Myopathies in the adult patient

David Hilton-Jones

Abstract

About 70,000 people in the UK (around 62 million) have a peripheral neuromuscular disorder, with about one-half of them having a myopathy. They can be acquired or inherited. Most of the former respond to removal of the cause or specific treatment, whereas most of the latter have no specific treatment. Much can be done to improve quality of life and reduce morbidity and mortality in hereditary myopathies, particularly relating to cardiac and respiratory management. Precise molecular diagnosis is essential for accurate genetic counselling and the provision of reproductive options. All of these diseases are best managed by a multidisciplinary team led by a specialist clinician. Many individual myopathies are extremely rare, and the generalist cannot be expected to identify all of them. However, generalists should have the generic skills to be able to recognize the broad nature of the problem and to refer on as appropriate. It is indefensible to miss a treatable disorder such as myositis or drug-induced myopathy, and the generalist should be aware of the major clinical features and management issues of the more common disorders, notably myotonic dystrophy and those with multisystemic manifestations, such as the mitochondrial cytopathies.

Keywords Dermatomyositis; facioscapulohumeral muscular dystrophy; inclusion body myositis; mitochondrial cytopathy; muscular dystrophy; myopathy; myositis; myotonic dystrophy; polymyositis; statins

Key points

- Serum alanine aminotransferase comes from muscle as well as liver — think of measuring serum creatine kinase if alanine aminotransferase elevated in absence of other signs of liver disease
- Statins are the most common cause of rhabdomyolysis
- Myotonic dystrophy can affect every body system and may present with non-myopathic problems
- Genetic myopathies may not present until middle age or later
- Even experts miss myotonic dystrophy type 2
- Inclusion body myositis is the most common acquired myopathy in late middle age and beyond
- It is indefensible to miss myositis but many other myopathies share similar clinical features

Introduction

Myopathies can be classified as acquired or inherited (Table 1). Adult neuromuscular clinics comprise conditions presenting in childhood (e.g. Duchenne and Becker dystrophy, congenital myopathies) and those, forming the basis of this article, that present for the first time in adulthood.

Investigations

The serum creatine kinase (sCK) concentration can be likened to the erythrocyte sedimentation rate in rheumatological/inflammatory disorders — an indicator of abnormality but totally lacking any specificity. Most laboratories quote an incorrect (too low) upper limit of normal.[1] The upper limits of normal (97.5th percentile) for non-black women and men are 217 U/litre and 336 U/litre, and for black women and men 414 U/litre and 801 U/litre, respectively. Grossly elevated (e.g. >5000 U/litre) concentrations are seen in Duchenne dystrophy and in all causes of rhabdomyolysis. Intermediate concentrations are seen in Becker dystrophy, various forms of limb-girdle dystrophy, acute myositides and acute episodes associated with metabolic myopathies. However, the activity can be normal in myotonic dystrophy, facioscapulohumeral dystrophy (FSHD) and some forms of limb-girdle dystrophy.

Neurophysiological studies are generally of less value in studying myopathies than neurogenic disorders. The unexpected finding of myotonic discharges may be the first pointer to a diagnosis of myotonic dystrophy type 2.

Increasingly, DNA analysis is the investigation of choice for inherited disorders.

Muscle biopsy remains an important tool in investigating suspected myopathy.

Idiopathic inflammatory myopathies

These autoimmune disorders include dermatomyositis (DM), polymyositis (PM) and myositis associated with connective tissue disorders. The cardinal features are proximal muscle weakness, skin changes in DM, inflammatory changes on muscle biopsy, and response to immunosuppression. DM is associated with a complement-mediated microangiopathy, whereas PM is caused by T-cell-mediated cytotoxicity (Figure 1).

Proximal limb weakness, and weakness of neck flexion, evolves acutely or subacutely in DM, and more insidiously in PM. In DM, the characteristic rash is similar to that seen in systemic lupus — erythema of sun-exposed parts (face, neck, shoulders) and, most characteristically, erythema over the knuckles and dilatation of nail-bed capillaries. Pain is not usually a major feature. About 20% of cases of DM are paraneoplastic, and screening for cancer at the time of diagnosis and vigilance for the following couple of years is required.

The sCK concentration is usually elevated. Muscle biopsy is usually diagnostic. Various serum antibodies have been noted in association with myositis: anti-Jo1 is associated with interstitial lung disease, and p155 with malignancy in DM.

Treatment is with immunosuppression.

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Classification of the myopathies and their major subtypes

Acquired myopathies

Idiopathic inflammatory myopathies
- Dermatomyositis
- Polymyositis
- Myositis associated with connective tissue disease

Inclusion body myositis

Drug- and toxin-induced myopathies

Endocrinopathies

Secondary metabolic myopathies

Myopathies associated with infections

Inherited myopathies

Myotonic dystrophy
- Types 1 and 2

Muscular dystrophy
- Duchenne
- Becker
- Emery—Dreifuss
- Facioscapulohumeral
- Limb-girdle
- Oculopharyngeal
- Congenital

Congenital (ultrastructural) myopathies
- Nemaline
- Central core disease
- Fibre-type disproportion

Myofibrillar myopathies

Distal myopathies

Metabolic myopathies

Disorders of glycogen metabolism
- McArdle's disease

Disorders of fatty acid metabolism
- Carnitine palmitoyltransferase deficiency
- Very long-chain acyl CoA dehydrogenase deficiency

Channelopathies
- Periodic paralyses
- Myotonia congenita

Mitochondrial cytopathies
- Chronic progressive external ophthalmoplegia

Table 1

Inclusion body myositis

This is the most common myopathy presenting after the age of about 45 years.[2] Despite some histological changes similar to those of PM, there is a lack of response to immunosuppression, and such treatment should not be given. Additional features (e.g. rimmed vacuoles, accumulation of abnormal proteins including amyloid) suggest a degenerative component to the disorder (Figure 1).

The clinical features are essentially pathognomonic — highly selective involvement of the finger flexor muscles (with preservation of the deltoid) and quadriceps (with preservation of iliopsoas), causing eventually profound disability due to impaired hand function (Figure 2) and falls as a result of the knees 'giving way'. Dysphagia is common. Diagnosis is based on a combination of the characteristic clinical features and histology.

Drug- and toxin-induced myopathies

Numerous toxins and drugs can induce myopathy via a wide range of pathological mechanisms. Clinical syndromes include painful and painless proximal myopathy, myalgia without weakness, rhabdomyolysis, malignant hyperthermia and myotonia. Acute alcohol intake can induce rhabdomyolysis, but chronic alcoholic myopathy is a more nebulous entity.

Of the many drug-induced myopathies, statin-induced myopathy is arguably the most prevalent.[3] Three main situations are recognized:

1 non-specific myalgia, without weakness, showing a modest elevation of sCK concentration
2 acute rhabdomyolysis
3 an autoimmune necrotizing myopathy that can persist after statin withdrawal.

The first is by far the most common (approximately 5% of patients). Acute rhabdomyolysis carries a risk of renal failure and death. Only a tiny percentage of users are affected, and it usually relates to very high dosages or the concomitant administration of other drugs that inhibit statin metabolism (e.g. ciclosporin). Situations (1) and (2) are metabolic in origin, whereas (3) is immune, and antibodies against the enzyme that statins inhibit (hydroxymethylglutaryl-CoA reductase) have recently been identified. There is little evidence that having a pre-existing myopathy increases the risk of statin-induced muscle problems.

Endocrine myopathies

Virtually every endocrinopathy has been associated with myopathy, the most common pattern being proximal weakness and muscle biopsy showing type 2 muscle fibre atrophy. The myopathy tends to be observed after the endocrine diagnosis has been established, but rarely it is the presenting feature.

Corticosteroid excess, whether iatrogenic or related to Cushing's syndrome, causes proximal weakness (pelvic more than shoulder girdle) that is almost invariably associated with other clinical features of corticosteroid excess. sCK concentration is normal (which can help in determining if increasing weakness in a patient being treated with corticosteroids for myositis is caused by worsening of the myositis or corticosteroid myopathy).

Hypothyroidism is more often associated with myalgia and stiffness than frank weakness. sCK is elevated, and occult hypothyroidism is an important cause of unexplained sCK elevation.

Hyperthyroidism often causes subclinical proximal weakness.

Thyrotoxic periodic paralysis (PP) describes the association of thyrotoxicosis with episodes of PP. It is largely confined to young adult men of Asian origin.

Thyroid ophthalmopathy (Graves' disease) is an autoimmune disorder involving shared antigens in the thyroid and orbital tissues. The patient may not be dysthyroid at the time of presentation. Major features include proptosis, diplopia, lid retraction, chemosis and visual loss.

Miscellaneous acquired myopathies

Systemic metabolic dysfunction can affect muscle, perhaps the most common being weakness resulting from hypokalaemia. Hypophosphataemia also causes weakness.