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The Floppy Infant: Evaluation of Hypotonia

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Author Disclosure
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Objectives

After completing this article, readers should be able to:

1. Characterize the distinguishing features of hypotonia and muscle weakness.
2. Describe the differences between central and peripheral causes of hypotonia.
3. Generate a differential diagnosis of hypotonia in infants.
4. Discuss the appropriate medical and genetic evaluation of hypotonia in infants.
5. Understand the need to suspect infant botulism in an infant younger than 6 months of age who has signs and symptoms such as constipation, listlessness, poor feeding, weak cry, a decreased gag reflex, and hypotonia.

Introduction

The "floppy infant" represents a diagnostic challenge to general pediatricians. Infants can present with hypotonia that is due to central or peripheral nervous system abnormalities, myopathies, genetic disorders, endocrinopathies, metabolic diseases, and acute or chronic illness (Table 1). A systematic approach to a child who has hypotonia, paying attention to the history and clinical examination, is paramount in localizing the problem to a specific region of the nervous system.

It is important to distinguish weakness from hypotonia. Hypotonia is described as reduced resistance to passive range of motion in joints; weakness is reduction in the maximum power that can be generated. A more useful definition of hypotonia is an impairment of the ability to sustain postural control and movement against gravity. Thus, floppy infants exhibit poor control of movement, delayed motor skills, and hypotonic motor movement patterns. The abnormal motor patterns include alterations in postural control, increased range of motion of joints, and abnormal stability and movement mechanics. Weak infants always have hypotonia, but hypotonia may exist without weakness.

Because dysfunction at any level of the nervous system can cause hypotonia, the differential diagnosis is extensive. Central causes, both acute and chronic, are more common than are peripheral disorders. Central conditions include hypoxic-ischemic encephalopathy, other encephalopathies, brain insult, intracranial hemorrhage, chromosomal disorders, congenital syndromes, inborn errors of metabolism, and neurometabolic diseases. Peripheral disorders include abnormalities in the motor unit, specifically in the anterior horn cell (ie, spinal muscular atrophy), peripheral nerve (ie, myasthenia), neuromuscular junction (ie, botulism), and muscle (ie, myopathy). Several studies have shown that central causes account for 60% to 80% of hypotonia cases and that peripheral causes occur in 15% to 30%. The most common central cause of hypotonia is cerebral palsy or hypoxic encephalopathy in the young infant. However, this dysfunction may progress in later infancy to hypertonia. The most common neuromuscular causes, although still rare, are congenital myopathies, congenital myotonic dystrophy, and spinal muscular atrophy. Some disorders cause both central and peripheral manifestations, such as acid maltase deficiency (Pompe disease).

Differentiating Central Versus Peripheral Causes

Infants who have hypotonia and do not track visually, fail to imitate facial gestures, or appear lethargic are more likely to have cerebral or central disorders. Central causes of hypotonia often are associated with a depressed level of consciousness, predominantly axial

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Table 1. Differential Diagnosis of Neuromuscular Disorders Presenting in Newborns

Anterior Horn Cell Disorders

- Acute infantile spinal muscular atrophy
- Traumatic myelopathy
- Hypoxic-ischemic myelopathy
- Neurogenic arthrogryposis
- Infantile neuronal degeneration

Congenital Motor or Sensory Neuropathies

- Hypomyelinating neuropathy
- Congenital hypomyelinating neuropathy
- Charcot-Marie-Tooth disease
- Dejerine-Sottas disease
- Hereditary sensory and autonomic neuropathy

Neuromuscular Junction Disorders

- Transient acquired neonatal myasthenia
- Congenital myasthenia
- Magnesium toxicity
- Aminoglycoside toxicity
- Infantile botulism

Congenital Myopathies

- Nemaline myopathy
- Central core disease
- Myotubular myopathy
- Congenital fiber type disproportion myopathy
- Multicore myopathy

Muscular Dystrophies

- Dystrophinopathies
- Congenital muscular dystrophy with merosin deficiency
- Congenital muscular dystrophy without merosin deficiency
- Congenital muscular dystrophy with brain malformations or intellectual disability
- Walker-Warburg disease
- Muscle-eye-brain disease
- Fukuyama disease
- Congenital muscular dystrophy with cerebellar atrophy/hypoplasia
- Congenital muscular dystrophy with occipital argyria
- Early infantile facioscapulohumeral dystrophy
- Congenital myotonic dystrophy

Metabolic and Multisystem Diseases

- Disorders of glycogen metabolism
- Acid maltase deficiency
- Severe neonatal phosphofructokinase deficiency
- Severe neonatal phosphorylase deficiency
- Debrancher deficiency
- Primary carnitine deficiency
- Peroxisomal disorders
- Neonatal adrenoleukodystrophy
- Cerebrohepatorenal syndrome (Zellweger)
- Disorders of creatine metabolism
- Mitochondrial myopathies
- Cytochrome-c oxidase deficiency

weakness, normal strength with hypotonia, and hyperactive or normal reflexes. Other clues to central hypotonia are abnormalities of brain function, dysmorphic features, fisting of the hands, scissoring on vertical suspension, and malformations of other organs. A newborn who has cortical brain dysfunction also may have early seizures, abnormal eye movements, apnea, or exaggerated irregular breathing patterns. Central disorders can result from an injury or an ongoing injury or they can be static, predominantly genetic or developmental. Hypoxic-ischemic encephalopathy, teratogens, and metabolic disorders may evolve into hyperreflexia and hypertonia, but most syndromes do not. Infants who have experienced central injury usually develop increased tone and deep tendon reflexes; infants who have central developmental disorders do not (Table 2).

If a hypotonic infant is alert, responds appropriately to surroundings, and shows normal sleep-wake patterns, the hypotonia likely is due to involvement of the peripheral nervous system, specifically the motor unit, which includes the anterior horn motor neurons of the spinal cord. Peripheral causes are associated with profound weakness in addition to hypotonia and hyporeflexia or areflexia. Disorders of the anterior horn cell present with hypotonia, generalized weakness, absent reflexes, and feeding difficulties. In the classic infantile form of spinal muscular atrophy, fasciculations of the tongue can be seen as well as an intention tremor. Affected infants have alert, inquisitive faces but profound distal weakness. Peripheral causes also are associated with muscle atrophy, lack of abnormalities of other organs, the presence of respiratory and feeding impairment, and impairments of ocular or facial movement. Children who have motor unit disorders are less likely to show involvement of the brain and spinal cord (Table 2).

Clinical Aspects

The first step in evaluating an infant who exhibits hypotonia is to take a family and past medical history (prenatal, perinatal, and neonatal assessment). The prenatal history should include information on fetal movement in utero, fetal presentation, and the amount of amniotic fluid present. The obstetric history occasionally may identify both a cause and the timing of onset. Maternal exposures to toxins or infections suggest a central cause. Low Apgar scores may suggest floppiness from birth, and a hypotonic newborn should be considered septic until proven otherwise. A term infant who is born healthy but develops floppiness after 12 to 24 hours may have an inborn error of metabolism. Cervical spinal cord trauma is a complication of a breech delivery or cervical presen-

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Table 2. **Localization of Disorders Producing Hypotonia**

Variable	Central Injury	Central Developmental	Anterior Horn Cell	Peripheral Nerve	Neuromuscular Junction	Muscle
Strength	Normal or slight weakness	Normal or slight weakness	Weakness	Weakness	Weakness	Weakness
Deep tendon reflexes	Normal to increased	Normal	Decreased	Decreased	Normal to decreased	Decreased to absent
Babinski sign	+/−	+/−	Absent	Absent		
Infantile reflexes	Persistent	Persistent/Absent	Absent	Absent	Absent	Absent
Muscle fasciculations	Absent	Absent	Prominent	Absent	Absent	Absent
Muscle mass	Normal or disuse atrophy	Normal or disuse atrophy	Prominent atrophy (proximal)	Distal atrophy	Normal or decreased	Proximal atrophy; increased or decreased distal pseudohypertrophy
Sensation	Normal	Normal	Normal	Increased or decreased	Normal	Normal
Tone	Decreased evolving to increased	Decreased	Decreased	Decreased	Decreased or normal	Decreased

tation and can present with hypotonia, with other neurologic signs appearing days to weeks later. After the newborn period, the course of floppiness can be revealing. Central congenital hypotonia does not worsen with time but may become more readily apparent, whereas infants suffering central injury usually develop increased tone and deep tendon reflexes.

The physical examination should include the assessment of pertinent clinical features (eg, the presence of fixed deformities), a comprehensive neurologic evaluation, and an assessment for dysmorphic features. The diagnosis of myotonic dystrophy in a floppy newborn is suggested by a history of uterine dystonia and a difficult delivery, as well as by examination of the handshake of the mother, who demonstrates an inability to relax her hand.

Clinical evaluation includes a detailed neurologic assessment examining tone, strength, and reflexes. To begin assessing tone, a clinician should examine an infant's head size and shape, posture, and movement. A floppy infant often lies with limbs abducted and extended. Plagiocephaly frequently is present. Additional techniques for positioning and examining tone include horizontal and vertical suspension and traction. To demonstrate decreased tone, an infant is suspended in the prone position with the examiner's palm underneath the chest (horizontal suspension). The head and legs hang limply, forming an inverted "U" posture (Fig. 1). An infant who has hypotonia "slips through" at the shoulders when the examiner grasps him or her under the arms in an upright position (vertical suspension) (Fig. 2). Head lag or hyperextension is evident when the infant is pulled by the arms from a supine to sitting position (traction) (Fig. 3).

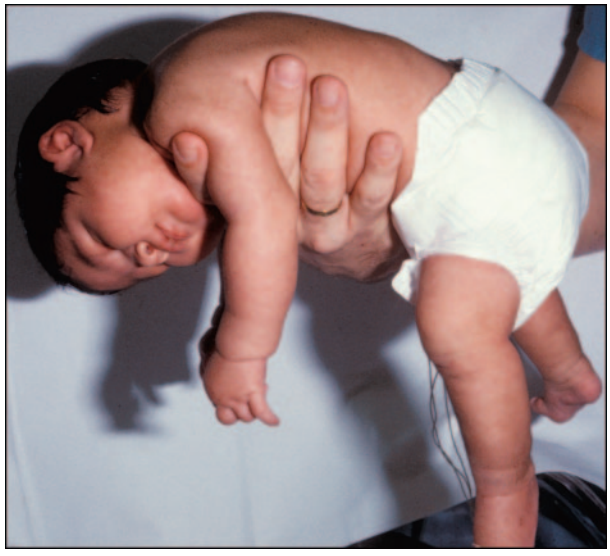

Figure 1. Infant who has trisomy and hypotonia, showing "U" posture with horizontal suspension.

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Figure 2. A 2-year-old girl who has developmental delay and hypotonia, as evidenced by the "shoulder slip through" response with vertical suspension.

Other pertinent findings may include poor trunk extension, astasias (inability to stand due to muscular incoordination) in supported standing, decreased resistance to flexion and extension of the extremities (Figs. 4, 5), exaggerated hip abduction, and exaggerated ankle dorsiflexion. Abnormalities in stability and movement may manifest in an older infant as a combat crawl, W-sitting (Fig. 6), a wide-based gait, genu recurvatum, and hyperpronation of the feet. In addition, the child who has hypotonia may exhibit oral-motor dysfunction, poor respiratory support, and gastroesophageal reflux. Deep tendon reflexes (DTRs) often are hyperactive in central conditions, and clonus and primitive reflexes persist; DTRs

Figure 3. A 15-month-old boy who has developmental delay and hypotonia, as evidenced by significant head lag with traction.

Figure 4. Hyperlaxity of the finger/wrist joints.

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Figure 5. Hyperlaxity of hand/wrist/finger joints.

are normal, decreased, or absent in peripheral disorders. Hypotonia also may manifest in the face (Figs. 7, 8).

Weakness also can manifest as decreased strength and frequency of spontaneous movements. A complete assessment for weakness includes evaluating for cry, suck, facial expressions, antigravity movements, resistance to strength testing, and respiratory effort. Infants who can generate a full motor response when aroused are more likely to be hypotonic than weak. The distribution and course of weakness is crucial to note, that is, if the face is spared versus the trunk and extremities.

The clinician should note if the hypotonia is fluctuating, static, or progressive. This differentiation discriminates between a static encephalopathy (as is seen in intellectual disability) and a degenerative neurologic condition (eg, spinal muscular atrophy). The presence or absence of dysmorphic features also should be noted on physical examination.

Figure 6. "W" sitting, a physical finding indicative of joint hyperlaxity, which can accompany hypotonia.

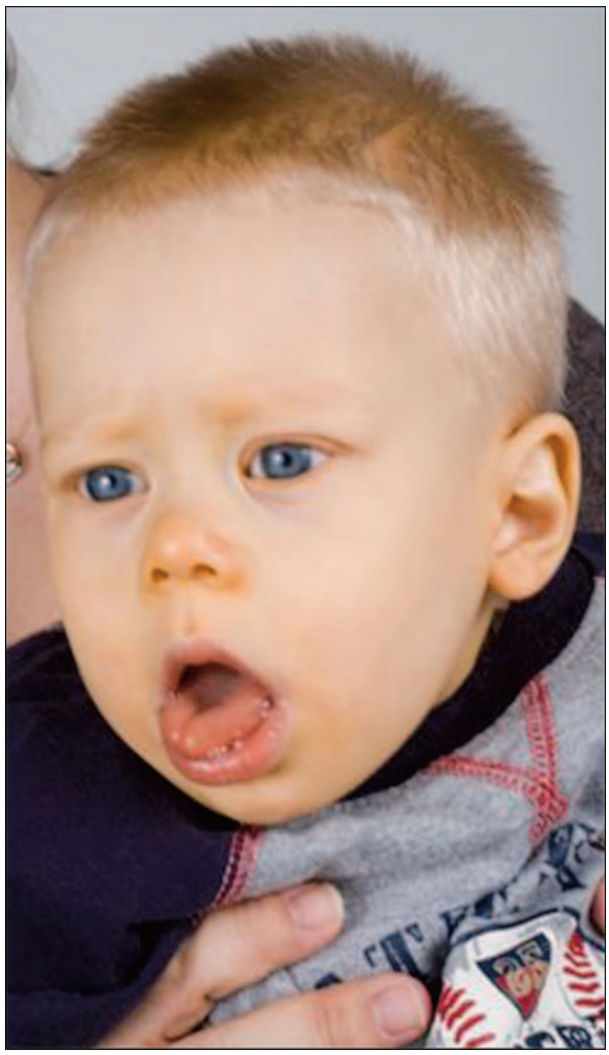

Figure 7. A 15-month-old boy who has developmental delay, hypotonia, and hypotonic facies.

Many heritable disorders are associated with hypotonia. The more common syndromes should be considered with the initial evaluation. Some of these disorders are described in this article, and frequencies are presented in Table 3. Refer to specific *GeneReviews* articles (*www.genetests.org*) for additional details.

Specific Disorders

Trisomy 21 (Down syndrome) is the most common chromosomal abnormality causing developmental disability. It is characterized by hypotonia, intellectual disability, and congenital heart defects (in 50%). Particular physical features in the neonate include flattened posterior occiput with brachycephaly, flat facial profile and nasal bridge, upslanting palpebral fissures, small or

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Figure 8. A 3-year-old girl who has global developmental delay and hypotonic facies. Note the shape of the mouth and the eyelid lag.

anomalous ears, short neck with excess nuchal folds, single transverse palmar creases, hypoplasia of the midphalanx of the fifth digit with clinodactyly, joint hyperextensibility, dysplasia of the pelvis, and a poor Moro reflex. A high-resolution chromosomal study is diagnostic for most patients. If chromosomes are normal on high resolution and concern remains, a trisomy screen or fluorescence in situ hybridization (FISH) testing should be requested for partial mosaic trisomy.

Fragile X syndrome is another genetic condition characterized by mild-to-profound intellectual disability, poor eye contact, autistic features, macrocephaly, large ears, epicanthal folds, a thickened nasal bridge, and increased testicular size in puberty. An expansion of a trinucleotide repeat (CGG) in the promoter region of the *FMR1* gene at Xq27.3 is responsible for the phenotype and is the basis for the molecular diagnosis of the disorder. Affected individuals have more than 200 repeats. Premutation carriers also can be detected in this manner. Although hypotonia generally is a feature during infancy, it is mild, and most children who have fragile X syndrome are not diagnosed early in life until a delay in developmental milestones is detected.

Prader-Willi syndrome is characterized by hypotonia, hypogonadism, intellectual disability, short stature, and obesity. Affected patients present at birth with profound hypotonia and feeding problems until 8 to 11 months of age, when they develop low-normal muscle tone and insatiable appetites. Prominent physical features during childhood include a narrow bifrontal diameter, strabismus, almond-shaped eyes, enamel hypoplasia, and small hands and feet. The genetic abnormality in 75% of patients is a deletion of the long arm of chromosome 15 at q11-q13. In all cases studied, the paternally derived chromosome has been deleted. Maternal uniparental disomy accounts for an additional 20% of cases. The remaining 5% are due to a mutation of the imprinting center or to a chromosomal translocation. Methylation analysis can detect all three molecular defects. If the methylation study result is abnormal, a FISH study can be used to define the diagnosis further.

Kabuki syndrome is a multiple congenital anomaly syndrome associated with hypotonia and feeding problems and is characterized by specific facial features (Fig. 9), mild-to-moderate intellectual disability, postnatal growth delay, skeletal abnormalities, and unusual dermatoglyphic patterns that have prominent fingertip pads. Physical features include long palpebral fissures with eversion of the lateral lower eyelid, large protuberant ears, cleft palate, tooth abnormalities, skeletal abnormalities, and cardiac and renal defects. Blue sclerae and a tethered nasal tip also are present. In the absence of major birth defects, this syndrome is difficult to recognize in neonates. No definitive genetic test or mechanism of inheritance has been determined, but research is ongoing.

Hypotonia in infancy and developmental delays are common manifestations in individuals afflicted with X-linked mental retardation (XLMR). Affected children typically present with decreased muscle tone early in life, and striking progression to spasticity may occur. Thirty syndromes exist in which infantile hypotonia is associated with XLMR, and recent studies have identified five genes associated with syndromal intellectual disability. Early diagnosis often is difficult because distinctive syndromic findings may be absent in the early years and only hypotonia and developmental delays may exist. One such disorder is the ATRX syndrome (alpha thalassemia-

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Table 3. Prevalence of Causes of Hypotonia

Cause of Hypotonia	Percentage in Three Hypotonic Series (n=277)	Prevalence	Distinguishing Features	Test Available?
Hypoxic-ischemic Encephalopathy	19%			
Genetic/Chromosomal Syndromes	31%			
Down syndrome	13%	1:800 to 1:1,000		Karyotype
Prader-Willi syndrome	5%	1:10,000 to 1:30,000		Methylation
Other dysmorphic syndromes	9%			
Other chromosomal anomalies	4%			Karyotype
Fragile X syndrome		1:4,000 males 1:8,000 females		*FMR1* test
Trisomy 18 (Edwards syndrome)		1:5,000 to 1:6,000		Karyotype
1p36 deletion syndrome		1:5,000 to 1:10,000		Array CGH
22q13 deletion syndrome		*		Array CGH
22q11.2 deletion syndrome (velocardiofacial/DiGeorge syndrome)		1:4,000 to 1:6,400		Array CGH
Williams syndrome		1:7,500		Array CGH
Trisomy 13 (Patau syndrome)		1:10,000		Karyotype
Smith-Magenis syndrome		1:15,000 to 1:25,000		Array CGH
Sotos syndrome		1:14,000		Array CGH
Wolf-Hirschhorn syndrome		1:50,000		Array CGH
Kabuki syndrome		1:30,000		None
Cri du chat syndrome		1:20,000 to 1:50,000		Karyotype
Brain anomalies	13%			
Myopathies	5%			
Central core disease		**		
Nemaline myopathy		1:50,000		
X-linked myotubular myopathy		1:50,000		
Congenital myotonic dystrophy	4%	1:100,000		
Metabolic disorders	3%			
Peroxisome biogenesis disorders, Zellweger syndrome spectrum		1:50,000		
Smith-Lemli-Opitz syndrome		1:20,000 to 1:60,000		
Glycogen storage disease Pompe (Type II)		1:14,000 to 1:100,000 1:40,000 (in United States)	Cardiomegaly	GAA gene; Alpha glucosidase
Benign neonatal hypotonia	3%			
Spinal muscular atrophy	2%	1:10,000		
Muscular dystrophies	2%	1:20,000 to 1:40,000		
Joint laxity	1.4%			
Neuropathy	1.4%			
Teratogens	1%			
Brain tumor	0.4%			
Myoclonic encephalopathy	0.4%			
Neuromuscular junction disorder	0.4%			
Familial infantile myasthenia (not transient)		1 to 4.4:1,000,000		Decremental EMG, negative antibodies, multiple gene tests for AcHR
Unknown	13%			

AcHR=anticholine receptor, EMG=electromyography, CGH=comparative genomic hybridization
*Second most common subtelomeric deletion after 1p36 deletion syndrome (*GeneReviews*)
**Most common congenital myopathy (*GeneReviews*)

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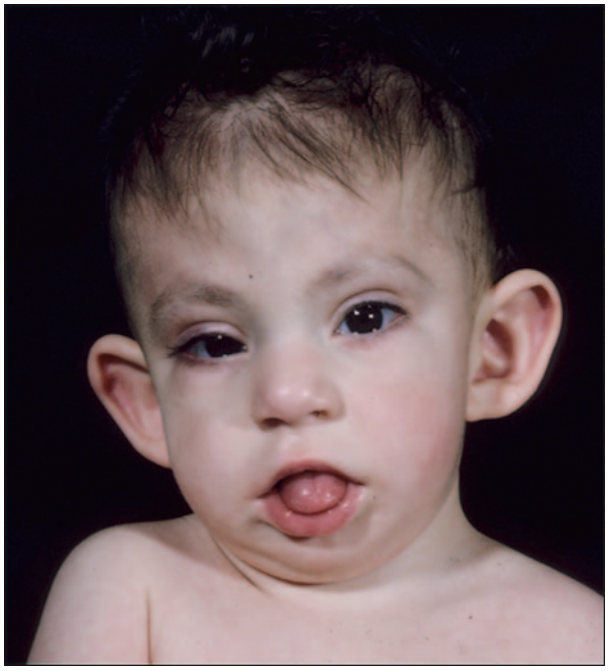

Figure 9. Child who has Kabuki syndrome. Note epicanthal folds, eversion of lateral half of eyelids, and hypotonic facies with protuberant tongue.

intellectual disability), which is associated with hypotonic facies and developmental delays. *XNP* is the causative gene.

Myotonic dystrophy is a multisystem disorder transmitted by autosomal dominant inheritance and caused by an unstable DNA trinucleotide repeat on chromosome 19 that can expand in successive generations. Symptoms usually begin in young adult life and include weakness of the face and distal limb muscles, cataracts, multiple endocrinopathies, frontal baldness in males, and myotonia. Congenital myotonic dystrophy (Steinert disease) can afflict infants born to affected mothers. Polyhydramnios is common, labor is prolonged, and delivery usually requires mechanical assistance. Severely affected infants have inadequate diaphragm and intercostal muscle function and require assisted mechanical ventilation. Perinatal asphyxia can be a consequence of a prolonged and difficult delivery and resuscitation. Facial diplegia, generalized muscular hypotonia, joint deformities, gastrointestinal dysfunction, and oral motor dysfunction can occur. Affected infants have a characteristic facial appearance, with tenting of the upper lip, thin cheeks, and wasting of the temporalis muscles. They also tend to have dislocated hips, arthrogryposis, and club feet. Limb weakness is proximal, tendon reflexes usually are absent, and myotonia may not be elicited on electromyography (EMG). The patients tend to have intellectual deficits. Cardiomyopathy contributes to early death, and the long-term prognosis is poor. Respiratory failure and an increased risk of aspiration also lead to early death. If the infant survives the first 3 postnatal weeks, motor function may improve, although facial diplegia usually persists.

Spinal muscular atrophies are a heterogeneous group of disorders, usually genetic in origin, characterized by the degeneration of anterior horn cells in the spinal cord and motor nuclei of the brainstem. Symptoms can present from birth to adult life. Disorders that begin in infancy are marked by a generalized distribution of weakness. Several clinical syndromes of infantile spinal muscular atrophy exist, one form manifesting between birth and 6 months of age (Werdnig-Hoffmann disease). Inheritance is autosomal recessive. Newborns often have arthrogryposis at birth, and weakness progresses rapidly to respiratory insufficiency and death.

Myasthenia syndromes can be caused by genetic defects or can occur as a transitory phenomenon in 10% to 15% of infants born to women who have myasthenia. Most myasthenia syndromes are transmitted via autosomal recessive inheritance and are rare (Table 3). Many infants require assisted ventilation at birth. Arthrogryposis may be present, as well as ptosis and generalized weakness. The infants are able to be weaned from mechanical ventilation in weeks, but persistent episodes of weakness and apnea may occur. The diagnosis is established by the patient's response to an intravenous or subcutaneous injection of edrophonium chloride (0.15 mg/kg). Ptosis and oculomotor paresis are the only functions that can be tested reliably.

The transitory myasthenic syndrome is due to the passive placental transfer of antibodies against the acetylcholine receptor protein from the mother who has myasthenia to her unaffected fetus. The severity of symptoms correlates with the newborn's antibody concentration. Difficulty feeding and generalized hypotonia are the major clinical features. Symptoms usually occur within hours of birth or up to 3 days later. Respiratory insufficiency is uncommon. Although weakness initially worsens, dramatic resolution subsequently occurs. The duration of symptoms averages 18 days, and recovery is complete. The transitory disorder is diagnosed by the presence of antibodies in the infant's blood and the temporary reversal of weakness with injection of edrophonium.

Laboratory Evaluation

The initial laboratory evaluation of the hypotonic newborn is directed at ruling out systemic disorders. Routine studies should include an evaluation for sepsis (blood culture, urine culture, cerebrospinal fluid culture and

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analysis); measurement of serum electrolytes, including liver functions and ammonia, glucose, calcium, magnesium, and creatinine; a complete blood count; and a urine drug screen. If hepatosplenomegaly is present and calcifications are noted on head ultrasonography, TORCH titers (toxoplasmosis, rubella, cytomegalovirus infection, herpesvirus infections) and a urine culture for cytomegalovirus should be undertaken.

If the hypotonia is considered to be central, the practitioner should evaluate for genetic and metabolic causes. A karyotype is indicated when several significant dysmorphic features are present and can disclose any obvious cytogenetic defects. Array comparative genomic hybridization study, methylation study for 15q11.2 (Prader-Willi/Angelman) imprinting defects, and testing for known disorders with specific mutational analysis are now available. Molecular genetic testing provides the advantage of speed and diagnostic specificity without invasive procedures. These tests should be chosen according to the clinical presentation of the infant.

If the clinical evaluation suggests complex multisystem involvement, screening for inborn errors of metabolism is indicated. If acidosis is present, plasma amino acids and urine organic acids (aminoacidopathies and organic acidemias), serum lactate (disorders of carbohydrate metabolism, mitochondrial disease), pyruvate, ammonia (urea cycle defects), and acylcarnitine profile (organic acidemia, fatty acid oxidation disorder) should be measured. Very long-chain fatty acids and plasmalogens are specific for the evaluation of a peroxisomal disorder. A creatine kinase and acylcarnitine/carnitine concentration should be determined if the child is weak and exhibits hypotonia to aid in diagnosis of a muscular dystrophy or carnitine deficiency. The list of neurometabolic conditions associated with hypotonia is immense and beyond the scope of this review.

To evaluate causes of peripheral hypotonia, creatine kinase concentrations should be measured. This value is elevated in muscular dystrophy but not in spinal muscular atrophy or in many myopathies. Specific DNA testing can be performed for myotonic dystrophy and for spinal muscular atrophy. Other potentially useful screening tools include electrophysiologic studies, which show abnormalities in nerves, myopathies, and disorders of the neuromuscular junction. With the exception of a few myopathies, normal EMG findings suggest that the hypotonia is central in origin. Muscle biopsy with immunohistochemical staining and electron microscopy is the method of choice for differentiating myopathies and muscular dystrophies, although it is more invasive. If biopsy shows specific abnormalities, it can be an essential part of the diagnostic evaluation in the newborn to guide subsequent DNA molecular diagnostic studies.

Radiologic Evaluation

Neuroimaging is a valuable tool for detecting central nervous system abnormalities. Magnetic resonance imaging can delineate structural malformations, neuronal migrational defects, abnormal signals in the basal ganglia (mitochondrial abnormalities), or brain stem defects (Joubert syndrome). Deep white matter changes can be seen in Lowe syndrome, a peroxisomal defect. Abnormalities in the corpus callosum may occur in Smith-Lemli-Opitz syndrome; heterotopias may be seen in congenital muscular dystrophy. Magnetic resonance spectroscopy also can be revealing for metabolic disease.

Other Diagnostic Considerations

The findings of an enlarged heart in a floppy, weak infant who has delayed milestones should alert the clinician to the possibility of a glycogen storage disease (type II Pompe disease or acid maltase deficiency). This condition is caused by a deficiency in the lysosomal enzyme acid alpha glucosidase, present in all tissues, which hydrolyzes maltose to yield glucose but has no function in maintaining blood glucose. Absent enzyme activity in the infantile form of Pompe disease results in abnormal glycogen deposition in the skeletal, cardiac, and smooth muscles, leading to hypertrophic cardiomyopathy, feeding abnormalities, hypotonia, weakness, respiratory insufficiency, and ultimately, death. Inherited in an autosomal recessive pattern, the infantile form may present perinatally, but onset of symptoms usually occurs in the second postnatal month. Profound generalized hypotonia without atrophy and congestive heart failure are the initial signs. Hypotonia is the result of glycogen storage in the brain, spinal cord, and muscle, producing a mixed central and peripheral clinical picture. Cardiomegaly almost always is diagnostic. Most patients die of cardiac failure by 12 months of age.

The diagnosis of Pompe disease is established by muscle biopsy, with a definitive diagnosis being demonstrated by deficient acid maltase activity in fibroblasts or other tissues. Early diagnosis of Pompe disease results in early institution of enzyme replacement therapy, which minimizes morbidity and prolongs survival. However, improving the function of skeletal muscle has proven to be a more challenging prospect for enzyme replacement therapy, which has not been shown to affect outcomes in severe cases presenting in the first few postnatal months with associated congenital anomalies or ventilator dependence. Recent assays using

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tandem mass spectrometry are likely to prove useful for early diagnosis and institution of therapy.

Other important diagnostic considerations for the primary care clinician include the presentation of an acute or subacute episode of hypotonia. Human botulism ordinarily results from eating foods contaminated by preformed exotoxin of the organism *Clostridium botulinum*. The exotoxin blocks the release of acetylcholine at the neuromuscular junction, which results in cholinergic blockade of skeletal muscle and end organs innervated by autonomic nerves. Infantile botulism is an age-limited disorder in which *C botulinum* is ingested, colonizes the intestinal tract, and produces toxin in situ. In only 20% of cases, contamination with honey or corn syrup is identified.

Historically, infants afflicted with botulism are between 2 and 26 weeks of age, usually live in a dusty environment adjacent to construction or agricultural soil disruption, and become symptomatic between March and October. A prodrome of constipation, lethargy, and poor feeding is followed in 4 to 5 days by progressive bulbar and skeletal muscle weakness and loss of DTRs. Progressive muscle paralysis can lead to respiratory failure. Symmetric bulbar nerve palsies manifested as ptosis, sluggish pupillary response to light, ophthalmoplegia, poor suck, difficulty swallowing, decreased gag reflex, and an expressionless face are primary features of infantile botulism.

The differential diagnosis includes sepsis, intoxication, dehydration, electrolyte imbalance, encephalitis, myasthenia gravis, and polyneuropathies such as Guillain-Barré syndrome. Spinal muscular atrophy type I and metabolic disorders can mimic infantile botulism. Patients who have spinal muscular atrophy type I generally have a longer history of generalized weakness, do not typically have ophthalmoplegia, and have normal anal sphincter tone. Treatment for infantile botulism should be instituted promptly with intravenous human botulism immune globulin, which neutralizes all circulating botulinum toxin, and supportive therapy for airway maintenance, ventilation, and nutrition. Infantile botulism usually is a self-limited disease lasting 2 to 6 weeks, and recovery generally is complete, although relapse can occur in up to 5% of infants.

The most common clinical condition, although a diagnosis of exclusion, is benign congenital hypotonia. This nonprogressive neuromuscular disorder presents at birth with delays in achieving developmental milestones. Benign congenital hypotonia improves with the maturity of the central nervous system. Characteristics include generalized symmetric flaccidity of muscles and hypermobile joints. Because this is a diagnosis of exclusion, the history must not suggest any neurologic or metabolic disorders. Muscle stretch reflexes are normal or only slightly exaggerated, and routine laboratory test results are within normal limits. Patients must be counseled about the possibility of joint dislocations in the future. An increased incidence of intellectual disability, learning disability, or other sequelae of cerebral abnormality often is evident later in life, despite the recovery of normal muscle tone. A high familial incidence also is reported. This condition must be differentiated from congenital muscular dystrophy, which has a high risk of life-threatening malignant hyperthermia from anesthesia.

The cause of hypotonia in most affected patients is central. The greatest diagnostic yield starts with a detailed medical history and examination, including a neurologic evaluation and the search for dysmorphic features. The selective use of neuroimaging, genetic studies, and biochemical investigations can contribute to a diag-

Table 4. Diagnostic Yield

Method of Diagnosis	% Successfully Diagnosed
History and Physical Examination (Step 1) Family history Pregnancy and delivery Clinical and neurologic examination	50%
Imaging Study (CT or MRI/MRS) (Step 2)	13%
Clinical Genetic Evaluation (Step 3)	9%
Genetic Testing (Step 4) Karyotype, FISH, CGH	6%
Biochemical Evaluation (Step 5) Amino acids, organic acids, peroxisomes, carnitine, CDG test	6%
Neuromuscular Testing (Step 6) CK, EMG, NCV, DNA for SMA and CMD, muscle biopsy	6%
Follow-up Testing Some tests repeated/Further tests	7%

CK=creatine kinase, CMD=congenital muscular dystrophy, CDG=congenital disorder of glycosylation, CGH=comparative genomic hybridization, CT=computed tomography scan, EMG=electromyography, FISH=fluorescence in situ hybridization, MRI=magnetic resonance imaging, MRS=magnetic resonance spectrography, NCV=nerve conduction velocity, SMA=spinal muscular atrophy,
Adapted from Paro-Panjan D, Neubauer D. Congenital hypotonia: is there an algorithm? *J Child Neurol.* 2004;19:439–442

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nosis in an additional subset of patients. Invasive studies with EMG and muscle biopsy only contribute to a small fraction of diagnoses. A suggested algorithm by Paro-Panjan is detailed in Table 4.

Treatment

Treatment of the infant who has hypotonia must be tailored to the specific responsible condition. In general, therapy is supportive. Rehabilitation is an important therapeutic consideration, with the aid of physical and occupational therapists. Nutrition is of primary importance, often achieved through nasogastric or percutaneous gastrostomy tubes for additional caloric supplementation. It also is important to maximize muscle function and minimize secondary crippling anatomic deformities. Genetic counseling is an important adjunct for the family.

Summary

- Hypotonia is characterized by reduced resistance to passive range of motion in joints versus weakness, which is a reduction in the maximum muscle power that can be generated. (Dubowitz, 1985; Crawford, 1992; Martin, 2005)
- Based on strong research evidence, central hypotonia accounts for 60% to 80% of cases of hypotonia, whereas peripheral hypotonia is the cause in about 15% to 30% of cases. Disorders causing hypotonia often are associated with a depressed level of consciousness, predominantly axial weakness, normal strength accompanying the hypotonia, and hyperactive or normal reflexes. (Martin, 2005; Igarashi, 2004; Richer, 2001; Miller, 1992; Crawford, 1992; Bergen, 1985; Dubowitz, 1985)
- Based on some research evidence, 50% of patients who have hypotonia are diagnosed by history and physical examination alone. (Paro-Panjan, 2004)
- Based on some research evidence, an appropriate medical and genetic evaluation of hypotonia in infants includes a karyotype, DNA-based diagnostic tests, and cranial imaging. (Battaglia, 2008; Laugel, 2008; Birdi, 2005; Paro-Panjan, 2004; Prasad, 2003; Richer, 2001; Dimario, 1989)
- Based on strong research evidence, infant botulism should be suspected in an acute or subacute presentation of hypotonia in an infant younger than 6 months of age who has signs and symptoms such as constipation, listlessness, poor feeding, weak cry, and a decreased gag reflex. (Francisco, 2007; Muensterer, 2000)

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The Floppy Infant: Evaluation of Hypotonia

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