Muscular Dystrophies

Sathasivam S

The Walton Centre NHS Foundation Trust, Lower Lane, Liverpool L9 7LJ, United Kingdom

ABSTRACT
Huge strides have been made in the last two decades in our understanding of muscular dystrophies. This has led to better classification of this group of heterogeneous neuromuscular disorders based on clinical features, investigation results, and molecular and genetic pathophysiology. This review aims to discuss the major forms of muscular dystrophies, the useful investigations to diagnose them and the management strategies available at present.

REVIEW ARTICLE

INTRODUCTION

Muscular dystrophies are an inherited group of disorders characterised by variable distribution of muscle wasting and weakness, age of onset, pattern of inheritance, rate of progression and clinical severity. Over the last two decades, enormous strides have been made in our understanding of the cellular, molecular and genetic pathophysiology of this heterogeneous group of disorders, thus expanding the phenotype spectrum and allowing better diagnostic and therapeutic capabilities. This article is not intended to be an exhaustive review of the muscular dystrophies but rather an overview of the more common and important forms to allow non-specialists
to recognise them and appreciate the potential benefits of referring these cases to specialist centres. Apart from highlighting the major clinical features of the different forms of muscular dystrophies, this article will briefly discuss (where available) the genetic and pathophysiological aspects, diagnostic tests and management strategies for these conditions.

Major forms of muscular dystrophies

Congenital muscular dystrophies (CMDs)
These are a clinically, biochemically and genetically heterogeneous group of disorders with a preferentially autosomal recessive inheritance. Typically, CMDs present at birth or within the first few months of life with hypotonia or muscle weakness. One possible way of classifying CMDs is on its pathophysiological basis (Table 1).[1] In some CMDs, the molecular defects are yet to be defined, making the diagnosis difficult to ascertain.

Different populations can have different prevalences of CMDs. For example, merosin-deficient CMD is common in the Caucasian population, accounting for around 30-40% of CMD cases,[2] but is less common in the Asian population.[3] On the other hand, Fukuyama CMD is the second most common cause of muscular dystrophy in Japan, but is rare in other countries. Prognosis depends on the type of CMD, for example, the Walker-Warburg syndrome is associated with a life expectancy of less than 3 years while Bethlem myopathy can be a relatively mild disease.

Duchenne and Becker muscular dystrophies
The X-linked Duchenne muscular dystrophy (DMD) is the most severe dystrophinopathy with an incidence of about 1 in 3500 male births. It presents with abnormal gait, difficulty in rising from the floor (Gowers' sign) and hypertrophy of calf muscles by the age of 3¬ – 5 years, leading to a loss of independent ambulation by the age of 13 years. If a boy is still walking independently at age 16 years, the clinical phenotype is Becker muscular dystrophy (BMD), which is a milder allelic form of DMD with an incidence of about 1 in 19 000 males. Some degree of brain dysfunction is common in DMD/BMD. Respiratory muscle weakness, cardiomyopathy and orthopaedic complications (osteopaenia, osteoporosis, contractures and scoliosis) emerge without treatment, and death occurs at around the age of 19 years in DMD. Progression is slower in BMD with patients having a mean age of 30 years.[4]

Mutations (mainly deletions) in the dystrophin gene lead to an absence of the protein dystrophin in DMD, and a reduction in, or internally truncated, dystrophin in BMD, which results in muscle degeneration. Around 10% of female carriers of DMD/BMD show some disease manifestations such as muscle weakness, enlarged calves, cognitive impairment and cardiac dysfunction.[5] The latter may occur even in the absence of other manifestations, thus the importance of cardiac surveillance in these patients.[6]

Emery-Dreifuss muscular dystrophy (EDMD)
EDMD is an autosomal dominant, or less commonly an X-linked recessive, disorder with a variable age of onset and disease progression. Contractures usually develop in the second decade of life, affecting the elbows, ankles, posterior cervical muscles (limiting

Corresponding author:
Sivakumar Sathasivam
The Walton Centre NHS Foundation Trust,
Lower Lane
Liverpool L9 7LJ, United Kingdom
Telephone:+44 1515298267
Fax:+44 1515295513
Email: s_sathasivam@hotmail.com

neck flexion), and eventually restricting forward flexion of the whole spine. Progressive muscle wasting and weakness typically affect the peroneal (distal lower limb muscles) and humeral (proximal upper limb muscles). Cardiomyopathy, especially cardiac conduction defects, are very common and may be evident before muscle weakness develops.[7] Evidence of cardiac disease is usually present by the age of 30 years.[8] The major risk with EDMD is sudden death, which pacemaker implantation does not always prevent.[9]

Autosomal dominant EDMD is caused by mutations in the LMNA gene, while X-linked EDMD is caused by mutations in the emerin gene. More recently, mutations in the nuclear membrane-associated proteins (the nesprins) are thought to be associated with EDMD-like phenotypes.[10]

Limb girdle muscular dystrophies (LGMD)

LGMDs are characterised by wide clinical and genetic heterogeneity. They are classically grouped into autosomal dominant LGMD (LGMD1) and autosomal recessive LGMD (LGMD2), and further divided into subtypes, each of which is known by a designated suffix allocated in chronological order of gene discovery. The age of onset of symptoms in LGMD ranges from early childhood to adulthood, but the onset is not typically congenital. The combination of clinical features and the result of investigations such as serum creatine kinase (CK), muscle biopsy (discussed below) and genetic testing are needed to diagnose the different disorders (Table 2).[11,12]

Table 1. Pathophysiological classification of congenital muscular dystrophies (common examples of each category are given)

Pathophysiology	Disorder/inheritance	Affected protein(s)	Clinical features
Defects of glycosylation	Walker-Warburg syndrome/ autosomal recessive	Protein-O-mannosyltransferase 1 & 2, fukutin, fukutin-related protein, LARGE	Muscular dystrophy, type II lissencephaly/agyria, hydrocephalus, eye abnormalities, life expectancy <3 years
	Muscle-eye-brain disease/ autosomal recessive	O-linked mannose β1,2-N- acetylglucosaminyltransferase	Muscular dystrophy, significant hypotonia, eye abnormalities, abnormal neuronal migration
	Fukuyama CMD/autosomal recessive	Fukutin	Muscular dystrophy, severe brain involvement with mental retardation, cardiomyopathy, epilepsy, eye abnormalities
Defects of extracellular matrix proteins	Merosin-deficient CMD/ autosomal recessive	Laminin α2	Muscular dystrophy, respiratory insufficiency and nocturnal hypoventilation, neuronal migration abnormalities, epilepsy, peripheral neuropathy
	Ullrich syndrome/ autosomal recessive	Collagen VI	Neonatal muscle weakness, kyphosis of spine, joint contractures, torticollis, hip dislocation, hyperextensibility of distal joints, follicular hyperkeratosis, keloid formation, restrictive respiratory insufficiency, normal intelligence
	Bethlem myopathy/ autosomal dominant	Collagen VI	Milder phenotype of Ullrich syndrome
Defects of nuclear envelope proteins	LMNA-deficient CMD/ autosomal recessive	Lamin A/C	Muscular dystrophy, scoliosis, contractures, restrictive respiratory insufficiency
Defects of endoplasmic reticulum proteins	Rigid spine syndrome/ autosomal recessive	Selenoprotein N 1	Muscular dystrophy, axial hypotonia and weakness, lumbar scoliosis, cervical spine stiffness, restrictive respiratory insufficiency

Table 2. Common forms of limb girdle muscular dystrophies

LGMD type	Predominant clinical features	CK level	Affected protein
LGMD1A	Presents from age 20 years onwards, proximal or distal limb weakness, dysarthria, cardiac and respiratory complications commoner in non-myotilin myofibrillar myopathies	Normal to <5x upper limit of normal	Myotilin
LGMD1B	Presents before age 20 years, neonatal hypotonia, proximal or distal limb weakness, spinal rigidity, contractures, cardiac and respiratory complications	Normal to <5x upper limit of normal	Lamin A/C
LGMD1C	Presents at any age, proximal or distal limb weakness, rippling muscle disease, percussion-induced repetitive muscle contractions	5x to >10x upper limit of normal	Caveolin-3
LGMD2A	Presents before age 40 years, proximal limb weakness, scapular winging, early contractures, focal muscle atrophy	5x to >10x upper limit of normal	Calpain-3
LGMD2B	Presents at age 10 – 40 years, proximal or distal limb weakness, difficulty standing on tiptoe, may be associated with normal sporting ability before abrupt onset of difficulty	>10x upper limit of normal	Dysferlin
LGMD2C-F	Presents before age 20 years, proximal limb weakness, scapular winging, hypertrophy of calves and other muscles, macroglossia, scoliosis, cardiac and respiratory complications	5x to >10x upper limit of normal	Sarcoglycan
LGMD2I	Presents at any age, proximal limb weakness, hypertrophy of calves and other muscles, macroglossia, cardiac and respiratory complications	5x to >10x upper limit of normal	Fukutin-related protein

LGMD2A is the commonest form of LGMD in most populations, but specific mutations may show a high frequency in certain populations. It is useful to correctly diagnose them (if possible) because some of these are more commonly associated with cardiac or respiratory complications and thus benefit from appropriate cardiorespiratory surveillance.[12]

Distal muscular dystrophies

Distal muscular dystrophies (also sometimes known as distal myopathies) are an expanding group of disorders, which share the clinical pattern of weakness predominantly affecting the feet and/or hands.[13] Factors that help current classification of this group of disorders include the age at onset, pattern of muscle involvement, CK level, muscle biopsy (discussed below) and mode of inheritance (Table 3).

The genes responsible for distal muscular dystrophies preferentially involve sarcomeric proteins, in contrast to sarcolemmal protein defects which are more commonly associated with proximal muscular dystrophies – the reason for this is unknown.[14] Some distal muscular dystrophies have only been described in certain populations, but this may change as genetic analysis becomes increasing available worldwide.

Facioscapulohumeral muscular dystrophy (FSHD)

This autosomal dominant condition, up to 30% of cases are sporadic and therefore, may not have a family history,[15] can be subclinical with patients not realising they have the condition for years or even, for life. Weakness is often asymmetrical. It usually starts with asymptomatic facial weakness, sequentially followed by scapular fixator, humeral, truncal and lower extremity weakness. Bulbar and extraocular muscles are spared. High-frequency hearing loss and asymptomatic retinal telangiectasias are common. Cardiac and respiratory involvements are unusual.[16]

Table 3 Distal muscular dystrophies (common examples of each category are given)

Types	Age of onset (years)	Early symptoms	CK level	Affected protein
Early onset autosomal dominant forms				
Laing distal myopathy	1 – 25	Anterior lower leg, neck flexors	1 – 8x	Beta myosin heavy chain
Adult onset autosomal dominant forms				
Desminopathy	Variable	Anterior lower leg, scapular, cardiomyopathy	Variable	Desmin
Late adult onset autosomal dominant forms				
Welander distal myopathy	>40	Finger and wrist extensors, hands	1 – 4x	Not known
Tibial muscular dystrophy	>35	Anterior lower leg	1 – 4x	Titin
Distal myotilinopathy	50 – 60	Posterior lower leg	1 – 2x	Myotilin
ZASPopathy	>40	Anterior lower leg	1 – 3x	Z-disk alternatively spliced PDZ-domain containing protein (ZASP)
Early onset autosomal recessive forms				
Distal nebulin myopathy	1 – 20	Anterior lower leg	1 – 3x	Nebulin
Early adult onset autosomal recessive forms				
Miyoshi myopathy	15 – 30	Posterior lower leg, calf	10 – 100x	Dysferlin
Distal myopathy with rimmed vacuoles	15 – 30	Anterior lower leg	1 -5x	UDP-N- acetylglucosamine 2 epimerase/N-acetyl mannosamine kinase (GNE)

FSHD patients have a deletion of a repetitive element of chromosome 4q35 known as D4Z4, with an inverse relationship between the residual repeat number and disease severity.[17] Nevertheless, the molecular mechanism of the pathological effects of this deletion remains largely unknown.

Oculopharyngeal muscular dystrophy (OPMD)
OPMD usually manifests in the fifth or sixth decade with eyelid ptosis and dysphagia. The progression of ptosis may lead to patients trying to compensate their limitation of the visual field by contracting the frontalis muscle and reclining the head. Extraocular muscles may gradually become involved, but complete external ophthalmoplegia is rare. The dysphagia is typically noticed for solid foods before liquids. Tongue weakness and atrophy, and dysarthrophonia can be observed. OPMD is a myopathy that affects voluntary muscles, but spares smooth and cardiac muscles.[18]

Autosomal and recessive forms of OPMD have been described and found to be allelic. OPMD is caused by expansions of the short (GCN) trinucleotide repeat in the coding sequence of the poly (A) binding protein nuclear 1 (PABPN1) gene. Gene dosage influences the onset of age and severity of OPMD.[19]

Myotonic dystrophies (DMs)
There are two clinically and molecularly defined types of DMs, known as DM1 and DM2, which are both autosomal dominant disorders. Common clinical features of DM1 are weakness and wasting muscles in the distal limbs, face (facial and temporalis muscles) and neck (sternocleidomastoid muscle), ptosis, frontal balding, precussion myotonia, cataracts, cardiac conduction defects, intellectual impairment, testicular atrophy in men, and insulin insensitivity.

Congenital DM1, which occurs almost exclusively when the mother is the transmitting parent, is associated, with decreased fetal movements and polyhydramnios, and after delivery, with severe generalised weakness, hypotonia and respiratory compromise. In contrast, DM1, DM2 has a milder phenotype, is less common, and has a later onset of symptoms (usually in the third decade). It is more slowly progressive, associated with predominant weakness and wasting of proximal muscles, and muscle pain, and less associated with facial and bulbar muscle involvement.[20,21]

The mutation of DM1 is an expansion of the unstable CTG trinucleotide repeat in the 3' untranslated region (UTR) of the myotonic dystrophy protein kinase (DMPK) gene, which codes for a myosin kinase expressed in skeletal muscle. Longer CTG repeat expansion size tends to correlate with an earlier onset age and more severe disease. DM2 is caused by an expansion of an intronic CCTG tetranucleotide repeat in the zinc finger 9 (ZNF9) gene. The size of the repeated DNA expansion in DM2 does not correlate with onset age or disease severity. Anticipation occurs more evidently in DM1 than DM2.[20]

Investigations

Several investigations are useful for diagnosing and differentiating between the different forms and subtypes of muscular dystrophies.

The CK concentration is the most sensitive and specific marker for muscle damage. In most muscular dystrophies, the CK level is raised, but it can be normal or only minimally raised in indolent disorders such as OPMD. The level of CK may also be helpful in distinguishing between the different forms and subtypes of muscular dystrophies (Table 2, Table 3).

In the presence of a family history, electrodiagnostic testing is of limited value. Electromyography may be useful in sporadic cases or to exclude neurogenic cases of weakness such as spinal muscular atrophy. However, electromyography may be less suitable for children because of the invasive nature of the investigation.

Ultrasound and computed tomography have been widely used in the past to evaluate patients with suspected muscle disorders. However, magnetic resonance imaging is being increasingly used to characterise the severity and pattern of muscle involvement which can help in narrowing the differential diagnoses of the muscular dystrophies. Diagnostic algorithms are being developed to guide physicians through the diagnostic process.[22]

Muscle biopsies play an important role in the diagnostic process of muscular dystrophies and are best done in specialised centres. Study of muscle histology, in conjunction with immunohistochemistry and immunoblotting analyses of the proteins involved in the various forms and subtypes of muscular dystrophies, permit a more refined diagnostic approach, and guide physicians towards appropriate genetic testing in conditions where the latter are available.[23] Detailed descriptions of muscle biopsy findings in muscular dystrophies are beyond the scope of this article.

Molecular genetic testing is the gold standard of diagnosis and may obviate the need for invasive investigations such as electromyography or muscle biopsy. Large, untargeted genetic testing panels are inappropriate. The gender, inheritance pattern, pattern of muscle involvement, muscle biopsy results (where appropriate), and occasionally ethnicity of patients, guides physician towards the appropriate genetic test(s). Genetic testing may be needed to detect carriers in families of affected patients and to offer appropriate genetic counselling. Genetic testing is available for many, but not all, muscular dystrophies –this is best discussed with the local genetics service. Molecular prenatal diagnosis, where available, is very useful in helping families of affected patients, to make informed decisions with regard to unborn children.[24]

Management

Medical treatment of muscular dystrophies is limited. Corticosteroids have been shown to improve muscle strength and function in the short-term (six months to two years) in randomized controlled trials in DMD.[25] There is no evidence that corticosteroids are beneficial in other forms of muscular dystrophies.

Supportive and symptomatic management is very important in muscular dystrophies. A multidisciplinary approach is the best management strategy for the vast majority of patients with muscular dystrophies. Physiotherapy is the key for many of these patients to prevent contractures and promote mobility. Occupational therapists, psychologists, speech therapists and dietitians provide invaluable input towards improving the physical and mental health, and quality of life, of these patients. Genetic counselling is an important service that should be available for affected and potentially affected families.

Neurologists and geneticists are important in helping to diagnose these conditions. Cardiologists and respiratory physicians are crucial in monitoring and managing the cardiac and respiratory complications that arise in certain forms and subtypes of muscular dystrophies. Orthopaedic management for complications such as scoliosis is important. Surgical treatments may be useful in specific situations, for example, to correct eyelid ptosis in OPMD.

There is intense research going on into the effectiveness of genetic and cell-mediated approaches in muscular dystrophies, in particular for DMD. It is hoped that some of these emerging therapies will prove to be beneficial for patients with muscular dystrophies.[26,27]

CONCLUSION

Improved understanding and better classification of muscular dystrophies will enable earlier and more accurate recognition of these disorders. This will allow physicians to give patients a better idea of prognosis and to offer useful interventions, such as cardiorespiratory surveillance, for at risk groups.

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