A schematic approach to hypotonia in infancy

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Hypotonia may be the presenting sign for many systemic diseases and diseases of the nervous system. The present paper discusses a rational, simple and accurate diagnostic approach to hypotonia in infancy, illustrated by the case of a five-month-old infant girl recently referred to the IWK Health Centre in Halifax, Nova Scotia. Key points in the history and physical examination are outlined to allow a tailored investigation both for the patient and for other hypotonic infants. A discussion of an important neuromuscular disease, diagnosed in the present patient, concludes the paper.

Key Words: Hypotonia; Infant; Spinal muscular atrophy

Infants with hypotonia pose challenges for clinicians because hypotonia may be the presenting sign of both benign and serious conditions. On first glance, the magnitude of the differential diagnosis, the rarity of associated illnesses, and the ongoing advances in diagnosis and management may appear overwhelming.

The present paper discusses a practical approach to hypotonia in infancy. Key elements in the child’s developmental and medical history and physical examination are outlined. The case of a five-month-old infant girl, recently seen at the IWK Health Centre in Halifax, Nova Scotia, provides a basis for discussion.

CASE PRESENTATION

A five-month-old infant girl was brought to her family physician after a family friend expressed concern that she was unable to raise her upper body when lying prone. Her parents stated that she had made no attempts to roll over, rarely moved her legs and made no attempts to push with her feet when held upright. She put toys into her mouth using both hands but did not reach farther than 10 cm for objects before her. She laughed and interacted with those around her and became excited at the sight of food. She breastfed well and seemed to have tolerated the recent introduction of rice cereal without coughing, choking or vomiting. She often squealed and seemed to respond to her name. No loss of milestones was reported.

She had been born at 38 weeks by spontaneous vaginal delivery with no prenatal or postnatal concerns. Apgar scores were 8 at 1 min and 5 min, with points lost for colour and tone. At three months, she had been hospitalized for respiratory syncytial virus-positive bronchiolitis. The family history was unremarkable and there was no consanguinity. The infant’s mother had antiphospholipid syndrome. There was a seven-year-old, healthy male sibling.

On examination, the infant looked well, with no dysmorphic features. Height, weight and head circumference were between the 75th and 90th percentiles. She had a strong cry and no fasciculations of the tongue were noted. Respiratory, cardiovascular and abdominal examinations were normal. Cranial nerves were normal, including extraocular movements. She had marked hypotonia on horizontal and vertical suspension. Tightness of the hip adductors and knee extensors was noted. She had a weak grasp and was unable to reach forward. Primitive reflexes were absent. Deep tendon reflexes could not be elicited.

Step 1: Understanding the terminology

A key distinction is to determine whether the infant has low tone with or without muscle weakness. Tone is defined as the resistance of muscles to stretch (1); therefore, hypotonia is diminished resistance of muscles to passive stretching. With respect to infantile hypotonia, it may be considered the “least resistance that an alert (but not overstimulated) infant generates while opposing passive movement” (2). In contrast, weakness is diminished muscle power or strength. While weak infants are always hypotonic, hypotonia is often present with normal strength (2).

Hypotonia is caused by disorders that affect any level of the nervous system – brain, brain stem, spinal cord, peripheral nerves, neuromuscular junction and muscle. Figure 1
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illustrates common diseases with hypotonia as a prominent feature and their anatomical correlates.

The term 'benign congenital hypotonia' was historically used as a diagnosis for infants who were hypotonic in the absence of other signs and symptoms, and who had normal tone in later childhood. We urge caution in the use of this 'diagnosis of exclusion', especially because it requires many months of follow-up for confirmation. One author argues that benign congenital hypotonia has not been an appropriate diagnosis since the 1960s, when central core disease and a number of other congenital myopathies were described (3).

Step 2: Key elements in the patient's history

Although the list of conditions to be considered in the differential diagnosis of hypotonia in infancy is long, the patient's history may narrow the possibilities significantly. Details of the pregnancy, delivery and postnatal period are important – a history of preterm delivery; toxoplasmosis, rubella, cytomegalovirus infection and other infections; maternal smoking; products with honey or corn syrup consumption; contamination of these products with Clostridium botulinum; or any other pre- or postnatal insult increases the probability of central nervous system (CNS) dysfunction as the underlying etiology for low tone. A history of hip subluxation or developmental delay (a chromosomal abnormality), delayed motor milestones (a congenital myopathy) and premature death (metabolic or muscle disease).

The deep tendon reflexes are likely the most valuable aspect of the physical examination. Brisk reflexes or clonus indicate CNS dysfunction, while diminished or absent reflexes point strongly to disorders of the lower motor unit. Dysmorphic features sharply increase the likelihood of CNS dysfunction as an explanation for hypotonia, although a long, narrow face may indicate muscle weakness. Anterior horn cell disease usually spares extracocular muscles, while diseases of the neuromuscular junction may be characterized by ptosis and extraocular muscle weakness (2). Attention to the quality of the cry is important because a high-pitched or unusual-sounding cry suggests CNS pathology, a weak cry may reflect diaphragmatic weakness, and a fatigable cry may suggest a congenital myasthenic syndrome.

A head-to-toe physical examination is required to assess for potentially associated organ dysfunction and to recognize existing syndromes. Abnormalities of internal organs such as the heart or liver are more likely to be associated with a number of metabolic diseases. In the presence of hypotonia, signs of cardiac failure suggest muscle or mitochondrial disease. Hepatosplenomegaly suggests a lysosomal or glycogen storage disease (4).
Physical examination of the parents may also provide important diagnostic information, especially because a parent may have very mild symptoms of a serious disorder. For example, transitory neonatal myasthenia may be suspected if the mother displays fatigability of the eyelids with upward gaze or fatigueability of the arms with sustained forward extension. Infants with congenital myotonic dystrophy have severe hypotonia but their mothers are typically only mildly affected and unaware of their disorder. Mothers with myotonic dystrophy may show grip myotonia, percussion myotonia, ptosis and/or distal weakness that they were unaware of. Although myotonic dystrophy is inherited as an autosomal dominant disorder, when a newborn inherits the gene and shows the striking weakness and bulbar difficulties of congenital myotonia, the mother, not the father, is nearly always affected (5,6).

Step 4: Investigations

The history and physical examination should guide the investigations. If there is good evidence for CNS dysfunction, brain imaging may be the first step. Suspicion of metabolic disease will trigger the appropriate tests; an immediate search for disorders of energy metabolism, amino acid metabolism, fatty acid metabolism and urea cycle function should be undertaken immediately if the child presents in metabolic crisis. These types of disorders may be more readily detected during metabolic crisis than once the child has been stabilized. The presence of particular dysmorphic features may prompt karyotype testing. Screening for hypothyroidism should be performed in all infants for whom an etiology is not clear. If a disorder of the muscles, nerves or neuromuscular junctions seems likely, a creatine phosphokinase (CPK) test may be useful, keeping in mind that most congenital myopathies are associated with a normal CPK level, while anterior horn cell disease may be associated with mild increases. A significant increase in CPK suggests a form of congenital muscular dystrophy.

Following initial screening tests and noninvasive investigations, electromyography (EMG), nerve conduction studies and muscle biopsy may be considered. If muscle biopsy or EMG are considered, blood for a CPK test should be drawn before these procedures because the procedures may cause a short-term elevation of the CPK level (1). Given the advances in genetic testing, muscle biopsies are not performed with the same frequency as they were in the past. Specific genetic tests are available for various disorders such as Prader-Willi and the spinal muscular atrophies (SMAs). However, many muscular disorders that present with hypotonia in the newborn or infancy period can only be diagnosed specifically using a muscle biopsy. Processing of the biopsy must include sophisticated electron microscopy and special staining – a ‘routine’ biopsy may miss significant pathology (7).

**REVIEW OF THE CASE**

Reviewing our case presentation in the context of the above discussion and Figure 2, a number of points become relevant. First, the infant’s social and communication skills were age-appropriate, while her hypotonia was associated primarily with marked gross motor delay. This increases the likelihood of a disorder of the lower motor neuron unit. A diagnosis of lower motor neuron disease is also supported by the unremarkable pregnancy and early postnatal course. The physical examination provides further support: absent reflexes with decreased strength points decisively to diseases of the motor unit. The absence of ptosis, early severe feeding difficulties and extraocular muscle weakness suggests that problems in the neuromuscular junction are unlikely and increases the likelihood of motor neuron disease.

Given the results of the history and physical examination, a diagnosis of SMA seemed very likely. EMG confirmed dysfunction in the anterior horn cells, and blood sent for genetic testing confirmed a diagnosis of SMA type 1. Parents were counselled regarding the nature of the disease and the value of supportive care.

**DISCUSSION**

The SMAs are a group of diseases characterized by a progressive loss of spinal anterior horn cells, leading to muscular denervation, atrophy and weakness. It is the second most
common hereditary neuromuscular disease, with a carrier frequency of one in 50 to one in 80 and an incidence of one in 10,000 to one in 25,000 (8). The most common forms of SMA are transmitted by autosomal recessive inheritance, with the gene defect localized to the motor neuron survival gene (SMN gene) on chromosome 5q. Rare X-linked and autosomal dominant forms have been recognized.

SMA type 1, also known as Werdnig-Hoffman disease, is most commonly described as the acute, infantile form of the disease, with symptoms recognized within the first six months of life. Patients with SMA type 1 rarely develop the ability to sit unassisted and usually die by two years of age (9). SMA type 2 has intermediate severity, often following a more chronic course. Patients may be able to sit unassisted, are generally unable to stand or walk without assistance, but may survive well into adolescence or young adulthood (10). SMA type 3, Kugelberg-Welander disease, generally manifests after 18 months of age and follows a slower disease progression, with survival into adulthood.

Children with SMA type 1 are most frequently perceived by parents to be normal during the first months of life, with subsequent development of dramatic hypotonia, proximal muscle weakness and absent deep tendon reflexes. The disease is not associated with sensory loss or intellectual impairment. Like our patient, most infants presenting with SMA type 1 appear normal on first glance because extraocular movements are spared and muscles of facial expression relatively so. As weakness develops, fasciculations of the tongue and fingers may be noted. With disease progression, feeding and swallowing are compromised, and death usually results from aspiration and respiratory insufficiency.

Treatment of SMA type 1 is supportive. Although the disease is generally described as rapidly progressive, the course may be quite variable. Counselling, respite care, physiotherapy, occupational therapy and other necessary supports should be made available.

Several studies have addressed the relative frequency of the various causes of neonatal/infantile hypotonia (11,12). Cerebral causes predominate and one series (12) suggested that this group of disorders might explain up to 88% of cases. Prader-Willi syndrome was particularly important. Paro-Panjan and Neubauer (12) suggested a six-step approach to diagnosis. Step 1 was simply the clinical examination, which allowed a successful diagnosis in 50% of 138 cases. Step 2 was neuroimaging, which diagnosed 13% of cases. Step 3 involved a search for dysmorphic syndromes, which diagnosed 9%. Step 4 involved karyotyping and fluorescence in situ hybridization tests, which diagnosed an additional 6.5%. Step 5 was made up of biochemical testing, which diagnosed 6%. Step 6 involved muscle and/or nerve biopsy, which diagnosed 6%. The remaining patients were only diagnosed with prolonged follow-up. Clearly, a careful history and physical examination will provide most of the clues.

REFERENCES