

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 clear¹⁻³ 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 forearm 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 **humero-peroneal** (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,

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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

TABLE 1: Inherited myopathies presenting with proximal weakness

Inset: Massive calf hypertrophy in DMD

PROXIMAL INHERITED MYOPATHIES	CHARACTERISTIC MUSCLE INVOLVEMENT	INHERITANCE <i>age at onset</i>	MOLECULAR DIAGNOSIS
DMD Duchenne's muscular dystrophy	toe-walking calf hypertrophy Gower's manoeuvre cardiomyopathy	X-linked 3-5y	mutations in dystrophin gene • absent staining • DNA studies
BMD Becker's muscular dystrophy	as for DMD but much milder post-exercise cramps cardiomyopathy	X-linked 3-20+y	mutations in dystrophin gene • normal/reduced staining • DNA studies
LGMD Limb-girdle muscular dystrophies	pelvic>>shoulder girdle can look like DMD, BMD or humero-peroneal weakness sparing face no cardiac involvement	AR (AD) 3-20+y	various mutations incl. calpain-3, / -, E, S, sarcoglycans • absent/reduced staining • Western blotting
PROMM Proximal myotonic myopathy (DM2)	limb-girdle stiffness, pain myotonia cardiac conduction defects can be similar to DM1	AD 20-60y	quadruplet expansions in ZNF9 • DNA studies



TABLE 2: Inherited myopathies presenting with distal weakness
Inset: Early selective posterior compartment weakness and wasting in LGMD2B

DISTAL INHERITED MYOPATHIES	CHARACTERISTIC MUSCLE INVOLVEMENT	INHERITANCE <i>age at onset</i>	MOLECULAR DIAGNOSIS
Myotonic dystrophy	myotonia bilateral ptosis masseter/temporalis sternocleidomastoid bulbar muscles cardiomyopathy	AD <i>any age</i>	triplet expansions in DM-PK • DNA studies
Distal myopathies • Welander • Nonaka • Miyoshi/LGMD 2B	no cardiac involvement • forearm extensors • anterior compartment leg • posterior compartment leg	AD >40y AR <30y AR <30y	few identified genes • myopathic biopsy ± inclusion bodies • Miyoshi/LGMD2B allelic disorders with decreased/absent dysferlin



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 US⁴ 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.

LEMB-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 [CCTG]_n repeats in the gene encoding zinc finger protein 9 (ZNF9). While there is some intergenerational instability in the size of the repeat, anticipation is not a prominent clinical feature.

Inherited myopathies presenting with distal limb weakness

MYOTONIC DYSTROPHY

The clinical features of myotonic dystrophy (DM1) are among the most characteristic of any neurological disease and include extramuscular manifestations such as frontal balding, cataracts and diabetes. Myotonia, best sought in the thenar eminence and

wrist extensors, is accompanied by strikingly distal limb weakness affecting particularly the foot extensors and the forearms but initially sparing the intrinsic muscles of the foot and hand.

Molecular genetic confirmation of the diagnosis of myotonic dystrophy is made by the demonstration of an expansion in the number of [CTG]_n triplet repeats in a non-coding region of the dystrophin myotonia protein kinase (DM-PK) 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 invariable.

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 3.3kb repeats at 4q35 but no single gene defect has been identified.

