in Children with Neurological Disorders

Nutritional status of children with cerebral palsy: A single center study

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Objective: To investigate the nutritional status of children with cerebral palsy from a tertiary center in Western Turkey, and to evaluate their risk of malnutrition based on their Gross Motor Function Classification System (GMFCS) level.

Methods: The study was designed as a descriptive retrospective study. Forty-three children who were followed-up with the diagnosis of cerebral palsy in pediatric neurology outpatient clinics were included. Anthropometric measurements, demographic, clinical and brain magnetic resonance imaging (MRI) findings, nutritional status were evaluated. Malnutrition was defined by height, weight, body mass index, and triceps skinfold thickness for age z-scores using Centers for Disease Control and Prevention (CDC) growth charts. The data were analyzed using SPSS 28 statistical software.

Results: Of the patients, 62.8% were spastic quadriplegic/hemiplegic and 37.2% were dyskinetic. Mean decimal age was 9±4.6 years with a mean gestational age of 34.5±5.4 weeks at birth. Twenty-eight of 43 patients were GMFCS levels IV and V. Mean weight-for-age z-score was found -3.12±5.19 for levels IV and V, and -0.39±2.02 for levels I-II-III ($p=0.024$). Mean height-for-age and triceps skinfold thickness for age z-scores were also lower in GMFCS level IV-V patients. Malnutrition was detected in 30.2% of the study population, based on CDC weight-for-age z-scores. Malnutrition rate was higher in GMFCS level IV-V patients. There was a strong inverse relationship between the weight-for-age z-scores and GMFCS IV-V levels ($p=0.02$; $r= -0.35$). Epilepsy was the most common comorbidity. Five patients had normal brain MRI findings, while 88.4% of the patients had abnormal MRI findings.

Conclusions: The majority of the children with cerebral palsy are prone to malnutrition. Moreover, risk of malnutrition increases with increased motor compromises. This study showed that children classified in GMFCS levels IV and V have more risk for malnutrition. We underscore the need for more emphasis on nutrition assessment and counseling in cerebral palsy patients.

Keywords:

Cerebral palsy, gross motor function, malnutrition,

EPNS23-2044 Oral or e-Poster

Quality of Life in Children with Neurological Disorders

It's not 'just a headache'- Quality Improvement Project on 'Headaches in children'

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Objective: To improve the efficiency of management of headaches in children presenting to Children's Assessment Unit (CAU) in a District General Hospital (DGH).

To implement strategies to improve the quality of care and ensure patient safety.

Methods: Retrospective data were collected for 6 months (from September 2020 to February 2021). Documentation, diagnosis, and management plans were audited. This was compared against NICE guidelines on headaches in children and young people.

Results: We had 23 children from 6-16 years. Documentation was 92% compliant in elaborating symptoms and 100% in eliciting red flags and neurological examination. Major diagnoses were migraine, tension, and cluster headaches. We had 3 (13%) children with Benign Intracranial Hypertension who were referred to tertiary hospital. We identified the following areas for improvement:

Unclear management plans where the type of headache is a dilemma in the first presentation.

Lack of written information given to parents.

Difficulty in referral to the urgent eye clinic for fundoscopic examination.

The following changes were implemented:

Trust guidelines were revised giving easy access to the registrars by including a flow chart that covered headaches of diagnostic dilemmas and follow-up plan.

We created an eco-friendly COVID-19 safe QR-coded parent information sheet for headaches in children with a symptom diary as an annexure.

We involved the opthalmology department and a referral form for an urgent eye clinic was created to facilitate easier communication between the departments.

Conclusions: In summary, good quality of care was met in terms of diagnosis and documentation but needed improvement in management. The lack of pathways and access were identified as the major cause for this. Following the implementation of the above changes, the audit will be repeated.

Keywords:
headache, children, audit, fundoscopy

EPNS23-2653 Oral or e-Poster
Sleep Disorders

The sleep problems in patients with Rett syndrome

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Objective: To investigate sleep problems of individuals with Rett syndrome (RTT) in Taiwan

Methods: In this cross-sectional study, twenty-nine Rett syndrome individuals with MECP2 mutation were included. They were divided into two groups (childen, adult) according to age. Demographic data, clinical manifestations and clinical severity were evaluated. The sleep condition were assessed using the children sleep habits questionnaire (CSHQ), seven-day data from actiwatch 2 and sleep diary. Pearson correlation analysis and linear multiple regression test were used to define the relationship between clinical characteristics and actigraphic parameters.

Results: Total 29 individuals with RTT were included in this study. Among them, twenty-two (75.9%) patients were found to have sleep disturbance by using the CSHQ. Further, the subscales, including bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night-waking, parasomnia and sleep breathing disorders, scored higher in younger RTT. The actigraphy in both the childen and adult groups demonstrated short total sleep duration (mean±SD, 480.4±98.0 minutes, 488.0±128.2 minutes, respectively), low sleep efficiency (73.6±12.9%, 70.8±14.7%), long sleep-onset latency(43.4±42.2 minutes, 47.3±67.0 minutes), long awaking duration (56.3±36.6 minutes, 74.9±56.1 minutes) and fragmented sleep(48.8±21.5 minutes, 67.0±32.2 awakening per night). We found that smaller head circumference was associated with shorter total sleep duration, while motor dysfunction was associated with longer wake after sleep onset, worsen scoliosis was associated with more awakenings per night. In addition, sleep efficiency was inversely associated with epilepsy and positively associated with somatic growth.

Conclusions: Sleep disturbances are common in RTT. Further, in these study, we identified factors that may be associated with sleep disturbance, which may reflect the underlying pathophysiology of altered sleep-wake mechanisms in RTT.

Keywords:
Rett syndrome, MECP2 mutation, sleep disturbance

EPNS23-2594 Oral or e-Poster
Sleep Disorders

Post-acute COVID-19 sleep disturbances in preschool children

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Case study: Objectives: Although sleep patterns and disturbances in children during the COVID-19 outbreak has been reported, the sleep disturbances of children with COVID-19 infection need further investigation compared with children without COVID-19 infection.

Methods: Preschool full-term children with COVID-19 infection were recruited during January to June, 2022, in a medical center in Northern Taiwan. Age- and gender-matched full-term children without COVID-19 infection were also enrolled for comparison. Their medical records were reviewed and recorded. All parents of all participants completed the Children's Sleep Habits Questionnaire (CSHQ), which was collected two to three months after COVID infection in infected children.

Results: Totally, 36 children (30 boys and 6 girls) with COVID-19 infection and 36 age- and gender-matched children without infection were enrolled. The mean age was 3.9 years. The only significant differences of sleep disturbances between these two groups were sleep duration and daytime sleepiness. Infected children showed more sleep duration but less daytime sleepiness than noninfected children.

Conclusions: During the COVID-19 pandemic, preschool children with COVID-19 infection showed more sleep duration and less daytime sleepiness than noninfected children. In addition to the environmental factor, our study showed that the virus per se contributed to the sleep disturbances in preschool children. We should pay more attention to the sleep quality in preschool children with COVID-19 infection.

Keywords:
COVID-19, sleep disturbance, preschool children

EPNS23-2510 Oral or e-Poster
Sleep Disorders

Evaluation of Sleep and Factors Affecting Sleep and Comorbid Conditions in Children with Cerebral Palsy

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Objective: The aim of this study was to evaluate sleep and sleep-affecting pain and comobid conditions in a group of children with cerebral palsy (CP) using a questionnaire administered to parents or caregivers.

Methods: The caregivers or parents of patients aged 2-18 years with CP who were admitted to the Pediatric Neurology outpatient clinic were asked to complete a questionnaire including questions about 'Children's Sleep Habits' and pain. Medical information of the patients was recorded during the outpatient clinic visit.

Results: 106 patients with CP participated in the study (mean age ± standard deviation: (116 ± 56 months) 53 of the patients were girl (50%) and 53 were boy (50%). According to the total score of the questionnaire, sleep disturbance was detected in 85 patients (81%). In addition, when the risk factors affecting sleep disturbance were examined, it was observed that increasing age decreased the risk of sleep disturbance. Considering comorbid conditions, evaluation was made according to the subscales of the questionnaire. The score in the area of waking up from sleep at night was higher in non-ambulatory patients than in ambulatory patients and in individuals with bladder-related disorders than in those without, and a statistically significant difference was found (p=0.002, respectively).

Conclusions: Sleep disturbance is common in patients with CP and should be part of routine evaluation. Steps should be taken by healthcare professionals to improve this area.

Keywords:
serebral palsy, child, sleep disturbance, questionnaire

EPNS23-2588 Oral or e-Poster
Sleep Disorders

Sleep disturbances in children after the COVID-19 in Crimea

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Case study: Sleep disorders may be a significant source of distress for children and consequently for their families. Several systematic reviews and meta-analyses examining the impact of COVID-19 on sleep disturbances have been conducted.

The study aim is to investigate sleep disturbances in children after the COVID-19 in Crimea.

Material and methods: 170 case reports was retrospectively collected and analyzed data in Crimean pediatric hospital from 2020 to 2022. The final sample consisted of 170 children after the COVID-19 disease (90 females and 80 males; mean age ± SD: 9.5 ± 2.5 years; age range: 6.4-12 years). Ethical approval was for this study because of the retrospective design. The Sleep Disturbances Scale for Children (SDSC) was used in this investigation for assessing sleep difficulties over the past 6 months in children after COVID-19 disease. T-scores are clinically significant when they are or more than 70 like normal sleep condition, whereas less than 60 was sleep disorders. To have a measure of sleep disturbance, we analyzed the results of all six subscales of the disorder.

Results: Before the COVID-19, there were no problems with sleep in the examined children. Means and standard deviations in SDSC subscales were calculated with p-values in standard statistical program. The disorders in initiating and maintaining sleep was in 45 % of children with means score - 62.76 (p=0,001), nocturnal hyperhidrosis was in 25% of children with mean score - 53.29 (p=0.001), the disorders of arousal was in 15% with mean score - 57.73 (p=0.001), the sleep-wake transition disorder - 7% with mean score - 57.91 (p=0.05), the disorders of excessive somnolence - 5% with mean score - 56.41 (p=0.05), the sleep breathing disorders -3% with mean score - 52.95 (p=0.05).

Conclusions: children who have had COVID-19 infection have demonstrated different types of sleep disorders. The predominant number of children had the disorders in initiating and maintaining sleep. Consequently, the sleep disorders in children after COVID-19 require longer observation and careful investigation in future.

Keywords:
sleep disturbances, COVID-19, children

EPNS23-2777 Oral or e-Poster
Sleep Disorders

Neural signatures of primary nocturnal enuresis: a polysomnography and autonomic

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Objective: To simultaneously evaluate overnight polysomnography (PSG) and autonomic function (AF) in children and adolescents with primary monosymptomatic nocturnal enuresis (PMNE) for better understanding of pathophysiology.

Methods: Subjects- Cases with PMNE, aged 5-18 years, presenting at a tertiary care teaching hospital in north India, between March 2021-November 2022 (exclusion criteria: chronic systemic illness, IQ>70, daytime symptoms and received any therapy for PMNE in last 6 months).
Evaluations done
- Intelligence quotient (IQ) using MISIC (Malint's Intelligence Scale for Indian Children),
- Childhood Behaviour Checklist (CBCL),
- House Tree Person Testing (HTP) to look at stressors in life,
- Childhood and adolescent sleep evaluation questionnaire (CASEQ), and
- Overnight PSG and AF

Subsequently, the cases received standard behavioural therapy for 12 weeks.

Results: Demography: 21 children enrolled (26 screened, 10.6+/-3.2 years, 16 boys); mean IQ of 86.6+/- 8.9 (median: 86.5, IQR:79.5-90.5); impaired CBCL in 47.6% (10/21) with inattention in 42.9% (9/21), hyperactivity in 9.5% (2/21) and aggression in 4.8% (1/21); stressors on HTP in 42.9% (9/21)- academics related in 42.9% (9/21), family related in 28.6% (6/21) and poor self-esteem in 9.5% (2/21)
On CASEQ and overnight PSG evaluation- sleep related breathing disorder and sleep related movement disorder (SRMD) in 71.4% (15/21) and 61.9% (13/21) respectively.
Significant findings ($p<0.05$) on PSG compared to normal controls
- lower sleep efficiency (72.3+/-10.9% versus 80.6+/-9.1%),
- higher proportion of N2 (76.4+/-2% versus 63.1+/-2.8%) and
- lower proportion of N3 (16.3+/-1.7% versus 28.2+/-1.5%).

Salient AF findings
- During sleep, higher sympathetic compared to parasympathetic tone (LF/HF of 1.2)
- Overall higher awake parasympathetic tone compared to sleep (RMSSD: 194.5ms versus 89.1ms)
- These findings are opposite to normal individuals described in literature.

One-third responded well to standard behavioural therapy. Presence of other primary sleep disorders, particularly SRMD was significantly associated with poor response.

Conclusions: This study simultaneously evaluated PSG and AFT in PNE for the first time highlighting relative sympathetic excess leading to lighter, fragmented sleep with reduced sleep efficiency. This fact can be used in early therapeutic management of PNE. They should be screened for other primary sleep disorders using simple questionnaire like CASEQ.

Keywords:
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EPNS23-2972 Oral or e-Poster
Sleep Disorders

Narcolepsy Type 2 Onset Following Treatment for a Tectal Glioma

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Case study: Objective: To demonstrate the occurrence of central hypersomnia following treatment of tectal glioma, a benign midbrain tumor

Method: Case report of a 14-year-old female seen in consultation by Sleep Medicine regarding daytime sleepiness and episodes of sleep paralysis that occurred following tectal glioma treatment with endoscopic 3rd ventriculostomy and proton beam radiation

Result: Narcolepsy type 2 diagnosis was made based on results of polysomnogram and multiple sleep latency test combined with clinical history

Conclusion: Narcolepsy may occur secondary to brain tumors and their treatment. Recognizing that neuroanatomical regions affected by tumor may predispose to sleep disorders is an important consideration in brain tumor patients. Daytime sleepiness and fatigue are common in survivors of pediatric brain tumors. Awareness of these symptoms and initiation of appropriate diagnostic evaluation and treatment will significantly improve daytime functioning and quality of life in this patient population.

Keywords:
tectal glioma, narcolepsy, quality of life

EPNS23-2195 Oral or e-Poster
Miscellaneous

A pharmacometric approach to predict pharmacokinetics and serum oligosaccharide concentrations in children under 6 years of age with alpha-mannosidosis treated with velmanase alfa

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Objective: Alpha-mannosidosis (AM) is a systemic, ultra-rare, progressive disorder. AM causes a lysosomal alpha-mannosidase deficiency, leading to an accumulation of oligosaccharides (OLS) in the lysosomes of various tissues. Clinical presentations include intellectual disability, hearing loss, facial dysmorphia, skeletal abnormalities, and ataxia. AM can manifest at a young age, with earlier onset associated with more-severe disease progression. Velmanase alfa (VA) is an intravenously administered recombinant human alpha-mannosidase enzyme replacement therapy authorized to treat AM in Europe and other countries. Approval was based on a placebo-controlled study (rhLAMAN05) in patients 6-35 years of age; at Week 52, VA led to marked reduction in OLS levels in the overall population. A small clinical study (rhLAMAN08) evaluated pharmacokinetics (PK), efficacy, and safety data in 5 patients <6 years of age. The objective of this modelling exercise was to confirm that VA 1.0 mg/kg weekly maintains the same efficacy in children aged <6 years as in patients ≥ 6 years.

Methods: A population PK model was developed based on samples collected from patients (N=39) in all 7 VA clinical trials that included PK sampling. Twelve patients were ≥ 18 to ≤ 35 years old and 27 were ≥ 3 to <18 years old. The model was used to extrapolate the PK of VA to patients aged <6 years from the National Health and Nutrition Examination Survey database. The exposure-response (E-R) relationship of serum OLS with average VA concentrations at steady state was assessed using a maximum inhibitory effect (Emax) model. Based on the E-R model, serum OLS concentrations were simulated in children aged <6 years using the data from the PK extrapolation.

Results: The similarity in disease pathophysiology, pharmacology, and response to intervention between reference and target populations supported extrapolation of PK and E-R models to patients aged <6 years. We analysed exposure to VA and found that clinically relevant reduction of OLS was not dependent on body weight or age. Using the model to extrapolate to patients aged <6 years, we found that the predicted mean serum OLS level after VA treatment dropped ~3 µmo/L, as observed in older patients.

Conclusions: We showed that a pharmacometric approach can be used to extrapolate PK and efficacy data for paediatric populations with AM. Extrapolations based on our PK and E-R models support use of VA 1.0 mg/kg across all ages, including patients aged <6 years.

Keywords:
Alpha-mannosidosis, velmanase alfa, pharmacokinetic population model, exposure-response analysis, extrapolation, pharmacometrics, paediatrics.

EPNS23-2166 Oral
Miscellaneous

The Effect of the Lunar Cycle of Pediatric Vasovagal Syncope Attacks

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Objective: The purpose of this study was to evaluate the relationship between the lunar cycle and attacks in cases of pediatric vasovagal syncope.

Methods: The attack durations, ages at onset of attacks, and personal and family histories of patients diagnosed with vasovagal syncope and followed-up at the Balikesir University Medical Faculty neurology clinic, Turkey, between 01.08.2019 and 01.04.2022 were recorded and analyzed. Patients' vasovagal syncope attacks were investigated retrospectively, and the phase of the lunar cycle during they took place was determined.

Results: The mean age of the 49 patients with vasovagal syncope in this study was 13.34±4.77 (5-18). The 12-18 age group represented the majority of cases in all lunar phases. Length of syncope attack was highest in the third quarter and shortest in the full moon. Age at onset of attacks was lowest in the third quarter and highest in the new moon. No statistically significant differences were observed between the groups in terms of age, attack duration, or age at onset of attack

Conclusions: Studies have shown that vasovagal syncope exhibits a circadian rhythm and that the lunar cycle can result in cardiovascular changes. Syncope cases have been shown to be affected by circadian, seasonal, and diurnal variations. However, no previous studies have examined the relationship between the lunar cycle and pediatric vasovagal syncope cases. The distinguishing features of the present study is that it the first on this subject

Keywords:
children, syncope, lunar cycle

EPNS23-2291 Oral or e-Poster
Miscellaneous

Rare case report : EVEN-Plus Syndrome.

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Case study: Introduction:
EVEN- Plus syndrome is characterized by its involvement of the Epiphyses, Vertebrae, Ears, and Nose, plus other associated findings. This syndrome was first described by Royer Bertrand et al. in 2015. They described three cases with this syndrome. Later on a fourth case was described by Nagrani et al. in 2018 with many of the characteristic features in addition to a laterally dislocated patella leading to scoliosis, leg-length discrepancy, and an abnormal gait. In 2020, a fifth case was described by Younger et al, which was the first male patient with this syndrome. EVEN- Plus Syndrome is caused by HSPA9 gene variants. Here we are presenting a clinically identified female patient with EVEN-Plus syndrome.
Case Report :
We are presenting the case of a, 8 year old female patient, product of non-consanguineous marriage presented with global developmental delay (predominant motor delay). She had microtia , hypoplastic nasal septum, maxillary hypoplasia, brachydactyly , scoliosis, absent coccyx , dysplastic acetabulum & femur with dislocated hip and anal atresia. MRI brain suggestive of corpus callosum agenesis.
Conclusion :
EVEN Plus syndrome is a rare syndrome and our patient had
characteristic facial features , skeletal abnormalities , ear and nose abnormalities described in EVEN-Plus syndrome along with corpus callosum agenesis . Whole exome sequencing is needed to confirm the diagnosis and to differentiate this case from a close differential, CODAS syndrome.

Keywords:
EVEN PLUS SYNDRME, Absent cocyx, Anal atresia, dysmorphism

EPNS23-2415 Oral or e-Poster
Miscellaneous

Use of anti-CGRP monoclonal antibodies in pediatric migraine: first evaluations of a phase 3, randomized, double-blind, placebo-controlled study.

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Case study: Objectives: to date, prophylactic therapies for migraine include the use of antiepileptic drugs, calcium antagonists or antidepressants. In recent years, studies have been conducted on adults with the monoclonal antibody that binds the receptor of the peptide related to the calcitonin gene (GCRP), which competes specifically with the binding of CGRP to its receptor by inhibiting its function. CGRP modulates the nociceptive signal and is associated with the pathophysiology of migraine. Therapies currently available in children have limited efficacy. There is therefore a need for additional drugs.
Methods: 8 patients with chronic migraine and 1 patient with episodic migraine were enrolled in the study according to the criteria of the International Classification of Headaches (ICHD-III). Patients with chronic migraine are in the following phases: 1 finished the study, 1 dropped out, 2 in the double-blind phase, 3 in the open-label and dose-blind phase, and 1 moved from the episodic migraine study to chronic.
Results: among the 8 patients with chronic migraine, it can be stated that 4 patients reported a reduction in the frequency and intensity of monthly migraine attacks, 2 patients reported the ineffective therapy and 2 patients, in whom the double-blind phase was not started, are being evaluated. In three of the four patients with chronic migraine, who had a good response to therapy, a reduction in the frequency and intensity of monthly attacks was observed starting from the double-blind phase.
Conclusion: to date our preliminary data on the efficacy of anti-CGRP antibodies in pediatric age, even if under evaluation, confirm what has been found in double-blind studies on the adult population, or the possibility of having a prophylactic drug specific and efficacy for migraine. However, more pediatric studies will be needed to confirm these preliminary results.

Keywords:
migraine, children, prophylactic therapies

EPNS23-2049 Oral
Miscellaneous

A comparison between Amitriptyline and Riboflavin (vitamin B2) for being used in child Abdominal Migraine Prophylaxis

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Objective: Riboflavin (vitamin B2) and Amitriptyline are used as prophylactic medications for childhood migraine headaches. This study has been done to compare both drug effects on child abdominal Migraine (AM) prophylaxis.

Methods: This hospital study was conducted from June 2021 to March 2022. Patients were recruited after formal consent, the clinical trial was conducted on 56 participants.34 females (60.7%) and 22 males (39.3%), with ages ranging from 8 to 14 years (mean 10.6 ± 3.4 years) with abdominal migraine. They were randomly assigned in a 1:1 ratio into 2 groups Amitriptyline group and Riboflavin (vitamin B2) group. Both groups have no other medical background and were explained the possible side effects of both drugs. The diagnosis of abdominal migraine was based on Rome IV Diagnostic Criteria for Child Abdominal Migraine .A good response to treatment was defined as more than a 50% decrease in the monthly abdominal ache frequency during follow-up. The Amitriptyline group received it in a dose of 1 mg/kg daily for 6 months. The Riboflavin group received it in a dose of 200 mg for the same period. The primary outcomes were a monthly frequency of abdominal pain attacks, a good response to intervention, and a reduction in migraine severity, duration, and disability before and after treatment.

Results: A good response was observed in 75% of patients (21 children) in the Amitriptyline group and 53.5% of patients (15 children) in the Riboflavin group, and Amitriptyline was significantly more effective than Riboflavin(P =.01). Side effects were observed in 2.1% (6 children) in the Amitriptyline group mainly mild constipation &sedation. The Riboflavin group has almost no side effects except in 0.7% (2 children) who felt urine is more yellow than usual. Comparisons of abdominal migraine characteristics before and after intervention in both
groups showed that Amitriptyline was more effective than Riboflavin in the reduction of monthly frequency, severity, duration, and disability for abdominal migraines.

Conclusions: Accordingly, Amitriptyline may be used with caution for child Abdominal Migraine (AM) prophylaxis, Daily administration of 1mg/kg with the good outcome rather than Riboflavin.

Further randomized controlled trials with larger sample sizes and a longer duration of follow-up are recommended,

Keywords:
Abdominal Migraine, Amitriptyline, Riboflavin

EPNS23-2741 Oral or e-Poster
Miscellaneous

The British Paediatric Neurology Association and James Lind Alliance Priority Setting Partnership: UK research priorities for childhood neurological disorders.

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Objective: The main aim of this Priority Setting Partnership (PSP) was to set research priorities focusing on the evaluation and effectiveness of interventions for children and young people (CYP) with Childhood Neurological Disorder (CNDs).

CNDs are a wide and heterogeneous group of conditions affecting a child's central and peripheral nervous system and include many rare as well as common diseases.

The James Lind Alliance (JLA) and National Institute for Health Research (NIHR) have a highly successful method to support patients, carers and clinicians to work together to agree on the most important research questions. This PSP was set up as a collaboration between the James Lind Alliance (JLA) and the British Paediatric Neurology Association (BPNA).

Methods: We adopted the JLA-PSP methodology. This includes 2 sequential surveys: to identify unanswered research questions, and then prioritise them. A final workshop of stakeholders then selects the top ten priorities.

Results: 701 participants generated 1800 uncertainties in survey one. Following analysis and literature search 44 research questions were taken to survey two, the prioritisation survey. This was completed by 1451 participants.

27 purposely sampled stakeholders (professionals, parent-carers and CYP) attended the final workshop and created the top ten list from the highest ranked 26 priorities in survey two.

Conclusions: The top ten list has identified research questions of significant importance regarding interventions for CYP with CNDs, their families and professionals working with them.

There is a balance regarding questions about a variety of interventions for more common conditions (e.g. medicinal and non-medicinal interventions for CYP with motor disorders), questions regarding interventions for co-morbidities relevant to CYP with many CNDs (e.g. sleep, emotional well-being, pain) and specific CNDs (e.g. neonatal seizures.)

It will inform researchers and funders to drive meaningful future research and improve clinical care for CYP with childhood neurological disorders.

Keywords:
Childhood Neurological Disorders, Interventions, Research, Priorities

EPNS23-2429 Oral or e-Poster
Miscellaneous

Letter Template for Paediatric Epilepsy Clinic

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Objective: (1) assess the need for a letter template among doctors working in the paediatric epilepsy clinic, (2) develop a letter template adopting International League Against Epilepsy (ILAE)classifications, and (3) gather feedback on the content and format of the letter.

Methods: A survey was conducted among doctors working in the paediatric epilepsy clinic in the East of England region (EOE). The survey included both closed-ended and open-ended questions. We got responses from paediatric epilepsy specialists working in different eleven hospitals in(EOE). The results of the survey were analysed using descriptive statistics.

Results: The survey results showed that there was a strong need for a letter template among doctors working in the paediatric epilepsy clinic. Specifically, the doctors reported that a letter template would be helpful in standardising communication with referring physicians, providing clear and concise information about the patient's epilepsy status, following (ILAE) multi-axis seizure classification, and improving the efficiency of the clinic.Based on the feedback from the survey, the letter template was developed and included the ILAE multi-axis classification. The survey results and proposed templated were introduced to Eastern Paediatric Epilepsy Network (EPEN) members and their feedback on the letter format and content was collected and analysed.

Conclusions: The development of a letter template for paediatric epilepsy clinics is important for improving communication and care coordination among healthcare professionals, patients and their families. The use of the ILAE multi-axis classification system in the template helps to standardize the description of seizures and facilitate the development of effective treatment plans. Further research is needed to assess the impact of the letter template on patient outcomes and the overall management of paediatric epilepsy.

Keywords:
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EPNS23-2728 Oral or e-Poster
Miscellaneous

Hemiplegic migraine with fever, impaired consciousness and cognitive dysfunction: a case report

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Case study: Objectives: Hemiplegic migraine is a rare entity in children. We present a case report of a patient not only with motor but also prolonged cognitive deficit and quantitative impairment of consciousness.Methods: We report a case of a girl with right-sided central motor deficit associated with fever, headache, vomiting, aphasia, impaired consciousness and prolonged cognitive deficit. Brain MRI, angiography and lumbar puncture were normal. We ruled out cerebral infarction, vasculitis, demyelination and others. The single-photon emission computerized tomography performed did not show a cerebral perfusion disorder. EEG showed a right-sided hemispheric abnormality correlated to a suspected diagnosis of migraine. Serum was sent to investigate the most common mutations associated with hemiplegic migraine (CACNA1A, ATP1A2, SCN1A). During the psychological examination, impaired visuomotor and abstract-visual functions were detected. A 6-week follow-up psychological examination showed improvement in all areas. However, slightly impaired visual differentiation still persisted. In the acute phase, before a definitive diagnosis was made, the girl was treated empirically with antibiotics, antivirals and anopyrine and had three doses of intravenous methylprednisolone. Valproate and non-steroidal analgesics had no effect on the headache. The neurological finding were almost normalised with this therapy and rehabilitation within 12 days of the first difficulties, but there was still a persistent impairment in the perceptual part of the intellectual functions. The second attack occured in three months as a hemiplegia and aphasia. Results: The patient was diagnosed with hemiplegic migraine asssociated with ATP1A2 mutation. The gene encodes protein for sodium/potassium-transporting ATPase subunit alpha-2. The same mutation was also found in the patient's father, who had similar problems into early adulthood. In an acute phase, treatment with lacosamide and magnesium sulphate demonstrated a positive effect. Verapamil was chosen as a chronic medication. Since she has been on chronic medication, she did not have another hemiplegic migraine attack for two years. Conclusion: A prominent clinical sign in our patient with ATP1A2 mutation was prolonged cognitive dysfunction. In addition to calcium channel blockers, antiepileptic drugs or betablockers are used in the treatment. The monoclonal antibodies seem to be the promise for the future of migraine therapy in children.

Keywords:
hemiplegic migraine, ATP1A2, cognitive dysfunction

EPNS23-2919 Oral or e-Poster
Miscellaneous

Infantile Neuroaxonal dystrophy case report

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Case study: Infantile neuroaxonal dystrophy (INAD) is a rare neurodegenerative disorder with autosomal recessive inheritance, generally with onset in the first 3 years of life. INAD belongs to the family of phospholipase A2 group 6-associated neurodegeneration (PLAN) related to PLA2G6 gene mutation, with particularly high detection rate (80-90%). Individuals have rapid motor and development delays, cognitive regression, with hypotonia evolving into spasticity. Before the molecular era, diagnostic criteria for INAD, were based on clinical and neurophysiologic findings, but the occurrence of atypical cases, made the diagnosis difficult. The definitive diagnosis, required histological study of the brain. On brain magnetic resonance imaging (MRI) cerebellar cortex atrophy findings made early suspicion of INAD. In 2006, PLA2G6 genetic mapped mutations were identified for the first time. We report a genetic confirmed INAD case, highlighting the key role of MRI diagnostic workup to help decide for PLA2G6 genetic testing.
A 3-years-old male, leucodermic child, with no relevant family or past medical history, presented loss motor skill, he walked at 18 months, but at 2 years started falling, and progressive gait disturbances and difficulty on climbings also evident language delay. On physical examination: obesity, atypical facies, convergent strabismus on the right eye, hypotonia, moderate weakness and hyperreflexia of the lower limbs, with mild hypertonicity, and bilateral Babinski. Presented gower's maneuvers, tip toe and large gait.
No laboratorial changes were found, including metabolic, genetic nuclear mitochondrial study.
Electroencephalogram and electromyogram were unremarkable.
On MRI relevant cerebellar atrophy, and signs of precocious claval or gracile nucleus hypertrophy imaging, highly suggestive of PLAN/INAD. These finding were useful for the differential diagnosis of symmetrical cerebellar atrophy and iron deposits in the basal ganglia. A molecular genetic testing confirmed the diagnosis (heterozygous: c.2032A>G and c.2370T>G pathogenic variants in the PLA2G6 gene).
One year later, he maintains with regular physiotherapy, and clinically progressed to severe axial hypotonia, hypertonia, hyperreflexia of the lower limbs, and loss of walking ability.
Despite no treatment exists, palliative support and physiotherapies can be offered, and genetic diagnosis is promising for reproductive options to young couples.

Keywords:
Infantile neuroaxonal dystrophy, PLA2G6, NBIA, neurodegerative diseases.

EPNS23-2618 Oral or e-Poster
Miscellaneous

A SURVEY ON THE IDENTIFICATION OF THE NEEDS FOR GUIDELINES IN PAEDIATRIC NEUROLOGY (PN)

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Objective: Clinical Practice Guidelines (CPGs) are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. The development of good quality guidelines is a time and resource consuming process requiring a prioritization of the diseases. The aim of this questionnaire was thus to investigate the needs for PN CGPs and to identify the topics of interest for paediatric neurologists and their daily clinical practice.

Methods: An online Google form was created by the authors and endorsed by the two scientific committees co-authoring the abstract. The link to the survey was distributed by email to all EPNS members (including all members of the Committee of National Advisors) during April 2022 with regular reminders for completion. A QR code with direct link to the survey was also intermittently displayed on screens during the 14th EPNS Congress (Glasgow, 2022). SPSS 21.0 was used for descriptive statistics.

Results: We have collected 310 answers from 64 countries around the world (84.2% of the respondents practicing in Europe representing 38 countries). More than half (53.9%) of the respondents are senior paediatric neurologists with more than 10 years of clinical experience in the field. The vast majority (96.1%) of the clinicians think that CPGs/official protocols on diagnosis and management in PN are lacking. All of the clinicians look for CPGs on specific conditions in their daily practice: often (60.3%), sometimes (34.8%) or rarely (4.8%). Most of the them use the available guidelines only if they are created/endorsed by an official International/European PN society or by their own country's PN society (81.9% and 50.3% of the respondents accordingly). Regarding the PN areas that CPGs are most lacking, the five topics most chosen by the clinicians (between a pre-defined list of 17 topics) are as follows : movement disorders (61.3%), neurodegenerative and neurometbolics disorders (52.3%) and neuroinflammation/neuroinfection (51.6%), neurovascular disorders (43.9%) & developmental neurology (42.6%).

Conclusions: PN conditions represent a big proportion of the global burden of disease in Europe and worldwide. The need of CPGs in the field is highly recognized even amongst experienced clinicians. CPGs and clinical decision tools created/endorsed by official international/European PN societies are essential for ensuring optimal and equitable healthcare provision, especially in rare and complex PN disorders.

Keywords:
clinical practice guidelines, clinical decision tools, healthcare provision, complex PN disorders

EPNS23-2278 Oral or e-Poster
Miscellaneous

BELATED PHENYLKETONURIA DIAGNOSIS IN A 9-MONTH-OLD INFANT OF AN IMMIGRANT FAMILY WITH WEST SYNDROME: A CASE REPORT

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Objective: Infantile Spasms correspond to 2 - 3,5 infants per 10000 live births and 4,8% are associated with metabolic diseases . West syndrome is reported in up to 12% of phenylketonuria cases. Since phenylketonuria is the most prevalent inborn error of metabolism, newborn screening is applied in most countries.
We present the case of a nine - month old girl, in which West syndrome manifestation preceded the phenylketonuria diagnosis.

Methods: A nine - month old girl, was referred to our clinic because of neurodevelopmental retardation and epileptic spasms. It is important to mention that the child belonged to a family of immigrants originating from a developing country.
According to her parents, at the age of 2 months the child was diagnosed with atopic dermatitis and by the age of 6 months she was started showing signs of developmental delay. After being evaluated in their country of origin, the child was diagnosed with West Syndrome and started treatment with vigabatrin.

Results: When the child was admitted to our clinic, she continued to manifest epileptic spasms and did not meet the corresponding milestones. She was not able to sit independently, she did not follow objects with her gaze and reacted poorly to stimuli. The EEG study that was conducted showed typical hypsarrhythmia. CT scan of the brain was normal, as were the initial serological tests that were performed. The phenylketonuria diagnosis was confirmed by the significantly increased levels of serum phenylalanine.

Conclusions: Although phenylketonuria has been linked to West Syndrome, most of the cases have shown symptoms prior to the diagnosis of their metabolic disease. Studies have shown that early diagnosis and treatment of phenylketonuria could prevent the manifestation of epileptic spasms and the establishment of neurodevelopmental deficits.
The preventive results of early treatment is the main reason why in most countries phenylketonuria is included in newborn screening. There are still a few developing countries, though, where newborn screening is not mandatory. The large immigration waves of the recent years and the population shifts they cause, could be the reason why undiagnosed phenylketonuria could exist everywhere.
The case we present, demonstrates the need to expand phenylketonuria screening in newborns worldwide. Until the time that is achieved, physicians everywhere should always consider phenylketonuria as a possible underlying diagnosis.

Keywords:
west syndrome, phenylketonuria, newborn screening

EPNS23-2284 Oral or e-Poster
Miscellaneous

Impact of COVID-19 on health utilisation and services in paediatric neurosciences

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Objective: To evaluate the impact of COVID-19 on paediatric neurosciences services worldwide.

Methods: Systematic literature review (PROSPERO 2022 CRD42022326953) of reports evaluating the impact of COVID-19 on paediatric neuroscience provision (January 2020 - April 2022). Changes compared to a pre-pandemic period were classified as mild (1-39%), moderate (40-69%) or severe (70% or higher).

Results: Of 10473 papers screened, 62 were eligible for inclusion. Reports were from North America (33.8%; 21/62), Europe (30.6%; 19/62), and worldwide (8.1%; 5/62). Epilepsy was the most common area of neuroscience evaluated (48.3%; 30/62) followed by general neurological conditions (17.7%; 11/62), neurodisability (12.9%; 8/62) and neuromuscular conditions (8.1%; 5/62). 19.3% (12/62) of studies reported ethnicity, 17.7% (11/62) social class and 10.0% (6/62) reported both. 14.5% (9/62) studies made direct comparison between health utilisation or health seeking behaviour pre and during the pandemic.
Key themes:-
1. 12.9% (8/62) studies reporting mild (3 studies), moderate (3 studies) or severe (2 studies) reduction of neurological emergency department attendance pre and during pandemic of which 50% (4/8) focused on seizure presentations.
2. 5.0% (3/62) studies reported mild (1 study), moderate (1 study) or severe (1 study) reduction of neurology admissions compared to pre-pandemic period. 5.0% (3/62) were patients or caregiver's experience surveys, reporting moderate impact (45%-52%) with delayed admission or cancellation of appointments.
3. 21.0% (13/62) studies reported on neurology clinic visits of which 7 compared pre-pandemic attendance. There were mild (3 studies), moderate (3 studies) and severe (1 study) reductions in in-person neurology clinic visits.
4. 46.7% (29/62) studies reported upscaling telemedicine. 10.3% (3/29) studies reported on acute presentations following telemedicine. 66.6% (2/3) found no impact on acute presentations but 33.3% (1/3) identified an increase in presentation with status epilepticus. A single study reported the need for in-person follow-up after telemedicine. In-person follow-up were associated with lower income, ethnicity, neuromuscular disorders and developmental delay.

Conclusions: Health utilisation in paediatric neurosciences was moderately to severely impacted by the pandemic. Telemedicine should be systematically evaluated to ensure implementation does not increase inequality in paediatric neuroscience service provision.

Keywords:
COVID-19; Health services utilisation; Paediatric neurosciences; Telemedicine

EPNS23-2850 Oral or e-Poster
Miscellaneous

WERNICKE'S ENCEPHALOPATHY IN 16 YEARS OLD GIRL

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Case study: Objectives:
Wernicke's encephalopathy is a degenerative brain disorder caused by the deficiency of vitamin B1 (thiamine). It is observed in patients with alcohol abuse, prolonged vomiting, dietary deficiencies, eating disorders, and after chemotherapy.
Methods:
The authors present a case of an adolescent girl with Wernicke's encephalopathy.
Results:
16-years old girl with obesity, insulin resistance,
Hashimoto disease, with loss of appetite, chronic vomiting, and loss of weight (about 20 kg) during 3 months before the hospitalization was admitted to the hospital for diagnosis and treatment. Also, she presented with headaches and dizziness. In MRI the edema of the cerebellum was found. The wide diagnostic tests were done and the typical treatment for encephalitis was applied. Despite this, during a few days, the worsening of neurological status was observed (quadriplegia, disturbances of consciousness, seizures) was observed and the progression of changes in MRI (edema of the brain) was described. The intravenous treatment with thiamine was administered and the improvement of the clinical status and regression of the brain changes in MRI scans have been obtained.
Conclusions:
In case of severe encephalitis symptoms with previously observed chronic vomiting and/or loss of appetite and with no improvement after the typical treatment the deficiency of B1 vitamin should be considered.

Keywords:
encephalopathy, thiamine

EPNS23-2249 Oral
Miscellaneous

Amantadine drug therapy for pediatric neurologic disorders: The experience in a pediatric rehabilitation center

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Objective: To assess the effectiveness, feasibility, and compliance of Amantadine treatment in pediatric patients who present with one of the following clinical symptoms: refractory seizures, movement disorder, attention disorder, behavioral regulation disorder or altered conscious state, within the setting of a pediatric rehabilitation hospital.

Methods: A retrospective study, including 61 patients - 36 males (59%) and 25 females (41%), 1.7 to 17.9 years old, who were prescribed with Amantadine. Retrospective data (Demographic, clinical, and radiologic) was retrieved from the patient's medical records, in addition - a designated questionnaire was filled by the patient's parents regarding their subjective and retrospective evaluation of treatment effectiveness.
Descriptive statistics and fisher exact test were used for analysis, p-value less then 0.05 was considered significant.

Results: Treatment compliance was observed in 87% (53) of the patients. Mild to moderate adverse side effects (ASE) were reported by 55% (29) of the patients. 61% (32) of the patients manifested improvement in at least one target symptom. The degree of improvement reported for different symptoms: altered consciousness states - 71%, seizures - 60%, movement and behavioral disorders - 50%, balance disorders - 38% and attention disorders - 37%. A significant association (p=0.02) was found between renewal or continued use of Amantadine treatment and improvement in target symptoms: among the 13 patients who renewed or continued amantadine treatment, improvement was observed in 92% (12).

Conclusions: These results provide important evidence demonstrating that amantadine may be effective in the treatment of a range of pediatric neurological disorders, especially in cases of refractory convulsions and behavioral disorders. Amantadine's adverse side effects are relatively mild. Further investigation is needed to confirm the effectiveness and safety of amantadine and define new biomarkers for treatment specification and
precision to determine which patients are the best candidates for this drug therapy.

Keywords:
Amantadine, seizures, dyskinesia, behavioral dysregulation, pediatric rehabilitation

EPNS23-2644 Oral or e-Poster
Miscellaneous

Video Diagnostics in Neurological, Muscle and Neurodevelopmental Disorders: A Multicentre, International Test of Change Project

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Objective: To describe the design, development and results of an international project evaluating the utility of carer-recorded smartphone video in neurological disease and neurodevelopmental disorder diagnosis and management. Test of change projects included epilepsy, movement disorders, muscle disease, autism, speech & language therapy, physiotherapy, orthotics and high-risk neonatal follow up.

Methods: Technology facilitating a secure carer/patient recorded smartphone video transfer classification was supported by government funding in the Covid-19 pandemic primarily to support epilepsy and paroxysmal disorder diagnosis. Subsequently funding for a further 18 test of change pilots was awarded. International projects were funded locally. Projects in low resource settings were supported without cost by the technology provider. Each service, in collaboration with user groups, determined disorder specific metadata uploaded by carers/patients with the video, the pathway for analysis and the clinician's classification system following video review. Clinicians designing pathways included neurologists, physiotherapists, speech therapists (SLT), neuro-developmentalists and psychiatrists. Pathways were developed to aid diagnosis, triage and management. Test of change evaluations including electronic questionnaires for carers and clinicians were embedded in pathways allowing qualitative and health economic evaluation.

Results: 23,976 videos uploaded by 9042 patients to 64 services with 1052 participating clinicians. Services include paediatric neurology (25), mental health & autism (4), high-risk neonatal follow up (16) speech & language therapy (5), specialist neuromuscular (1), orthotics (1). Patients recruited and videos uploaded include: paediatric neurology - 5787 / 17,650, mental health & autism - 139 / 384, neonatal follow up - 677 / 1563, SLT - 856 / 1901. Selected survey results: SLT saved face to face appointment in 73% of cases and 76% therapists felt the video aided clinical decision making. In paediatric neurology 90% of videos led to reduced waiting times and 93% were helpful in making a diagnosis. 20% patients / carers did not miss a day off school or work. Themes of improved access, reassurance & empowerment emerged in free text questionnaire analysis.

Conclusions: Carer-recorded video can aid diagnosis and management in a variety of neurological and neurodevelopmental disorders. Bespoke clinician-designed systems and pathways facilitate engagement and rapid uptake by clinical services.

Keywords:
Video, technology, diagnosis

EPNS23-2549 Oral
Miscellaneous

Neurological Problems of Patients Followed Up in the Palliative Care Unit

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Objective: Due to advances in neonatal and pediatric intensive care, infant mortality rates have dropped significantly all over the world. The number of children living with chronic diseases is increasing. Many of these children do not suffer from cancer, but from syndromes and neurometabolic diseases. Pediatric palliative care (PPC) is necessary to manage the severe symptoms of these patients and to ensure the participation and well-being of the whole family. Up to 40% of patients cared for by PPC teams have severe neurological impairment. Children with neurological disorders often have complex care coordination and symptom management needs. We are monitoring the patients who applied to our unit prospectively for 1 year with our ongoing study. The underlying diagnoses, medications, symptoms, physical examinations and neurological examinations of the patients will be evaluated with the 0., 6. and 12-months examinations. In this one-year period, we aim to determine the change in the consciousness of the patients and the status of their neurological symptoms.

Methods: All patients who were followed up in our PPC unit between 15.09.2022 and 15.12.2022 were included. These patients will be followed up prospectively for 1 year if death does not occur. The initial assessment was considered G0, then patients will be reassessed at 6, and 12 months. Demographic data of the patient (age, gender, nationality, diagnosis of the disease, date of admission to PPC), current medications, nutritional status, medical devices used, current physical examination, will be retrieved. The patient's current consciousness status will be evaluated using the Glasgow coma scale, AVPU and Consciousness Level Scale for Palliative Care. The patient's neurological drugs, the patient's sleep pattern, neurological examination will be retrieved in detail. The patient's examination (conscious, minimally conscious state, persistent vegetative state, complete unresponsive state) will be evaluated.

Results: We included 32 children in the Month 0 assessment. Twenty-four of these patients had primary neurological and 8 had metabolic disease. Detailed evaluations and statistical analysis of the patients are ongoing

Conclusions: : In this study, the neurological status and symptoms of the patients followed in the PPC unit will be examined. We aim to better control the neurological symptoms of these patients. To the best of our interest, our study is the first study that examine the neurological status of the patients who are undergoing PPC.

Keywords:
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EPNS23-2831 Oral or e-Poster
Miscellaneous

TO STUDY THE PREVALENCE OF LEARNING PROBLEMS IN CHILDREN WITH EPILEPSY

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Objective: Primary: To study the prevalence of learning problems in children with epilepsy.
Secondary: To co-relate the occurrence of the learning problems in epilepsy with factors such as anti-epileptic drugs, duration of epilepsy, dosage of drugs, age and gender, primary diagnosis and socio-economic status.

Methods: Children with epilepsy who presented in OPD were enrolled. Epilepsy and demographic details were noted on a predesigned pro forma.
For purpose of assessment of school performance over the last one year, the most recent examination marks and marks of final exams of the previous year were noted in aggregates and school attendance was procured.
Audio and visual screening was done and the socioeconomic status of the family was noted. IQ assessment was done by Seguin form board test. Behaviour, emotional and psychological problems were assessed by Strengths and Difficulties Questionnaire.
Children with poor school attendance and falling grades were considered as children with learning problems.

Results: Of the 90 children enrolled, 66.6% of children had generalized seizures while 33.3% had focal seizures, dosage of antiepiletic's was changed in 13.3%, 7% required additional AED, 38% of children had poor seizure control , 64.4% had abnormal EEG findings, 34% had abnormal MRI findings, Sleep problems were seen in 32%,IQ assessment showed 28.8 % had IQ levels below average. On SDQ scale 22.2% had emotional, 14.4% had conduct problems, 14.4% were hyperactive, 18.8% had peer problems and 16.6% were not pro social. Overall 14.4% children had difficulty detected with SDQ screening score. All these correlates were studied and it was seen in this study that 44 children out of the 90 children enrolled with epilepsy were found to have learning problems. The prevalence came out be 48.8%. Poor seizure control, low socioeconomic status, poly drug therapy , anti epileptic (Clobazam) , change in dosage were statistically significant and likely co relates of learning problems.

Conclusions: During this study it was concluded that learning problems are prevalent in children with epilepsy. The like correlates of these problems were studied and children with learning problems were compared with controls from the same study. This study recommends the regular screening of children with epilepsy for development of learning problems and early rehabilitation and likely cause should be resolved.

Keywords:
Epilepsy, Learning problems, children

EPNS23-2071 Oral or e-Poster
Miscellaneous

Bumetanide, a Diuretic That Can Help Children with Autism Spectrum Disorder

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Objective: Background: Autism Spectrum Disorder (ASD) is a common child neurobehavioral disorder, which pathogenesis is not completely understood. Until now, there is no proven treatment for the core symptoms of ASD. However, some evidence indicates a crucial link between this disorder and GABAergic signals which are altered in ASD. Bumetanide is a diuretic that reduces chloride, shifts gamma-amino-butyric acid (GABA) from excitation to inhibition, and may play a significant role in the treatment of ASD.
Objective: To assess the safety and efficacy of bumetanide as a treatment for ASD.

Methods: Methods: Eighty children, aged 3-12 years, with ASD diagnosed by Childhood Autism Rating Scale (CARS), ⩾30 were included in this double-blind, randomized, and controlled study. Group 1 received Bumetanide, Group 2 received placebo for 6 months. Follow-up by CARS rating scale was performed before and after 1, 3, and 6 months of treatment.

Results: Results: The use of bumetanide in group 1 improved the core symptoms of ASD in a shorter time with minimal and tolerable adverse effects. There was a statistically significant decrease in CARS and most of its fifteen items in group 1 versus group 2 after six months of treatment (p-value <0.001).

Conclusions: Conclusion: Bumetanide has an important role in the treatment of core symptoms of ASD.

Keywords:
Keywords: ASD (Autism Spectrum Disorder), CARS (Childhood Autism Rating Scale), GABA(Gamma -amino-butyric acid), Bumetanide.

EPNS23-2432 Oral or e-Poster
Miscellaneous

Value of diagnostic evaluations in school-aged children with syncopal symptoms

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Objective: Syncope and presyncope are common chief complaints in pediatric neurologic clinics or emergency rooms. We investigate clinical characteristics associated with syncopal falls and diagnostic values of diagnostic tools in neuropediatric clinics.

Methods: We collected retrospectively the pediatric patients (age range 6-18) who first visited a pediatric neurology clinic or emergency room with a chief complaint of syncope or presyncope from July 2020 to July 2022 in a single center. We excluded patients who had underlying diseases, including epilepsy, psychiatric disorders, and cardiac diseases, and who were under severe dehydration or medication overuse.

Results: We classified 89 patients into three groups. The orthostatic intolerance group (89%) was the major group, consisting of 64 vasovagal syncope (64 patients), postural orthostatic tachycardia syndrome (10 patients), and orthostatic hypotension (5 patients). The cardiac arrhythmia-related syncope included 3 patients (3%), and the other group, including seizure, hyperventilation, or somatization disorder, included 7 patients (8%). Sixty-one patients (68.5%) reported trigger factors causing syncope and presyncope. The orthostatic position was the most common trigger factor, followed by emotional stress, pain, and bathing. Significant prodromal symptoms before presyncope/syncope were dizziness, visual change, and unsteadiness. The diagnostic tools showing high diagnostic yield were tilt table test, electrocardiogram, electroencephalogram, and hemoglobin/ferritin.

Conclusions: An initial impression in the clinic based on the history taking, including triggering factors and prodromal symptoms, is important for selecting of the primary diagnostic tools reaching an accurate diagnosis, and providing proper management.

Keywords:
presyncope, pediatric, vasovagal syncope, orthostatic hypotension, postural orthostatic tachycardia syndrome

EPNS23-2146 Oral or e-Poster
Miscellaneous

Long-term Efficacy of Velmanase Alfa in Patients With Alpha-Mannosidosis: Retrospective Analysis of a French Registry for up to 9.5 Years

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Objective: Alpha-mannosidosis is a rare lysosomal storage disorder caused by deficient alpha-mannosidase activity. Clinical presentations include skeletal abnormalities, hearing impairment, and recurrent infections. Velmanase alfa is a recombinant human alpha-mannosidase replacement therapy approved in Europe for alpha-mannosidosis treatment. The longest trial with velmanase alfa occurred over a mean of 2.4 years in the rhLAMAN-10 study and demonstrated improvements in patient mobility and serum oligosaccharides. To evaluate long-term efficacy of velmanase alfa in patients from France with alpha-mannosidosis, a retrospective 9.5-year registry analysis was performed.

Methods: Velmanase alfa was administered in accordance with the summary of product characteristics and usual clinical practice, as authorized by the EMA. Efficacy measures (biochemical, mobility, pulmonary function) were collected from 2010 to June 2020.

Results: This analysis included 16 patients-8 in clinical trials and 8 under temporary utilization authorization; mean age, 26 years (range: 10-52y; 69% >18y); 9 (56%) were male. Mean velmanase alfa treatment duration was 54 months (range: 13-114 months). There was a mean change in serum oligosaccharides of -78.5% at the last evaluation vs baseline. Mean serum IgG levels were increased at the last evaluation (10.99 g/L) vs baseline (7.98 g/L). In 11 evaluable patients, mobility was improved at the last evaluation vs baseline: mean 3-Minute Stair-Climb Test (3MSCT) was 182 steps vs 163 steps at baseline (n=4 improved, n=3 stable) and mean 6-Minute Walk Test (6MWT) was 411m vs 395m at baseline (n=6 improved, n=3 stable). A small percentage of patients declined (3MSCT, n=4; 6MWT, n=2). Overall, pulmonary function (forced vital capacity, forced expiratory volume in 1 second, and peak expiratory flow) improved ~45.5% from baseline.

Conclusions: Although the sample size is small, improvements in biochemical measures and pulmonary function were seen in all evaluable patients, whereas improvements or stabilization in mobility assessments were observed in most. These findings suggest that long-term treatment with velmanase alfa can improve symptoms or stabilize alpha-mannosidosis in most patients in key clinical outcomes.

Keywords:
Alpha-mannosidosis, lysosomal storage disorder, velmanase alfa, enzyme replacement therapy, registry

EPNS23-2402 Oral or e-Poster
Miscellaneous

Development of a patient-led, physician-supported foundation for the care of a developmental and epileptic encephalopathy in Latin America: The Syngap1 experience

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Objective: Global access to targeted genetics has increased the diagnosis of developmental and epileptic encephalopathies (DEEs). Low and middle-income countries (LMICs) have seen emerging patient groups seeking access to specialized care. Syngap1 is a highly prevalent DEE. The first known Latin American (LatAm) case was identified in 2017 in Argentina. Since, the identification of several dozen patients broadened interest and awareness among families/medical community. We describe the development of The Fondo de Investigacion Syngap LATAM (FIS), including patient support/advocacy, education, clinical development, and research initiatives over its first 3 years.

Methods: FIS was developed in 2020 as an affiliate to Syngap Research Fund, a nonprofit founded in 2018 in California. FIS supports families across the region, raising awareness and promoting genetic testing to identify those affected. FIS also provides education and support to families/clinicians in Spanish. FIS has established a regional scientific/medical advisory board of families and local, Spanish-speaking clinicians and scientists. Administrative/legal status in select countries has been pursued, as have collaborations with clinicians and institutions across LatAm, Spain, and the US.

Results: FIS has united patients/families across 6 countries. One clinical site has been established for dedicated care in Colombia. FIS clinicians have presented information on Syngap1 in 2 regional meetings. A 1st Spanish-speaking Syngap scientific congress was held virtually in February 2021, with 450 clinicians and scientists attending, and 11 panelists from 6 countries. Other activities include: family webinars (10). Monthly family zoom meetups (since June 2020); in-person family meetups (1, Colombia, 2022). Family video testimonials (website, YouTube). A 2nd Spanish-speaking congress is due to be held in 2023, as is another Colombian family meetup.

Conclusions: The FIS experience demonstrates collaborative patient/families-clinicians-scientists work around a single DEE, capitalizing on a common language and digital resources. Despite growing visibility and access, significant limitations in local access to care (including funding of clinical sites), and support/access to research, remain. Multiple logistical/legal barriers are identified. FIS' programmatic outlook includes continued creation and access to educational resources, focusing on raising awareness, early identification, comprehensive treatment, and future access to research.

Keywords:
syngap; syngap1; developmental and epileptic encephalopathies; global health; neurogenetics; genetics; low and middle income countries; LMICs; latin america; latam

EPNS23-2211 Oral or e-Poster
Miscellaneous

Baseline Characteristics of a Real-World Population With Alpha-Mannosidosis: Insights From the SPARKLE Registry

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Objective: Alpha-mannosidosis is an ultra-rare disorder caused by lysosomal alpha-mannosidase deficiency, with an estimated prevalence of 1:500,000. Clinical presentations vary and include recurrent infections, hearing impairment, facial dysmorphism, cognitive impairment, impaired speech, skeletal abnormalities, diminished motor function, ataxia, and psychiatric symptoms. The rarity of this disease and the heterogeneity of the clinical symptoms of alpha-mannosidosis often lead to delayed diagnosis, hindering timely treatment. Velmanase alfa is a recombinant human alpha-mannosidase, intravenously administered, enzyme replacement therapy authorized to treat alpha-mannosidosis in Europe. This study evaluated baseline characteristics, genetics, and enzymatic activity of patients enrolled in the SPARKLE (EUPAS29038) registry.

Methods: SPARKLE, which started December 10, 2019, will follow up to 100 patients with alpha-mannosidosis with or without velmanase alfa treatment for ≤ 15 years. Descriptive analysis of baseline characteristics of all currently enrolled patients are reported. As of September 16, 2022, 59 patients with a mean ± standard deviation (SD) age of 21.9 ± 12.2 (median 20.0 [3.0-51.0]) years were enrolled at 23 European sites.

Results: Mean ± SD age at first alpha-mannosidosis manifestation and age at diagnosis were 1.9 ± 3.3 (median 1.0 [0-15]) and 8.4 ± 10.5 (median 4.0 [0-50]) years, respectively, revealing a mean 6.5-year delay in diagnosis. Genetic information was available for 46 patients (78.0%), including 22 patients with homozygous variants, 20 patients with compound heterozygous variants, and 4 patients with only 1 reported pathogenic variant. The most frequent variant was c.2248C>T (30.5% of patients; heterozygous n=10; homozygous n=5; unknown n=3). Of 22 participants with relative alpha-mannosidase activity data, 20 had <5% relative alpha-mannosidase activity, 1 had 8.1% relative activity and 1 had 11.3% residual, relative activity. The most common symptoms were related to cognitive disabilities, hearing impairment, and dysmorphic facial features.

Conclusions: A 6.5-year window from first alpha-mannosidosis manifestation to diagnosis indicates a need for improved awareness of alpha-mannosidosis signs and symptoms. Genetic results are consistent with the most frequently reported variant (c.2248C>T) in the literature. SPARKLE will provide new insights into natural history and disease progression of alpha-mannosidosis, as well as long-term velmanase alfa safety and effectiveness.

Keywords:
Alpha-mannosidosis, lysosomal storage disorder, velmanase alfa, enzyme replacement therapy, registry, genetic variant, enzyme activity

EPNS23-2907 Oral or e-Poster
Miscellaneous

The Knowledge of Mothers About Child Development

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Objective: Development is a process which begins at birth and continues until adolescence. The first 2 years hold an important place in this process. Developmental stages can be evaluated in 4 main aspects, including fine motor and gross motor skills, language development and personal-social development. Developmental delays can be observed in one or more than one aspect of developmental steps. These delays in childhood are seen at a rate of 1-15%. Early detection of these developmental delays warrants better outcomes. Studies on mothers knowledge is various and inadequate knowledge had been shown within the literature. The aim of the present study was to asses knowledge of mothers about developmental steps in children for previously mentioned 4 main aspects.

Methods: The number of participants was 218. They were asked about developmental steps in children in fine motor, gross motor, linguistic and social developmental steps. The questionnaire involved questions about 8 domains in social, 6 domains in fine motor, 8 domains in linguistic and 7 domains in gross motor development obtained from Denver 2 test. Additionally demographic data obtained. Questionnaires were collected via Google Forms and face to face with print-outs. SPSS 26.0 used for analysis.

Results: Among 218 participants most of the mothers were aged between 35-44 (39.4%). Most of the mothers had 2 children (44.4%). More than half of the participants' education level was university or above (70.6%). Stay-at-home wives were 44% of the participants. Most common type of access to information was the internet (33.9%). The mean of correct answers were 9.4 ±3.4. Mostly fine motor skills had been known. Mothers who had more than 2 children had better knowledge on language development when compared to mothers with single child (p:0.038). No correlation about knowledge and age, educational status, working status, source of information and occupation had been demonstrated.

Conclusions: In conclusion, with increasing number of children the knowledge about linguistic development increases. The educational status did not correlate with knowledge about child development within this study and the overall scores were low. It can be postulated that higher educational status about one topic does not necessarily correlate with knowledge about child development. Increasing awareness is important for all mothers including the ones with higher educational level. Additionally participants received correct answers that served for public education.

Keywords:
development, denver 2, mothers knowledge, developmental delay

EPNS23-2503 Oral or e-Poster
Miscellaneous

Influence of vitamin D on presentation of headaches in children and adolescents

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Objective: Primary headache is a common diagnose in the pediatric population. Vitamin D deficiency is common in the Slovenian population. Vitamin D has an impact on many functions and can worsen headaches.
The aim of this study was to determine the impact of deficiency and replacement of vitamin D on the clinical picture of headache. By replacing vitamin D, the frequency and severity of headaches should decrease. We were interested in whether vitamin D deficiency is related to the season of the year.

Methods: A prospective clinical study, which included all children and adolescents who were examined because of headache for the first time at the Ljubljana Pediatric Clinic during the time of on going research. 87 patients met the inclusion criteria. After informed consent to participate in the study, all participants had the value of vitamin D measured in the serum. In case of vitamin D deficiency, it was medically replaced. After four to five months, we checked changes in headache presentation. In order to evaluate the connection between different variables Mann-Whitney test, Chi-square test of independence and Unconditional exact test were performed. An overall level of significance of $p < 0,05$ was used for all tests.

Results: Vitamin D deficiency was found in 17 patients. We demonstrated the variability of the serum value of the vitamin D depending on the season of the year, with more deficiency during the winter. Vitamin D deficiency was not associated with a higher frequency of headaches at the first treatment (Mann-Whitney U test, $p=0.296$), neither with a higher severity of migraine attacks (Chi-square test of independence, $p=0.770$). It was interesting to note that patients with serum vitamin D deficiency had a greater intensity of tension-type headaches (Unconditional exact test, $p=0.030$). After replacement with vitamin D preparations in 17 patients, the clinical picture of headaches improved: the severity decreased in 88.2 % and the frequency of headaches in 94.1 % out of 17 patients.

Conclusions: Vitamin D deficiency is related to the season of the year. Serum vitamin D deficiency is not associated with higher frequency of headaches or greater severity of migraine attacks but is associated with greater severity of tension-type headaches. By replacing vitamin D, the frequency and severity of headaches was reduced.

Keywords:
vitamin D deficiency, headache, pediatric/children and adolescents

EPNS23-2369 Oral or e-Poster
Miscellaneous

Family led care and advocacy for Developmental and Epileptic Encephalopathies in Latin America: A survey of the virtual landscape

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Objective: The diagnosis of Developmental and Epileptic Encephalopathies (DEEs) has greatly increased worldwide over the past decade. Etiologic diagnosis has led to growing condition-specific care and advocacy, often led by families of those affected. While this has facilitated access to care and research in high-income countries (HICs), differences with low and middle-income countries (LMICs) have accentuated significantly. The Latin America region (LatAm) offers an example of such growing access and disparities vis-à-vis the United States and Europe, and even within the region. The goal of this study is to understand the current state of patient-led advocacy in LatAm, available resources and possible areas of future work and partnership.

Methods: A convenience sample of 12 DEEs was selected, based on general awareness and prevalence. A systematic query was conducted across select web and social media platforms (google, facebook, Instagram) to identify patient/advocacy groups in 18 predominantly Spanish-speaking countries in LatAm. Within, we collected information on advocacy, support, education, research, and clinical access, based on group models of these conditions existing in the US/Europe. Descriptive statistics and basic analyses were conducted.

Results: 12 identified DEEs (Rett, Angelman, Dravet, Tuberous Sclerosis, Syngap1, CDKL5, STXPB1, Lennox-Gastaut, Doose, SCN2A, SCN8A, West syndrome) were studied. A total of 67 online groups were identified; 64 of which had publicly available information. All groups had available data on family support/education; however, only a minority (19%) had healthcare provider education information. Strikingly, only 9% had available professional advisory council information, and fewer than 5% shared data on disease-specific local/regional clinics or research endeavors.

Conclusions: While there is increasing identification of DEEs in different regions, the approach and opportunities for grassroots advocacy, clinical, and research support, are very asymmetric. Endeavors in LatAm have been largely informal. Few examples of more structured groups have allowed for regional conferences and identification of scientific and medical advisory boards, essential for progress in clinical care and opening the region for research. This presents an opportunity for development, with support from HICs and structured groups in LMICs, taking advantage of the cultural, linguistic and socioeconomic similarities across the region.

Keywords:
global health; latin america; developmental and epileptic encephalopathies; low and middle income countries; LMICs; virtual

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