Myopathies in the adult patient

David Hilton-Jones

Abstract

Primary muscle disorders (myopathies) are rare, even within a neurology clinic. It has been estimated that there are about 70,000 people in the UK (population ~62 million) with a peripheral neuromuscular disorder, with about one-half of them having a myopathy. A fundamental distinction is between acquired and inherited myopathies. Currently, a majority of the former will respond to removal of the cause or specific treatment, such as immunosuppression, whereas despite the hopes of 'genetic engineering' the majority of the latter have no specific treatment, although appropriate interventions can greatly improve both morbidity and mortality. For the latter group, genetic counselling issues are of fundamental importance. All of these diseases are best managed by a multidisciplinary team led by a clinician with a specific interest in neuromuscular disease.

Many individual myopathies are extremely rare and will not be seen by most neurologists during their careers. The tyro cannot be expected necessarily to identify these rarities, but should have the generic skills to be able to recognize the broad nature of the problem and to refer on as appropriate. However, it would be indefensible to miss a treatable disorder such as myositis, and they should certainly 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

Introduction

Many individual myopathies are extremely rare but can be classified as either acquired or inherited. Within each of these categories there are only a few major subdivisions, but within each of those an enormous range of clinical presentations (Table 1). Not surprisingly, inherited disorders tend to present earlier, and acquired disorders later, in life but with certain notable exceptions. The adult neuromuscular clinic will be populated by those who presented in childhood but are transitioning to adult services (e.g. Duchenne and Becker dystrophy, congenital myopathies including congenital and childhood onset myotonic dystrophy) and those, forming the basis of this article, who present for the first time in adulthood. Management issues are similar for both groups.

David Hilton-Jones *MD FRCP FRCPE is a Consultant Neurologist at the John Radcliffe Hospital, Oxford, and Milton Keynes Hospital Foundation Trust, UK. Conflicts of interest: none declared.*

Investigations

Most patients will have their serum creatine kinase (sCK) estimated. The sCK can be likened to the erythrocyte sedimentation rate or C-reactive protein in rheumatological/inflammatory disorders – an indicator of abnormality but totally lacking any specificity. Most laboratories quote an upper limit of normal based on inappropriate populations and ignoring racial and sex differences, the net result of which is to quote an inappropriately low upper limit, leading to 'false-positive' results.[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. Such apparently precise figures are somewhat misleading and need to take into account sometimes marked day-to-day variability, particularly relating to levels of physical activity. Grossly elevated (e.g. >5000 U/litre) concentrations are seen in Duchenne dystrophy, and in any cause of rhabdomyolysis. Intermediate but substantially raised concentrations are seen in Becker dystrophy, various forms of limb-girdle dystrophy, acute myositides, and in acute episodes associated with metabolic myopathies. However, the concentration can be normal in myotonic dystrophy, facioscapulohumeral dystrophy and some forms of limb-girdle dystrophy.

Neurophysiological studies are generally of less value in studying myopathies than neurogenic disorders and sometimes the results are frankly misleading. The typical signature of a myopathic process is short-duration polyphasic motor unit potentials. Inflammatory myopathies may also show 'irritative' phenomena (positive sharp waves and fibrillation potentials). Demonstrating myotonia is entertaining, but not necessary when the clinical picture indicates myotonic dystrophy, when the only investigation should be DNA testing. On the other hand, the unexpected finding of myotonic discharges may be the first pointer to a diagnosis of myotonic dystrophy type 2.

Specific metabolic studies, for example when investigating a suspected metabolic myopathy, will be discussed later. Plasma lactate may be elevated in mitochondrial disorders but is a poor screening test.

Increasingly, for suspected inherited disorders, DNA analysis is the investigation of choice, and rapid advances in technology will soon see the introduction of DNA microchips that will look at all known myopathy-related genes, although analysis of the large amount of data generated will in itself create new problems.

For the time being, muscle biopsy remains an important tool in investigating suspected myopathy. However, most clinicians will have experienced the problem of misleading 'minor changes' in a biopsy report and the need for close clinicopathological correlation remains paramount. Biopsies should be processed only in suitably experienced laboratories, able to handle frozen specimens appropriately and to undertake the wide range of necessary specific stains and immunological studies.

Acquired myopathies

Although the term may imply that anybody could be affected, there is evidence for genetic predisposition for many of these disorders (e.g. association with particular human leukocyte antigen (HLA) types). Some closely mimic inherited disorders, particularly the rather non-specific phenotype of limb-girdle muscular dystrophy.

Classification of the myopathies and their major sub-types

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 (CPT) deficiency*
    - *Very long-chain acyl CoA dehydrogenase (VLCAD) deficiency*
- Channelopathies
  - *Periodic paralyses*
  - *Myotonia congenital*
- Mitochondrial cytopathies
  - *Chronic progressive*

Table 1

Idiopathic inflammatory myopathies

These are autoimmune disorders, although rather little is known about the afferent and efferent pathways. The group includes dermatomyositis (DM), polymyositis (PM) and myositis associated with connective tissue disorders.[2] Previous classifications have included inclusion body myositis but this is best considered separately (see below). The cardinal features are proximal muscle weakness, inflammatory changes on muscle biopsy, skin changes in DM, and response to immunosuppression. DM is associated with a complement-mediated microangiopathy (in the muscle biopsy B-lymphocytes predominate, and tend to cluster around blood vessels, and there is evidence of ischaemic damage to muscle fibres) (Figure 1), whereas PM is caused by T-cell mediated cytotoxicity (in the biopsy foci of predominantly T-cells are seen in the endomysium and may be seen to be invading muscle fibres).

Proximal limb weakness, and weakness of neck flexion, evolves acutely or sub-acutely 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. Contrary to popular belief, pain is not usually a major feature. In DM of acute onset proximal discomfort may be evident, exacerbated by muscular effort. About 20% of cases of DM, more in the elderly and never in childhood, are paraneoplastic, but not associated with any specific cancer type. Therefore, screening for cancer at the time of diagnosis and vigilance for the following couple of years is required.

The serum creatine kinase is usually elevated, more so when the myopathy is of acute onset. Electromyography shows features of myopathy with positive sharp waves and fibrillation potentials. Muscle biopsy is usually diagnostic, but due to sampling artefact may be normal or show only minor non-specific abnormalities. In the absence of frank inflammation, up-regulation of sarcolemmal MHC1 expression can be taken as a surrogate marker of inflammation. Various serum antibodies have been noted in association with myositis, but they are not in themselves pathogenic. Anti-Jo1 is associated with interstitial lung disease, and p155 with malignancy in DM.

Treatment is with prednisolone, with or without the addition of a second-line immunosuppressant (e.g. methotrexate or azathioprine).

Inclusion body myositis

This is the commonest myopathy presenting after the age of about 45 years. Males are more frequently affected than females. Despite some histological changes similar to PM, the lack of response to immunosuppression and additional features (e.g. rimmed vacuoles and accumulation of abnormal proteins including amyloid) suggest the primary process may be degenerative, with secondary immune changes (Figure 1).

The established clinical features are essentially pathognomonic — highly selective involvement of the finger flexor muscles (with preservation of deltoid) and quadriceps (with preservation of iliopsoas), causing eventually profound disability due to impaired hand function (Figure 2) and falls due the knees 'giving way'. Dysphagia is common, rarely the presenting feature, and may require intervention (e.g. balloon dilatation).

Diagnosis is based on a combination of the characteristic clinical features and histology.[3]

No drug therapy has been found to be effective. Although leading to profound disability after 10 or more years, life expectancy is not reduced, although some will succumb to pneumonia due to ventilatory muscle weakness and aspiration.[4]

Drug- and toxin-induced myopathies

Numerous toxins and drugs may induce myopathy through a wide range of pathological mechanisms, many not fully understood.[5] Clinical syndromes induced by drugs include painful and painless myopathy (almost invariably proximal),