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Neonatal presentations of neuromuscular disorders

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ABSTRACT

The term 'neuromuscular diseases' defines disorders of the extended motor unit. Newborns with disorders of peripheral nervous system (PNS) (motor neurons, nerve roots, plexuses, peripheral nerves, neuromuscular junction, and skeletal muscles) present most frequently with hypotonia, weakness, contractures, respiratory and feeding difficulties.

Challenge in the newborn period is, hypotonia may also occur with more common central causes such as; electrolyte disturbances, sepsis, hypoxic-ischemic encephalopathy (HIE), congestive heart failure, and inborn errors of metabolism. Moreover, newborns with PNS involvement and/or genetic neuromuscular disorders (NMD) can also be prone to intrapartum asphyxia which further masks an underlying condition. This is why, NMD is also described as one of the 'HIE-mimics'.

Genetic counseling, individualized treatment strategies, standards of care require accurate diagnosis. Neuromuscular field is moving to screening programs and pre-symptomatic diagnosis with promising disease-modifying treatments. The aim of this paper is to discuss approach to NMD within the newborn period in line with clinical history, examination findings, and diagnostic tests.

1. Introduction

Neuromuscular disorders (NMD) in the newborn period present significant diagnostic and therapeutic challenges for neonatologists and pediatric neurologists. Considering normal evolution of muscle tone with gestational age and the limited repertoire of newborns, hypotonia and weakness being the most common presentations of NMD in the newborn period, require evaluation of an extensive differential diagnostic list. As in other age groups, a structured approach including history, family history and pedigree, presenting symptoms, physical examination findings, skin, dysmorphic features and other organ/system involvement is a critical first-step [1,2]. Anatomic localization of the pathology helps to develop a differential diagnostic list, and use diagnostic tests accurately [3–6]. Central and/or peripheral; acquired and/or genetic etiologies require different routes of evaluation in terms of accurate genetic diagnosis, therapeutic approaches and genetic counseling.

Despite advances in molecular diagnostic modalities and access to next generation sequencing (NGS) technologies, it is very important to recognize the phenotype, since these tests may miss spinal muscular atrophy (SMA), congenital myotonic dystrophy type 1 (DM1), and severe forms of facioscapulohumeral muscular dystrophy (FSHD) [5–7]. On the other hand, 'time matters' in terms of response to disease modifying treatments and early interventions, as in the case of SMA and Pompe disease [8,9].

This teaching review aims to discuss approach to early-onset NMD without discussing individual diseases in detail. The reader is referred to elegant and comprehensive book chapters as a complementary tool for further reading [3,4,10,11].

2. History and physical examination

The most common presentations of NMD in the newborn period are presented in Fig. 1. Since these features can be present in a variety of systemic, acquired, genetic and inborn errors of metabolism, careful history and examination may help to narrow the differential diagnostic list. The classical scenario 'floppy baby' is challenging for the neonatologist and pediatric neurologist, since hypotonia is a nonspecific sign which does not help for localization [1,4,6,10]. Moreover, intensive care unit environment where most of these babies require ventilatory and feeding support, sedation and/or hypothermia for hypoxic-ischemic insult may further complicate evaluation of neurological features. Considering maternal diseases (diabetes, myasthenia gravis, myotonic dystrophy, epilepsy), drugs, withdrawal, serological testing and infectious exposures, systemic diseases, sepsis, hypoglycemia, fluid/-electrolyte disturbances, hypoxic-ischemic encephalopathy (HIE),

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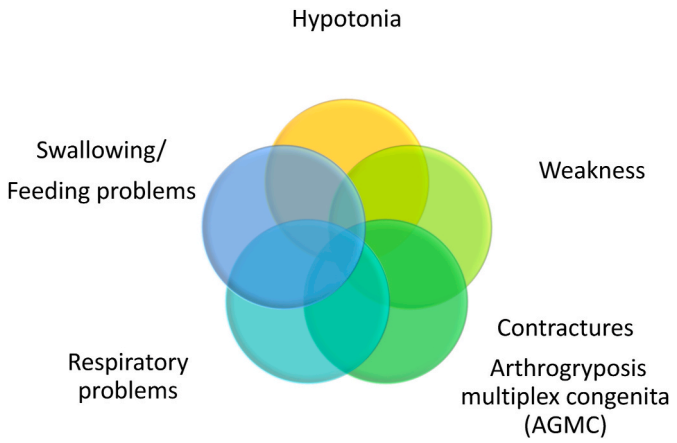

Fig. 1. Common neonatal neuromuscular presentations.

intraventricular hemorrhage, congestive heart failure, hypothyroidism are important, since these conditions require different management [6,12].

Pregnancy, delivery and family history combined with peripartum and early neonatal history serve as an invaluable background before physical and neurological examination (Table 1) [10,11].

Fetal behavior and evolution of embryonic/fetal movements are central for typical development, since skeletal, muscular, and neural developments are activity-dependent [13,14]. Frequency and any change in intrauterine movements (body and respiratory movements, sucking/swallowing) depending on the gestational age may serve to evaluate physical examination correlates in the newborn period [13–15]. Maternal perception of intrauterine movements and comparison with the previous pregnancies should be questioned. Anything that interferes with and/or limits normal intrauterine movement, including pregnancy-related and maternal factors, result in multiple congenital contractures (MCC) or arthrogryposis multiplex congenita (AGMC), which can be defined as contractures in more than two different body parts (excluding club foot deformity and congenital hip dislocation), not associated with each other [14,15]. Fetal akinesia deformation sequence (FADS) is the most severe end of the spectrum, and although contractures at birth including congenital torticollis, scoliosis, or multiple joint contractures indicate prenatal onset, they are not specific for NMD, and can be a part of malformations of cortical development, genetic syndromes, skeletal dysplasias and inborn errors of metabolism [14,15]. Pena-Shokeir syndrome phenotype includes AGMC with craniofacial abnormalities (hypertelorism, low set malformed ears, depressed tip of the nose), polyhydramnios, short umbilical cord, pulmonary hypoplasia, intrauterine growth retardation and osteoporosis with a wide clinical and genetic heterogeneity [14,15].

Gestational age, delivery history, the Apgar score may further help to determine the onset of hypotonia and other presenting features [3,10,11]. Of note, clinical and laboratory confirmation of an acute perinatal and intrapartum hypoxic insult does not rule out an underlying primary disease. This is often described as ‘double-trouble’, and ‘HIE-mimics’ should be considered in the presence of clues and any mismatch between history, examination, laboratory and imaging features and the course [12,16]. Maternal history (exposure to teratogens and infections, chronic illness, substance abuse, magnesium sulfate administration for preeclampsia), family history of consanguinity and an affected sibling may help to narrow the differential diagnostic list [1,2,6].

Not all recurrences are genetic in origin, such as maternal antibodies with or without myasthenia gravis to fetal isoform of acetylcholine receptor should also be considered [10,14].

Neonatal neuromuscular examination depends on evaluation of developmental maturity [4,6,10]. Assessment of the tone depends on gestational age for premature infants and can change with the state of

Table 1
Key elements in history for evaluation of neuromuscular disorders.

Pregnancy history	Delivery history	Family history	Peripartum and early neonatal history
Chronic or acute diseases of the mother (diabetes, myasthenia gravis, myotonic dystrophy)	Presentation (breech, transverse)	Consanguinity	Asphyxia
Infections	Length of gestation	Positive family history	Decreased Apgar scores
Fever	Traumatic delivery	Increased stillbirths or miscarriages	Fetal acidosis
Nausea	Intrauterine mass	Advanced paternal age	Signs of encephalopathy/ seizures
Drugs	Abnormal uterine structure or shape		Gestational age
Fetal movement	Abnormal placenta, membranes, cord length, position		A sign for a metabolic disorder
Polyhydramnios, hydrops			Intrauterine growth retardation
Trauma during pregnancy			Dysmorphic features
			Other organ/ system involvement
Bleeding, abnormal lie, threatened abortion			Breathing pattern
			Thin ribs
			Respiratory insufficiency/ ventilator dependence
Prenatal diagnosis			Sucking/ swallowing and feeding difficulties
			Contractures
			Congenital torticollis
			Arthrogryposis
			Fractures
			Neonatal kyphosis/scoliosis
			Joint hyperlaxity

the baby. To examine the baby in a quiet and awake state, to note the relation of the examination to feeding and medications, and if possible, re-evaluation at a different time point can be informative. Observation and inspection help to assess posture, spontaneous motor activity, motor repertoire, respiratory effort and feeding of the baby. Movements are complex, asynchronous, symmetric and consist of normal patterns, variable in nature, involving the arms, legs and trunk. Mental state, dysmorphic features, micro- and macrocephaly, other organ/system involvements provide valuable information in terms of ‘central’ vs ‘peripheral’ localization (Table 2) [1,2,4,11]. Central hypotonia is characterized by more pronounced axial involvement or truncal hypotonia. Distinctive dysmorphic features may point toward chromosomal disorders such as Down syndrome, or Prader-Willi syndrome, among the most common genetic causes of hypotonia in the newborn period [1,2,5,6]. Cranial nerve involvement (ptosis, facial weakness, ophthalmoplegia, ability to suck and swallow, strength of cry, tongue fasciculations), fluctuation of symptoms and observation of fatigue during the course of examination, sensory examination provide valuable clue for the differential diagnosis of early-onset NMD. Presence of tongue fasciculations

Table 2
Clues for differentiating cerebral and peripheral hypotonia[4].

Cerebral hypotonia	Peripheral hypotonia
Developmental delay	Weakness with paucity of spontaneous movement
Normal CK	Raised or normal CK
Decreased level of consciousness	Alert
Increased deep tendon reflexes, clonus	Decreased deep tendon reflexes
Seizures	Muscle fasciculations
Dysmorphic facial features	Myopathic facies
Microcephaly	Ophthalmoplegia
	Ptosis
	Bulbar dysfunction
Apneas, irregular respiration	Prolonged breathing difficulties
	Ventilator dependence
High pitched/unusual cry	Fatigable or weak cry
Multiple congenital anomalies	History of polyhydramnios

CK: creatine kinase
From Reference 4, Table 138-1.

and paradoxical abdominal breathing may directly lead to *SMN1* gene analysis in a hypotonic newborn baby. Myopathic facies, long face, dolichocephaly, high arched palate, tented upper lip, open mouth, lower facial involvement can serve to differentiate early-onset NMD, including congenital myopathies, congenital myasthenic syndromes and congenital myotonic dystrophy (MD1). Presence of lower facial weakness with hypotonia, and contractures such as club foot deformity require examination of the mother in terms of MD1, since congenital forms are inherited from the mother [1–6]. A fatigable cry, ptosis and external ophthalmoplegia in a newborn baby with apneas may require consideration of congenital myasthenic syndromes. Muscle bulk and quality (atrophy, hypertrophy), joint mobility and tone (hypotonia, hypertonia, joint contractures, joint hyperlaxity, distribution of contractures), assessment of muscle weakness provide additional clues, and should be evaluated in the context of developmental features, primary neonatal reflexes and postural responses which can be further evaluated through maneuvers and positioning [3,4,10].

In a 'floppy infant' presenting in the newborn period it is very important to differentiate 'muscle tone' from 'muscle strength'; 'paralytic' from 'non-paralytic' muscle weakness. Tone is defined as a skeletal muscle's inherent resistance to passive movement with axial and appendicular components, and muscle strength is defined as a muscle's maximum voluntary resistance to movement [4,10,11]. There is an evolution of muscle tone with gestational age (GA); at the GA of 28th weeks, there is a 'frog-leg' posture with low axial (postural) and peripheral tone, without flexion of the arms or legs, at the GA of 32nd weeks flexor tone appears in the lower extremities, with full flexion of the hips and knees around GA of 36th weeks with flexor tone in the upper extremities, and a full flexor tone at the elbow level by the GA of 40th weeks [10]. Pronation/supination should be evaluated to bypass flexor predominance, and head should be in the midline position to overcome activation of tonic neck reflex [4,6,10]. 'Frog-leg' posture with flask extension of the arms and external rotation and abduction of the hip which is normal for a 28th gestational week baby, is abnormal in a term baby. Presence and distribution of contractures, congenital torticollis, hip dislocation, neonatal-onset kyphosis/scoliosis, joint hyperlaxity, skin features, muscle bulk and consistency may help for further phenotyping [4–6,10]. During maneuvers and postural/elicited responses, it is very helpful to note weakness, asymmetry or fatiguability. Maneuvers that are used include; pull to sit, shoulder suspension or vertical suspension, ventral suspension and the scarf-sign [2–4]. Distal joint laxity is a non-specific sign which can accompany congenital myopathies, congenital muscular dystrophies and connective tissue disorders including Ehlers-Danlos syndrome spectrum. It is important to assess passive range of motion and resistance in all joints. Arm and leg recoil tests, and objective measures such as popliteal angle can be used to evaluate tone in the lower extremity. For objective serial evaluation, neonatal scoring scales such as the Hammersmith Infant Neurological Examination can also be used [1,3,5,6].

Although it is often unreliable in the newborn period, deep tendon reflexes should be evaluated after assessment of tone. Increased deep tendon reflexes and sustained clonus suggest upper motor neuron dysfunction with brain or spinal cord involvement, whereas hyporeflexia may indicate a lower motor neuron involvement (Table 2) [2,6,10,11]. Asymmetry is a clue for focal CNS or nerve root/plexus injury [5,6,10]. Primary neonatal reflexes and evolution according to GA serve as an important clue for differential diagnosis [4,6,10,11].

3. Localization based etiological classification

Neuromuscular disorders presenting in the newborn period are classified according to localization within the motor unit. History and physical examination as presented in Tables 1 and 2, may help to narrow the extensive differential diagnostic list. As in other age groups, acquired and genetic etiology should be considered for each domain of the motor unit in the newborn period [3–6]. Although muscle weakness and contractures in a newborn baby presenting with hypotonia may reliably suggest NMD, careful evaluation of clues from the history and physical examination may dictate further disease-specific targeted testing and diagnostic evaluation [1–6]. Looking at case series, etiological distribution of hypotonia is different at different settings, although cerebral hypotonia is more common than peripheral hypotonia, and multisystem and systemic disorders should be considered as mentioned above [4–6,16]. Table 3 represents an etiological classification according to central nervous system (CNS) and peripheral nervous system (PNS) involvement [4,11].

In a complex scenario, a newborn baby may have symptoms and signs indicating both CNS and PNS involvement (Table 4) [4–6]. In such a newborn baby, presenting with suggestive clues for cerebral hypotonia such as encephalopathy, seizures, dysmorphic features and upper motor neuron signs, a PNS involvement should be considered in case of low muscle bulk, proximal or distal predominant weakness pattern, hyporeflexia or absence of deep tendon reflexes, contractures and increased serum creatine kinase (CK) level [3,4]. One such example will be congenital muscular dystrophies (CMD) with CNS involvement within the group of alpha-dystroglycanopathies [1–6,17]. A newborn baby with a PNS disorder such as a congenital myopathy or MD1 may be prone to prolonged labor and perinatal/intrapartum asphyxia, and given the diagnosis of HIE [6,12,16]. There is a growing list of inborn errors of metabolism affecting both CNS and PNS within the group of metabolic myopathies including mitochondrial diseases, peroxisomal disorders (Zellweger syndrome), lysosomal storage disorders [4,6,12,16].

4. Diagnostic approach to neuromuscular disorders in the newborn period

Appropriate diagnostic testing depends on phenotype and yield of diagnostic procedure. There is a wide range of laboratory investigations, electrophysiological studies, muscle biopsy, imaging procedures and molecular genetic tests in the context of a newborn baby with hypotonia and a suspected NMD [1–6]. Table 5 summarizes a list of first and second-tier diagnostic assessment for cerebral and peripheral hypotonia. Instead of complementary testing, it is important to consider diagnosis-oriented laboratory investigations, since it may be invasive and/or not cost-effective.

4.1. Basic laboratory investigation

Serum creatine kinase (CK) level elevation can be due to birth trauma, which usually normalizes within a week. Intramuscular injection of Vitamin K may cause an increased serum CK level. Congenital hypothyroidism, Pompe's disease may present with a high serum CK

Table 3
Summary of localization based etiological classification (acquired/genetic) of neonatal neuromuscular disorders.

Upper Motor Neuron (Supraspinal/ Suprasegmental)	Lower Motor Neuron (Segmental/ Motor unit)			
	Anterior horn cell	Peripheral Nerve	Neuromuscular junction	Muscle
Hypoxic-ischemic encephalopathy	Hypoxic-ischemic injury	AIDP	Transient MG	Congenital myotonic dystrophy
Intracranial hemorrhage				
Perinatal stroke	Neonatal poliomyelitis	Neonatal-onset Guillain-Barre syndrome	Infantile botulism	Congenital muscular dystrophies
Intracranial infection				
Sepsis	Spinal muscular atrophy type 0, 1	Inherited CD59 deficiency	Hypermagnesemia	Congenital myopathies
Trauma				
	SMA variants (SMA with respiratory distress-SMARD; SMA, X-linked; SMA-LED; SMA with pontocerebellar hypoplasia)	Congenital hypomyelinating and axonal neuropathies	Congenital myasthenic syndromes	Metabolic myopathies
MCD				
Chromosomal disorders	Glycogen storage disease type 2	Congenital sensory neuropathies		
IEM (Peroxisomal disorders, Zellweger syndrome, CDG, organic acidurias, aminoacidopathies, CCDS, neurotransmitter defects)				
	Neurogenic AGMC			
Spinal cord disorders				

MCD: malformations of cortical development; IEM: inborn errors of metabolism; CDG: congenital disorders of glycosylation; CCDS: cerebral creatine deficiency syndromes; SMA: spinal muscular atrophy; SMARD: spinal muscular atrophy with respiratory distress; LED: lower extremity predominant; AGMC: arthrogryposis multiplex congenita; AIDP: acute inflammatory demyelinating polyneuropathy; MG: myasthenia gravis.

Table 4
Neuromuscular disorders causing combined central and peripheral nervous system involvement.

Motor neuron	Peripheral nerve	Neuromuscular junction	Muscle

• Acquired: Enterovirus encephalitis/ acute flaccid paralysis
• Hereditary: SMA with pontocerebellar hypoplasia
	• Lysosomal storage disorders
	• Congenital disorders of glycosylation
	• Congenital disorders of deglycosylation
	• Peroxisomal disorders (Zellweger's disease, Infantile Refsum's disease)
	• Hypomyelinating neuropathy
	• Giant axonal neuropathy
	• Infantile neuroaxonal dystrophy
	• Andermann syndrome
	• Hereditary sensory and autonomic neuropathy
		• Subgroups of congenital myasthenic syndromes	• Congenital myotonic dystrophy
			• Congenital muscular dystrophy with CNS involvement (alpha DG-, LAMA2-RD)
			• Inborn errors of metabolism
			  • Mitochondrial disorders
			  • Fatty acid oxidation disorders
			  • Congenital autophagy disorders
			• Marinesco-Sjögren syndrome

SMA: Spinal muscular atrophy; CNS: Central nervous system; DG: dystroglycan; LAMA2-RD: laminin alpha2-related dystrophy.

Table 5
Diagnostic tests for central and peripheral nervous system involvement in a newborn baby with hypotonia.

Central nervous system involvement	Peripheral nervous system involvement
Thyroid function tests	Thyroid function tests
Intrauterine infections (TORCH complex-Zika virus)	Serum electrolytes
Serum and urine aminoacids	Serum magnesium
Tandem mass spectrometry	Serum creatine kinase
Toxicology	Serum 25-OH-Vitamin D
Metabolic screening	Serum Vitamin B12
Newborn screening	Serum AChR antibody
Chromosomal studies (Karyotyping, array CGH, FISH analysis DNA probes)	Chest radiograph
Magnetic resonance imaging	Electromyography
Magnetic resonance spectroscopy	Neostigmine test
	Muscle biopsy/ Tissue analysis
	Genetic testing

TORCH: toxoplasmosis, others (Syphilis, Hepatitis B), rubella, Cytomegalovirus (CMV), and herpes simplex; CGH: comparative genomic hybridization, FISH: florescent in situ hybridization; AChR: acetylcholine esterase

level. However, marked serum CK elevation in the context of peripheral hypotonia, paralytic weakness and contractures require further evaluation for CMD [1–6,17]. Asymptomatic serum CK elevation with increased transaminases may suggest muscular dystrophies, such as dystrophinopathies (Duchenne muscular dystrophy: DMD, Becker muscular dystrophy: BMD) in the differential diagnosis. Sustained high serum CK level can be rarely due to channelopathies that present in the newborn period, or rare forms of congenital myopathies or myofibrillar myopathies, due to hypertonia as a rare manifestation [1–6]. A normal serum CK level does not rule out NMD.

4.2. *Electrophysiological tests*

Electrophysiological tests including electromyography (EMG) and nerve conduction velocity (NCV), although very valuable for localization in the PNS a) require experience, b) are invasive and challenging, since in the newborns signal amplitudes are smaller than those of older children and it is difficult to voluntarily activate muscles during the study, which may also interfere with electrical noise in neonatal

intensive care unit setting [4–6]. Despite these challenges, even a limited study in selected newborn babies may document signatures for motor neuron diseases, neuropathies and congenital myasthenic syndromes.

There are recommendations on the use of cholinesterase inhibitors as a diagnostic test [18]. In the newborn period, it is challenging to assess results in the absence of a specific fatigable weakness (ptosis, extra-ocular muscle involvement, dysphagia) that can be measurable. Among these recommendations the following can be highlighted: a) test should be performed in the neonatal intensive care unit, b) an intravenous line should be started as a rapid route for medications in the event of an adverse event, c) electrocardiographic monitorization, d) edrophonium is not recommended to be used in infants-its effect is too brief, and incidence of acute cardiac arrythmias is especially reported in neonates, e) premedication with atropine (20 μg/kg/dose, intramuscular) 30 min before a test dose of neostigmine methyl sulfate) (150 μg, intramuscular) before 30 min feeding is recommended, f) long-acting cholinesterase inhibitors administered orally, such as pyridostigmine (mestinon) are not very useful since onset and duration of response is less predictable [18]. Of note, rare forms of congenital myasthenic syndromes can get worse with cholinesterase inhibitors [5,6,18].

4.3. Imaging procedures

Muscle imaging with ultrasonography may aid to describe selective involvement and pattern in congenital myopathies presenting in the newborn period. Cranial imaging (ultrasonography, computed tomography and/or magnetic resonance imaging) may help to differentiate an acquired lesion, hypoxic-insult, intracranial hemorrhage, malformations of cortical development, and additional clues of CNS involvement such as pontocerebellar hypoplasia, brainstem kinking, cerebellar cysts, encephalocele which may lead to the diagnosis of alpha-dystroglycanopathies on the severe end of the spectrum with muscle, eye and brain abnormalities in different combinations [1–6,17].

If clinical history and neurological examination is suggestive, MRI of the spine can be performed to rule out traumatic myelopathy, syrinx or spinal dysraphism [3–6].

4.4. Genetic testing

Chromosomal studies including karyotyping, microarray-based comparative genomic hybridization and fluorescence in situ hybridization (Prader-Willi syndrome) can be considered in a newborn baby with central hypotonia [1–6]. Single gene testing for SMA, DNA probes for congenital myotonic dystrophy type 1 (MD1), and DMD can be used [1–7,11].

Availability and access to molecular genetic testing through directed gene testing, targeted-gene panels, whole exome and genome sequencing (WES, WGS) replaced invasive procedures such as muscle biopsy in the newborn period. In a large-cohort of patients presenting with NMD before or at birth, NGS through either WES or a custom-designed neuromuscular sub-exomic supercapture array containing 277 genes, confirmed by using Sanger sequencing revealed a conclusive genetic diagnosis in 18/38 families with a 47% yield [19].

Efficiency of NGS in ventilated newborns with peripheral hypotonia was evaluated and compared with Sanger sequencing, and Myopanel increased the diagnosis of NMD with neonatal respiratory distress with a yield of 43% (12/28 patients) compared to Sanger sequencing with a yield of 26% (5/19) [20]. In different series, for neuromuscular diseases, targeted-gene panels and WES offer a diagnostic yield of between 15-83% and 29–67%, respectively [7,20]. If panel testing is negative, comparative genomic hybridization/single nucleotide polymorphism arrays should be considered in the presence of dysmorphic features and additional organ/system involvement [1–7,20]. Further analysis can be performed by WES, including at least two first-degree relatives (trio analysis), to filter non-pathogenic polymorphisms. Molecular genetic testing strategy and data analysis should be performed with an input from molecular geneticists and physicians working in the bioinformatics field. Advanced molecular technologies including WGS and transcriptome sequencing, collectively require experience in terms of interpretation of the results and genotype-phenotype correlations in the clinical setting [7]. It is very important to combine clinical phenotype with diagnostic strategy. Of note, NGS alone may miss MD1 and severe form of FSHD in the newborn period [5–7]. MD1 is an autosomal dominant trinucleotide repeat expansion disease, and severe FSHD is characterized by chromosome 4q D4Z4 repeat contraction, both of which require a different testing strategy [5–7].

Evaluation of the molecular genetic data requires a multidisciplinary team approach, including input from the fields of genetics and bioinformatics. These molecular diagnostic modalities are becoming available and less expensive, however turn-around time, and evaluation may limit and explain different approaches in the diagnostic pathway.

4.5. Muscle biopsy

In order to define the etiology of genetically heterogeneous early-onset NMD, there is a shift between traditional and genomic diagnostic modalities which is reflected to recent practice. Muscle biopsy, as an invasive procedure, is not essential for all newborns with congenital myopathies, congenital muscular dystrophies and metabolic myopathies. Muscle biopsy evaluation is reserved for newborn babies with inconclusive and/or negative initial molecular genetic work-up, and valuable for deep-phenotyping and further correlations. Because of the overlap between histopathological features within the group of congenital myopathies and congenital muscular dystrophies, precise diagnosis depends on molecular genetic testing. Of note, muscle biopsy is not diagnostic for congenital myasthenic syndromes and MD1, which are among the most common NMD in the newborn period [1–6].

5. Current and future landscape of neuromuscular disorders in the newborn period

Broad phenotypic spectrum and genetic heterogeneity of the NMD combined with intrauterine and early-fetal presentations make evaluation of this rare and complex group challenging for physicians involved in the care of newborns from pre-conceptional to neonatal period. During the last several years, there has been a tremendous progress in our understanding of NMD and individualized treatments changing natural history and diseases' trajectories. Such examples include SMA, riboflavin-transporter disorders, DMD, MD1, X-linked myotubular myopathy, lysosomal storage disorders (Pompe and Krabbe diseases), and other metabolic diseases [5–9].

Infantile SMA serves as a prototype example for aforementioned discussion [8,9]. Symptoms in infantile SMA may appear in utero or the first weeks of life. Abnormalities in *SMN1* gene cause reduced levels of survival motor neuron (SMN) protein and a paralogue gene *SMN2* produces low levels of functional protein. Infantile SMA is a spectrum from SMA type 0 on the severe end of the spectrum to SMA type 1. In about 50%, affected newborns are symptomatic at birth or within the first month of life [8]. Patients with SMA type 0, usually harbor one or two *SMN2* copies, and present with decreased intrauterine movements, fetal-onset, contractures, respiratory insufficiency and very limited life expectancy [8]. Most SMA type 1 patients will have two or three *SMN2* copies [8]. Beyond hypotonia, areflexia, hypotonia and weakness, bell-shaped thorax, paradoxical abdominal breathing, other SMA manifestations in the newborn period can be; weak cry, swallowing or feeding difficulties, dysautonomic manifestations (increase of sweating, bradycardia, distal necrosis, impaired regulation of vascular tone, irregular skin responses to temperature changes), cardiac defects (septal defects and abnormalities of the cardiac outflow tract), metabolic problems (hypoglycemia, hypercalcemia), joint contractures, osteopenia and bone fractures [8].

Common to current disease-modifying drugs (nusinersen, onasemnogene abeparvovec, risdiplam) approved by the FDA and EMA is that, there is clearly a difference in terms of response in the presymptomatic and symptomatic patients [1,5–9]. This implies the critical 'therapeutic window' for increased efficacy, which can be targeted through NBS programs [8,9]. With that not only the natural course of the disease but also developmental trajectories, care guidelines, patient management and historical classifications are changing. The concept of NBS switching from a biochemical to genetic-based approach is also described in DMD, where mutations amenable to exon-skipping can be diagnosed at birth, and early therapeutic interventions can increase effectiveness of combined-treatment strategies [9].

6. Conclusions

None of the neonatal manifestations are unique to NMD in the newborn period. The aim of this teaching review is to emphasize the importance of a comprehensive history including conception, fetal movement, gestation, natal and postnatal history with a three-generation pedigree which may be helpful in directing the diagnostic pathway. Full clinical assessment includes; a) observation, b) provocative maneuvers, c) resistance to passive range of motion, d) motor repertoire of the newborn baby, e) full range of joint extension to evaluate subtle contractures. Of note, evolution of tone and maturity according to gestational age should be taken into account. Dysmorphic features, myopathic face, other organ/system involvement, eye abnormalities, extraocular eye movements, facial diplegia, tented upper lip, tongue fasciculations, feeding and/or swallowing problems, respiratory insufficiency, failure to wean from the ventilator, hypotonia, weakness and contractures may provide clues for anatomic location and etiology. Acquired, systemic, infectious and metabolic diseases should also be considered since they require different management. Despite increased access to advanced molecular diagnostic strategies, in an era with evolving techniques, it is helpful to use a combined approach, based on clinical findings and traditional diagnostic tests. 'Hunting for the perfect diagnostic strategy' especially in the newborn period still requires experience and recognition of these clinical entities in the neonatal intensive care unit with a combined multidisciplinary effort.

Declaration of competing interest

I have no disclosures and no conflict of interest to declare.

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