

# Cerebral hypotonia

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Originally released July 12, 2006; last updated February 1, 2016; expires February 1, 2019

## Introduction

This article includes discussion of cerebral hypotonia, central hypotonia, essential hypotonia, benign congenital hypotonia, and [floppy infant](#). The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

## Overview

Hypotonia is a clinical manifestation of numerous diseases affecting the central and/or peripheral motor nervous system. The key to accurate diagnosis involves integral steps of evaluation that include a detailed history, examination, and diagnostic tests. "Cerebral" (or central) hypotonia implies pathogenesis from abnormalities from the central nervous system, and related causal disorders include cerebral dysgenesis and genetic or metabolic disorders. Patients with central hypotonia generally have hypotonia without associated weakness, in contrast to the peripheral (lower motor neuron) causes, which typically produce both hypotonia and muscle weakness. Hypotonia is a clinical manifestation of over 500 genetic disorders; thus, a logical, stepwise approach to diagnosis is essential. With recent advances in the field of genetic testing, diagnostic yield will undoubtedly improve. There is no cure, but treatment includes supportive therapies, such as physical and occupational therapy, and diagnosis-specific management.

## Key points

- Hypotonia is reduced tension or resistance of passive range of motion.
- The first step in the evaluation of a child with hypotonia is localization to the central ("cerebral") or peripheral nervous system, or both.
- Central hypotonia is more likely to be noted axially with normal strength and hyperactive to normal deep tendon reflexes.
- Other clues to central hypotonia include dysmorphic facies, macro or [microcephaly](#), developmental delay (global, motor, or cognitive), seizures, malformations of other organs, altered level of consciousness, abnormal eye movements, abnormal breathing pattern, or other signs of central nervous system dysfunction.
- A majority of diagnoses arise from history and physical exam, but neuroimaging, genetic testing, and other laboratory evaluations are also important in diagnosis.

## Historical note and terminology

The term "cerebral hypotonia" describes a symptom complex concerning the contribution of higher cortical functions to muscle tone and motor development.

Literature in the 1960s reflects an understanding of the cerebral influences on tone and motor control. In 1961, Jebsen and colleagues suggested classification of the causes of hypotonia into 3 broad categories: (1) central nervous system diseases, (2) motor unit diseases, and (3) metabolic disorders ([Jebsen et al 1961](#)). Furthermore, the monograph by Victor Dubowitz in the late 1960s entitled "The Floppy Infant" provided a practical approach to the diagnosis and classification of a child with hypotonia ([Dubowitz 1969](#)). He emphasized 2 main questions when confronted with a floppy baby or child: (1) "Is this a paralyzed child with incidental hypotonia?" and (2) "Is this a hypotonic child without significant muscle weakness?" His categorization of the paralytic conditions of children with hypotonia with weakness with "incidental" hypotonic was found to be most often lower motor neuron diseases: proximal spinal muscular atrophies, congenital myopathies, and other neuromuscular disorders. The infants with nonparalytic conditions who had hypotonia without significant weakness included disorders of the central nervous system, connective tissue disorders, metabolic, nutritional, and endocrine disorders, acute illness, and essential (or benign) hypotonia. This subdivision, central versus peripheral hypotonia, remains clinically useful. Two thorough reviews of the genetic evaluation of hypotonia provide diagnostic algorithms based on the original distinction of symptom manifestations: central, peripheral, or both ([Lisi and Cohn 2011](#); [Prasad and Prasad 2011](#)). A concise overview of neonatal hypotonia is also presented in a recent review article ([Sparks 2015](#)).

At the end of his monologue Dubowitz stated, "It is important for the clinician to remember that when he makes the diagnosis of floppy infant syndrome, he is only at the beginning of the diagnostic exercise not at the end."

## Clinical manifestations

### Presentation and course

Hypotonia is an end product of multiple diseases affecting the upper and/or lower motor nervous system. Accurate diagnosis involves key steps of evaluation that include a detailed history, examination, and diagnostic tests.

Assessing a child with "hypotonia" typically takes place in the immediate postnatal period, in early infancy, or within the first 1 to 2 years of life. It may be readily apparent at birth or may be noted as a child fails to make normal developmental progress. Central hypotonia is more common, accounting for 60% to 80% of presentation of hypotonia (Peredo and Hannibal 2009). Despite an extensive differential diagnosis list for central hypotonia, genetic and metabolic diagnoses have been reported to account for up to 60% of these cases (Prasad and Prasad 2011).

Clinical signs of low tone in infancy include hip abduction with legs externally rotated in the supine infant ("frog-leg posture"), arms extended at rest, head lag greater than expected for age when arm traction applied, increased distance of arm pull with the anterior scarf sign, and low tone notes on both vertical ("slip through" at the shoulders) and horizontal (c-curve over hand) suspension. Central hypotonia is more typically axial in distribution, although infants with significantly low tone may have a paucity of antigravity movements similar to a child with weakness and hypotonia. Muscle power (strength) and deep tendon reflexes are preserved in disorders with central hypotonia.

Low tone, however, may also present as a child ages with delayed motor milestones (along the spectrum of mildly delayed walking or impaired handwriting to significantly impaired milestones). Hypotonia can affect both gross and fine motor movements. Hypotonia may also manifest with oromotor symptoms, including poor feeding, drooling, swallowing problems, or speech difficulty. Abnormal posture can also pose difficulty to feedings, and joint laxity places the child at increased risk for dislocations or other skeletal abnormalities.

Other clinical signs used to support a diagnosis of central hypotonia include encephalopathy, [global developmental delay](#), seizures, dysmorphic features or other organ structural abnormalities, visual or hearing impairment, and hyperreflexia. On the other hand, hypotonia may be a sign of central nervous system pathology in a certain population. Although it was a small study, Wessel found the association between hypotonia and glioma in children with [neurofibromatosis type 1](#) and suggested that hypotonia might be a clinically useful indicator of brain tumor in this population (Wessel et al 2013).

Other clinical signs will vary by the specific diagnosis of each patient. However, these other symptoms are important in the algorithms for diagnosis. For example, central hypotonia associated with normal creatine kinase and global developmental delay leads down a different diagnostic pathway than hypotonia associated with weakness, but no cognitive impairment (Lisi and Cohn 2011). Algorithms for diagnostic evaluation both by Lisi and Cohn and Prasad and Prasad are highly recommended references when considering a patient with hypotonia (Lisi and Cohn 2011; Prasad and Prasad 2011).

Clinical history. When evaluating a patient with hypotonia important questions to help elucidate the diagnosis would include:

#### *Prenatal history.*

- (1) Age of mother at time of birth: increased odds of chromosomal disorders with advanced maternal age.
- (2) Nature of baby's intrauterine movements: neuromuscular disorders may have decreased movements or hypoxia may cause sudden change in movements.
- (3) History of infections or teratogens during pregnancy: rhythmic movements in utero may represent intrauterine seizures and increased risk of cerebral abnormalities. [TORCH](#) infections and teratogens increase risk of cerebral abnormalities and hypotonia.
- (4) History of polyhydramnios or oligohydramnios: maternal history of previous miscarriages and fetal demise. May represent inheritable metabolic or genetic conditions.

(5) Abnormalities on screening ultrasounds: congenital brain and other organ anomalies are more often linked to central causes of hypotonia, whereas arthrogryposis multiplex is often linked to peripheral/neuromuscular disorders.

(6) Presentation at birth: breech presentation is common in hypotonia and/or neuromuscular disorders.

(7) Positive family history of neuromuscular disorders: ie, [myotonic dystrophy](#) in the mother.

#### *Birth/perinatal history.*

(1) History of prematurity: increased risk for cerebral abnormality, complications, and [cerebral palsy](#).

(2) Mode of delivery, complications/difficult birth: hypoxic-ischemic encephalopathy may lead to [CNS](#) damage.

(3) Difficulties sucking/swallowing: may be seen with hypoxic ischemic injury, cerebral palsy, cerebral disorders, and neuromuscular causes.

(4) Poor respiratory effort: may be seen with hypoxic ischemic injury but if not in context with overall clinical picture, reflects possible neuromuscular cause.

(5) Encephalopathy: if out of context of birth history, may reflect underlying metabolic disorder or severe cerebral dysgenesis.

(6) Neonatal seizures: if out of context of birth history, may reflect underlying metabolic disorder or cerebral dysgenesis.

(7) Unexplained metabolic “lab” abnormalities: consider metabolic disturbances and inborn errors of metabolism.

#### *Developmental history.*

(1) Moderate to severe developmental delay and retardation: genetic, cerebral dysgenesis.

(2) Normal previous development and loss of previously acquired motor skills: consider muscular dystrophies, progressive/intermittent metabolic disorders, or neurodegenerative disorders.

(3) Mild delay in motor development with normal [IQ](#) and social development: “benign hypotonia” or normal variation in development.

#### *Medical history.*

(1) Seizure disorders: cerebral dysgenesis, genetic, metabolic, chromosomal disorders.

(2) Learning disabilities and behavioral disorders such as attention deficit hyperactivity disorder: reflect overall abnormality of brain development often associated with mild hypotonia.

(3) Recurrent respiratory infections: neuromuscular dysfunction, possible central dysfunction.

(4) Detailed review of systems: determine other associated malformations or systemic involvement.

#### Pertinent exam findings.

(1) Vital sign disturbance: may reflect severe cerebral dysgenesis, neuropathy, effects from hypoxia, acute illness.

(2) General: dysmorphic features point to possible genetic abnormality.

(3) Skin: neurocutaneous abnormalities may reflect underlying genetic syndrome (neurofibromatosis, tuberous sclerosis).

(4) Ocular exam: retinal findings, “cherry red spot,” optic nerve exam (atrophy, pale disc) may reflect underlying metabolic abnormality. Abnormal optic nerve may indicate “central causes,” septo-optic dysplasias, etc.

(5) Hepatosplenomegaly: TORCH infections, [glycogen storage diseases](#), inborn errors of metabolism.

(6) Extremities: abnormal digits, etc., may be characteristic of genetic syndromes.

(7) Other organ abnormalities (cardiovascular, genitourinary): genetic syndromes or associations.

### *Neurologic exam.*

#### (1) Head circumference:

Microcephaly: more common in central causes such as TORCH infections, genetic syndromes.

Macrocephaly: neurocutaneous genetic syndromes, possible CNS disturbance such as [hydrocephalus](#).

#### (2) Mental status: normal IQ points to neuromuscular causes.

#### (3) [Nystagmus](#), erratic eye movements, strabismus: more common in central causes.

(4) Prominent facial weakness: congenital myopathies, [myasthenia gravis](#). Possible brainstem effects from hypoxia or cerebral dysgenesis. "Hypotonic facies" typically describe a child with open, downturned mouth and eyelid lag (secondary to hypotonia of facial muscles).

(5) Other dysfunctions of cranial nerves (ie, [Mobius syndrome](#), hearing loss): more likely central causes, genetic causes.

### *Motor system evaluation.*

#### (1) General observation:

(a) Resting position: Frog-leg position indicates significant hypotonia, especially in neonates when baseline tone is flexor "W." Sitting in an older child is indicative of proximal hypotonia.

(b) Muscle atrophy or fasciculations: more common in neuromuscular disorders.

(c) Extent of movement: hypotonia is often associated with a lack of spontaneous movement.

(d) Distribution of movement: In certain conditions such as anterior horn disease, there may be only movement of the distal extremities. Wide-based gait and genu recurvatum are also indicative of hypotonia.

(2) Ventral suspension: an infant is typically held in ventral suspension, in which the infant is supported by a hand under the chest. Head control, trunk curvature, and movement of the extremities can be readily assessed ([Dubowitz 1969](#); [Bluestone 1999](#)). A normal newborn will hold the head about 45 degrees or less to the horizontal, the back will be straight or only slightly flexed, the arms flexed at the elbows and partially extended at the shoulder, and the knees partially flexed. An infant with hypotonia may look like a "rag doll" and slump forward and need more support. An infant with possible central cause of hypotonia may scissor in ventral suspension ([Bluestone 1999](#)).

(3) Traction of the hands in the supine position will typically result in some degree of flexion in full-term and premature infants, but a hypotonic infant may have prominent head lag.

(4) Muscle strength: may be more difficult to assess. One method to gauge movement is the ability of the neonate to sustain the posture of a limb against gravity ([Bluestone 1999](#)). In older children, strength may be more easily tested.

(5) Reflexes: more typically diminished or absent in neuromuscular disorders; likely to be increased in central disorders.

(6) Sensory disturbance: may reflect nutritional causes, neuropathies, patterns of abnormalities suggestive of central causes (previous [stroke](#), etc.).

(7) Coordination: a hypotonic patient may be more uncoordinated from muscle tone abnormalities, but frank [ataxia](#) would make one consider more prominently cerebellar disorders or central causes.

### **Prognosis and complications**

The prognosis of centrally based hypotonia may be significantly different based on the etiologic process ([Menkes 1990](#); [Miller 1998](#)). For cases of children with cerebral dysgenesis, the symptoms of hypotonia are often not as disabling as the other developmental problems that may accompany the disorder, such as static encephalopathy and [intellectual disability](#).

A hypotonic patient may be at risk for musculoskeletal problems such as contractures, joint dislocation, respiratory

compromise, and orthopedic complications based on abnormal postures and positions (Vries 1998; Rosenbaum 2004).

### **Clinical vignette**

A 4-month-old female presented with hypotonia, poor ocular fixation, and a history of “spasms” at 3 months of age. Her prenatal history was relevant for premature birth at 32 weeks' gestation, with postnatal hospitalization only relevant for poor sucking/swallowing that resolved within the expected timeframe. There were no perinatal seizures or known intraventricular hemorrhage from prematurity.

The first 3 months of her life were noted for mild irritability but were otherwise unremarkable.

The patient then started developing clusters of spasms on awakening from sleep that got progressively more intense, sometimes lasting almost 10 minutes.

On EEG she showed classic findings of hypsarrhythmia and was diagnosed with infantile spasms. She was started on adrenocorticotropic hormone injections after a short course of phenobarbital. Her flexor spasm seizures subsided and she was maintained on 2 antiepileptic drugs, Zonigran and phenobarbital, and did well from a seizure standpoint from that point on.

On diagnostic testing, it was revealed she had septo-optic [dysplasia](#) and some findings of bilateral [periventricular leukomalacia](#). {embed="pagecomponents/media\_embed" entry\_id="8152"} Because of the seizures and this midline defect, she was referred to the genetic and metabolic clinic. There were no other associated metabolic or genetic problems identified after extensive evaluations. She had endocrine testing done because of this midline defect; to this point these tests have been normal, although she does have some failure to thrive.

Now at 17 months, she is demonstrating severe developmental delay. She cannot sit without support and has head lag when pulled from prone. She has strabismus with prominent right esotropia. She does have a social smile and is babbling some.

She demonstrates mixed tone pattern with prominent truncal hypotonia and some extension pattern to her legs at times. Reflexes are present and slightly brisk at the knees.

She has guarded long-term developmental outcome and has been involved with physical, occupational, and visual therapies.

This patient's hypotonia would be thought to be centrally based secondary to her brain dysmorphology (septo-optic dysplasia) and periventricular leukomalacia.

### **Biological basis**

#### **Anatomic localization**

Disorders which may mimic central hypotonia typically can be excluded by careful history, the clinical exam, and supportive diagnostic testing.

Usually, symptoms of a patient with central hypotonia have a generalized hypotonic pattern. The symptoms are usually present in infancy or noted in early development with delayed acquisition of developmental milestones.

Unilateral weakness in an infant or child would typically make this diagnosis more unlikely and would suggest other etiologies of unilateral weakness, including things such as brachial plexus injury at birth, broken clavicle, early presentation of [stroke](#), etc.

Localization patterns include:

Conditions affecting the lower motor neuron (peripheral hypotonia).

*Myopathic diseases.* Severe congenital myopathies may present in the newborn period, with decreased movements of the face and body, hypotonia, ptosis, and decreased deep tendon reflexes. The mother may have reported decreased intrauterine movements.

Myopathies or muscular dystrophies presenting later in childhood or adulthood may present with delayed acquisition of typical motor milestones or loss of previously acquired motor milestones.

Often patients with a primary myopathic process have an abnormal creatine phosphokinase, possibly abnormal transaminases, abnormal EMGs, and may have characteristic patterns seen on muscle biopsy.

Examples of myopathies and or muscular dystrophies include: [nemaline myopathy](#), metabolic myopathies, [myotonic dystrophy](#), [central core disease](#), [Duchenne muscular dystrophy](#), and limb girdle muscular dystrophies. Infectious (postviral) metabolic disturbances (potassium, calcium abnormalities) and medications (prednisone) may affect muscle function but are generally reversible and are preceded by normal muscle function.

*Neuromuscular junction disease.* These patients may have a [waxing and waning](#) weakness. Ptosis may be involved in an infant with this condition. Weakness may be more prominent at the end of the day or after feeding. Weakness can generally be improved by administration of medications such as Tensilon. Genetic testing is commercially available for the acetylcholine receptor antibody binding, transmission, and uptake. EMG/nerve conduction velocity may show characteristic findings.

*Anterior horn cell disease.* Anterior horn cell disease, such as the spinal muscular atrophies, can present with a prominent hypotonia and can be a progressively fatal disease, which can be rapid in early infancy and childhood. [Amyotrophic lateral sclerosis](#) would be a disease of adulthood characterized by previously normal motor function.

*Spinal cord disease.* "Spinal shock" may acutely present as hypotonia from an injury. A child may be born with congenital abnormalities of the spinal cord that may present with hypotonia affecting the legs more than the arms. Higher spinal cord defects may affect the arms and chest. Typically, below the area of the "lesion" there are decreased reflexes and hypotonia accompanied by motor paresis or paralysis. There may be accompanying bowel and bladder dysfunction.

Examples of spinal cord disorders are [spina bifida](#), congenital maldevelopment, or damage to the spinal cord.

*Neuropathies.* Abnormal nerve function may be distinguished by abnormal sensory patterns and response of the infant or child. There may be accompanying autonomic dysfunction. Reflexes are typically diminished. Neuropathies may also present as a "stocking/glove" pattern of motor weakness.

Maldevelopment and damage to the brain (central hypotonia). Disorders affecting the brain structure account for a majority of cases with cerebral hypotonia. These disorders are typically classified into the cerebral dysgenesis or dysplasias and conditions in which the developing brain may have been damaged, such as in prematurity. [Lissencephaly](#), [holoprosencephaly](#), and [Joubert syndrome](#) are examples of conditions of cerebral dysgenesis that may present with hypotonia.

A factor analysis of neuroanatomical and clinical characteristics of a series of patients with holoprosencephaly showed a high variance in terms of which motor abnormalities may present with cleavage of the cerebral hemispheres. [Other deep brain structures can often be affected, such as the basal ganglia, thalami, and hypothalamic nuclei. The motor abnormalities ranged dramatically from hypotonia to dystonia to spasticity.](#)

Joubert syndrome is an autosomal recessive disorder with familial vermian [cerebellar hypoplasia](#) and other brainstem malformations. [Symptoms of presentation may include hyperpnea, apnea in the neonatal period, abnormal eye movements, hypotonia, and mental retardation.](#) Observed abnormalities in the posterior fossa include cerebellar vermian dysgenesis, dilatation of the fourth ventricle, and thickened stretched cerebral peduncles shown by CAT scan or MRI of the brain ([Alorainy 2006](#)).

In some pontocerebellar hypoplasias, other possible associated disorders must be excluded including carbohydrate-deficient glycoprotein disorder and respiratory chain defects.

Midbrain disconnection syndrome was described involving a peculiar anatomic entity in which a child was born with congenital absence of the midbrain and upper pons along with remarkable disconnection between the midbrain, with the right cerebral peduncle missing and the left cerebral peduncle very thin and dysplastic ([Bednarek 2005](#)). [There was a thinned brainstem and small pons](#)

but cortical structures were otherwise remarkably intact. The clinical presentation was that of a full-term girl infant with severe massive hypotonia. The mother had a relatively unremarkable pregnancy and birth. Her orbitofacial cleft was normal, without prominent dysmorphic features. External stimuli provoked jitteriness but no facial or visual responses. She had no oculocephalic or corneal responses; there was no [myoclonus](#) or dyskinesias. She did have positive deep tendon reflexes. [CT](#) showed a large prepontine cistern but [MRI](#) helped to clarify this remarkable case of cerebral hypotonia.

[Cerebral palsy](#) typically denotes a heterogeneous collection of clinical syndromes that are characterized by abnormal motor and postural mechanisms ([Miller 1998](#)). Cerebral palsy as a term typically applies to children with motor symptoms presenting before 2 years of age and often reflective of underlying [CNS](#) maldevelopment or damage to the developing nervous system, such as in cases of extreme prematurity, hypoxic ischemic encephalopathy, or other etiologies. Typically, cerebral palsies are divided into the subgroups of spastic, dyskinetic, ataxic, atonic, and mixed.

Patients with ataxic cerebral palsy are usually term infants with an early prenatal etiology of their motor disability. They can be a clinically and heterogeneously diverse group. Some patients with this disorder may have underlying conditions such as cerebral dysgenesis syndromes. Most patients with ataxic cerebral palsy are hypotonic from birth and display cognitive and language delays.

Atonic cerebral palsy again can be a heterogeneous group of infants who are usually full-term and remain hypotonic for many months, prominently so after birth. Often, these children do not ever stand or walk and commonly have [microcephaly](#) and cerebral dysgenesis. The tone of these children may be called paratonic—when a joint is moved passively, increased resistance occurs that is proportional to the amount of pressure applied. This atonic group has been recognized for years and, until recently, was not mentioned in typical classifications of the cerebral palsy syndromes ([Miller 1998](#)).

Genetic and metabolic disorders (central or cerebral hypotonia). Hypotonia can be a clinical manifestation of over 500 genetic disorders. With recent advances in the field of genetic testing, many new disorders are being identified, and attempts are being made to find candidate genes responsible for the pathophysiology of these genetic disorders. For example, in a case report of 6p22.3 deletion syndrome, the authors proposed that deletion of genes, *DTBNP1* or *JARID2* may be contributing to the hypotonia phenotype ([Di Benedetto et al 2013](#)). Some inheritable recognized disorders of inborn errors of metabolism may present with hypotonia. Some typical disorders include peroxisomal disorders, [mitochondrial disorders](#), and organic and amino acidurias. Some of these disorders may cause reversible severe hypotonia in the newborn period and need to be recognized in the first 1 to 3 days of life. Infants with [pyruvate carboxylase deficiency](#) may present with axial hypotonia and tachypnea ([Garcia-Cazorla 2006](#)). Bizarre ocular movements may be described as well as abnormal movements to the limbs (high amplitude tremor and hypokinesia). This complex of movements may be called hypokinetic rigid syndrome. [MRI](#) in these infants can show cystic [periventricular leukomalacia](#). Laboratory tests typically reveal lactic acidosis, hypercitrullinemia, and hyperammonemia. Treating these patients with triheptanoin and citrate may be life-saving.

Other metabolic disturbances that may present with a generalized hypotonia include some disorders of potassium, calcium, and magnesium. Some of these may be transitory attacks of weakness such as in the periodic paralysis caused by abnormal potassium regulation and are distinguished from a central persistent hypotonia by the reversibility of the weakness. A case of severe hypermagnesemia resulting in development of acute hypotonia and reversibility of its clinical symptoms after correcting metabolic disturbance has been described ([Hyun e al 2011](#)).

Although a rare x-linked disorder, MCT8 (monocarboxylate transporter 8) deficiency or Allan-Herndon-Dudley syndrome (AHDS) presents with global hypotonia and psychomotor delay. All affected males present with a typical thyroid profile including elevated serum level of [T3](#) values ([Rodrigues et al 2014](#)). It may be important to include [T3](#) values when obtaining a thyroid panel as part of laboratory evaluation in the diagnostic workup for hypotonia.

[Down syndrome](#) is an example of a chromosomal disorder that causes hypotonia, static encephalopathy, and [intellectual disability](#). Many genetic syndromes have hypotonia as a symptom. Another important chromosomal abnormality to consider in a child with hypotonia of infancy is [Prader-Willi syndrome](#) (15q11-13 deletion or disruption). [Fragile X syndrome](#), X-linked intellectual disability syndromes, and Kabuki syndrome also have associated hypotonia. Tetrasomy 15q presents with [global developmental delay](#), hypotonia, [epilepsy](#), and autistic-like features ([Battaglia 2008](#)).

[Cerebral folate deficiency](#) has also been shown to present with hypotonia, as well as with global developmental delay, agitation, [ataxia](#), slowed head growth, and later with epilepsy, spasticity, speech disorder, and dyskinesias ([Gordon 2009](#)). Similarly, the disorders of bipterin metabolism, leading to defective tyrosine and tryptophan hydroxylases, leads to progressive cognitive and motor decline, central hypotonia with peripheral spasticity, and epilepsy ([Longo 2009](#)).

Conditions affecting both the lower and the upper motor neuron (combined peripheral and central hypotonia). When the underlying cause of hypotonia is a combined lower and upper motor neuron problem, it may present with developmental delay and cognitive impairment in addition to muscle weakness or increased creatine kinase level. Examples of such conditions are dystroglycanopathies (Walker-Warburg syndrome, muscle-eye-brain disease, Fukuyama-type congenital muscular dystrophy), [congenital disorders of glycosylation](#), mitochondrial encephalomyopathies, [Pelizaeus-Merzbacher disease](#), Marinesco-Sjögren syndrome, and [Canavan disease](#) ([Lisi and Cohn 2011](#)).

The condition Fukuyama-type congenital muscular dystrophy is characterized by both dystrophic changes in the skeletal muscle and CNS migration disturbances. This disorder is characterized by severe infantile hypotonia, symmetrical generalized weakness, and mental retardation. The cerebral migrational disturbances normally seen are cobblestone [lissencephaly](#) along with other cerebral and cerebellar dysgenesis. A genetic test is available for this disorder located at the Fukuyama congenital muscular dystrophy gene at chromosome 9q31-q33 by genetic linkage analysis ([Saito 2006](#)).

*Other: orthopedic/joint laxity.* Abnormally free moving joints and flexibility may be confused with hypotonia but can usually be distinguished by proper assessment of the joints and flexibility of the patient. Hyperflexibility or hypermobility is usually secondary to "joint laxity." Hypermobile people are stated to be at one extreme of the normal distribution curve, but this can rarely be due to pathological conditions such as Ehlers Danlos syndrome. Typically those conditions are associated with other abnormalities. Interestingly, hypermobility is twice as common in females as males. Hypermobile people are prone to a variety of musculoskeletal complaints such as patella dislocations and joint effusions. Some clinical tests that may indicate a patient is hypermobile include whether a patient is able to press the thumb to the forearm, hyperextend the fingers almost completely backwards, touch the floor with the palms of the hands, and whether or not the knees hyperextend ([Walsh 1992](#)).

## **Pathophysiology**

Tone can be influenced by many factors such as sleep, hypoxia, metabolic factors, and position at the time of testing. Tone is thought to be influenced by many interrelating pathways: hierarchical controls, muscle feedback through the muscle spindle arc, and genetic and metabolic influences.

Hierarchical theory of control of motor pathways. The reflex model of motor control shows that different reflex pathways may share common interneurons and the neuron is a nodal point for control by spinal neurons by descending pathways ([Sherington 1947](#); [Galea 2004](#)). The neurologist Hughlings Jackson (1835-1911) formulated the idea that there are successive levels of motor control in the nervous system, with the control of automatic movements by lower levels and of purposeful movements by higher levels ([Galea 2004](#)). Higher levels normally exert control (either excitatory or inhibitory) over lower levels. It was later found that there are both serial and parallel pathways affecting these lower and higher motor control centers. It is postulated that the influence of abnormal functioning "higher centers" affecting "lower centers" may be the basis of abnormal tone in patients with cerebral dysgenesis syndromes.

Muscle spindle feedback loop and effects on tone. The importance of the muscle spindle in the control of tone has been clearly established. The muscle spindle is thought to provide a feedback system for regulating the length of the muscle and the reflex arc. The spindle fibers have a rich supply of afferent nerve endings that pass to the anterior horn cells of the gamma fibers innervating the spindles and of the alpha nerve fibers innervating ordinary (extrafusal) muscle fibers, and form the reflex arc ([Dubowitz 1969](#)). The gamma efferent system has slowly conducting, small-diameter motor nerves supplying the striated intrafusal fibers of the muscle spindles. It has been suggested that floppiness in some children may be related to the hypoactivity of the gamma efferent system.

Genetic and biochemical influences on muscle tone. Other major contributing factors relating to the understanding of muscle tone are how genetic and biochemical factors influence muscle tone. Conditions affecting the cerebral cortex,

either by metabolic and cellular disturbances or abnormal formation of these intricate pathways, affect typical sequencing of evolution of motor control.

## Differential diagnosis

Dubowitz, in 1980, related:

It (hypotonia) may be the presenting feature of a neuromuscular disorder; it may occur in mentally retarded children or in the early presenting phase of cerebral palsy; it may be a manifestation of a connective tissue disorder; it may be associated with various metabolic disturbances in infancy; it may be an incidental and non specific sign in an acutely ill child; it may be completely physiological in the premature infant; and it may occur as a completely isolated symptom in an otherwise normal child.

Birdi provides a retrospective analysis of [floppy infants](#) seen in a tertiary care facility (Birdi 2005). Cases were gathered by a systemic evaluation of clinical databases, EMG analysis, and case reports of evaluations of “floppy infants” under 1 year of age. The cases were 47% female, 52% male. A definitive diagnosis was established in 67% of cases, in 24 cases (40%) purely on clinical grounds. In 60% of the cases, additional testing was required. Genetic disorders were discovered in 20%, congenital or acquired disorders of the CNS in 24%, and disorders of the lower motor neuron unit in 10%. If the infant survived 1 year of life, 62% were found to be globally delayed and 49% achieved independent ambulation. Another review indicates that history and exam may provide diagnosis in children with congenital hypotonia in 50% of cases, whereas imaging contributes to 13% of diagnoses, clinical genetic evaluation 9%, genetic testing 6%, biochemical testing 6%, neuromuscular testing 6%, and follow-up or repeated testing 7% (Peredo 2009).

As a tertiary facility, however, this series may reflect more severe cases of hypotonia and possibly not the more wide variation in presentation and outcome seen in a general child neurology practice.

Discussion of disorders that may cause hypotonia was noted in the localization area of this article.

**Table 1. Central versus Lower Motor Neuron Causes of Hypotonia**

|                                          | <b>“Central causes” of hypotonia</b>                                                                                                                                                                                                                          | <b>“Neuromuscular causes” of Hypotonia</b>                                                                                                                                                                           |
|------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Perinatal and birth history risk factors | ++++ Risk for genetic disorders<br>++++ Intrauterine seizures<br>++++ Hypoxic ischemic injury<br>++++ <a href="#">Neonatal seizures</a><br>++++ Encephalopathy<br>+++ Prematurity<br>++ Arthrogryposis multiplex<br>++ Abnormal brainstem/ autonomic features | +++ Poor feeding, swallowing, or breathing out of context of birth history<br>+++ Arthrogryposis multiplex<br>+++ History of ptosis<br>+++ Breech presentation                                                       |
| Exam features                            | ++++ No muscle weakness<br>+++ Dysmorphic features<br>+++ Fisting of hands “mixed tone”<br>+++ Impaired cognition<br>++ Muscle reflexes present<br>++ Crossing of adductors in ventral suspension<br>++ <a href="#">Nystagmus</a> , strabismus                | ++++ Muscle weakness<br>++++ <a href="#">Waxing and waning</a> course of weakness (NMUSC)<br>+++ Normal intelligence<br>++ Characteristic dysmorphic features<br>++ Typically decreased muscle reflexes<br>++ Ptosis |

|                     |                                                                                                                                                                                                       |                                                                                                                                                                                                                                   |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Evaluation features | <p>++++ Abnormal neuroimaging</p> <p>++++ Abnormal metabolic and serologic tests</p> <p>++++ Abnormal genetic tests</p> <p>+++ Reversible with correction of identified problem (sepsis, hypoxia)</p> | <p>++++ Abnormal creatine phosphokinase</p> <p>+++ EMG/nerve conduction velocity/muscle biopsy generally more helpful</p> <p>+++ Typically not reversible (NMUSC JXN/drug effect: exception)</p> <p>++ Abnormal genetic tests</p> |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Key: ++++=highly associated, +++=generally associated, ++=less strongly associated, +=possibly associated

**Table 2. Differential Diagnosis of a Child with Central Hypotonia**

- Central nervous system malformation
  - cerebral dysgenesis, neuronal migrational disorders
- Acute systemic disturbance
  - electrolyte disturbance
- Endocrine disorders
  - thyroid disturbance
- Infectious causes
  - sepsis
- Hypoxia
  - birth injury
- Chromosomal and genetic disorders
  - Down syndrome, Prader-Willi syndrome, fragile X syndrome
- Metabolic disorders
  - Cerebral folate deficiency, bipterin disorders
- Toxin exposure
- Vascular
  - stroke, hemorrhage
- Inborn errors of metabolism
  - mitochondrial, respiratory chain
- Cyanotic congenital heart disease
- Normal variation in tone
- Connective tissue disorders
- Rule out lower motor neuron cause
  - anterior horn cell, neuromuscular junction, neuropathy, myopathic processes
- Consider mixed disorders with both central and neuromuscular causes of hypotonia
  - hypoxic-ischemic encephalopathy, metabolic and storage disorders

Holoprosencephaly

Joubert syndrome

Cerebellar hypoplasia,

Down syndrome

Fragile X Disorder

Fukuyama muscular dystrophy

Ataxic cerebral palsy

Spina bifida

Rett syndrome

Lissencephaly

Porencephaly

Pontocerebellar hypoplasia

Mid brain disconnection syndrome  
Neuronal migrational disorders

## Diagnostic workup

**Table 3. Diagnostic Testing to Consider in Evaluation of a Patient Thought to Have Central Hypotonia**

|                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Neuroimaging:                                                                       | May reveal cerebral dysgenesis, previous or acute vascular event, evidence of hypoxic insult.                                                                                                                                                                                                                                                                                                                                                                              |
| Initial metabolic labs:                                                             | Complete metabolic profile, with liver panel, bilirubin, lipid profile, thyroid panel, calcium, magnesium, complete blood count with differential. Drug/toxin screen, infectious labs.                                                                                                                                                                                                                                                                                     |
| Muscle enzyme test:                                                                 | Creatine phosphokinase.                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Initial chromosomal / genetic screening:                                            | High resolution karyotype, <a href="#">SNP</a> array.                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Secondary metabolic labs or tests of inborn error of metabolism:                    | Depending on the clinical picture, tests to consider include: plasma amino acids, urine organic acids, arterial blood gas, lactic acid, pyruvate, lactate/pyruvate ratio, <a href="#">CSF</a> analysis for neurotransmitters and amino acids and glucose (along with other routine studies), white blood count enzymes, test for <a href="#">congenital disorders of glycosylation</a> , urine <a href="#">mucopolysaccharides</a> , ammonia, very long chain fatty acids. |
| Metabolic/genetic consultation recommended.                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Secondary genetic screening to consider:                                            | FISH 15Q Prader-Willi, <a href="#">fragile X syndrome</a> , or whole exome sequence                                                                                                                                                                                                                                                                                                                                                                                        |
| May need evaluation to rule out or consider component of lower motor neuron disease |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

**Table 4. Diagnostic Testing to Consider in Evaluation of a Patient Thought To Have Lower Motor Neuron Hypotonia**

|                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Serum creatine phosphokinase                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Initial metabolic labs:                                               | Complete metabolic profile, calcium, phosphorus, magnesium, complete blood count                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| EMG/nerve conduction velocity                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Muscle biopsy                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Genetic tests:                                                        | Tests will vary depending on clinical situation, for example <ul style="list-style-type: none"><li>• Anterior horn cell disease: <a href="#">SMA</a> Werdnig-Hoffmann disease 5q 11-13.</li><li>• Congenital myopathies: <a href="#">central core disease</a> 19 q13, myotubular myopathy Xq28.</li><li>• Muscular dystrophies: <a href="#">DMD</a> Del/Dup/Sequencing, <a href="#">myotonic dystrophy DM1</a> and <a href="#">DM2</a>, mitochondrial enzyme deficiency myopathy panel</li><li>• Peripheral neuropathy panels: <a href="#">CMT</a> panel</li></ul> |
| Neuromuscular consultation recommended                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Consider neuroimaging                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Consider further evaluations to rule out central causes of hypotonia. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

## Management

Typically central hypotonia is treated by supportive and rehabilitative efforts that aim to establish improved muscle tone and strength ([Clark 1998](#); [Scrutton 2004](#)). There may be oral motor dysfunction that requires evaluation and

management due to the risk of aspiration and reflux (Lifschitz 1998). There may be reversible metabolic conditions that present as hypotonia; these disorders need to be excluded.

Genetic testing may be available for some of the genetically acquired hypotonia cases, including some cases of inherited inborn errors of metabolism, to help advise and manage future pregnancies.

Rehabilitative services would include physical, occupational, and speech therapy. Children may need adaptive devices. The use of orthoses such as foot orthoses or supramalleolar orthoses is considered the standard of care to promote stability and functional mobility in children with hypotonia (Weber and Martin 2014).

## Outcomes

Outcome or the response to treatment will depend on the underlying etiology and severity of hypotonia. However, although some cases of idiopathic or benign congenital hypotonia will improve or recover completely, many demonstrate persistent problems in motor coordination, language, and learning difficulties later in life (Strubhar et al 2007).

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\*\*References especially recommended by the author or editor for general reading.

## Former authors

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## ICD codes

### ICD codes

Congenital hypotonia/essential hypotonia/neonatal hypotonia: P94.2

## Profile

## Age range of presentation

01-23 months

02-05 years

06-12 years

13-18 years

## Differential diagnosis list

neuromuscular disorders

intellectual disability

cerebral palsy

connective tissue disorders

metabolic disturbances in infancy

prematurity

brachial plexus injury at birth

broken clavicle

early presentation of stroke

severe congenital myopathies

myotonic dystrophy

central core disease

Duchenne muscular dystrophy

limb girdle muscular dystrophies

Fukuyama congenital muscular dystrophy

anterior horn cell disease

Werdnig Hoffmann disease

spinal cord disease

spinal bifida

congenital malformation of the spine

neuropathies

cerebral dysgenesis

cerebral dysplasias

lissencephaly

holoprosencephaly

Joubert syndrome

pontocerebellar hypoplasias

midbrain disconnection syndrome

peroxisomal disorders

mitochondrial disorders

organic and amino acidurias

pyruvate carboxylase deficiency

disorders of potassium, calcium, magnesium

orthopedic/joint laxity

acute systemic disturbance (electrolyte disturbance)

endocrine disorders (thyroid disturbance)

infectious causes (Sepsis)

cyanotic congenital heart disease

normal variation in tone

## Associated disorders

Holoprosencephaly

Joubert syndrome

Cerebellar hypoplasia,

Down syndrome

Fragile X Disorder

Fukuyama muscular dystrophy  
Ataxic cerebral palsy  
Spina bifida  
Rett syndrome  
Lissencephaly  
Porencephaly  
Pontocerebellar hypoplasia  
Mid brain disconnection syndrome  
Neuronal migrational disorders

### **Other topics to consider**

Cerebral palsy  
Disorders of peroxisome assembly  
Down syndrome  
Holoprosencephaly  
Intellectual disability  
Joubert syndrome

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