Inherited Myopathies

Dystrophic and non-dystrophic inherited muscle diseases have traditionally been defined by the presence or absence of prominent muscle fibre degeneration on biopsy. Huge advances in our molecular genetic understanding of the inherited myopathies have made this nosological distinction less clear but the recognition of characteristic phenotypes is still an important part of the diagnosis.

Presentations of inherited myopathies

Inherited myopathies commonly present with weakness, contractures or cardiac dysfunction, frequently only in adulthood. In the absence of a family member with a confirmed diagnosis, individuals are investigated with measurement of the serum creatine kinase level (typically extremely high), EMG, (immuno)histochemical analysis of a muscle biopsy specimen, ECG and echocardiography. Genetic testing may also be required.

PATTERNS OF WEAKNESS

The early involvement of selective muscle groups is a prominent feature of the inherited myopathies. Limb-girdle (shoulder and pelvic girdles) weakness, a non-specific finding in muscle disease, is more likely to be due to an inherited myopathy if associated with toe-walking (Table 1). The weakness in distal myopathies (Table 2) typically affects muscles in the fore-arm and lower leg more than the intrinsic muscles of the feet and hands, distinguishing it from neurogenic processes. Early selective facial weakness, ocular and bulbar, periscapular and humeroperoneal (e.g. biceps and tibialis anterior) weakness are strongly suggestive of inherited myopathies (Table 3). Prominent asymmetry is a distinctive and necessary feature of facioscapulohumeral dystrophy.

CONTRACTURES

Contractures, caused by tendon shortening and restrictive changes in the joint capsule, can occur in any immobile joint but are particularly common in inherited myopathies. The result is a fixed reduction in the range of joint movement that feels more like bone than a tight tendon, for instance at the ankle, knee, hip or elbow. Ankle contractures due to shortening of the Achilles' tendon give rise to the toe-walking so characteristic of boys with Duchenne's muscular dystrophy. It is rare for contractures to be prominent early in the course of neuromuscular disease but they are a presenting feature of Emery-Dreifuss muscular dystrophy and Bethlem myopathy at a time when muscle weakness is minimal or absent.

CARDIAC INVOLVEMENT

Many of the inherited myopathies are associated with cardiac dysfunction which must be sought with ECG and echocardiography and may require the insertion of a pacemaker. Cardiomyopathy in the dystrophinopathies may present with tachycardia at rest. Cardiac conduction defects are frequently seen in myotonic dystrophy and may be followed by the development of a cardiomyopathy. Individuals with Emery-Dreifuss muscular dystrophy are particularly prone to bradycardia that may present with syncope or sudden death.

Inherited myopathies presenting with limb-girdle weakness

DUCHENNE'S (DMD) & BECKER'S (BMD) MUSCULAR DYSTROPHIES

DMD and BMD are allelic variants in which mutations of the dystrophin gene give rise respectively to absent or reduced protein expression. Mutations generating a premature stop codon abolish dystrophin expression and result in the more severe DMD phenotype. Residual expression of dystrophin, typically a truncated protein, gives rise to BMD which can be very mild indeed, including individuals with cramps and post-exercise myalgia or myoglobinuria. Cardiac involvement is frequent in DMD and BMD and can even affect carriers of the mutation, the severity of the cardiomyopathy bears no relation to the degree of limb weakness.

Due to the size of the dystrophin protein, three antibodies (directed against the -NH2/-COOH terminals or the rod domain) are used to demonstrate the immunohistochemical absence of

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TABLE 1: Inherited myopathies presenting with proximal weakness

Inset: Massive calf hypertrophy in DMD

<table>
<thead>
<tr>
<th>PROXIMAL INHERITED MYOPATHIES</th>
<th>CHARACTERISTIC INVOLVEMENT</th>
<th>INHERITANCE</th>
<th>MOLECULAR DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMD</td>
<td>Duchenne's muscular dystrophy</td>
<td>toe-walking calf hypertrophy Gower's manoeuvre cardiomyopathy</td>
<td>X-linked</td>
</tr>
<tr>
<td>3-5y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD</td>
<td>Becker's muscular dystrophy</td>
<td>as for DMD but much milder post-exercise cramps cardiomyopathy</td>
<td>X-linked</td>
</tr>
<tr>
<td>3-20y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGMD</td>
<td>Limb-girdle muscular dystrophies</td>
<td>pelvic-&gt;shoulder girdle can look like DMD, BMD or humeroperoneal weakness sparing face no cardiac involvement</td>
<td>AR (AD)</td>
</tr>
<tr>
<td>3-20y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROMM</td>
<td>Proximal myotonic myopathy (DM2)</td>
<td>limb-girdle stiffness, pain myotonia cardiac conduction defects can be similar to DM1</td>
<td>AD</td>
</tr>
<tr>
<td>20-60y</td>
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and diabetes. Myotonia, best sought in the thenar eminence and the full-length molecule in DMD. Staining may be normal or only minimally reduced in BMD. A detectable deletion or duplication in the dystrophin gene is found in 70% of DMD, the remainder being due to point mutations or small rearrangements that cannot be routinely screened in such a large gene. Treatment with oral or pulsed intravenous steroids is routine in the US but not in the UK. With more attention to multidisciplinary, and especially respiratory, care many boys with DMD are living well into their third decade.

LIMB-GIRDLE MUSCULAR DYSTROPHY (LGMD) SYNDROMES

The LGMDs are a large group of inherited disorders with a range of presentations including phenotypes indistinguishable from DMD or BMD as well as non-specific limb-girdle weakness. In an undiagnosed early-onset myopathy disproportionate pelvic girdle weakness is suggestive of a LGMD where proximal lower limb weakness often predates shoulder girdle weakness even by many years (e.g. calpainopathies, LGMD2A). The dysferlinopathies (LGMD2B) differ from other LGMD syndromes with a later (adolescent) onset and striking distal weakness, particularly in the gastrocnemii (cf. distal myopathies).

Most LGMDs have an autosomal recessive pattern of inheritance. They are frequently associated with deficiencies in dystrophin-associated proteins, especially the sarcoglycans (LGMD2C-F). Diagnosis currently depends on demonstrating absent or reduced protein expression on muscle immunohistochemistry or Western blotting. It is recognised, however, that a reduction in protein expression is not always the primary molecular defect but may be secondary to another pathogenic process.

PROXIMAL MYOTONIC MYOPATHY (PROMM)

PROMM (or DM2) is an autosomal dominant disorder that gives rise to muscle weakness, stiffness or pain in a limb-girdle distribution and cataracts. The distribution of weakness, frequent calf hypertrophy, normal face and absence of central nervous system involvement distinguish PROMM from myotonic dystrophy (DM1). This distinction, however, is not absolute and distal weakness similar to DM1 can also be seen. PROMM is caused by an expansion in the number of [CTG]n triplet repeats in a non-coding region of the DM2 gene. The phenomenon of genetic anticipation (earlier symptom onset in successive generations) is the result of an intergenerational increase in the number of repeats.

DISTAL MYOPATHIES

The distal myopathies can be divided into autosomal dominant disorders with late (>40 years old) onset (e.g. Welander-type) and autosomal recessive disorders with earlier (<30 years old) onset (e.g. Miyoshi- and Nonaka-type). The biopsy is myopathic rather than dystrophic and frequently contains inclusion bodies reminiscent of those seen in (sporadic) inclusion body myositis and hereditary inclusion body myopathies. Welander distal myopathy is unusual in that weakness starts in the arms (especially wrist and finger extensors) rather than the legs and, in contrast to other distal myopathies, wasting of the intrinsic muscles of the hand occurs early. Nonaka distal myopathy (also known as hereditary inclusion body myopathy type 2) starts in the legs with preferential involvement of muscles in the anterior compartment. Miyoshi-type distal myopathy is allelic with LGMD2B (dysferlinopathy) with which it shares distal leg onset in the posterior compartment (i.e. wasted as opposed to hypertrophied gastrocnemii).

Distinctive inherited myopathy phenotypes

FACIOSCAPULOHUMERAL (FSH) MUSCULAR DYSTROPHY

FSH is a relatively benign asymmetric myopathy with no cardiac involvement, a normal life expectancy and only 20% lifetime risk of being wheelchair-bound. Although symptom onset is most typically during adolescence, individuals with FSH frequently present to adult neurology clinics with sporadic (10% of mutations are new) asymmetric muscle weakness: the absence of asymmetry makes the diagnosis unlikely. Facial weakness is invariably found on examination but may be very mild and shoulder girdle symptoms, including pain, are more likely to trigger presentation. Impaired shoulder abduction with elevation of the shoulder blades (‘triangular shoulders’) is the result of reduced scapular fixation and not weakness of the deltoids which are characteristically spared. Scapular winging is frequently observed but not invariably.

Limb weakness is in a humeroperoneal distribution and can result in a symptomatic footdrop. FSH is diagnosed by the demonstration of a chromosomal deletion, a reduced number of 3 kb repeats at 4q35 but no single gene defect has been identified.
OCULOPHARYNGEAL MUSCULAR DYSTROPHY (OPMD)

Late-onset ptosis (often asymmetric) and dysphagia are characteristic of OPMD in which ophthalmoplegia and limb-girdle weakness can also be present to a variable degree. The main differential diagnoses are myasthenia gravis, mitochondrial myopathy and myotonic dystrophy. Polymyositis and motor neuron disease can cause progressive dysphagia but not ptosis. OPMD is now known to be a triplet-repeat disease affecting a non-coding portion of the poly[A] binding protein 2 (PABP2) gene. The [GGG]n expansion differs from that seen in other neurological conditions in being short (8-13 repeats) and stable.

EMERY-DREIFUSS MUSCULAR DYSTROPHY (EDMD) and BETHLEM MYOPATHY

EDMD is characterized by the triad of (i) early contractures (especially in the elbows and neck); (ii) progressive humeroperoneal weakness and wasting; (iii) cardiac conduction defects. The flexed elbows and stiff neck so characteristic of the condition are not seen in BMD. Atrial paralysis with small or absent P-waves (leading to a sinus bradycardia) is almost pathognomonic of the condition and requires cardiac pacing. EDMD is usually X-linked and due to mutations of the STA gene which give rise to absence of the nuclear membrane protein emerin on immunohistochemistry.

Rare autosomal dominantly inherited EDMD is due to mutations in a different gene encoding lamins A and C. AD-EDMD has to be distinguished from Bethlem myopathy, another rare dominantly-inherited condition with prominent early contractures, particularly in the interphalangeal joints of the fingers and in the wrists and elbows. It is associated with mild limb-girdle weakness and the heart is not affected. Bethlem myopathy is caused by mutations in the gene for collagen VI.

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TABLE 3: Inherited myopathies presenting with distinctive patterns of weakness

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