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Diagnostic Approach to Children with Unexplained Global Developmental Delay in Pediatric Neurology Outpatient Clinic

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Abstract

Background Global developmental delay (GDD) is a common pediatric disorder that affects up to 3% of children. Due to the heterogeneous etiology of GDD, diagnostic procedures and algorithms are complex and diverse. The aim of our study was to investigate the diagnostic yield of genetic, metabolic, and imaging studies in establishing the etiology of unexplained GDD (UGDD).

Methods In this retrospectively observational study, we examined the medical records of all children diagnosed with UGDD at the Department of Pediatric Neurology, University Medical Centre Ljubljana, Slovenia, between January and December 2019. We evaluated the effectiveness of various genetic, metabolic, and magnetic resonance imaging (MRI) tests in identifying the underlying cause of GDD. Additionally, we assessed subgroups of patients to determine whether any of the studied tests were particularly beneficial based on their clinical symptoms.

Results A total of 123 patients met the inclusion criteria, with a median age of 4.3 years (range, 0–16 years), of which 71 (57.7%) were males. Genetic diagnosis was established in 47.1% (58/123) of patients. Metabolic laboratory testing did not identify a metabolic disease in any of the tested participants (114/123) and MRI was critical for diagnosis in only 1/81 (1.2%) patient.

Conclusion Our findings strongly suggest that genetic testing surpasses MRI and metabolic testing in establishing the etiology of UGDD in a pediatric neurology outpatient setting. This information will help guide the diagnostic evaluation of these children.

Keywords
- unexplained global developmental delay
- diagnostic yield
- genetics
- MRI
- metabolic screening

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Introduction

Global developmental delay (GDD) is defined as a significant delay in two or more developmental domains namely gross or fine motor skills, language, cognition, social/personal skills, or activities of daily living. It affects up to 3% of children under the age of 5.[1,2] Many of these children will present with intellectual disabilities (ID) identified in the school years.[3,4] Determining the underlying cause of GDD is crucial, as it enables accurate prognosis, avoidance of unnecessary and costly testing that can be burdensome for the child and family, prevention of complications, initiation of potential causal and supportive treatment, genetic counselling, access to disease-specific family support groups, and evaluation of treatment protocols for research purposes.[4–7] However, due to the heterogeneous etiology of GDD, a universal diagnostic algorithm does not exist, and multiple diagnostic tests are often utilized. Discernible history or clinical features, such as preterm birth, hypoxic-ischemic encephalopathy, asphyxia, congenital infections, exposure to various environmental toxins in utero, head trauma, epileptic encephalopathy, central nervous system (CNS) infections, typical syndromic features, etc. can provide clues to the etiology of GDD.[8] When thorough history and clinical examination fail to identify a probable underlying etiology, the term unexplained GDD (UGDD) is employed. Genetic and metabolic disorders account for the majority of UGDD cases and genetic, metabolic, and radiological tests are commonly applied in the diagnostic evaluation of affected individuals.[1,4,9] The diagnostic yield of these tests in children with GDD has been influenced by the rapid advancements in genetic diagnostic technologies. Due to the previous limitations of available genetic tests and methods, the real contribution of genetics to the GDD etiology was underestimated. While array comparative genomic hybridization (aCGH) is often the initial screening test for GDD due to its high detection rate and cost-effectiveness,[10] a recent meta-analysis has shown that exome sequencing (ES) outperforms aCGH in diagnosing previously unexplained neurodevelopmental disorders.[11]

The primary objective of this study was to determine the diagnostic yield of genetic tests, metabolic tests, and brain magnetic resonance imaging (MRI) in establishing the etiology of UGDD in a cohort of pediatric patients. A secondary objective was to identify subsets of patients in which specific investigations may yield higher diagnostic rates. Based on the new insights, we reassessed the current diagnostic algorithm and proposed an alternative diagnostic approach for children with UGDD in our country, considering the diagnostic yield of the investigated methods and an expanded neonatal metabolic screening.

Methods

The ethical approval of the National Medical Ethics Committee of the Republic of Slovenia (No. 0120-321/2023/6 of October 4, 2023) was obtained for the study.

This retrospective, cross-sectional cohort study included all patients diagnosed with GDD who were treated between January 2019 and December 2019, at the Department of Child, Adolescent and Developmental Neurology, University Medical Centre Ljubljana (UMCL), Slovenia primarily in the outpatient setting. The UMCL serves as a tertiary referral center for children with neurological disorders in Slovenia.

The children with GDD included in this study were primarily referred to our tertiary institution by pediatricians working at outpatient developmental clinics. Despite a thorough history and physical examination, a specific cause of GDD could not be established. Consequently, our cohort represents the second-tier evaluation in a tertiary care pediatric neurology clinic. The hospital's electronic health record system was searched for patients with any of the following diagnoses according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10): R62.0, GDD; R62.8, Other deviation from expected normal physiological development; R62.9, Deviation from expected normal physiological development, unspecified. Assessment of developmental milestones was based on Denver Developmental Screening Test II and/or Bayley Scales of Infant and Toddler Development IIIrd Editon, which was used especially when cognitive delay was suspected. Only children who met GDD criteria were included in the study, even children older than 5 years of age, who met the criteria in the past, according to their medical records. Exclusion criteria were all conditions that could potentially contribute to acquired causes of GDD, such as epileptic encephalopathy, epilepsy as a key feature, prematurity, congenital infections, hypoxic-ischemic encephalopathy, asphyxia, head trauma, previously detected inborn errors of metabolism (IEM) based on Slovenian neonatal metabolic screening program,[12] CNS infections. Patients with the history of developmental regression and children with autism spectrum disorder as the principal diagnosis were excluded as well. The clinical characteristics and results of diagnostic methods were recorded for each patient.

Genetic analyses were performed at the Clinical Institute of Genomic Medicine and the Centre for Medical Genetics of the University Children's Hospital Ljubljana of UMC Ljubljana and were based on aCGH and ES techniques. The DNA was isolated from peripheral blood samples, according to the manufacturer's protocol using the Qiagen Mini kit (Qiagen, Valencia, California, United States). Following the sample extraction, the DNA was processed according to recommended protocols and as previously described by the group using aCGH and/or ES approach.[13,14] Briefly, the Agilent protocol (Version 7.3 March 2014) was used with commercially available male and female genomic reference DNA and Agilent SurePrint G3 Unrestricted CGH 4×180K microarrays. The array images were acquired using the Agilent laser scanner G2565CA, the image files quantified with Agilent Feature extraction software and analyzed using the Agilent Cytogenomics software (all Agilent Technologies). The genome wide average aCGH resolution was 50 kb, with significantly higher resolution in regions of known microdeletion/microduplication syndromes and in some disease-causing genes. Most of the ES tests were done as singletons, 10% were performed as trio approach. The samples were enriched

using TruSight One, TruSight Exome, and Nextera Coding Exome capture kits by Illumina or Agilent SureSelect Human All Exon v2 and Agilent SureSelect Human All Exon v5 capture kits by Agilent Technologies and sequencing on either Illumina MiSeq or Illumina HiSeq 2500 platforms was employed. Processing of raw sequence files was done by custom exome analysis pipeline and aligned to UCSC hg19 human reference genome as previously described. In the first step in silico panel interpretations were done. The open exome analyses were performed, if panel approach did not establish the diagnosis. Variant filtering and interpretation were performed as previously described[13,14] and according to the current recommendations.[15]

Metabolic screening of blood/urine samples were performed at the Special Laboratory Diagnostics Unit of UMCL. Standard metabolic screening consisted of urine and plasma analyses for complete blood count, blood biochemical tests, liver function tests, lactate, pyruvate, ammonium, homocysteine, uric acid, plasma amino acids, urinary organic acids, acylcarnitine profile, and transferrin glycosylation. Blood and urine samples were collected when the patients were in a stable condition, i.e., outside a metabolic crisis. The results were interpreted by an experienced biochemist specialized in metabolic diseases in collaboration with an expert in the field of pediatric metabolic disorders.

MRI of the head was performed in selected patients with Siemens 1.5-T Avanto or 3.0-T Trio (Siemens Medical, Erlangen, Germany) scanners. The standard MRI protocol included axial T1-weighted images or inversion recovery-weighted images, T2-weighted images and diffusion-weighted images. The custom diffusion sequence consisted of $2 \times 2 \times 2$ mm voxels, 9300-ms repetition time, 96-ms echo time, 1710 Hz/Px and 2 b values, 0 and 1000. Images were interpreted by different pediatric neuroradiologists as normal, abnormal, or equivocal, indicating that the significance of the finding was uncertain and might suggest a normal variant.

A chi-square test of independence was performed to examine the relation between the group of patients with and without dysmorphic features with genetic etiology of GDD. R version (4.2.2) and the following R packages were used for statistical analysis and generation of images: Package "circlize" version 0.4.15, Package "dplyr" version 1.1.2, Package "RColorBrewer" version 1.1–3.

Results

Patients

An initial cohort of 425 pediatric patients diagnosed with developmental delay by a pediatric neurologist was identified. After reviewing their medical data, we excluded 302 patients who met at least one of the predefined exclusion criteria, which indicated a specific cause of GDD. A final number of 123 patients with UGDD were included in the study: 71 males (57.7%) and 52 females (42.3%). The median age at the time of the study was 4.3 years (range, 0–16 years). All patients were diagnosed with developmental delay in at least two domains. The most frequently reported combination was gross motor and language delay (37%), followed by other combinations (►**Fig. 1**).

In our cohort of patients 121 (98.4%) children had speech, 106 (86.2%) gross motor, 59 (48%) cognition, 38 (30.9%) fine motor, and 31 (25.2%) social developmental delay.

At least one dysmorphic feature was detected in 91 (74%) children. Genetic etiology of UGDD was found in 44/91 (48.3%) children with dysmorphic signs, compared with 14/32 (43.7%) children without dysmorphic signs. Using chi-square test, the difference was not significant. The most frequently described dysmorphic signs were frontal

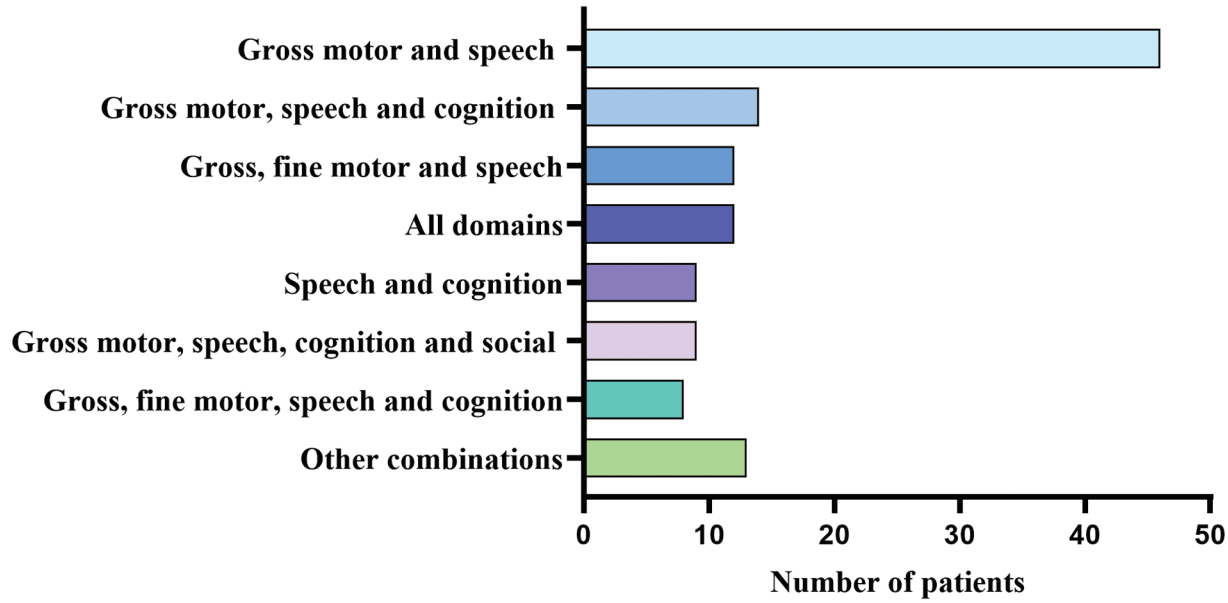

Fig. 1 Patients' affected developmental domains.

bossing, hypertelorism, low set ears, epicanthus, wide nasal bridge.

Genetic Testing

At least one genetic test was performed in all children and a specific diagnosis was obtained through genetic testing for 58/123 (47.1%) children. Several genetic tests were employed in the diagnostic evaluation (►**Fig. 2**).

The initial genetic evaluation typically involved aCGH, which was performed in 113 (91.8%) children. The diagnostic yield of aCGH in establishing the genetic etiology of UGDD was 23.9% among the tested individuals. Overall, aCGH contributed to the final diagnosis in 21.9% of all children included in the study. Pathogenic copy number variations (CNVs) were found in 27/113 (23.9%) children, constituting 23 patients with deletions and 5 patients with duplications. One child presented with both a pathogenic deletion and a duplication (►**Fig. 3**). Additionally, 18 variants of unknown significance (VUS) were found in 16 children.

ES was conducted in 74 participants, typically following a normal result of aCGH. Pathogenic variants were identified in 29/74 (39.2%) children and VUS were found in 15 children. Therefore, the diagnostic yield of ES was 39.2%, and it contributed to the final diagnosis in 23.6% of our cohort. Both aCGH and ES were performed in 66 patients. In one child 1/66 (1.5%), both aCGH and ES yielded positive results. In 11 patients, other genetic tests were performed. One patient was found to have aneuploidy based on karyotyping and fluorescence in situ hybridization analysis. Subtelomere analysis revealed a diagnostic deletion in another child (►**Fig. 2**). Detailed descriptions of the genetic findings for each patient with a pathogenic variant are given in the ►**Supplementary Table S1** (available in the online version only).

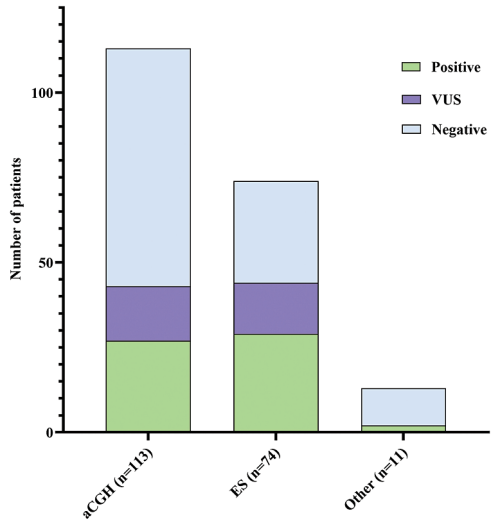

Fig. 2 Number of children with a specific genetic test performed. Number of children with pathogenic variations (green), VUS (violet), and negative results (blue). aCGH, array comparative genomic hybridization; ES, exome sequencing; VUS, variant of unknown significance; Other, subtelomere analyses and karyotype.

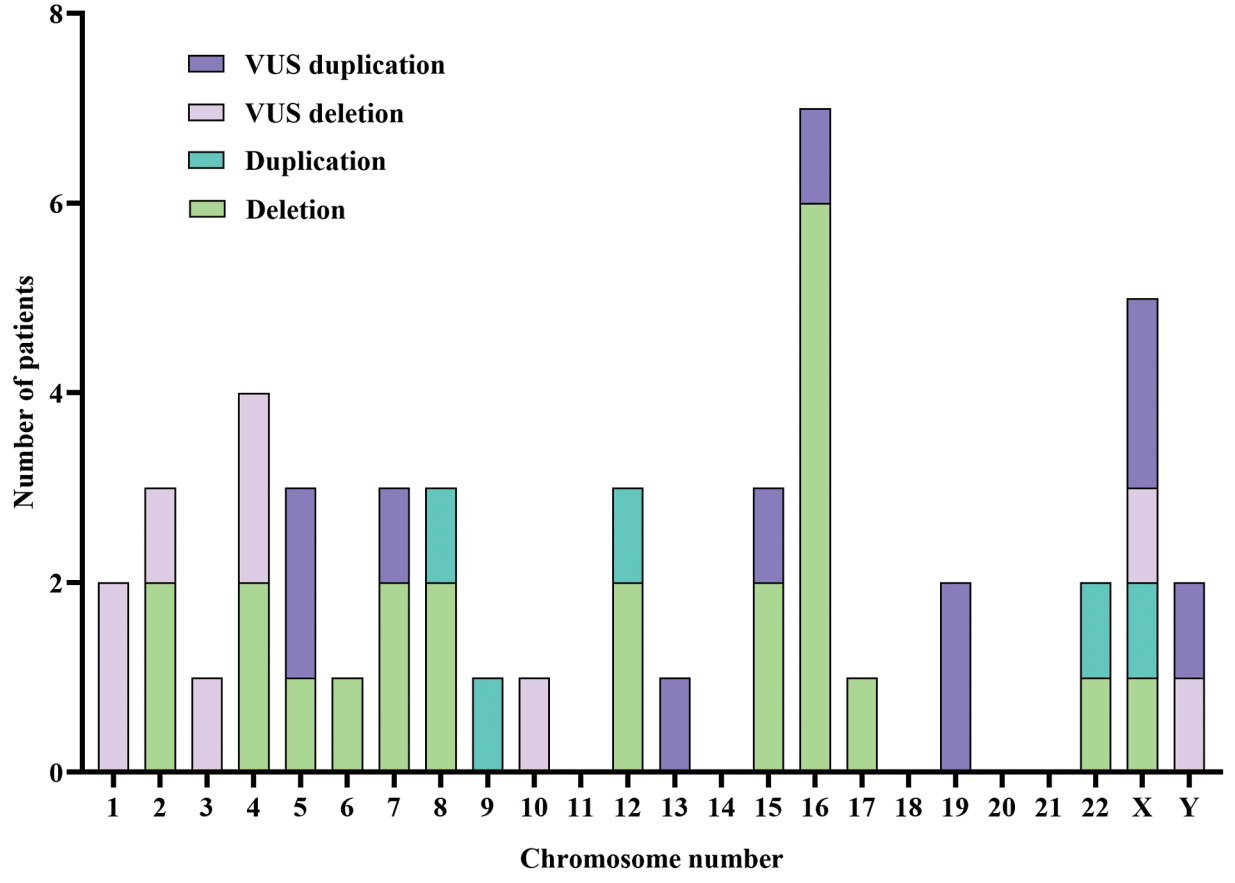

Fig. 3 Chromosomal distribution of deletions and duplications based on aCGH analyses. aCGH, array comparative genomic hybridization.

Metabolic Screening

Metabolic screening was performed as one of the standard diagnostic procedures in 114/123 (92.7%) children and additional specific metabolic tests were performed in 38/114 (33.3%). A total of 25/114 (21.9%) children had enzymatic tests for lysosomal storage disorders; 18/114 (15.8%) had peroxisomal diseases screening; 12/114 (10.5%) had enzymatic tests for Pompe's disease; 8/114 (7%) had biotinidase deficiency tests; 7/114 (6%) had neurotransmitter analysis of cerebrospinal fluid; 3/114 (2.6%) had purines and pyramidines analysis of urine. Metabolic screening did not reveal etiological cause of UGDD in any of the participants.

Brain Imaging

MRI of the head was performed in 81/123 (65.8%) patients. Normal MRI was found in 36/81 (44.4%). Imaging revealed the etiological cause of UGDD in only 1/81 (1.2%) child with a Dandy–Walker spectrum disorder. Structural brain abnormalities were found on MRI in 45/81 (55.5%) of the patients, but the changes were unspecific and did not point to a certain diagnosis in any but one child. White matter (WM) abnormalities, e.g., hypoplastic corpus callosum, dysmyelination, WM hyperintensities, WM atrophy, were the most commonly described pathological findings, followed by cerebellar pathologies such as vermis or cerebellar hemispheres hypoplasia/atrophy and brain stem abnormalities (pons/mesencephalon atrophy). Other findings such as ventriculomegaly and hippocampal malrotation were also noted in a few patients.

Among the patients with abnormal findings on MRI, genetic tests were positive in 30/45 cases (66.7%). Conversely, among patients with positive genetic tests, 30/58 cases (51.7%) exhibited abnormal findings on MRI. Detailed descriptions of MRI findings for each patient with a pathogenic variant are listed in the ►**Supplementary Table S1** (available in the online version only).

Head circumference abnormalities were observed in 22/81 (27%) children who underwent imaging. Among the 15/81 (18.5%) children with microcrania, 9/15 (60%) exhibited abnormalities on MRI. One of these patients was diagnosed with Dandy–Walker spectrum disorder. In the remaining 6/15 (40%) children with microcrania, MRI findings were normal. Macrocrania was present in 7/81 (8.6%) patients who underwent imaging. Among these, 5/7 (71.4%) displayed unspecific abnormal findings on MRI, whereas in the remaining 2/7 (28.5%) children, MRI findings showed normal anatomical variants of persistent cavum verge and septum pellucidum (►**Fig. 4**).

Discussion

The main finding of our study is that in our cohort of patients evaluated at a tertiary care pediatric neurology center, genetic tests were superior to metabolic testing, and MRI in establishing the cause of UGDD. Metabolic screening did not lead to diagnosis in any patient, questioning its historical role as a first-line test in children with UGDD.

Overall, genetic tests combined resulted in establishing a diagnosis of a single gene or a chromosomal abnormality in 47.1% of patients. The diagnostic yield of aCGH in children with UGDD in our pediatric neurology practice was found to

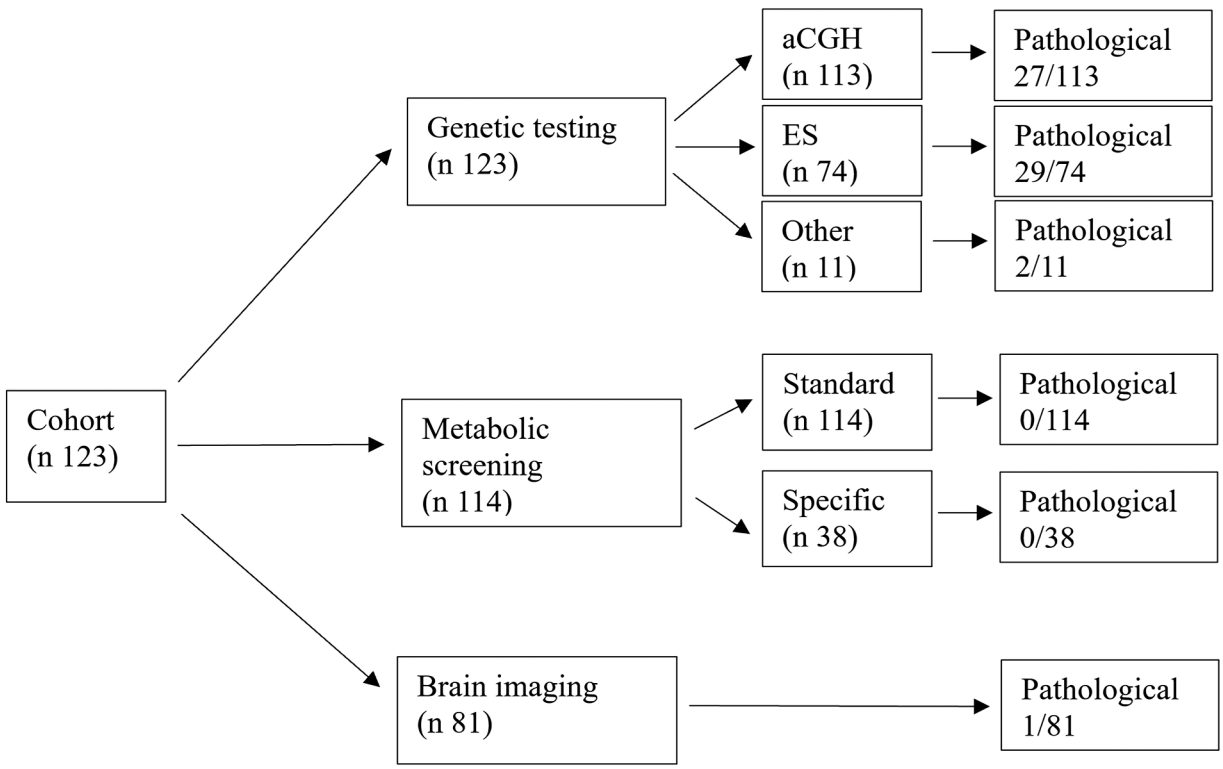

Fig. 4 Flowchart representing the results of performed tests in our cohort. aCGH, array comparative genomic hybridization; ES, exome sequencing; Other, subtelomere analyses and karyotype.

be 21.9%, which falls on the higher end of the reported spectrum in literature.[5,16] The high yield of aCGH in our study may be due to the strict criteria of patient selection used by pediatric neurologists, excluding children with acquired causes of GDD. Variations in patient selection criteria and clinical settings can contribute to differences in diagnostic yields observed across studies. In addition, various aCGH platforms exist and resolution of this method has significantly improved during the past decade.

ES yielded a diagnosis in 39.2% of the tested patients and contributed to the final diagnosis in 23.6% of patients in our cohort. It is worth noting that further genetic testing was only conducted on selected patients, as determined by geneticists. Over the past decade, aCGH has been considered a first-choice genetic test in children with GDD.[1,4,9,17–19] However, a few studies have recently reported that ES consistently outperforms aCGH in evaluating UGDD and even proposed a diagnostic algorithm that places ES at the forefront of the evaluation process for UGDD.[11,19] Although ES demonstrates a higher utility than aCGH, our study suggests that aCGH remains a reasonable first-line genetic test for children with UGDD due to its lower cost, better accessibility, shorter turnaround time, and significant diagnostic yield. However, with the improved accessibility and reduced costs of next-generation sequencing testing, it is possible that sequencing methods will see a wider adoption in the near future.

Additionally, apart from the definitive pathogenic results, aCGH identified VUS in 16 patients, which accounted for 13% of the cohort. Similarly, ES detected VUS in a comparable percentage of patients (12.2%). Although these findings were not considered positive at the time, they might prove so in the future—as our understanding of phenotypes associated with different genetic/chromosomal disorders continues to expand, reanalysis (usually performed at least 2 years after the initial interpretation) could alter the clinical interpretation of VUS. We aimed to identify subgroups of patients in which genetic tests would have a higher yield. The combination of GDD with dysmorphic features and abnormal head circumference was predictive of pathogenic CNV and higher diagnostic yield according to studies by Misra et al and Savatt and Myers.[17,20] However, our results did not confirm the significant difference between two groups. We identified a genetic etiology in 48.3% of children with dysmorphic features, compared with 43.7% in those without dysmorphic features. This finding could be attributed to the specific characteristics of our study cohort, as children were typically assessed by developmental pediatricians before their referral to our clinic. Notably, those children who exhibited dysmorphic signs indicative of specific syndromes were more likely to have been referred directly to clinical geneticists. The majority of children evaluated at our center displayed minor dysmorphic features, such as frontal bossing, hypertelorism, and low-set ears. These dysmorphic signs were primarily documented by child neurologists, who may not possess the same level of expertise as geneticists in identifying such features. Consequently, some children may have been classified as nondysmorphic due to the potential oversight of subtle features.

In our study, children presenting with epileptic encephalopathy or epilepsy during their initial visit to our center were excluded. However, four patients were subsequently diagnosed with epilepsy during annual follow-up visits. Interestingly, all four patients tested positive for genetic abnormalities, leading to the following diagnoses: Rett syndrome, variant in *SYNGAP1* gene, variant in *SEMA6B* gene, and 16q23.2q23.3 deletion (►**Supplementary Table S1**, available in the online version only).

All the children included in our study were examined during prearranged appointments, mainly in an outpatient facility, and none of them were in an acute, decompensated state. This setting primarily caters to patients with a more chronic and indolent course of the disease. This may be one of the reasons why metabolic testing did not identify any patients with metabolic diseases. However, one patient was diagnosed with a metabolic disease through ES (0.8%), which revealed a pathogenic homozygous variant in pyruvate dehydrogenase complex component X (PDHX) gene. Our findings are consistent with a Canadian study conducted by Djordjevic et al, which explored the utility of metabolic screening in childhood neurological diseases. The diagnosis of IEM through metabolic screening was only made in children who presented with acute neurological signs, such as encephalopathy, persistent seizures, etc. during metabolic crises. They concluded that the yield of metabolic screening tests in infants with hypotonia and/or developmental delay outside the context of clinical decompensation or multisystem involvement is exceedingly low, approaching zero. Additionally, whole-exome sequencing, microarray, or genetic panel testing identified IEM in 6/53 (11%) outpatients that had been missed by screening in the metabolic laboratory.[21] These findings contradict numerous recommendations that still consider metabolic screening tests as a first-line approach for evaluating children with GDD.[1,2,9] The primary argument in favor of routine metabolic screening for treatable IEM is the availability of targeted treatments or disease-modifying agents that can significantly alter the disease course. However, with the expansion of metabolic screening for newborns in economically privileged countries and the increased accessibility of genetic testing, diagnostic algorithms for children with GDD are likely to change. A reasonable approach would be to adapt diagnostic algorithms to the specifics of each country. In Slovenia, the current panel for newborn screening includes 18 metabolic diseases.[12] Considering the aforementioned arguments and our own results, we recommend metabolic screening in children with UGDD only if they present with an acute deterioration, involvement of multiple organ systems, or exhibit typical features suggestive of a metabolic disease.

The role of neuroradiological studies in the etiologic diagnosis of GDD has undergone significant changes, with genetic testing now taking the lead in terms of efficacy and priority. MRI has replaced computed tomography as the preferred imaging modality due to its higher sensitivity in

detecting CNS abnormalities and a better safety profile. The rate of abnormalities detected by MRI ranges from 6 to 48% and is more commonly observed in children with profound ID, abnormal head circumference, or focal neurological signs.[7,22,23] According to the comprehensive clinical report and guidelines from the American Academy of Pediatrics, approximately 30% of children with GDD/ID exhibit abnormal findings on MRI, but these findings are typically nonspecific and only contribute to understanding the etiology of GDD/ID in a small percentage of cases (0.2–2.2%).[18] Our findings are consistent with this observation, as MRI played a crucial role in the diagnosis of only one patient in our cohort. Nevertheless, none of our patients exhibited focal neurological signs. Nonspecific abnormalities on structural MRI were observed in 45/81 (55.5%) of the children, WM abnormalities being the most common. However, these MRI findings did not provide insights into the underlying etiology of GDD in these patients.

In published guidelines for the evaluation of children with GDD, it is suggested that MRI of the brain should be performed when microcephaly, macrocephaly, or abnormal findings on neurological examination (focal motor findings, pyramidal signs, extrapyramidal signs), intractable epilepsy, or focal seizures are present.[1,18] Our findings support this recommendation, as we found limited diagnostic benefit from MRI in children without specific neurological signs.

This study has several limitations. It is retrospective in nature, relying on data collected from the hospital's electronic health record system, inevitably leading to recall and selection biases. Some participants were examined solely by child neurologists, indicating that geneticists were not involved in the diagnostic process. This could potentially lead to variations in the genetic methods employed. Unfortunately, we were unable to assess how the severity of the delay might have impacted the yield of the tests, primarily due to the lack of standardized psychological evaluations at the initial clinic visit.

When interpreting our results, it is crucial to consider various factors rather than generalizing our conclusions to all children with GDD. Our cohort is unique, representing children with UGDD evaluated by child neurologist after excluding acquired causes of GDD. Furthermore, as neonatal screening for IEM is standard practice in Slovenia, our proposed algorithm for investigations may not be directly applicable to countries without comprehensive newborn screening programs.

Conclusion

Our findings strongly suggest that genetic testing surpasses MRI and metabolic testing in establishing the etiology of UGDD in a pediatric neurology outpatient setting. Additionally, genetic testing can identify IEM in children with UGDD outside of the specific contexts of acute decompensation or an overwhelmingly suggestive clinical picture, where specialized metabolic screening laboratory tests might yield false-negative results.

Note

The work was performed at the Department of Pediatric Neurology, University Children's Hospital, University Medical Centre Ljubljana.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest

None declared.

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