Muscular dystrophies

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Muscular dystrophies are a heterogeneous group of inherited disorders that share similar clinical features and dystrophic changes on muscle biopsy. An improved understanding of their molecular bases has led to more accurate definitions of the clinical features associated with known subtypes. Knowledge of disease-specific complications, implementation of anticipatory care, and medical advances have changed the standard of care, with an overall improvement in the clinical course, survival, and quality of life of affected people. A better understanding of the mechanisms underlying the molecular pathogenesis of several disorders and the availability of preclinical models are leading to several new experimental approaches, some of which are already in clinical trials. In this Seminar, we provide a comprehensive review that integrates clinical manifestations, molecular pathogenesis, diagnostic strategy, and therapeutic developments.

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Introduction

Muscular dystrophies are a clinically, genetically, and biochemically heterogeneous group of disorders that share clinical and dystrophic pathological features on muscle biopsy.[1] They are characterised by progressive muscle weakness that affects limb, axial, and facial muscles to a variable degree. In specific forms, other muscles, including respiratory muscles, cardiac smooth muscles, and swallowing muscles, can also be affected. In rare variants, the disorder is associated with involvement of other organs or tissues, such as the brain, inner ear, eyes, or skin. The severity, age of onset, rate of progression, and consequent complications and prognosis vary greatly in the different forms of the disorder.

In the past two decades, a better understanding of the mechanisms underlying muscular dystrophies, improvements in standards of care, and new treatment approaches have changed both the natural history and long-term perspectives of these disorders. The identification of the genetic basis of the most common forms of muscular dystrophy has also resulted in an unexpected expansion of the clinical range of variants, including allelic disorders that share no features with the first muscular dystrophy described.[2,3] The availability of clinical guidelines based on expert consensus[4–8] has led to harmonisation of standards of care, with implementation of anticipatory care done on the basis of knowledge about individual disorder complications. This development allows improved prevention and management of complications, often followed by improved clinical course and better survival.[9–14] Finally, knowledge about the molecular basis of these disorders has led to the development of new treatment approaches, several of which are already in clinical trials. This progress is triggering unprecedented international cooperation between clinicians, scientists, industry, and advocacy groups to attempt to further improve international standards of care, outcome measures, and other aspects related to clinical trial readiness.[15]

In this Seminar, we discuss the most recent advances in this area, with a focus on clinical aspects that can help with the differential diagnosis and clinical management of muscular dystrophies, and we draw attention to topics that remain controversial. We also provide a framework to help to improve the understanding of the mechanisms and the possible treatment approaches for these disorders.

Classification

Historically, muscular dystrophies have been classified according to the main clinical findings and age of onset (eg, limb girdle muscular dystrophies, Emery-Dreifuss muscular dystrophy, and congenital muscular dystrophies). Heterogeneous groups such as limb girdle muscular dystrophies or congenital muscular dystrophies were subclassified further according to their inheritance and the genetic defect responsible for the individual forms (eg, *LGMD1A*, *LGMD1B*, *LGMD2A*, and *LGMD2B*), in which the number 1 indicated dominant inheritance and the number 2 recessively inherited disorders. A, B, and C were labelled consecutively according to when the individual genes were identified.

The improved understanding of the mechanisms underlying these forms provided new clues about their classification that cannot be based only on the previous assumption that every clinical phenotype is related to a distinct genetic defect.[2,3,16] Individual phenotypes are often associated with mutations in different proteins that share similar cellular functions. For example, in the variants associated with structural CNS involvement, such as muscle-eye-brain disease and Walker-Warburg syndrome, which were initially thought to be related only to mutations in genes with glycosyltransferase

Search strategy and selection criteria

To identify data for this Seminar, we searched Medline, Current Contents, and PubMed with the search terms "muscular dystrophy", " Duchenne", "congenital", "limb girdle", "therapy", and "care". We included abstracts and reports from meetings only when they related directly to previously published work. We included only articles published in English between 1980 and 2012. We identified ongoing trials from the ClinicalTrials.gov and clinicaltrialsregister.eu websites.

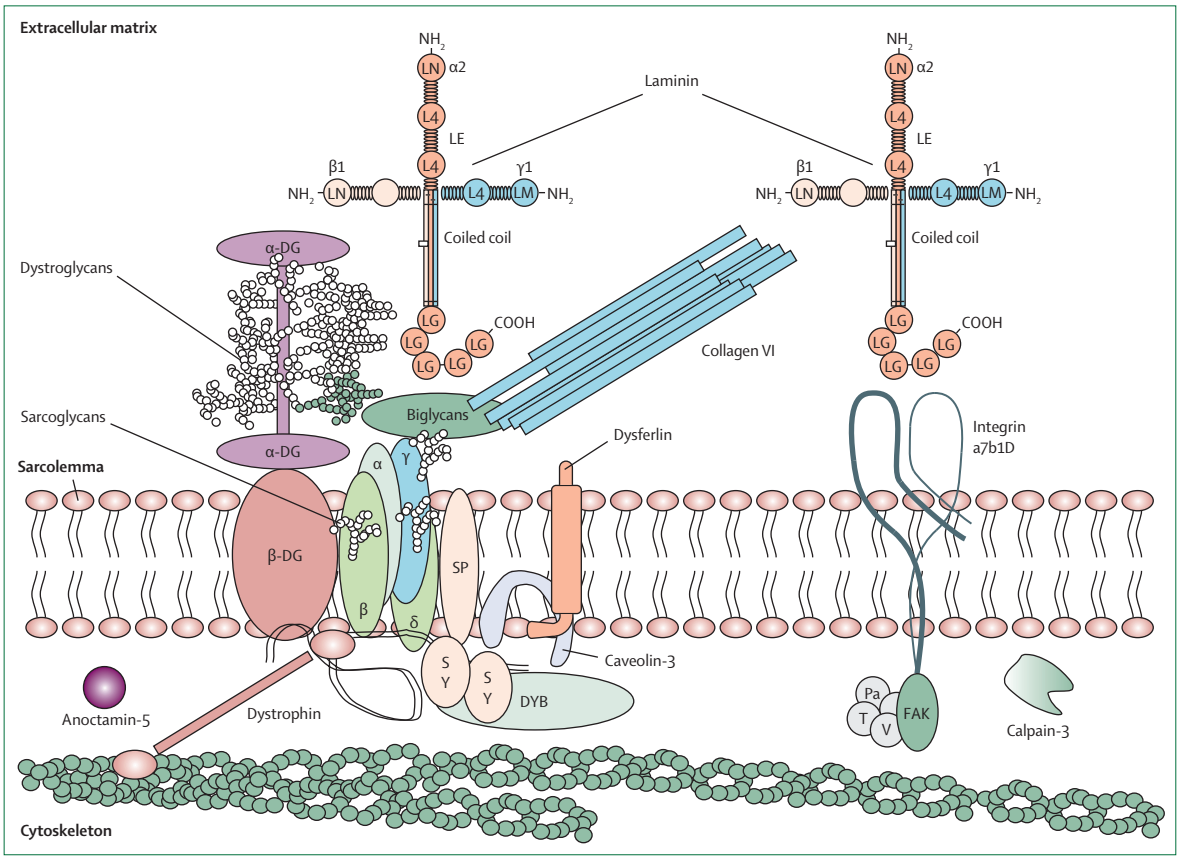

Figure 1: **Sarcolemma and proteins involved in muscular dystrophies**
DG=dystroglycan. SP=sarcospan. SY=syntrophin. DYB=dystrobrevin. Pa=paxillin. T=talin. V=vinculin. FAK=focal adhesion kinase. Not all proteins mentioned in this figure are primarily affected by muscular dystrophies.

activity (*POMT1* for Walker-Warburg syndrome and *POMGnT1* for muscle-eye-brain disease), many other genes involved in convergent glycosylation steps have since been shown to result in the same phenotypes.[17–21] Conversely, allelic disorders can give rise to divergent diseases. Mutations in the *LMNA* gene, which causes Emery-Dreifuss muscular dystrophy, have since been described in several other phenotypes with no muscle involvement.[22–25] Supplementation of the old classification, which was based on the main clinical findings, with information about the primary protein defects and their localisation or function (figure 1) is useful (table 1).

Epidemiology

Duchenne muscular dystrophy is the most common inherited muscle disease of childhood, with an estimated point prevalence in northern England of 8·29 per 100 000 boys; a milder allelic variant, Becker muscular dystrophy, has a slightly lower prevalence of 7·29 per 100 000 boys. Myotonic dystrophy is the most common form in adults, with an estimated prevalence of 10·6 per 100 000 men, followed by facioscapulohumeral muscular dystrophy, with an estimated prevalence of three per 100 000 men.[8,26] Of the limb girdle muscular dystrophies, the recessive forms are more common than the dominant variants. Limb girdle muscular dystrophy 2A seems to be more prevalent in southern Europe, whereas limb girdle muscular dystrophy 2I is common in northern Europe, followed by limb girdle muscular dystrophy 2B.[27–31]

Similarly, the frequencies of the different forms of congenital muscular dystrophy vary by region. Fukuyama congenital muscular dystrophy is the most common form of congenital muscular dystrophy in Japan and is caused by a founder recessive mutation, whereas Ullrich congenital muscular dystrophy is the most frequent type in most other countries for which data are available. Laminin α2-deficient congenital muscular dystrophy, originally reported to be one of the most common subtypes,[32–34] accounts for between about a fifth and a quarter of all cases of the disorder.[34,35]

Clinical manifestations

The onset of clinical signs varies, ranging from birth or childhood to adulthood (table 2). Generally, congenital muscular dystrophies have obvious clinical signs at birth or in the first few months of life. Many other forms, such as Duchenne muscular dystrophy or some of the limb

	Inheritance	OMIM number	Locus	Gene symbol	Protein	Main localisation
Duchenne or Becker muscular dystrophy	X-R	310200 (Duchenne); 300376 (Becker)	Xq21·2	*DMD*	Dystrophin	Sarcolemma-associated protein
Limb girdle muscular dystrophy						
Type 1A	AD	159000	5q31	*MYOT*	Myotilin	Sarcomere-associated protein (Z disc)
Type 1B	AD	159001	1q21·2	*LMNA*	Lamin A/C	Nuclear lamina-associated protein
Type 1C	AD	607780	3p25	*CAV3*	Caveolin-3	Sarcolemma-associated protein
Type 1D	AD	603511	7q	*DNAJB6*	Co-chaperone DNAJB6	Sarcomere-associated protein (Z disc)
Type 1E	AD	602067	6q23	*DES*	Desmin	Intermediate filament protein
Type 1F	AD	608423	7q32	Unknown	Unknown	Unknown
Type 1G	AD	609115	4p21	Unknown	Unknown	Unknown
Type 1H	AD	613530	3p23–p25	Unknown	Unknown	Unknown
Type 2A	AR	253600	15q15·1	*CAPN3*	Calpain-3	Myofibril-associated proteins
Type 2B	AR	253601	2p13	*DYSF*	Dysferlin	Sarcolemma-associated protein
Type 2C	AR	253700	13q12	*SGCG*	γ-sarcoglycan	Sarcolemma-associated protein
Type 2D	AR	608099	17q12–q21·33	*SGCA*	α-sarcoglycan	Sarcolemma-associated protein
Type 2E	AR	604286	4q12	*SGCB*	β-sarcoglycan	Sarcolemma-associated protein
Type 2F	AR	601287	5q33	*SGCD*	δ-sarcoglycan	Sarcolemma-associated protein
Type 2G	AR	601954	17q12	*TCAP*	Titin cap (telethonin)	Sarcomere-associated protein (Z disc)
Type 2H	AR	254110	9q31–q34	*TRIM32*	Tripartite motif-containing 32 (ubiquitin ligase)	Sarcomeric-associated protein (Z disc)
Type 2I	AR	607155	19q13·3	*FKRP*	Fukutin-related protein	Putative glycosyltransferase enzymes
Type 2J	AR	608807	2q31	*TTN*	Titin	Sarcomeric protein
Type 2K	AR	609308	9q34	*POMT1*	Protein-1-O-mannosyl-transferase 1	Glycosyltransferase enzymes
Type 2L	AR	611307	11p14·3	*ANO5*	Anoctamin 5	Transmembrane protein, possible sarcoplasmic reticulum
Type 2M	AR	611588	9q31	*FKTN*	Fukutin	Putative glycosyltransferase enzymes
Type 2N	AR	613158	14q24	*POMT2*	Protein-O-mannosyl-transferase 2	Glycosyltransferase enzymes
Type 2O	AR	613157	1p34	*POMGNT1*	Protein-O-linked mannose β 1,2-N-aminyltransferase 1	Glycosyltransferase enzymes
Type 2P	AR	613818	3p21	*DAG1*	Dystrophin-associated glycoprotein 1	Sarcomeric-associated protein
Type 2Q	AR	613723	8q24	*PLEC1*	Plectin 1	Sarcolemma-associated protein (Z disc)
Facioscapulohumeral muscular dystrophy						
Type 1	AD	158900	4q35	Unknown	DUX4 and chromatin rearrangement	Nuclear
Type 2	AD	158901	18	Unknown	SMCHD1	Structural maintenance of chromosomes flexible hinge domain containing 1
Emery-Dreifuss muscular dystrophy						
X-linked type 1	X-R	310300	Xq28	*EMD*	Emerin	Nuclear membrane protein
X-linked type 2	X-R	300696	Xq27·2	*FHL1*	Four and a half LIM domain 1	Sarcomere and sarcolemma
Autosomal dominant	AD	2181350	1q21·2	*LMNA*	Lamin A/C	Nuclear membrane protein
Autosomal recessive	AR	604929	1q21·2	*LMNA*	Lamin A/C	Nuclear membrane protein
With nesprin-1 defect	AD	612998	6q25	*SYNE1*	Spectrin repeat containing, nuclear envelope 1 (nesprin-1)	Nuclear membrane protein
With nesprin-2 defect	AD	5612999	4q23	*SYNE2*	Spectrin repeat containing, nuclear envelope 2 (nesprin-2)	Nuclear membrane protein
Congenital muscular dystrophy with merosin deficiency (MDC1A)	AR	607855	6q2	*LAMA2*	Laminin α2 chain of merosin	Extracellular matrix proteins
Congenital muscular dystrophy	AR	604801	1q42	Unknown	Unknown	Unknown
Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (MDC1C)	AR	606612	19q13	*FKRP*	Fukutin-related protein	Putative glycosyltransferase enzymes
Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (MDC1D)	AR	608840	22q12	*LARGE*	Like-glycosyl transferase	Putative glycosyltransferase enzymes
Fukuyama congenital muscular dystrophy	AR	253800	9q31–q33	*FCMD*	Fukutin	Putative glycosyltransferase enzymes

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	Inheritance	OMIM number	Locus	Gene symbol	Protein	Main localisation
(Continued from previous page)						
Walker–Warburg syndrome						
With fukutin defect	AR	236670	9q31–q33	*FCMD*	Fukutin	Putative glycosyltransferase enzymes
With protein-O-mannosyl-transferase 1 defect	AR	236670	9q34	*POMT1*	Protein-1-O-mannosyl-transferase 1	Glycosyltransferase enzymes
With protein-O-mannosyl-transferase 2 defect	AR	236670	14q24	*POMT2*	Protein-O-mannosyl-transferase 2	Glycosyltransferase enzymes
With protein-O-linked mannose β 1,2-N-aminyltransferase 1 defect	AR	236670	1p34	*POMGNT1*	Protein-O-linked mannose β 1,2-N-aminyltransferase 1	Glycosyltransferase enzymes
With fukutin-related protein defect	AR	236670	19q13	*FKRP*	Fukutin-related protein	Putative glycosyltransferase enzymes
Muscle-eye-brain disease						
With protein-O-linked mannose β 1,2-N-aminyltransferase 1 defect	AR	253280	1p34	*POMGNT1*	Protein-O-linked mannose β 1,2-N-aminyltransferase 1	Glycosyltransferase enzymes
With fukutin-related protein defect	AR	253280	19q13	*FKRP*	Fukutin-related protein	Putative glycosyltransferase enzymes
With protein-O-mannosyl-transferase 2 defect	AR	253280	14q24	*POMT2*	Protein-O-mannosyl-transferase 2	Glycosyltransferase enzymes
Congenital muscular dystrophy due to glycosylation disorder	AR	NA	9q34·1	*DPM2*	Dolichyl-phosphate mannosyltransferase polypeptide 2	Glycosyltransferase enzymes
Congenital muscular dystrophy due to glycosylation disorder	AR	NA	1q21·3	*DPM3*	Dolichyl-phosphate mannosyltransferase polypeptide 3	Glycosyltransferase enzymes
Congenital muscular dystrophy with mitochondrial structural abnormalities	mtDNA	602541	22q13	*CHKB*	Choline kinase	Sarcolemmal and mitochondrial membrane
Congenital muscular dystrophy with rigid spine syndrome	AR	602771	1p36	*SEPN1*	Selenoprotein N1	Endoplasmic reticulum protein
Ullrich syndrome						
With collagen type VI subunit α1 defect	AR	254090	21q22·3	*COL6A1*	Collagen type VI, subunit α1	Extracellular matrix proteins
With collagen type VI subunit α2 defect	AR	254090	21q22·3	*COL6A2*	Collagen type VI, subunit α2	Extracellular matrix proteins
With collagen type VI subunit α3 defect	AR	254090	2q37	*COL6A3*	Collagen type VI, subunit α3	Extracellular matrix proteins
Congenital muscular dystrophy with integrin α7 defect	AR	613204	12q13	*ITGA7*	Integrin α7	External sarcolemmal protein
Congenital muscular dystrophy with integrin α9 defect	AR	NA	3p21·3	*ITGA9*	Integrin α9	External sarcolemmal protein
Muscular dystrophy with generalised lipodystrophy	AR	NA	17q21–q23	*PTRF*	Polymerase I and transcript release factor (cavin-1)	T tubules and sarcolemma
Oculopharyngeal muscular dystrophy	AD or AR	164300	14q11·2	PABPN1	Polyadenylate binding protein nuclear 1	Unknown

X-R=X-linked recessive. OMIM=Online Mendelian Inheritance in Man. AD=autosomal dominant. AR=autosomal recessive. NA=not assigned.

Table 1: **Classification of muscular dystrophies**

	Motor function	Distribution of weakness	Rigid spine	Cardio-myopathy	Respiratory impairment	Disease course	Increased CK	Other signs
Congenital-onset muscular dystrophy								
Congenital muscular dystrophy with merosin deficiency	Independent ambulation generally not achieved in patients with absent merosin	Upper limbs>lower limbs	–	Not frequent	++	Slowly progressive	++	White matter changes on brain MRI
Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (Walker-Warburg syndrome, muscle-eye-brain disease, congenital muscular dystrophy type 1C, etc)	Independent ambulation generally not achieved	Upper limbs>lower limbs	–	Not frequent	+	Slowly progressive	++	Frequent structural brain changes
Congenital muscular dystrophy with rigid spine syndrome type 1 (SEPN1)	Ambulation achieved	Axial muscles>limbs	++	–	Early respiratory failure	Progression of respiratory signs>motor signs	N or +	Scoliosis
Ullrich syndrome	Ambulation achieved in ~50% but lost by middle teens	Proximal and axial	++	–	Early respiratory failure	Progression of respiratory and motor signs	N or +	Distal laxity

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	Motor function	Distribution of weakness	Rigid spine	Cardio-myopathy	Respiratory impairment	Disease course	Increased CK	Other signs
(Continued from previous page)								
From early-onset to childhood-onset muscular dystrophy								
Duchenne muscular dystrophy	Independent ambulation achieved, but lost before age of 13 years	Proximal>distal (pattern A)	–	++	++	Progression of motor, cardiac, and respiratory signs	++	Mental retardation in 30%
Emery-Dreifuss muscular dystrophy with lamin AC deficiency (type 2)	Ambulation achieved in all cases except for rare cases with congenital onset	Scapulo peroneal (pattern B)	++	++	In adulthood in the typical form, but also in childhood (congenital variants)	Slowly progressive	+ (+)	Frequent association with Dunningham type lipodystrophy
Limb girdle muscular dystrophy with lamin AC deficiency (type 1B)	Independent ambulation achieved, variable progression	Proximal>distal (pattern A)	+	++	In adulthood	Progression of cardiac signs>motor signs	+ (+)	None
Limb girdle muscular dystrophy with calpain deficiency (type 2A)	Ambulation achieved	Proximal>distal (pattern A)	+	–	Not frequent	Slow progression	++	None
Childhood-onset and adulthood-onset muscular dystrophy								
Becker muscular dystrophy	Independent ambulation achieved, variable progression	Proximal>distal (pattern A)	–	++	Not frequent	Progressive with substantial variability	++	None
Limb girdle muscular dystrophy with sarcoglycan deficiency (type 2C , 2D, 2E, 2F)	Independent ambulation achieved, generally lost in the second decade	Proximal>distal (pattern A)	–	++	++	Progression of motor, cardiac and respiratory signs	++	None
Limb girdle muscular dystrophy with abnormal glycosylation of dystroglycan (type 2I, 2K, 2L, 2M, 2N, 2O)	Independent ambulation achieved, variable progression	Proximal>distal (pattern A)	–	++	+(+)	Progressive	++	Mental retardation reported in some cases
Limb girdle muscular dystrophy with dysferlin deficiency (type 2B)	Independent ambulation always achieved	Both pattern A and pattern E	–	–	–	Progressive in adulthood	++	None
Limb girdle muscular dystrophy with telethonin deficiency (type 2G)	Independent ambulation achieved, generally lost in the fourth decade	Proximal>distal (pattern A); in some pattern B	–	+	+	Progressive in adulthood	+ (+)	None
Limb girdle muscular dystrophy with titin deficiency (type 2J)	Independent ambulation achieved	Proximal>distal (pattern A) but also pattern E	–	–	–	Roughly half lose ambulation in adulthood	++	None
Facioscapulohumeral dystrophy	Independent ambulation achieved, variable progression	Pattern D	–	–	Uncommon and mild	Slowly progressive	N or +	Neurosensory hearing loss and retinal degeneration
Emery-Dreifuss muscular dystrophy with merin deficiency (type 1)	Independent ambulation achieved, variable progression	Scapuloperoneal (pattern B)	+	++	Not frequent	Progression of cardiac signs>motor signs	+ (+)	None
Adult-onset muscular dystrophy								
Limb girdle muscular dystrophy with anoctamin deficiency (type 2L)	Onset in adulthood, 8:1 ratio of men:women	Mainly lower limbs pattern A, rarely pattern E	–	–	–	Slowly progressive in adulthood	++	None
Limb girdle muscular dystrophy type 1A (myotilin)	Independent ambulation achieved	Proximal>distal (pattern A)	–	–	–	Generally slowly progressive in adulthood	+	Dysarthria in some cases
Limb girdle muscular dystrophy with caveolin deficiency (type 1C)	Independent ambulation achieved; rippling might be seen before weakness	Proximal and distal	–	+	–	Slowly progressive, variable	++	Cramps, rippling, percussion-induced repetitive contractions

CK=creatine kinase. –=absent. ++=severe. +=mild. N=normal. +(+)=variable.

Table 2: **Clinical signs of muscular dystrophy**

girdle muscular dystrophies, manifest in early or late childhood or adolescence after independent ambulation has been achieved; milder, later onset limb girdle muscular dystrophies and most cases of myotonic dystrophy and facioscapulohumeral muscular dystrophy do not manifest until adulthood.

Weakness of the skeletal muscles is a consistent finding, and the distribution of weakness can help to distinguish between different forms of muscular dystrophy (figure 2).[1,36] In several variants, the peculiar distribution of weakness allows the disorder to be suspected rapidly, as is the case for facioscapulohumeral

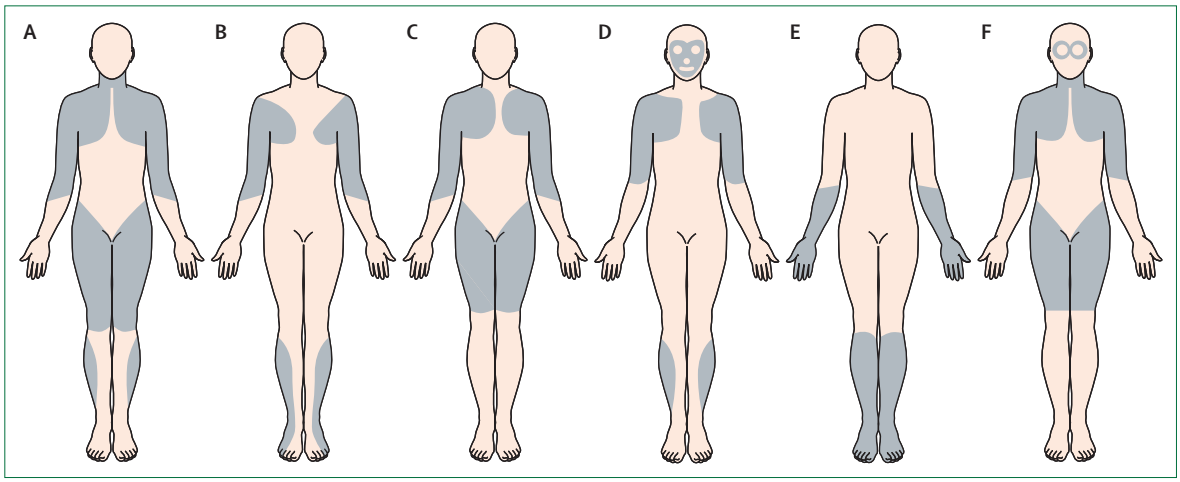

Figure 2: **Patterns of distribution of weakness**
(A) Duchenne and Becker muscular dystrophy. (B) Emery-Dreifuss muscular dystrophy. (C) Limb girdle muscular dystrophy. (D) Facioscapulohumeral muscular dystrophy. (E) Distal muscular dystrophy. (F) Oculopharyngeal muscular dystrophy. Shading represents affected areas. Reproduced from reference 36, by permission of the BMJ Publishing Group.

muscular dystrophy and oculopharyngeal muscular dystrophy. Muscle weakness is often associated with either muscle atrophy or the presence of relative muscle hypertrophy, or both, as is seen in Duchenne muscular dystrophy, Becker muscular dystrophy, and several limb girdle muscular dystrophies. Myotonic dystrophy is unique because it is associated with stiffness of various muscles (and difficulties in relaxation of grip)—a phenomenon known as myotonia. Joint contractures are common and often have a distinctive pattern that allows specific disorders to be suspected. Progressive rigidity of the elbow, Achilles tendon, and spine almost invariably occurs in Emery-Dreifuss muscular dystrophy and in Ullrich congenital muscular dystrophy, but is less common in limb girdle muscular dystrophy 2A and is rare in other variants.

Scoliosis occurs frequently in wheelchair-dependent children, especially during the pubertal growth spurt; it can also be common in ambulant patients affected by specific forms of muscular dystrophy, such as Ullrich congenital muscular dystrophy or rigid spine congenital muscular dystrophy, but is unusual in other disorders in which ambulation is not affected.

Progression of the disease is variable and is controlled mainly by the severity of the individual mutation affecting each gene. In most patients affected by congenital muscular dystrophy variants, ambulation is never achieved; in the childhood-onset forms, ambulation is achieved but will be invariably lost in the rapidly progressive variants such as Duchenne muscular dystrophy or some of the limb girdle muscular dystrophies. In these forms, affected children become progressively weaker by the end of the first decade, and loss of ambulation occurs by the early or middle teenage years. In the other forms of limb girdle muscular dystrophies and in most cases of facioscapulohumeral muscular dystrophy, ambulation can be maintained and wheelchair assistance is needed only later in life. Clinical severity in myotonic dystrophy is extremely varied, ranging from severely affected infants with fatal outcome to minimally affected adults with only cataracts and grip myotonia.

Respiratory impairment is frequent, but the onset, distribution of respiratory muscle weakness, and progression can vary greatly, and its severity is not always related to the degree of motor impairment. In most muscular dystrophy variants in which this complication occurs, respiratory insufficiency happens only after loss of ambulation as a result of generalised weakness of inspiratory and expiratory muscles. In other forms, respiratory insufficiency can develop in ambulant patients as a result of selective diaphragmatic weakness. Knowledge of these differences allows implementation of disease-specific anticipatory respiratory care. Respiratory insufficiency typically starts at night, resulting in disturbed sleep, morning drowsiness and headaches, loss of appetite, and frequent chest infections. These patients are at particular risk because they are often hypoxic and, unless their carbon dioxide levels are monitored, they will usually be offered supplementary oxygen, which can have major consequences because the oxygen suppresses the respiratory drive, leading to respiratory arrest.

Cardiac involvement is common in many muscular dystrophies, but is not a consistent finding (table 3).[37–39] Age of onset, progression, and type of cardiac involvement are variable. Although in Duchenne muscular dystrophy and other limb girdle muscular dystrophy variants dilated cardiomyopathy is the main presenting cardiac concern, in others, such as Emery-Dreifuss muscular dystrophy, conduction defects are a severe and invariable feature.[23]

	Onset and first signs	Progression	Cardiac death	Surveillance
Duchenne muscular dystrophy	Dilated cardiomyopathy with reduced left-ventricular ejection fraction after 10 years of age	Dilated cardiomyopathy in almost all patients by 18 years of age. Ventricular dysrhythmias occur in older patients	Congestive heart failure or sudden death in 20% of patients, although the contribution of heart to death of ventilated patients is now well established	Echocardiography every 2 years in the first decade of life and annually after 10 years of age (or more frequently if abnormalities are identified)
Becker muscular dystrophy	Dilated cardiomyopathy, generally after 10 years of age	Present in 40% of patients older than 18 years and more than 80% of those older than 40 years. Most patients develop dilated cardiomyopathy followed by ventricular arrhythmias	Death from congestive heart failure and arrhythmias is estimated to occur in up to 50% of cases. Cardiac transplants reported	Echocardiography at least every 5 years
Myotonic dystrophy	Cardiac abnormalities can occur as early as the second decade of life	Conduction deficits occur in about 65% of adult patients	20–30% of patients; mean 54 years of age. Sudden death is mainly due to conduction blocks, but ventricular tachyarrhythmias are also a possible cause of death	ECG yearly. Holter monitoring is recommended in patients with ECG abnormalities to detect asymptomatic conduction blocks and arrhythmias
Emery-Dreifuss muscular dystrophy				
X-linked recessive Emery-Dreifuss muscular dystrophy (type 1)	Conduction disturbances generally in the second decade	Ventricular myocardium might become involved, leading to mild ventricular dilatation and low-to-normal systolic function	Sudden death is by far the most common cause of death and can be very unpredictable	ECG and yearly Holter monitoring are indicated. Pacemaker implantation should be considered if sinus node or atrioventricular node disease develops. Defibrillator might be needed in some patients
Emery-Dreifuss muscular dystrophy 2 and limb girdle muscular dystrophy 1B	Conduction disease and cardiac failure	Dysrhythmias (sinus bradycardia, atrioventricular conduction block, or atrial arrhythmias) present in 92% of patients older than 30 years	Sudden death reported also in patients with pacemaker. Rare death with defibrillator also reported. Cardiac failure. Cardiac transplants reported	ECG and yearly Holter monitoring are indicated. Defibrillator implantation should be considered since pacemaker does not have a substantial effect on mortality
Limb girdle muscular dystrophy				
Sarcoglycanopathies	ECG and/or echocardiographic abnormalities reported in 20–30% of patients (especially β and δ variants, less common in α variant)	Severe dilated cardiomyopathy and lethal ventricular arrhythmias might occur in patients with Duchenne muscular dystrophy-like dystrophy	Typically by cardiac failure. Cardiac transplants reported	No evidence-based standards of care exist, but experts have made recommendations
Limb girdle muscular dystrophy 2I	Cardiac involvement reported in 29–62% of limb girdle muscular dystrophy 2I. Dilated cardiomyopathy may start in teenage years	Symptomatic cardiac failure over time, at a mean age of 38 years (range 18–58 years)	Cardiac failure. Cardiac transplants reported	No evidence-based standards of care exist, but experts have made recommendations
Limb girdle muscular dystrophy 1E	Dilated, restrictive, hypertrophic cardiomyopathies and arrhythmias. Cardiac involvement can precede muscle weakness in some patients	Major cardiac signs, such as atrioventricular block, can be the presenting symptom or occur within a decade of onset of muscle weakness	Life-threatening cardiac complications in roughly 50% of patients, at a mean age of 40 years, including sudden death, end-stage heart failure, atrioventricular block, and syncope	No evidence-based standards of care exist, but experts have made recommendations
Congenital muscular dystrophy				
Congenital muscular dystrophy merosin muscular dystrophy type C1A	Occasional reports of reduced left ventricular systolic function	Not well characterised	Rare by cardiac failure	No evidence-based standards of care exist, but experts have made recommendations
Fukuyama congential muscular dystrophy	Systolic left-ventricular dysfunction may develop in the second decade	Symptomatic cardiac failure over time	Death from congestive heart failure might occur by the age of 20 years	No evidence-based standards of care exist, but experts have made recommendations
Muscular dystrophy type C1C	Dilated cardiomyopathy reported in young children	Not well characterised	Not reported	No evidence-based standards of care exist, but experts have made recommendations
Facioscapulohumeral muscular dystrophy	Uncommon	Not well characterised	Not reported	No evidence-based standards of care exist, but experts have made recommendations

ECG=electrocardiogram.

***Table 3*: Cardiac involvement in muscular dystrophies**

In some congenital muscular dystrophies and rarely in limb girdle muscular dystrophy variants, functional or structural brain involvement occurs. The best examples of functional involvement are myotonic dystrophy and Duchenne muscular dystrophy. In Duchenne muscular dystrophy, a third of boys have non-progressive mental retardation and associated behavioural or psychiatric comorbidities (eg, attention-deficit disorder or autism).[40,41] Structural brain defects have also been recorded in congenital muscular

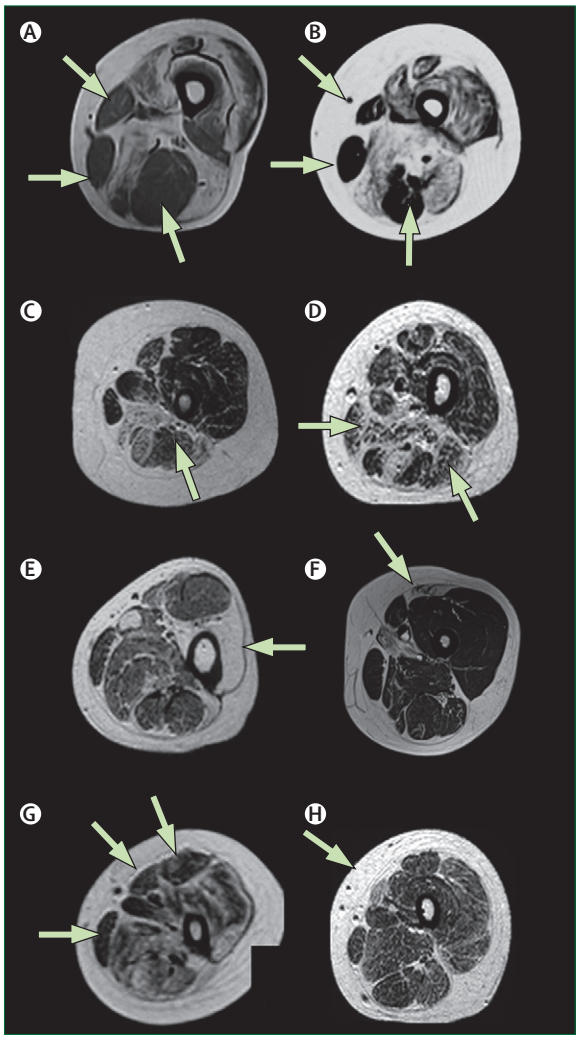

Figure 3: **Muscle MRI showing different patterns of involvement in various types of muscular dystrophy**
(A) Becker muscular dystrophy. (B) Duchenne muscular dystrophy. (C) Limb girdle muscular dystrophy 2A. (D) Limb girdle muscular dystrophy 2I. (E) Emery-Dreifuss muscular dystrophy. (F) Facioscapulohumeral muscular dystrophy. (G) Ullrich congenital muscular dystrophy. (H) Congenital muscular dystrophy with rigid spine and SEPN1 mutations. Arrows indicate selectively spared or affected muscles that have been reported as the typical pattern in each of these forms. An overview of pelvis, thigh, and calf muscles increases the possibilities of detection of disease-specific patterns of muscle involvement.

See Online for appendix

dystrophy subtypes such as Walker-Warburg syndrome, Fukuyama congenital muscular dystrophy, or muscle-eye-brain disease.[42]

Facioscapulohumeral muscular dystrophy and severe congenital muscular dystrophy variants are associated with retinal involvement or myopia; cataracts are common in myotonic dystrophy, hearing loss can occur in facioscapulohumeral muscular dystrophy, and skin involvement (cheloids and atrophic skin lesions) is common in Ullrich congenital muscular dystrophy. Smooth muscle involvement leading to slow gastric emptying, constipation, and urinary retention is a feature of the advanced stages of Duchenne muscular dystrophy and of myotonic dystrophy. Diabetes and hypogonadism also occur in myotonic dystrophy.

Diagnosis

The combination of clinical signs and an analysis of the possible mode of inheritance allows suspicion of specific forms of muscular dystrophy and direction of further analyses, although the overlaps between genetically distinct forms complicate the diagnostic pathway. Serum creatinine kinase concentrations are often more than ten times higher than normal values, but do not suggest a specific disorder. Normal creatinine kinase concentrations do not rule out some of the muscular dystrophies such as Ullrich congenital muscular dystrophy or facioscapulohumeral muscular dystrophy. Electromyography might help in the identification of myotonic discharges in myotonic dystrophy, but has low value in the diagnosis of a specific disorder in patients with elevated serum creatinine kinase.

Muscle biopsy allows assessment of morphology and exclusion of disorders with overlapping features, such as myofibrillar myopathies. The use of a range of antibodies to assess level and localisation of different muscle proteins (appendix), and western blot analysis to calculate their abundance, will often help to identify the underlying primary protein defect and to direct genetic testing. However, not all dystrophies have a protein deficiency signature; thus, identification of the genetic defect is the gold-standard diagnostic method.

Increasing evidence suggests that muscle imaging to identify disease-specific patterns of muscle involvement[43–48] can be used in the differential diagnosis of many neuromuscular diseases (figure 3). A precise genetic diagnosis is essential for accurate genetic counselling of affected patients, and systematic referral to the appropriate counselling services is necessary.

As evidence of the efficacy of early intervention accumulates, the importance of early diagnosis has been emphasised. However, the mean age of diagnosis even for common variants such as Duchenne muscular dystrophy is delayed by about 2 years after manifestation of the early clinical signs.[49] Neonatal screening programmes for Duchenne muscular dystrophy have been piloted, but no consensus exists about whether these studies should be widely implemented. Some of these programmes were terminated because, with no available treatment, the benefits of screening seemed to be limited to a better informed choice for subsequent pregnancies. However, even in the absence of a definitive cure, neonatal screenings and early recognition of patients with Duchenne muscular dystrophy would allow implementation of recommendations for early aspects of care, including physiotherapy, corticosteroids, and proactive treatments for psychosocial and behavioural issues.

Management and prevention

Consensus meetings and documents that focus on individual aspects of care (eg, management of respiratory, cardiac, and bone complications)[6,50,51] or that provide general standard-of-care recommendations for specific forms of muscular dystrophy are available.[4,5,7,8] Although consensus exists about many of these aspects, others are controversial.

Respiratory insufficiency

The introduction of non-invasive ventilation and of manually and mechanically assisted cough techniques improves respiratory function and survival in patients with a range of neuromuscular disorders. Non-invasive ventilation is now used widely;[11] its effect on survival has been documented clearly[10] and its use in symptomatic patients is not controversial. However, the precise timing of its implementation is still under investigation, since premature introduction can be counterproductive.[52] Nevertheless, patients with nocturnal hypoventilation could benefit from the introduction of nocturnal non-invasive ventilation before daytime hypercapnoea ensues.[53]

The use of mechanical assisted cough devices varies by centre and country. Most people agree that mechanical assisted cough devices can be used in patients with severe neuromuscular cases, but systematic randomised clinical trials and full economic analysis of their effect in patients with milder disease are not yet available.

Cardiac involvement

Guidelines for surveillance and introduction of appropriate interventions are available (table 3).[7,37,39,51] However, consensus is still not complete in some areas, and additional work is in progress. One such topic relates to the timing of the optimum intervention for disorders characterised by invariable cardiomyopathy, such as Duchenne muscular dystrophy. Standards of care suggest that cardiac protection treatment (angiotensin-converting-enzyme inhibitors, β blockers, or both) should be started when echocardiography detects signs of cardiac dysfunction. Some evidence suggests that initiation of treatment before any detectable sign (by echocardiography) of left-ventricular dysfunction occurs is associated with better long-term outcome,[54,55] and early-intervention randomised trials are underway to confirm this theory (appendix). Parallel efforts that use techniques such as echocardiographic colour Doppler or cardiac MRI to identify early markers of cardiac involvement and response to treatment are also underway.

Results of several studies have shown that the implantation of pacemakers does not effectively prolong life in people with Emery-Dreifuss muscular dystrophy secondary to *LMNA* mutations and that a defibrillator should be used.[56,57] Some people also advocate this intervention in the X-linked variant of the disease but more evidence is needed to support this notion. Nevertheless, even defibrillators cannot always prevent sudden cardiac death in patients with Emery-Dreifuss muscular dystrophy.[58] Prospective international registries are needed to collect survival data for patients with implantable defibrillators. A list of the ongoing clinical trials on cardiac function is available in the appendix.

Bone metabolism

Reduced bone density and increased rate of peripheral and vertebral fractures are well documented in boys with Duchenne muscular dystrophy, as a result of their relative immobility and chronic daily steroid use,[6,59–62] but little systematic research has been done for other disorders.[63] Results of recent studies support the negative effect of cumulative doses of steroids.[59,60] Serum concentrations of inflammatory markers have been related to bone involvement.[64,65] The standards of care in Duchenne muscular dystrophy suggest that personalised physical exercises, appropriate calcium and protein intake, and vitamin D supplementation (after measurement of serum concentrations of 25-hydroxyvitamin D), should be started as soon as possible.[4] Bisphosphonates are used routinely as a preventive measure in adults receiving chronic corticosteroids; however, they are only indicated for children after spontaneous fractures and established osteopenia. In some centres, bisphosphonates are used as a preventive strategy in children,[66,67] but no consensus for this strategy exists and further studies are needed to establish the efficacy and safety of early use of these drugs in growing bones.[68] No systematic study about other muscular dystrophies is available.

Natural history data

The need for clinical trial readiness has been an impetus for natural history studies.[13,69–71] Large, albeit retrospective, datasets have been published that describe the clinical course, frequency, and age at onset of complications in patients with facioscapulohumeral muscular dystrophy,[72,73] Ullrich congenital muscular dystrophy,[71] dysferlinopathy,[74] laminin α2-deficient congenital muscular dystrophy,[69] and limb girdle muscular dystrophy 2A and 2B.[75,76] Meanwhile, national and international registries have been established for longitudinal prospective data collection.[76,77]

Updated information about progression rate is essential to power interventional studies appropriately. Recent studies in patients with Duchenne muscular dystrophy have shown that deterioration in young ambulant boys with Duchenne muscular dystrophy starts after the age of 7 years, with an increasing number of patients on daily steroids able to walk independently after the age of 13 years, by which point all boys with untreated Duchenne muscular dystrophy should, by definition, have lost ambulation.[13,14,78–80] Although several different corticosteroid regimens have

been published, only one is recommended in a recent standard-of-care consensus document.[5] A randomised controlled clinical trial will compare existing regimens and will hopefully provide a definitive answer about the advantages and disadvantages of the most frequently used regimens (ClinicalTrials.gov trial number: NCT01603407).

Long-term survival anticipatory care

The increased life expectancy of patients with Duchenne muscular dystrophy has had a notable effect on the number of patients referred to adult services and the need to understand how to improve health and quality of life at the transition to adulthood.[81,82]

Because survival can now be prolonged, emerging features of cardiac involvement can be severe ventricular dysrhythmias and the first cardiac symptom can be sudden death in disorders not usually associated with these complications. The standards of cardiac care will need to change to take these emerging aspects into consideration,[83] including the complications of smooth muscle dysfunction.

Pathogenesis and associated treatment approaches

The classifications of muscular dystrophies that take into account the location or function of the primary protein defect (table 1) allow assignment of a rational framework for most muscular dystrophy variants. The main classes of proteins involved in these conditions are: extracellular matrix and external membrane proteins, enzymes or proteins with putative enzymatic function, sarcolemma-associated proteins, nuclear membrane proteins, sarcomeric proteins, and others.

Proteins of the extracellular matrix and external membrane

Abnormalities in this group of proteins often result in congenital onset of weakness, which suggests an important role of these proteins in prenatal skeletal muscle development and function, rather than in only skeletal muscle maintenance.

Muscular dystrophy variants due to collagen VI deficiency can be inherited both as autosomal recessive or autosomal dominant traits in any of the three collagen VIA chain genes.[84–86] The range of severity encompasses the congenital muscular dystrophy variant Ullrich congenital muscular dystrophy and a milder form with later onset (Bethlem myopathy). Collagen VI is present in most extracellular matrices (figure 1), where it interacts with a wide range of molecules; disturbed cell matrix interactions are believed to be an important feature of this disorder.

A link between collagen VI deficiency and myofibre degeneration secondary to mitochondrial damage, apoptosis, and autophagy has been suggested.[87,88] This association results from disruption of the potential controlled by the mitochondrial permeability transition pore and the subsequent defective activation of the autophagic machinery. Pharmacological agents acting on the mitochondrial permeability transition pore are being used in preclinical models.[89] In a mouse model of collagen VI deficiency, forced reactivation of autophagy by nutritional and pharmacological approaches also improved outcome.[90,91] Clinical trials with drugs that inhibit apoptosis are being planned.

Regarding laminin α2 deficiency, autosomal recessive mutations in this gene cause the severe congenital muscular dystrophy variant known as laminin α2-deficient congenital muscular dystrophy.[92] Laminin α2 assembles with the laminin subunits β1 and γ1 (figure 1) and is the main isoform in the basement membrane of muscle fibres. Pathogenesis of the dystrophic process in the laminin α2-deficient muscle is multifactorial, but the main mechanism of muscle fibre death is apoptosis, rather than necrosis.

Treatment approaches that aim to replace laminin α2 with wild-type protein or with engineered proteins to restore a link between the extracellular matrix and the cell receptors have been developed in the mouse model of laminin α2-deficient congenital muscular dystrophy. Examples of the engineered protein approach exploit a modified agrin mini-gene,[93] which is easier to pack into viral vectors than the full-length laminin α2 cDNA. Other genetic studies focus on reduction of fibrosis or inhibition of apoptosis.[94] A clinical trial of a drug that inhibits apoptosis in laminin α2-deficient congenital muscular dystrophy is in the planning stages.

Enzymes or proteins with putative enzymatic function

This group of proteins can be divided into two categories: proteins involved in the glycosylation of α dystroglycan and those that are not involved in this glycosylation. Defects in the glycosylation of α dystroglycan are one of the major factors causing congenital muscular dystrophy and limb girdle muscular dystrophies; these disorders are referred to as dystroglycanopathies because the primary defect is the post-translational modification of dystroglycan.[95,96] α dystroglycan is an essential component of the dystrophin-associated glycoprotein complex (figure 1); it links to β dystroglycan, a sarcolemma-spanning protein part of the complex, which in turn binds to dystrophin. α dystroglycan is highly glycosylated, mostly by O-mannosylation; this process, which is not completely understood, needs many enzymatic steps that are regulated in a developmental and tissue-specific manner. Binding of α dystroglycan to its extracellular matrix partners—laminins, perlecan, agrin, neurexin, and pikachurin—depends on its proper glycosylation, regulated by an increasingly long series of proteins with demonstrated or putative enzymatic function, which—when mutated—give rise to a dystroglycanopathy. Their clinical features are similar: mild allelic mutations cause an adult-onset limb girdle muscular dystrophy phenotype

(LGMD2I is the most common variant); moderate-severity mutations are associated with a congenital muscular dystrophy variant, without (congenital muscular dystrophy type 1C) or with structural brain involvement (muscle-eye-brain disease, Fukuyama congenital muscular dystrophy, and others); the most severe disease types are the severe, lethal, congenital forms with invariable serious structural eye and brain malformations, in addition to congenital muscular dystrophy (eg, Walker-Warburg syndrome).[97–99] This clinical range is associated with different degrees of α dystroglycan glycosylation and emphasises a fundamental role of this glycosylation, not only for muscles but also for the basal membrane maintenance and function of other organs.[100]

In addition to the gene therapy approaches that are being investigated in animal models, pharmacological upregulation of one of the glycosyltransferases involved in a dystroglycanopathy, LARGE, is being investigated because this enzyme has the unexpected capacity to increase the glycosylation of α dystroglycan in fibroblasts of patients affected by other genetically determined dystroglycanopathies, and in animals.[101]

The main protein in the group of enzymes not involved in α dystroglycan glycosylation is calpain 3, which belongs to a family of calcium-activated neutral proteases. Calpain 3 interacts with several proteins that are crucial for muscle function (figure 1); it is a component of the skeletal muscle triad that causes calcium release, and is also a part of the dysferlin complex (disruption of which also results in a limb girdle dystrophy). Calpain 3 also interacts with titin, a giant myofibrillar protein that serves as a scaffold for sarcomeric organisation.[102–104] Despite the clear role of calpain 3 as a protease and the identification of several targets for its function, the precise pathophysiology of limb girdle muscle dystrophy A is still incompletely understood; the mechanisms involved implicate dysfunction in calcium–calmodulin protein kinase II signalling, loss of enzymatic function (eg, loss of nuclear protein AHNAK cleavage), and abnormal response to stretch-induced muscle adaptation.[105]

Sarcolemma-associated proteins

The major subcomplex in this category is the dystrophin-associated glycoprotein complex, which comprises dystrophin and sarcoglycans, in addition to dystroglycan (figure 1). Proteins in this group give rise to the most common forms of muscular dystrophy in childhood, Duchenne muscular dystrophy and Becker muscular dystrophy, and to four autosomal recessive phenocopies called sarcoglycanopathies, which are all secondary to mutations in one of the four sarcoglycans. The dystrophin-associated glycoprotein complex has an important role in stabilisation of the muscle fibre against the mechanical forces of muscle contraction by providing a shock-absorbing connection between the cytoskeleton and the extracellular matrix; however, it is also believed to have several other roles, from signalling to molecular ruler inside the sarcolemma.[106] The destabilisation of proteins of the dystrophin-associated glycoprotein complex renders muscle cells susceptible to stretch-induced damage and necrosis, although the precise series of events leading to muscle weakness and degeneration is still not completely understood.

Dysferlin is another sarcolemma-associated protein that is frequently mutated in adults with limb girdle muscular dystrophy; it interacts with caveolin 3, which is also implicated in a less common limb girdle muscular dystrophy variant. Dysferlin has a crucial role in muscle repair.[107–109] The pathogenesis of muscle degeneration secondary to the deficiency of caveolin 3 is multifactorial, which is indicative of the many cellular processes that involve caveolae (invaginations of the plasma membrane), including clathrin-independent endocytosis, regulation and transport of cellular cholesterol, and signal transduction. Mutations in the human *PTRF* gene (also known as cavin), which is a component of caveolae with an essential role in caveolar formation, results in a secondary deficiency of caveolin 3 and muscular dystrophy.[110,111] Another protein located in the sarcolemma and other cellular membranes or vesicles is anoctamin 5. Although the function of this protein is unknown, it belongs to a family of proteins that are thought to function as calcium-activated chloride channels.[112,113] Defective membrane repair similar to that seen in dysferlinopathies has also been reported in patients affected by this variant.

Gene and stem cell therapy approaches are being pursued in animal models of muscular dystrophies,[114] and a few phase 1 trials have been done in human beings (appendix). These approaches are complicated by the large size of the transgenes, the complexity of targeting the most abundant tissue in the body (muscle) with viral vectors, and the challenges in identification of an effective stem cell that targets muscle after systemic delivery (and, in the case of a homologous cell, after genetic correction). Regional delivery protocols of gene therapy products are being explored by a few groups, often with mini-genes that can be packed in the adenoviral vectors. Clinical trials with this approach are in the advanced planning stage.[115,116]

Pharmacological approaches that interfere with the secondary processes involved in dystrophic progression are being investigated in preclinical models, including strategies to facilitate membrane resealing in dysferlinopathies,[117–119] and drugs aimed at reducing nitrosylation of the ryanodine receptor, a protein involved in excitation coupling for which secondary dysfunction occurs in several muscular dystrophies.[120,121] In Duchenne muscular dystrophy, pharmacological upregulation of the dystrophin-related protein utrophin is being investigated, because this protein could compensate for dystrophin deficiency.[122,123]

One exciting development has been the targeting of mutant RNA in Duchenne muscular dystrophy by use

of antisense oligonucleotides to induce exon skipping and to restore the reading frame in boys with eligible deletions.[15,124–127] Since roughly 70% of boys with Duchenne muscular dystrophy have out-of-frame deletions, the strategy to restore the open reading frame with antisense oligonucleotides and generate internally deleted molecules (mimicking what happens naturally in the milder disorder Becker muscle dystrophy) has progressed rapidly to phase 1, 2a, 2b, and 3 clinical trials.[128–130] Initial efforts focused on boys with deletions that respond to skipping exon 51, since this targets the largest percentage of boys with Duchenne muscular dystrophy (about 13%), whereas targeting of another nine exons would achieve correction in roughly 70% of boys with Duchenne muscular dystrophy who carry deletions. Outcomes of randomised placebo-controlled efficacy studies in Duchenne muscular dystrophy are expected in the second quarter of 2013, and the process of targeting other exons has begun. Similar approaches are being explored in other muscular dystrophies (myotonic dystrophy and dysferlinopathies) and motor neuron diseases.[124,131,132]

Nuclear membrane proteins

The nuclear envelope consists of two membranes: the outer nuclear membrane, which is continuous with the rough endoplasmic reticulum; and the inner nuclear membrane, which contains integral membrane proteins. These proteins interact with the underlying nuclear lamina and contribute to maintenance and regulation of the nuclear architecture. Mutations in proteins located in different subdomains of the nuclear envelope, such as lamin A or C, emerin, nesprin 1 or 2, and LUMA, all result in disorders that share a progressive muscular dystrophy phenotype originally described by Emery and Dreifuss,[133] with humeroperoneal weakness and invariable coexistent cardiac involvement.[22,23] Mutations in another nuclear membrane protein, matrin 3, have also been described in a family with a distal myopathy associated with vocal cord paralysis.[134] Although the core phenotype of mutations in these proteins is Emery-Dreifuss muscular dystrophy, the phenotypes are notably divergent because of allelic mutations in many of these genes.[25] An extreme example relates to mutations in *LMNA*, which can give rise to Emery-Dreifuss muscular dystrophy, cardiomyopathy with cardiac conduction system disease, muscular dystrophy plus lipodystrophy, lipodystrophy with isolated mandibuloacral dysplasia, congenital muscular dystrophy, peripheral neuropathy, lethal restrictive dermopathy, and Hutchinson-Gilford progeria. These diverse phenotypes are associated with specific mutations, which emphasises the specific roles of different protein domains. Although the precise pathogenesis of these nuclear envelopathies is still elusive, evidence exists for a role of the nuclear envelope proteins in stabilisation of the nuclear membrane (with mutations giving rise to increased nuclear fragility), organisation of specific chromatin domain localisation, and consequently in involvement in specific gene expression effects. The development of specific therapeutic interventions for these conditions is in its infancy, but knowledge of natural history of the condition with disease-specific complications has revolutionised the clinical management of these patients.

Sarcomeric proteins

Sarcomeric proteins are a new addition to the class of proteins involved in muscular dystrophies. The resulting phenotypes often have a mainly distal distribution of weakness.[135,136] Some of these disorders invariably progress to involve proximal muscle, whereas others, such as tibial muscular dystrophy titinopathy, Welander distal myopathy, and distal myosinopathy, often remain distal throughout the patient's lifetime, although proximal variants have been recorded.[137] In some of these disorders, severe cardiomyopathy can also be present. In some of these gene mutations, isolated cardiomyopathy can also be a feature, such as for MYH7 and titin.[138]

Others

For a few proteins, the cellular localisation and presumed function do not fit easily into the proposed classification scheme. One example is facioscapulohumeral muscular dystrophy, one of the most common adult variants with autosomal dominant inheritance. The identification of the genetic defect of the disorder is proving to be very complex, despite the finding of telomeric deletions on chromosome 4q for more than 20 years; even now, the precise mechanism of disease is not completely clear. Incremental understanding of the role of genes such as the retrogene *DUX4*, first with the demonstration of its transcription regulation of the paired-like homoeodomain transcription factor 1,[139] and more recently the demonstration of a single nucleotide polymorphism within the chromosome 4q permissive deleted haplotype, which results in inefficient repression of *DUX4*.[140] Although no information about how inefficient *DUX4* repression leads to progressive muscle weakness is available, investigators are studying downregulation of the *DUX4* mRNA for therapeutic intervention.[141] The appendix contains a list of recent and ongoing clinical trials.

Conclusions

The area of muscular dystrophy has advanced greatly in the past decade. From a clinical perspective, the recognition of specific subtypes of the disorder has allowed refinement of standards of care and provision of anticipatory interventions.

The identification of genes that cause the most common disorders followed by availability of adequate preclinical models has allowed an extensive framework to be built in which pathogenesis can be studied and therapeutic

applications developed. Multiple therapeutic approaches are now in clinical trials, some of which focus on secondary aspects of muscle degeneration whereas others target particular mutations, such as antisense oligonucleotides in Duchenne muscular dystrophy; a list of the ongoing clinical trials is available in the appendix.

Although these developments are exciting, the pathway to effective treatments is lengthy and ambitious, and efforts are needed to continue to improve and implement standards of care and collect prospective natural history data from these patients.

Contributors

Both authors contributed to the systematic review and to the writing of the paper. FM had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflicts of interest

FM has served on scientific advisory boards for Acceleron Pharma, Genzyme, AVI BioPharma, Debiopharma Group, GlaxoSmithKline, Prosensa, Servier, and Santhera Pharmaceuticals; he receives research support from the European Union, the UK Medical Research Council, the Wellcome Trust, the Association Française Contre les Myopathies, the Muscular Dystrophy Campaign, the Great Ormond Street Hospital Biomedical Research Centre, and the Muscular Dystrophy Association USA; he is receiving funding for trials from GlaxoSmithKline, Trophos, and the British Heart Foundation; and has received funding for trials from AVI BioPharma and PTC Therapeutics. EM has served on scientific advisory boards for Acceleron Pharma, Prosensa, and PTC Therapeutics; he receives research support from the European Union, Parent Project NL, SMA Europe, and Italian Telethon; he is receiving funding for trials from GlaxoSmithKline; and has received funding for trials from Trophos and PTC Therapeutics.

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