CHAPTER 15

Congenital myopathies

Introduction

The congenital myopathies are a clinically, genetically and pathologically heterogeneous group of muscle disorders defined by the presence of particular histopathological features. They emerged as a group of disorders with the wider application of histochemistry and electron microscopy in the 1950s and 1960s, when abnormal structural defects were identified in association with a particular phenotype. Historically the recognition of this group of disorders probably dates from the description of ‘a new congenital non-progressive myopathy’ by Magee and Shy (1956), later named central core disease, and the subsequent demonstration of the striking histochemical picture by Dubowitz and Pearse (1960). Presentation of congenital myopathies is often at birth or in early childhood, but some cases may have adult onset and are thus not strictly ‘congenital’. It is not yet clear if all of these are parts of clinical spectra or if they are genetically distinct entities, sharing pathological features with congenital cases. Clinically, the congenital myopathies often fall into the ‘floppy infant’ category with a variable degree of hypotonia (Dubowitz 1969, 1995). Muscle weakness is often, but not always, relatively non-progressive but diaphragmatic weakness and respiratory insufficiency may be disproportionate. Structural abnormalities in the central nervous system or peripheral nerves are absent and congenital myopathies are therefore regarded as primary myopathies.

Advances in molecular analysis have led to the identification of several causative gene mutations associated with the morphological features and this has led to a wider appreciation of the clinical phenotype associated with them. Some of the more common forms are now relatively well defined disorders whilst others are very rare and may be based on very few isolated patients. In these it is not yet clear if all are distinct genetic entities. Few of the pathological features are specific for a particular disorder and all are a secondary consequence of the gene mutation. It is now apparent that there is considerable pathological overlap between the various congenital myopathies and the pathological
distinction between them is not always clear. Mutations in different genes can lead to the presence of the same histopathological feature, sometimes as a result of functional association of the gene products, and mutations in the same gene can give rise to a variable clinical phenotype. The pathogenic mechanisms underlying the presence of the structural abnormalities are not fully understood, although several hypotheses have been put forward.

Inheritance may be autosomal recessive, autosomal dominant or X-linked and there is a high incidence of de novo dominant mutations.

In this chapter we describe the pathology of the more common congenital myopathies that a pathologist is likely to encounter. We have deliberately steered away from a molecular categorization as it is the pathology in association with the clinical phenotype that usually leads to identification of the causative gene defect. Molecular advances, however, have led to greater knowledge of the range of morphological features that can occur in association with a broad range of clinical phenotypes.

The most common congenital myopathies are central core disease, multi-minicore disease, nemaline myopathy, and myotubular and centronuclear myopathies (see below; Table 15.1; North 2004). Additional rare disorders characterized by other morphological features are also listed in Table 15.1.

**Clinical features**

In addition to hypotonia, which is usually present at birth or early infancy, there are several additional clinical features that distinguish the various congenital myopathies. Muscle weakness may be predominantly proximal and of girdle distribution, thus resembling muscular dystrophy or mild forms of spinal muscular atrophy, or it may be more generalized. In some, weakness may show marked involvement of the axial muscles and the face and a few may show prominent distal involvement. A long ‘myopathic’ face is a common feature, particularly in nemaline myopathy and in some cases with mutations in the ryanodine receptor gene (RYR1). Structural abnormalities of the central nervous system or peripheral nerves do not usually occur and intelligence is usually normal. Although generally non-progressive, diaphragmatic involvement may be disproportionate to overall muscle weakness, in particular in some cases of nemaline myopathy and multi-minicore disease.

Arthrogryposis may occur in some severe cases of nemaline myopathy (Lammens et al 1997) and central core disease (Romero et al 2003). Lordosis, spinal rigidity, scoliosis and joint laxity are common and hip dislocation is a particular feature of central core disease.

**Investigations**

Serum creatine kinase levels are usually normal and electrophysiological studies rarely help in diagnosis. Ultrasound imaging often shows increased echo and
# TABLE 15.1 The congenital myopathies

<table>
<thead>
<tr>
<th>Disorders with known gene defects</th>
<th>Gene</th>
<th>Gene locus</th>
<th>Inheritance</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central core disease</td>
<td>RYR1</td>
<td>19q13.1</td>
<td>AD or AR</td>
<td>Ryanodine receptor</td>
</tr>
<tr>
<td>Multi-minicore disease</td>
<td>SEPN1</td>
<td>1p36</td>
<td>AR</td>
<td>Selenoprotein N1</td>
</tr>
<tr>
<td>Nemaline myopathy</td>
<td>ACTA1</td>
<td>1q42.1</td>
<td>AD or AR</td>
<td>Skeletal α-actin</td>
</tr>
<tr>
<td></td>
<td>NEB</td>
<td>2q.21.2-22</td>
<td>AR</td>
<td>Nebulin</td>
</tr>
<tr>
<td></td>
<td>TPM3</td>
<td>1q21-q23</td>
<td>AD</td>
<td>α-Tropomyosin</td>
</tr>
<tr>
<td></td>
<td>TPM2</td>
<td>9p13</td>
<td>AD</td>
<td>β-Tropomyosin</td>
</tr>
<tr>
<td></td>
<td>TNNT1</td>
<td>19q13</td>
<td>AR</td>
<td>Slow troponin T</td>
</tr>
<tr>
<td>Myotubular myopathy</td>
<td>MTM1</td>
<td>Xq28</td>
<td>XL</td>
<td>Myotubulin</td>
</tr>
<tr>
<td>Hyaline body myopathy</td>
<td>MYH7</td>
<td>14q</td>
<td>AD</td>
<td>Slow myosin heavy chain</td>
</tr>
<tr>
<td>Sarcotubular myopathy</td>
<td>TRIM32</td>
<td>9q31-34</td>
<td>AR</td>
<td>TRIM32</td>
</tr>
<tr>
<td>Fibre type disproportion</td>
<td>ACTA1</td>
<td>1q42.1</td>
<td>?</td>
<td>Skeletal α-actin</td>
</tr>
</tbody>
</table>

## Disorders with structural defects but unknown gene defects*

- Broad A-band disease
- Cap disease
- Cylindrical spirals myopathy†
- Cytoplasmic or spheroid body myopathy
- Fingerprint body myopathy†
- Lamellae body myopathy
- Myopathy with muscle spindle excess
- Reducing body myopathy†
- Trilaminar fibre myopathy
- Tubular aggregate myopathy†
- Zebra body myopathy

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked; ?, inheritance currently uncertain.

* A genetic basis for some of these is uncertain and only sporadic cases reported.
† Familial cases reported.
may reveal differential involvement of muscles. This can be helpful in deciding which muscle to sample. The differential involvement of muscles is clearly seen with magnetic resonance imaging (MRI) and emerging data indicate that particular patterns of selective involvement of thigh and lower leg muscles are associated with mutations in certain genes and are helpful in directing molecular analysis (Jungbluth et al 2004a,b,c). Muscle biopsy, with detailed histochemical studies, supplemented by immunohistochemistry and electron microscopy, is essential for the diagnosis of congenital myopathies and for directing molecular analysis.

### Pathological features of congenital myopathies

Hypotrophy of type 1 fibres is seen in several congenital myopathies, and there is often a marked predominance or uniformity of type 1 fibres. Although the fibres appear to be type 1 with stains for oxidative enzymes and for adenosine triphosphatase (ATPase), the intensity of staining is often less than that seen in normal muscle and intermediate between type 1 and 2 fibres. Antibodies to myosin isoforms confirm the slow phenotype of most fibres but again the intensity of labelling may be less than in normal muscle. Necrosis and regeneration are not typical features of congenital myopathies. Scattered, very small fibres containing neonatal myosin, however, are often seen (see Ch. 6), but it is not clear if these represent attempts at regeneration. Fibrosis is also rare in congenital myopathies but can occur (see section on central core disease). Centrally placed nuclei are a particular feature of myotubular and centronuclear myopathies (see below) and we are now aware that they are also common in association with mutations in the *RYR1* gene (see below).

### Central core disease

In 1956 Magee and Shy described a ‘new congenital non-progressive myopathy’ affecting five patients in three generations of the same family, ranging in age from 2 to 65 years. The main clinical features were hypotonia and delay in motor milestones in infancy, and a mild non-progressive weakness, affecting proximal muscles more than distal, and the legs more than the arms. The muscle was characterized by amorphous-looking central areas within the muscle fibres. Greenfield et al (1958) subsequently suggested the name ‘central core disease’. A second case documented by Engel et al (1961) was studied histochemically (Dubowitz and Pearse 1960) and the classical histochemical features noted, in particular well delineated areas that ran down a considerable length of the fibres that were devoid of oxidative enzyme stain and phosphorylase. These core areas were not necessarily central and many fibres had multiple cores. In addition, the normal fibre typing was lost and the fibres had a uniform appearance of only
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Electron microscopy showed a virtual absence of mitochondria and sarcoplasmic reticulum in the core region, a marked reduction in the intermyofibrillar space and an irregular pattern (streaming) of the Z lines (Engel et al 1961, Seitelberger et al 1961).

Since these early reports there have been many additional cases with this phenotype associated with the prominent core lesions. With the advent of molecular genetics there has been a greater understanding of the clinical and pathological phenotype of central core disease (Muntoni and Sewry 2003).

The inheritance of most cases is autosomal dominant with variable penetrance; many sporadic de novo dominant cases have also been reported and there are also some recessive cases (Jungbluth et al 2002, Ferrerio et al 2002a). Central core disease is one of the most common congenital myopathies. Initial linkage studies assigned a locus to chromosome 19q13.1, and these cases showed a fairly consistent clinical phenotype, presenting with hypotonia and developmental delay. Cases with a severe presentation with features of the fetal akinesia sequence have been reported and some are associated with recessive inheritance (Monnier et al 2003, Romero et al 2003). Most of these severely affected infants require ventilation at birth and follow a downhill course, leading to death in infancy. Other cases, in contrast, may show considerable improvement and it may be possible to wean them off tracheostomy ventilation; one reported child eventually became independently ambulant (Romero et al 2003).

Weakness in most familial cases is pronounced in the hip girdle and in the axial muscle groups and may be associated with muscle wasting. Facial involvement is usually mild and lack of complete eye closure may be the only finding. Orthopaedic complications are common and include congenital dislocation of the hips and scoliosis. Contractures, other than Achilles tendon tightness, are rare, and many affected individuals have marked ligamentous laxity, occasionally associated with patellar instability. Apart from the most severe neonatal cases, and some of those with congenital dislocation of the hips (Manzur et al 1998), most patients achieve independent walking. The course of central core disease is often static, or only slowly progressive, even over prolonged periods of time (Lamont et al 1998). Primary cardiac involvement is rare and respiratory involvement is usually milder than other congenital myopathies, except in the severe neonatal cases. Serum creatine kinase activity is usually normal or only mildly elevated. A striking feature of central core disease is the differential muscle involvement, which can be shown on muscle ultrasound and, more strikingly, with MRI of muscle which reveals a characteristic pattern of selective involvement, even within the quadriceps (Jungbluth et al 2004b). This is helpful when selecting the site for a muscle biopsy and interpreting results.

Histopathology

Fibre size variation occurs but is often mild. Fibre hypertrophy is common, particularly in adults (Fig. 15.1). When fibre typing is retained the cores have a predilection for type 1 fibres but fibre type uniformity is common with most fibres
staining as type 1 fibres, with the associated properties of slow fibres (Fig. 15.1). A few fibres may co-express fast myosin and there may be a few very small fibres with neonatal myosin scattered through the biopsy. The intensity of stain of the type 1 fibres, however, may not always be as strong as in normal muscle. Classical cores may be central or peripheral, single or multiple, but clearly demarcated cores are not always evident in all cases (Fig. 15.1). Very young cases, in particular, may only show type 1 uniformity or predominance, suggesting there is an age-related development of the cores (Fig. 15.1; Sewry et al 2002). Other cases may show only subtle unevenness in oxidative enzyme stains (Fig. 15.2) or multiple focal areas of disruption, resembling minicores, making a histopathological distinction difficult (Fig. 15.1; Sewry et al 2002; see below). It is important to remember that core formation is a secondary morphological phenomenon and may not itself be the reason for the muscle weakness.

In most cases of central core disease the cores are of the ‘structured’ type, as they retain a striated myofibrillar pattern and myofibrillar ATPase activity, although myofibrils of the core are often very contracted (Fig. 15.3). In ‘unstructured cores’ myofibrillar ATPase activity is lost (Fig. 15.4) and there is severe myofibrillar disruption with pronounced accumulation of smeared Z-line material. The length of the cores can be variable but they typically extend down an appreciable length of a fibre. The area devoid of mitochondria may be more extensive than the apparent ultrastructural myofibrillar disruption. Sarcoplasmic reticulum and T tubules may also be reduced in cores but some tubular structures may be apparent within them. Cores are often delineated by a rim of periodic acid-Schiff (PAS) stain (see Ch. 4) and immunohistochemistry shows that desmin may accumulate at their perimeter or within them (Fig. 15.5). Other proteins that have been shown to accumulate in cores are αB-crystallin, γ-filamin, small heat shock proteins and myotilin (Sewry et al 2002, Shröder et al 2003, Bönnemann et al 2003).

Internal nuclei had not been considered a feature of central core disease in studies of early cases but it is now appreciated that they can be an important indicator of central core disease (Fig. 15.6a,d). In some they may be numerous, and several may be in a central position. Similarly, an increase in connective tissue was not considered a feature of ‘classical’ cases but can occur, and in some samples there may also be extensive adipose tissue (Fig. 15.6d,e). In these samples the separation of fascicles of fibres by adipose tissue and fibrous tissue may cause

**FIG. 15.1** Biopsies of the quadriceps from three members of the same family with central core disease with a dominant mutation in the ryanodine receptor gene showing the range of appearance that can be seen with oxidative enzyme stains. (a) Female aged 4 months showing variation in fibre size (fibre diameter range 5–40 μm) and fibre type uniformity but no clear-cut cores; (b) the brother aged 3 years showing mild variation in fibre size (fibre diameter range 15–65 μm), fibre type uniformity and numerous cores of varying size centrally or peripherally; (c) the mother aged 32 years showing hypertrophy of most fibres (fibre diameter range 85–120 μm), type 1 fibre predominance and unevenness of stain or small areas devoid of stain but no pronounced cores.
FIG. 15.2 Quadriceps biopsy from a female aged 28 years with typical clinical features of central core disease and a mutation in the RYR1 gene showing (a) occasional central nuclei (arrow) (Gomori trichrome); (b) indistinct fibre typing and mild unevenness of oxidative enzyme stain (*) and only one core-like area (red arrow) (NADH-TR); but (c) type 1 predominance and variation in size of the dark type 1 fibres (ATPase preincubated at pH 4.6).
FIG. 15.3 Electron micrograph of a structured core (arrows) in a case of central core disease showing pronounced contraction of the myofibrils in the core (*) compared with those either side (●), a little disruption of the Z line and an absence of mitochondria from the core.

FIG. 15.4 Unstructured cores in a severely affected case of central core disease showing an absence of ATPase stain in the cores and uniform fibre typing with an intermediate intensity, and a rather brown colour compared with normal (ATPase 9.4).
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Diagnostic confusion with a muscular dystrophy. Some of these samples may show only subtle unevenness of oxidative enzyme stains, whilst others show large classical cores or multiple small cores (minicores; see Fig. 15.6 b,c,f).

Although cores are the characteristic feature of central core disease caused by mutations in the gene encoding the ryanodine receptor (RYR1), core formation can also occur following tenotomy, following neurogenic atrophy (see Ch. 9) and in association with several other gene defects such as the ACTA1 and MYH7 genes, encoding skeletal α-actin and β-myosin heavy-chain, respectively (Jungbluth et al 2001, Kaindl 2004, Fananapazir 1993). Cores can also co-exist with rods (Fig. 15.7) and be associated with RYR1 mutations (Monnier et al 2000). In some cases with RYR1 mutations only a few fibres may show rods (Fig. 15.8; Jungbluth et al 2002). The coexistence of rods and cores is likely to be genetically heterogeneous as there are examples of cases where linkage to RYR1 and to the loci of nemaline myopathy (see below) have been excluded.

**Molecular genetics**

Central core disease is caused by mutations in the gene for the skeletal muscle ryanodine receptor (RYR1) on chromosome 19q. The same gene is responsible for malignant hyperthermia, although additional loci are also linked to this. The precise association between central core disease and malignant hyperthermia is not clear but all patients with central core disease are considered at risk and appropriate precautions need to be taken.

The RYR1 gene contains 106 exons and encodes the skeletal muscle ryanodine receptor protein (RyR1), named after the fact that it binds ryanodine. The receptor is a large transmembrane, tetrameric structure of the sarcoplasmic
FIG. 15.6 Quadricep biopsies from two cases of central core disease aged 18 months (a)–(c) and 11 years (d)–(f) with proven mutations in the RYR1 gene. Note the excess internal nuclei, some of which are central, in both cases [arrows; (a), (d)], and the pronounced increase in fat and connective tissue seen at low power in case 2 (e). Case 1 shows multiple cores with oxidative enzyme stains (c) which are particularly apparent in longitudinal section (b), and case 2 shows more classical cores (f) [(a), (d), (e) H&E; (b), (c), (f) NADH-TR. Fibre diameter range (a), (b) 25–40 μm; (d) 10–105 μm; (f) 15–85 μm].
FIG. 15.20 Muscle biopsy from a 9-year-old girl with autosomal centronuclear myopathy. Note in (a) numerous central nuclei (H&E) and (b) core-like areas devoid of cytochrome oxidase activity (fibre diameter range 10–25 μm). A mutation in the myotubularin gene was excluded but a mutation in the ryanodine receptor gene (RYR1) has been identified.
**Hyaline body myopathy**

This rare disorder has been described with other congenital myopathies and the original patients described presented at birth with hypotonia. The molecular basis of this disorder has recently been identified as a mutation in the gene encoding slow/β-cardiac myosin (MYH7). It can therefore be considered as a myofibrillar myopathy and will be discussed further in Chapter 16. Pathologically the muscle is characterized by accumulations of areas of granular material that stain for myosin ATPase and myosin.

**Sarcotubular myopathy**

In 1973 Jerusalem and co-workers described a congenital myopathy in two Hutterite brothers in whom a proportion of muscle fibres showed focal dilation of the sarcoplasmic reticulum. Two further German cases were also described (Muller-Felber et al 1999). A mutation in the TRIM32 gene has recently been found in these families (Schoser et al 2005). The same mutation in TRIM32 causes limb-girdle muscular dystrophy 2H (see Ch. 11), which is restricted to the Hutterite population. Schoser et al (2005) have suggested that sarcotubular myopathy and LGMD2H are the same disorder.

**Congenital fibre type disproportion**

In the course of their histographic analysis of muscle biopsies, Brooke and Engel (1969d) suggested that children’s biopsies could be classified into five categories according to their histographic characteristics. It was noted that in most normal children, the type 1 and type 2 fibres were of roughly equal size and had a variability coefficient which was less than 250. Children suffering from neurogenic disease were usually found to have histograms characterized by one population of large fibres and another of small fibres, thus giving a ‘twin-peaked’ appearance to the histogram of an individual fibre type (see Ch. 4). Biopsies from myopathic patients were found to exhibit an increased variability in the size of fibres, without a twin-peaked appearance in the histogram. Thus, the histogram maintained its bell-shaped appearance. A large number of children were seen in whom the type 2 fibres were smaller than the type 1 fibres and this was found in conditions as varied as simple disuse and mental retardation. Some of the biopsies, however, were characterized by the fact that the type 1 fibres were smaller than type 2 fibres, and in 10 of these children a relatively non-progressive weakness was found which was usually present at birth. Brooke (1973) subsequently delineated a fairly consistent clinical picture based on a further 12 cases, and suggested the name ‘congenital fibre type disproportion’.

All of the children were floppy babies, the condition being noted at or shortly after birth. In 50% of the cases, contractures of various muscles of either the
hands or feet were noted. One patient had a torticollis due to a contracted sternomastoid. Congenital dislocation of the hip, either bilaterally or unilaterally, was also found in 50% of the patients. The degree of weakness varied quite considerably. It seemed to involve all the muscles of the trunk and extremities, although in some patients the legs seemed to be more involved than the arms. It was so severe in one patient that little voluntary movement of the arms or legs was possible until almost 2 years of age. In other cases, the weakness was mild enough to cause only a delay in the development of the motor milestones, rather than any obvious paralysis. In some, there appeared to be an initial progression of the weakness during the first year of life, but in no case was there any progression once the child had attained 2 years of age. As the child grew older, the disease became static or improvement took place.

Recurrent respiratory infections were frequently a problem during the first year of life. There was an associated abnormality in stature, and most patients were below the third percentile in weight, even though the birth weight was normal in most cases, and below the tenth percentile in height. Commonly occurring anomalies included a high arched palate, kyphoscoliosis and deformities of the feet – either flat feet or occasionally high arched feet.

Although the genetics of this disease was not clear cut, about half of the patients had a relative with a similar clinical condition. In some, there were affected siblings only, suggesting an autosomal recessive pattern of inheritance, but one patient had both a father and brother affected, suggesting a dominant mechanism.

A similar histochemical pattern was documented in female siblings with a non-progressive congenital myopathy (see Dubowitz 1980) and in the cases reported by Caille et al (1971). Several reports have subsequently documented further cases, including a number of familial ones (see Clarke and North 2003).

The pathological criterion for determining fibre type disproportion that is often quoted is the presence of type 1 fibres that are at least 12% smaller in diameter than type 2 fibres and the absence of any other pathological feature, but Brooke acknowledged subsequently that this is too narrow a distinction and agreed to at least 25%.

Small type 1 fibres are a feature of several disorders and it is important to exclude other conditions such as congenital myotonic dystrophy, and the various congenital myopathies mentioned above. It is also important to restrict the diagnosis to ‘pure’ cases with no change histologically other than the variation in fibre size.

There has been a long debate on whether fibre type disproportion is a disease entity or if it is ‘pathology in search of a disease’. Recent molecular data, however, has thrown some light on this and mutations in the ACTA1 gene have been found in a small proportion of cases that only showed small type 1 fibres (Fig. 15.21; Laing et al 2004). The clinical phenotype in the cases identified to date is variable and the absence of a detectable mutation in additional cases suggests further genetic heterogeneity.
Congenital myopathies with ultrastructural abnormalities

A number of rare cases have been reported in which a biopsy has been characterized by, and the disorder named after, the presence of a particular ultrastructural abnormality (see Table 15.1). It is not clear if all are genetic entities as some are sporadic, non-familial cases (Goebel and Anderson 1999, Taratuto 2002). The clinical presentation of these cases is variable and not all may fall into the ‘congenital myopathy’ category, and are perhaps more strictly ‘myopathies with structural abnormalities’. Many of the structures are highlighted by the Gomori trichrome stain and stains that use a tetrazolium salt. Examples of the ultrastructure of several of these structures are shown in Chapter 5.

The morphological structures that have given their name to a disorder that may have a genetic basis include fingerprint bodies (Engel et al 1972, Fardeau et al 1976, Curless et al 1978), cylindrical spirals (Carpenter et al 1979, Bove et al 1980), tubular aggregates (de Groot and Ants 1982, Rohkman et al 1983, Cameron et al 1992) and reducing bodies (Brooke and Neville 1972, Dubowitz and Brooke 1973, Sahgal and Sahgal 1977, Nomiizu et al 1992, Bertini et al 1994). Tubular aggregates are a non-specific finding which often occur in cases with periodic paralyses where they are restricted to type 2 fibres. In familial tubular aggregate myopathy, they occur in both fibre types. Reducing bodies are intracytoplasmic...
bodies that are non-reactive for oxidative enzymes and ATPase, but are able to reduce nitroblue tetrazolium directly when mediated by menadione – hence the suggested name of ‘reducing-body’ myopathy.

Other structures that have given their name to a myopathy have been seen in rare sporadic cases and a genetic basis is far from clear (see Table 15.1). These include cap disease (Fidzianska et al 1981), characterized by crescent-shaped granular areas at the periphery of several fibres; and zebra body myopathy (Lake and Wilson 1975).