CASE REPORT

Hypotonia: A Clinical Sign, Different Etiologies

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Abstract

Hypotonia is a nonspecific sign with many possible underlying etiologies. The clinical history and neurological examination are vital, providing clues to a methodical and systematic investigation. It is essential to accomplish an early etiological diagnosis to implement adequate therapy (when available), establish prognosis, and offer genetic counseling. The authors present two clinical cases that reflect the diagnostic challenge in evaluating a newborn or an infant with hypotonia.

Keywords: Infant; Newborn; Muscle Hypotonia/etiology; Myotonic Dystrophy/diagnosis; Myotonic Dystrophy/genetics; Spinal Muscular Atrophies of Childhood/diagnosis; Spinal Muscular Atrophies of Childhood/genetics

Introduction

Hypotonia is defined as a decrease in muscle resistance to passive movement.[1-3] It is easily recognized in the observation of the newborn and infant, being a frequent sign of disease in this age group.[1] This sign, although extremely important, lacks specificity, appearing in association with neurologic, genetic, endocrinologic, metabolic and many other pathologies.[1-6] As such, when it is found, a physician must use all of the strategies in order to clarify its etiology.

The most important aspect to be considered for assessing the diagnosis is to differentiate between a primary cause of hypotonia due to a neuromuscular disorder (involvement of the structures that comprise the peripheral motor unit, from the motor neuron to the muscle) and a secondary cause due to non-neurological conditions, chromosomal abnormalities or central nervous system involvement (central causes).[1,2,4-6] Central causes are more common than peripheral ones (60%-88% *vs.* 15%-30%).The prognosis is more severe in the latter.[1,2,5,7]

The first step in the evaluation of the hypotonic newborn or infant is to perform a thorough analysis of the family, prenatal, perinatal, and neonatal history.[1-8] A detailed family history is imperative in order to exclude hereditary disorders.[3,6] The obstetric and perinatal history is essential in order to identify prenatal exposure to infectious or toxic agents, and may also provide information that supports the diagnosis of a neuromuscular disorder, since affected infants frequently have a history of polyhydramnios (caused by decreased fetal swallowing), fetal hypokinesia (paucity of movement), fetal growth restriction, arthrogryposis, and malpresentation (often in the breech position).[1,3-6]

The physical examination begins with an assessment of the infant's general health.[4] Dysmorphic features and congenital defects should be identified.[4] Signs, such as depressed consciousness, poor eye contact (in the infant), preserved or hyperactive reflexes, axial hypotonia, preserved active strength, irregular respiratory patterns, and anomalous primitive reflexes, should alert physicians to a central cause.[1,2,4,6,7] Conversely, if the patient shows generalized hypotonia and muscular weakness, hyporeflexia/areflexia, hypomobility, normal sleep-wake patterns, and responds appropriately to outside stimulation (in some of the cases), a peripheral cause becomes more likely.[1,2,4,6,7]

The authors present two clinical cases of infants simultaneously admitted to a pediatric ward who had hypotonia as a primary cause, in which the differential diagnosis was essential to administer the appropriate therapy and to establish the prognosis.

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Case Report 1

Newborn male, the first child of nonconsanguineous parents, with unremarkable family history. The pregnancy was followed up on without analytical alterations, but a multicystic left kidney and hydramnios were noticed in the ultrasound evaluation. Childbirth was by cesarean section at 35 weeks due to fetal heart decelerations. The Apgar score was 2 at the first minute and 8 at the fifth minute, needing hospitalization in the neonatal intensive care unit and ventilatory support. Hypotonia, muscular weakness, and weak primitive reflexes were observed that led to a neuropediatric evaluation on the second day of life. The observation revealed batrachian position, facial hypomimia, bilateral eyelid ptosis without ophthalmoparesis and reactive pupils, sialorrhea, compromised swallowing and cough reflexes, narrow chest with predominantly abdominal breathing, poor muscle mass, flaccid quadriparesis, absent reflexes, and arthrogryposis (Fig. 1). Toward the hypotheses of congenital myopathy or congenital myasthenic syndrome, the mother of the newborn was examined, revealing a myopathic face as well as the failure of spontaneous release of the hands following strong handshakes due to delayed relaxation.

Newborn blood tests revealed creatinine kinase (CK) 256 U/L (reference values 29-168 U/L), lactate dehydrogenase (LDH) 952 U/L (reference values < 248 U/L), aspartate aminotransferase (AST) 56 U/L (reference values 13-36 U/L), alanine aminotransferase (ALT) 12 U/L (reference values 8-24 U/L). Genetic studies (next generation sequencing for congenital myopathy including genes for congenital myasthenic syndrome) confirmed the diagnosis of myotonic dystrophy type 1. In a subsequent triplet repeat primed polymerase chain reaction (TP-PCR) technique, the presence of a normal allele of the gene *DMPK* with 12 trinucleotide repetitions was detected, and a pathogenic allele, with 1,270 repetitions, was also identified, corresponding to the genotype c.*224_*226CTG[12];(1270).

The infant was discharged from the hospital in day 113 of life under non-invasive ventilation, physiotherapy, and nasogastric tube feeding.

Case Report 2

A 41-day-old male infant with healthy parents and brother, as well as normal gestational and neonatal periods, was derived for a neuropediatric observation with 1 month of age due to hypotonia, hyporeflexia, and poor active movements and primitive reflexes. On neurological examination, he presented good fixation and eye movements, fasciculation of the tongue, severe axial and peripheral hypotonia, without spontaneous movement observed, bell-shaped chest, inter-bone muscle amyotrophy, areflexia, and paradoxical breathing (Fig. 2).

Analytically, a CK value of 837 U/L (reference values 29-168 U/L) was found. Since the diagnostic hypothesis of spinal muscular atrophy was immediately considered, a quantitative analysis of survival motor neuron genes (*SMN*) with the amplification of exons 7 and 8, followed by differential restriction to distinguish *SMN1* gene from *SMN2* was required and supported the diagnosis of a type 1 spinal muscular atrophy (a homozygous deletion was detected, which covers exons 7 and 8 of the *SMN1* gene and the presence of two copies of the *SMN2* gene, exons 7 and 8). He was started on physiotherapy and intrathecal nusinersen (16 days after genetic diagnosis). Both cases maintain a multidisciplinary follow-up by pneumology, physiotherapy, neurology, and genetics, among others.

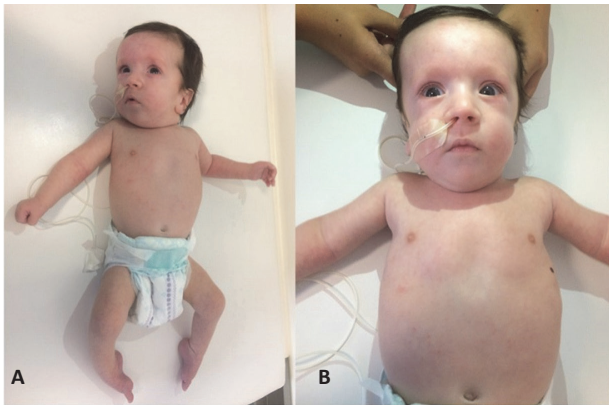

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Figure 1. Batrachian position, poor muscle masses, arthrogryposis (A), and facial hypomimia (B).

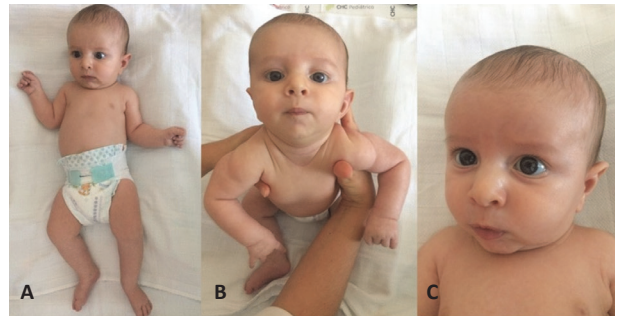

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Figure 2. Severe axial and peripheral hypotonia and amyotrophy (A, B). Normal face and good eye movements (C).

Discussion

Neuromuscular diseases are frequently present in newborns or infants with hypotonia and muscle weakness.[4,5,9] These two signs were present in both individuals and led to the clinical suspicion of the diagnosis in each case. However, hypotonia and weakness also occur in many common disorders such as sepsis, organ failure, and metabolic dysfunction that need to be excluded in order to consider the diagnosis of a primary neuromuscular disorder.[1,2,4-6] Primary neuromuscular disorders are classified according to the topography of the lesion within the motor unit: motor neuron affections, hereditary sensory-motor polyneuropathies, disorders of the neuromuscular junction, and myopathies.[1,2,8-11] The clinical approach, valuing certain signs or symptoms, is essential for improved targeting of each type of neuromuscular disorder, especially when there is suspicion of a disease that is susceptible to molecular diagnosis, which avoids invasive methods, e.g. muscular and/or nerve biopsy.[1,2,5,6]
Muscular dystrophies are an inherited group of progressive myopathic disorders resulting from defects in numerous genes required for normal muscle function.[11] Myotonic dystrophy is a clinically and genetically heterogeneous disorder with two major autosomal dominant forms myotonic dystrophy type 1 (Steinert disease) and myotonic dystrophy type 2.[8,10-14] Myotonic dystrophy affects at least 1:8,000-20,000 people worldwide.[10] The prevalence of the two types varies among different geographic and ethnic populations. In most populations, myotonic dystrophy type 1 is the most common form of the disease.[12,14] The age of onset, presentation, severity, and progression of symptoms varies according to the myotonic dystrophy type.[8,12] Myotonic dystrophy type 2 is generally a less severe disease, resulting from a pathological expansion (cytosine-cytosine-thymine-guanine, CCTG) in the *CNBP* gene.[10,12,14] Myotonic dystrophy type 1 is further divided into congenital, childhood, classic, and mild phenotypes.[13,14] In general, the severity of the myotonic dystrophy type 1 phenotype correlates loosely with the cytosine-thymine-guanine (CTG) repeat size in the *DMPK* gene.[8,10-14]
The first case described relates to a newborn with myotonic dystrophy type 1. The congenital form of this disease is characterized by profound hypotonia, muscular weakness, areflexia or marked hyporeflexia, facial diplegia, poor feeding, arthrogryposis, and respiratory failure.[9-11,13,14] Myotonic dystrophy type 1 may present before birth as polyhydramnios, talipes (clubfoot), and reduced fetal movement. Infants with congenital myotonic dystrophy type 1 often present with respiratory and feeding difficulties and may require neonatal intensive care, ventilatory support, and gastrostomy tube feeding. Respiratory involvement is the leading cause of death in the neonatal period.[9,14]
Inheritance of congenital myotonic dystrophy type 1 is maternal in approximately 90% of cases.[14] This phenomenon stems from the much greater likelihood for anticipation (that is, expansions of CTG repeats) to occur in maternal versus paternal transmissions.[13] It is common for an adult (typically the mother) to be diagnosed with myotonic dystrophy only after giving birth to an affected neonate, as verified in the presented case, and underscoring the potential for subclinical presentation of this disorder.[1,3,11,13,14]
Average life expectancy is reduced for patients with myotonic dystrophy type 1. No disease-modifying therapy is available and only supportive treatment is warranted.[10,14]
Spinal muscular atrophy is characterized by the degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem, which results in progressive muscle weakness and atrophy.[3,8,9,11,15-20] The incidence of spinal muscular atrophy ranges from 4-10:100,000 live births.[15] The inheritance pattern of the common forms of spinal muscular atrophy is autosomal recessive.[9,11,15-20] These forms are caused by biallelic deletions or mutations in the *SMN1* gene on chromosome 5q13.[11,15-20] The differences in SMN protein and phenotypic expression appear to be related in part to a modifying gene (*SMN2*) that lies close to the *SMN1* gene.[15,16,18-20] Disease severity in spinal muscular atrophy generally correlates inversely with *SMN2* gene copy number.[9,15-20] Spinal muscular atrophy phenotypes are classified as types 0 through 4 depending upon the age of onset and clinical course. Spinal muscular atrophy type 0 (prenatal onset) and spinal muscular atrophy type 1 (infantile onset) are the most common and severe types.[9,15,16,20] These subtypes are clinically useful for prognostic and therapeutic considerations.[19]
Our second case is an infant with spinal muscular atrophy type 1, also known as infantile spinal muscular atrophy or Werdnig-Hoffmann disease.[3,9,15] It typically presents after birth but before 6 months of age.[3,9] Affected infants may appear normal before the onset of symptoms. This condition should be suspected in infants with diffuse symmetric proximal muscle weakness that is greater in the lower versus upper limbs and absent or markedly decreased deep tendon reflexes.[9,15,17] Because the upper cranial nerves are mostly spared, patients usually have an alert expression, furrowed brow, and normal eye movements. However, weakness

of the bulbar muscles results in a weak cry, poor suck and swallow reflexes, pooling of secretions, tongue fasciculation, and an increased risk of aspiration and failure to thrive. Respiratory muscle weakness leads to progressive respiratory insufficiency.[9] Intercostal muscles are typically more affected than the diaphragm, resulting in paradoxical breathing and the development of a characteristic bell-shaped chest deformity.[15] The severe hypotonic leg weakness often manifests as a "frog-leg" posture when lying. Before any treatment was available, the natural history of the disease led to a very rapid death for these children (usually before 2 years of age), mainly from respiratory failure.[9,15]

Like myotonic dystrophy, spinal muscular atrophy needs supportive therapy that is directed at providing adequate nutritional and respiratory support and treating or preventing complications of the muscle weakness.[2,5,9-11,17] However, contrary to myotonic dystrophy, a disease-modifying therapy exists for spinal muscular atropy and, if the diagnosis is considered, should be promptly administered.[9,15,18-20] Nusinersen is an antisense oligonucleotide that modifies the splicing of the *SMN2* gene to increase the production of normal, full-length survival motor neuron protein, which is deficient in spinal muscular atrophy.[15,19-21] This intrathecally administered therapy is approved for marketing in several countries, including Portugal.[15,19,21] Infants treated with nusinersen demonstrated improved motor milestones and permanent ventilation-free time. However, the treatment requires multiple loading doses followed by repeated administration for life to maintain elevated levels of functional SMN protein.[22] Another approach to treating spinal muscular atrophy involves the gene replacement of the mutated *SMN1* gene with the normal gene delivered by intravenous administration, via an adeno-associated virus 9 vector that can cross the blood-brain barrier (onasemnogene abeparvovec).[15,20,21] This treatment has been already administered in Portugal but larger and longer-term studies are still needed to clearly define the benefits and risks of this therapy.[21] So far, the data presented (and not yet published) on this therapeutic intervention support a very important clinical benefit, if it is performed early in the lives of these children (before 6 months of age). Some cases presented at international meetings support a benefit that allows these children to develop motor skills close to normal. Moreover, a single administration of the drug may be sufficient.[23] However, the scientific community looks forward to receiving the definitive publication of the results of these clinical trials, with the respective analyses of efficacy and the safety of the drug.

Because these diseases are heterogeneous and variable, their management requires an interdisciplinary approach among health professionals and involves many different skills and services from community resources, like pneumology, physiotherapy, neurology, genetics, and others.[5,10,12,15] A prompt diagnosis is needed in order to provide a directed treatment in selected cases.[5] Both in myotonic dystrophy and spinal muscular atrophy, genetic counseling is mandatory to parents and close relatives.[5,10,15]

Table 1. Differential diagnosis between a myopathy and spinal muscular atrophy[11,17]

	Spinal muscular atrophy	Myopathy
Clinic		
Weakness	Persistent	Persistent
Cramps	Often	Rare
Myoglobinuria	No	Yes/No
Sensory changes	No	Myalgia
Bladder incontinence	Rare	No
Clinical exam		
Paralysis	Yes	Yes
Amyotrophy	Yes	Yes
Fasciculation	Yes	No
Tendon reflexes	Diminished	Diminished
Complementary exams		
Creatinine kinase	Normal or somewhat elevated	Normal to very high
Slow stimulus conduction velocity	No	No
Electromyography	Neuropathic	Myopathic
Muscular biopsy	Neurogenic traits	Myopathic

Table 1 summarizes the main clinical aspects that differentiate these two types of neuromuscular disorders and the results of the diagnostic methods.

WHAT THIS CASE REPORT ADDS

- Hypotonia can be a diagnostic challenge, as its differential diagnosis is extensive, requiring a methodical and systematic approach.
- In general, in a central nervous system disorder, tone is reduced relatively more than muscle strength, and the limbs retain antigravity power. In contrast, neuromuscular disorders are more likely to exhibit profound weakness, manifested by the inability to move the limbs against gravity.
- Infants with a neuromuscular disorder frequently have a history of polyhydramnios, fetal hypokinesia, and malpresentation. A family history of neuromuscular abnormalities may be present.
- Physical findings that may be helpful in making the diagnosis of a specific neuromuscular disorder include dysmorphic features, bruising or petechiae, respiratory abnormalities, cardiomyopathy, organomegaly, defects of the genitalia, and joint contractures or laxity.
- It is essential to accomplish an early etiological diagnosis to implement adequate therapy (when available) and support, establish prognosis, and offer genetic counseling.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Hipotonia: Um Sinal Clínico, Etiologias Diferentes

Resumo
A hipotonia é um sinal inespecífico e são várias as etiologias que a podem explicar. A história clínica e o exame objetivo são fundamentais, fornecendo pistas para uma investigação minuciosa e sistemática. É essencial realizar um diagnóstico precoce para instituir a terapêutica adequada (quando disponível), estabelecer o prognóstico e oferecer aconselhamento genético. Os autores apresentam dois casos clínicos que refletem o desafio diagnóstico na avaliação do recém-nascido ou do lactente com hipotonia.

Palavras-chave: Atrofias Musculares Espinhais da Infância/diagnóstico; Atrofias Musculares Espinhais da Infância/genética; Distrofia Miotónica/diagnóstico; Distrofia Miotónica/genética; Hipotonia Muscular/etiologia; Lactente; Recém-Nascido