Congenital muscle fiber-type disproportion

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Introduction

This article includes discussion of congenital muscle fiber-type disproportion, congenital fiber-type disproportion myopathy, type I fiber hypotrophy with central nuclei, CMFTD, congenital muscle fiber-type disproportion, and fiber-type predominance. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Congenital muscle fiber-type disproportion is a condition that can be defined only in the muscle biopsy by 2 obligatory criteria of “disproportion”: (1) a massive type I myofiber predominance of 80% or more, and (2) myofibers of type I are uniformly smaller than normal for age by 2 standard deviations or more, but are not necessarily angular or rounded as in myofiber atrophy. Internal sarcolemmal nuclei are an inconstant additional feature in a minority of cases, but myofiber necrosis, inflammation, and fibrosis are not typical features. This condition may be isolated as a nonprogressive congenital myopathy inherited as an autosomal dominant or recessive trait; may be associated with other congenital myopathies, such as nemaline rod myopathy, minicore myopathy, and infantile myotonic dystrophy; and may present with a variety of genetic metabolic diseases, including Krabbe leukodystrophy in early stages and insulin-resistant diabetes mellitus. It also is associated with congenital malformations of the brain, particularly cerebellar hypoplasia. Clinically, patients often have dysmorphic facies with facial wasting similar to that of nemaline myopathy or myotonic dystrophy. Serum creatine kinase is normal and EMG is nondiagnostic. Congenital muscle fiber-type disproportion, thus, is best regarded as a syndrome, and not a specific disease, except for isolated familial cases.

Key points

- Pathological major criteria are: (1) uniform smallness of type I myofibers and (2) type I myofiber predominance. Pathological minor criteria are: (3) small myofibers remain polygonal, not angular, in transverse contour; (4) myofiber necrosis and degeneration is not a feature; (5) centronuclear fibers occur in a minority of cases.
- Congenital muscle fiber-type disproportion associated with several congenital myopathies (neonatal myotonic dystrophy; nemaline myopathy) may occur as an isolated congenital myopathy, is associated with several systemic inborn metabolic diseases (multiple sulfatase deficiency; some mitochondrial cytopathies; Krabbe disease), and may be secondary to suprasegmental abnormal influences on the motor unit in midfetal life, particularly cerebellar hypoplasia and other posterior fossa malformations; this is not due to denervation or reinnervation of muscle (spinal muscular atrophy, congenital or genetic polyneuropathies).
- Many diverse genes are now known to be associated, in addition to those that cause nemaline myopathy.
- Serum CK is normal; EMG is nondiagnostic; NCV is normal.
- Clinical phenotype is variable, depending on the associated disease (facial weakness and wasting in myotonic dystrophy and nemaline myopathy). Arthrogryposis is rare, but isolated contractures of proximal and distal joints may occur, and scoliosis is a frequent complication; cardiomyopathy is rare.

Historical note and terminology

The unique ratio of histochemical fiber types and sizes in the muscle biopsy of infants and children was described by Brooke and Engel (Brooke and Engel 1969), Farkas-Bargeton and colleagues (Farkas-Bargeton et al 1968), Karpati and colleagues (Karpati et al 1971), and Caille and colleagues (Caille et al 1971), but was first recognized as a distinct entity and called “congenital fiber-type disproportion” by Brooke (Brooke 1973). He initially defined a difference in fiber size, type I smaller than II by 12% or more, but in later publications, he reconsidered and changed his criteria to 25% or more because the earlier difference was too little and, in most cases, even 25% was a conservative ratio. The 25% difference in fiber size is now accepted as the standard (Clarke and North 2003). By definition, it is a muscle biopsy diagnosis of selective uniform smallness of type I fibers relative to those of type II by 25% or more and also
type I myofiber predominance of 80% or more. “Partial congenital muscle fiber-type disproportion” may be defined by
uniform type I myofiber smallness but without the numerical predominance of classical congenital muscle fiber-type
disproportion. This form is more usual in systemic metabolic diseases. An additional feature in some patients with
congenital muscle fiber-type disproportion is the presence of large numbers of centrofibrillar fibers that are not
regenerative fibers (Sarnat 1984; Sharma et al 2004; Camacho et al 2005). In rare cases, type II fibers, rather than
undergoing the usual compensatory hypertrophy, may become atrophic and angular (Rao et al 2005).

Because the genetics are uncertain in most cases, despite the discovery of many new genetic mutations (see below),
and because congenital muscle fiber-type disproportion is found in association with many other myopathies and
diseases, Dubowitz characterized this unique histopathological pattern as “a pathology in search of a disease
(Dubowitz 1995). The ultrastructure of muscle in congenital muscle fiber-type disproportion shows only subtle changes without myofiber
necrosis. The Z-band tends to be less regular than normal, and excessive Z-band streaming sometimes is seen
(Carpenter and Karpati 2001). This finding is of interest because congenital muscle fiber-type disproportion is a
constant feature in nemaline rod myopathy (see below), and nemaline rods are derived from Z-band material. Other
findings by electron microscopy are abnormal exchanges of bundles of myofilaments between adjacent myofibrils and
occasional peripheral sarcoplasmic masses containing bundles of disoriented myofilaments (Carpenter and Karpati
2001). In cases with demonstrated genetic mutations in the molecular structure of contractile proteins (see below),
these specific myofilaments of actin or myosin are ultrastructurally altered and may predict the genetic defect.

Both the clinical features and the muscle biopsy findings were subsequently confirmed by many other authors. The
diverse etiologies of the disorder as a syndrome rather than a disease and its association in some cases with specific
metabolic diseases were first recognized by Martin and colleagues (Martin et al 1976). The association with cerebellar
hypoplasia was documented by Sarnat (Sarnat 1985). A review of the known genetic mutations was provided by
DeChene and colleagues (DeChene et al 2008).

Clinical manifestations

Presentation and course

The diagnosis of congenital muscle fiber-type disproportion must be established by muscle biopsy, and one may
distinguish the “pure congenital myopathy” from the congenital muscle fiber-type disproportion syndrome associated
with a large number of other hereditary and nonhereditary conditions. Even the pure myopathic form might be denied
as a “congenital myopathy” if genetic transmission is used as an obligatory criterion. Only rarely is Mendelian
transmission demonstrated (Klein et al 1999; Kim et al 2000). In some families, nevertheless, autosomal dominant
inheritance is clearly demonstrated (Sobrido et al 2005); in other families an autosomal recessive trait is suspected
from similar involvement of siblings of both genders.

The clinical expression varies with the diverse etiologies of this syndrome in those cases with identified metabolic or
neurologic diseases. Among patients in whom congenital muscle fiber-type disproportion occurs as an apparent
isolated “congenital myopathy,” the clinical presentation is variable. Manifestations may be severe at birth and in
infancy or may be mild. The severe clinical pattern often, but not always, has an additional muscle biopsy finding of
disproportion is associated with nemaline rods, as it nearly always is in nemaline myopathy, the clinical pattern also is
usually one of severe weakness. Even as an isolated congenital myopathy, weakness may be generalized and severe,
but static, though most cases have only mild weakness and a benign clinical course (Clarke and North 2003). In a
study of 67 cases of idiopathic congenital muscle fiber-type disproportion, 25% had contractures, scoliosis, or other
deformities, and failure to thrive was common in infancy. The diagnosis of clubfoot with polyhydramnios can be made
prenatally at times by ultrasound (Bignier et al 2000). About 25% had a severe clinical course and 10% died in
childhood, usually of respiratory insufficiency or pneumonia (Clarke and North 2003). Ophthalmoplegia, facial weakness, and other bulbar motor deficits were associated with a poorer prognosis.

Most patients present at birth with hypotonia, proximal generalized weakness, and small muscle mass. Intelligence is normal and there are no other indications of cerebral dysfunction (Clarke and North 2003; Igarashi 2004). In the severe infantile form of the syndrome, the weakness at birth involves axial and appendicular muscles, facial and other bulbar-innervated muscles, and may require ventilatory support and gavage feeding. In some cases, gastrostomy may be recommended because of feeding difficulties with dysphagia, aspiration, and frequent pulmonary infections secondary to aspiration. The facial weakness is prominent, but the typical inverted V-shaped upper lip is usually seen when congenital muscle fiber-type disproportion is due to myotonic dystrophy, and the everted lips characteristic of facioscapulohumeral muscular dystrophy do not occur. Ptosis and variable external ophthalmoplegia are often present, and pharyngeal muscles are weak (Cavanagh et al 1979; Owen et al 1981; Lo et al 1990; Torres and Moxley 1992). The tongue is thin but no fasciculations are seen. The muscle mass of the trunk and extremities is thin. Tendon reflexes are hypoactive or absent. Congenital contractures, scoliosis, and deformities of the feet or clubfoot may be present (Lenard and Goebel 1975; Clancy et al 1980; Loren et al 1998; Clarke and North 2003). Severe arthrogryposis is exceptional but is reported (Vanek et al 1986; Gerdes et al 1994). In reading case reports, one must carefully evaluate whether the muscle biopsy fulfills the histochemical criteria of congenital muscle fiber-type disproportion because titles of some articles use this term rather indiscriminately.

In early infancy, congenital muscle fiber-type disproportion may have a clinical presentation suggestive of congenital myasthenia gravis, particularly if associated with the tropomyosin 3 (TPM3) gene (Munot et al 2010). The discovery of autosomal recessive mutations in the RYR1 gene product associated with defective motor end plates of ryanodine receptors in some cases of congenital muscle fiber-type disproportion further explains this similar clinical picture (Clarke et al 2010; Clarke 2011).

Cardiomyopathy is rare in congenital muscle fiber-type disproportion, but exceptional cases with dilated cardiomyopathy and intractable congestive heart failure requiring cardiac transplantation in early adolescence are described (Banwell et al 1999). Cardiomyopathy also was a feature in 3 Dutch families in whom myofibrillar lysis was an additional feature (Barth et al 1998). Cardiomyopathy also may be less severe, but sufficient to cause mild congestive heart failure with pedal edema (Igarashi 2004). Some cases with cardiomyopathy are so mild in childhood that they are not recognized until adult life (Fujita et al 2005).

Respiratory weakness, ranging from mild to severe, occurs in 30% of children with congenital muscle fiber-type disproportion (DeChene et al 2008).

Gastrointestinal tract dysmotility with poor peristalsis and fecal impaction in the bowel is not a characteristic feature, but it is found in occasional cases (Kubota et al 2005), similar to the smooth muscle dysfunction in infantile myotonic dystrophy. Mild to severe feeding difficulties occur in nearly 30% of affected individuals (DeChene et al 2008).

Some infants die in the neonatal period or early infancy. Those who survive stabilize clinically and may eventually breathe adequately without ventilator support and are able to feed slowly, but continue to have severe generalized weakness, poor head control, and delayed gross motor development. Others remain ventilator-dependent for years (Glick et al 1984; Torres and Moxley 1992). Signs of central nervous system disease such as mental retardation, seizures, or corticospinal tract signs do not appear unless hypoxia is superimposed as a secondary insult. In later childhood, they require an electric wheelchair because they never walk and their arms remain too weak to use a manual wheelchair, but they may feed themselves with specially designed aids and learn to use a computer keyboard for schoolwork.

The muscle biopsy not only confirms the diagnosis of congenital muscle fiber-type disproportion, but also may have some predictive value of the severe or mild clinical expression of the myopathy. However, the muscle biopsy finding may change in time so that most patients continue to show smallness of type I fibers, but the type I predominance becomes even greater after several years (Spiro et al 1977; Sarnat unpublished observations). In other patients, by contrast, the type I fiber hypoplasia may resolve so that infants with typical congenital muscle fiber-type disproportion no longer have small type I fibers by adolescence, and the type I fibers may indeed actually become larger than the type II fibers; it is postulated that after the type II fibers have undergone as much compensatory hypertrophy as they can, the type I fibers then grow in size and become hypertrophic (Bartholomeus et al 2000). Some of these patients also show improvement in their strength and stamina (Bartholomeus et al 2000). Brooke found a relative absence of
If the severe form is accompanied by many centronuclear fibers in the muscle biopsy, there may be progressive changes in serial muscle biopsies over time, with a decrease in type II myosin light chains 2 and 3 that suggest type I fiber deficiency in terms of total volume of type I myofibrils. Such children are severely disabled, never walk, and may require chronic ventilatory support (Danon et al 1997). Even in mild, clinically nonprogressive cases, there may be a histochemical continuation of the process of conversion of type II fibers to type I so that the ratio becomes even more extreme during later childhood and adolescence (Shibata et al 1998).

In the mild clinical form of congenital muscle fiber-type disproportion, the body habitus and phenotypic features are similar to those of the severe form: a generally thin muscle mass at birth, generalized hypotonia often of severe degree, hypoactive tendon reflexes, poor head control in infancy, and mild generalized weakness (Cavanagh et al 1979; Clancy et al 1980; Peyronnard et al 1982; Chang et al 1990; Simon et al 1991; Shishikura et al 1994). Though gross motor development may be delayed, mildly affected children learn to walk, often with a Trendelenburg gait, and have no difficulty in using their arms for ordinary activities. Inability to lift their arms above their heads is explained by prominent scapular winging, indicating poor fixation of the scapula for rotation. As with the severe form, marked dolichocephaly and facial weakness are present, and the facies are accentuated by the deficient mass of the temporalis muscles in particular. The palate is narrow and high-arched. Severe skeletal open bite, incompetent lips, maxillary arch, and EMG evidence of weakness of masticatory muscles are present. These congenital craniofacial features are similar to the neonatal form of myotonic dystrophy (Baccetti et al 1997). Ptosis and weakness of extraocular muscles may be present but are less common than in the severe form. In the neonatal period, there are no difficulties with respiration or feeding. Intellectual development is normal, and no signs of central nervous system disease are evident.

The myopathy is nonprogressive and may even improve clinically as the child grows (Curless and Nelson 1977; Clancy et al 1980; Iannaccone et al 1987; Akiyama and Nonaka 1996). In some cases, myopathy is not even detected until midchildhood, when it presents as a slowly progressive or nonprogressive mild proximal weakness (Eisler and Wilson 1978). Even a 20-year-old adult man with a "marfanoid habitus" was found to have congenital muscle fiber-type disproportion on muscle biopsy (Haltia et al 1988). In some cases, episodic progressive weakness is reported, but these cases are usually associated with additional myopathic findings such as centronuclear fibers or cytoplasmic bodies in myofibers, or an excessive number of immature myotubes (Shishikura et al 1994).

Congenital muscle fiber-type disproportion as an isolated myopathy, without other associated conditions, thus, is not fundamentally a progressive disease and is not a necrotizing myopathy or a muscular dystrophy. Patients who exhibit centronuclear myopathy in addition to congenital muscle fiber-type disproportion generally experience greater weakness, including dysphagia and respiratory muscle weakness, than do patients with only rare centronuclear muscle fibers. Some patients appear to show increasing numbers of centronuclear fibers over years with serial muscle biopsies and may exhibit some additional clinical weakness as well, as already noted (Akiyama and Nonaka 1996; Danon et al 1997). In addition, most children show a progressive conversion of more type I fibers to type I, so biopsies in older children may show almost exclusively type I fibers and only rare scattered type II fibers. Progressive clinical signs do not necessarily accompany this change in the ratio of fiber types, however, and clinical course and histochemical change over time should be considered separately and not equated. The clinical variability and apparent clinical progression might be due in part to growth spurts. Whereas histochemical fiber types are traditionally determined by myosin (calcium-mediated) ATPase stains preincubated at acid and alkaline pH ranges, heavy-chain myosin immunocytochemical antibodies against type II fibers in paraffin sections demonstrate the same pattern of fiber type differentiation in congenital muscle fiber-type disproportion as in normal muscle biopsies (Rojiani and Cho 1998).

Complications include dislocations of the shoulder or other joints because of severe hypotonia, fractures of long bones because of thin and weak muscle cylinder, respiratory infections, and, in the severe form, aspiration. Scoliosis and other spinal deformities occur in 25% of patients (DeChene et al 2008). Scoliosis is a serious complication in patients confined to a wheelchair, but kyphoscoliosis sometimes develops in ambulatory patients as well (Lenard and Goebel 1975). Contractures may also occur in the hips, knees, ankles, elbows, and fingers in approximately 25% of cases.
Patients requiring chronic ventilator support for years may develop cardiac complications, but cardiac and smooth muscles are not primarily involved. Congenital anomalies of other organ systems do not usually occur, but 1 case is reported with coarctation of the aorta (Noda et al 1990). Cardiomyopathy has already been discussed. Myotonia occurs only in those cases associated with myotonic muscular dystrophy and rarely before 5 years of age.

Cases associated with cerebellar hypoplasia are difficult to distinguish in early infancy because of the shared clinical findings of delayed gross motor development and generalized hypotonia, but infants follow the mild rather than the severe form of congenital muscle fiber-type disproportion. Ataxia and intention tremor may become evident as the child matures, and nystagmus is uncommon (Sarnat and Alcala 1980). Facial weakness and dolichocephaly are often absent in congenital muscle fiber-type disproportion associated with cerebellar hypoplasia. In some cases, intellectual deficits and seizures may provide additional distinguishing features of CNS involvement, and delayed corticospinal tract maturation may result in hyperreflexia.

Congenital muscle fiber-type disproportion is not regularly associated with systemic malformations of other organ systems except for the central nervous system dysgeneses already mentioned. A few cases are reported in patients with congenital heart disease or mitral valve prolapse (Darsee et al 1980), and rare patients with chromosomal disease and congenital muscle fiber-type disproportion have anomalies of other organs.

**Prognosis and complications**

Severely involved infants with congenital muscle fiber-type disproportion are at risk for early respiratory failure or aspiration leading to death. Congenital muscle fiber-type disproportion is generally not a progressive disease, however, and patients stabilize with persistent hypotonia and weakness that may even improve mildly with time and growth (Curless and Nelson 1977; Clancy et al 1980; Iannaccone et al 1987). The muscle biopsy generally remains unchanged, but in some cases the disproportion in size and types of myofibers may diminish or even resolve, though fiber-type predominance usually persists (Rickey and Cabello 1985; Iannaccone et al 1987; Mizuno and Komiya 1990; Bartholomeus et al 2000). In some cases, the quantitative disproportion may even intensify with time and become more pronounced after 6 months of age on repeat muscle biopsy (Iannaccone et al 1987), or the size ratio remains unchanged, but the type I predominance becomes more pronounced. In this regard, a nonprogressive "congenital myopathy" is described that is characterized by uniform type I myofibers and lack of differentiation of type II fibers (Dinn and O’Doherty 1980; Oh and Danon 1983; Vallat et al 1983); whether such children had congenital muscle fiber-type disproportion earlier in life with this single fiber type as the end result is speculative. Some children with nemaline rod myopathy show just such a pattern of evolution in their repeat muscle biopsy years later (Sarnat 1983).

If congenital muscle fiber-type disproportion is associated with another neuromuscular, neurologic, or metabolic disease, the prognosis is that of the primary disease. In congenital muscle fiber-type disproportion secondary to cerebellar hypoplasia, the muscle findings do not appear progressive either clinically or histologically (Sarnat 1985; Sarnat 1986).

Cardiac involvement in congenital muscle fiber-type disproportion is rare, except if secondary to a systemic metabolic disease with cardiomyopathy, such as Pompe disease (glycogenosis II). Nevertheless, some cases of isolated congenital muscle fiber-type disproportion are described with cardiac involvement in later childhood or adolescence (Moore et al 2002).

**Biological basis**

**Etiology and pathogenesis**

Both genetic and epigenetic causes of this muscle biopsy phenotype are well documented. Congenital muscle fiber-type disproportion can be divided into several etiologic categories: (1) an isolated “congenital myopathy,” probably an autosomal recessive trait for which the genetic mutation is not yet known; (2) associated with other better defined myopathies including nemaline rod myopathy, the severe congenital form of myotonic dystrophy, rigid spine myopathy, and some centronuclear myopathies; (3) association with suprasegmental developmental malformations of the CNS, particularly cerebellar hypoplasia and Moebius syndrome; (4) association, in some cases, with systemic metabolic diseases, including Krabbe disease (globoid cell leukodystrophy), multiple sulfatase deficiency, mitochondrial cytopathies, Lowe disease, and glycogenoses II, III, and IX; and (5) association with acquired perinatal
disorders, such as fetal alcohol syndrome.

In most cases, congenital muscle fiber-type disproportion is a "congenital myopathy" of unknown etiology that occurs sporadically without an identified genetic trait. Rare families with congenital muscle fiber-type disproportion are described (Barth et al 1998). Fiber-type disproportion is not confined to human myopathies but is also described in a juvenile canine (Rodenas et al 2012). Fiber-type disproportion is not confined to human myopathies but is also described in a juvenile canine (Rodenas et al 2012). Fiber-type disproportion is not confined to human myopathies but is also described in a juvenile canine (Rodenas et al 2012). Fiber-type disproportion is not confined to human myopathies but is also described in a juvenile canine (Rodenas et al 2012). Fiber-type disproportion is not confined to human myopathies but is also described in a juvenile canine (Rodenas et al 2012).

Some cases are associated with other neuromuscular or metabolic diseases (Table 1), which include (1) all cases of nemaline rod myopathy, except for those in which no type II myofibers are differentiated (Sarnat 1983; Shimomura and Nonaka 1989); (2) the infantile form of myotonic dystrophy (Sarnat and Siebert 1976; Argov et al 1980; Tominaga et al 2010); (3) Krabbe globoid cell leukodystrophy (Martin et al 1976; Dehkharhigni et al 1981; Marjanovic et al 1996); (4) multiple sulfatase deficiencies (Tachi et al 1985); (5) a minority of cases of glycogenosis II (infantile acid maltase deficiency or Pompe disease) (Martin et al 1976), a minority of cases of glycogenesis III (debrancher enzyme deficiency or Cori-Forbes disease) (Martin et al 1976), and rare cases of glycogenesis IX (phosphorylase kinase B deficiency) or of muscle phosphoglyceromutase deficiency (Sarnat unpublished data); (6) rarely in hypothyroidism (Simon et al 1991); (7) rarely in mitochondrial disorders (Naumann et al 1995); (8) a genetic form of congenital muscle fiber-type disproportion with additional muscle biopsy findings of myofibrillar lysis but not myofiber necrosis, and cardiomyopathy (Barth et al 1998); (9) fetal alcohol syndrome (Martin et al 1976); (10) rigid spine syndrome (Goebel et al 1977; Seay et al 1977; Sulaiman et al 1983); (11) oculocerebrorenal disease of Lowe (Kohyama et al 1989); (12) cerebellar hypoplasia (Sarnat 1985; Sarnat 1986) and other cerebral dysgeneses with involvement of posterior fossa neural structures (Garcia-Alix et al 1992; Nakagawa et al 1996); (13) Emery-Dreifuss X-linked muscular dystrophy (type I fiber atrophy or hypotonia is a typical feature of the muscle biopsy, and some patients also have type I fiber predominance or frank congenital muscle fiber-type disproportion) (Voit et al 1988); (14) coexistence of congenital muscle fiber-type disproportion with minicore myopathy (Jongpiputvanich et al 2008). Over 60% of children with hypotonia and type I muscle fiber predominance, perhaps an incompletely expressed congenital muscle fiber-type disproportion, have central nervous system disease (Kyriakides et al 1993).

**Table 1. Differential Diagnosis of Congenital Muscle Fiber-type Disproportion Syndrome**

<table>
<thead>
<tr>
<th>Associated condition or disease</th>
<th>Reference</th>
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<tr>
<td>Isolated congenital myopathy</td>
<td>(Farkas-Bargeton et al 1968; Brooke and Engel 1969; Caille et al 1971; Karpati et al 1971; Brooke 1973; Iannaccone et al 1987; Kissiedu and Prayson 2016)</td>
</tr>
<tr>
<td>Centronuclear myopathy</td>
<td>(Peyronnard et al 1982; Lo et al 1990; Danon et al 1997; Romero 2010)</td>
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<tr>
<td>Nemaline rod myopathy (with ACTA1, TPM2, TPM3, SEPM1 or NEB1 mutations)</td>
<td>(Sarnat 1983; Iannaccone et al 1987; Shimomura and Nonaka 1989; North and Laing 2008; Feng and Marston 2009; Lawlor et al 2010; Munot et al 2010; Waddell et al 2010; Clarke et al 2012; Nowak et al 2012; Maggi et al 2013; Rodriguez Cruz et al 2014)</td>
</tr>
<tr>
<td>Infantile myotonic dystrophy</td>
<td>(Sarnat and Silbert 1976; Argov et al 1980; Tominaga et al 2010)</td>
</tr>
<tr>
<td>Emery-Dreifuss muscular dystrophy</td>
<td>(Voit et al 1988)</td>
</tr>
<tr>
<td>Infantile facioscapulohumeral muscular dystrophy</td>
<td>(Brooke et al 1979)</td>
</tr>
<tr>
<td>Ulrich disease (collagen VI mutation)</td>
<td>(Schessl et al 2008)</td>
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<tr>
<td>Myofibrillar lysis and cardiomyopathy</td>
<td>(Barth et al 1998)</td>
</tr>
<tr>
<td>Myofibrillar myopathy (with ACTA1 mutation)</td>
<td>Selcen 2015</td>
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<tr>
<td>Calpain 3 deficiency</td>
<td>(Vattemi et al 2009)</td>
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</table>
• Distal myopathy (autosomal dominant MYH7 mutation)  (Ruggiero et al 2015a)
• Globoide cell leukodystrophy (Krabbe disease)  (Martin et al 1976; Dehkharghani et al 1981; Marjanovic et al 1996)
• Laminopathy with LMNA gene mutations in the lamin A/C protein)  (Ruggiero et al 2015b)
• Minicore myopathy  (Jongpiputvanich et al 2008)
• Multiple sulfatase deficiency  (Tachi et al 1985; Macaulay et al 1998)
• Pompe disease (glycogenosis II)*  (Martin et al 1976)
• Cori-Forbes disease (glycogenosis III)*  (Martin et al 1976)
• Phosphorylase-B-kinase deficiency (glycogenosis IX)*  (Sarnat et al unpublished data)
• Phosphoglyceromutase deficiency*  (Simon et al 1991)
• Hypothyroidism*  (Vestergaard et al 1995; Clarke et al 2006)
• Mitochondrial cytopathy*  (Naumann et al 1995)
• Fetal alcohol syndrome  (Martin et al 1976)
• Rigid spine syndrome  (Goebel et al 1977; Seay et al 1977; Sulaiman et al 1983)
• PHOX2B mutation  (Khan et al 2008)
• RYR1 mutation  (Clarke et al 2010; Wilmshurst et al 2010)
• MYH7 mutation (and myosin excess)  (Ortolano et al 2011; Clarke 2011b; Pajusalu et al 2016)
• MYH2 mutation  (Willis et al 2016)
• Oculocerebrorenal disease of Lowe  (Kohyama et al 1989)
• Cerebellar hypoplasia and other dysgeneses of brainstem or cerebellum, diabetes mellitus, insulin-resistant*  (Sarnat 1985; Sarnat 1986; Garcia-Alix et al 1992; Nakagawa et al 1996; Vorwerk et al 1999; Klein et al 1999)
• Hypertrophic polyneuropathy  (Fardeau et al 1975)
• Spinal muscular atrophy  (Glick et al 1984)

* rare or inconstant

Postmortem examination of the spinal cord and peripheral nerves of a few patients showed no abnormalities, and the number and morphology of motor neurons in particular were normal (Spiro et al 1977; Sarnat unpublished data). Atrophy and degeneration of the medial neuronal group of the ventral horn in lumbosacral segments was found in a patient with congenital muscle fiber-type disproportion and rigid spine syndrome (Sulaiman et al 1983).

An association was made in a child with congenital muscle fiber-type disproportion who had congenital melanocytic nevi that underwent malignant degeneration to melanoma (Seigler et al 1997).

In some of the metabolic disorders cited in Table 1, the congenital muscle fiber-type disproportion may not be as "pure" as in the uncomplicated genetic forms of the disease in that the ratio of fiber type I and II may be somewhat less than 80%, not all of the type I fibers may be hypoplastic, or the small type I fibers may be angular rather than retaining the normal polygonal contour. Whether these conditions should be classified as congenital muscle fiber-type disproportion or whether strict and absolute criteria should be upheld varies among authors.

**Genetic etiologies.** Several genetic mutations are now recognized in which congenital muscle fiber-type disproportion is a component (Clarke 2011a). The SEPN1 gene at locus 1p36-p35 is associated with insulin resistance in diabetic children (Clarke et al 2006), and congenital muscle fiber-type disproportion was previously known to be associated with insulin resistance (Vestergaard et al 1995). In some cases of central congenital hypoventilation
syndrome, the PHOX2B gene has been implicated (Khan et al 2008). In nemaline myopathy with congenital muscle fiber-type disproportion, ACTA1 (skeletal alpha-actin) and TPM3 (tropomyosin alpha-3 chain) at 1q22-q23 are now well documented (Clarke et al 2008; North and Laing 2008; Feng and Marston 2009; Vandamme et al 2009; Munot et al 2010; Nowak et al 2013). The latter has been confused clinically with congenital myasthenia gravis (Munot et al 2010). Other genes implicated in congenital muscle fiber-type disproportion include beta-tropomyosin (TPM2) (Brandis et al 2008; Clarke et al 2012; Rodriguez Cruz et al 2014) and TPM3, which as with TPM2 mutation, can also present in the muscle biopsy as a “cap myopathy” (Waddell et al 2010; Maggi et al 2013; SEPN4 (Maggi et al 2013); and beta-myosin (MYH7), with a muscle biopsy phenotype of myosin excess or “storage” (Ortolano et al 2011; Clarke 2011b). Testing is available for these genes. Some, such as the cap myopathies due to TPM mutations, can have secondary features of neuromuscular transmission defects and, thus, resemble myasthenia; these are important to recognize because they may respond to cholinesterase inhibitors (Rodriguez Cruz et al 2014).

Among the most important genetic mutations demonstrated to cause the congenital muscle fiber-type disproportion phenotype are those exhibiting molecular structural alterations in the contractile proteins. Those affecting actin filaments and tropomyosin were noted in the preceding paragraph. Myosin heavy chain (MYH), another major contractile component of muscle, is also demonstrated to be affected in other cases with normal actin. MYH7 is a beta-myosin gene that clinically causes a distal myopathy with autosomal dominant transmission (Ruggiero et al 2015a; Pajusalu et al 2016). This MYH7 myopathy may present clinically in infancy with diffuse weakness and hypotonia of axial and appendicular muscles; congenital muscle fiber-type disproportion is seen pathologically in the muscle biopsy, and exon skipping has been demonstrated by whole exome sequencing (Pajusalu et al 2016). A novel MYH2 mutation causes ophthalmoplegia and facial weakness in patients and family members, with muscle biopsy demonstrating absence of type IIA myofibers and genetic analysis showing exon skipping (Willis et al 2016). The LMNA gene, which is also associated with Emery-Dreifuss muscular dystrophy, limb-girdle dystrophy, and autosomal recessive axonal neuropathy, can be expressed as congenital muscle fiber-type disproportion in the muscle biopsy (Ruggiero et al 2015b).

RYR1 mutations, transmitted as an autosomal recessive trait, are another genetic association with congenital muscle fiber-type disproportion that has been documented in several families; some of these patients also have centronuclear myopathy, but in others, the sarcolemmal nuclei remain peripheral with only occasional scattered centronuclear fibres (Clarke et al 2010; Wilmshurst et al 2010). Still another mutation, MYH7 of autosomal dominant transmission, associates congenital muscle fiber-type disproportion with myosin increase or storage in the muscle (Ortolano et al 2011). In other cases, the specific mutation or deletion is unknown, but the chromosomal locus has been identified, as in the 1p36 deletion syndrome with congenital muscle fiber-type disproportion (Okamoto et al 2002).

The phenotype-genotype correlation is, therefore, highly variable because congenital muscle fiber-type disproportion is a multietiological syndrome rather than a single disease and can be due to either genetic causes or to developmental malformation of the brain, particularly the cerebellum (Ravenscroft et al 2015).

**Fetal development pathogenesis.** Congenital muscle fiber-type disproportion is probably a developmental disorder of muscle arising during the histochemical stage of muscle maturation, between 20 and 28 weeks’ gestation, though the disparate growth of myofibers may continue in late fetal life (Sarnat 1994). Congenital muscle fiber-type disproportion is not, however, a simple arrest in a normal stage of muscle ontogenesis (Sarnat 1992; Sarnat 1994; Sarnat 2016). Disturbances in muscle fiber-type differentiation occur in congenital neuropathies beginning in fetal life, such as congenital hypomyelinating neuropathy due to genetic SOX10 or myelin protein zero (MPZ0) mutations, but this is more of a delayed histochemical differentiation than congenital muscle fiber-type disproportion (Szigi et al 2003). Congenital muscle fiber-type disproportion does occur, however, in infantile polyneuropathies (Fardeau et al 1975; Igarashi 2004), occasionally in spinal muscular atrophy (Glick et al 1984), and in globoid cell leukodystrophy (Krabbe disease), though usually in a stage when the CNS white matter is more affected than peripheral nerve (Dehkharghani et al 1981; Marjanovic et al 1996). Amongst the congenital muscular dystrophies, the most frequent associations are with neonatal myotonic dystrophy, and it has been shown to be a component of Ullrich muscular dystrophy due to a defect in collagen VI (Schessl et al 2008). Calpain-3 deficiency causes myopathy and also may present as fiber-type disproportion (Vattemi et al 2009). Fiber-type disproportion also is found in many congenital centronuclear myopathies (Sharma et al 2009; Romero 2010). Defects of excitation-contraction components in extraocular muscles may occur in congenital muscle fiber-type disproportion as well as several other congenital myopathies (Sekulic-Jablanovic et al 2015). Congenital ptosis may accompany ophthalmoplegia in these cases because the striated levator palpebrae muscle of the upper eyelid is also involved, and both this muscle and the smooth Müller...
In rigid spine myopathy, a gene has been identified as mutated at the 1p35-36 locus (Moghadaszadeh et al 1998). The significance of this finding is uncertain. Phosphoprotein B-50 may serve a local function involving transmembrane myofibers of type I in congenital muscle fiber-type disproportion (Laing et al 2004). A defect in tropomyosin 3 (TPM3) is more frequent than previously thought and shows a stronger association with fiber-type disproportion (Lawlor et al 2010). The gene of TPM3 is mutated in some cases of nemaline myopathy, which constantly has fiber-type disproportion as a histopathological feature of muscle. ACTA1 is another gene expressed in actin filaments in which mutations are associated with nemaline rod disease including intranuclear rods, central core disease, myofibrillar myopathy, and congenital muscle fiber-type disproportion (Selcen 2015).

Phosphoprotein B-50 is reported to be immunocytochemically demonstrable on the inner face of only the small myofibers of type I in congenital muscle fiber-type disproportion (Heuss and Schlotzer-Schrehardt 1998). The significance of this finding is uncertain. Phosphoprotein B-50 may serve a local function involving transmembrane signaling by means of calmodulin binding or phosphorylation, but this role still does not explain the pathogenesis of congenital muscle fiber-type disproportion (Heuss and Schlotzer-Schrehardt 1998).

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The association with cerebellar hypoplasia suggests that suprasegmental influences on the motor neuron during the histochemical stage of muscle maturation may dictate the aberration in differential growth and maturation of types I and II myofibers (Sarnat 1985; Sarnat 1986). The bulbospinal tracts form before 20 weeks’ gestation and, during the critical histochemical period of 20 weeks to 28 weeks, they form important relations with motor neurons and spinal interneurons because of the sprouting of axonal collaterals, synaptogenesis, and myelination. The cerebellum projects no direct descending "cerebellospinal" fibers. Efferent axons of the cerebellar nuclei synapse in the red, vestibular, inferior olivary, and tegmental reticular nuclei, however. All of these structures mediate cerebellar impulses through descending bulbospinal projections. The corticospinal tract, by contrast, has few axonal ramifications or synaptic contacts at this age and is still completely unmyelinated and probably nonfunctional (Sarnat 1989); ascending cerebellar connections with the cerebral cortex, via relay in the thalamus, do not, therefore, likely influence the developing motor unit. Hypotonia is a constant feature of human cerebellar hypoplasia (Sarnat and Alcala 1980); experimental studies in the monkey demonstrate that the mechanism is diminished fusimotor activity by spinal gamma motor neurons (Gilman 1969). In animals, repetitive stimulation of motor nerves results in conversion of type II muscle fibers to type I (Kugelberg 1976; Salmons and Sreter 1976); hence, the pathogenesis of congenital muscle fiber-type disproportion in cerebellar hypoplasia may be abnormal suprasegmental stimulation of spinal motor neurons (Sarnat 1985; Sarnat 1986). Congenital muscle fiber-type disproportion does not occur in children with spastic or hypotonic diplegia due to cortical or corticospinal tract lesions in the perinatal period (Sarnat 1983).

The pathogenesis and pathophysiology of congenital muscle fiber-type disproportion in the various metabolic diseases that are not primary myopathies are unknown. Congenital muscle fiber-type disproportion occurs in some cases of Moebius syndrome, consistent with a developmental brainstem disorder (Simon et al 1991). The basis for congenital muscle fiber-type disproportion as an isolated congenital myopathy is uncertain, but it is likely an autosomal recessive trait for which the genetic mutation is not yet identified.

The finding of congenital muscle fiber-type disproportion in a family with a balanced chromosomal translocation of t(10;17) suggested that a genetic locus responsible for the myopathy might be on 1 of these chromosomes (Gerdes et al 1994), but the consistent association of congenital muscle fiber-type disproportion with Krabbe leukodystrophy, in which chromosome 14 is implicated by linkage studies, suggests another locus if indeed the genetic defect is directly responsible for the myopathy.

The great majority of cases of congenital muscle fiber-type disproportion are sporadic, but some familial cases appear to be transmitted as an autosomal dominant trait (Kim et al 2000), and other families with similarly involved siblings suggest an autosomal recessive inheritance (Fardeau et al 1975). Two brothers with a defect of the insulin receptor gene have a 91% to 95% reduction in receptor kinase activity; their father shows a similar 70% reduction in the insulin receptor kinase with an Arg1174-Gln mutation. The mother, however, also shows a genetic defect related to insulin receptor kinase, with a point mutation at the last base pair in exon 17 (Klein et al 1999). This molecular genetic defect of alternative splicing of exon 17 and a missense mutation in exon 20 of the insulin receptor gene is expressed as insulin-resistant diabetes mellitus and congenital muscle fiber-type disproportion (Vestergaard et al 1995; Vorwerk et al 1999).

Abnormal actin filaments due to a genetic mutation are found in some cases of congenital muscle fiber-type disproportion (Laing et al 2004). A defect in tropomyosin 3 (TPM3) is more frequent than previously thought and shows a stronger association with fiber-type disproportion (Lawlor et al 2010). The gene of TPM3 is mutated in some cases of nemaline myopathy, which constantly has fiber-type disproportion as a histopathological feature of muscle. ACTA1 is another gene expressed in actin filaments in which mutations are associated with nemaline rod disease including intranuclear rods, central core disease, myofibrillar myopathy, and congenital muscle fiber-type disproportion (Selcen 2015).

In rigid spine myopathy, a gene has been identified as mutated at the 1p35-36 locus (Moghadaszadeh et al 1998;
Moghadaszadeh et al. 2001a; Moghadaszadeh et al. 2001b). Though some authors characterize this myopathy as a “muscular dystrophy,” it is not a necrotizing myopathy; hence, it does not fulfill the criteria of a true dystrophy. In addition to muscular rigidity in axial muscles, a restrictive respiratory syndrome is characteristic (Moghadaszadeh et al. 2001a; Moghadaszadeh et al. 2001b). The congenital muscle fiber-type disproportion in these cases is not always classical and may be partial, with uniform smallness of type I myofibers but without the other histopathological criterion of type I predominance (Dawson in preparation). In a family, a father and son both had congenital muscle fiber-type disproportion, and the father developed rigid spine syndrome in adult life (Sulaiman et al. 1983). Another mechanism of the congenital muscle fiber-type disproportion in rigid spine syndrome may be altered motor unit stimulation by spinal interneurons, similar to cerebellar hypoplasia.

In multiple sulfatase deficiency, the defective SEPN1 gene encodes selenoprotein-N (Macaulay et al. 1998). Not all cases of this metabolic disease show congenital muscle fiber-type disproportion, however.

Many, though not all, infants with mitochondrial cytopathies, including Leigh encephalopathy, show congenital muscle fiber-type disproportion as an histopathological feature, but whether the hypotonia and weakness in these cases is due to myopathy or encephalopathy is not certain (Sarnat unpublished data).

Phylogenetically, congenital muscle fiber-type disproportion is the normal condition of rodents such as the rat, but the evolutionary relevance to the human disorder remains speculative (Sarnat and Netsky 1984).

**Epidemiology**

The incidence is unknown because many cases are not recognized or muscle biopsy is not performed. Congenital muscle fiber-type disproportion was once thought to be a rare myopathy, but is an increasingly frequent association in the investigation of the “floppy infant.” It affects both genders, but some series show a female preponderance (Cavanagh et al. 1979).

Most commonly, congenital muscle fiber-type disproportion not associated with myotonic dystrophy or other identified genetic diseases occurs sporadically. In some families, an autosomal dominant trait is suggested by involvement of a parent and child of either gender, or an asymptomatic parent has an abnormal muscle biopsy showing fiber-type predominance or scattered centronuclear fibers (Eisler and Wilson 1978; Kula et al. 1980; Peyronnard et al. 1982). Sibships of congenital muscle fiber-type disproportion with or without centronuclear fibers in the muscle biopsy are described, consistent with either autosomal dominant or recessive inheritance (Hernandez et al. 1978; Clancy et al. 1980; Jaffe et al. 1988; Marolda 1992). An X-linked trait is not suspected.

**Differential diagnosis**

The clinical suspicion of congenital muscle fiber-type disproportion is often made on the basis of clinical features and morphology of the face and head; other cases are diagnosed by muscle biopsy for infantile hypotonia and weakness. The diagnosis of congenital muscle fiber-type disproportion must be confirmed by muscle biopsy; clinical features and other laboratory tests are not diagnostic.

Because congenital muscle fiber-type disproportion is a syndrome, the specific diseases with which it is associated must be excluded: myotonic muscular dystrophy, nemaline rod myopathy, glycogenoses, Krabbe leukodystrophy, Lowe disease, rigid spine syndrome, cerebellar hypoplasia, and fetal alcohol syndrome. The muscle biopsy alone does not distinguish these disorders except for nemaline rod myopathy and glycogenosis II.

The muscle biopsy of congenital muscle fiber-type disproportion with centronuclear fibers might be confused with that of X-linked myotubular myopathy, but many histological and histochemical features distinguish the two, including the strong immunoreactivity for vimentin and desmin in myotubular myopathy and the expression of desmin alone in some but not all cases of congenital muscle fiber-type disproportion (Lo et al. 1990; Sarnat 1990; Sarnat 1992).

The muscle biopsy of infantile myotonic dystrophy showing congenital muscle fiber-type disproportion may be indistinguishable from other causes of congenital muscle fiber-type disproportion or may show maturational arrest in various stages of muscle ontogenesis (Sarnat and Silbert 1976).

Perinatal denervation of muscle, such as in infantile spinal muscular atrophy (Werdnig-Hoffmann disease), also shows 2 populations of fiber sizes, but the hypertrophic fibers are grouped rather than scattered and are type I fibers rather
than type II. Ultrastructurally, the sleeves of empty basement membranes projecting from the surface of myofibers in spinal muscular atrophy are not found in congenital muscle fiber-type disproportion (Zalneraitis et al 1989). Atrophic muscle fibers in denervate neurogenic atrophy often have an angular contour in cross-section, whereas the hypoplastic type I fibers in congenital muscle fiber-type disproportion retain the normal polygonal shape.

A congenital familial myopathy involving an infant girl and her mother was described as type II fiber hypoplasia and type I fiber predominance (Muranaka et al 1997). This nonprogressive and nondegenerative myopathy is not, however, congenital muscle fiber-type disproportion by definition, even though many clinical features, including facial weakness, are similar.

**Diagnostic workup**

No molecular genetic marker of congenital muscle fiber-type disproportion exists because of multiple etiologies, both genetic and developmental. The diagnosis of congenital muscle fiber-type disproportion thus remains a histopathological finding in the muscle biopsy with a characteristic histochemical pattern of the ratio and sizes of the 2 major myofiber types (Sarnat and Carpenter 2015). Though “reverse fiber type disproportion” is published as a metabolic response to incremental exercise, with a 75% predominance of type II myofibers (Cooper et al 2016), this is not true congenital muscle fibre-type disproportion. In this regard, type II fibres are more variable in size in relation to exercise and undergo work hypertrophy or disuse atrophy more readily than type I fibres (Sarnat and Carpenter 2015). This important distinction requires knowledge and experience by the pathologist reporting the muscle biopsy.

The serum creatine kinase is nearly always normal in congenital muscle fiber-type disproportion, though mild transient elevations are reported in a few patients (Cavanagh et al 1979). More constant increases in serum creatine kinase may occur in congenital muscle fiber-type disproportion secondary to metabolic diseases and are reported in a few familial cases without identified metabolic defects (Eisler and Wilson 1978).

The EMG is usually normal or shows mild, nonspecific myopathic features (Eisler and Wilson 1978; Cavanagh et al 1979; Rowinsky-Marcinska et al 1990). A reduced interference pattern with complex high-amplitude motor unit potentials is described in some patients (Lenard and Goebel 1975). Fibrillations, positive sharp waves, and other signs of denervation of muscle are described only rarely, including in the rigid spine syndrome (Sulaiman et al 1983). Single fiber EMG in congenital muscle fiber-type disproportion is normal or mildly myopathic (Rowinsky-Marcinska et al 1991). It is important to identify secondary neuromuscular transmission defects that are potentially treatable (Rodriguez Cruz et al 2014). ECG is recommended for cardiomyopathy, even if no cardiac murmur or other clinical evidence of heart disease is evident (Moore et al 2002).

The muscle biopsy is obligatory and diagnostic of this condition. The "disproportion" involves 2 aspects: size and histochemical fiber type. There is a predominance of 80% or more of small myofibers that are uniformly type I; the remaining hypertrophic fibers are type II, particularly subtype Ib (Brooke 1973; Sarnat 1983; Argov et al 1984; Iannaccone et al 1987). A detailed morphometric study including comparisons of repeat muscle biopsies at different ages is provided by Iannaccone and colleagues (Iannaccone et al 1987). The reverse pattern (small type II fibers and large type I fibers) is not congenital muscle fiber-type disproportion. The distribution of the 2 populations of fibers is relatively uniform and involves all fascicles. Necrosis and myofiber degeneration and regeneration are not found. Perimysial connective tissue may be mildly increased or normal. In some cases, probably constituting less than 20%, between 10% and 70% of myofibers of both sizes have central nuclei, but other cytoarchitectural alterations are rare except for occasional "moth-eaten" fibers with zones of disorganized myofilaments (Karpati et al 1971; Inokuchi et al 1975; Sarnat 1983). The presence of nemaline rods identifies the congenital muscle fiber-type disproportion as nemaline rod myopathy and the subtype Ib hypertrophic fibers are often absent in nemaline myopathy, the hypertrophic fibers being mainly Ic (Shimomura and Nonaka 1989). Congenital muscle fiber-type disproportion in metabolic myopathies may be accompanied by myopathic changes characteristic of those diseases, such as vacuoles in glycogenesis II. Minicores may coexist in some familial forms of congenital muscle fiber-type disproportion (Jongpiputvanich et al 2008). Discoveries in genetic mutations and mechanisms still require muscle biopsy to demonstrate and clarify the pathogenicity of gene variants as well as directing molecular analysis (Sewry and Wallgren-Pettersson 2017).

The congenital muscle fiber-type disproportion or fiber-type preponderance associated with cerebellar hypoplasia lacks distinctive features that distinguish the muscle biopsy from congenital muscle fiber-type disproportion as an idiopathic congenital myopathy (Sarnat 1985). The shape of the small type I fibers is a secondary feature that helps distinguish
type I hypoplasia of true congenital muscle fiber-type disproportion from acquired type I atrophy: in pure congenital muscle fiber-type disproportion, the small type I fibers retain their polygonal contour in transverse section, whereas secondarily atrophic fibers are more often sharply angular.

In some cases, genetic studies for particular mutations are indicated. Examples include the genes associated with nemaline myopathy, such as ACTA1 and TPM3 if nemaline rods are noted in the muscle biopsy, PHOX2B gene mutations, particularly if respiratory insufficiency is a prominent clinical feature, and SEPN1 if insulin resistant diabetes mellitus is the presentation. MYH genes of the myosin heavy chain also merit genetic analysis by whole exon sequencing to demonstrate exon skipping in selected cases.

**Management**

Treatment is symptomatic, with attention to respiratory and feeding care in infancy. In older children, prevention and treatment of scoliosis and contractures by good orthopedic care and physiotherapy are important. An electric wheelchair and aids for feeding and body hygiene may be required. A computer with word-processing capability is often helpful for schoolwork. Because of a normal intellectual status, special education is not usually required, although the physical limitations must be accommodated. No medications or special dietary supplements or exclusions are needed. However, a minority of patients may have secondary myasthenic effects, which are treatable with cholinesterase inhibitors. Discoveries of genetic and molecular mechanisms that can lead to congenital fiber type disproportion enable the development of specific gene-editing and metabolic therapies in some cases, at least theoretically, but clinical trials are just being initiated and data are too sparse for conclusions (Jungbluth et al 2017).

**Special considerations**

**Pregnancy**

Little information is available regarding reproductive limitations, complications of pregnancy, or the status of infants born to mothers with congenital muscle fiber-type disproportion. A mother and daughter with congenital muscle fiber-type disproportion are reported, but few obstetrical details are provided (Kula et al 1980). Fetuses with congenital muscle fiber-type disproportion may have decreased activity in late gestation.

**Anesthesia**

Precautions should be taken as with any child with generalized weakness who requires a general anesthetic, particularly if bulbar weakness is present. Congenital muscle fiber-type disproportion is not especially susceptible to malignant hyperthermia, and pretreatment with dantrolene sodium before an anesthetic is not required, though not contraindicated. Neuromuscular blockade with curare or succinylcholine does not have the prolonged effects that patients with myasthenia gravis experience.

**References cited**


Clarke NF. Congenital fiber-type disproportion. Semin Pediatr Neurol 2011a;18(4):264-71. PMID 22172422

Clarke NF. Congenital fibre type disproportion--a syndrome at the crossroads of the congenital myopathies. Neuromuscular Disorders 2011b;21(4):252-3. PMID 21420627


Clarke NF, North KN. Congenital fiber type disproportion--30 years on. J Neuropathol Exp Neurol 2003;62(10):977-89. PMID 14575234

Clarke NF, Waddell LB, Cooper ST, et al. Recessive mutations in RYR1 are a common cause of congenital fiber type disproportion. Hum Mutat 2010;31(7):E1544-50. PMID 20583297


Dehkharghani F, Sarnat HB, Brewster MA, Roth SI. Congenital muscle fiber type disproportion in Krabbe’s leukodystrophy. Arch Neurol 1981;38:585-91. PMID 7271538


Feng JJ, Marston S. Genotype-phenotype correlations in ACTA1 mutations that cause congenital myopathies. Neuromusc Disord 2009;19(1):6-16. PMID 18976909


Goebel HH, Lenard HG, Gorke W, Kunze K. Fibre type disproportion in the rigid spine syndrome. Neuropadiatrie 1977;8:467-77. PMID 579444


Hernandez M, Ricoj JR, Santolaya JM, Escudero R. Miopatías congénitas con hipotrofia de fibras tipo I. An Esp Pediat 1978;11:471-84. PMID 697216


Iannaccone ST, Bove KE, Vogler CA, Buchino JJ. Type I fiber size disproportion: morphometric data from 37 children with myopathic neuropathic, or idiopathic hypotonia. Pediatr Pathol 1987;7:395-419. PMID 2451237


Inokuchi T, Umezaki H, Santa T. A case of type I muscle fiber hypotrophy and internal nuclei. J Neurol Neurosurg
Psychiatry 1975;38:475-82. PMID 168319


Jongpiputvanich S, Walsh PJ, Kakulas BA. Minicores and congenital fibre-type disproportion observed in a family. J Paediatr Child Health 2008;31(3):253-7. PMID 1769390


Lawlor MW, Dechene ET, Roumm E, et al. Mutations of tropomyosin 3 (TPM3) are common and associated with type 1 myofiber hypotrophy in congenital fiber type disproportion. Hum Mutat 2010;31:176-83. PMID 19953533


Martin JJ, Clara R, Ceuterick C, Joris C. Is congenital fibre type disproportion a true myopathy. Acta Neurol Belg 1976;76:335-44. PMID 1070214


Ravenscroft G, Laing NG, Bönnermann CG. Pathophysiologica concepts in the congenital myopathies: blurring the boundaries, sharpening the focus. Brain 2015;138(Pt 2):246-68. PMID 25552303


Sarnat HB. Cerebral dysgeneses and their influence on fetal muscle development. Brain Dev 1986;8:495-9. PMID 3541664


Seigler RS, Golding EM Jr, Rogers C. A child with both congenital fiber type disproportion and giant congenital melanocytic nevi with malignant melanoma. J S C Med Assoc 1997;93(10):374-6. PMID 9343958


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

ICD and OMIM codes

ICD codes

ICD-9:
Congenital hereditary muscular dystrophy: 359.0

ICD-10:
Congenital muscular dystrophy: G71.2

OMIM numbers

Myopathy, congenital, with fiber-type disproportion: #255310

Profile

Age range of presentation

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years

Sex preponderance

male=female

Family history

family history may be obtained

Heredity

heredity may be a factor
autosomal recessive

Population groups selectively affected

none selectively affected

Occupation groups selectively affected

none selectively affected

Differential diagnosis list

myotonic muscular dystrophy
nemaline rod myopathy
glycogenoses
Krabbe leukodystrophy
Lowe disease
multiple sulfatase deficiency
mitochondrial cytopathies
rigid spine myopathy
cerebellar hypoplasia
fetal alcohol syndrome
Werndig-Hoffmann disease
x-linked myotubular myopathy
infantile myotonic dystrophy
infantile spinal muscular atrophy
**Associated disorders**

Trendelenburg gait  
Krabbe globoid cell leukodystrophy  
Pompe disease  
Mitochondrial cytopathies  
Moebius syndrome  
*Myasthenia gravis, congenital*  
Cori-Forbes disease  
Emery-Dreifuss X-linked muscular dystrophy  
Ullrich (collagen VI) muscular dystrophy  
Nemaline rod myopathy  
Cerebellar hypoplasia  
Multiple sulfatase deficiencies  
Debrancher enzyme deficiency  
Calpain 3 deficiency  
PHOX2B mutation

**Other topics to consider**

Cerebellar hypoplasia, dysplasia, and enlargement  
Congenital muscular dystrophy: merosin deficient form  
Nemaline myopathy  
X-linked myotubular myopathy

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