Genetic evaluation of the pediatric patient with hypotonia: perspective from a hypotonia specialty clinic and review of the literature

EMILY C LISI | RONALD D COHN

Johns Hopkins Center for Hypotonia, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Correspondence to Dr Ronald D Cohn, Johns Hopkins University School of Medicine, 733 N Broadway, Room 529, Baltimore, MD 21205, USA. E-mail rcohn2@jhmi.edu

AIM Hypotonia is a symptom of diminished tone of skeletal muscle associated with decreased resistance of muscles to passive stretching, which can be caused by abnormalities of the central nervous system, any element of the lower motoneuron, or both. Hypotonia is not a specific diagnosis, but can be part of over 500 different genetic disorders, with many other conditions waiting to be identified. This review proposes a pragmatic approach to evaluating hypotonia in neonatal and pediatric populations by using a diagnostic algorithm.

METHOD We use a dedicated literature review combined with clinical experience in a newly established multidisciplinary center for hypotonia to establish a diagnostic algorithm.

RESULTS Hypotonia can be a symptom of over 500 different genetic disorders. It can present as peripheral, central, or combined hypotonia, providing necessity for rational and systematic diagnostic testing.

INTERPRETATION Our analyses demonstrate that a staged diagnostic approach categorizing patients as having peripheral, central, or combined hypotonia is the most efficient to providing a rational work-up. Establishing a diagnosis is crucial for prognosis, management, and treatment strategies, and for ascertaining an accurate recurrence risk for future offspring in a family.

‘Hypotonia’ is a general term used to denote decreased tone in the limbs, trunk, or craniofacial skeletal muscles. It can be detected at birth or later in childhood. The incidence of hypotonia is difficult to determine, owing to its presence as a feature of many distinct disorders. Severity is extremely variable and depends on the underlying etiology. Establishing a diagnosis is crucial for prognosis, management, and treatment strategies, and for ascertaining an accurate recurrence risk for future offspring in a family. Because of the growing and increasing complex list of conditions that must be considered in a child with hypotonia, a rational approach to diagnosis should be taken. Here, we provide a diagnostic algorithm for the genetic evaluation of the child with hypotonia with a staged approach for diagnostic testing and a brief overview of the most common genetic conditions associated with hypotonia (Figs 1–3). Appropriate genetic counseling is crucial for the family after a diagnosis for ongoing management, psychosocial support, family planning, and patient/family advocacy.

The first distinction to make when assessing a child with hypotonia is whether decreased muscle tone is a result of an abnormality of the central nervous system (CNS), peripheral neuromuscular system, or a combined abnormality involving both. Clinical findings suggestive of an abnormality of the CNS may include hyperreflexia, cognitive developmental delay, and seizures. In contrast, physical findings pointing towards a neuromuscular origin may include weakness, lack of antigravity movements, muscle atrophy, fasciculations, and/or diminished reflexes, most often in the context of normal cognitive function. However, it is important to note that there are occasional exceptions to this rule, particularly in cases of congenital myotonic dystrophy or severe cases of congenital myopathies. In such instances, patients may present with significant hypotonia associated with swallowing and respiratory difficulties, but yet demonstrate the ability of antigravity movements with reasonable amounts of muscle power, in particular during later stages of the disease.

During the first evaluation of an infant or child with hypotonia, a careful history is taken of pregnancy and delivery, as well as a medical and three-generation family history, and dysmorphological clinical/neurological history. A pregnancy history should ascertain complications including polyhydramnios, abnormalities on prenatal ultrasound, frequency and quality of fetal movements, maternal exposures, and gestational length. Lack of fetal movements in utero may indicate congenital muscular dystrophies, congenital myotonic dystrophy, or other primary myopathies. Delivery history should include mode of delivery, complications, evidence of asphyxia, and Apgar scores. Evidence of asphyxia and low Apgar scores are common presentations of hypoxic–ischemic encephalopathy, which is one of the most common causes of neonatal
hypotonia. Additionally, preterm infants often have secondary hypotonia, and corrected gestational age should be considered before ordering a genetic evaluation of a preterm infant. Hypoxic–ischemic encephalopathy should also be considered in the preterm infant with hypotonia, often elucidated by ultrasound and/or brain magnetic resonance imaging (MRI) for morphological abnormalities indicative of ischemia. The clinical course of the hypotonia should be elucidated, such as age at onset and whether the hypotonia has improved or worsened. It is essential to obtain a detailed review of systems to determine the presence of other associated malformations or health conditions. A three-generation family history should be obtained, specifically inquiring about a history of skeletal muscle disease, birth defects, mental retardation,* and consanguinity, the last of which can lead to consideration of an autosomal recessive disease. A careful clinical examination should first determine physical findings suggestive of an upper motoneuron versus a lower motoneuron problem or both. A thorough examination for dysmorphic features may lead to a particular syndromic diagnosis.

Generally, all patients with hypotonia should be tested for elevations of serum creatine kinase, which can be detected in a variety of neuromuscular disorders and warrants further diagnostic work-up.

**CENTRAL HYPOTONIA**

The presence of global developmental delay and/or seizures with a lack of peripheral muscle weakness and normal creatine kinase is highly suggestive of a central form of hypotonia caused by a defect in the CNS. An MRI of the brain should be obtained to look for structural abnormalities. Other ancillary testing such as careful evaluation of vision and hearing, echo-cardiogram, or an abdominal ultrasound should be considered based on the clinical examination and medical history, as multiple congenital anomalies can be part of a chromosome abnormality or a syndromic disorder.

In the presence of developmental delay with dysmorphic features or birth defects, laboratory testing should include a high-resolution karyotype and array comparative genomic hybridization, or single nucleotide polymorphism array, to detect gains and losses in DNA copy number. With or without dysmorphic features/birth defects, biochemical testing including plasma amino acids, urine organic acids, and an acylcarnitine profile, and testing for congenital disorders of glycosylation and lactate/pyruvate should be considered. Depending on the clinical findings, specific testing such as methylation testing for Prader–Willi/Angelman syndrome, very long-chain fatty acids, 7-dehydrocholesterol, urine metabolites of creatine synthesis, MECP2 and/or cyclin-dependent kinase-like 5 (CDKL5) gene testing, and specific metabolic studies of CSF may need to be considered (see Fig. 1 and details below).

Treatment for patients with central hypotonia is largely supportive and symptomatic. Physical, occupational, and speech therapy are the most beneficial modes of improving central hypotonia and are relatively effective (unpublished

---

**What this paper adds**

- A systematic review of the genetic syndromes associated with hypotonia.
- It develops distinctions between various etiologies for hypotonia and provides tools for clinicians to determine these distinctions.
- It presents the first algorithms for diagnostic testing of patients with hypotonia.
- It draws on the clinical experience from the only hypotonia specialty clinic in the world.

---

**Figure 1:** Central hypotonia.

*UK usage: learning disability.
Aquatic therapy and/or hippotherapy have also been shown to increase function and endurance in some children with disabilities such as cerebral palsy, but are understudied in children with central hypotonia. Other treatments should be given based on symptomatology regardless of the etiology of the hypotonia unless otherwise specified below.

**Congenital central hypotonia**

**Chromosomal abnormalities**
General salient features include the following: central hypotonia, dysmorphic features, birth defects, micro/macrocephaly, growth anomalies, global developmental delay with cognitive impairment, typically negative family history. The presence of dysmorphic features, birth defects, or failure to thrive may indicate a chromosomal abnormality.
detectable by karyotype, array comparative genomic hybridization, or single nucleotide polymorphism array. Down syndrome is the most common chromosomal cause of central hypotonia and can be recognized clinically with characteristic features such as upslanting palpebral fissures, epicanthal folds, midface hypoplasia, single transverse palmar creases, and the so-called sandal gap between the toes. Williams syndrome, a relatively common contiguous gene deletion caused by a microdeletion on 7q11.23, is associated with central hypotonia, mild to moderate mental retardation, and characteristic facial features including epicanthic folds with periorbital fullness, stellate irises, and midface hypoplasia.

Hypotonia is a feature of many other chromosome abnormalities; the availability of comparative genomic hybridization or single nucleotide polymorphism arrays will undoubtedly lead to the discovery of many more deletion/duplication syndromes, such as the recently identified 17q21.31 microdeletion syndrome and Phelan–McDermid syndrome (22q13 deletion), both with hypotonia as a major clinical feature.4,5 There is growing concern about the occurrence of copy number variants of uncertain clinical significance found on chromosomal array testing.6 Genetic counseling can be difficult in these cases, as it is unclear whether the abnormality found on array testing is causative of the patient’s features. Fortunately, several steps can be taken to determine likely association, including searching genome browsers such as that at the University of California, Santa Cruz website (http://genome.ucsc.edu) for known genes associated with hypotonia or other features in the copy-number variant interval, searching databases of known polymorphic copy number variants such as DECIPHER (https://decipher.sanger.ac.uk), and parental testing to see if the copy number variant was inherited from a phenotypically normal parent.

**Prader–Willi syndrome/Angelman syndrome** Salient features of Prader–Willi syndrome are central hypotonia, short stature, genital hypoplasia, and failure to thrive in infancy leading to hyperphagia at approximately 1 year of age.

Salient features of Angelman syndrome include the following: central hypotonia (most), global developmental delay, acquired microcephaly, seizures, prognathism, and skin hypopigmentation.

The clinical findings of generalized hypotonia, global developmental delay, genital hypoplasia, and associated feeding difficulties warrants methylation testing for the Prader–Willi/Angelman syndrome region. The Prader–Willi critical region on chromosome 15q11-13 is subject to parent-specific imprinting. Failure of maternal expression of this region because of a deletion, imprinting defect, uniparental disomy, or mutation in the UBE3A gene causes Angelman syndrome, whereas Prader–Willi syndrome is caused by deletion or uniparental disomy of the paternal allele. The two conditions are phenotypically distinct but both can be associated with various degrees of hypotonia. Thus, it is important to note that if a deletion of the 15q11-13 region is discovered by karyotype and/or fluorescence in-situ hybridization testing in a hypotonic infant, it is crucial to perform methylation testing to distinguish the two, as prognosis and management are very different.

Prader–Willi syndrome is characterized by severe neonatal hypotonia and failure to thrive due to poor suck, improving with age. The diagnosis can be made in approximately 99% of cases by methylation testing, which detects deletions and uniparental disomy.7 Subtle dysmorphic features may be present, and mild to moderate mental retardation occurs in almost all individuals. At approximately 1 year of age, hyperphagia starts with rapid weight gain leading to central obesity. Short stature is also present, with average adult heights of 155cm and 148cm for males and females respectively. Growth hormone has been shown to increase final height to an average of 171cm in males and 158cm in females and may increase muscle strength in these children.8,9

Angelman syndrome is characterized by severe mental retardation with severe speech impairment, gait ataxia with limb tremulousness due to distal cortical myoclonus, and acquired microcephaly. Seizures are present in approximately 80% of affected individuals and may present as absent, myoclonic, or grand mal seizures.10 Hypotonia is not present in all individuals with Angelman syndrome, although recent studies have shown that it occurs with a higher frequency in those with a deletion than in those with uniparental disomy (73% vs 29%).11 The diagnosis can be made by methylation testing in 80% and UBE3A gene sequencing in another 5% to 10% of cases. Ten to 15% of cases of presumed Angelman syndrome remain undiagnosed by molecular methods, presumably because of yet undetermined genetic etiologies such as the recently discovered X-linked ‘Angelman-like’ syndrome caused by mutations in the SLC9A6 gene.12

**MECP2 disorder spectrum**

Salient features of this disorder include the following: central hypotonia, acquired microcephaly, seizures, repetitive hand movements, and regression.

Classic Rett syndrome, an X-linked dominant disorder caused by mutations in MECP2, is characterized by a normal prenatal and perinatal history with a loss of developmental skills and acquired microcephaly between 6 and 18 months of age. Affected females typically lose purposeful hand actions substituted by repetitive stereotyped hand movements. Seizures occur in up to 90% of affected females but may decrease in the late stages of deterioration.13 Variant Rett syndrome can be associated with a less aggressive disease course or with neonatal hypotonia and developmental delay with no real acquisition of skills. Males with Rett syndrome have a severe neonatal-onset encephalopathy with hypotonia, microcephaly, and seizures; typically they do not survive past 2 years of age.14 Males with duplication of the MECP2 gene have hypotonia, severe mental retardation, absent speech, and frequent infections. Recently, mutations in the X-linked gene CDKL5 have been detected in patients presenting with seizures in the first few months of life and features of Rett syndrome.15 Given the current clinical experience, screening for CDKL5 mutations can be useful in females with a history of early-onset...
intractable seizures and becomes mandatory when idiopathic infantile spasms and/or atypical features of Rett syndrome are present.

**Peroxisomal disorders**

Salient features include the following: central hypotonia, liver abnormalities, seizures, cataracts/retinal dystrophy, hearing loss, chondrodysplasia punctata, and flattened facies with large anterior fontanelle.

Infants with hypotonia, abnormal liver function tests, jaundice, and/or seizures require quantification of very long-chain fatty acids, which can be elevated in peroxisome biogenesis disorders. These disorders fall along a spectrum of severity, with the classic form of Zellweger syndrome being the most severe and infantile Refsum disease the least. Dysmorphic features can include flattened facial profile, large anterior fontanelle, widely split sutures, and a broad nasal bridge. Zellweger syndrome typically presents in the neonatal period with severe hypotonia and inability to feed, dysmorphic features, congenital cataracts, chondrodysplasia punctata, and seizures. Death typically occurs in the first year of life from apnea or respiratory compromise. Neonatal adrenoleukodystrophy and infantile Refsum disease may present in infancy or early childhood with hypotonia, developmental delay, and progressive hearing loss and vision impairment from retinal dystrophy. These patients may develop leukodystrophy with developmental regression and ultimate death. All forms are autosomal recessive, resulting from mutations in one of 12 PEX genes, the most common being mutations to PEX1. Diagnosis is made by measuring plasma concentrations of very long-chain fatty acids, phytanic acid, and pristanic acid. Elevated C26 and C22, ratios of C24/C22 and C26/C22, and concentrations of phytanic acid and pristanic acid are diagnostic.

**Smith–Lemli–Opitz (SLO) syndrome**

Salient features of SLO syndrome include the following: central hypotonia, growth delay, global developmental delay, Y-shaped two/three-toe syndactyly, cleft palate, cataracts, heart defects, genital abnormalities, down slanting palpebral fissures with epicanthial folds, and anteverted nares.

Infants with hypotonia and pre- and postnatal growth retardation with or without associated malformations require quantification of 7-dehydrocholesterol for SLO syndrome. Features of SLO syndrome include moderate to severe mental retardation, microcephaly, intrauterine and postnatal growth retardation, and characteristic Y-shaped two/three-toe syndactyly. Of affected individuals, 25 to 50% have postaxial polydactyly, 40 to 50% have cleft palate, 20% have congenital cataracts, and 40 have heart defects. Dysmorphic facial features include bitemporal narrowing, down slanting palpebral fissures, epicanthal folds, blepharoptosis, anteverted nares, cleft palate, and micrognathia. Urogenital anomalies are common in males: 50% with SLO syndrome have hypospadias and/or cryptorchidism. Combined treatment of SLO syndrome with a cholesterol-enriched diet and simvastatin has been suggested to reduce 7-dehydrocholesterol and increase cholesterol levels in patients with this syndrome.

**Creatine deficiency disorders**

Salient features include central hypotonia, global developmental delay, seizures, and delayed myelination on MRI of the brain.

Creatine deficiency disorders, including guanidinoacetate methyltransferase and creatine transporter deficiencies, can present with infantile or childhood hypotonia. Guanidinoacetate methyltransferase deficiency is an autosomal recessive disorder of creatine synthesis. All individuals have some degree of cognitive impairment, with most having severe mental retardation. Many patients also have seizures and/or an extrapyramidal movement disorder. Abnormalities on MRI of the brain may consist of myelination delay or increased signal intensity in the globus pallidus in T2-weighted images. The substrate guanidinoacetate accumulates in urine, plasma, and cerebrospinal fluid (CSF); elevation in these fluids is diagnostic of guanidinoacetate methyltransferase deficiency. Oral substitution of creatine and dietary restriction of arginine (a required substrate for guanidinoacetate production) have been shown to be effective in improving seizures, hypotonia, movement disorder, and abnormal signal intensities in the basal ganglia in a subset of patients, but do not correct the mental retardation. Creatine transporter deficiency is caused by mutations in SLC6A8 and is an X-linked disorder presenting in males with developmental delay most prominently in speech, mild seizures, and central hypotonia. MRI of the brain shows increasing brain atrophy, possibly indicating a slowly progressive disorder. Creatine concentration is elevated in both plasma and urine; however, guanidinoacetate is normal, in contrast to guanidinoacetate methyltransferase deficiency. Confirmatory diagnosis is made by measuring the deficiency of creatine uptake in fibroblasts. Owing to the inability to transport creatine across the membrane, oral creatine treatment is not helpful in creatine transporter deficiencies.

**Benign congenital hypotonia**

The term ‘benign congenital hypotonia’ has been a controversial entity since its initial description by Walton in 1971. It has most recently been used to describe children with mild central hypotonia, normal or mild motor delay which shows improvement, and normal muscle enzymes. However, care must be taken to eliminate other causes of hypotonia first, because many patients who carry this diagnosis have subsequently been diagnosed with specific single-gene disorders. Therefore, this term should no longer be considered as a specific diagnostic entity.

**Peripheral Hypotonia**

The clinical presentation of skeletal muscle weakness associated with an impairment to or inability to move extremities against gravity, with or without an elevated creatine kinase, is highly suggestive of a lower motoneuron dysfunction, which can include pathological abnormalities of the anterior horn segment, peripheral nerves, neuromuscular junction, or skeletal muscle (Fig. 2). Individuals with peripheral muscle weakness generally do not show signs of cognitive impairment, although gross and fine motor skills can be delayed depending on the
severity of the weakness and pattern of muscle involvement. The diagnostic work-up for peripheral hypotonia often requires electromyography (EMG) studies and a skeletal muscle biopsy. Some conditions warrant specific ancillary testing to aid in diagnosis, such as an echocardiogram and electrocardiogram in Pompe disease, or an echocardiogram and ophthalmology evaluation in Marfan syndrome. If a particular diagnostic entity is suspected, molecular genetic testing may be available for diagnosis, prognosis, and prenatal testing options in future pregnancies.

**Congenital peripheral hypotonia**

**Spinal muscular atrophy (SMA)**

Salient features of SMA include the following: peripheral hypotonia with proximal weakness, absent deep tendon reflexes, tongue fasciculations, and contractures.

SMA is an autosomal recessive condition characterized by progressive muscle weakness caused by degeneration and loss of lower motoneurons in the spinal cord and brainstem. SMA is one of the most common causes of peripheral hypotonia, with an incidence between 4 and 10 per 100 000. Onset can be variable, from pre/perinatal (SMA 0) to adulthood (SMA IV), and considerable overlap exists between the subtypes, particularly in prognosis, in light of the identical underlying etiology for each subtype. In all types, patients have normal cognition. The prenatal form of SMA includes arthrogryposis multiplex congenita and hypotonia at birth, with minimal facial weakness. SMA I, also called Werdnig–Hoffman disease, presents within the first 6 months of life with hypotonia, gross motor delay, mild contractures, particularly at the knees, and absence of tendon reflexes. Fasciculations of the tongue are seen commonly, though not universally. Individuals exhibit paradoxical breathing, owing to intercostal muscle weakness. Swallowing and feeding are affected owing to weakness, and adequate nutritional support should be addressed promptly. These patients never achieve the ability to sit without support, and death occurs because of swallowing dysfunction and respiratory compromise in infancy. SMA II presents after 6 months of age with muscle weakness and absent tendon reflexes in 70%. Finger trembling is almost always present. Individuals achieve the ability to sit without support when placed in a sitting position. Life expectancy for SMA II can vary from 30 to 50 years, depending on the severity of the disease, which can be quantified even during infancy. Onset of SMA III, also called Kugelberg–Welander syndrome, is typically after 10 months of age and some ambulation is achieved. Proximal muscle weakness is evidenced by frequent falls or trouble climbing stairs around 2 to 3 years of age, and the legs are more severely affected than the arms. Life expectancy is normal. SMA IV is characterized by adult-onset muscle weakness. Diagnosis of SMA is made by genetic testing of the *survival motor neuron (SMN1)* gene. SMN1 is the primary disease-causing gene, and 95 to 98% of individuals with SMA have a homozygous deletion of exon 7 in this gene, whereas 2 to 5% are compound heterozygotes with deletion in one gene and a point mutation in the other. SMN2, located next to SMN1 on chromosome 5q, is homologous to SMN1 but lacks exon 7, thus is less stable. It can be present in multiple copies in tandem. Recent studies have suggested that having more than two copies of the SMN2 gene can correlate with a milder phenotype; approximately 90% of patients with SMA I have two copies, whereas 97% of patients with SMA III have three or more copies. Prior et al. demonstrated that individuals homozygous for the SMN1 deletion who have five copies of SMN2 were completely asymptomatic, giving further credence to the importance of SMN2 as a modifier gene. A multidisciplinary approach should be used to provide optimal care to patients with SMA. Owing to lack of consistency in care among providers, a consensus statement was developed by Wang et al. for standard of care in SMA for medical management, diagnostic strategies, monitoring, and therapeutic interventions. Importantly, the team should be cognizant of issues related to prolonging life by ventilatory support or other means, particularly in patients with SMA I, when quality of life is being undermined. Consensus statements cannot be developed for this indication as family members and caregivers must make decisions on a case-by-case basis. Appropriate direction and counseling should be given, however, to aid the family in making the best decision for their child.

**SMA with respiratory distress syndrome**

Salient features of SMA with respiratory distress syndrome include peripheral hypotonia with distal weakness, hemidiaphragmatic palsy, and absent deep tendon reflexes.

Diaphragmatic SMA or infantile SMA with respiratory distress is a rare variant of infantile SMA affecting approximately 1% of patients with early-onset SMA. The clinical picture is characterized by initial respiratory insufficiency due to diaphragmatic palsy and often followed by distally pronounced weakness and wasting, which is in contrast to SMA type I, where weakness is predominantly present in proximal muscles. The prognosis is usually poor, with early death unless mechanical ventilation is provided. The disease can be mistaken for infantile SMA and follows an autosomal recessive mode of inheritance. There is both clinical and genetic heterogeneity within this group of conditions, in that age at onset can range from birth to 6 months, and that the gene identified as causing SMA with respiratory distress type 1 (*immunglobulin µ-binding protein 2 (IGHMBP2)*) has not been found to cause all cases of SMA with respiratory distress.

**Congenital myotonic dystrophy**

Salient features include the following: peripheral hypotonia, facial diplegia, weak cry/poor suck, possible developmental delay/cognitive impairment, maternal family history of facial weakness and contraction myotonia, diabetes type II, and/or cataracts.

Myotonic dystrophy type 1 is a multisystem disorder causing peripheral skeletal and smooth muscle weakness involving the eye, heart, and other organs. It is classified into three subtypes: mild, classic, and congenital, with a combined incidence of approximately 1 in 20 000 worldwide. Congenital myotonic dystrophy should be in the differential diagnosis of any neonate with severe muscle weakness and respiratory compromise. Prenatal history may be significant for lack of fetal
movement and/or polyhydramnios. Infants also have facial paresis with a tented upper lip and highly arched palate. A weak cry and poor suck occur in approximately 75% of affected infants. Respiratory failure causes a high rate of mortality, owing to diaphragmatic and intercostal muscle involvement, pulmonary immaturity, aspiration pneumonia, and/or cerebral disturbances. However, those who survive generally show improvement in hypotonia. Facial weakness may remain stable or become more significant, causing speech delay and the risk of aspiration remains high. Electrocardiograms are crucial for evaluation of syncope and palpitations, and annual screening should occur for potential asymptomatic cardiac conduction defects. Mental retardation of varying severity occurs in approximately half of affected children; the cause of this is currently being elucidated.

Congenital myotonic dystrophy is an autosomal dominant condition caused by an expansion of the CTG trinucleotide repeat in the 3’ untranslated region of the DMPK gene. Normal repeat sizes vary from 5 to 35 CTG repeats, whereas having 35 to 49 repeats results in no symptoms but is less stable and creates the possibility of expanding in offspring. Congenital myotonic dystrophy results from more than 200 CTG repeats. Expansions occur more commonly from maternal transmission, and an affected infant’s mother is likely to have a milder form of myotonic dystrophy, whether or not it has been diagnosed. Suspicion of myotonic dystrophy type 1 should prompt an evaluation of the mother for myopathic facies, sustained muscle contraction demonstrated by inability to release a hand grip quickly (grip myotonia), or release a muscle tapped with a reflex hammer (percussion myotonia). Mild forms present in adulthood with mild myotonia, cataracts, and/or diabetes mellitus, whereas classic myotonic dystrophy causes those features with muscle weakness and wasting and cardiac conduction defects. A family history elucidating these features should warrant further studies for myotonic dystrophy.

**Congenital muscular dystrophies**

The congenital muscular dystrophies are a heterogeneous group of inherited disorders. The clinical features range from severe and often early fatal disorders to relatively mild conditions compatible with survival into adult life. Until recently, patients with different variants of congenital muscular dystrophy were assigned to a specific category on the basis of the main clinical features and country of origin. More recently, however, molecular genetic data have indicated that this approach, although still valid in many respects, has its limitations when applied to genetic counseling. The classification of congenital muscular dystrophies, therefore, has to rely on the clinical features of affected individuals and the identification of the genetic and biochemical defects.

**Congenital muscular dystrophy type 1A (MDC1A)** Salient features of MDC1A include peripheral hypotonia, kyphoscoliosis, joint contractures, and increased signal intensity of white matter on MRI of the brain. Primary deficiency of laminin-z2 (MDC1A) accounts for 30 to 40% of all patients with congenital muscular dystrophy although regional variations do occur. Patients with MCD1A experience a variety of symptoms beginning in infancy or early childhood including hypotonia, kyphoscoliosis, and joint contractures. They have delayed motor milestones and often do not achieve ambulation. Respiratory insufficiency is a common manifestation and often progresses to the requirement of supportive ventilation. Serum creatine kinase levels are generally markedly elevated. The brain is affected in numerous ways, with notable variation in severity. After 6 months of life most patients have a specific pattern of changes to the white matter on MRI of the brain, with increased signal intensity on T2-weighted images. Normal intelligence is found in most patients, although a few may present with seizures and mental retardation. In addition, signs of dysmyelinating motor neuropathy with reduced nerve conduction velocity can be observed.

Biopsy of skeletal muscle of patients with this disorder demonstrates dystrophic changes such as muscle fiber necrosis with signs of ongoing degeneration and regeneration. A significant increase in muscle fibrosis is often a sign of end-stage muscle disease. Immunohistochemical studies in a subset of patients show absence and/or marked reduction in the carboxy (C)-terminal product of laminin-z2, whereas isolated reduction of only the amino (N)-terminal 300-kilodalton portion can be seen in patients with a milder phenotype. Therefore, antibodies directed against the C- and N-terminal portions of laminin-z2 must be used in the diagnostic work-up of patients with suspected MDC1A.

**Ullrich congenital muscular dystrophy** Salient features include the following: peripheral hypotonia, joint contractures of proximal joints, joint hypermobility of distal joints, torticollis, and kyphoscoliosis.

Ullrich congenital muscular dystrophy is thought to be the second most common form of congenital muscular dystrophy. It is characterized by the combination of congenital contractures of the proximal joints, torticollis, and kyphoscoliosis associated with hyperelasticity of the distal joints. Spinal kyphosis and proximal contractures can be transient or at least improve under physiotherapy. However, there is a tendency for contractures to recur and eventually also affect the previously lax ankles, wrists, and fingers. Achievements of motor function are very variable. Some patients never walk whereas others achieve ambulation in time or with delay up to the fourth year of life. Additional manifestations in this condition include follicular hyperkeratosis of the skin, softer consistency of the palmar and plantar skin, and scoliosis. Normal intelligence and respiratory failure are also integral features.

Creatine kinase levels are normal or elevated up to five times the normal level within five times above the normal level. Diagnosis often requires a combination of genetic testing and muscle biopsy with immunohistochemical analysis of collagen VI in tissue and cultured fibroblasts. Histological abnormalities of skeletal muscle in Ullrich congenital muscular dystrophy include variation in fiber size, muscle fiber...
necrosis, and increased accumulation of connective tissue. Muscle MRI has also been proposed as a diagnostic tool, specifically when collagen VI expression is normal in skeletal muscle and/or skin.\textsuperscript{46} Patients show diffuse patches of abnormal signal in the thigh muscles and display the pattern regardless of the level of collagen expression.\textsuperscript{46} The genetic heterogeneity of this disorder causes difficulties for molecular testing. Only a portion of the known cases have either collagen VI deficiency or mutations in the genes coding for collagen VI \( \alpha \)-chains, but mutations in each of the three genes have been characterized and could potentially be used for genetic testing.

**Rigid spine with muscular dystrophy** Salient features of the disorder include axial hypotonia, progressive spinal rigidity, and scoliosis.

Rigid spine syndrome is caused by mutations in a gene encoding selenoprotein N (SEPN1), which maps to 1p35-36.\textsuperscript{47} Interestingly, mutations in this gene have also been identified as a cause for congenital fiber type disproportion, desmin-related myopathy, and multi-minicore disease.\textsuperscript{48} The most common clinical findings of patients with this disorder include axial hypotonia and weakness, often noticed in the first year of life, but usually in a child with otherwise normal motor milestones and no significant contractures. Ambulation is usually maintained into adulthood unless a severe progressive scoliosis develops that cannot be treated surgically. The overall muscle mass is reduced, especially in the medial aspects of the thighs. The most prominent clinical feature is spinal rigidity and scoliosis due to contractures of the spine extensor muscles, which may develop between 3 and 12 years.

Vital capacity due to stiffness of the rib cage is low and decreases over time; this is almost invariably aggravated by diaphragmatic weakness leading to respiratory failure. It is important to emphasize that there is often a significant clinical discrepancy between the functional abilities of affected individuals who are able to walk and the compromise of respiratory function. Many patients require ventilatory assistance as early as the first decade. It is imperative to consider instigation of ventilatory support early, so an active life with good quality and reasonable muscle function can be maintained over many years or possibly decades.

Creatine kinase levels can be normal or mildly elevated. Skeletal muscle biopsy reveals myopathic findings with increased variation of fiber size and some increase in endomysial fibrosis. Expression for laminin-\( \alpha \)-2 and collagen VI is normal. There are many clinical similarities to Emery–Dreifuss syndrome, although rigid spine syndrome generally has an earlier age at onset.

**Congenital myopathies**

The congenital myopathies are a class of muscle diseases normally present at birth and marked by characteristic, but not pathognomonic, structural abnormalities in muscle fibers. Major progress within the past few years has been made by identifying causative genes for many congenital myopathies (for reviews see Lisi and Cohn\textsuperscript{39} and Laing\textsuperscript{49}). Patients generally present with congenital hypotonia, muscle weakness, delayed motor milestones, feeding difficulties, and facial and oral muscle weakness. Serum creatine kinase may be normal or slightly raised, and deep tendon reflexes may be diminished or abolished. There is heterogeneity even among affected members from the same family, in terms of progression, age at onset, and presence of other complications such as respiratory impairment.

**Central core/multi-minicore disease** Salient features of the disease are peripheral hypotonia, congenital hip dislocation, and scoliosis.

Central core disease is characterized by congenital hypotonia, weakness, and delayed motor milestones together with congenital hip dislocation and scoliosis. The disease is mainly non-progressive or slowly progressive, and families with asymptomatic individuals have been described. It is inherited as an autosomal-dominant trait with variable penetrance (although an autosomal-recessive form has been suggested), and is associated with malignant hyperthermia due to calcium dysregulation caused by defects of the sarcoplasmic reticulum calcium-release channel, the ryanodine receptor.\textsuperscript{50} Muscle biopsy demonstrates specific rounded areas that lack oxidative enzyme activity in type 1 muscle fibers. Cores are mostly centrally placed, though they may be eccentric. More than 90% of cases of central core disease are due to mutations in the \textit{RYR1} gene.\textsuperscript{51} Zhou et al. showed that epigenetic mechanisms can determine congenital myopathies as some patients with recessive central core disease transcribed only the mutated \textit{RYR1} allele in skeletal muscle with the normal allele (which would otherwise prevent disease) being silenced, possibly as a result of imprinting.\textsuperscript{52}

**Nemaline myopathy** Salient features of nemaline myopathy include peripheral hypotonia, facial weakness, scoliosis, and joint contractures.

Nemaline myopathy is a group of conditions characterized by the presence of subsarcolemmal, intermyofibrillar, or intranuclear rod-like structures that are reactive for \( \alpha \)-actinin and related to the Z band in continuity with actin filaments.\textsuperscript{49} Congenital hypotonia, generalized muscle weakness, scoliosis, and facial muscle involvement with a highly arched palate are commonly present. On occasion, patients may present with skeletal and joint deformities, including arthrogryposis multiplex congenita. Hypertrophic cardiomypathy has been observed in a subset of patients.\textsuperscript{53} Clinical heterogeneity ranges from severe neonatal cases with generalized weakness, and diaphragmatic and respiratory involvement, to late-onset, slowly progressive cases. Severe neonatal, milder congenital ‘classic’ and late-onset forms are of autosomal-recessive inheritance, but there is also an autosomal-dominant form with childhood onset.\textsuperscript{54} ‘Nemaline’ rods may occur in type I fibers alone or in fibers of both types I and II. Type I predominance or normal distribution of fiber types with type I hyotrophy is usually present; the amount of rods in different muscles from the same patient may vary widely, but does not correlate with clinical severity. Asymptomatic members from affected families may exhibit only type I predominance and no rods. Causa-
Myotubular myopathy Myotubular myopathy affects mainly males causing severe to mild peripheral hypotonia, respiratory insufficiency when severe, macrocephaly, and arachnodactyly.

X-linked myotubular myopathy is characterized by muscle weakness that ranges from severe to mild. Severe (classic) X-linked myotubular myopathy presents prenatally with polyhydramnios and decreased fetal movement, and in neonates with severe hypotonia and respiratory insufficiency. Affected males have chronic ventilator dependency and grossly delayed motor milestones, and mortality in infancy can be high if respiratory support fails. Males with moderate X-linked myotubular myopathy achieve motor milestones more quickly than males with the severe form and may require no ventilator support or intermittent support in the newborn period or at night. They usually demonstrate only minimally delayed motor milestones, are able to walk, and lack myopathic facies. Muscle strength generally improves over time. Female carriers of X-linked myotubular myopathy are in general asymptomatic, although rare manifesting heterozygotes have been described. The diagnosis of X-linked myotubular myopathy should be considered in any male with significant neonatal hypotonia and/or muscle weakness, particularly if a positive family history is suggestive of X-linked inheritance and/or length and head circumference are greater than the 90th centile in association with cryptorchidism and/or long fingers and toes. Histopathology typically shows small rounded muscle fibers with varying percentages of centrally located nuclei that resemble fetal myotubes, with patchy central clearing on ATPase staining indicating absence of myofibrils. Molecular genetic testing of MTM1 detects mutations in 60 to 98% of affected individuals.

Congenital myasthenia syndromes
Salient features of these syndromes include peripheral weakness, poor suck/weak cry, ptosis, facial weakness, and possible arthrogryposis.

Congenital myasthenic syndromes are a group of disorders characterized by fatigable weakness of the ocular, bulbar, and limb muscles with sparing of the cardiac and smooth muscles. Age at onset ranges from birth or shortly after birth to early childhood, or rarely in later childhood. Symptoms occurring in the neonatal presentation can include feeding difficulties, poor suck, weak cry, ptosis, and facial weakness. Respiratory insufficiency can occur rapidly with apnea and cyanosis, and arthrogryposis can be present. A child with this syndrome may present with increased fatigability and difficulty with running or climbing stairs. Prolonged or intermittent extraocular muscle weakness may be present as well. Diagnosis of myasthenia can be made by EMG, showing abnormal compound action potential on low-frequency stimulation, negative anti-acetylcholine receptor testing, and lack of improvement on immunosuppressive therapies. Most forms of congenital myasthenic syndrome are autosomal recessive; however, some autosomal dominant types have been documented, either inherited from a parent or as a de novo mutation. Several genes have been identified as causative of congenital myasthenic syndrome, each with protein expression at the neuromuscular junction. Some genotype–phenotype correlation exists. Most patients will benefit from treatment with acetylcholinesterase inhibitors, though patients with certain subtypes may deteriorate on this medication. 3,4-Diaminopyridine has shown benefit in some patients instead of, or in addition to, acetylcholinesterase inhibitors; however, two children with fast-channel disease died after starting this treatment. Other treatments that have shown some benefit include quinidine (though this has potential serious side effects such as arrhythmia, hypotension, and hypersensitivity) and fluoxetine in patients with slow channel syndrome.

Carnitine palmitoyltransferase deficiency type 2/metabolic myopathies
Salient features of the neonatal phenotype include the following: peripheral hypotonia, liver failure, hypoketotic hypoglycemia, cardiomyopathy, respiratory distress, liver calcifications, cystic/dysplastic kidneys, and neuronal migration defects.

Salient features of the infantile phenotype are peripheral weakness, acute liver failure with hypoketotic hypoglycemia, and cardiomyopathy.

Salient features of the myopathic phenotype include exercise-induced muscle weakness and cramping with possible myoglobinuria.

Carnitine palmitoyltransferase deficiency type 2 (CPT II) is an autosomal recessive disorder of fatty-acid oxidation, essential in energy homeostasis during periods of simultaneous energy demands and glucose sparing. Most fatty acids are catabolized in the mitochondria through the β-oxidation pathway, and long-chain fatty acids must be imported into the mitochondrial matrix by the CPT enzyme complex. This complex is made of two proteins, carnitine palmitoyltransferase 1 and 2. CPT II deficiency is recognized in three phenotypes: a neonatal lethal form, an infantile hepatocardiomuscular form, and a myopathic form with variable age at onset. The neonatal lethal form presents with liver failure, hypoketotic hypoglycemia, cardiomyopathy, and respiratory distress from birth to 4 days of life. Other congenital abnormalities can include liver calcifications and cystic dysplastic kidneys, or neuronal migration defects such as polymicrogyria, glial heterotopias, and cystic dysplasia of the basal ganglia. Hyperammonia and metabolic acidosis are common, with reduced serum total and free carnitine and increased serum long-chain acylcarnitines and lipids. The infantile form of CPT II presents at 6 months to 2 years with acute liver failure with hypoketotic hypoglycemia, transient hepatomegaly, and peripheral myopathy. Heart involvement, occurring in approximately 50% of cases, can include dilated or hypertrophic cardiomyopathy (which can spontaneously improve) or arrhythmias. These attacks may be caused by fasting or illness, or occur without known precipitating factors. Laboratory values are similar to those seen in the neonatal form. Sudden death may occur owing to cardiac arrhythmias or Rye syndrome. The myopathic form of CPT II is quite variable in onset, from 4 to 50 years of age.
Symptoms include recurrent attacks of myalgias with accompanying muscle weakness and possible myoglobinuria in most individuals. There are no clinical symptoms between episodes. The most common trigger is exercise (ranging from mild to long-term), followed by infections and fasting. Other precipitating factors can include cold, anesthesia, sleep deprivation, stress, or symptoms can be present with no known etiology. Life-threatening events may occur owing to acute renal failure following myoglobinuria, or respiratory insufficiency if respiratory muscles become involved. Diagnosis is made first by a screening acylcarnitine profile revealing a characteristic pattern, then by CPT II enzyme assay or molecular testing, which identifies more than 95% of disease-causing mutations. Genotype-phenotype correlations exist, with missense mutations more commonly associated with the myopathic form and truncating mutations with the neonatal or infantile form. Heterozygotes typically do not present with symptoms, though symptomatic individuals have been documented. Management of CPT II involves avoiding fasting and restriction of long-chain fatty acid intake. High-carbohydrate and low-fat diets are recommended for the myopathic form, particularly before and after exercise. Additionally, carnitine deficiency occurs in a subset of patients, and supplementation for the correction of carnitine deficiency may be necessary. Highly concentrated glucose infusions (D10) should be given during intercurrent infections, and hydration should be maintained during myoglobinuria to prevent renal failure.

Pompe disease

Salient features include the following: severe peripheral hypotonia, hypertrophic cardiomyopathy, hepatomegaly, and shortened P–R interval on the electrocardiogram.

Pompe disease is a rare autosomal recessive condition characterized by hypotonia, generalized muscle weakness, and hypertrophic cardiomyopathy. It is caused by the accumulation of glycogen in the lysosomes, primarily in skeletal and cardiac muscle tissue owing to acid-α-glucosidase deficiency. The infantile form, caused by less than 1% activity of the enzyme, presents neonatally and leads to death in the first year of life from cardiorespiratory failure or respiratory infection by 1 year of age when untreated. The juvenile- and adult-onset forms present with progressive skeletal muscle dysfunction and less severe cardiac involvement. Enzyme activity can range from 1 to 40% and generally correlates with age at onset and disease severity. Myopathy is present in all affected individuals eventually, with progressive muscle weakness in the trunk, lower limbs, and diaphragm. Severe cardiomyopathy from glycogen accumulation in cardiac muscle causes thickening of the ventricles and interventricular septum. It is present only in the infantile form, occurring before 6 months of age. Infants have profound hypotonia with head lag, failure to thrive owing to feeding difficulties, and respiratory difficulties. Electrocardiographic findings are pathognomonic, with a shortened P–R interval and likely large QRS complexes due to accelerated atrioventricular conduction. More than half of infants have macroglossia and/or moderate hepatomegaly from glycogen accumulation.

Enzyme replacement therapy with cell-derived recombinant human guanidinoacetate from Chinese hamster ovary (Myozyme) is a promising new therapy, approved by the US Food and Drug Administration for use in infantile Pompe disease in 2006, whereas studies for the later-onset forms are pending. Kishnani et al. performed the first clinical trial using guanidinoacetate in eight patients with infantile Pompe disease at various ages and severity of manifestations. The three who achieved ambulation were under 6 months of age when treatment was started, thus suggesting that earlier treatment provides optimum outcome. Markedly decreased left ventricular mass and a normal Bayley Mental Developmental Index were noted. In a follow-up trial, 18 patients were started on estrogen replacement therapy before the age of 6 months. All 18 patients survived to 18 months of age, and the risk of death or requirement for any type of ventilation was reduced by 88%. Eleven of the 18 experienced infusion-related reactions that were not significant enough to stop treatment.69 More studies are needed to determine the physical and cognitive characteristics of the chronic nature of this previously lethal condition.

Barth syndrome

Salient features include the following: males with peripheral hypotonia, cardiomyopathy, neutropenia, and growth delay.

Barth syndrome is an X-linked disorder characterized by skeletal myopathy, cardiomyopathy, neutropenia, and growth delay. Muscle weakness and exertional fatigue (owing to skeletal myopathy and cardiomyopathy) are characteristic, and delayed motor milestones and/or facial weakness may be the presenting features. The weakness is not progressive (and can improve over time), and ambulation is typically reached by 2 years of age. The most significant clinical finding is cardiomyopathy, which typically presents as either biventricular dilation or left-ventricular compaction. Cardiac dysfunction usually presents within the first year of life and has been seen in the last trimester of pregnancy by prenatal ultrasound. The cardiomyopathy has been shown to be responsive to medical therapy for heart failure in many cases and can remain stable or slowly improve. However, some patients have developed severe cardiomyopathy, necessitating transplant, and sudden ventricular tachycardia has been documented. Neutropenia can vary from mild to complete absence, especially during infection. Most patients have proportionate growth deficiency, though endocrine deficiencies or skeletal dysplasias are found. Some school-age children have shown a mild learning disorder; however, cognition is typically normal. Biochemical abnormalities include 3-methylglutaconic acid on urine organic acids and low levels of plasma cholesterol. Barth syndrome is caused by mutations in the tafazzin (TAZ) gene on Xq28.

Infant botulism

Salient features include the following: normal tone at birth with development of peripheral hypotonia, hyporeflexia, constipation, respiratory difficulties, and eye motility abnormalities.

Infant botulism is caused by a neurotoxin produced by the spore-forming, anaerobic, Gram-positive bacillus Clostridium
botulinum, which is found globally in soil and honey. Ingestion of spores leads to toxin synthesis and absorption from the infant’s intestinal tract. Infants who acquire botulism range in age from 6 weeks to 9 months, with the peak incidence occurring at 2 to 3 months of age. The classic clinical features include constipation, cranial nerve abnormalities, hypotonia, hyporeflexia, and respiratory difficulties. Constipation may be present in affected infants for a variable length of time and can precede weakness by several weeks. The infant may develop a weak cry, poor sucking ability, impaired gag reflex, pooling of secretions, and decreased oral intake. Loss of ocular motility, ptosis, mydriasis, and facial weakness may also occur. In severe cases of infant botulism, respiratory difficulties begin as a late sign of disease, quickly leading to respiratory arrest. A definitive diagnosis can be made with the detection of botulinum toxin and the isolation of C. botulinum from stool samples. Additionally, EMG can support an early diagnosis. The prognosis is excellent, with a case fatality rate of less than 2%. 

Hypotonia diagnosed in infancy and/or childhood
Charcot–Marie–Tooth polyneuropathies
Salient features include peripheral hypotonia with distal weakness, atrophy, sensory loss, and decreased deep tendon reflexes.

Hereditary motor and sensory neuropathies or Charcot–Marie–Tooth polyneuropathies are a heterogeneous group of conditions associated with demyelinating distal muscle weakness and atrophy with accompanying sensory loss, decreased deep tendon reflexes, and reduced nerve conduction velocities (<38 m/s). They are the most common type of hereditary neuropathy as a whole, with an incidence of approximately 1 in 3300 (http://www.genetests.org). Typical onset of this slowly progressive group of conditions is the first to third decade, and most subtypes do not have a reduced lifespan. Inheritance can be autosomal recessive, autosomal dominant, or X-linked. Dejerine–Sottas syndrome, or hereditary motor and sensory neuropathy type III, is a severe demyelinating subtype with onset in infancy and nerve conduction velocities less than 10 m per second. Periperal nerve biopsy shows a severely decreased number of myelinated fibers and ‘onion bulb’ formations, or flattened Schwann cells. Inheritance is typically autosomal recessive, with mutations in either PMP22, MPZ, or EGR2, sometimes caused by locus heterozygosity. Congenital hypomyelinating neuropathy is characterized by severe hypotonia and distal muscle weakness with areflexia, and slow nerve conduction velocities of less than 10 m per second. It is clinically difficult to distinguish from Dejerine–Sottas syndrome. Patients with congenital hypomyelinating neuropathy have ‘onion bulb’ formations with lack of active myelination and often total amylination. Inheritance is also autosomal recessive, and mutations have been found in both MPZ and EGR2 in congenital hypomyelinating neuropathy. It should be noted that currently some controversy exists over the naming of both Dejerine–Sottas syndrome and congenital hypomyelinating neuropathy. Because they have the same underlying genetic etiologies, they may both represent the severe end of the spectrum of Charcot–Marie–Tooth type 1 disease, which should be further elucidated.

Connective tissue disorders
Marfan syndrome and Loeys–Dietz syndrome
Salient features of Marfan syndrome include mild peripheral hypotonia, joint hypermobility, aortic root or dilatation, scoliosis, pectus excavatum or carinatum, arachnodactyly, and tall stature.

Salient features of Loeys–Dietz syndrome are mild peripheral hypotonia, hypertelorism bifid uvula or cleft palate, tortuous blood vessels on magnetic resonance angiography, and craniosynostosis.

In children with mild hypotonia and a constellation of features such as pectus excavatum, pes planus, joint hypermobility, craniosynostosis, and cardiac abnormalities such as aortic root dilation or mitral valve prolapose, a disorder of the connective tissue should be considered.

Marfan syndrome is a systemic disorder of the connective tissue with autosomal dominant inheritance and significant clinical variability. Though mutations in the FBN1 gene have been established as causative, diagnosis is typically made on a clinical basis, following established Ghent criteria. Typical presenting features can include ectopia lentis, pectus carinatum or excavatum, a reduced upper segment:lower segment ratio (<0.85) or increased arm span:height ratio (>1.05), arachnodactyly, scoliosis of more than 20°, medial rotation of the medial malleolus causing pes planus, and/or dilatation of the ascending aorta involving the sinuses of Valsalva or dissection of the ascending aorta. The major source of morbidity and mortality among patients with Marfan syndrome is significant risk for aortic dissection once the maximal dimension of the aorta reaches 5.0cm. If aortic root replacement occurs before this point and the other cardiovascular complications are managed properly, life expectancy is not reduced. Decreased muscle bulk is a well-described phenomenon in these patients, and significant hypotonia and myopathy have been documented in a subset of the population. Joyce et al. were among the first to describe abnormal muscle biopsies, including atrophy and type 1 fiber preponderance in a family with Marfan syndrome and progressive weakness. Myopathy with associated respiratory failure was documented in a family of three individuals with Marfan syndrome. Hypotonia has been documented in the neonatal form of Marfan syndrome, the most severe form associated with mutations in exons 24 to 32 of the FBN1 gene.

Loeys–Dietz syndrome is a newly described autosomal dominant disorder of the connective tissue characterized by hypertelorism, bifid uvula and/or cleft palate, and generalized arterial tortuosity with ascending aortic aneurysm and dissection. Other findings can include craniosynostosis, structural brain abnormalities, mental retardation, patent ductus arteriosus, and aneurysms with dissections occurring anywhere along the arterial tree. Mutations in TGFBR1 and TGFBR2 have been shown to be causative of this syndrome. Since the original description, individuals with Loeys–Dietz syndrome have been shown to have hypotonia in addition to the above findings.
(unpublished personal observation). If this syndrome is suspected, an echocardiogram should be ordered for possible aortic enlargement, and computed tomography angiography or magnetic resonance angiography of the entire aorta to look for arterial tortuosity and/or aortic aneurysms with or without the presence of an identified TGFBI or TGFBI2 mutation.

COMBINED PERIPHERAL AND CENTRAL HYPOTONIA

The clinical presentation of global developmental delay with cognitive impairment, with muscle weakness and/or paralysis as well as an increased creatine kinase level (albeit not necessary), is highly suggestive of combined abnormality of upper and lower motoneurons as the underlying cause. MRI of the brain and pertinent ancillary studies should be ordered as indicated by examination. Similar laboratory studies as mentioned above should be ordered in this group of patients (Fig. 3). Often, EMG and/or muscle biopsy is very helpful in establishing a diagnosis. An example of disorders that present with a combined picture of hypotonia include dystroglycanopathies, such as Walker–Warburg syndrome and Fukuyama-type congenital muscular dystrophy, mitochondrial encephalomyopathies, congenital disorders of glycosylation, Pelizaeus–Merzbacher disease, Marinesco–Sjögren syndrome, and Canavan disease.

Congenital combined hypotonia

Dystroglycanopathies

Salient features of the dystroglycanopathies include combined hypotonia, ‘cobblestone’ lissencephaly, neuronal migration abnormalities, and ocular abnormalities.

Dystroglycanopathies include Walker–Warburg syndrome, muscle–eye–brain disease, Fukuyama-type congenital muscular dystrophy, congenital muscular dystrophy types 1C and 1D, and limb-girdle muscular dystrophy type 2I. Presentation is variable, even within the same condition, but the group has common clinical characteristics. Hypotonia is common in any type, and elevated creatine kinase levels with muscular pathology indicative of dystrophy including necrosis, fibrosis, and muscle degeneration is present in all forms. Type II, or ‘cobblestone type’ lissencephaly, is pathognomonic and is characterized by multiple coarse gyri and/or agyric regions with variable thickness and disorganization of the cerebral hemispheres and cerebellum. Other brain abnormalities can include dilation of the cerebral ventricles, flattened brainstem, absent corpus callosum, aberrant myelination, or occipital encephalocoele. Ocular abnormalities, more common in Walker–Warburg syndrome and muscle–eye–brain disease, are variable, including milder abnormalities such as myopia or more clinically severe findings such as cataracts, glaucoma, retinal detachment, or microphthalmia. The most severe form of the group is Walker–Warburg syndrome, with a life expectancy of less than a year, whereas the least severe is limb-girdle muscular dystrophy type 2I, which may not even manifest until the fourth or fifth decade of life. The genetic etiology of dystroglycanopathies shows significant overlap. The first dystroglycanopathy described was Fukuyama-type congenital muscular dystrophy, a relatively common condition in the Japanese population, which is caused by mutations in the fukitin gene. Walker–Warburg syndrome can be caused by mutations in one of the six related genes, including protein-O-mannosyltransferase I and II (POMT1 and POMT2), fukitin, fukitin-related protein (FKRP), protein-O-mannose 1,2,3-N-acetylgalactosaminyltransferase 1 (POMGnT1), and acetylgalactosaminyltransferase-like protein (LARGE). Muscles–eye–brain disease is caused by mutations in POMGnT1, FKRP, or POMT1, and MDC1C is caused by mutations in FKRP as well. Other mutations cause the milder limb-girdle muscular dystrophy type 2I (most commonly L276I). Finally, congenital muscular dystrophy type 1D can be caused by mutations in the LARGE gene. The most frequent causative gene for dystroglycanopathies in the Caucasian population is FKRP. The genotypic heterogeneity and phenotypic overlap of these disorders are due to the common pathogenetic nature of all these gene mutations: association with abnormalities in the glycosylation of α-dystroglycan, thus the use of ‘dystroglycanopathy’ as nomenclature of the group of disorders as a whole (see reviews by Martin, Lisi and Cohn, and Muntoni et al.). See Table I for clinical features and genetic etiology of each form of dystroglycanopathy.

Congenital disorders of glycosylation

Salient features of congenital disorder of glycosylation type 1a include the following: combined central hypotonia and weakness, global developmental delay, dysmorphic features, inverted nipples, and abnormal fat distribution.

Congenital disorders of glycosylation is a rapidly expanding family of multisystem genetic diseases caused by defects in the biosynthesis of the glycan moiety of glycoproteins and other glycoconjugates. These disorders comprise defects in protein N-and O-glycosylation. Deficiencies of N-glycosylation represent multisystem diseases with involvement of the central and peripheral nervous, the gastrointestinal, endocrine, immune, and coagulation/anticoagulation systems. All forms are autosomal recessive in inheritance, although X-linked recessive inheritance has been suggested for a few cases of congenital disorders of glycosylation type 1X (Freeze H, personal communication 2009). Congenital disorder of glycosylation type 1a is the most common form. It is characterized by moderate to severe mental retardation, severe hypotonia, dysmorphic facial features, inverted nipples, and abnormal fat pad distribution. Congenital disorder of glycosylation type IId was described by Peters et al., with hydrocephalus requiring shunting, transient cholestatic syndrome, coagulation abnormalities, and significant myopathy. Isoelectric focusing revealed a type 2 pattern of abnormality not described previously, caused by a deficiency of β-1,4-galactosyltransferase. Additionally, congenital disorder of glycosylation type Ie, caused by a deficiency of dolichyl-phosphate-mannose synthase 1, has been described in a few patients. These children presented with severe developmental delay, hypotonia, intractable seizures, and postnatal microcephaly. Frontal atrophy is a common finding on MRI. A relatively inexpensive screening test for congenital disorders of glycosylation requires only a small amount of serum and has used isoelectric focusing in the past, and currently electrospray ionization–mass spectrometry, to evaluate the glycosylated state of serum transferrin.
**Table 1: Etiologies and clinical features of dystroglycanopathy**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Inheritance</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walker–Warburg syndrome</td>
<td>POMT1, POMT2, FKTN, FKRP, POMGnT1, LARGE</td>
<td>Autosomal recessive</td>
<td>Progressive muscle deterioration, type II lissencephaly, eye abnormalities, life expectancy less than 3y</td>
</tr>
<tr>
<td>Muscle–eye–brain disease</td>
<td>POMGnT1, FKRP, POMT1</td>
<td>Autosomal recessive</td>
<td>Progressive muscle deterioration, neuronal migration defects, eye abnormalities, variable severity</td>
</tr>
<tr>
<td>Fukuyama congenital muscular dystrophy</td>
<td>FKTN</td>
<td>Autosomal recessive</td>
<td>Progressive muscle deterioration, severe neuronal migration defects, seizures, eye abnormalities, cardiomyopathy</td>
</tr>
<tr>
<td>Congenital muscular dystrophy type 1C</td>
<td>FKRP</td>
<td>Autosomal recessive</td>
<td>Progressive muscle deterioration, variable white-matter abnormalities/magnetic resonance imaging or normal central nervous system, (CNS) eye abnormalities less common</td>
</tr>
<tr>
<td>Congenital muscular dystrophy type 1D</td>
<td>LARGE</td>
<td>Autosomal recessive</td>
<td>Progressive muscle deterioration, white matter abnormalities/neuronal migration abnormalities, eye abnormalities less common</td>
</tr>
<tr>
<td>Limb-girdle muscular dystrophy type 2l</td>
<td>FKRP (L276I common mutation)</td>
<td>Autosomal recessive</td>
<td>Milder progressive muscle deterioration, dilated cardiomyopathy, onset at 1–40y with normal life expectancy, no abnormalities of the CNS</td>
</tr>
</tbody>
</table>

**Canavan disease**

Salient features of Canavan disease include the following: combined hypotonia, global developmental delay, macrocephaly, optic atrophy, seizures, ‘spongy’ degeneration of white matter on MRI of the brain, and Ashkenazi Jewish ethnicity.

Canavan disease is an autosomal recessive condition characterized by macrocephaly, severe hypotonia with head lag, and developmental delay. It is more common in the Ashkenazi Jewish population, with a carrier rate of 1:57 (Feigenbaum et al. 111). Optic atrophy and seizures may also be present.112 Patients make developmental progress; some interact with their environment. Three distinct forms are described based on age at onset, including neonatal, infantile, and juvenile Canavan, and lifespan is variable depending on onset and severity of disease. Pathophysiology includes cortical and subcortical ‘spongy degeneration’ of the white matter in the brain, dysmyelination, and astrocyte abnormalities.113 A deficiency of the enzyme aspartoacylase, encoded by ASPA, causes an increase in N-acetyl aspartic acid which can be measured in the urine. N-acetyl aspartic acid is also elevated in blood, CSF, skin fibroblasts, and on proton nuclear magnetic resonance spectroscopy.112 Ninety-eight per cent of Ashkenazi Jewish patients have mutations at E285A or Y231X owing to a founder effect, whereas only 3% of non-Jewish patients have a mutation in one of these two genes.114 The A305E mutation is most common in the non-Jewish population, with a 40 to 60% detection rate.114

**Marinesco–Sjögren syndrome**

Salient features include central hypotonia and myopathy, global developmental delay, cerebellar atrophy, and ataxia, cataracts. Marinesco–Sjögren syndrome is a rare autosomal recessive disorder characterized by cerebellar atrophy and ataxia, myopathy with hypotonia, early-onset cataracts, and developmental delay. Hypotonia is evident in early infancy, and muscle biopsy can reveal myopathic features such as variation in fiber size, an increased number of fibers with centralized nuclei, and scattered necrotic and regenerating fibers. Ragged red fibers have also been documented on muscle biopsy in this condition.115 Bilateral cataracts are typically present and though not necessarily congenital, progression is rapid and requires lens removal in the first decade. Short stature, scoliosis/kyphosis, and hypogonadism are also documented. Cerebellar atrophy, particularly of the vermis, is the most common finding on MRI, though Reinhold et al. reported that this finding is not obligatory for making a diagnosis of Marinesco–Sjörgen syndrome.116 Neurological manifestations can include truncal or limb ataxia, dystarthis, intention tremor, and nystagmus.117 Other brain MRI findings can include cortical atrophy and periventricular white-matter lesions. Cognitive development can vary from mild to severe mental retardation. In 2005, Sendeck et al. discovered mutations in the SIL1 gene in nine patients with this syndrome, implicating this as the causative gene.118 SIL1 encodes for a heat-shock protein with an essential role in activity of the endoplasmic reticulum.

**Mitochondrial encephalomyopathies**

Salient features include the following: central hypotonia or myopathy, exercise intolerance, seizures and/or migraines, ataxia, cardiomyopathy, external ophthalmoplegia, sensorineural hearing loss, optic atrophy, hypothryoidism, diabetes mellitus, and maternal family history of any of the above.

Mitochondrial disorders are caused by dysfunction of the respiratory chain, which is predominantly responsible for oxidative phosphorylation and the production of adenosine triphosphate. Though mitochondrial conditions are extremely variable and can affect almost any organ system, brain and skeletal muscle are typically affected owing to their high demand on oxidative metabolism.119 Mitochondrial conditions are classified into two groups: conditions due to abnormalities in the mitochondrial DNA and disorders caused by mutations in nuclear DNA. Of the five complexes required for ATP production in the inner mitochondrial membrane, complex II is encoded only by nuclear DNA, whereas I, III, IV, and V have both nuclear and
mitochondrial gene-encoding subunits. The mitochondrial genome encodes for 13 proteins and 24 RNAs, and is present in multiple copies within cells. Most mitochondrial DNA disorders occur when a fraction of the mitochondria within a certain cell type are abnormal, called heteroplasmy, whereas some conditions such as Leber hereditary optic neuropathy can occur when all mitochondria are abnormal (homoplasmy).

Mitochondrial disorders have extremely variable presentations, with almost any organ system possibly being affected at any age. Common clinical features can include hypotonia at birth or in the first 2 years of life, myopathy with exercise intolerance, encephalopathy with seizures and/or migraines, ataxia, cardiomyopathy, external ophthalmoplegia, sensorineural hearing loss, optic atrophy, diabetes mellitus, and other abnormalities.112 Obtaining a three-generation pedigree is essential if a mitochondrial disorder is considered; mitochondrial DNA mutations are inherited only from the maternal line: evidence of paternal inheritance would eliminate this possibility (though a nuclear DNA abnormality should still be considered). Serum lactate may be elevated whereas serum pyruvate is decreased, giving an increased lactate:pyruvate ratio. Other helpful laboratory tests include plasma acylcarnitine profile, plasma amino acids, and urine organic acids. Genetic testing sequencing the whole mitochondrial genome or mitochondrial DNA point-mutation screening is now available. Muscle biopsy can be extremely valuable, even in the absence of clinical symptoms of muscle disease. Pathological features in the muscle in mitochondrial disorders can include ragged red fibers, accumulation of structurally abnormal mitochondria, and cytochrome c oxidase (COX)-negative fibers. Unfortunately, all these diagnostic tests can be normal in individuals with suspected or known mitochondrial disease owing to family history of the disorder, proving diagnostic testing for mitochondrial disease to be quite elusive.

Clinically recognizable mitochondrial disorders with myopathic features include the following: chronic progressive external ophthalmoplegia; Kearns–Sayre syndrome; mitochondrial DNA deletion syndromes; mitochondrial encephalopathy lactic acidosis and stroke-like episodes; myoclonus epilepsy with ragged red fibers; Leigh syndrome; and neuropathy, ataxia, and retinitis pigmentosa. Sequencing the whole mitochondrial DNA or a specific nuclear gene is warranted if one of these conditions is suspected. It needs to be emphasized that a definitive diagnosis of mitochondrial disease (as well as its elimination) can often not be established, which needs to be explained to the patients and their families. A variety of vitamins and co-factors have been used to treat patients with a known or suspected mitochondrial disorder, including coenzyme q10, creatine, and various vitamins. However, despite quite significant anecdotal reports about therapeutic benefits, a systematic review by Chinnery et al. did not show clear improvement of symptoms after administration of these supplements.120

**Childhood-onset combined hypotonia**

**Pelizaeus–Merzbacher disease**

Salient features of this disease include the following: males with progressive central and peripheral hypotonia, spasticity, ataxia, dysarthria, and cognitive impairment with dysmyelination on MRI of the brain.

Pelizaeus–Merzbacher disease arises from mutations or duplications in the proteolipid protein (PLP) gene on the X chromosome. There is considerable variability between patients, who are diagnosed on a spectrum of clinical severity. Congenital Pelizaeus–Merzbacher disease is the most severe form, whereas the mildest phenotype is classified as spastic paraplegia type 2. The disease is described as a progressive dysmyelinating disorder in which myelin is not formed correctly, distinguishing it from other leukodystrophies caused by degeneration of normally formed myelin. It is characterized by the development of nystagmus, hypotonia, and dysarthria in early infancy to childhood, progressing to spasticity, ataxia, intention tremor of the upper limbs, and cognitive impairment. MRI of the brain demonstrates lack or reduction of myelin sheaths in the white matter (usually more prominently in the periventricular regions), preservation of the neurons and axons, and patchy areas of thin but conserved myelin (‘tigroid’).121 Individuals with classic Pelizaeus–Merzbacher disease can survive into mid-adulthood, with a tigroid appearance of the brain, whereas the congenital form typically results in death in the first decade and shows complete absence of myelin. The most severe forms of the disease are typically caused by missense mutations in the PLP1 gene, though a missense mutation can cause variable phenotypes, from mild to severe.122 Null mutations typically result in a milder phenotype, presumably owing to nonsense-mediated decay.121 The most frequent alterations found in the disease are duplications on the X chromosome containing the PLP1 gene, accounting for approximately 60 to 70% of cases; deletions can also be present.123 This gives credence to the importance of gene dosage in this disorder. Most carrier females for Pelizaeus–Merzbacher disease are asymptomatic, though some females can present with mild symptoms.

**CONCLUSION**

This review is written to present a logical and systematic approach to the hypotonic infant or child. As outlined above, a careful and thorough approach is important for the diagnosis, management, and future prenatal diagnosis for patients and their families. However, it is important to emphasize that often, despite a thorough work-up, a diagnosis cannot be established. Nevertheless, this should not interfere with the ability to manage hypotonia and additional medical problems individually in these patients. A careful explanation to the patients and their families that symptomatic treatment can and needs to be tailored toward the individual is of utmost importance and is essential for a productive long-term physician–patient relationship.

**ONLINE MATERIAL/SUPPORTING INFORMATION**

The references for this article may be found in the online version.