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The Genetic Approach to Hypotonia in the Neonate

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Author Disclosure
Drs Zadeh and Hudgins have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives After completing this article, readers should be able to:
1. Describe the genetic approach to hypotonia in the newborn.
2. Discuss the most common presentations of genetic disorders associated with hypotonia in the newborn period.
3. Review the genetic basis of neuromuscular disorders that present with hypotonia in the newborn period.
4. Understand the definition of anticipation with respect to trinucleotide repeat disorders.

Abstract
Numerous genetic syndromes present with hypotonia during the neonatal period, including Prader-Willi syndrome, myotonic dystrophy, spinal muscular atrophy, congenital muscular dystrophies, nemaline myopathy, congenital hypomyelinating neuropathy, congenital disorders of glycosylation, and Pompe disease. This article reviews neonatal presentations and appropriate diagnostic tests and examinations for each. Awareness of possible underlying genetic causes for neonatal hypotonia can aid physicians in general pediatric practice, neonatology, and other specialties in making a timely diagnosis for what may be considered rare conditions. Furthermore, early diagnosis allows for improved management of affected infants while providing invaluable information to their families with respect to potential recurrence risks in future generations.

Introduction
Hypotonia is defined as a subjective decrease of resistance to passive range of motion in a newborn (Fig. 1). Knowledge of genetic disorders that present most commonly with hypotonia during the immediate newborn period is imperative because early diagnosis and initiation of appropriate supportive therapies allows the most beneficial outcomes for affected individuals. Molecular testing for most of these disorders is a rapid, cost-effective diagnostic approach. Most molecular tests involve acquiring a modest amount of blood, which is significantly less invasive and more cost effective than prior practices of obtaining muscle via surgical biopsy for similar diagnostic purposes.

Prader-Willi Syndrome (PWS)
Prenatal hypotonia is evident with PWS, resulting in decreased fetal movement as well as abnormal positioning (ie, breech) at parturition, which causes difficulty with delivery, often necessitating cesarean section. Delivery typically is at term, with normal birth length and weight, although early failure to thrive may result in both parameters falling below the third percentile. During the immediate neonatal period, infants exhibit profound central hypotonia, lethargy, decreased spontaneous movement, and weak cry. Hypogonadism is a common feature; cryptorchidism is present in 80% to 90% of affected males. Characteristic facial features of PWS in the newborn period include dolichocephaly with narrowed bifrontal diameter, “almond-shaped” palpebral...
fissures, and a narrow nasal bridge. Infants who have PWS have poor suck and swallow, with severe cases warranting surgical insertion of a gastric tube. However, affected infants do not have respiratory insufficiency and do not require ventilatory assistance.

Hypotonia improves by 2 to 3 years of age, although adolescents and adults may have evidence of mild hypotonia, with subtly decreased muscle tone and bulk. Global developmental delay and excessive eating with central obesity is not seen until early childhood.

PWS is caused by lack of paternal contribution of 15q11, which can be related to:

- Chromosome deletion of the Prader-Willi critical region (chromosome 15q11-q13) from the paternal allele
- Maternal uniparental disomy in which there are only two maternally derived copies of chromosome 15
- Mutations of the genes responsible for imprinting control (1% of all cases)
- Structural chromosome abnormality (eg, translocation, duplication) involving the critical region, resulting in deletion of the paternal allele.

Due to multiple causes, a number of different diagnostic tests can be undertaken to confirm the presence of PWS. Methylation study or SNRPN expression is used as first-line testing. Both forms of testing detect all four of the previously cited causes, but they cannot distinguish between the causes that have different recurrence risks. Accordingly, they often are followed by high-resolution chromosome analysis to rule out a structural chromosome abnormality involving chromosome 15, which could have implications for recurrence if one of the parents carries a balanced rearrangement.

Myotonic Dystrophy (DM1)
DM1 is an autosomal dominant condition that may present with hypotonia and respiratory insufficiency in the neonatal period. Decreased fetal movement and polyhydramnios in utero result in breech positioning at delivery. As a result, positional malformations (clubfoot) and congenital contractures are common. At birth, infants have little-to-no spontaneous movement because of generalized muscle weakness. Bitemporal wasting, a masklike facies, and tented upper lip also may be evident. Most affected infants require respiratory assistance because of weak respiratory muscles and underdeveloped lungs. Attempts at feeding are very poor initially due to weak suck and swallow, but they improve gradually over time.

Clinical diagnosis is based on facial features and the
characteristic pattern of muscle weakness. DM1 is caused by expansion of the CTG trinucleotide repeat in the DMPK gene. Detection of trinucleotide repeat size is considered the “gold standard” for molecular diagnostic testing. Alleles greater than 34 repeats in length are unstable and have the ability to expand during female germline cell division (miosis), which is also known as anticipation. Individuals who have mild DM1 possess 50 to 150 repeats; those who have the classic form have repeat sizes of 100 to 1,000. Congenital DM1 is the most severe form, with greater than 1,000 repeats. Individuals who have expansion in the pre-mutation range frequently are asymptomatic or have very subtle clinical features.

Infants who have congenital DM1 are born to affected mothers with very few exceptions. Maternal examination may reveal mild myopathic facies and sustained grip during hand shake (Fig. 2). Parents of an affected infant routinely are offered testing for recurrence risk purposes and health surveillance because those who have the mild and classic forms are at risk for cataracts and arrhythmias.

**Spinal Muscular Atrophy (SMA)**

SMA is an autosomal recessive disorder characterized by symmetric and progressive muscle weakness and atrophy resulting from degeneration of anterior horn cells in the brainstem and spinal cord. There are four clinical forms of SMA; in this article, we discuss SMA type 0 and SMA I.

The prenatal form of SMA (type 0) is the most severe, characterized by generalized weakness at birth as well as multiple congenital joint contractures involving at least two areas of the body (arthrogryposis multiplex congenita). Furthermore, motor milestones are not achieved and infants have a poor prognosis. Demise typically occurs at 6 months of age.

SMA I also manifests early, between birth and 6 months of age. Affected infants have hypotonia, muscle weakness, and mild contractures of the large joints. Deep tendon reflexes usually are absent, and on close observation, fasciculations of the tongue may be observed. This type of SMA also manifests with lack of motor development and failure to meet gross motor milestones. Intellect is usually normal.

The two genes associated with SMA are known as survival motor neuron (SMN) genes. Normally, individuals have two copies of the SMN gene arranged in tandem on each chromosome, known as SMN1 (telomeric copy) and SMN2 (centromeric copy). SMA arises with the loss of function of the SMN1 gene. The remaining functional SMN2 genes cannot compensate without expression of SMN1. Molecular testing is available via blood sample for targeted mutation analysis.

**Congenital Muscular Dystrophy (CMD)**

CMD is a group of autosomal recessive disorders characterized by hypotonia, joint contractures, brain malformations, eye abnormalities, generalized weakness, and elevated serum creatine kinase (CK) concentrations. We discuss merosin-deficient muscular dystrophy, Walker-Warburg syndrome, muscle-eye-brain (MEB) disease, and Fukuyama CMD (FCMD).

Merosin-deficient CMD is the nonsyndromic member of this group. Affected infants have hypotonia, proximal muscle weakness, and multiple large joint contractures, which worsen with age. Brain imaging results may be normal for the first 6 months after birth, followed by progressive characteristic changes of hypomyelination.
and hypodensity of the white matter. These specific central nervous system findings have been attributed to blood-brain barrier dysfunction causing abnormal water distribution in the cerebral white matter. Nocturnal hypo-o-nnea is a common occurrence and may require respiratory assistance via mechanical ventilation. Gross motor milestones develop poorly, with lack of ambulation during childhood. Cognitive impairment is usually mild but depends greatly on the presence and severity of brain abnormalities. The lifespan is shortened, with death occurring between the first decades of life and early adulthood. Diagnostic testing requires a muscle biopsy to evaluate histology and immunostaining for merosin and other muscle proteins. Molecular testing on a clinical basis involves sequencing of the laminin, alpha-2 chain (LAMA2) gene known to be associated with the disorder.

Walker-Warburg syndrome presents with generalized neonatal hypotonia and weakness as well as contractures at the elbows. Eye findings may include congenital cataracts, microphthalmia, and Peter anomaly (an anterior segment defect with corneal opacities). Severe brain malformations are common and include absence of the corpus callosum, fusion of cerebral hemispheres, and lissencephaly. Prognosis is poor, with demise occurring during early infancy. Molecular diagnostic testing for Walker-Warburg syndrome involves sequencing of protein O-mannosyl-transferase (POMT1 and POMT2) genes.

MEB disease manifests with generalized neonatal hypotonia, muscle weakness, eye malformations (glaucoma, progressive retinal atrophy, and juvenile cataracts), hydrocephalus, and cerebral white matter changes. There is also global developmental delay, with a very slow natural progression of milestones. Most affected individuals are nonambulatory by the third decade of life. Molecular diagnostic testing for MEB is by gene sequencing of the laminin, alpha-2 chain (LAMA2) gene known to be associated with the disorder.

Nemaline Myopathy

Nemaline myopathy may present early in utero with poor fetal movement and polyhydramnios. The neonatal period is notable for severe proximal muscle weakness, hypotonia, dilated cardiomyopathy, arthrogryposis multiplex congenita, and absence of deep tendon reflexes. Due to generalized weakness and poor suck and swallowing coordination, feeding difficulties are expected. The prognosis is poor, with demise during the first postnatal year.

Screening studies reveal a normal serum CK value. If a muscle biopsy is performed, histology is abnormal on modified Gomori trichrome staining, with illustration of nemaline inclusion bodies (which appear “rodlke”) scattered throughout muscle fibers. These inclusion bodies are made up of several Z-line proteins and alpha actinin and are not unique to this disorder.

Five genes are known to be associated with nemaline myopathy. Unfortunately, only two tests, ACTA1 sequencing and NEB deletion/duplication analysis, are available on a clinical basis at the time of this writing.

Congenital Hypomyelinating Neuropathy (CHN)

CHN is an autosomal recessive disorder that presents with neonatal hypotonia, generalized weakness, arthrogryposis multiplex congenita, areflexia, and respiratory insufficiency. These findings are evident during the newborn period in the neonatal form of this disorder. CHN is considered a neuromuscular disorder and usually is associated with an early demise due to the need for mechanical ventilation and subsequent complications of respiratory infections.

Diagnostic evaluation should begin with molecular testing rather than more invasive methods. Molecular testing involves sequencing of MPZ, PMP22, or EGR2 genes, which are known to be associated with CHN. We do not recommend the more invasive diagnostic methods of electromyography (EMG) and nerve biopsy as first-line testing. Peripheral nerve biopsy reveals thin-to-absent myelin sheaths consistent with hypomyelination and suggestive of an intrinsic defect of myelin synthesis. Of interest, EMG often shows normal patterns when sampled at a proximal muscle site and denervation at distal muscle sites.

The evaluation strategy for this group of disorders includes neuroimaging (preferably magnetic resonance imaging), serum CK assessment, and ophthalmology and neurology evaluations. Molecular testing for Walker-Warburg syndrome, MEB disease, and FCMD are clinically available, as described previously.

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Congenital Disorders of Glycosylation (CDGs)

CDGs are a group of disorders inherited in an autosomal recessive pattern and caused by defective synthesis of N-linked oligosaccharides, which play an important role in the synthesis of glycoproteins and glycolipids throughout the body. A CDG may manifest during early infancy with hypotonia and microcephaly. Examination of an affected neonate reveals an abnormal distribution of fat, most prominently notable in the suprapubic, iliac, and buttock regions, as well as the finding of inverted nipples (Fig. 3). Strabismus is very common. Other potential systemic manifestations include cardiomyopathy, protein-losing enteropathy, hypoglycemia, coagulation defects, and seizures. Neuroimaging often reveals progressive diffuse cerebellar atrophy. The variable neurologic phenotype ranges from mild impairment to severe psychomotor retardation, with motor skills more severely affected than cognition. CDG type Ib is treatable with mannose supplementation, but no curative treatment exists for the other forms.

Ophthalmology, hematology, cardiology, and endocrinology evaluations are warranted. First-line diagnostic testing for CDG is carbohydrate-deficient transferrin analysis, which is detected by mass spectrometry. Mutation analysis of PMM2 is reserved for second-tier testing. The causative enzymes are known for most CDG subtypes, but enzymatic assays are not available on a clinical basis. Thus, clarification of particular CDG subtype requires molecular testing of the specific gene associated with the subtype.

Pompe Disease

Pompe disease is an autosomal recessive disorder manifested by profound central hypotonia along with generalized weakness, respiratory insufficiency, cardiomegaly, and feeding difficulties. The condition is also known as glycogen storage disease type II and is caused by deficiency of the lysosomal enzyme acid alpha glucosidase. Dysfunction of this enzyme leads to abnormal lysosomal glycogen storage throughout the body, with skeletal, cardiac, and smooth muscle involved most prominently. Additional manifestations include macroglossia, hepatomegaly, and hearing deficits.

The initial evaluation for affected infants involves echocardiography to screen for hypertrophic cardiomyopathy, assessment of pulmonary function, and measurement of serum transaminases and CK. CK concentrations may be elevated in this disorder, which is a sensitive but nonspecific marker for Pompe disease. Characteristic electrocardiographic findings include tall QRS complexes, shortened PR intervals, and arrhythmias that include Wolf-Parkinson-White syndrome. Arrhythmias are due to glycogen deposition in cardiac muscle, which acts as an electrical conductor. Untreated cardiac insufficiency may lead to heart failure and rapid demise. Molecular testing should be performed for diagnostic confirmation. The possibility of mass spectrometry newborn screening is on the horizon and may be performed on all infants to screen for this disorder in the near future.

Molecular testing is GAA gene sequencing or skin fibroblast culture for enzymatic assay. Prompt diagnosis of this disorder can lead to early referral to a metabolic center for initiation of enzyme replacement therapy.

Approach to the Hypotonic Infant

Because neonatal hypotonia has many different genetic causes, thorough physical and neurologic examinations are warranted before embarking on diagnostic testing. Careful attention should be paid to overall appearance, facial features, respiratory status, muscle bulk and tone, joint assessment for contractions, and genital development.

After ruling out infection, infarction, perinatal trauma, electrolyte abnormalities, or isolated congenital
brain malformations as the cause for hypotonia, the neonatologist should consider a number of genetic disorders. For infants who have normal respiratory function and evidence of hypogonadism, PWS should be considered. Neonates who have large joint contractures should be evaluated for possible SMA and syndromic forms of CMDs. Neonates who have respiratory deficiency should be evaluated further for any underlying abnormality affecting muscle, including DM1, CHN, SMA, and nemaline myopathy.

Laboratory evaluations should include serum CK. CK is present in cardiac and skeletal muscle and is a nonspecific marker of muscle breakdown. Mild-to-moderate elevations should raise the suspicion for CMD such as MEB disease and Walker-Warburg syndrome. Of note, the expected CK concentrations in these disorders are not as severely elevated as would be expected in males who have Duchenne muscular dystrophy, which usually is greater than 10 times the normal value. Thus, laboratory findings of elevated CK should prompt neuroimag- ing and formal ophthalmologic evaluation. Other laboratory evaluation should include chromosome analysis and possible comparative genomic hybridization if dysmorphic features are present. If a particular disorder is being considered, specific single gene testing is more appropriate.

Congenital hypothyroidism also should be considered in the diagnostic evaluation of an infant exhibiting hypotonia. Serum thyroid-stimulating hormone and free thyroxine are measured easily. Hypothyroidism is important to consider because this condition has a much better prognosis when detected early.

Conclusion

Many genetic and metabolic conditions may present with signs of hypotonia and generalized muscle weakness. The cause and mechanism of muscle weakness depends on the disorder and underlying associated genetics. Furthermore, lack of cellular energy, abnormally functioning proteins, or accumulation of toxic metabolites may result in a similar clinical picture.

The genetic approach to hypotonia includes knowledge of presenting signs/symptoms of some of the most common inheritable disorders and the appropriate diagnostic tools that are available (molecular and biochemical testing) (Table). Awareness of these possible underlying causes may prove very beneficial to physicians in general pediatric practice, neonatology, and other specialties in making a timely diagnosis for conditions that may be seen more rarely and often not considered. Such early consideration allows further management and provides invaluable information to

Table. Genetic Conditions and Appropriate Diagnostic Testing

<table>
<thead>
<tr>
<th>Genetic Disorder</th>
<th>Diagnostic Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prader-Willi syndrome</td>
<td>First tier: Methylation studies or SNRPN expression</td>
</tr>
<tr>
<td></td>
<td>Second tier: High-resolution chromosome analysis</td>
</tr>
<tr>
<td>Myotonic Dystrophy</td>
<td>Detection of trinucleotide CTG repeat expansion in DMPK</td>
</tr>
<tr>
<td>Spinal Muscular Atrophy</td>
<td>Targeted mutation analysis for SMN1 and SMN2</td>
</tr>
<tr>
<td>Congenital Muscular Dystrophies</td>
<td></td>
</tr>
<tr>
<td>Merosin-deficient CMD</td>
<td>LAMA2 gene sequencing</td>
</tr>
<tr>
<td>Walker-Warburg syndrome</td>
<td>POMT1 and POMT2 gene sequencing</td>
</tr>
<tr>
<td>Muscle-eye-brain</td>
<td>POMGNT1 gene sequencing</td>
</tr>
<tr>
<td>Fukuyama CMD</td>
<td>Fukutin gene sequencing</td>
</tr>
<tr>
<td>Nemaline myopathy</td>
<td>ACTA1 sequencing and NEB deletion/duplication analysis; consider muscle histology</td>
</tr>
<tr>
<td>Congenital hypomyelinating neuropathy</td>
<td>MPZ, PMP22, or EGR2 gene sequencing</td>
</tr>
<tr>
<td>Congenital disorders of glycosylation</td>
<td>First tier: Carbohydrate-deficient transferrin analysis, which is detected by mass spectrometry</td>
</tr>
<tr>
<td></td>
<td>Second tier: Mutation analysis of PMM2</td>
</tr>
<tr>
<td>Pompe disease</td>
<td>GAA gene sequencing or skin fibroblast culture for enzymatic assay</td>
</tr>
</tbody>
</table>

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the etiology, molecular phenotype, and clinical manifestations of disorders associated with uniparental disomy.
- Recognize the DNA findings, clinical manifestations, and inheritance of expanding genes, such as myotonic dystrophy.
- Know the basis for (including genetic), clinical and laboratory features (including associated abnormalities), differential diagnosis, management, and outcomes of neonatal hypotonia/neuromuscular weakness.
families regarding genetic counseling with respect to recurrence risk in future pregnancies.

**Suggested Reading**

- Thomas NH, Dubowitz V. The natural history of type 1 (severe) spinal muscular atrophy. *Neuromuscul Disord*. 1994;4:497–502
NeoReviews Quiz

4. While discussing the causes of neonatal hypotonia with medical students, you raise the possibility of Prader-Willi syndrome in a patient. Of the following, the most accurate statement regarding Prader-Willi syndrome is that:

A. A characteristic cranial feature is brachycephaly.
B. Deletion of the maternal allele from chromosome 15 is the genetic cause.
C. Cryptorchidism is present in nearly all affected males.
D. Hypotonia worsens with age.
E. Prolonged ventilatory assistance is often necessary.

5. Molecular genetic testing is a rapid and cost-effective means of making a diagnosis in cases of neonatal hypotonia. Of the following, an expansion of the CTG trinucleotide repeat in the DMPK gene is most consistent with the diagnosis of:

A. Congenital hypomyelinating neuropathy.
B. Merosin-deficient congenital muscular dystrophy.
C. Myotonic dystrophy.
D. Nemaline myopathy.
E. Spinal muscular atrophy.

6. A term newborn presents with severe proximal muscle weakness, arthrogryposis multiplex congenita, and dilated cardiomyopathy. Maternal history is significant for poor fetal movement and polyhydramnios from fetal dysphagia, suggestive of prenatal onset of the neuromuscular disease. A muscle biopsy using Gomori trichrome staining reveals rodlike bodies scattered throughout the muscle fibers. Of the following, the most likely diagnosis in this infant is:

A. Fukuyama congenital muscular dystrophy.
B. Merosin-deficient congenital muscular dystrophy.
D. Nemaline myopathy.
E. Walker-Warburg syndrome.

7. A 3-month-old male infant is being evaluated for severe hypotonia. Physical examination reveals an abnormal distribution of fat, especially in the suprapubic, iliac, and gluteal regions. The infant has inverted nipples, strabismus, and microcephaly. Cranial magnetic resonance imaging shows diffuse cerebellar atrophy. Of the following, the most likely diagnosis for this infant is:

A. Congenital disorder of glycosylation.
B. Congenital hypomyelinating neuropathy.
C. Congenital hypothyroidism.
D. Pompe glycogen storage disease.
E. Prader-Willi syndrome.
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