

The Evaluation of the Hypotonic Infant

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The pediatric neurologist is regularly asked to evaluate a hypotonic patient. This consultation request usually occurs in 2 different situations; the first is in the newborn period when the neurologist is asked to evaluate the "floppy infant," and the second is in the latter half of the first year of life and is usually accompanied by concern about the developmental progress of the infant and, in particular, the motor development of the infant. In this article, I will try to outline the factors related to the production of muscle tone in infants and children. The elements of the clinical evaluation of the hypotonic child including those clinical tests most helpful in the measurement of tone will be reviewed. A scheme for localizing the origin of the disturbance in muscle tone is presented, many of the known causes of the tone abnormalities are reviewed, and a rational approach to the diagnostic evaluation of these children is offered.

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One of the most difficult tasks the general pediatric neurologist is asked to undertake is the evaluation of the hypotonic child. In the newborn, the differential must include acute illnesses and systemic diseases such as sepsis and congestive heart failure. Both categories are beyond the scope of this article. The second situation in which the neurologist is asked to evaluate a hypotonic child is usually in the later half of the first year when the issue is not only tone but also delay in the acquisition of psychomotor developmental milestones. To construct a meaningful differential diagnosis and eventually arrive at an appropriate diagnosis, the clinician must ascertain whether the patient is hypotonic or hypotonic and weak together. The physician must also ascertain whether the delay, when present, is just a motor delay or motor and cognitive delay together. These may seem to be straightforward determinations but, in fact, are among the more difficult clinical determinations clinicians are called on to make, requiring careful history and examination and frequently requiring serial examinations to be confident of the result.

In addition to the determination of tone and strength as well as motor versus psychomotor delay, the physician must try to localize the process within the nervous system. I find it most useful to divide the localization into 2 large groups: the supraspinal conditions (the brain, brainstem, and cervical spinal junction) that we can call central hypotonia and the segmental conditions, which are more appropriately called

motor unit hypotonia (including anterior horn cell, peripheral nerve, neuromuscular junction, and muscle). To successfully undertake this process with the minimum of false starts and unnecessary investigations, the clinician must have an understanding of the nature of tone itself as well as some of the specifics of the conditions in the differential of each type of hypotonia.

Muscle Tone

Muscle tone is usually defined as the resistance to passive movement. Muscle tone is most easily shown as movement of an extremity but certainly including the trunk, neck, back and the shoulder, and pelvic girdles. In the clinical setting, we speak of 2 types of tone: phasic tone and postural tone.¹⁻⁶ Phasic tone may be thought of as the passive resistance to movement of the extremities (appendicular structures), whereas postural tone may be thought of as the resistance to passive movement of the axial muscles (neck, back, trunk, and so on). There may be a discrepancy between phasic tone and postural tone in a given patient. The most common example might be in the 3- or 4-month-old infant who has suffered an hypoxic-ischemic insult at birth and now has poor head and trunk control (postural hypotonia) but is beginning to become stiff (hypertonic) in the extremities (phasic tone) and will eventually develop increased reflexes and tone (spasticity) in the appendicular and axial muscles.

The neurologic inputs that influence muscle tone are divided into 2 major categories for convenience; these are supraspinal or suprasegmental structures and motor unit or segmental structures. Supraspinal influences represent those inputs from the central nervous system (CNS) in general as

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well as discrete structures within the brain that have to do with movement and motor control. This influence is exerted on the axial and appendicular muscles but is most easily appreciated in the appendicular portion of the motor system. For example, the motor strip is normally a facilitator of muscle tone, and a discrete surgically produced lesion in the motor strip will result in decreased tone in the corresponding portion of the body. There are many other CNS structures that have well-known influences on the tone of the individual including, but not limited to, the basal ganglia and striatum, the red nucleus, and the cerebellum. The basal ganglia and red nucleus are normally inhibitors of somatic tone, and damage or dysfunction of these structures is typically associated with increased resistance to passive movement of the extremities. The cerebellum normally is a powerful facilitator of tone and damage to the organ produces decreased tone. Midline cerebellum damage may relate most to axial hypotonia and lateral cerebellar damage causing appendicular hypotonia.

Motor unit or segmental structures related to tone include the reflex loop and the components thereof. The reflex loop is influenced by discrete supraspinal or suprasegmental inputs (the sum of the discrete CNS inputs) as well as diffuse cerebral inputs such as level of consciousness, anxiety, and so on, and all are eventually translated into the resting rate of discharge of the anterior horn cell or motor neuron. A commonly observed change in tone and reflex activity related to diffuse cerebral inputs is observed in teens or preteens who are anxious about the examination and as a result have increased tone and brisk, although not pathologic, myotatic

reflexes. More discrete lesions of the motor unit may affect either the afferent or efferent limb of the reflex arc or the muscle itself. These lesions almost always result in the loss of the myotatic reflex as we commonly measure it. Lesions of the neuromuscular junction may also be associated with hypotonia and weakness but may have preserved reflexes. This is particularly true unless special examinations are performed to test the limits of the neuromuscular transmission in the form of repetitive stimulation and single-fiber jitter. Peripheral lesions that might increase tone include visceral pain, which may cause increased sensitivity and increased resting discharge in the spinal segments involved. An example of this would be the “splinting” that occurs with pleural inflammation associated with an increased discharge of the motor units in the area of the pain.

Measures of Muscle Tone

The quantification of tone, particularly in the typical clinical setting, is and has always been problematic. Attempts to objectify the assessment of tone with scales like the Ashworth scale are only moderately reliable and repeatable even between serial examinations by the same individual.⁷ Nevertheless, in older infants and children, such scales are more useful than cumbersome attempts at more precise assessments. In the newborn, tone measurement is even more subjective and dependent on the experience and attitude of the examiner. There are several maneuvers that have been generally found to be useful in the demonstration of tone and the detection of abnormalities of tone, particularly low tone. These maneu-

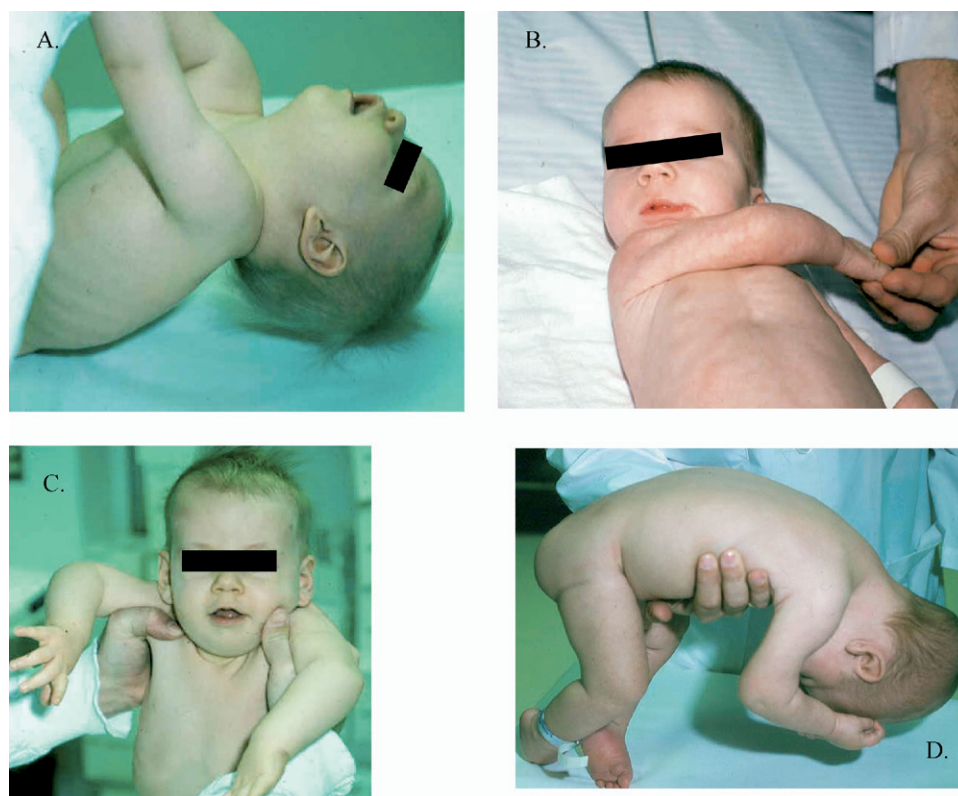


Figure 1 Measures of hypotonia: (A) pull to sit, (B) scarf sign, (C) shoulder suspension, and (D) ventral suspension.

vers include (1) “pull to sit,” (2) the “scarf sign,” (3) “shoulder suspension,” and (4) “ventral suspension” (Fig 1).

The “pull to sit” maneuver is performed by grasping the supine infant’s hands and gently pulling them to a sitting position. The normal newborn will have a head lag, but, by about 2 months of age, this should be minimal if still present at all. Premature infants will have lower tone than term infants, and term infants will have lower tone than postterm infants normally. The “pull to sit” maneuver tests axial tone of the neck and back and appendicular tone of the shoulder and arms and also tests strength to some extent because the normal response from the infant being tested is to resist the pull on the arms and shoulder.

The “scarf sign” is performed by grasping the supine infant’s hand and pulling it across the chest as far as it will go without significant resistance. Normally, the elbow can be brought to the midline of the baby’s chin and chest. In the hypotonic infant, the elbow can easily be brought well beyond the midline before encountering resistance. This test measures the appendicular tone in the shoulder and is somewhat sensitive to the gestational age of the infant, the degree of laxity of the ligaments, and the state of alertness of the child.

The examiner performs the shoulder suspension test by picking the infant up holding them under the arms. The hypotonic infant tends to slip through the examiners hands, and the maneuver is a test of appendicular tone but can also give some indication of head control (axial) as well as strength because the normal infant provides some resistance in the shoulders when being lifted.

In ventral suspension, the infant is lifted off the table by 1 hand under the chest and abdomen. The position the infant assumes is quite dependent on the gestational age and state of alertness. Normally, the term infant will keep the arms and legs flexed some and is able to lift the head above the horizontal, although not indefinitely. The premature infant will just drape over the hand, and the postmature infant would be able to keep the arms and legs flexed and the head above horizontal indefinitely. In older children (eg, 2 to 4 months

old), this maneuver is also a reasonably good measure of strength.

The examiner who regularly performs these 4 maneuvers will soon develop a sense of what is normal and what is not. Unfortunately, there is no substitute for experience in making this judgment in the clinical setting, and there is no objective measurement of the result either.

Clinical Evaluation

Now that we have some understanding of how tone is generated and measured, it is appropriate to discuss the key components of the clinical evaluation of the hypotonic patient and then discuss the localization of the cause of the tone abnormality and conclude with considerations in the differential diagnosis based on the clinical features and localization.

Once the patient has been clearly identified as hypotonic using the procedures listed previously, the examiner must ascertain 2 important features before addressing the diagnosis or differential diagnosis. The examiner must determine if the patient has weakness in addition to a tone abnormality or if the patient is just hypotonic but normally strong. This sounds easier than it actually is because strength, defined as the maximum voluntary resistance to a movement, requires that the patient actively resist with maximum effort. This almost never occurs in the infant or young child outside of the setting in which the examiner applies a noxious stimulus that the patient tries to avoid. Furthermore, this process can be difficult in the presence of the parent for obvious reasons. Thus, we are frequently left with indirect measures of the strength and thus are vulnerable to misinterpretations and judgmental errors. Once again, there is no substitute for experience, and I strongly recommend that the patient be examined on 2 or more occasions to minimize the effects of the confounding elements such as the state of alertness of the child. This will decrease the likelihood of making major misinterpretations of the clinical findings. The second important feature to determine is the presence or absence of myotatic

Table 1 Localization in the Floppy Infant

| Origin of Hypotonia | Structural Localization | Clinical Pathological Conditions |
|---|--------------------------|---|
| Supraspinal/suprasegmental hypotonia (preserved DTR) | Brain Brainstem | Systemic illness (sepsis, CHF, HIE) Syndromic hypotonia Cerebral dysgenesis Grossly normal brain |
| Segmental or motor unit hypotonia (DTR depressed or lost) | Craniovertebral junction | Spinal cord injury |
| | Anterior horn cell | Spinal muscular atrophy |
| | Peripheral nerve | HMSN |
| | Neuromuscular junction | Myasthenia gravis, congenital myasthenic syndromes, botulism |
| | Muscle | Congenital myopathies, metabolic myopathies, neonatal presentation of muscular dystrophy |

DTR = myotatic reflexes (deep tendon reflexes); CHF = congestive heart failure; HIE = hypoxic ischemic encephalopathy; HMSN = hereditary motor sensory neuropathy.

Table 2 Central Hypotonia

| Syndromic Hypotonia | Nonsyndromic Hypotonia |
|---|--|
| Dysmorphic features (constellations of features in recognizable combinations followed by genetic confirmation in many) Dozens of syndromes, Prader-Willi, Smith-Lemli-Opitz, Angelman, Down, Sotos, Coffin-Lowry, cerebro-oculo-facioskeletal, many deletion syndromes | No recognizable dysmorphic features Reflexes often depressed but present MRI in the first 6 to 8 months may show delayed myelination or may show cerebral dysgenesis |

MRI = magnetic resonance imaging.

reflexes. Most hypotonic individuals will have depressed reflexes requiring that the examiner be careful to test the patient in the proper state, proper position, striking the appropriate tendon at the correct place, and delivering the proper stimulus strength to elicit the reflexes. If the myotatic reflexes are truly absent, it suggests that the difficulty lies somewhere in the motor unit, and thus the differential is narrowed considerably.

Localization of Hypotonia

Localization of the lesion or disease process has traditionally been a useful exercise in neurology. This remains the case in dealing with the hypotonic infant or child as well. A scheme of localization based on the division of potential causes into 2 general categories is presented in Table 1. Those conditions that affect the brain and brainstem, either diffusely or focally, and in which the myotatic reflexes are preserved, I call supraspinal or suprasegmental conditions, although, the term “central hypotonia” is frequently used when the cause of the hypotonia is thought to be due to the effect a condition has on the CNS. We also have those conditions that affect the motor unit that I call segmental or motor unit conditions. In the latter conditions, reflexes are usually lost completely, with the exception of the myasthenic syndromes in which standard testing of myotatic reflexes is usually unremarkable.

Central Hypotonia

Systemic Disease

Using the localization scheme to organize the discussion of individual entities from the top down, the most important and by far the most frequent cause of hypotonia in the newborn infant is systemic disease that influences the entire CNS (brain and brainstem) diffusely to cause hypotonia. The most frequent examples include congestive heart failure in an infant with significant congenital heart disease. These infants spend all of their energy breathing and pumping blood. They do not move much; they may be profoundly hypotonic and diffusely weak as well, although the assessment of strength is not possible because of the lack of voluntary effort on the part of an acutely ill infant. The infant with sepsis will also have hypotonia that is sometimes quite severe, but they usually have other features that allow the physician to suspect a systemic illness as the culprit. The infant who has suffered a hypoxic-ischemic insult will have altered consciousness in the immediate newborn period, but when they seem to regain consciousness, the hypotonia will persist for months

sometimes until they begin to get increased tone and reflexes and become spastic after the first 2 to 3 months of life. The number of hypotonic infants with systemic disease is larger than the number of all of the other conditions discussed here put together. This fact makes the assessment of the infant’s general health imperative as the first step in the evaluation of the floppy infant.

Another category of systemic disease would be those infants with inborn errors of metabolism. These infants certainly may be hypotonic, although usually there is a prominent alteration of mental status; an infant with a metabolic abnormality such as hyperammonemia may appear to be septic, and the distinction will usually not be clear until the results of the metabolic screens are available.

Syndromic Central Hypotonia

A significant cause of hypotonia in both infants and children is the presence of one of the genetic syndromes known to be associated with hypotonia. The list of possibilities here is extensive, and it is unlikely that any single physician could identify all of them without considerable help from the genetics laboratory. The most common conditions include Down syndrome and other chromosomal anomalies. Smith-Lemli-Opitz, Prader-Willi syndrome, cerebro-oculo-facial syndrome, Coffin-Lowry syndrome, Angelman syndrome, Sotos syndrome, Joubert syndrome, Shprintzen syndrome, Marfan syndrome, and osteogenesis imperfecta (Table 2). The physician must search carefully for somatic anomalies or dysmorphic features during the examination of the patient. Many infants will have 1 anomalous or dysmorphic feature, only a few will have 2 such features, and 3 or more are highly associated with malformations in major organ systems and

Table 3 Nonsyndromic Hypotonia

| Cerebral Dysgenesis | No Morphologic Abnormality on MRI |
|--|--|
| Developmental anomalies of the brain, most of which are not in the category of namable cerebral malformations but represent more subtle anomalies of brain formation These children will not probably be normal though tone may improve with maturation | Grossly normal brain (GNB) With or without delayed myelination on MRI (scan done in the first 8 months) |

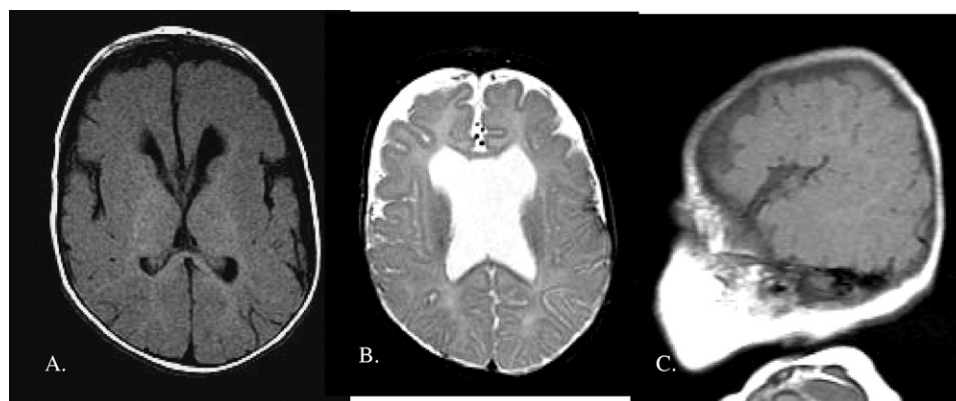


Figure 2 Three examples of abnormal brain structure on magnetic resonance imaging. None are sufficiently distinctive to be “named” by the neuroradiologist.

suggest that its not inappropriate to search for a syndromic cause of the hypotonia.

Nonsyndromic Central Hypotonia

This diverse group of conditions has never been carefully studied or characterized. These are patients who do not have a recognizable collection of somatic dysmorphic features but still have anomalies or abnormalities of the CNS that result in hypotonia. In my experience, they can be placed into 2 major categories based on the neuroimaging (MRI) findings.

Cerebral Dysgenesis

One group of patients with nonsyndromic hypotonia has MRI evidence of developmental abnormalities of the brain. These are most often minor anomalies that are not recognizable or classifiable as a specific malformation such as schizencephaly, lissencephaly, or holoprosencephaly but represent a larger group with less specific and less clearly defined anomalies that we might lump into the title “cerebral dysgenesis” (Table 3). The diagnostic yield from MRI studies in patients with nonsyndromic hypotonia is dependent to some extent on the skill, interest, and experience of the individual assessing the neuroimaging studies (Fig 2). It would come as no surprise that although the outcome is quite variable and one must be very careful making structure/function correlations based on the neuroimaging, infants and children with cerebral dysgenesis frequently have cognitive as well as motor deficits and most often do not catch up to age-matched peer groups over time.

Grossly Normal Brain

The second major category of nonsyndromic central hypotonia patients is those whose neuroimaging studies show no obvious evidence of cerebral dysgenesis (Table 4). These children have a grossly normal brain from the standard imaging standpoint. Some of these infants will be delayed in the development/maturation of myelin if they are assessed in the first few months of life.

With Delayed Myelination

Admittedly, myelination standards are not well established (with standard deviations and so on) so it is difficult to quantify the status of development/maturation of myelin with any

objectivity. Furthermore, if one images these children later in life, they almost always are within the normal range of myelination for age. Clinically, the children with delayed myelination fall into 2 general groups. One group has hypotonia with motor delay and normal language and social skills. The second group is globally delayed. Both groups will improve with respect to muscle tone over time, but the first group with motor delay only will tend to catch up to their peers and although they will likely be among the less gifted when it comes to motor coordination, they function adequately. The second group of infants with delayed myelination, those who are also globally delayed, also catch up with respect to the degree of myelination of the cerebral white matter; however, they do not usually catch up in motor and cognitive skills and are in for difficulties if they are expected to function in the normal school setting.

There is another, somewhat uncommon entity, that was described in 1997 as the macrocerebellum.⁸ In patients with this condition, the volume of the brain is normal, and the size of the major components of the supratentorial brain (cerebrum) is normal but the size of the cerebellum is more than 2 standard deviations above the age-matched control values for

Table 4 Central Hypotonia With Grossly Normal Brain

| Delayed Myelination | Myelination Within Normal Range |
|--|--|
| Motor Delay Only (Usually catch up to peers in tone and development by school age) | Developmental Delay (May later be diagnosed as nonsyndromic mental retardation, frequently labeled as autistic) |
| Global developmental delay (Although they frequently catch up to peers in tone by school age, they usually do not catch up intellectually and cognitively) Chromosomal microarray studies will be abnormal in 12% to 15% of these children) | Normal development (Essential hypotonia, Oppenheim's disease?) |

the structure. Infants with a macrocerebellum are delayed in meeting developmental and cognitive milestones, and who are imaged with MRIs in the first 6 months of life have delayed myelination in the cerebrum, which catches up with the normal range sometime in the second year of life. Thus, if one assesses the myelination at 2 or 3 years, it is within the normal range, but the children remain somewhat behind in achievement.

Without Delayed Myelination

Children with central hypotonia with grossly normal brains without delayed myelination can be divided into 2 groups just as those with delayed myelination and the prognosis can be roughly defined by the same criteria (ie, those with just motor delay will likely catch up and those with global delay will likely not catch up). I think it is in the infants with only motor delay that one can recognize the entity that Oppenheim was describing in 1900 and that has gone by many names including benign congenital hypotonia and essential or primary hypotonia.⁹

There is another somewhat uncommon but certainly underrecognized condition that can result in hypotonia. The first patients with congenital malformations of the petrous portion of the temporal bone involving the labyrinth were described by Rapin.¹⁰ These children usually have congenital hearing loss as well as striking hypotonia and are often identified mistakenly as retarded because of the language delay secondary to the hearing loss and the motor delay that is secondary to the hypotonia that is, in turn, caused by the maldevelopment of the labyrinth.^{10,11} In children with central hypotonia in whom a specific syndromic diagnosis cannot be made, with or without cerebral dysgenesis, the application of chromosomal microarray analysis should be considered because the yield is higher than most of our diagnostic tests.¹² Although more frequently mentioned in the evaluation of nonspecific mental retardation, there is considerable overlap between that group of patients and those who come to medical attention for hypotonia evaluation. This is particularly true for those hypotonic children with motor and psychomotor delays.

Hypotonia Caused by Craniocervical Junction Lesions

Injury to the craniocervical junction may occur in infants without evidence of disruption of the spinal ligaments or the bony structures of the spine. This is presumably caused by the flexibility and distensibility of the immature spine compounded by the relatively large size of the head and relatively poor muscle support of the neck in infancy.

Injury to the spine in the newborn is followed by a period of flaccidity in the arms and legs. This fact is not always recognized early in the clinical course because the detailed examination necessary to identify this lesion is not always performed because the infant is often acutely ill and requires extensive support. After 1 to 3 weeks, the spinal shock disappears and is replaced by gradually increasing reflex hyperactivity. Again, the detailed examination may not be possible because of the general status of the infant. Certainly, the infant will be very hypotonic at first, and it is not usually until

the development of the hyperactive reflexes and the lack of the expected maturation of the corticospinal tract influences on the motor unit that the nature of the injury is suspected. Another cause of hypotonia involving the craniocervical junction is the presence of a Chiari I or II malformation. The Chiari II is usually associated with spina bifida and easily suspected, but the Chiari I may be an isolated finding that may cause hypotonia early on by compression of the lower brainstem at the level of the foramen magnum. Chronic compression of the craniocervical junction may result in increased tone and reflexes as well so one has to keep this entity in the differential diagnosis of spasticity in older infants and children; it is to be considered when localizing the cause of hypotonia in infants.

Motor Unit Hypotonia

Any of the components of the motor unit can be the site of involvement in conditions resulting hypotonia. A sequential scheme of localization would begin with the anterior horn cell and progress to the peripheral nerve, neuromuscular junction, and the muscle itself. Involvement of the sensory limb of the reflex arc of the motor unit is very uncommon as a cause of hypotonia but can occur in rare circumstances. The characteristic features that would allow localization of the problem to the motor unit would be the absence of features of central hypotonia, the absence of reflexes, and convincing weakness. Of lesser importance but still a consideration would be abnormal size and/or texture/consistency of the muscle on observation and palpation. When the clinician is convinced the patient has a motor unit hypotonia, the next step is to consider going directly to genetic testing for specific diseases. The physician should consider short circuiting the usual sequential evaluation if it is clear that the mother has myotonic muscular dystrophy or in the situation in which there is a known family history of a neuromuscular disease such as Charcot-Marie-Tooth (CMT), spinal muscular atrophy (SMA), or one of the known congenital myopathies.

If the clinician cannot identify one of the previously described situations, faced with a motor unit hypotonia, the clinician should do a serum creatine kinase determination and an EMG/MNCV (Fig 3). A modest elevation of creatine kinase is not very helpful, although it does suggest the problem is in the muscle, whereas a striking elevation of this enzyme in the serum is very suggestive of a dystrophinopathy

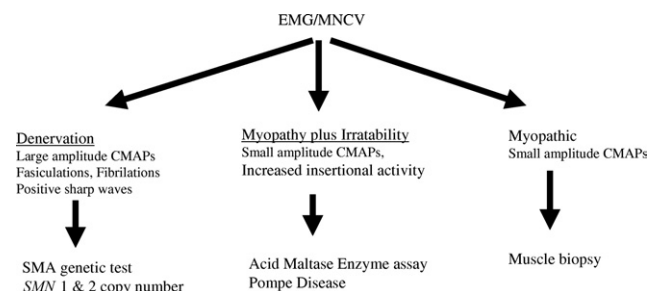


Figure 3 Evaluation of motor unit hypotonia.

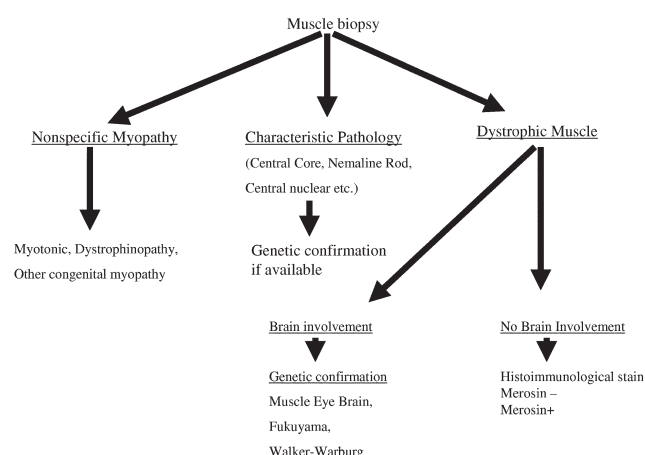


Figure 4 Muscle biopsy.

or some other myopathy with membrane instability as a pathophysiological feature. Perhaps the most important test in the evaluation of the patient with motor unit hypotonia, the EMG/MNCV, is also the most often omitted component of the evaluation. In my experience, the failure to proceed in a logical sequential fashion is the most common reason for failure to make a proper diagnosis for most pediatric neurologists not fellowship trained in neuromuscular disease. The EMG/MNCV can establish the presence of denervation of the muscle, the presence of myopathic features with additional features of muscle irritability, or the presence of a myopathy without evidence of increased irritability of the muscle (Fig 3). The EMG can also be very useful in the choice of muscle for biopsy so as to avoid or minimize the likelihood of not finding diagnostically useful changes in the muscle.

Muscle biopsy, once the most useful test in the diagnosis of motor unit hypotonia, is used much less often today with the availability of specific gene tests for many of the conditions under consideration. Still, however, there are many situations in which a muscle biopsy is essential to guide the completion of the evaluation. A sequential scheme for the proper use of the muscle biopsy is presented in Figure 4.

Anterior Horn Cell

The chief cause of hypotonia because of conditions involving the anterior horn cell is SMA. SMA is the most common serious cause of hypotonia in the infant and child. Regardless of the age at which they present, children with SMA are weak as well as hypotonic. The gene mutation that leads to SMA is in the survival motor neuron gene (*SMN*). Each of us has 2 copies of the *SMN* gene: *SMNt* or *SMN1* is the telomeric copy and *SMNc* or *SMN2* is the centromeric copy. All patients with SMA have deletions or mutations of *SMN1*, and the major phenotype determinant is the number of copies of *SMN2* present. If the individual has no copies of the *SMN2*, the situation usually results in spontaneous abortion or fetal wastage. One copy is likely to produce SMA I, and 5 or 6 copies might allow normal survival with little or no progressive weakness. There are very few other conditions other than SMA that would result in widespread denervation on EMG in the clinical setting of hypotonia and weakness in infancy. In

this clinical situation, muscle biopsy is no longer necessary to make the diagnosis of SMA.

Peripheral Nerve

Hypotonia in infancy is rarely caused by peripheral nerve disease. There are well-documented cases of CMT causing hypotonia in the first 6 months, but this is the exception rather than the rule. In the newborn, the electrophysiological hallmark of CMT 1A, the slowing of nerve conduction secondary to a demyelinating neuropathy, is not identifiable because the speed of conduction is not different than that of the normal unaffected infant. By 6 months of age, however, the normal nerve-conduction velocity has increased sufficiently to distinguish the normal from the affected.^{13,14} It would be appropriate to do the genetic studies to investigate the possibility of CMT with a positive family history with or without electrophysiological confirmation, but muscle biopsy is not the appropriate diagnostic tool in this clinical setting. The genetics of CMT have become fairly complicated, and to do all of the gene tests without knowing what specific defect to look for is quite expensive (Table 5). Thus, it is less expensive and more efficient if the family knows what their mutation is; a single test can be performed to confirm the presence of the same mutation in the patient.

Neuromuscular Junction

Although not common as a cause of hypotonia in infancy, the myasthenia-like conditions must be in the differential diagnosis in this clinical setting. These represent the only category of motor unit diseases in which the reflexes may be preserved. Neonatal myasthenia gravis, the condition in which the mother has autoimmune myasthenia gravis and the antibodies to the AChR are passively transferred to the infant, is very uncommon in recent years. Much more common now is the group of conditions called congenital

Table 5 The Genetics of Charcot-Marie-Tooth Hereditary Motor Sensory Neuropathies

| Type of CMT | Chromosome | Protein | Mutation |
|------------------|--------------------|-------------|--|
| CMT 1A | 17p11.2 | PMP22 | Dup = CMT Absent = HNPP Point = Dejerine Sottas |
| CMT 1B | 1q22 | MPZ | 50+Point mutations CMT, CHMN, HNPP And Dejerine Sottas |
| CMT 2B CMT 4A | 3q13 to 22 8q13 | | Peroneal muscular atrophy |
| CMT-X | X 13.1 | Connexin 32 | X-linked CMT |

CMT = Charcot-Marie tooth; PMP = peripheral myelin protein; MPZ = myelin protein zero; HNPP = hereditary neuropathy with pressure palsies; CHMN = congenital hypomyelinating neuropathy.

Table 6 Selected Congenital Myasthenic Syndromes

| Type of CMS | Clinical Features | Gene Defects |
|---|--|---|
| AchR deficiency | Early onset Variable severity Ptosis, extraocular palsy Bulbar, arm, and legs involved | AchR subunit genes <i>CHRNE</i> <i>CHRNA1</i> <i>CHRNA1</i> <i>CHRNA1</i> <i>CHRNA1</i> <i>CHRNA1</i> |
| Slow-channel syndrome (SCCMS) | Selective severe weakness of neck, wrist, finger extensor Onset variable Severity variable Ventilatory problems common and may be progressive | |
| Fast-channel syndrome | Variable onset and severity May respond to AchE inhibitors | |
| Endplate rapsyn deficiency (EP rapsyn deficiency) | Early onset with hypotonia, respiratory failure, apnea, arthrogryposis Mild or severe involvement | <i>RAPSN</i> |
| CMS with episodic apnea (CMSEA) | Respiratory failure early Episodic apnea Improvement with age May respond to AchE inhibitors | <i>CHAT</i> |
| Endplate acetylcholinesterase deficiency (EP AchE deficiency) | Severe Ophthalmoparesis Severe axial musculature weakness Slow pupillary responses | <i>COLQ</i> C-terminal missense mutations may be milder |

The *CHRN* genes code for different subunits of the AchR. *COLQ* codes for the collagenic tail subunit of the acetylcholinesterase. *CHAT* is the gene for choline acetyltransferase, *RAPSN* codes for rapsyn, and the *SCN4A* gene encodes the sodium channel in skeletal muscle.

myasthenic syndromes (CMSs). The CMS conditions represent genetic defects of neuromuscular transmission resulting in a decrease in the safety margin in neuromuscular transmission. This is manifested clinically by easy fatigability and weakness to variable degree depending on the severity of the defect in transmission. These children may be very sensitive to neuromuscular-blocking agents and may respond to AchE antagonists.

The clinical diagnosis of a congenital myasthenic syndrome is based on the history of fatigue with exercise. Many cases have a decremental response to repetitive stimulation on EMG and the absence of AchR and MuSK antibodies in the serum. To date, there are several mutations in several genes associated with the ion channel, the AchR receptor, or the recycling mechanism for the acetylcholine itself. Some of the more widely recognized CMSs are listed in Table 6. Gene tests are available for those conditions listed. Investigation of individuals with CMS will detect one of the known mutations in about 50% of the cases.^{15,16}

Muscle

Abnormalities of muscle structure or function are a major cause of motor unit hypotonia, second to SMA in overall

frequency. Although children with dystrophinopathy usually do not present until later in life, some will be hypotonic in the first year. In addition, because they are frequently slow in psychomotor development, they may indeed come for evaluation even before they are noted to be weak.

More likely than Duchenne type muscular dystrophy as a cause of hypotonia in the first year are the congenital myopathies. The congenital myopathies are a group of primary muscle diseases that, although present at birth with variable severity, are typically only slowly progressive over time. They represent abnormalities of muscle structure or defects in muscle function that are mostly genetically determined. Originally, they were classified according to the morphology of the muscle fibers on histochemical study of muscle biopsy tissue. Thus, you had central core disease, nemaline rod disease, and centronuclear disease. In recent years, the genetic basis of many of these conditions has been delineated, and classification will change but some of the old terms are retained for clarity. Table 7 lists some of the “classical” congenital myopathies along with gene defect and clinical information. Table 8 lists similar information about other congenital

Table 7 The Classical Congenital Myopathies

| | Central Core Disease | Nemaline Myopathy | Centronuclear (myotubular) Myopathy |
|------------------------------|--|--|---|
| Presentation/Severity | | | |
| Infantile | Severe | Severe | Severe |
| Childhood | Moderate | Moderate | Moderate |
| Adult | Mild | Mild | Mild |
| Muscle wasting | No | Yes | Yes |
| Somatic abnormalities | Yes | Yes (infantile) | Yes (dominant) |
| Ocular muscle weakness | No | Yes | Yes with ptosis |
| Pain/cramps | No | Yes (adult onset) | No |
| Malignant hyperthermia | Yes (characteristic) | No | No |
| Cardiomyopathy | Occasionally | Rare | No |
| Mental retardation | No | No | No |
| Genetic defect(s) | Dominant: 19q13.1 (<i>RYR1</i> gene) Ryanodine receptor, Dihydropyridine-sensitive L-type Ca channel gene. ?beta myosin heavy chain (cardiomyopathy) | Dominant: 1q42, 1q22-q23 <i>TPM3</i> (tropomyosin-3 gene), <i>ACTA-1</i> gene Recessive: <i>NEB</i> (Nebulin)gene, <i>ACTA-1</i> gene | Dominant: 11q22 Xlinked: <i>MTM1</i> (myotubularin gene) |

myopathies that are generally recognized to be distinct clinical pathologic entities.

The 1 metabolic disease that may be easily mistaken for a primary myopathy in the first year is Pompe disease. The diagram in Figure 3 indicates that the EMG findings in Pompe (acid maltase deficiency) are very distinct and should allow the clinician to proceed in the proper diagnostic path. Pompe patients also have large hearts and firm skeletal muscles because of the glycogen stored in the muscle fibers. These factors occasionally are useful in making the diagnosis in these patients.

An important subgroup of congenital myopathies are the congenital muscular dystrophies (CMDs). The CMDs are a

group of conditions that are usually present at birth, often quite severe with muscle weakness, wasting, respiratory difficulty, and contractures, with variable involvement of the brain, eyes, and other tissues. These conditions all have what looks like dystrophic muscle on biopsy with muscle fiber necrosis and regeneration with replacement of muscle with fibrous and fatty connective tissue. The understanding and evaluation of the CMDs has, perhaps more than any other area of myology, been aided by the recent advances in molecular genetics. Typically, CMDs have been divided into 2 large categories; those with brain involvement (syndromic CMD)¹⁷⁻¹⁹ and those without brain involvement (nonsyndromic CMD)^{20,21} (Tables 9 and 10).

Table 8 Well-Established Congenital Myopathies

| | Multicore | CFTD | Reducing Body | Fingerprint | Cytoplasmic Body |
|------------------------------|---|-------------------------------------|------------------------------|-------------------------------------|--|
| Presentation/Severity | | | | | |
| Infantile | Mild | Severe | Severe | Mild | Severe |
| Childhood | Mild | Moderate | Moderate | | Moderate |
| Adult | | Mild | Mild | | |
| Muscle wasting | No | Yes | — | Yes | No |
| Somatic abnormalities | Yes | Yes | Yes | Yes | Yes |
| Ocular muscle weakness | Yes (ptosis) | No | Yes (ptosis) | No | No |
| Pain/cramps | — | Stiffness | — | — | — |
| Malignant hyperthermia | Reported | — | — | — | — |
| Cardiomyopathy | Reported | No | Reported | No | Yes |
| Mental retardation | No | Yes | No | Yes | No |
| Genetic defect(s) | AD: possible AR: SCAD (short chain Acyl CoA dehydrogenase) | AR: Reported Most cases sporadic | XN AR: Maps to 9p1 to 9q1 | AR: Reported Most cases sporadic | AD: 2q35 Desmin Several allelic disorders, variable clinical features |

Table 9 The Nonsyndromic Congenital Muscular Dystrophies

| Disease | Gene/Protein/Testing | Clinical Features |
|---|--|--|
| Merosin-deficient CMD (MDC1A) | LAMA2/Alpha-2 Laminin/+ | Severe, hypotonia, global weakness, Contractures, Scoliosis, MRI = abn white Matter signal, Do not walk, NL IQ |
| CMD with partial merosin deficiency (MDC1B) | LAMA2/Alpha-2 Laminin/- research only | Milder Sx, most do walk, NL IQ, MRI normal, cardiomyopathy, contracture of elbow, knees, fingers |
| CMD type 1C (MDC1C) | FKRP/fukutin-related protein/+ | Severe weakness, global involvement Contractures of elbows, knee, finger MRI normal, NL IQ, cardiomyopathy |
| CMD with ITGA7 mutations | ITGA7/Integrin alpha-7/- | Proximal weakness, torticollis, congenital hip dislocation |
| CMD with spine rigidity (CMD RSS) | SEPN1/Selenoprotein N/+ | Rigid spine, elbow, hip, and ankle Sleep hypoventilation, progressive |
| Ullrich CMD | COL6A1&2/Alpha 1 & 2 Collagen VI or COL7A3/Alpha 3 collagen VI | Global weakness with contractures, Distal hyperextensibility, calf atrophy, NL IQ |

CMD = congenital muscular dystrophy; NL IQ = normal intelligence; abn = abnormal.

The most prominent member of the CMDs without brain involvement or the nonsyndromic group of congenital muscular dystrophies is merosin-deficient CMD, also called laminin A2-deficient CMD. This condition is more common than the other nonsyndromic CMDs combined. Clinically, the most striking feature that distinguishes merosin-deficient CMD from others is the finding of “leukodystrophy” on magnetic resonance imaging of the brain in the context of a weak, hypotonic infant with absent reflexes but preserved cognition when assessing psychomotor development. Although the other members of the CMDs are less common, some features that might be helpful in the differential are listed in [Tables 9](#) and [10](#).

Conclusion

Although the evaluation of the hypotonic infant is sometimes very complex and confusing, in my experience, if the clini-

cian can localize the abnormality to the suprasegmental etiology or motor unit etiology, the most difficult part of the diagnostic process is already achieved. The suprasegmental or central causes of hypotonia are much less well defined currently than the motor unit causes of hypotonia. In the future, we will be able to identify an increasing number of specific causes of central hypotonia, but it is unlikely that we will ever get as good at delineating the central causes as we will be with the motor unit causes of hypotonia. Thus, it is sometimes not as diagnostically precise to find a central hypotonia. Because there is the possibility, however, that some of the patients with central hypotonia will catch up to the normal range, the clinician should be somewhat familiar with those features that allow the appropriate diagnosis and prognosis to be determined. It is my hope that this article will help the reader to be more comfortable and knowledgeable when faced with the problem of a hypotonic infant.

Table 10 Syndromic Congenital Muscular Dystrophies (Those With Brain Involvement)

| Disease | Gene/Protein/Testing | Clinical Features |
|---|---|--|
| Fukuyama CMD (FCMD) | FCMD/fukutin/+ | Generalized weakness (severe), Contractures, Cobblestone Lissencephaly |
| Muscle eye brain disease (MEB) | POMGNT1/protein -O-Mannoside beta-1,2-N-Acetylglucosaminyltransferase/+ | Eye malformations without cataracts, Hydrocephalus, white-matter abn Cobblestone lissencephaly, milder as some walk but lose walking by age 20 |
| Walker-Warburg syndrome | POMT1/protein-O-mannosyl-transferase -1/+ | Severe generalized weakness, Contractures at elbows only, lissencephaly, Dandy-Walker or cerebellar hypoplasia, flat pons, early demise |
| Walker-Warburg syndrome 2 | POMT2/protein-O-mannosyl-transferase -2/+ | Clinically indistinguishable from W-W-1 |
| Congenital muscular dystrophy 1D (CMDC1D) | LARGE/glycosyltransferase-like protein (LARGE)/+ | Global delay, muscle hypertrophy, Facial sparing, MRI changes in white matter, proximal > distal weakness |

References

1. Fenichel GM: The newborn with poor muscle tone. *Sem Perinatol* 6:68-88, 1982
2. Dubowitz V: *The Floppy Infant* (ed 2). Philadelphia, PA, JB Lippincott, 1980, pp 1-9
3. Bodensteiner JB: Symptoms of Neurologic Disorders: Neurologic Symptoms, in Finberg L, Kleinman RE (eds): *Saunders Manual of Pediatric Practice*. Philadelphia, PA, Saunders, 2002, pp 953-955
4. Bodensteiner JB: Neurologic Examination, in Finberg L, Kleinman RE (eds): *Saunders Manual of Pediatric Practice*. Philadelphia, PA, 2002, pp 1017-1018
5. Bodensteiner JB: Neurologic examination of the neonate, in Finberg L, Kleinman RE (eds): *Saunders Manual of Pediatric Practice*. Philadelphia, PA, Saunders, 2002, pp 1018-1020
6. Bodensteiner JB, Riggs JE, Schochet SS: Congenital myopathies, in Katurji B, Kaminski HJ, Preston DC, et al (eds): *Neuromuscular Diseases*. Newton, MA, Butterworth Heinemann, 2002, pp 1114-1127
7. Kaufman HH, Bodensteiner JB, Burkhart B, et al: Treatment of spastic gait in cerebral palsy. *W Va Med J* 90:190-192, 1994
8. Bodensteiner JB, Schaefer GB, Keller GM, et al: The macrocerebellum: Neuroimaging and clinical features of a newly recognized condition. *J Child Neurol* 12:365-368, 1997
9. Dubowitz V: *Muscle Disorders in Childhood* (ed 2). Philadelphia, PA, Saunders, 1995
10. Rapin I: Hypoactive labyrinths and motor development. *Clin Pediatr* 13:922-937, 1974
11. Bodensteiner JB, Smith DS, Schaefer GB: Hypotonia, congenital hearing loss and hypoactive labyrinths. *J Child Neurol* 18:171-174, 2003
12. Bhavana JD, Sanger WG: Role of cytogenetics and molecular cytogenetics in the diagnosis of genetic imbalances. *Semin Pediatr Neurol* 14:2-6, 2007
13. Gutmann L, Fakadej A, Riggs JE: Evolution of nerve conduction abnormalities in children with autosomal dominant hypertrophic neuropathy of the Charcot-Marie-Tooth type. *Muscle Nerve* 6:515-519, 1983
14. Zellweger H, Schochet S, Pavone L, et al: Malattia di Charcot-Marie-Tooth ad insorgenza precoce presentazione di una famiglia. *Pediatria* 79:198-214, 1971
15. Engel AG, Sine SM: Current understanding of congenital myasthenic syndromes. *Curr Opin Pharmacol* 5:308-321, 2005
16. Beeson D, Hantai D, Lochmuller H, et al: 126th International Workshop: Congenital myasthenic syndromes, 24-26 September 2004, Naarden, the Netherlands. *Neuromuscul Disord* 15:498-512, 2005
17. Kobayashi K, Nakahori Y, Miyake M, et al: An ancient retrotransposon insertion causes Fukuyama-type congenital muscular dystrophy. *Nature* 394:388-392, 1998
18. Kirschner J, Bonnemann CG: The congenital and limb-girdle muscular dystrophies: Sharpening the focus, blurring the boundaries. *Arch Neurol* 61:189-199, 2004
19. Villanova M, Mercuri E, Bertini E, et al: Congenital muscular dystrophy associated with calf hypertrophy, microcephaly and severe mental retardation in three Italian families: Evidence for a novel CMD syndrome. *Neuromuscul Disord* 10:541-547, 2000
20. Pegoraro E, Marks H, Garcia CA, et al: Laminin alpha2 muscular dystrophy: Genotype/phenotype studies of 22 patients. *Neurology* 51:101-110, 1998
21. Muntoni F, Voit T: The congenital muscular dystrophies in 2004: A century of exciting progress. *Neuromuscul Disord* 14:635-649, 2004