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REVIEW ARTICLE

The role of the pediatrician in suspected neuromuscular diseases in childhood

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Development Indicators, Child Development, Muscle Hypotonia.

Abstract

Objective: Help the pediatrician in the suspicion of neuromuscular diseases when the child has complaints or altered findings in neuropsychomotor development, presenting one review on the topic. **Methodology:** Non-systematic literature review using articles published between 2015 and 2021 obtained with the terms “neuromuscular disorders” and “children”; “neuromuscular disorders” and “pediatric”; “milestones” and “delay”; “motor development” and “delay”; “development”and “neuromuscular disorders”; “neuromuscular disorder” and “evaluation”; “neuromuscular disorders” and “examination” in the Lilacs, Medline, Paho, Wholis and Scielo research bases. **Results:** Data found in the review were compiled and divided into three topics: (1) Warning signs for neuromuscular diseases: how history and physical examination help define hypotonia and signs of muscle weakness; (2) Differential Etiological Diagnoses: most common clinical presentations and brief description of the main diseases with available therapies; and (3) Investigation of Neuromuscular Diseases: examples of situations divided between those with central or peripheral hypotonia, the use of creatine phosphokinase dosage in cases of muscle weakness and motor delay and examples of confirmatory tests of neuromuscular diseases with therapeutic possibilities. **Conclusion:** Although neuromuscular diseases are individually rare, they may have specific treatment that modifies their natural history, then the important differential diagnosis when there is a delay in neuropsychomotor development. It is imperative that the pediatrician, as a reference professional for families, have a high degree of suspicion and knowledge that allows initial assessment and referral to a specialized service.

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INTRODUCTION

Pediatric neuromuscular disorders consist of different diseases originating in the spinal cord anterior horn, the peripheral nervous system, the neuromuscular junction or skeletal muscle, with estimated prevalence of 0.3:1,000 children[1]. Overall, the signs and symptoms are not specific and overlap. A combination of hypotonia, muscle weakness, hyporeflexia/areflexia and delay in neurodevelopmental milestones is seen in childhood as initial clinical manifestations, although other complaints such as myalgia, exercise intolerance and rhabdomyolysis may also be present. Many can lead to systemic impairment, affecting the respiratory, cardiovascular, osteometabolic, nutritional and psychiatric systems[2,3].

In this group of diseases, a financial and emotional burden commonly occurs on families, given their chronic and progressive nature. Early diagnosis enables the start of multidisciplinary management, access to care services, as well as the initiation of treatment with slowing disease progression and often attenuation of the clinical phenotype (such as corticosteroids in Duchenne muscular dystrophy, enzyme replacement in Pompe disease, drugs for myasthenia gravis, gene therapies in spinal muscular atrophy etc.)[4,5].

This article is targeted to the general pediatrician, in his/her critical role in monitoring and welcoming families and children, whose practice closely observes neuropsychomotor skills and their domains. The appreciation of family complaints about child neurodevelopment should lead to prompt investigation and referral to the specialist.

METHODOLOGY

This article was built from a non-systematic bibliographic review in the main databases in the health area: Latin American and Caribbean Health Sciences Literature (Lilacs), Medical Literature Analysis and Retrievel System Online (Medline), Pan American Health Organization (Paho); World Health Organization Library and Information Services (Wholis) and Scientific Electronic Library Online (Scielo) in the period between 2015 and 2021.

The compilation was structured in three parts: (1) Main warning signs for neuromuscular disease, in which the most typical signs/symptoms verified in this group of diseases are described; (2) Etiological differential diagnoses, in order to describe the main characteristics of diseases for which there is phenotype-modifying treatment; (3) Complementary investigation, which aims to establish the correct flow of tests for diagnostic elucidation.

To this end, the following search terms (titles and abstracts) were placed in the aforementioned databases: "***neuromuscular disorders***" and "***children***"; "***neuromuscular disorders***" and "***pediatric***"; "***milestones***" and "***delay***"; "***motor development***" and "***delay***"; "***development***" and "***neuromuscular disorders***"; "***neuromuscular disorder***" and "***evaluation***"; "***neuromuscular disorders***" and "***examination***".

Warning signs for neuromuscular disease

Hypotonia

Hypotonia is defined as the reduction in muscle resistance to passive movement of the joint, leading to flaccidity. It may or may not be associated with weakness, which is the reduction in the maximum muscle contraction power.[6] Clinical neurological assessment allows the identification of some signs of hypotonia and muscle weakness (Table 1).

As for the topographic diagnosis, hypotonia can be divided into central (or secondary or a non-paralytic group) or peripheral (or primary or a paralytic group), with clinical characteristics that help distinguish between them (Table 2)[8,9].

Delayed neuropsychomotor development and muscle weakness

Neuromuscular diseases in childhood, when not presenting with the classic signs of hypotonia, can manifest with delayed motor development (gross or fine) with or without cognitive impairment. Parents and caregivers who express concerns about neurodevelopment are correct more than 80% of the time, warning us on the importance of the complaint and the correct approach[11]. Table 3 shows the main family complaints related to some of the neuromuscular diseases of childhood, while in Table 4 the pediatrician can find clinical evaluations to be made according to the child's age.

Paying attention to all neurodevelopmental milestones and their areas (gross motor, fine motor/adaptive, personal-social and language) is critical to determine the level of suspicion and allow for early diagnosis. Table 5 shows the main characteristics of the development and clinical signs in Duchenne muscular dystrophy.

Differential etiological diagnosis

Neuromuscular diseases manifest themselves clinically through congenital hypotonia, neurodevelopmental delays or classic signs of muscle weakness. As previously described, the history and neurological physical examination help to produce diagnostic reasoning and guide further investigation, which will be discussed below. Table 6 summarizes the main neuromuscular diseases and their forms of presentation.

As described, there are numerous differential diagnoses of diseases that lead to hypotonia, developmental delay or weakness. Most of the time, hypotonia is of central origin (66% to 88%), and only 15% to 30% are of peripheral or neuromuscular topography[10]. Although rare, neuromuscular diseases are progressive and associated with a number of systemic repercussions, adding important morbidity and mortality to the patient and their families. Currently, there are treatments for some neuromuscular diseases based on the correction of the genetic alteration or its molecular consequences, providing phenotype modification and better quality of life (Table 7).

Table 1. Neurological assessment in infants with suspected hypotonia and muscle weakness.

Signs of muscle hypotonia	
	• Pull-to-sit maneuver: the examiner holds the infant's hands in the supine position, pulling to the sitting position, evaluation the tone/strength of the neck, paravertebral, shoulders and arms. • Normal answer: around 2 months, head drop is minimal, and the child presents with semi-flexion of shoulders and elbow. • Signs of hypotonia: head hangs completely back and upper limbs stretch out without any resistance.
	• Scarf maneuver: the examiner holds the infant's hands in a supine position, crossing them in front of the chest, evaluating the strength/tone of the shoulders and arms. • Normal answer: resistance from the elbow, preventing it from going beyond the midline. • Signs of hypotonia: Elbow is extended beyond midline.
	• Shoulder suspension maneuver: the examiner holds the infant by the chest, in a vertical position, evaluating the strength/tone of the axial muscles. • Normal response: resistance in the upper limbs and semi-flexion of the lower limbs. • Signs of hypotonia: limbs are stretched out, without resistance, and the child appears to "slip" by the examiner's hands.
	• Ventral suspension maneuver: the examiner holds the infant by the chest and abdomen in a horizontal position to assess the strength/tone of the axial muscles. • Normal response: semi-extension of the neck and pelvis with relative spinal straightening. • Signs of hypotonia: the spine remains flexed, head and pelvis drooping, with upper and lower limbs extended, as if the infant's body formed an inverted "C".
Signs of muscle weakness	
• Weak cough, with difficulty removing upper airway secretions. • Difficulties swallowing, leading to an accumulation of secretions in the oral cavity. • Faint cry. • Paradoxical breathing: during inspiration, there is greater abdominal expansion than the thoracic one due to the weakness of the intercostal respiratory muscles and the relative preservation of diaphragmatic strength. • Batrachian position: lower limbs abducted and lateralized. • Reduced spontaneous movements. • Excessive head drop during pull-to-sit maneuver; minimal trunk and limb support during the semiological maneuvers mentioned above.	

Source: Bodensteiner (2008)[7].

Investigation of neuromuscular diseases

As discussed in the previous topics, we will emphasize the clinical conditions for which natural history modifying therapy exists. The selection of tests is ideally guided by the clinical presentation, with localization diagnosis derived from the neurological examination (sequence of presentation will be guided by the likely topography of the clinical condition, determined, as described in topics 1 and 2, by the characteristics of the neurological examination).

Hypotonia is a clinical presentation of neuromuscular disorders in infants. Nevertheless hypotonia may also be a feature of many other conditions located in the central nervous system. The neuromuscular disorders will show, in addition to the low motor tone, signs of weakness, may have diminished to absent tendon reflexes and, in the presence of spinal muscular atrophy, tongue fasciculations might be depicted. Those distinct findings in physical examination define the peripheral hypotonia. Thus, the diagnostic approach for hypotonia is based on history and physical examination data, (following a sequence of complementary tests that must follow the syndromic and topographic diagnosis logic). Further tests differ according to the topographic definition of central or peripheral hypotonia (Table 8).

If topographical location is not defined by the neurological examination in the diagnostic approach to motor weakness or delay, low-cost, non-invasive screening tests

Table 2. Topographic diagnosis of hypotonia in childhood.

Primary/central hypotonia	Secondary/peripheral/neuromuscular hypotonia
• Represent 60% to 88% of cases. • Topography: CNS alterations, genetic syndromes: − Down syndrome (trisomy of chromosome 21): brachycephaly, slanted palpebral fissures, single palmar crease, and weak Moro's reflex. - Prader-Willi syndrome: hypotonia, eating difficulties, obesity/binge eating in preschool age. - Peroxisomopathies (mutations in 12 PEX genes): in the severe form (Zellweger syndrome) there is severe hypotonia, large anterior fontanelle, liver, kidney, eyes, brain, bone and adrenal impairment	• Represent 15% to 30% of cases. • Topography: changes in the motor unit (lower motor neuron, nerve roots, peripheral nerves, neuromuscular junction and muscles): -Lower motor neuron: presence of myofasciculations (such as spinal muscular atrophy). -Peripheral nerves: changes in sensitivity and predominance of distal weakness (such as sensorimotor neuropathies). -Motor endplate: presence of fatigue and weakness fluctuation throughout the day (such as myasthenic syndromes; botulism; use of aminoglycosides; hypermagnesemia). -Muscles: myopathic facie (poor facial mimicry, tent mouth, eyelid ptosis and high-arched palate), proximal weakness, arthrogryposis (such as myopathies and congenital dystrophies).
Hypotonia: • Axial predominance. • Presence of antigravity appendicular movements. • Thumbs in abduction. • Association with encephalopathy (changes in the consciousness level, behavior and cognitive level). • Association with seizures. • Association with metabolic disorders. • Suction-swallowing incoordination.	Hypotonia: • Axial and appendicular. • Diffuse muscle weakness, with absence or significant reduction in antigravity movements. • Possible involvement of eye, facial or bulbar muscles. • Tendinal retractions at birth; hip dislocation or arthrogryposis; high-arched palate.
Deep reflexes: exacerbated or reduced. Persistence of primitive reflexes (such as Moro, ATNR). Chest: normal shape.	Deep reflexes: absent or greatly reduced. Poor primitive reflexes. Chest: Bell-shaped, narrow, with paradoxical breathing.
Prenatal history: • Exposure to infectious or toxic agents. • Family history of genetic syndromes.	Prenatal history: • Reduction of fetal movements. • Polyhydramnios.

Key: ATNR: asymmetrical tonic neck reflex; CNS: central nervous system.
Adapted from: Duarte (2018)8, Reed (2007)9, Harris (2008)10.

Table 3. Main complaints related to the two most common neuromuscular diseases.

Disease	Family complaints
Spinal muscular atrophy	• "Unable to support the neck" • "Unable to lie down on their stomach" • "Crawls slowly and not able to support weight on the legs" • "Hands shake, falls a lot and walks in a strange way"
Duchenne muscular dys-trophy	• "Delayed walking and talking 'mom' and 'dad'" • "Falls a lot" • "Difficulty running, jumping and climbing stairs" • "Walks on tiptoe"

Source: Lurio, Peay and Matheus (2015)12 with additions by the authors.

should be requested. Serum creatine phosphokinase levels should be the first screening test[25]. The following flowchart (Figure 2) illustrates the sequence of diagnostic tests to be requested in the face of a suspected neuromuscular disease: Suspected neuromuscular disease without topographic definition: most myopathies (muscle topography diseases), whether congenital or acquired, present with higher levels of creatine phosphokinase in the blood, intermittently or continuously, and should deserve further investigation[25].

Suspected neuromuscular disease with topographical definition:

- **Anterior horn:** initially address treatable disease, performing genetic testing (MLPA) for homozygous deletion in the *SMN1* gene, followed by sequencing of the *SMN1* gene if necessary. In spinal muscle atrophy, there may be an increase in creatine phosphokinase, but never more than five times the normal limit[17].

- **Peripheral nerve: clinical diagnosis with topographical definition on physical signs together with inheritance pattern defines** hereditary sensorimotor neuropathies of autosomal recessive/dominant or X-linked inheritance. Genetic testting/inherited neuropathy panel may be requested. Not all have an identified gene.
- **Neuromuscular junction:** with symptom onset of less than 2 years, the focus should be on congenital

Table 4. Clinical assessment of motor delay and weakness according to age.

Age	Assessment
<6 months	Perform pull maneuvers to sit, scarf, shoulder suspension and ventral suspension. • If there is delay in head support, sit with support or roll over, refer to motor physiotherapy and reassess in 1 month. • If delays persist after 1 month, request serum creatine phosphokinase dosage and refer the child to a pediatric neurologist.
6-12 months	Assess the ability to sit unsupported at 6 months, go from lying down to sitting at 9 months and remain in this position with hands free to grasp objects. • If the infant does not sit unsupported at 7 months of age or moves to a sitting position at 9 months of age, request serum creatine phosphokinase dosage, refer to physical therapy and reassess in 1 month. • If motor delays persist after 1 month, refer the child to a pediatric neurologist.
> 12 months	Assess gait and move from sitting to standing (stand-up test). • If the infant is not walking at 15 months of age, request creatine phosphokinase dosage and refer to stimulation with motor physical therapy, followed by reassessment in 3 months. • If at 18 months of age the child is not walking well and if there is any regression, refer to the pediatric neurologist. • If in the standing up test the child is only able to stay the standing position using sequential hand supports on legs, knees and thighs (Gowers sign), request creatine phosphokinase dosage and refer to the pediatric neurologist. • Whenever there are serum creatine phosphokinase values above 2,000 IU/L, refer to a pediatric neurologist.

Source: Lurio, Peay and Matheus (2015)12 with additions by the authors

Table 5. Neurodevelopment and clinical signs in Duchenne muscular dystrophy

Duchenne Muscular Dystrophy
Aspects of neurodevelopment
There is a delay in all domains of neurodevelopment (gross motor, fine motor/adaptive, language and social-personal) from 3 months of age onwards. After 12 months of life, the gross motor domain delay becomes more pronounced. • Average age for acquisition of the first words: around 16.1 months would be the tolerable. • Average age for acquisition of unsupported walking: around 16.27 months would be the tolerable. • 70% of patients acquire independence for activities of daily living at 5 years of age. • 30% of patients have intellectual disability.
Clinical signs • Gowers Sign (Figure 1). • Pseudohypertrophy of the calves.

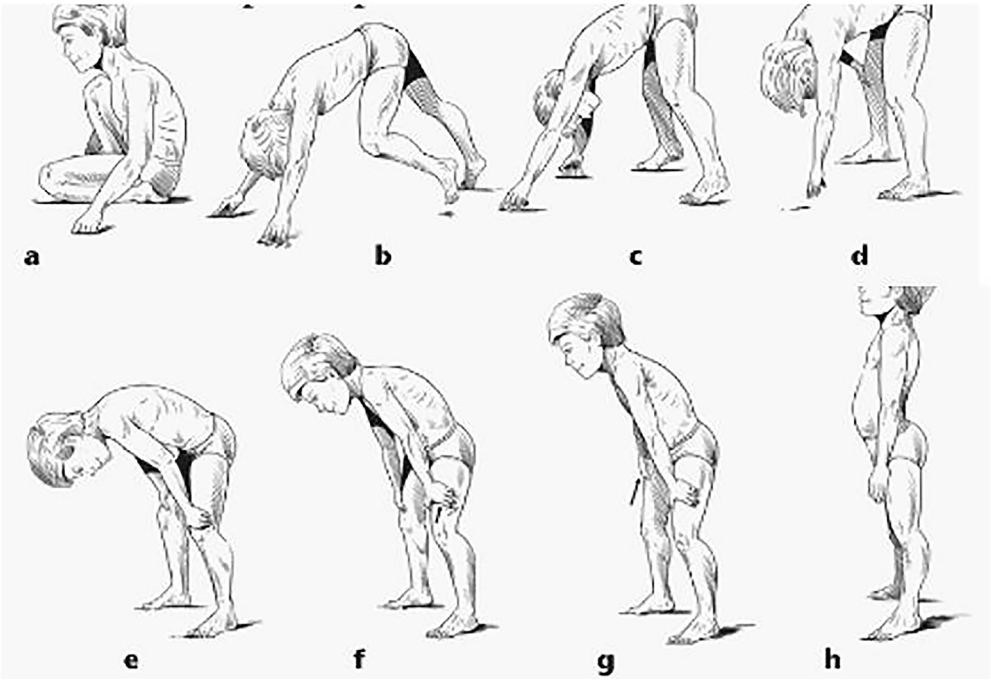
Source: Dommellen et al., 2020; Nardes et al., 2018; Chang et al., 2012.13-15

myasthenic syndromes, including treatable ones (such as those related to the *DOK7* gene). If the age of onset of symptoms is above 2 years, consider the possibility of congenital or acquired myasthenic syndrome, including screening for anti-acetylcholine receptor antibody (anti-AchR).

- **Muscle:** initially address the treatable causes:
  - Use clinical data to separate acquired conditions (infectious or non-infectious inflammatory myositis) from congenital (dystrophinopathies, Pompe disease, lim-girdle dystrophies).
  - As screening tests, creatine phosphokinase level above ten times the normal limit occurs in most cases of myopathy, elevated transaminases may also be present in dystrophinopathies, elevated erythrocyte sedimentation rate (ESR) in inflammatory myopathies.
  - To confirm dystrophinopathies and limb-girdle dystrophies, genetic specific test (as MLPA followed by *DMD* gene sequencing) or a genetic panel for myopathies should be requested[20].
  - If a metabolic myopathy is suspected, investigate with a myopathy genetic panel that includes Pompe genes, multiple acyl-CoA dehydrogenase deficiency and primary carnitine deficiency, (*GAA, ETFDH, SLC22A2)* those can be treated with respectively replacement enzyme, riboflavin supplementation, carnitine supplementation[26].

Anterior horn

Spinal muscular atrophy must be investigated if this topographical diagnosis is present. Speaking up the diagnosis is critical, because when symptoms are present, there is already dysfunction of motor neurons. Next step will be cell



Source: Chang et al. (2012)[15].
Figure 1. Gowers sign. Acquires the prone position, then performs the triangle posture (a-d); continues to support on knees and thigh, until assuming the standing position (e-h).

Table 6. Differential diagnoses of neuromuscular diseases.

Clinical presentation	Etiological diagnosis
Hypotonia at birth	- Atrofia muscular espinhal 0 e 1. - Distrofias musculares congênitas. - Miopatias congênitas. - Miopatias metabólicas. - Síndromes miastênicas congênitas.
Gross engine delay with or without language delay	- Distrofia muscular de Duchenne. - Atrofia muscular espinhal 2 e 3. - Miopatias metabólicas.
Muscle weakness	- Duchenne muscular dystrophy. - Waist dystrophy. - Myasthenia gravis. - Inflammatory myopathies (such as dermatomyositis infectious myopathies).

degeneration and death and the progression is extremely fast in earlier onset cases. The best therapeutic results depend on still having motor neurons. Therefore, if suspected, immediately genetic testing is mandatory[17].

Mutation of the two alleles of the *SMN1* gene confirms this diagnosis. In most cases homozygous deletion is the mutation, and the genetic test to detect a deletion uses the MLPA technique. If this test is negative and the diagnostic suspicion remains, a compound heterozygosity may be present. In these cases, one of the alleles may have, for example, a deletion in exon 7 and the other allele, a different mutation such as a point mutation. Confirmation in this situation is carried out by *SMN1* gene sequencing. Either blood in EDTA, or, less invasively, cells from the oral mucosa can be collected with a specific *swab* for this purpose[17].

Genetic counseling for families who have a confirmed case cannot be forgotten. Future pregnancies of the couple or the father and mother in another relationship are at great recurrence risk. Genetic testing is indicated for the newborn baby, using the same methods. If a pre-symptomatic diagnosis is achieved the best therapeutic window for specific therapy is present. Some countries are including genetic testing in the neonatal screening procedure. In Brazil, this inclusion is expected in the expansion of the neonatal screening program[27].

Peripheral nerves

Hereditary polyneuropathies do not yet find natural course modifying specific treatments. Nevertheless, genetic tests (molecular genetic panel for peripheral neuropathy) for

Spinal muscular atrophy

5q spinal muscular atrophy is a genetic disease of autosomal recessive inheritance, determined by mutations in the *SMN1* gene and absence of the SMN (surviving motor neuron) protein, leading to degeneration of lower spinal and bulbar motor neurons. The clinical phenotype is variable in severity and greatly influenced by the number of copies of a pseudogene called SMN2, as seen below:

Classification and subtypes of spinal muscular atrophy

Subtypes of spinal muscular atrophy	Frequency	Onset of symptoms	Motor milestone reached	Subclassification
	***SMN2* gene copy number**			
Type 0	Unknown	Prenatal	None	-
1 copy in 100% of patients				
Type 1				
Werding-Hoffmann disease	60%	0-6 months	Some control the head	
Never sit down	1A: signs over 1 month			
1B: signs between 1-3 months				
1C: signs between 3-6 months	1-2 copies in 80% of patients			
Type 2				
Dubowitz's disease	27%	7-18 months	Sit down	
Never walk without support	2A: sit unsupported, but lose ability			
2B: sit unsupported and maintain ability	3 copies in more than 70% of patients			
Type 3				
Kugelberg-Welander Disease	12%	Older than 18 months	Stand up	
Walk without support	3A: signs between 18-36 months			
3B: signs older than 36 months	3-4 copies in more than 95% of patients			
Type 4	1%	10-30 years	Walk	-
More than 4 copies in more than 90% of patients				

It is a multisystem disease, requiring care by a multidisciplinary team. There are specific drugs that stimulate the production of SMN protein in patients with spinal muscular atrophy, either through antisense oligonucleotides or through gene therapy. Regardless of the therapeutic option, better results in terms of muscle and functional preservation of patients are related to early diagnosis and rapid institution of treatment. Disease course-modifying antisense oligonucleotide therapy is available in our public health system.

Duchenne muscular dystrophy

Duchenne muscular dystrophy is the most frequent childhood-onset dystrophinopathy. As an X-linked genetic and hereditary disease, it mainly affects boys. Mutations in the *DMD* gene, which encode the dystrophin protein, lead to muscle cell sarcolemma fragility, leading to cell destruction (dystrophic aspect to histology) and its liposubstitution.
There is progressive muscle weakness, leading to loss of gait at around 1-12 years of age and death from cardiac or respiratory complications in the third decade of life. Brazilian and international consensus recommend the use of corticosteroids in order to reduce the speed of disease progression and multidisciplinary care. Drugs that act directly on some of the Duchenne muscular dystrophy-defining mutations are now available for clinical use and show promising results.

Pompe Disease

Pompe disease is a lysosomal disorder caused by mutations in the *GAA* gene that encodes the acid alpha-glucosidase enzyme. Due to partial or total deficiency of the enzyme, glycogen accumulates pathologically in various tissues of the body, causing mainly cardiac and muscular dysfunction. There is a variable clinical spectrum: at the most severe extreme, starting before 12 months of life, there is cardiomyopathy, hypotonia, muscle weakness, difficulty eating and rapid progression to respiratory and cardiac failure, which, without treatment, determine death in the first year of life. A less severe form, of late onset (after 12 months of age), behaves like a waist myopathy, without significant cardiac impairment, but with progressive muscle weakness that ultimately leads to loss of gait and respiratory failure. Enzyme replacement therapy for disease course-modifying Pompe disease is available in our public health system.

Primary carnitine deficiency

Autosomal recessive disease leading to carnitine transport deficit. Half of the patients with primary carnitine deficiency have the infantile form, and recognition of metabolic crises and prompt correction of hypoglycemia are critical, preventing coma and death. Among the treatment recommendations in primary carnitine deficiency is the monitoring of plasma levels of carnitine and its supplementation (if necessary) with oral L-carnitine (50-400 mg/kg/day, in three doses). The main clinical forms are:

- Infant metabolic form (hepatic): onset between 3 months to 2.5 years of age; episodes of hypoketotic hypoglycemia, hyperammonemia, hepatomegaly, elevated transaminases, hepatic encephalopathy (lack of appetite, irritability, lethargy), which can be triggered by fasting or infection; cardiomyopathy, muscle weakness and increased creatine phosphokinase.
- Childhood myopathic form (cardiac): onset between 1 and 7 years of age (typically 4 years); dilated cardiomyopathy; hypotonia; muscle weakness.
- Adult form: low energy and exercise intolerance.

Myasthenia gravis
Myasthenia gravis is an autoimmune disease evolving with muscle weakness characterized by fatigue, diurnal variability, worsening after exercise and improving with rest. In 85% of cases, there are anti-acetylcholine receptor antibodies. Diagnosis begins with clinical suspicion in view of fluctuating weakness and is confirmed by a typical electroneuromyography pattern, with or without the presence of typical antibodies. Assessment of thyroid and thymus function in the investigation of myasthenia gravis is important. The first-choice treatment for myasthenia gravis is the use of acetylcholinesterase inhibitors (pyridostigmine). In cases refractory to the use of pyridostigmine, the use of prednisone or other immunosuppressants, such as cyclosporine, azathioprine or cyclophosphamide, is recommended. In acute clinical worsening, the use of immunoglobulin or plasmapheresis may be considered. It is important to highlight that congenital myasthenic syndromes are non-autoimmune genetic conditions, with different clinic and treatment from myasthenia gravis.

Source: Ministry of Health (2019)[16]; Mercuri et al. (2018)[17]; Finkel et al. (2017)[18]; Chen (2020)[19]; Araujo et al. (2017)[20]; Araujo et al. (2018)[21]; Kohler, Puertollano and Raben (2018)[22]; Magoulas et al. (2012)[23].

Table 8. Differential diagnosis of congenital hypotonias.

Central hypotonia	Peripheral hypotonia
• Hypoxic-ischemic encephalopathy: compatible prenatal or perinatal history • Bacterial infections (sepsis): blood tests, CSF and cultures • Congenital infections (TORCHSZ): serology and polymerase chain reaction (PCR) for toxoplasmosis, rubella, syphilis, HIV, hepatitis, herpes, Zika virus • Genetic diseases/dysmorphias: karyotype, fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH-array), panel for neuromuscular diseases and exome sequencing • Metabolic diseases: blood glucose, lactate, pyruvate, ammonia, amino acid chromatography in urine and blood; investigation of organic acids in urine; very long-chain fatty acids (C26, C24 and C22), phytanic and pristanic acids for suspected peroxisomopathies; acylcarnitines profile (suspected organic acid disturbances and beta-oxidation)	• Serum creatine phosphokinase: very high (> 10 ×) in congenital muscular dystrophies and moderately high (< 10 ×) in some congenital myopathies and metabolic myopathies • Magnesium: levels above 0.15 mmol/L (2.8 mg/dl) present with hypotonia, areflexia, paralytic ileus and bradycardia • Potassium: hyperkalemia can present with hypotonia, weakness and heart rhythm disturbances • Electroneuromyography (ENMG): may aid in the study of neuromuscular location (peripheral nerve, motor plate, or muscle) when physical examination is inconclusive, and is particularly useful in defining motor plate diseases • Electrocardiogram (ECG): short PR interval and high amplitude QRS (Pompe's disease) • Enzymatic/metabolic dosages: acid alpha-glucosidase (Pompe's disease); free and total carnitine dosage (primary carnitine deficiency) • Genetic tests: spinal muscular atrophy (multiplex ligation-dependent probe amplification [MLPA]/SMN1/SMN2 gene sequencing; Dejerine-Sottas disease (genetic tests for hereditary sensory-motor neuropathies); genetic tests for congenital dystrophies/myopathies • Muscle biopsy: suspected congenital myopathies

Source: Harris (2008)10; Kaler et al. (2020)24.

genes already known to be associated with these diseases can be ordered for diagnostic confirmation.[27]

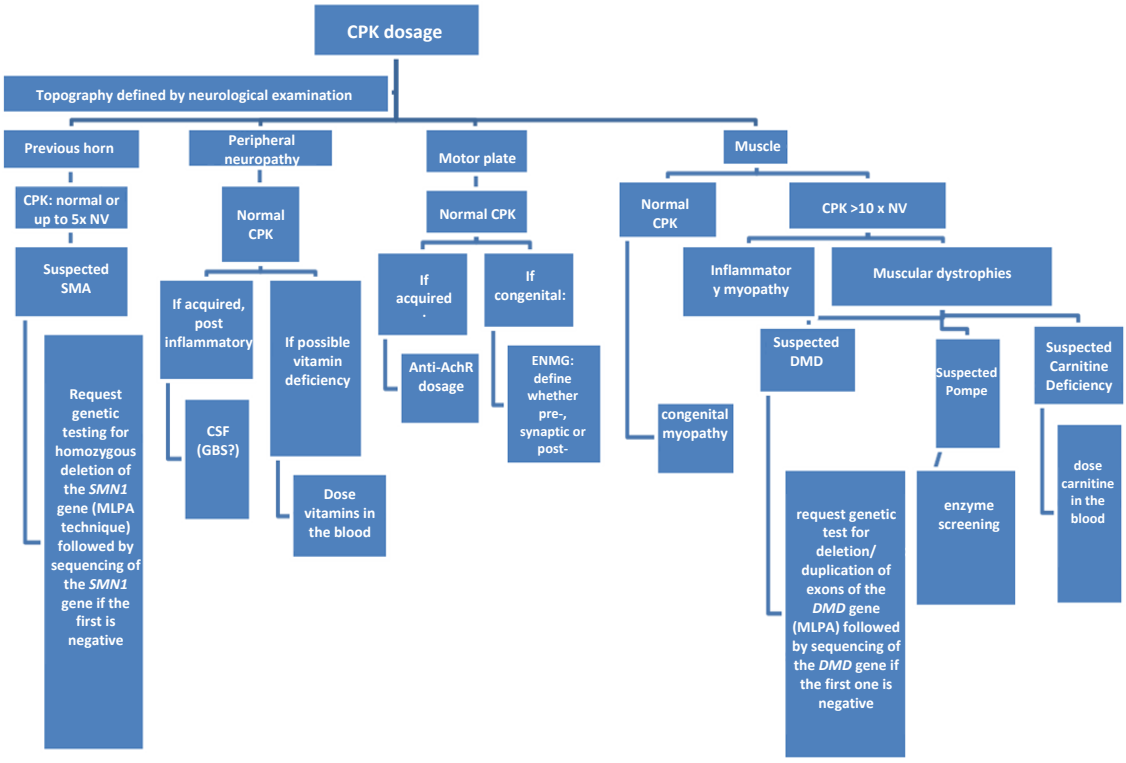
Neuromuscular junction

Myasthenic syndromes

A history of maternal myasthenia gravis should guide the care of newborns presenting with symptoms of a transient condition called "transient neonatal myasthenia". Anticholinesterase therapeutic test helps to confirm the suspicion. The reversal of symptoms can occur spontaneously, but impact on swallowing and breathing determines the transient use of anticholinesterases.

Muscle weakness with hypotonia that may begin soon after birth and throughout the first few years of life may represent a congenital myasthenia. As hereditary diseases, family data collection is also extremely important, helping to define the inheritance pattern, an autosomal dominant, X-linked or autosomal recessive. Some clinical features may point to specific conditions, such as slow photomotor pupillary response, congenital contractures, episodes of apnea related to fever, distribution of weakness, stridor, nephrotic syndrome, ocular malformations, association with convulsive seizures, intellectual disability or bullous epidermolysis. Symptom fluctuation is difficult depict in infants. Electroneuromyography contributes to the topographic diagnosis of these conditions, defining if it is a presynaptic, synaptic or postsynaptic condition. This test should be performed by experienced people. Congenital myasthenia panels can also be requested. Some of these conditions respond to treatment with cholinergic agonists, but in others these medications can make symptoms worse. For others, fluoxetine or quinine may be an option, as well as adrenergic agonists[28].

Juvenile myasthenia gravis is the acquired autoimmune form of myasthenia that can begin in childhood. Isolated ocular presentation is common in early onset cases. Applying ice on the eyes for five minutes reduces the ptosis. Fatigability can be tested either in ocular motor muscles or in proximal upper limbs muscles. Electroneuromyography, with repetitive stimulation, can confirm changes in the motor



Key: CPK, creatine phosphokinase; CSF, cerebrospinal fluid; NV, normal value.
Figure 2. Diagnosis in neuromuscular diseases.

plate. The presence of anti-acetylcholine receptor antibodies may be present, although a lower frequency of positivity is found in prepubertal children. Other antibodies may also be involved (anti-MuSK, for example). Tests with cholinesterase inhibitors, carried out in a hospital setting, also help to define the diagnosis[29].

Muscle

Duchenne muscular dystrophy

A great advance in the diagnosis of Duchenne muscular dystrophy came through with the access to genetic tests. Boys with neuropsychomotor development delay or motor difficulties (jumping, running, lifting from the floor, walking on toes or with frequent falls) should have their level of creatine phosphokinase screened. Levels above ten times the normal value are very indicative of the possibility of muscular dystrophies. The diagnosis can be confirmed either on a genetic test directed to the dystrophin gene (MLPA technique followed or not by sequencing), or on a genetic panel for myopathies that includes *DMD* gene. Other tests that were previously performed, such as electroneuromyography and muscle biopsy, are no longer necessary[20].

Pompe disease

In the suspicion of Pompe disease, in its early classic form or in its late form, the level of creatine phosphokinase is also a good screening test. If this disease is suspected, tests to verify the activity of the acid alpha-glucosidase enzyme must be ordered, either in blood collected on filter paper, or in enzymatic tests on leukocytes or fibroblasts. Finally confirmation should be sought with the genetic test in cases with enzyme deficiency[30].

Conclusion

In light of the advances in diagnostic technology and specific treatment of some neuromuscular diseases with high morbidity and mortality, it is imperative to advocate for the early recognition of this group of pathologies. It is believed that pediatricians, in their mission to monitor the neuropsychomotor development of children from their earliest ages, play a fundamental role in the suspected neuromuscular disease and in conducting the first steps towards diagnostic confirmation. Although individually these are rare diseases, a good history and careful physical examination can guide the request for useful and accessible tests, such as creatine phosphokinase dosage, for a child with muscle weakness.

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