Clinical review

Fortnightly review

The muscular dystrophies

Alan E H Emery

In 1954 based on their own detailed clinical studies and an extensive review of the earlier literature, Walton and Nattrass[1] proposed a new and valuable classification of the muscular dystrophies. Ten years later Walton reviewed advances in the subject in the *BMJ*.[2 3] Many developments have taken place since then during a period in which there have been important advances in the application of molecular biology to medicine. Using protein studies and gene studies it is possible in the majority of cases to establish the precise diagnosis of a particular type of dystrophy, and thus provide a prognosis as well as genetic counselling and a reliable prenatal diagnosis. These developments could hardly have been imagined 30 years ago.

Summary points

- The muscular dystrophies are a heterogeneous group of inherited disorders characterised by progressive muscle wasting and weakness
- The genes and the protein products that are responsible for the dystrophies have been identified for most types of dystrophy
- Using muscle protein studies and molecular genetic studies in the majority of cases it is possible to establish a precise diagnosis, provide a prognosis, detect preclinical cases, identify carriers, and offer prenatal diagnostic testing
- The quality of life of individuals with dystrophy can be much improved by a positive attitude to management which includes respiratory care, physiotherapy, and the surgical correction of contractures
- A molecular genetic approach seems to offer the best prospect for developing effective treatment in the future

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Methods

This brief review is partly based on a survey of the most recent literature and partly based on nearly 40 years of personal clinical and research experience of these disorders. During the past 10 years the European Neuromuscular Centre, now based in the Netherlands, has encouraged and coordinated both clinical and laboratory studies of dystrophy, many of which have led directly or indirectly to the advances reported here.

Definition of muscular dystrophy

The muscular dystrophies are a group of inherited disorders characterised by progressive muscle wasting and weakness. A unifying feature of the dystrophies is the histological analysis of muscle samples which typically includes variations in fibre size, areas of muscle necrosis, and, ultimately, increased amounts of fat and connective tissue. The diagnosis therefore requires a muscle biopsy (generally a needle biopsy under local anaesthesia) and possibly electromyography.

Classification

The original classification scheme proposed by Walton and Nattrass depended on two considerations: the distribution of predominant muscle weakness (whether mainly proximal or distal and whether facial muscles were affected) (fig 1) and the mode of inheritance. They identified three principal groups of muscular dystrophies (Duchenne-type, facioscapulohumeral, and limb girdle) and three comparatively uncommon forms (distal, oculopharyngeal, and congenital).

It soon became clear that the X linked muscular dystrophies included not only the severe Duchenne type but also milder forms such as Becker-type muscular dystrophy; also, the limb girdle dystrophies proved to be clinically and genetically very heterogeneous. This general classification has stood the test of time and proved an extremely useful basis for clinical and genetic research. However, recent advances are now blurring the distinctions previously made between many types.

Duchenne-type muscular dystrophy (Meryon's disease)

Duchenne-type muscular dystrophy (also known as Meryon's disease) is the commonest form of dystrophy; it is inherited as an X linked recessive trait and therefore predominantly affects boys. It is a serious condition with progressive muscle wasting and weakness which causes most boys to start using wheel-

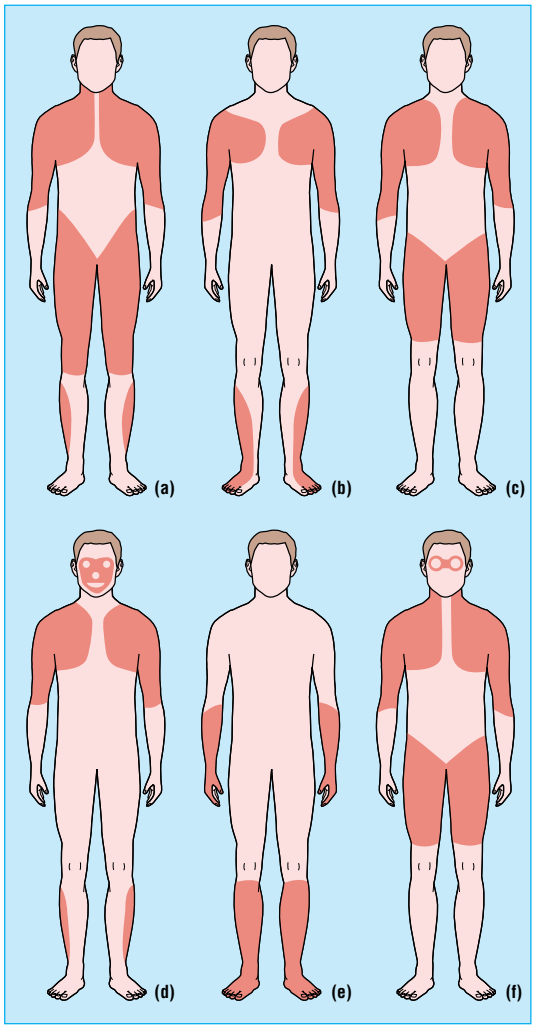

Fig 1 Distribution of predominant muscle weakness in different types of dystrophy: (a) Duchenne-type and Becker-type, (b) Emery-Dreifuss, (c) limb girdle, (d) facioscapulohumeral, (e) distal, and (f) oculopharyngeal

chairs by age 12 and to die in their 20s. Up to a third of boys with Duchenne-type dystrophy have some degree of intellectual impairment, and in severe cases special schooling may have to be considered. Becker-type muscular dystrophy is clinically similar but milder, with onset in the teenage years or early 20s. Loss of the ability to walk may occur later and many individuals with Becker-type dystrophy survive into middle age and beyond.

Much research over many years had failed to identify the basic biochemical defect in Duchenne-type dystrophy. However, in 1982 it was the first gene associated with a disease to be localised using chromosomally defined DNA markers.[4] Shortly thereafter the gene itself was isolated,[5 6] cloned, and sequenced. In 1987 its protein product was identified and termed dystrophin.[7]

The dystrophin gene remains the largest gene associated with a disease that has been identified (2.4 million base pairs). It takes more than 24 hours to be transcribed, and it consists of at least 85 exons with introns making up 98% of the gene.

Molecular diagnosis

Using labelled monoclonal antibodies to dystrophin, histochemical studies on muscle sections without muscular dystrophy indicate that dystrophin is localised at the periphery of muscle fibres. It is a cytoskeletal protein located beneath the sarcolemma. In Duchenne-type dystrophy the majority of fibres fail to show any staining; in the milder Becker-type dystrophy the intensity of staining is reduced and varies both between and within fibres, as it does also in the rare female carriers of Duchenne-type dystrophy who manifest symptoms of the disease (fig 2).

This immunohistochemical technique, first introduced for the diagnosis of Duchenne-type dystrophy in 1988,[8 9] is now widely used to help confirm the diagnosis of other dystrophies using labelled antibodies to specific muscle proteins that are absent in particular disorders. Alternatively, the deficiency of a particular protein can be biochemically shown by electrophoresis (western blotting). These techniques, as well as molecular genetic studies, provide the means of establishing a precise diagnosis and prognosis for many types of dystrophy in which the gene and its product have been identified.

Genetic counselling and prenatal diagnosis

Molecular genetic studies are essential for detecting female carriers of Duchenne-type dystrophy, Becker-type dystrophy, and for prenatal diagnostic testing.[10] It is often necessary to know the specific gene mutation occurring in a family, usually accomplished by having first studied an affected male in the family. However, a major problem in genetic counselling in Duchenne-type dystrophy is that some mothers have been identified who transmitted a mutation to more than one offspring which they themselves did not have in their somatic cells (in their peripheral blood leucocytes). This has been attributed to germline mosaicism.[11] In practice this means that prenatal testing might have to be considered in subsequent pregnancies if a mother has had an affected son, because it cannot be guaranteed that his dystrophy is the result of a new mutation and is therefore unlikely to recur. Preimplantation diagnosis could avoid the problem of selective abortion.[12]

Facioscapulohumeral muscular dystrophy

Over the past few years the essential clinical features of weakness of the facial, scapulohumeral, anterior tibial, and pelvic girdle muscles have been extended to include retinal vascular disease, sensory hearing loss (usually asymptomatic) and, in severe cases, even abnormalities of the central nervous system.[13] Many individuals are only mildly affected by these dystrophies though some may later become dependent on wheelchairs. This condition is always inherited as an autosomal dominant trait, and in 1990 the responsible gene was located on chromosome 4.[14] Restriction enzyme DNA fragments associated with the gene have been found to be greater than 35 kilobases in length in individuals who do not have muscular dystrophy; in affected individuals fragments are always less than this (as measured on an electrophoretic gel). This difference can be used to confirm the diagnosis in

suspected presymptomatic cases and for prenatal diagnosis. Furthermore, there is a general tendency for shorter fragments to be associated with earlier onset and more severe cases of the disease; in a sporadic case, for example, this can give an idea of the likely prognosis.

Limb girdle muscular dystrophy

As suspected by Walton,[2] limb girdle muscular dystrophy has turned out to be a clinically and genetically heterogeneous group of conditions. Less than 10% of cases are inherited as an autosomal dominant trait (type 1) and are relatively mild. One subtype (1B) may be allelic to autosomal Emery-Dreifuss dystrophy. All other cases are inherited as autosomal recessive traits (type 2) affecting both males and females; type 2 is often more severe and resembles Duchenne-type dystrophy. At least three dominant subtypes and eight recessive subtypes have been identified.

Apart from limb girdle muscular dystrophy 2A, which is caused by a muscle specific protease (calpain 3) deficiency, four other recessive subtypes have been found to be caused by deficiencies of particular sarcoglycans (dystrophin associated glycoproteins) which form part of the dystrophin associated protein complex of muscle membrane (fig 3). Each of these dystrophies can be diagnosed using a combination of protein studies and genetic studies.[15–17] The different types of limb girdle dystrophies can only be differentiated by laboratory studies carried out in specialised centres.

Distal myopathies

These rare forms of dystrophy are associated with wasting and weakness of the distal muscles, usually without the noticeable involvement of other muscle groups. For many years the only form that was recognised was that first described by Welander in Sweden.[18] However, four clinically and genetically different types are now recognised, although there may well be additional types that have not been identified.[19 20] Many individuals with distal myopathies are only mildly affected although some may ultimately develop serious problems in walking and everyday life.

Oculopharyngeal muscular dystrophy

This autosomal dominant disorder has been largely, but not exclusively, described as occurring in French Canadians descended from a couple who immigrated in 1634. This disorder was studied by Barbeau and is often referred to by patients as Barbeau's disease. It is characterised by onset in late adulthood of progressive ptosis and dysphagia which is followed by involvement of other cranial and limb muscles.[21] The gene associated with the disease is located on chromosome 14 not only among French Canadians but also in other populations; therefore it is likely to be genetically homogeneous but with different ancestral mutations in different populations. The gene has not yet been isolated but recent progress in isolating it is encouraging.[22] Like the milder dominant forms of limb girdle dystrophy and the distal myopathies, it is arguable whether prenatal testing is indicated for this disorder.

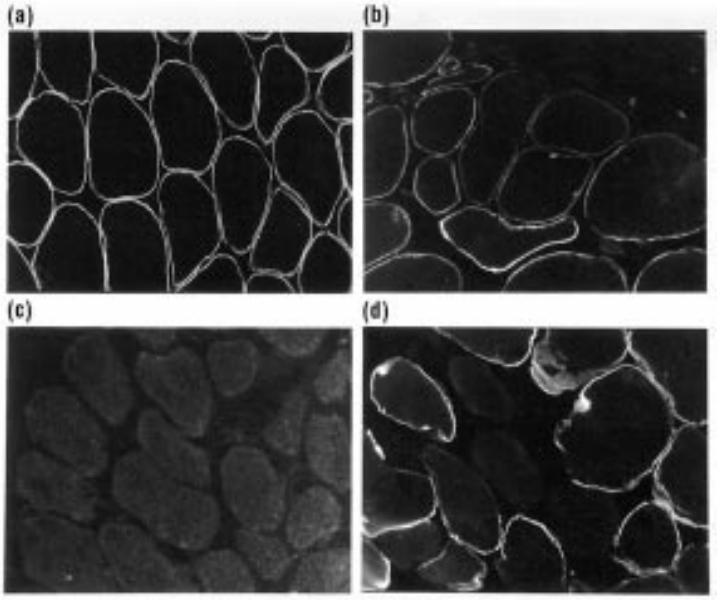

Fig 2 Cryostatic sections of muscle stained with fluorescent labelled monoclonal antibodies to dystrophin from (a) an individual without muscular dystrophy, (b) an individual with Becker-type dystrophy, (c) an individual with Duchenne-type dystrophy, and (d) a carrier of Duchenne-type dystrophy manifesting symptoms of the disease. (Reproduced with permission of Dr Louise Anderson)

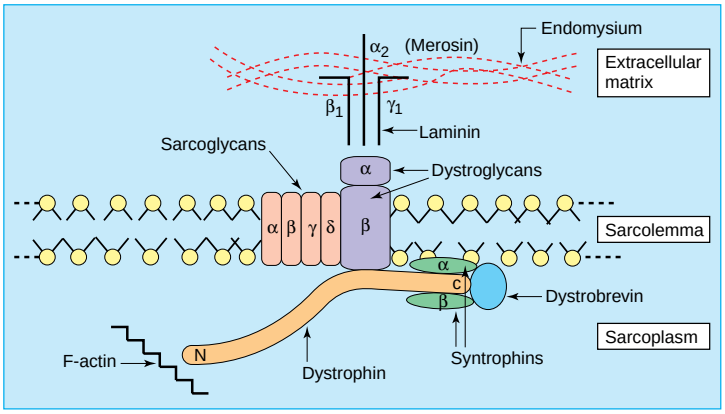

Fig 3 Muscle membrane proteins. Specific muscular dystrophies have been found to be caused by deficiencies of dystrophin, or a particular sarcoglycan, or merosin

Congenital muscular dystrophy

This relatively uncommon autosomal recessive form of dystrophy presents at birth or in early infancy with symptoms of hypotonia and generalised weakness which may be associated with joint contractures. Around 50% of cases are caused by a specific deficiency of the extracellular muscle protein known as laminin α 2 chain, or merosin (on chromosome 6).[23] Protein studies and genetic studies make it possible to establish a precise diagnosis in cases of congenital dystrophy and to offer prenatal testing and diagnosis either by direct staining of chorionic villi with labelled antibodies to merosin or by molecular genetic studies.[24 25] Some merosin positive cases are actually deficient in the protein receptor (integrin α 7). When compared with cases of congenital dystrophy that are merosin positive, cases of congenital dystrophy that are merosin negative are more uniform in their clinical features and tend to be more severe: there tends to be marked muscle weakness, few individuals with this

Muscular dystrophies

- At least 1 in 3000 people are affected by a serious inherited neuromuscular disorder; the muscular dystrophies make up an appreciable proportion of these
- Histological examination of muscle tissue and electromyography are used in the diagnosis of muscular dystrophy to exclude other causes of muscle wasting and weakness, such as spinal muscular atrophy, myopathies, and neuropathies
- On the basis of clinical and molecular genetic studies the following types of muscular dystrophy are recognised: X linked (Duchenne-type and at least two other subtypes), facioscapulohumeral, limb girdle (11 subtypes), distal (four subtypes), and oculopharyngeal
- A precise diagnosis is essential in order to provide a reliable prognosis and accurate genetic counselling

disorder are ever able to stand or walk without support, and they often have severe respiratory problems.[26]

Pathogenesis

The common clinical feature of these disorders is muscle weakness. Dystrophin and other associated proteins form a link between the extracellular matrix (endomysium) and intracellular F-actin (fig 3). It seems that the absence of any one of these proteins (and dystrobrevin might be the final common pathway[27]) would interfere with the integrity and the strength of the membrane and so result in muscle weakness. But at least in the case of dystrophin, the protein about which most is known, the evidence is still equivocal as to how its absence results in muscle weakness.[28] Furthermore, it is not clear how the deficiency of a muscle enzyme (such as the calpain 3 protease in limb girdle muscular dystrophy 2A) could result in muscle weakness similar to that which occurs in disorders that result from a defect in a structural protein.

X linked Emery-Dreifuss muscular dystrophy is also perplexing. This disorder is associated with early contractures of the Achilles tendons, elbows, and spine; humeroperoneal muscle weakness; and life threatening defects of cardiac conduction. The protein responsible for this dystrophy (emerin) is absent in the disease and is not part of the muscle cytoskeleton, despite progressive weakness being a feature of the disease. The protein is located on the inner surface of the nuclear membrane in skeletal and cardiac muscle. In cardiac muscle it is also associated with the intercalated discs which may partly explain the serious cardiac problems[29]; this raises important questions of the wider significance of this protein's role other than that which occurs in this relatively rare dystrophy.

Management

Molecular biological techniques make the prevention of most forms of dystrophy possible through genetic counselling and prenatal testing. But there have also been important advances in the management of the disease.[10 30]

Regardless of the type of dystrophy and stage of the disease certain general principles must be considered. A well balanced diet with adequate fibre to overcome problems of constipation is essential, especially when individuals become immobile. Excessive weight gain may also become a problem. Prolonged periods of bed rest should be discouraged because they can accelerate weakening of the muscles. Though everyday activity within the individual's limits should be encouraged, strenuous exercise should be avoided (although supervised swimming is excellent exercise). Passive exercises to prevent contractures that result from immobility can be carried out by parents, partners, or friends, but it is advisable to have a physiotherapist demonstrate the various procedures.

Lightweight polypropylene splints or orthoses, when used with appropriate surgical correction of contractures, can prolong ambulation. In the less severe forms of dystrophy such measures are particularly important in improving the individual's quality of life.

Of major importance in the treatment of almost all individuals with dystrophy is the preservation of respiratory function, which may be compromised by immobility and the chest deformity that results from scoliosis. All respiratory infections must be treated thoroughly, as soon as they occur, with postural drainage and antibiotics. The surgical correction of scoliosis makes sitting easier and more comfortable and also helps to preserve lung function. However, as the respiratory muscles become increasingly affected some form of assisted ventilation may have to be considered. In the late stages of the disease tracheostomy with artificial ventilation is an option. An increasing number of individuals with severe neuromuscular disorders are now being managed in this way.

Future treatment

Most of the research on treatment has concentrated on Duchenne-type muscular dystrophy because of its frequency and severity. Steroids may slow the progression of the disease for a time[31] but no drug has been found which appreciably affects the long term course of the disease.[10] When the pathogenic pathways in dystrophy are better understood it may be possible to design a drug that interrupts those pathways. Alternatively, the development of some form of gene therapy, in which a normal gene is inserted into cells in order to rectify the effects of a mutant gene, is proving technically challenging.[32]

Another approach might be to upregulate a protein that could compensate for the deficiency of dystrophin. Utrophin (on chromosome 6), which is normally localised at the neuromuscular junction, has a high degree of homology with dystrophin. When it is upregulated in genetically engineered mice with muscular dystrophy (mdx) and no dystrophin, the disease is ameliorated.[33] When utrophin and dystrophin are both deleted (in "double knockout" mice) the animals are much more seriously affected than mdx mice.[34] This is an encouraging approach to treatment because it avoids any potential immunological reaction since utrophin is normally ubiquitously expressed. The task is to find a safe compound which will upregulate utrophin in humans; this approach seems to offer the best prospect for finding an effective treatment.

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Observing patients

The chair sign

I have noticed in the past that if I do not remain visibly near my consulting room door when I call patients they go astray with regular monotony. I have even observed one patient stand up, turn 180 degrees, and head out of the building. By way of welcoming in new patients I ask them "to come and take a seat."

I was therefore a little taken aback a year ago when one patient proceeded quite casually to sit in my seat (a rather comfortable swivel chair) and explain what he had come to see me for. The patient had a flat affect and a history of psychosis so I conducted the rest of the consultation from the more miserable and tatty chair I usually reserve for patients.

Six weeks later a well dressed, polite patient said, "Good afternoon doctor," walked straight to my chair, and sat down in it comfortably. I wondered if this was a joke. I made a lighthearted reference to the large computer needed for printing prescriptions, the desk, prescription pad, and records. He just smiled. I asked him if he would prefer to sit in the other (tatty) chair. He looked disappointed. I lost my temper and demanded my chair back. He acquiesced. He had come in for a repeat prescription of antipsychotics and sleeping tablets.

Sitting in the doctor's chair by mistake can be a bit embarrassing for patients if it is not handled sensitively. I decided to conduct an observational study on new patients who used my swivel chair. Patients who first asked me where they should sit were excluded, along with those 3 year olds who were not big enough to climb up. Over the next nine months, eight new patients came in and sat in my chair. Seven had a diagnosis of schizophrenia or chronic psychosis and were receiving antipsychotic medication. The remaining patient consulted for a minor postoperative complication but had no psychiatric history. (One 5 year old also met the admission criteria but he needed the chair to check if the computer had the Lion King game on it.) I found the result of the postoperative patient a little disappointing and at this stage I resolved to discontinue the study. This week, however, a young man walked in, impeccably dressed and looking very well. He sat straight down in my chair and looked at me. "How can I help?" I asked from the tatty chair with a feeling of resignation. "I'd like some more olanzapine," he replied.

I admit that I am sometimes too hassled to read thick sets of notes before calling in new patients. Patients new to the practice will initially not have any records (until they arrive from the health authority). Either way, I was blinded to the diagnoses and drug histories before these patients sat down. Eleven patients have used my chair in the past year and 10 of these (91%) were taking antipsychotic medication. They were all men. The chair sign may be associated with psychiatric illness. It needs to be formally validated. We could study all new patients at the practice and in different consulting rooms. If all the partners were involved and were properly blinded to all patients' diagnoses and drug histories our practice manager could be overwhelmed with complaints. I worry about the long term implication of my findings. After all, I often walk into consulting rooms and sit in the comfortable looking chair.

Fiona Mackay, *part time general practitioner, Southampton*