Journal of Pediatric Neurology 5 (2007) 181–187
IOS Press

Review Article

The hypotonic infant: Clinical approach

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Received 27 November 2006
Revised 25 December 2006
Accepted 31 December 2006

Abstract. Hypotonia in infants can be a confusing clinical presentation leading to inaccurate evaluation and unnecessary investigations. Hypotonia can result from a variety of central or peripheral causes. Therefore, hypotonia is a phenotype of many clinical conditions with variable prognosis. It is important to recognize that hypotonia is not equivalent to weakness. Infants with central causes, such as Down syndrome, may have severe hypotonia with normal muscle strength. Peripheral hypotonia is frequently associated with weakness, which can be predominantly distal in neuropathies or predominantly proximal in myopathies. In general, central hypotonia is much more commonly encountered; however, the prognosis is worst for hypotonia secondary to neuromuscular pathology. The distinction between central and peripheral hypotonia is therefore critical for proper evaluation and management. Stepwise and accurate assessment is very important to reach the correct diagnosis promptly. In this review, I present a concise clinical approach for evaluating the hypotonic infant. Some practical tips and skills are discussed to improve the likelihood of obtaining an accurate diagnosis. Reaching a specific diagnosis is needed for providing appropriate therapy, prognosis, and counseling.

Keywords: Infant, child, hypotonia, floppy, examination, approach

1. Introduction

Neurological disorders are common in Saudi Arabia accounting for 25–30% of all consultations to pediatrics [1]. Consanguineous marriage is a common traditional practice followed within some sections of our community and results in the high prevalence of many inherited and genetic neurological disorders [1–3]. Diagnosing these disorders requires accurate assessment including detailed history, examination, and then formulation of a differential diagnosis list to guide laboratory investigations [4,5]. Many students, residents, and generalists consider the assessment of neurological disorders one of the most difficult aspects of their clinical practice [6–8]. Hypotonia in infants and children can be a confusing clinical presentation, which often leads to inaccurate evaluation and unnecessary investigations [9]. Stepwise and accurate assessment is important to reach the correct diagnosis promptly. Although specific treatments are not always available, accurate diagnosis is critical to predict the clinical course, associated manifestations, complications, prognosis, and provide genetic counseling [10]. In this review, I present a concise clinical approach for evaluating the hypotonic infant. Some practical tips and skills are discussed to improve the likelihood of obtaining an accurate diagnosis.

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2. Definition and classification

Muscle tone is defined as resistance to passive movement. Muscle tone develops in an orderly se-

Table 1
Summary of types of hypotonias

Central hypotonia
Site of lesion: Brain, brainstem, spinal cord (above the origin of the cranial nerve nuclei or anterior horn cells). Causes: Brain malformations, chromosomal aberration: e.g. Down's syndrome, Prader-Willi syndrome, cerebellar hypoplasia (see Figs 1–3). Clues to diagnosis: Histoy of brain insult, seizures, dysmorphic features, lack of interest in surroundings, abnormal head size, normal spontaneous movements, normal or increased reflexes, persistence of primitive reflexes, organomegaly.
Peripheral hypotonia
Site of lesion: Cranial nerve nuclei, anterior horn cell, nerve roots, peripheral nerves, neuromuscular junction or muscle. Causes: Spinal cord injury, spinal muscular atrophy, poliomyelitis, peripheral neuropathy, Guillain-Barre syndrome, myasthenia gravis, infantile botulism, congenital or metabolic myopathy, muscular dystrophy. Clues to diagnosis: Decreased fetal movements, alertness and responsiveness, weakness with little spontaneous movements, absent or decreased reflexes, fasciculations, muscle atrophy, and sensory loss.
Mixed hypotonia
Features of both central and peripheral hypotonia due to combined central and peripheral pathology (e.g. peroxisomal, lysosomal, and mitochondrial disorders, or any cause of peripheral hypotonia with an acquired hypoxic ischemic brain insult)

quence through gestation and continues to change after birth [11]. Increased muscle extensibility and passivity characterize infantile hypotonia. Hypotonia can be global, truncal, or predominantly involving the limbs. Hypotonia can result from a variety of central or peripheral causes (Table 1). Therefore, hypotonia is a phenotype of many clinical conditions with variable prognosis [12]. Central hypotonia results from global brain dysfunction due to toxic, metabolic, infectious, ischemic or hypoxic insult. Certain drugs, such as barbiturates and benzodiazepines, can be implicated. As well, congenital or developmental brain abnormalities can cause central hypotonia [13]. Down, Prader-Willi, and Smith-Lemli-Opitz syndromes are important examples. On the other hand, focal brain pathology usually results in hypertonia depending on the site and extent of the lesion (e.g., hemiplegia, diplegia, quadriplegia). It is important to recognize that hypotonia is not equivalent to weakness [14]. Infants with central causes, such as Down syndrome, may have severe hypotonia and normal muscle strength. Peripheral hypotonia is frequently associated with weakness and results from a lesion involving the peripheral nervous system (anterior horn cell, nerve roots, peripheral nerves, neuromuscular junction, or muscles). Hypotonia with weakness due to a peripheral nervous system lesion can be predominantly distal in neuropathies or predominantly proximal in myopathies.

The distinction between central and peripheral hypotonia is critical for proper evaluation and management as shown in Table 1. In general, central hypotonia is much more commonly encountered in general pediatric and neurology practices than peripheral hypotonia [15]. Mixed hypotonia occurs when primarily central disorders present with both profound hypotonia and weakness, particularly in the neonatal period. They include Prader-Willi syndrome and acute conditions such as intracranial hemorrhage or infarction of the deep central gray matter of the brain or spinal cord. As well, combined central and peripheral abnormalities can present with hypotonia and weakness. Examples include congenital muscular dystrophy, congenital myotonic dystrophy, cervical spinal cord injury, acid maltase deficiency, and some mitochondrial and peroxisomal disorders. Note that conditions such as Ehlers-Danlos syndrome or osteogenesis imperfecta can also present with hypotonia. In these disorders, hypotonia results from ligamentous laxity, rather than a neurological abnormality.

3. History taking

Detailed history is critical in the evaluation of the hypotonic infant [14,15]. It is important to identify whether the hypotonia was present at birth (congenital hypotonia) as seen in congenital myotonic dystrophy, Prader-Willi syndrome, and spinal muscular atrophy, or present later on. Hypotonia apparent in later infancy could result from muscular dystrophies or myopathies. However, the usual presenting complaint in these infants is motor delay rather than hypotonia per se. The distinction between a static course (e.g., due to brain insults, congenital structural myopathies) or progressive course (e.g., due to spinal muscular atrophy and dystrophies) is critical. Static causes usually results in slow improvements and developmental gains, while progressive causes results in relentless deterioration.

Perinatal history may provide information that supports the diagnosis. Infants with a peripheral neuromuscular disorder may have history of polyhydramnios (due to decreased fetal swallowing), decreased fe-

tal movements, and malpresentation [16]. History of birth trauma, asphyxia, or infection may predispose to central hypotonia. However, infants with congenital neuromuscular disorders may be less able to tolerate the stress associated with labor and thus, be more susceptible to birth depression. Seizures, cognitive dysfunction, vision or hearing impairment points towards a central etiology.

A family history of neuromuscular abnormalities may be informative because many disorders are inherited. Examples of familial neuromuscular diseases include congenital myotonic dystrophy, spinal muscular atrophy, metabolic disorders (e.g., mitochondrial disease, acid maltase deficiency, defects of creatine synthesis). It is important to draw complete three-generation family tree and a detailed maternal family history for X-linked disorders such as some dystrophies and mitochondrial disorders.

4. Assessment of muscle tone

Hypotonia can be identified readily by inspection [4]. In the normal term infant, both the upper and lower limbs have predominantly flexor tone with active limb movements. Normal muscle tone is decreased in the premature compared to the term infant. Flexor tone in premature infants diminishes with decreasing gestational age. Limb tone is examined by assessing the passive mobility in at least three joints in each limb (e.g., shoulder, elbow, wrist). Each joint is moved in all ranges of motion in a rapid manner and compared to the other side. Hand shaking is a useful initial step in an older child. Another useful maneuver is gentle shaking of both hands and feet to assess symmetry of the muscle tone. In the lower limb, rolling the leg (internal and external rotation at the hip) while the child is lying supine in bed, is easy and useful to assess more proximal tone. Before concluding the findings, truncal tone should be assessed. Pulling the infant from supine to sitting position results in a slight head lag at term. No head lag should be seen normally by the age of 3 months. The hypotonic infant lies supine in a frog leg position with the hips flexed and abducted [5]. Holding the infant in horizontal (ventral) suspension is accompanied by flexion of the limbs, straightening of the back, and maintenance of the head in the body plane for few seconds. By age 3 months, the head can be raised above the body plane momentarily on ventral suspension. Holding the infant under the arms identifies truncal resistance that allows the infant to be easily supported without slipping through the examiner's hands. Finally, it is important to evaluate the mother's muscle strength and tone to exclude myotonia (delayed muscle relaxation). This is usually tested by asking the mother to close her eyes tightly or make a tight fist then quickly opening it. This can be an important clue to congenital myotonic dystrophy.

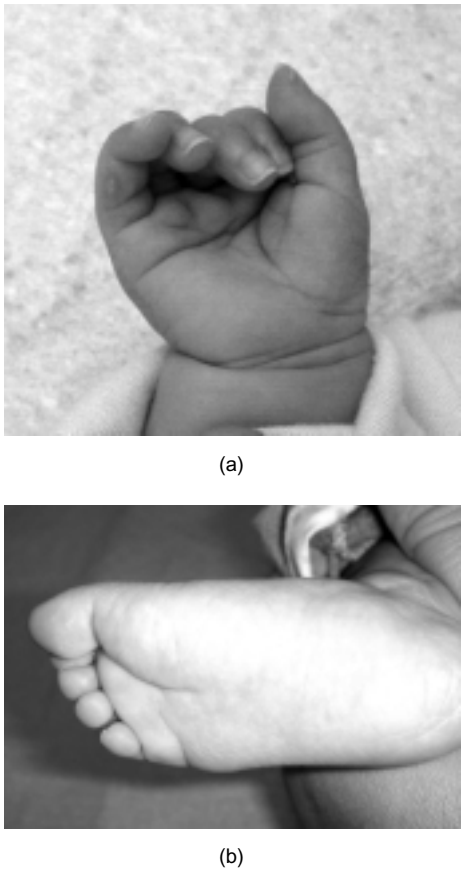

Fig. 1. Single palmar crease (a) and single plantar crease (b) in an infant with Trisomy 13.

5. Physical examination

Careful general examination is needed. Abnormalities of respiratory rate, pattern, or diaphragmatic movement can accompany congenital myopathies. Dysmorphic features and congenital defects points towards a central etiology (Fig. 1). Weight, length, and head circumference should be measured and plotted on percentile charts [4]. Abnormal head size could suggest a central cause (Table 1). Macrocephaly can be associated with an overgrowth syndrome such as Soto

Table 2
Differentiation of upper and lower motor motor neuron lesions

Features	Upper motor neuron lesion	Lower motor neuron lesion
Site of the lesion	Cerebrum hemispheres, cerebellum, brain stem, or spinal cord	Anterior horn cell, roots, nerves, neuromuscular junction, or muscles
Muscle weakness	Quadriplegia, hemiplegia, diplegia, triplegia	Proximal (myopathy) Distal (neuropathy)
Muscle tone	Spasticity/rigidity	Hypotonia
Fasiculations	Absent	Present (tongue)
Tendon reflexes	Hyperreflexia	Hyporeflexia/areflexia
Abdominal reflexes	Absent (depending on the involved spinal level)	Present
Sensory loss	Cortical sensations	Peripheral sensations
Electromyography	Normal nerve conduction	Slow nerve conduction
	Decreased interference pattern and firing rate	Large motor units Fasciculations and fibrillations

syndrome. Pallor and bruising could suggest an acute traumatic etiology. The skin should also be carefully examined to exclude neurocutaneous syndromes or dermatomyositis. Examination of the back is critical in children with paraplegia to exclude spina bifida.

The most important step in the initial neurological examination is to differentiate between upper and lower motor neuron lesions (Table 2). Abnormal eye fixation or follow suggests a lesion above the level of the brainstem. Examination of fundi is needed to exclude optic atrophy (demyelinating disorders) and retinal changes (metabolic or congenital infections). Facial diplegia occurs in some neuromuscular disorders (e.g., congenital myotonic dystrophy). This leads to a myopathic face, which is a long, flat, expressionless face associated with tented upper lip (fish mouth) and sometimes high-arched palate. Facial diplegia also can be associated with severe acute basal ganglia damage (e.g., mitochondrial disorders such as Leigh disease). The infant's ability to suck and swallow should be assessed. Difficulty with swallowing may lead to drooling. The character of the cry should be noted, and the tongue should be examined for fasciculations, which typically are associated with spinal muscular atrophy [5]. However, they can be seen with hypoglossal motor nerve dysfunction accompanying glycogen storage diseases, hypoxic-ischemic encephalopathy, and infantile neuroaxonal degeneration. Motor examination identifies the extent and distribution of hypotonia (limb, truncal, or global). By inspection, good level of alertness and little spontaneous movements suggest peripheral hypotonia. Most neuropathies (except spinal muscular atrophy) results in distal weakness. On the other hand, most myopathies (except myotonic dystrophy) results in proximal weakness. Central hypotonia is usually associated with reasonable power. Spontaneous fisting or an abnormal primitive reflex in response to handling also suggests cerebral dysfunction. Hypotonia can be a non-localizing initial motor presentation of a brain insult that may later evolve to hemiplegia, quadriplegia, or diplegia [17]. In these cases, neonatal hypotonia is followed by motor delay and subsequent spasticity [18]. Spasticity replaces neonatal hypotonia in children with cerebral palsy towards the end of the first year of life as myelination progress. Hypotonia predominantly involving the trunk and lower extremities may occur in premature babies as a result of insult to the periventricular germinal matrix. This region contains pyramidal fibers that descend through the internal capsule to supply the lower limbs. As mentioned above, spastic diplegia may develop later on. Contractures are mainly found in infants with peripheral nerve or muscle involvement. Arthrogriposis may be the presenting feature of a severe neuropathic or myopathic process of a prenatal onset. Deep tendon reflexes may help distinguish between upper and lower motor neuron lesions (Table 2). Abnormally brisk reflexes with clonus suggest central involvement, whereas absent reflexes are consistent with nerve or muscle disease. Sensations should be tested as sensory loss suggests peripheral neuropathy. Other system examination may provide important clues to the diagnosis [10]. Hepatomegaly and/or splenomegaly are evident in neurovisceral sphingolipidosis, mucopolysaccharidosis, peroxisomal, and mitochondrial disorders. Cardiomyopathy may suggest muscular dystrophy, mitochondrial disorders, lysosomal disorders, or Pompe disease. Features of renal failure are evident in Lowe syndrome.

6. Investigations

The required investigations depend on the findings on history and physical examination. Many times, the etiology is apparent and no further tests are needed. Im-

Table 3
Differentiating features of myopathies and dystrophies

Features	Myopathy	Dystrophy
Examples of disorders	Thyroid disease	Duchene
	Centronuclear	Becker
	Central core disease	Limb girdle
Etiology	Congenital	Genetic
	Metabolic	
	Endocrine	
Inheritance	Sporadic	Always inherited
	Autosomal recessive	
Progression	Static or improve with time or treatment	Always progressive
Muscle enzymes	Mildly increased (100s) or normal	Markedly increased (1000s)
Electromyography	No fibrillations	Fibrillations because of active muscle necrosis

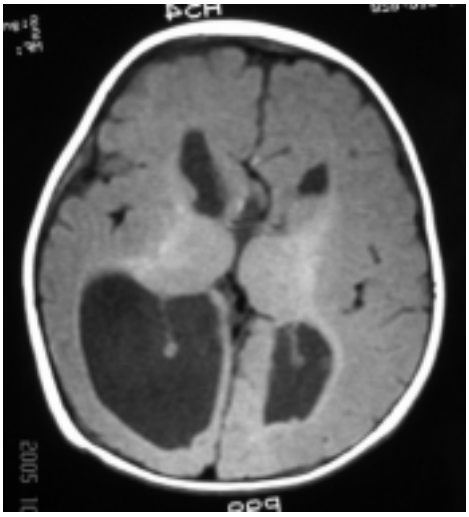

Fig. 2. MRI of a girl with developmental delay, hypotonia, infantile spasms, and retinal lacunae (Aicardi syndrome) showing absent corpus callosum.

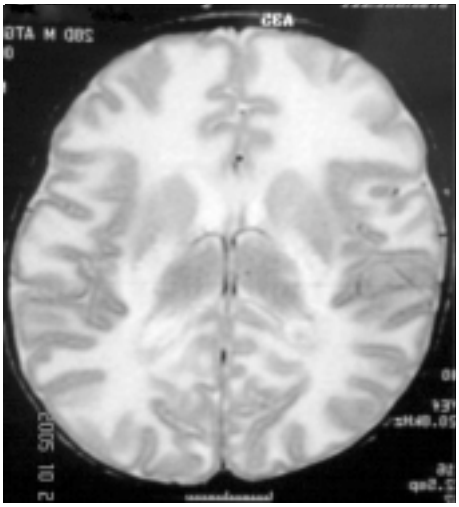

Fig. 3. MRI showing diffuse demyelination in an infant with Krabbe disease. The hypotonia was the result of associated peripheral neuropathy.

portant blood tests include muscle enzymes and thyroid function tests. Serum creatine kinase level is normal in central and neuropathic causes. It can be mildly elevated in myopathies (100s) and markedly elevated in muscular dystrophies (1000s) as shown in Table 3. Cardiac assessment including electrocardiography and echocardiography is needed in muscular dystrophy and mitochondrial disorders to exclude cardiac involvement. Neuroimaging, particularly magnetic resonance imaging, is needed in children with central hypotonia to exclude brain anomalies, degenerative disorders or acquired lesions (Figs 2-4). Recently, magnetic resonance spectroscopy was found to be diagnostic in some disorders. Specific examples include an increased N-acetylaspartic acid in Canavan disease and lactate peaks in mitochondrial disorders. If metabolic disorders are suspected, the following tests are indicated including serum ammonia, lactate, pyruvate, amino acids, and urine for amino acids and organic acids. These tests would screen for most amino acid disorders, organic acidopathies, and urea cycle abnormalities.

Electrodiagnostic studies include needle electromyography (EMG) and nerve conduction studies. This test is difficult to conduct reliably in young infants and uncooperative patients [12,19]. As well, the results are not specific. It can show denervation changes in spinal muscular atrophy and peripheral neuropathies [20]. Myopathic changes are expected in myopathies and muscular dystrophies. Therefore, EMG is sensitive but not specific. Other authors also stressed the controversy over the usefulness of EMG in the assessment of the hypotonic infant even if neuromuscular diseases were suspected [21]. Accurate clinical evaluation can replace this test with emphasis on more specific tests, such as muscle biopsy in peripheral hypotonia and brain magnetic resonance imaging in central hypotonia. However, EMG is important if myotonia, infan-

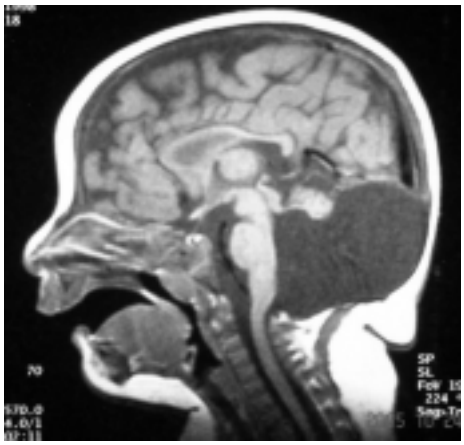

Fig. 4. An infant with incoordination and hypotonia due to congenital brain malformation (cerebellar hypoplasia).

tile botulism or congenital myasthenic syndromes are suspected. Decrement on repetitive nerve stimulation and clinical improvement with Tensilon are diagnostic of myasthenia.

Muscle biopsy is the gold standard for diagnosing muscle diseases. The surgeon should avoid taking the sample from a mildly involved muscle, because it may not reveal the pathology. As well, severely involved muscles should be avoided because of possible fibrosis and lack of the diagnostic characteristics. Finally, the surgeon should avoid sampling a muscle that was recently needled for EMG because of post-traumatic inflammatory changes that may confuse the picture. Specific histochemical staining is important to identify specific muscle disorders such as dystroglycans, merosin, and adhalin. In specialized laboratories, specific respiratory enzymes activities can be examined to classify mitochondrial disorders. Muscle biopsy can also help in some neuropathies such as spinal muscular atrophy showing group atrophy. However, note that many causes of hypotonia are central in origin and therefore a muscle biopsy is not indicated. Recently, DNA study for the specific genetic defect has replaced the need to do the invasive biopsy in some disorders, such as spinal muscular atrophy [22]. Rapid molecular diagnosis is also now possible for congenital muscular dystrophies, several forms of congenital myopathies, and congenital myotonic dystrophy [23]. Genetic tests are helpful when positive, however, muscle biopsy is indicated if the DNA testing is negative (false negative). Reaching a specific diagnosis is very important for providing appropriate therapy, prognosis, and genetic counseling. When possible, prenatal diagnosis can be offered in subsequent pregnancies.

7. Management

Hypotonia is an expression of many disorders involving the central and peripheral nervous system. Once the correct diagnosis is confirmed, specific treatments can be offered. The diagnosis of benign congenital hypotonia should be made only after excluding common etiologies. The disorder is rare with isolated hypotonia that recovers completely before 2 years of age [20,24]. Some studies have shown that a portion of these children may have additional motor deficits on long-term follow-up [24]. Central hypotonia due to static lesions and hypotonia secondary to congenital myopathies usually improves with time. The prognosis is worst for hypotonia secondary to neuronal pathology or other progressive central disorders. Treatment is directed towards the underlying etiology, clinical manifestations, or complications of the disease.

Some central causes are correctable neurosurgically such as hydrocephalus and posterior fossa arachnoid cyst. If the hypotonia is drug related, removing the drug is curative. However, frequently it is multifactorial. Some metabolic myopathies are correctable by specific treatments to counteract the offending metabolite, replace the dysfunctional enzyme, or vitamin therapy. Examples include the use of dichloroacetate, L-carnitine, and coenzyme Q10 in mitochondrial disorders, and the reduction of phytanic acid intake in Refsum disease [10]. However, there is no cure for mitochondrial disorders and most therapies only slow the progression of the disease. Other metabolic encephalopathies such as amino acid disorders and organic acidopathies have specific treatments that can be curative if provided early. Pediatricians and neonatologists must be vigilant in early detection as early diagnosis and intervention is crucial to avoid central nervous system sequelae and death. Treatment is also directed towards treatable complications such as epilepsy, sleep disorder, behavioral symptoms, feeding difficulties, skeletal deformities, and recurrent chest infections.

These children require a multidisciplinary team approach with the involvement of several specialties including pediatrics, neurology, genetics, orthopedics, physiotherapy, and occupational therapy [17,23]. Physiotherapy is mainly preventative to avoid contractures and wasting, but will not increase muscle tone. Occupational therapy is more important in terms of seating and mobility. Counseling the families about potentially preventable disorders is very important in the management of these children. Consanguinity needs to be strongly discouraged in order to prevent inherited causes in our region.

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