

24.19.2 Muscular dystrophy

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section 24 Neurological disorders 6310 FURTHER READING Hughes BW, Kusner LL, Kaminski HJ (2006). Molecular architecture of the neuromuscular junction. *Muscle Nerve*, 33, 445–61. Huxley HE, Hanson J (1972). The molecular basis of contraction. In: Bourne GH (ed). *The structure and function of muscle*, Vol 1, 2nd edition. Academic Press, New York, NY. Larsson L, et al. (1991). MHC composition and enzyme-histochemical and physiological properties of a novel fast-twitch motor unit type. *Am J Physiol*, 261, 93–101. Smerdu V, Karsch-Mizrachi I, Campione M (1994). Type IIx myosin heavy chain transcripts are expressed in type IIb fibers of human skeletal muscle. *Am J Physiol*, 267, C1723–8. Walton JN, Mastaglia FL (1980). The molecular basis of muscle disease. In: Thompson RHS, Davison AN (eds) *The molecular basis of neuropathology*. Edward Arnold, London. Wattjes MP, Kley RA, Fischer D (2010). Neuromuscular imaging in inherited muscle diseases. *Eur Radiol*, 20, 2447–60. 24.19.2 Muscular dystrophy Kate Bushby and Chiara Marini-Bettolo ESSENTIALS Muscular dystrophies are primary, genetically determined disorders of muscle. All cause muscle weakness, which is usually progressive. They are challenging to classify, but clinical characteristics can be combined with genetic and molecular information to obtain a useful operational nomenclature for prognosis and family counselling. In general, diagnosis is guided by the age at which clinical manifestations appear, the distribution of weakness, and the rate at which muscle function is lost, but unusual features such as muscle pain and rhabdomyolysis may also contribute to the identification of a particular hereditary muscle disorder. Congenital muscular dystrophies Congenital muscular dystrophies are defined by their very early childhood onset and dystrophic features on the muscle biopsy. Clinically patients present with early onset of muscle weakness and hypotonia, and contractures are common. Respiratory and cardiac involvement is common and can be severe. In some cases, the congenital muscular dystrophies can have overlapping genetic and clinical features with the congenital myopathies. Molecularly based subclassification allows the recognition of various subgroups including those associated with

mutations in/causing: (1) laminin A2 (LAMA2), (2) α -dystroglycan and glycosyltransferase enzymes (FKRP, FKTN, POMT1, POMT2, POMGnT1, LARGE, ISPD, GTDC2, DAG1, TMEME5, B3GALNT2, B3GNT1, GMPPB, SGK196, DPM1, DPM2, DPM3, DOLK) (3) collagen VI (COL6A1, COL6A2, COL6A3)—, (4) lamin A/C (LMNA), (5) selenoprotein 1 (SEPN1), (6) ryanodine receptor 1 (RYR1), (7) integrin A7 and A9 (ITGA7, ITGA9) (8) nesprin 1 (SYNE1) (9) choline kinase beta (CHKB), and (10) other congenital muscular dystrophies with no genetic diagnosis but compatible clinical and histological features. Table 24.19.2.1 gives an overview on the congenital muscular dystrophy classification including nomenclature, gene, phenotype, relative frequency in the UK population and diagnostic test. Dystrophin deficiency Mutations (mostly deletions) in the dystrophin gene result in deficiency of dystrophin protein and cause variable phenotypes ranging from the more severe form, Duchenne muscular dystrophy to the milder form, Becker muscular dystrophy. Despite these being X-linked diseases female carriers can also manifest the disorders. Cardiomyopathy can occur in conjunction with the skeletal muscle weakness, but also in the absence of overt weakness as X-linked dilated cardiomyopathy. Clinical features—(1) Duchenne muscular dystrophy—all affected boys are symptomatic within the first 3 years of life, although diagnosis is frequently delayed beyond this; motor milestones and speech are frequently delayed; there is a pronounced waddling gait on attempting to run. Hypertrophy of the calf muscles is almost universal. (2) Becker muscular dystrophy—mean age at onset is 11 years; typically manifests with difficulty with high steps and climbing hills; may suffer muscle pain after exercise; frequently have hypertrophy involving the same muscle groups as seen in Duchenne muscular dystrophy. (3) About 10% of female carriers can also present with variable skeletal and/or cardiac muscle involvement. Exercise induced muscle pain is common as well as calf hypertrophy. (4) X-linked dilated cardiomyopathy (XL-dCMP)—a distinct dystrophinopathy phenotype characterized by dilated cardiomyopathy and absence of overt skeletal muscle weakness. Treatment is similar to dilated cardiomyopathy and surgery may be necessary for refractory heart failure. Investigation, diagnosis, and prevention—serum creatine kinase is always massively elevated, but the level does not distinguish the severity of the disease. Molecular confirmation of the diagnosis is essential to assist in defining prognosis and allow provision of appropriate genetic counselling. Prognosis and complications—the prognosis of ‘dystrophinopathies’ is highly variable, especially among Becker MD and manifesting carriers. Untreated patients with Duchenne muscular dystrophy lose the ability to walk by the age of 12, but corticosteroids delay deterioration. Scoliosis, respiratory failure, and cardiomyopathy develop during the teenage years. With appropriate multidisciplinary supportive care, survival into or beyond the late twenties and thirties is becoming more common. Novel therapeutics directed to the mutations in the dystrophin gene or the downstream effects of dystrophin deficiency are a prospect for treatments in the future and are currently being tested in trials, with likely availability of these new drugs on the market in the coming years. At the time of writing, conditional marketing approval in Europe only has been granted for ataluren, though access remains restricted. Other muscular dystrophies Facioscapulohumeral muscular dystrophy is an autosomal dominant disease sometimes arising as the result of a new dominant mutation. Affected individuals manifest early symptoms, typically including facial weakness, shoulder girdle weakness, and foot-drop, often by their teens or twenties. Serum creatine kinase may be normal or mildly elevated. Diagnosis can be confirmed in 95%

24.19.2 Muscular dystrophy 6311 of cases by demonstration of a deletion close to the telomere of chromosome 4q: more complex analysis is required for the other cases. The condition is usually slowly progressive; complications rarely include scoliosis and respiratory failure. Emery–Dreifuss

muscular dystrophy—caused by mutation of any one of several genes encoding components of the nuclear envelope (e.g. emerin, lamin A/C). This may present at any age, with contractures of the ankles and elbows and rigidity of the spine often pre-dating any clear weakness. Prognosis is determined by ability to manage life-threatening cardiac arrhythmias and varies depending on the exact gene involved. Limb-girdle muscular dystrophies—these comprise a range of disorders that cause weakness of the proximal musculature. Important considerations in any case are (1) could it be a dominant disease? (e.g. limb-girdle muscular dystrophy 1B; allelic with autosomal dominant Emery-Dreifuss muscular dystrophy), Bethlem myopathy; (2) age of presentation and of rate of progression—these give important clues to likely diagnosis; (3) investigations—creatine kinase is greatly elevated in all forms of autosomal recessive limb-girdle muscular dystrophy; electromyography confirms a primary myopathic process; muscle biopsy shows dystrophic changes on standard analysis, with more specialized testing for diagnosis of, for example, sarcoglycanopathies, calpainopathy, or dysferlinopathy. Oculopharyngeal muscular dystrophy—typically presents in the sixth decade with ptosis, dysphagia to solids, and dysphonia. Associated with an expanded triplet repeat in the gene for poly(A) binding protein 2.

Introduction

Muscular dystrophy is not a single disease. Many different types of muscular dystrophy can be recognized: all are primary, genetically determined disorders of muscle and all cause muscle weakness and wasting, which is usually progressive. The various types of muscular dystrophy share several characteristic findings on muscle biopsy, most notably a variation of fibre size, evidence of muscle fibre necrosis, and usually replacement of muscle tissue by fat and fibrous tissue. These pathological findings are often, but not always, accompanied by elevation of the serum creatine kinase. Although the key clinical sign in muscular dystrophy is muscle weakness, the distribution of that weakness and the association with other features such as wasting, hypertrophy, and joint contractures are the most helpful defining features in making a clinical diagnosis, together with age at presentation and rate of progression. Unusual presenting manifestations of muscular dystrophy are muscle pain, rhabdomyolysis, myoglobinuria, and cardiomyopathy. Complications may include cardiac and respiratory failure or anaesthetic problems. These complications may be relatively specific to particular types of muscular dystrophy. Taken together with the clinical findings in any patient, precise diagnostic tests (through either DNA analysis or protein analysis of a muscle biopsy sample) are available for most of these disorders, as knowledge of the underlying mechanism of disease for each of these entities has increased. Confirmation of the type of muscular dystrophy in any individual patient is critical to the provision of appropriate management, prognostic advice, and genetic counselling. No form of muscular dystrophy is currently curable, although various experimental therapeutic procedures are under investigation.

Classification of the muscular dystrophies

Various classifications of the muscular dystrophies have been proposed, reflecting historical advances in the understanding of this group of diseases (Box 24.19.2.1). The current basis for classification combines an appreciation of the clinical features with the ability to determine the molecular basis for the disease. Therefore, the eponymous names (e.g. Duchenne muscular dystrophy) still in common usage reflect the detailed clinical descriptions provided by early clinicians; other disease names reflect the recognized pattern of muscle involvement in a particular condition (e.g. fascioscapulohumeral muscular dystrophy). Disease designations based on the genetic or protein defect in a particular disorder (e.g. dystrophinopathy) are becoming more widely used, reflecting the fact that some disorders previously believed to be clinically distinct actually represent different manifestations of lesions at the same locus. Genetic analysis has also revealed an unsuspected level of heterogeneity with different genetic causes for disorders that show superficial

clinical similarities. This can be seen most strikingly within the 'limb-girdle' and congenital groups of muscular dystrophies. The pathophysiology of the muscular dystrophies Biochemical and physiological experiments failed to shed any light on the mechanisms by which muscular dystrophy could arise, and it has only been since the identification of the dystrophin gene (DMD) in 1987 that progress has been made. It is now quite clear that proteins involved in several different functions within the muscle cell can, when altered or absent, cause muscle damage and account for the pathological and clinical features of a muscular dystrophy. Some of these proteins are components of the membrane of the muscle fibre that may have a structural or signalling role, others are components of the nuclear envelope or muscle-specific enzymes (Fig. 24.19.2.1). General points on the diagnosis of muscular dystrophy Box 24.19.2.2 summarizes some of the major considerations for arriving at the correct diagnosis of a muscular dystrophy. History taking at the time of presentation (Box 24.19.2.3) may be particularly informative. The clinical history may be pathognomonic. Detailed diagnostic information is given in the following text relating to specific diseases. The main tools for specific diagnosis in muscular dystrophy are the use of antibodies for immunolabelling of muscle biopsy sections and/or the application of specific DNA-based genetic analysis. Muscle MRI can also be helpful in achieving a diagnosis as it can show selective patterns of muscle involvement Box 24.19.2.1 Basis of the classification of muscular dystrophies • Clinical description • Genetics (autosomal dominant/recessive/X-linked) • Underlying gene/protein defect • Localization or function of the protein involved

section 24 Neurological disorders 6312 specific to various forms of muscular dystrophy and these specific patterns are increasingly well defined. General points on the management of the muscular dystrophies Despite the fact that no cures for muscular dystrophy have been established, there are many management issues that may be important or specific to the various types. However, as yet there is little systematic or comprehensive clinical research into management and randomized trials of management regimens are few and far between. It is nevertheless appropriate, where possible, that patients with a diagnosis or a suspected diagnosis of muscular dystrophy should be referred to a specialist clinic with access to the full range of specialists, who need to be involved in the coordinated care of these patients depending on their diagnosis and stage of disease. The multidisciplinary approach of these clinics ensures that patients have access to the full range of diagnostic facilities, are able to obtain specialized multidisciplinary care (including physiotherapy advice), and can obtain accurate genetic counselling where this is required. Access to patient support organizations and their staff is also of paramount importance. Patients should also be informed and offered the option to sign on to disease specific patient registries, as these are a powerful tool to collect information to gather better understanding of these rare conditions and help develop standards of care, identify participants for clinical trials, and update patients with relevant information to their condition. The diagnosis of any kind of muscular dystrophy, in that it inevitably implies a progressive and incurable disease, possibly with implications for children or other relatives, is a considerable burden and one that needs to be recognized and supported. The congenital muscular dystrophies The congenital muscular dystrophies (CMDs) are defined by their very early childhood onset. They comprise several disorders with different molecular pathological bases for the diseases. For their presentation, see Box 24.19.2.4. Extracellular matrix: Plasma membrane Cytoplasm Nuclear envelope Extracellular matrix Cytoplasm: Nuclear envelope: Plasma membrane: Collagen Laminin Fukutin FKRPM POMGnt LARGE Myotilin Emerin Dystrophin Integrins Caveolin Dysferlin Sarcoglycans Nesprins Lamin A/C Actin Telethonin TRIM32 Titin Calpain 3 Ab-crystallin Desmin Fig. 24.19.2.1

Schematic diagram to show localization within the muscle fibre (where known) of some of the proteins involved in producing a dystrophic phenotype. Box 24.19.2.2 Diagnosis of muscular dystrophy • History (especially motor milestones, age at onset, physical prowess as a child). • Age of patient (congenital/childhood/teenage/adult presentation). • Pattern of muscle involvement on examination (predominantly proximal/distal, upper limb/lower limb, symmetrical/asymmetrical). • Pattern of associated features on examination (contractures, muscle wasting, hypertrophy). • Level of serum creatine kinase in active disease (massive elevation in dystrophinopathy, sarcoglycanopathy, dysferlinopathy, calpainopathy, congenital muscular dystrophy (some); moderate elevation in facioscapulohumeral muscular dystrophy, Emery–Dreifuss muscular dystrophy, congenital muscular dystrophy (some); normal to mild elevation in autosomal dominant limb-girdle muscular dystrophy, facioscapulohumeral muscular dystrophy (some)). • Electromyography (to exclude neurogenic causes of weakness and congenital myasthenias, especially if serum creatine kinase is not markedly elevated). • Muscle imaging (ultrasound scans can confirm muscle involvement, but to confirm pattern of muscle involvement need MRI/CT). • Muscle biopsy, histology, and storage of frozen biopsy material for further analysis. • Specialized analysis of muscle biopsy (immunocytochemistry, immunoblotting, electron microscopy). • DNA analysis is now the gold standard for diagnosis. Box 24.19.2.3 History taking in muscle disease • Question in detail about early motor development. • Elicit what actually were the first symptoms experienced by a patient; this may be difficult but is important in highlighting the initial pattern of muscle involvement—lower limb vs. upper limb/ proximal vs. distal musculature. • Ask ‘When were you at your fastest?’; this may be informative in determining age of peak motor performance. • Ask about performance at school sports. • Particularly useful indicators in that respect are the ability to climb ropes (upper girdle weakness), muscle pain on running, a tendency to spend all the time in goal at football(!). • Do not assume that difficulty climbing stairs always indicates proximal muscle weakness—it may reflect an inability to push up on the toes. • Ask specifically about the ability to stand on tiptoe/stand on heels. The need to wear heels on shoes at all times may indicate Achilles tendon contractures. • Patients who had early Achilles tendon contractures may have had them operated on before being referred for diagnosis. Ask about this.

24.19.2 Muscular dystrophy 6313 Differential diagnosis In the neonatal and early childhood presentation the main clinical diagnostic confusion (after excluding central causes of hypotonia) may be with spinal muscular atrophy (check SMN gene for characteristic deletions), congenital myotonic dystrophy (facial weakness is usually more pronounced and diagnosis can be excluded on genetic testing), and congenital myopathy (may be distinguished on muscle biopsy). In all of these conditions, serum creatine kinase is either normal or much lower than seen in many congenital muscular dystrophies. With later childhood presentation the differential diagnosis is as already mentioned, plus Duchenne muscular dystrophy (though calf hypertrophy is usually more pronounced and serum creatine kinase is typically higher—biopsy will exclude the diagnosis) or childhood presentation of a limb-girdle type of muscular dystrophy. Classification There are several recognized forms of congenital muscular dystrophy and, as there is considerable heterogeneity in the group that remains, additional entities are ultimately likely to be distinguished at the genetic level. The diagnostic classification of this group of diseases was previously very clinically based, but is moving increasingly into a molecularly based. This allows the recognition of various subgroups of CMD: laminin $\alpha 2$ (LAMA2) associated CMD (MDC1A), the types of CMD involving abnormal glycosylation of α -dystroglycan (where there is frequent eye and/or brain involvement as well as muscle weakness), CMD associated with collagen VI mutations (Ullrich congenital

muscular dystrophy or UCMD), and rigid spine muscular dystrophy-1 (RSMD1) due to mutations in the selenoprotein-1 gene (Table 24.19.2.1). Cases of CMD due to mutations in genes also causing other types of muscular dystrophy are also increasingly recognized, for example with mutations in lamin A/C. Rare cases of CMD, mental retardation, and abnormal mitochondria (CMDmt) have been described associated with mutations in choline kinase beta (CHKB). Establishing the diagnosis Serum creatine kinase may, in some forms of congenital muscular dystrophy, be normal, but is typically elevated at least twofold, and up to twentyfold or more in the laminin A2-deficient group and the α -dystroglycanopathies. Muscle biopsy shows dystrophic changes and allows examination for LAMA2, α -dystroglycans, and collagen VI in muscle; skin is also used to distinguish cases with normal and abnormal or absent protein. MRI of the brain is a useful adjunct to diagnosis because it will confirm the presence of white matter changes, which are always present after age 6 months in primary LAMA2 deficiency, and the characteristic brain malformations in the types of CMD associated with α -dystroglycanopathy (see Table 24.19.2.1). Prognosis and management The overall prognosis depends on the type of CMD and individual severity in the patient because there can be major variability even within the different subgroups. Children with the most severe forms are at risk of dying in early childhood. If they survive this period, with appropriate management of feeding problems, and respiratory and (in a minority) cardiac complications, survival into adult life is the norm. The muscle weakness in congenital muscular dystrophy may be relatively static, but the complications of that weakness can be severe, and vary according to the precise diagnosis. The degree of muscle weakness is quite variable. In primary laminin A2-deficient CMD, the severity of the disease correlates roughly with the abundance of laminin A2 in the muscle, with children completely lacking laminin A2 rarely achieving independent ambulation. Others may

Box 24.19.2.4
Presentation of congenital muscular dystrophies
 Neonatal presentation • Hypotonia, which may be prenatal • Feeding problems (usually mild) • Joint contractures, especially knees, hips, and ankles (Fig. 24.19.2.2) • Joint laxity that may coexist with contractures at other joints
 Early childhood presentation • Delayed motor milestones • Failure to thrive • Repeated respiratory infections
 Later childhood presentation (rare) • Mainly proximal muscle symptoms • History of delayed motor milestones • Rigid spine, contractures of ankles, hips, and knees (a) (c) (b) Fig. 24.19.2.2 (a) Typical clinical picture of a baby presenting with MDC1A (muscular dystrophy, congenital, type 1a). Note the hypotonic posture, and mild contractures of the hips, knees, and ankles. (b, c) Immunofluorescence picture of skin biopsy labelled with an antibody to laminin A2 (merosin), showing normal (b) and absent labelling (c) patterns. This investigation can be carried out on a variety of tissues including skin, muscle, and placenta.

section 24 Neurological disorders 6314 Table 24.19.2.1 The congenital muscular dystrophies

Disease and nomenclature	Gene	Relative frequency in the UK population (expressed as % of CMD clinic population)	Diagnostic tests	Phenotype
Collagen VI related dystrophies (COL6-RD)	COL6A1, COL6A2, COL6A3	21%	Frequent absence or abnormality of collagen VI immunolabelling in muscle or cultured fibroblasts. Mutation testing	Characteristic pattern of joint hyperlaxity distally with proximal contractures. May be abnormal skin, including keloid scarring and hyperkeratosis
Can present as:				• Ullrich congenital muscular dystrophy (UCMD)– severe nonambulant and transient ambulant. UCMD is typically autosomal recessive, de novo dominant mutations are increasingly recognized • Intermediate phenotype • Bethlem myopathy (BM, milder allelic form)
CMD with abnormal glycosylation of α -dystroglycan (a dystroglycan-related dystrophy, α -dystroglycanopathy, a DGpathy)	fukutin, FKR, LARGE, POMT1, POMT2, POMGnT1, DAG1, DPM2/DPM3, GMPPB, ISPD, GTDC2, B3GNT1, SGK196, TMEM5, and others	15%	Abnormal labelling	

of α -dystroglycans in muscle, mutation testing Very variable brain phenotype ranging from normal to severe lissencephaly. Eye phenotype is also variable from normal to microphthalmia • Walker-Warburg syndrome • Muscle-eye-brain disease; Fukuyama CMD; Fukuyama-like CMD • CMD with cerebellar involvement; cerebellar abnormalities may include cysts, hypoplasia, and dysplasia • CMD with mental retardation and a structurally normal brain on imaging; (includes patients with isolated microcephaly or minor white matter changes on MRI) • CMD with no evidence of abnormal cognitive development Can present also as: • Limb-girdle muscular dystrophy (LGMD) with mental retardation • LGMD without mental retardation MDC1A (muscular dystrophy congenital type1A, Laminin A2 deficiency LAMA2- related dystrophy, LAMA2-CMD, merosin- deficient CMD) LAMA2 10% Absence of laminin A2 labelling in muscle and skin, mutation testing White matter radiolucency on MRI, approx 30% have epilepsy. May have restricted eye movements. Progressive development of severe contractures, scoliosis, feeding and respiratory problems require close follow-up Congenital laminopathy (LMNA related dystrophy, LMNA-CMD, LCMD, and Emery-Dreifuss) LMNA 3% Mutation testing in LMNA Very heterogeneous phenotype Early onset axial weakness with absent or early loss of ambulation, dropped head syndrome, feeding difficulties, and respiratory involvement Milder phenotypes Cardiac phenotype: arrhythmogenic cardiomyopathy with conduction block and also ventricular tachyarrhythmias requiring use of an AICD Selenoprotein 1 related myopathy presenting as CMD (SEPN1 related myopathy, RSMD1) SEPN1 1% Immunolabelling in muscle is typically normal. Diagnosis established on mutation in SEPN1 Typical rigid and side sliding spine develops in first decade. Early respiratory failure while ambulation maintained. Selenoprotein 1 gene mutations are also responsible for multiminicore disease RYR1 related myopathy presenting as CMD (RYR1-CMD) RYR1 n/a Muscle biopsy shows central core, multiminicore, centronuclear and nonspecific pathologies. which can assume CMD like characteristics Early scoliosis and absent or limited ambulation Others Various other causes of CMD have been described including mutations in integrin α -7 and α -9, nesprin 1, and CHKB ITGA7, ITGA9, SYNE1 CHKB n/a Depends on causative gene which will need to be detected by protein and mutation testing Depends on causative gene: ITGA7 related CMD: delayed motor milestones, respiratory impairment, scoliosis ITGA9 related CMD: similar to UCMD but no protruding calcanei, no respiratory failure, and acquired ability to walk SYNE1-related CMD: adducted thumbs, mental retardation, ophthalmoplegia CHKB-related CMD: large appearing mitochondria, cognitive impairment (with normal brain MRI), acanthosis nigricans like lesions and intense pruritus

24.19.2 Muscular dystrophy 6315 learn to walk independently but this is usually much later than usual, and these children may later lose this ability. For all types of CMD, joint contractures and scoliosis are major complications of the disease and cause much additional disability, requiring careful management by physiotherapy, standing regimens, orthoses, and surgery where appropriate. Feeding problems may be intractable and lead to chronic malnutrition unless treated by naso- gastric or gastrostomy feeding. Malnutrition may contribute to susceptibility to chest infections, which is also heightened by weakness of the respiratory muscles. These children are at risk of respiratory failure and their follow-up should include monitoring for this complication, which can be effectively managed by the provision of noninvasive home nocturnal ventilation. Cardiac failure is a relatively rare complication in CMD but has been reported in MDC1A and the α -dystroglycanopathies. Fukuyama congenital muscular dystrophy, muscle-eye-brain disease, Walker-Warburg syndrome, and other diseases within the α -dystroglycanopathy spectrum may be dominated by intellectual and visual impairment. In MDC1A, brain changes on MRI are typically

asymptomatic. In UCMD intellectual development is normal but respiratory failure is a major risk in the first decade. RSMD1 overall carries a generally much milder prognosis with respect to mobility, but this may mask a serious risk of respiratory failure and scoliosis, both generally necessitating intervention by the end of the first decade, often while still ambulant. Genetic counselling CMD are generally inherited in an autosomal recessive fashion, however dominant inheritance is possible and needs careful recognition to provide correct genetic counselling. Indeed, collagen VI and lamin A/C related disorders can be inherited in a recessive as well as a dominant pattern and these tend to be de novo mutations. It is, therefore, important to recognize dominant acting mutations—segregation studies are needed to determine whether the mutation is de novo, but the possibility of somatic or germline mosaicism in de novo mutations should always be considered to provide correct counselling. As the molecular basis for these disorders has recently become much better established, specific diagnosis should be attempted in all cases in order to allow proper direction of management, as well as prenatal and carrier testing where requested.

Dystrophin deficiency This group, including two of the most common forms of muscular dystrophy—Duchenne and Becker muscular dystrophy—involve the same gene and protein. These are X-linked diseases, caused by mutations, most of which are deletions, in the dystrophin gene (DMD). Presentation

Duchenne muscular dystrophy (OMIM 300377)

- All patients are symptomatic within the first 3 years of life, although the mean age at diagnosis is 51.7 months (4.3 years) with a range of 10–91 months.
- Motor milestones are often delayed (half the cases are not walking by 18 months).
- Speech is also frequently delayed.
- Patient is unable to run: there is a pronounced waddling gait on attempting to rush.
- Patient is unable to jump with both feet together or to hop: there is no spring in the step.
- ‘Climbs up legs’ on rising from the floor: Gower’s manoeuvre.
- Can present with anaesthetic complications. Anaesthesia guidelines can be found on

<http://community.parentprojectmd.org/profiles/blogs/revised-duchenne-anesthesia-recommendations-2015>

Becker muscular dystrophy (OMIM 300376)

- The mean age at onset of Becker muscular dystrophy is 11 years, although the range of age at presentation is extremely wide and the diagnosis may be made at any age, particularly if there is a family history.
- A proportion will have had delayed motor milestones (this may correlate as much with reduction in IQ as with major motor problems at that age).
- Many describe being unable to keep up with peers at school.
- There is difficulty with high steps and climbing hills.
- Muscle pains after exercise are a common complaint, especially in teenagers (rarely myoglobinuria).

Manifesting carriers of Duchenne muscular dystrophy/Becker muscular dystrophy A highly variable group, which may occasionally be as severely affected as those with Duchenne muscular dystrophy or more or less mildly than those with Becker muscular dystrophy. Up to 10% may be at risk of cardiac complications of their carrier status.

Dystrophin-associated cardiomyopathy OMIM 302045 There are symptoms and signs of hypertrophy progressing to dilated cardiomyopathy in the absence of major muscle symptoms. Some patients have an elevated serum creatine kinase. Establishing the diagnosis

The clinical presentation of Duchenne muscular dystrophy (DMD) is very characteristic. Hypertrophy of the calf muscles is almost universal (Fig. 24.19.2.3a), sometimes accompanied by muscle hypertrophy elsewhere, most frequently involving deltoid, parts of the quadriceps, the tongue, and masseters. Wasting of the pectoral and scapular muscles leads to hypotonia around the shoulders, detected as the child ‘slipping through the hands’ on being lifted. In the lower limbs, quadriceps power is weaker than that of the hamstrings. Formal examination of a small child may be difficult, and the main clinical tool is observation of walking, attempting to run, jump, and climb stairs, and to rise from the floor. It is imperative to give the child space to attempt to run, as this will bring out the lack of spring in the step and the lack of fluidity of the

attempted running. Becker muscular dystrophy (BMD) has been described as a 'slow motion version of Duchenne muscular dystrophy', in that the pattern of muscle involvement in these two allelic disorders is essentially identical (Fig. 24.19.2.3c), but progresses at a much slower rate in BMD. Patients with BMD may be quite strong on formal muscle examination, but tend to show subtle signs of proximal muscle weakness on climbing stairs or running. They frequently

section 24 Neurological disorders 6316 have hypertrophy involving the same muscle groups as seen in DMD. Some patients have pes cavus. Serum creatine kinase is always massively elevated, even to more than 200 times normal, but levels of serum creatine kinase do not distinguish the severity of the disease. Muscle biopsy and electro-myography are nonspecifically but generally severely dystrophic. The muscle biopsy in BMD may also show some grouped fibre atrophy reminiscent of a 'neurogenic' pathology. Molecular confirmation of the diagnosis is essential to assist in defining prognosis and to provide appropriate genetic counselling. In addition, current standards of diagnosis include detailed characterization of the mutation as it is essential in view of mutation-specific drugs that are now available or being developed for use, so far, in clinical trials. Multiple ligation probe amplification is a technique that can detect copy number of every exon and confirm the diagnosis in the 60–80% of patients in whom a deletion or duplication of the dystrophin gene is present, regardless whether the patient is a male or female—this was not the case with previously used techniques like multiplex polymerase chain reaction. For patients in whom deletion and duplication analysis are negative, testing for point mutations via direct sequencing techniques (Sanger sequencing or next-generation sequencing) of the entire coding region is mandatory. In dubious cases of unknown pathogenicity of the variant identified or in patients with no detectable mutation, it is useful to consider a muscle biopsy by which, in all patients, the diagnosis can be established by not finding or finding reduced dystrophin in the muscle biopsy (Fig. 24.19.2.3d). This analysis also allows the distinction of dystrophinopathy from the much rarer (in most populations) limb-girdle types of muscular dystrophy. Precision of the exact mutation is important for offering carrier testing to the mother and other family members (important to establish the risk of any cardiac problems as well as to allow genetic advice for future pregnancies) and also to allow future access to the mutation-specific treatments that are currently under development, such as antisense oligonucleotide-mediated exon skipping and stop codon suppression. Prognosis Within the 'dystrophinopathy' group the prognosis is highly variable. By definition, untreated patients with DMD lose the ability to walk by the age of 12, though this definition is now difficult to apply as the widespread use of corticosteroids has delayed the loss of ambulation in many patients well into their teenage years. The development of scoliosis, respiratory failure and cardiomyopathy (Box 24.19.2.5) are also delayed with the use of steroids, and improved overall management means that survival into or beyond the late 20s and 30s is becoming more common. Patients with BMD are ambulant beyond 16 years of age, and may remain able to walk independently into their fifth decade or later. These patients are susceptible to cardiac failure at any age from the teens onward and should be monitored for this complication on a regular basis (Box 24.19.2.5). Respiratory failure is a late complication in BMD and correlates with very late-stage disease. The lifespan in BMD may be normal, or reduced in more severe disease. An 'intermediate' group is also recognized, patients losing ambulation between age 12 and 16: their overall prognosis is also intermediate between DMD and BMD. Around 8% of carriers of (b) (a) (c) (d) Fig. 24.19.2.3 (a) Child with Duchenne muscular dystrophy at presentation, showing the marked calf and quadriceps hypertrophy and tendency to rise onto the toes. (b) Teenage boy in the later stages of the disease, showing the complications of marked immobility, scoliosis, and muscle

wasting. This young man has now been maintained on home nocturnal ventilation successfully for more than 7 years. (c) Clinical pattern at presentation in a young man with Becker muscular dystrophy. Note hypertrophic muscles in calves and quadriceps and mild wasting around the shoulder girdle. (d) Immunocytochemical analysis of dystrophin in normal muscle, Becker muscular dystrophy muscle, and Duchenne muscular dystrophy muscle. In normal muscle, dystrophin labels evenly around the periphery of the muscle fibres. This labelling is typically patchy and reduced in Becker muscular dystrophy, and is either completely or almost completely absent in Duchenne muscular dystrophy. Box 24.19.2.5 Practice point: cardiac involvement in dystrophinopathy • All patients with dystrophinopathy are at risk of developing cardio- myopathy which progresses with age. It is frequently asymptomatic, and needs to be sought through full cardiac assessment including echocardiography, as treatment with antifailure medication may improve function and prognosis. • Cardiac transplantation has been used successfully in patients with Becker muscular dystrophy and manifesting carriers of dystrophinopathy. It may be more utilized in DMD as other management modalities improve. • Cardiac compromise is the major determinant of operative risk in boys with Duchenne muscular dystrophy, and all should have a full cardiac assessment in advance of any surgery at any age.

24.19.2 Muscular dystrophy 6317 DMD or BMD may develop some signs of the disease: rarely this is in a full-blown form comparable to the disease in boys. In practice, there is a continuum of severity with the highest incidence in the DMD group (birth incidence 1 in 3500 male live births), while the estimated incidence in the BMD group is at 1 in 18 518 male births. As the lifespan is so much longer in the BMD group, however, the prevalence of the two conditions is roughly similar (about 24 per million population in north-east England). Over the whole group, there is a correlation between dystrophin abundance (as measured in a muscle biopsy sample) and severity: children with completely absent dystrophin tend to be confined to a wheelchair slightly earlier than children whose biopsies contain low levels of dystrophin. Patients with BMD have much higher levels of dystrophin (see Fig. 24.19.2.3). These dystrophin levels also correlate in most cases with the type of mutation found in the dystrophin gene—in DMD most deletions are out of frame, not supporting the production of dystrophin, whereas BMD patients typically have in-frame deletions, allowing the production of a reduced amount of dystrophin of a slightly smaller size. Although these correlations are useful in a general sense, they are not absolutely predictive of outcome in an individual case, and must always be taken in the context of the clinical features of the patient. Indeed, the move towards genetic testing as the primary step in diagnostics means that most patients now will not have a muscle biopsy routinely. They can be useful, however, in giving the best possible guide to prognosis, especially in those patients who present early with no clinical clues as to the severity of the disease, or who are identified by neonatal screening or the incidental finding of a high serum creatine kinase level. Management DMD is essentially a predictable disease with complications that need to be proactively sought and managed in different systems. Although, in the past, a nihilistic attitude to management in DMD was widespread, evidence of the benefits of proactive management is now available and all patients should have access to the highest possible care. The key to proper management is a team specializing in neuromuscular management, who can oversee the coordination of input from physiotherapy, orthopaedic, cardiac, respiratory and psychology specialists. Input from other specialties, including occupational therapy, educational psychology, gastrointestinal medicine, and palliative care, may also be required. Indeed, corticosteroids together with multidisciplinary management of DMD boys have led to changes of the natural history of this condition,

improvement of quality of life and prolonged survival with the possibility of life expectancy into the late thirties. Duchenne muscular dystrophy: the early stages Proper management of a child with DMD starts with awareness of the possibility of the diagnosis in any boy who is not walking by the age of 18 months or whose mobility is poor compared with that of his peers. The current mean age at diagnosis has improved over the last decade dropping from almost 5 years to 4.3 years with a range of 10–91 months, highlighting still unacceptable delays. The principal impetus to early diagnosis is currently the ability to offer parents the option of prenatal diagnosis in subsequent pregnancies. Early diagnosis is essential, as prompt management and interventions according to standards of care results in better outcomes. When specific treatments become available, there is likely also to be a need to implement such treatments before the disease is too advanced. Once the diagnosis has been considered, measurement of the serum creatine kinase will confirm the suspicion and ideally a referral to a specialist unit should be made at this stage. The specialist unit should have rapid-track access to DNA diagnostic and, if needed, muscle biopsy facilities to confirm the diagnosis as quickly as possible. DMD is a devastating diagnosis, and should be given to the family following guidelines for the best practice for disclosure of bad news: the parents should be seen together wherever possible in complete privacy, they should have time to sit and ask questions, and have access to experienced staff for support and further information. Access to support groups and the relevant national charity is appropriate. Supporting information should also be passed immediately to the GP, health visitor, and school who may never have looked after a child with this type of condition before. As DMD is an X-linked condition, early access to genetic counselling is also vital shortly after diagnosis (Box 24.19.2.6) and needs to be reinforced as the affected person and his siblings reach adulthood. Untreated, DMD has a rapidly progressive course with loss of ambulation in the first decade of life and death before the age of 20. Thanks to the introduction of corticosteroids and multidisciplinary management in boys with DMD the life expectancy and disease course have changed substantially. As part of the multidisciplinary management, the introduction of nocturnal noninvasive ventilation and scoliosis surgery has been shown to have a positive impact on survival, in particular if combined. In addition, early cardiac treatment with angiotensin converting enzyme (ACE) inhibitors and β -blockers can delay the progression of dilated cardiomyopathy. From Box 24.19.2.6 Genetic counselling

in dystrophinopathy Genetic counselling in dystrophinopathy is an essential part of the management of any family where a diagnosis of dystrophinopathy has been made because the potential implications go far beyond the index case.

- These are X-linked diseases.
- The new mutation rate in the dystrophin gene is high.
- Most cases of Duchenne muscular dystrophy are born now in families with no prior history of the disease.
- None the less, even in these families, other female relatives (through the maternal line) are at risk of being carriers.
- The essential piece of information is the delineation of the dystrophin mutation in the affected child (easy to find in the 60% in whom the mutation is a deletion, but point mutation testing by sequencing required in the remainder).
- In the presence of a known mutation, female relatives can be offered testing directly to see if they are carriers or not.
- They may choose to have prenatal diagnosis on the basis of that testing.
- Even if mothers of boys with Duchenne muscular dystrophy can be shown not to be somatic carriers of the mutation in their son, they still may have a proportion of egg cells containing the mutation (a situation known as ‘germline mosaicism’). They therefore remain at a 10–20% risk of having another affected child in a future pregnancy.
- Boys with Duchenne muscular dystrophy are increasingly surviving to adulthood with some having the opportunity to have children, and men with Becker muscular dystrophy often do (overall fitness reduced to around 2/3). All of their daughters are obligate carriers of Becker muscular dystrophy, but none of their

sons are at risk. Genetic counselling is an important part of transition planning.

section 24 Neurological disorders 6318 early stages physiotherapy management of ankle and hip contractures with regular stretching exercises is fundamental for maintenance ambulation. Boys frequently develop a toe-walking gait which partially compensates for their proximal muscle weakness—walking splints or ankle-foot orthoses are, therefore, not appropriate at this stage and any early Achilles tendon contractures are better managed through passive stretching and night-time below-knee splints. During the late ambulatory phase, at the point at which walking becomes impossible independently, knee-ankle-foot orthoses can be introduced to prolong ambulation, but are not essential. Corticosteroids are at present the sole available treatment that has been proven to slow down the decline in muscle strength and prolong ambulation. It is recommended that corticosteroids (prednisolone or deflazacort) are started between the age of 2 and 5 years (when strength is plateauing or declining) for the preservation of strength. An increasing consensus has developed that use of daily corticosteroids (prednisolone at a dose of 0.75 mg/kg per day or deflazacort at a dose of 0.9 mg/kg per day) is preferred to alternative regimes; however, intermittent regimens are currently being tested in a double-blind randomized trial which may potentially lead to changes in these recommendations. Controlled trials show a clear benefit for strength and respiratory function for up to 18 months, and uncontrolled long-term cohort studies report a significant delay in loss of ambulation, a reduction in the development of scoliosis, and a protective effect on respiratory and also cardiac function. Close monitoring for the side effects of corticosteroids is, of course, indicated, and crucial to minimize the potentially harmful effects of the treatment. In DMD the most commonly reported side effects are weight gain (which can be addressed with careful attention to diet), reduction in height, delayed puberty, and behavioural side effects, which may respond to a change in timing of dosage to evening instead of morning, as well as to standard psychological means to improve behaviour management. A further concern is the development of significant osteoporosis, which is a risk in any case in boys with DMD, but which may be exacerbated, particularly in the lumbar spine, by steroid usage. The prophylactic use of bisphosphonates in this patient group remains controversial, but intravenous bisphosphonate treatment is certainly indicated if there is a problem with symptomatic fracture, and this need not be an indication for discontinuation of steroid treatment. Prophylactic cardiac treatment with ACE inhibitors and β -blockers is currently being investigated in a double-blind, randomized, multicentre, placebo-controlled trial to assess whether this can prevent the development or delay the age of onset of cardiomyopathy in boys with normal left ventricular function on transthoracic echocardiography. Duchenne muscular dystrophy: after mobility is lost Despite optimal multidisciplinary management loss of ambulation inevitably occurs and interventions and adaptation should follow according to disease progression (early and late nonambulatory phase). The prompt provision of a powered wheelchair with indoor and outdoor access is critical to the best possible maintenance of independence and access to wheelchair sports. In the early non-ambulatory phase provision of a manual wheelchair may also be necessary, predominantly for indoor use and as a backup. With disease progression upper limb strength will inevitably decline and alternative control devices need to be considered to maintain independence. Regular assessment of the wheelchair, with particular attention to correct seating, promoting upright and symmetrical spine posture, is fundamental to reduce scoliosis, as well as lower limb neutral posture to limit foot deformities. Scoliosis is seen in around 90% of patients with DMD who have not been treated with steroids, though corticosteroid use reduces this risk dramatically. For patients with progressive scoliosis, spinal surgery in an experienced setting is a good way to

restore posture and comfort, and has an additive effect on survival. Physiotherapy priorities for all boys shift towards postural support, the prevention and containment of contractures, and respiratory maintenance. Alongside progressive loss of ambulation, respiratory muscle strength declines, and respiratory management and prompt intervention become fundamental. Regular measuring of respiratory muscle function (forced vital capacity) in order to monitor the progression of the disease and identification of early signs of respiratory failure is required in order for timely intervention and to improve the quality of life and longevity in these patients, since respiratory failure is still among the main causes of death in patients affected by DMD. As forced vital capacity falls further, boys are at serious risk of chest infections and ultimately nocturnal respiratory failure. Respiratory care should begin early with prompt access to antibiotics at the first sign of any infection, access to immunizations, support for and augmentation of coughing, and noninvasive ventilation. Patients are at risk of hypercapnia, and oxygen should not be administered without proper monitoring of blood gases and a low threshold for initiating respiratory support. Symptoms of respiratory failure may be extremely insidious and totally missed unless explicitly sought (Box 24.19.2.7). Routine overnight pulse oximetry (which can readily be carried out at home provided that the equipment is available) can show a trend of deteriorating overnight Box 24.19.2.7

Respiratory failure in neuromuscular disease Respiratory failure in neuromuscular disease is a complication which needs to be specifically sought.

- It may be the result of intercostal muscle or diaphragmatic weakness or a combination of the two. The presence of a scoliosis or other spinal deformity may be an additional factor.
- Nocturnal problems tend to dominate.
- Frank symptoms of morning CO₂ retention may be seen (poor colour, morning sickness, headaches, confusion) but these are late symptoms and the problem should be detected by investigation or careful history taking before this stage.
- Increasing frequency of chest infections may indicate incipient respiratory failure.
- Subtle signs include loss of appetite and weight loss, loss of energy and enthusiasm.
- Poor sleep, increasing wakefulness at night, inability to lie flat may also be seen together with a tendency to fall asleep during the day.
- Difficulties swallowing and difficulty completing sentences may also be seen.
- In many muscle diseases, the main risk of respiratory failure is when the patient is no longer able to walk independently and weakness is pronounced (for example Duchenne muscular dystrophy, Becker muscular dystrophy, congenital muscular dystrophy, facioscapulohumeral muscular dystrophy, limb-girdle muscular dystrophy, and so on).
- In other muscle diseases, respiratory failure may be an earlier feature and present while the patient is still ambulant (for example multicore and other congenital myopathies, some forms of congenital muscular dystrophy).

24.19.2 Muscular dystrophy 6319 oxygenation and, together with the monitoring of symptoms, highlight the time at which elective nocturnal respiratory support, ideally at least through noninvasive ventilation initially, should be provided. Such respiratory support abolishes symptoms, reduces the tendency to chest infections and undoubtedly improves life-span, in particular if combined with spinal surgery, with a good quality of life. In the late stages of DMD, nutrition may be of concern. Loss of weight occurs in most boys as a result of dysphagia, slow eating due to chewing difficulties and low mood as the disease progresses, and issues of diet and the possibility of supplemental nutrition (possibly by gastrostomy) need to be addressed. Patients may need referral to Speech and Language therapy to assess their swallowing function as dysphagia can lead to aspiration pneumonia. Constipation is also frequently reported in DMD and can be severe; it may also contribute to reduced appetite. Constipation is usually managed with laxatives or a combination of laxatives and rectal enemas; however, these should be used carefully as they can

lead to a vasovagal reaction. DMD patients have an increased anaesthetic risk and pre-anaesthetic cardiac and respiratory assessment is important. When exposed to inhalational anaesthetics or muscle relaxants like succinylcholine, patients can develop rhabdomyolysis. Non-depolarizing neuromuscular blockers can be used safely instead of succinylcholine. Inhalational anaesthetics should be avoided if possible and intravenous anaesthetics should be used instead. DMD patients are exposed to increased fracture risk due to steroids. Early mobilization and rehabilitation is essential. Internal fixation should be taken into consideration to shorten immobilization. There is also a high risk of vertebral fractures, and these can sometimes be asymptomatic. Fat embolism syndrome is extremely rare, though a life-threatening event, that usually presents following a fracture of long bones, but can present also after minor trauma. Signs and symptoms suspicious of fat embolism syndrome are shortness of breath and/or neurological symptoms following a fall or fractures. Respiratory function should be supported. A chest CT scan may be helpful to confirm the diagnosis. Thanks to improvements in care management life expectancy for patients with DMD has increased, and patients are now reaching adulthood with a relatively good quality of life. While this was not the case a few years ago, a young DMD man can now aim to reach higher education levels and also achieve independent living. Transition of care to adulthood needs timely planning, to allow care hand-over ideally to a multidisciplinary team, to monitor and promptly address care needs arising in an adult man with DMD in order to maximize health. While at present only few adult men with DMD achieve independent living, this is likely to become more common in future and represents a challenge for the patient and family; the team around the family should be able to provide adequate support to achieve this and overcome barriers. The actual cause and timing of death in DMD is hard to predict. Some patients will die of a particularly severe chest infection. In others cardiomyopathy may be difficult to control or a cardiac arrhythmia may arise. Any medical intervention at the later stages should be carefully managed by an experienced team. Early onset of cardiomyopathy is a poor prognostic sign. Talking about death to these patients and their parents, helping them to prepare and also address their fears and uncertainties, is another important but easily neglected aspect of management.

Education On average, children with DMD have an IQ around 1 standard deviation below the normal mean; often a striking verbal performance deficit is observed and there is a deficit in number span. Learning problems are not progressive. Additional behavioural phenotypes may complicate the pattern of learning needs, including a tendency to behaviour in the autistic spectrum in some children. Schooling should offer the best possible environment for learning, taking into account the profile of needs of the individual child, and including full attention to information technology equipment, while supporting the very real physical needs of the child. Families and areas vary as to whether this will be best provided through mainstream or special schooling. With a good education and medical support, boys with DMD and the appropriate intellectual potential can go on to higher education, and should be encouraged to do so.

Becker muscular dystrophy Management issues in BMD tend to cover the same broad areas as DMD, but with the deterioration in muscle function over a much longer timescale. Certain complications, such as scoliosis, are very unusual. Other complications, such as cramping muscle pains after exercise, which can be a particular problem in the teenage years, are more common. Despite the fact that BMD is much milder than DMD, it can represent a considerable and insurmountable disability for the person who has it, and problems with adjustment, poor self-esteem, and poor body image are all fairly common in this group. There are no hard data to define completely any intellectual problems in BMD, but on average it is likely that this group has a general reduction in IQ, although probably not to the extent seen in DMD. Cardiac complications may occur at any age in BMD and

require proactive surveillance and management (see Box 24.19.2.5): respiratory complications tend to be a feature of the late stages of the disease. Fascioscapulohumeral muscular dystrophy (FSHD) is an example of a muscular dystrophy named for the most characteristic pattern of muscle involvement observed (that of involvement of the facial, scapular, and humeral muscles predominantly). However, other muscle groups usually become involved with time and may even be involved at onset.

- Age at presentation is variable. Most affected individuals manifest some symptoms by their teens or twenties. Occasionally symptoms may be very minor, even late in adult life.
- Symptoms may, unusually for a muscular dystrophy, be very markedly asymmetrical. Early symptoms typically include facial weakness (inability to bury eyelashes or puff cheeks; this often goes unnoticed), shoulder girdle weakness manifesting as problems in reaching high shelves, changing light bulbs, or climbing ropes, and foot-drop.

section 24 Neurological disorders 6320 An infantile form of FSHD is recognized with early childhood onset, extremely marked facial weakness, and progressive weakness of both the shoulder and pelvic girdle musculature. Lumbar lordosis may be profound. Hearing loss and retinal telangiectasia may be seen in any patient with FSHD but are particularly associated with this most severe form of the disease.

Differential diagnosis The clinical pattern of FSHD can be very distinctive, and the asymmetry of muscle involvement is a major clue. However, facial weakness may be very variable and, if it is absent or subtle, confusion can arise with forms of limb-girdle muscular dystrophy.

Diagnostic investigations Serum creatine kinase may be normal or mildly elevated. Muscle biopsy and electromyography (EMG) provide supportive evidence for a muscular dystrophy; some inflammatory features are sometimes also seen in the biopsy. Most cases (if not all) of FSHD are linked to altered expression of the DUX4 gene in the macrosatellite repeat D4Z4 region chromosome 4q35. A DNA-based test is available that can confirm the diagnosis in 95% of cases. This test involves the demonstration of a DNA deletion that is consistently associated with the disease and shows a shortening of the D4Z4 allele, which causes altered expression of the DUX4 gene. This common form of FSHD is known as FSHD1. A smaller percentage of patients (about 3–5%) have epigenetic factors that alter the chromatin relaxation in the D4Z4 (DUX4 permissive allele) area, without a shortening of the D4Z4 allele; in this group of patients mutations have been identified in the chromatin modifier SMCHD1. This group of patients is known as FSHD2.

Prognosis and management Infantile FSHD is a progressive disease that leads to early confinement to a wheelchair and the development of such complications as scoliosis and respiratory failure. This condition is most frequently seen as a result of a new dominant mutation in cases with no family history, and these children often have particularly large DNA deletions on chromosome 4. The development of a lumbar lordosis, seen also in later-onset fascioscapulohumeral muscular dystrophy, together with secondary hip flexion contractures, can be very disabling. Bracing may be partially successful at controlling the lordosis, but at the expense of some loss of mobility. More typically, FSHD is a slowly progressive disease. As the disease progresses it can involve the proximal as well as the distal lower limb muscles. Around 20% of patients with FSHD will become unable to walk independently, most when aged over 40. Involvement of the proximal lower limbs before the age of 20 years is a poor prognostic sign, indicating an increased likelihood of wheelchair use. Some patients describe progression as being stepwise in nature, with periods of faster deterioration alternating with phases of plateauing of their symptoms. Foot-drop is a common complaint, which can be helped by the provision of daytime ankle-foot orthoses. A significant proportion of patients with FSHD complain of painful muscles, for which no cause can

be found and for which pain relief may be difficult. Some patients find swimming or a small dose of antidepressants useful for this symptom. More severely affected patients with FSHD may develop respiratory failure or swallowing problems, and these complications should be sought. Cardiomyopathy is rarely reported. Genetic counselling FSHD1 is an autosomal dominant disease and as such an affected person has a 50% chance of transmission to his or her offspring, regardless of sex. Use of the new DNA diagnostic techniques has shown that up to 30% of cases of FSHD may represent de novo dominant mutations. Germline mosaicism is also common. Genetic analysis has also shown a higher proportion of asymptomatic gene carriers than expected, with females overrepresented in this group. The availability of a relatively straightforward genetic test in this disorder has opened up the possibility of presymptomatic and pre-natal testing, which were previously impossible. However, despite an overall correlation between the size of the deletion found and the severity of the symptoms, the DNA test is not useful in predicting the severity of the disease—people in individual families with apparently the same sized deletion may have a very variable experience of the disease (Fig. 24.19.2.4). FSHD2 is inherited in a digenic manner, meaning that SMCHD1 and DUX4-permissive alleles segregate independently and each parent will carry either a SMCHD1 or a permissive DUX4 allele. Clinically, this means that heterozygous patients are asymptomatic. Putting this together, there is a risk to between 25 and 50% of the offsprings being affected, depending on the haplotypes in the wider Fig. 24.19.2.4 Mother and daughter with fascioscapulohumeral muscular dystrophy. The mother is extremely mildly affected and has minimal symptoms. By contrast the daughter was affected from early childhood and has been wheelchair dependent outside from her early teens. Note the daughter's expressionless face and her posture—she is leaning forward due to a combination of her marked lumbar lordosis, a major feature of the condition, and hip flexion contractures.

24.19.2 Muscular dystrophy 6321 family. As for FSHD1, there is variability in disease expression even within the same family. Emery-Dreifuss muscular dystrophy (OMIM 300384) Classic Emery-Dreifuss muscular dystrophy (EDMD) has a highly characteristic phenotype. X-linked recessive, autosomal dominant, and (very rare) autosomal recessive forms are recognized, and the genes involved in these conditions encode proteins that are components of the nuclear envelope (Fig. 24.19.2.5). The gene involved in X-linked EDMD is emerin (EMD), and that involved in autosomal dominant and autosomal recessive EDMD2 and 3 is lamin A/C (LMNA/LMNC). Other genes have also been implicated in patients with an Emery-Dreifuss phenotype, including nesprin 1 and 2 (SYNE1 and SYNE2), EDMD 4 and 5, four-and-a-half-LIM protein 1 (FHL1) EDMD6 and transmembrane protein 43 (TMEM43) EDMD7. Presentation • Patients may present at any age, most typically in the early teens, although symptoms may be present much earlier than that. • Contractures of the ankles and elbows and rigidity of the spine often predate any clear weakness. • Consequently, these patients have frequently had Achilles tendon release before the diagnosis is suspected. • Weakness and wasting are typically humeroperoneal in distribution. A key part of these conditions, which may rarely be seen at presentation, is cardiac involvement, most typically arrhythmias (see next). Several alternative phenotypes (a form of congenital muscular dystrophy limb-girdle muscular dystrophy 1B and a pure cardiac disease—Box 24.19.2.8 and see Fig. 24.19.2.5) exist in combination with mutations in the same gene as autosomal dominant EDMD (lamin A/C). Lamin A/C mutations are also described in several diseases where there is no predominant muscle phenotype, including partial lipodystrophy, some forms of progeria syndromes, mandibuloacral dysplasia, and a form of peripheral neuropathy. Some patients may show overlapping features of these different syndromes. Laminopathy is

much more phenotypically diverse than X-linked EDMD and a high index of suspicion of this disorder is necessary, especially due to the almost inevitable life-threatening cardiac complications. Confirming the diagnosis Serum creatine kinase is typically mildly elevated in EDMD. Muscle biopsy shows nonspecific histological features: in X-linked EDMD, emerin is absent in muscle and skin. Detection of mutation in the emerin gene is necessary to offer genetic counselling to female relatives at risk of being carriers. The involvement of lamin A/C (the gene responsible for autosomal dominant EDMD) cannot be determined by antibody analysis in muscle, but requires the demonstration of a lamin A/C mutation. Many lamin A/C mutations arise anew, and germline mosaicism is common. Use of specific genetic testing has shown that, in fact, in (a) (b) Fig. 24.19.2.5 Muscular dystrophy phenotypes characterized by prominent contractures. (a) This patient has autosomal dominant Emery–Dreifuss muscular dystrophy, with a proven mutation in his lamin A/C gene. The elbow and Achilles tendon contractures seen here, combined with his markedly rigid spine, are very similar to the pattern of contractures and weakness seen in the X-linked form of the disease. (b) Bethlem myopathy in a woman with marked contractures of the elbows, ankles, and spine. In addition she has finger flexion contractures, demonstrated here by attempting to straighten the fingers with the wrist extended. Box 24.19.2.8 The skeletal muscle laminopathies • Forms of congenital muscular dystrophy, Emery–Dreifuss muscular dystrophy and limb-girdle muscular dystrophy are all caused by mutations in lamin A/C, a component of the nuclear envelope. • The phenotype is variable, depending on age at onset and the presence or not of contractures as a major component of the phenotype. • Where contractures are present, these typically involve the elbows, Achilles tendons, and spine. In these patients, there is often a humeroperoneal pattern of muscle weakness as in X-linked Emery–Dreifuss muscular dystrophy. • Where contractures are less of a feature, patients typically present with proximal muscle weakness. • In all groups, cardiac involvement is the most important complication. Arrhythmias may lead to sudden death and should be sought and treated appropriately. • A phenotype with exclusively cardiac involvement has also been described. • New mutations and germline mosaicism is common in this group.

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contradistinction to what had been previously reported, autosomal dominant EDMD is more frequent than the classically described X-linked form.

Differential diagnosis In addition to previously mentioned other genes (SYNE1, SYNE2, FHL1, TMEM43) that can give rise to Emery–Dreifuss phenotype, other muscular dystrophies may present with contractures as an important component (see Fig. 24.19.2.5). Some forms of CMD may be associated with contractures and a rigid spine. Bethlem myopathy may present congenitally (often with torticollis) or in early childhood: here finger flexion contractures, elicited especially on wrist extension, are more prominent and cardiac involvement is not associated. Bethlem myopathy is itself genetically heterogeneous, involving mutations in any of the genes for collagen VI- α 1, - α 2, and - α 3. The condition is allelic to the much more severe CMD, UCMD. Unlike in UCMD, where examination of skin and muscle frequently shows an abnormality of collagen VI expression, in Bethlem myopathy collagen VI labelling in muscle may be normal. Immunoanalysis of cultured fibroblasts may be a useful diagnostic tool before proceeding to mutation analysis, which is time-consuming due to the large size of the three genes to be screened and the presence of many polymorphisms. Muscle MRI demonstrates a very characteristic pattern of muscle involvement that can be used to help diagnosis and guide mutation testing. Patients with Bethlem myopathy may show skin abnormalities such as follicular hyperkeratosis and abnormal scarring. In some cases, calpainopathy (limb-girdle muscular dystrophy 2A) may be associated with contractures of the

ankles, elbows, fingers, and paraspinal muscles. However, the associated weakness here is predominantly proximal and of a characteristic distribution (see next). These patients typically have a higher creatine kinase, absent calpain 3 on biopsy and CAPN3 mutations. Prognosis and management The prognosis in EDMD relates almost directly to the ability to manage the life-threatening arrhythmias to which every patient with either the X-linked or dominant form is susceptible. Severe arrhythmias are inevitable by the third decade. All patients with this diagnosis should, therefore, be under regular cardiological review, and once a rhythm disturbance has been detected cardiac pacing may be life saving. However, in autosomal dominant EDMD evidence suggests that the risk of ventricular arrhythmias necessitates the use of an implantable defibrillator. In this condition there is also a risk of cardiomyopathy, which may be less amenable to routine treatment. Management of the contractures in EDMD is the other main issue, and will involve close liaison with a physiotherapist. Operative treatment of contractures, especially at the Achilles tendons, is commonly performed, but, although such surgery does work in the short term, contractures often recur. With increasing age, however, contractures frequently stabilize. Muscle weakness may worsen but progression is usually very slow. Rigidity of the spine may complicate weakness of the respiratory muscles and nocturnal respiratory support may be needed. Monitoring should include regular assessment of forced vital capacity when sitting and lying, and symptom enquiry for any symptoms of respiratory impairment.

The limb-girdle muscular dystrophies The broad definition of the term 'limb-girdle muscular dystrophy' comes from the classification of Walton and Nattrass in 1954, when the term was suggested to describe those patients with weakness of the proximal musculature who did not fulfil the criteria for either the X-linked muscular dystrophies or fascioscapulohumeral muscular dystrophy. The term has always encompassed a heterogeneous group of disorders: now that many of them can be distinguished at the gene or protein level it is no longer sufficient to use it without qualification as to the specific type of disease (Table 24.19.2.2). The type of limb-girdle muscular dystrophy may be suggested by the precise pattern of muscle involvement, with confirmation from a combination of genetic and protein analysis. The ability to provide a precise diagnosis in limb-girdle muscular dystrophy has greatly improved the prognostic and genetic information that can be given to these patients. In recent years, thanks to the development and introduction of next-generation sequencing techniques for diagnostic purposes, this particular field of limb-girdle muscular dystrophies (LGMDs) has grown rapidly, and new genes have been identified as causative of LGMD, or known genes causative of other forms of muscular disorders were identified as responsible for the limb-girdle phenotype. Careful attention is needed when counselling about these newly identified conditions and prognostic implications. The approach to diagnosis in limb-girdle muscular dystrophy Could it be dominant disease? Autosomal dominant limb-girdle muscular dystrophy (LGMD) represents only around 10% of the total LGMD population, and LGMD1A, -1C, -1D, and -1E have been very rarely reported. In families with a dominant history the most likely diagnoses are fascioscapulohumeral muscular dystrophy (exclude fascioscapulohumeral muscular dystrophy on DNA analysis especially if there is any suspicion of facial weakness), LGMD1B (allelic with autosomal dominant EDMD—see Box 24.19.2.8), and Bethlem myopathy. New mutations are common, however, so, if the clinical features are suggestive of one of these disorders, the diagnosis should be pursued even in the absence of a family history. Features that should raise the suspicion of dominant disease are less marked elevation of creatine kinase (typically normal to five times normal in dominant disease and much higher than this in active recessive disease), or the presence of early and prominent contractures. As knowledge of the disorders within the autosomal dominant LGMD classification has grown, together with a greater understanding of the other

phenotypes that have been identified in association with mutations in the same genes, a key feature of these diseases has clearly emerged as variability. So, for example, LGMD1A is due to mutations in myotilin, which is also responsible for a form of myofibrillar myopathy. Patients in this group may have mutations in a range of different genes and the phenotypes may be very variable, including both proximal and distal muscle weakness, and cardiac and respiratory complications. LGMD1B or laminopathy has already been discussed in the section on EDMD—a very high index of suspicion of this diagnosis is definitely required. Caveolin 3 mutations, responsible for LGMD1C, are also now recognized in a form of rippling

24.19.2 Muscular dystrophy 6323 Table 24.19.2.2 The more prevalent autosomal recessive types of limb-girdle muscular dystrophy

Type of muscular dystrophy	gene symbol
Calpainopathy (LGMD 2A)	(CAPN3)
Dysferlinopathy (LGMD 2B/MM)	(DYSF)
Sarcoglycanopathies (LGMD 2C–2F)	(SGCA, SGCB, SGCC, SGCD)
Dystroglycanopathies (LGMD 2I, 2K, 2M, 2N, 2O, 2P, 2T, 2U)	(FKRP, POMT1, fukutin, POMT2, POMGnT1, DAG1, GMPPB, ISPD)
LGMD2L (ANO5)	

Distribution Worldwide, some isolates (e.g. Reunion, Amish, Basque) Worldwide. Founder effect in Libyan Jewish population. Others Worldwide. Regional differences in different types Worldwide. Founder mutation in Scandinavia for FKRP Worldwide. UK founder mutation Status of diagnosis Protein, mutations Protein, mutations Protein, mutations (may not be readily found in all patients) Abnormal glycosylation of α -dystroglycan and laminin A2, mutations in FKRP, POMT1, fukutin, POMT2, POMGnT1, DAG1, GMPPB, ISPD Mutation in ANO5 Protein Calpain 3 deficiency detectable by monoclonal antibody on blots Dysferlin deficiency detectable on sections and blots • Dystrophin may be mildly abnormal • γ and α : may see selective reduction • β and δ : mostly see depletion of all Secondary reduction in α -dystroglycan and laminin A2 in some muscle biopsies No protein test yet available: all antibody analysis normal Mutations Widely distributed, few recurrent. All types of mutation seen, large deletions rare. Changes may be non-pathogenic. Except in homozygotes, difficult to correlate mutation type with rate of progression Widely distributed, few so far recurrent • α R77C seen in 42% of chromosomes • γ two predominant mutations, N. African and gypsy. Otherwise mutations very heterogeneous • Missense mutations mainly in extracellular domain Depending on causative gene involved. FKRP common mutation (C826A) responsible for many cases Founder mutation in UK and other N. European groups Age at onset Typically 8–15, may be from early childhood or adulthood Most present around 20 ($\pm$ 5 years). Onset not in first decade α most variable—may be from childhood to adulthood. γ , β , δ tend to be more severe. Majority of all types will present in first decade Congenital form may be very severe: ranges to very mild disease in LGMD group Typically late adulthood; males usually younger than females Mode of presentation and selective Muscle involvement Highly selective pattern of muscle involvement wasting post. compartment of thighs, scapular winging. Sparing of hip abductors. Relative involvement of muscle groups important Variable. May be: • lower limbs first • proximal alone, mixed proximal/ distal alone • distal presentation most commonly posterior, may be anterior Weakness, toe walking, muscle pains/cramps are typical presentations. Main muscles—shoulder girdle involvement more prominent than DMD, scapular involvement, hamstrings more than quadriceps, lordosis, foot-drop in some before loss of mobility Proximal muscle weakness Asymmetrical muscle atrophy, may be proximal or distal, clinically may resemble LGMD2B Early development Motor milestones normal; physical prowess in childhood may be less good than peers Normal—good athletic prowess Motor milestones less delayed than DMD, even if later very severe Usually normal, but can be delayed in some forms Normal Rate of progression May not be linear—can see rapid change with no gender

effect. Otherwise gradual with time. Age at death probably typically in 60s Usually slow—some more rapidly progressive Cases have similar age at onset Variability main feature: • poor correlation between age at onset/ progression • rate of progression very variable • may be great intrafamilial variation, even with sibs Variable, usually mild Usually mild; typically maintain ambulation until old age, women may remain asymptomatic Age of confinement to wheelchair 20–30+ Typically beyond 30s. Seems to be normal lifespan Earliest 9 years. Variability in mild cases very marked. Occasional asymptomatic cases in adult life (esp. α). Typically even most severe cases live to 30s In mild cases 40+, in severe forms <20 Late adulthood if at all (continued)

section 24 Neurological disorders 6324 Atrophy Posterior compartment of thighs, latissimus dorsi Typically distal LL, biceps—may be very selective. Atrophy of proximal deltoid, hypertrophy of distal Anterior and posterior thighs, shoulder girdle Proximal Patchy and may be assymetrical Hypertrophy Occasionally see calf hypertrophy Very rare—a few cases have transient calf hypertrophy at presentation which may be painful Common in calves, also elsewhere. May be macroglossia Common in calf muscles May be seen in some muscle groups Contractures AT contractures common. Occasionally more widespread No AT contractures, lordosis, hip flexion contractures (may be problem in rehab.). Scoliosis less common than DMD even when WCB Not common in LGMD forms, reported in LGMDK, 2M, 2P Not common Facial involvement Mild facial weakness unusual. Also macroglossia very occasionally seen No facial weakness No facial weakness, may see macroglossia. In later stages typical transverse smile Mild facial weakness common No Cardiac status Normal Normal α usually not present (one Dutch patient). β , γ , δ may be important Cardiomyopathy significant complication Cardiomyopathy not reported to date Respiratory status Respiratory impairment may be significant in some Normal Common, may be at later stage than DMD Some cases require nocturnal ventilation Well-preserved respiratory status Intellectual function Normal Normal Normal Normal or mildly impaired Normal Creatine kinase 10–100 $\times$ normal May be low or mildly raised in young presymptomatic cases, rising to huge elevation by early teens. Very high in active phase of disease, falling with age 10–100 $\times$ normal 10–100 $\times$ normal 10–100 $\times$ normal Biopsy Dystrophic Dystrophic plus inflammation, may be perivascular or more widespread Dystrophic Dystrophic Dystrophic Other Muscle imaging confirms highly selective pattern of muscle involvement Muscle imaging may reveal asymptomatic proximal changes in distal onset and vice versa. Phenotypes may vary with same mutation and between sibs Genotype–phenotype correlations: α -null tend to be more severe; β truncating very severe, huge variation with missense. Majority in γ are truncating mutations. δ mutations so far are rare Allelic with forms of congenital muscular dystrophy Muscle imaging can be quite specific Note Finnish anterior tibial MD homozygotes may show reduction of calpain on blots May have been misdiagnosed as polymyositis or distal myopathy Main differential diagnosis is with dystrophinopathy. Occasional cases may resemble calpainopathy. No clinical guidelines to distinguish subgroups, though very mild disease most likely to be α N/K Females may remain asymptomatic with hyperCKaemia LGMD, limb-girdle muscular dystrophy; DMD, Duchenne muscular dystrophy; WCB, wheelchair bound; N/K, not known; LL, lower limbs; AT, Achilles tendon.

Table 24.19.2.2 Continued

24.19.2 Muscular dystrophy 6325 muscle disease, as well as in patients presenting with myalgia or hypercalcaemia. Therefore, a broad level of knowledge about the possible diagnostic features in these different disorders is necessary when taking the family tree for these patients, as well as is in the individual clinical assessments required—rippling, for example, may be seen only if

specifically elicited. What is the age and nature of the presentation? Variability in the age of presentation and the rate of progression is usual in the various autosomal recessive types of LGMD. However, some broad conclusions can be helpful (Fig. 24.19.2.6). Childhood presentation is most common in sarcoglycanopathy, which may superficially resemble dystrophinopathy, with frequent calf (and other muscle) hypertrophy. Adult-onset cases are less frequent and are essentially 'Becker-like' in presentation. However, whatever the age at presentation, in sarcoglycanopathy, quadriceps is almost always stronger than the hamstrings. This is the reverse of the pattern seen in dystrophin deficiency. Another important differential diagnosis in a 'Becker-like' (including the presence of calf hypertrophy and cardiomyopathy) presentation is LGMD2I, which is the most common form of LGMD in northern Europe. Calpainopathy may present with early childhood symptoms, especially contractures of the Achilles tendons, but onset is most commonly between 8 and 15 years of age. Dysferlinopathy typically presents in the late teens or early twenties, and early features may include proximal weakness or distal involvement (usually manifesting as difficulty standing on tiptoe). LGMD2L can resemble dysferlinopathy in many ways. Which investigations should be performed? Serum creatine kinase is greatly elevated in all forms of autosomal recessive LGMD, but may be only marginally elevated or within the normal range in autosomal dominant LGMD. EMG confirms a primary myopathic process. Standard analysis of the muscle biopsy together with immunohistochemistry analysis has been so far necessary to confirm dystrophic changes (which, especially in dysferlinopathy, can be accompanied by evidence of inflammation) and attempt to determine the type of LGMD together with the clinical features (Fig. 24.19.2.7). Gene analysis is required to confirm the diagnosis. However, if so far the muscle biopsy analysis together with the clinical picture were directing the targeted genetic testing, with the advent of novel sequencing techniques, allowing a simultaneous testing of multiple known genes causative of muscular dystrophy, genetic testing is going to replace some of the more invasive investigations (i.e. muscle biopsy). Nevertheless, muscle (a) (b) (c) (d) Fig. 24.19.2.6 Typical clinical pictures of patients with different types of autosomal recessive limb-girdle muscular dystrophy (LGMD). (a) Calpainopathy or LGMD2A. Note the predominantly atrophic pattern of muscle involvement and Achilles tendon contractures. The stance is often wide based due to the imbalance of the hip abductors and adductors and tight Achilles tendon. (b) Dysferlin deficiency or LGMD2B. Note the wasting of the posterior calf muscles and flat-footed stance. (c) Child with γ -sarcoglycanopathy or LGMD2C. Note the lordotic posture and scapular winging, both of which may be more marked at presentation in sarcoglycanopathy than in dystrophin deficiency. (d) Adult with γ -sarcoglycanopathy, to illustrate the variability in severity of sarcoglycan deficiencies and the muscular hypertrophy, which may be as marked or more marked than in dystrophin deficiency. Fig. 24.19.2.7 Multiplex western blotting as an approach to diagnosis in limb-girdle muscular dystrophy. Two strips of a western blot of control human skeletal muscle protein extracts immunostained with a mixture of antibodies to the proteins indicated. Absence or reduced intensity of a particular species, compared with the other proteins labelled in the same lane, can indicate which gene and protein are implicated in that patient's disease. Courtesy of Dr L V B Anderson, University of Newcastle upon Tyne.

section 24 Neurological disorders 6326 biopsy and immunohistochemistry analysis may be still necessary and fundamental to interpret genetic variants of unknown clinical significance. Scheme for specialized investigations Do the clinical features or family history suggest a specific disorder (Boxes 24.19.2.9–24.19.2.11)? If so, look for that first. The sarcoglycanopathies Dystrophin staining may be mildly abnormal in these patients, reflecting the close and interdependent relationship

between the proteins of the dystrophin-associated complex; however, the predominant abnormality on immunolabelling or immunoblotting will be the absence or reduction of one or more of the sarcoglycans. The pattern of reduction of these proteins may give a clue as to the primary gene involvement. Detection of the mutation is necessary to offer prenatal diagnosis and specific genetic counselling.

Calpainopathy Here the sarcoglycans are normal, as is dystrophin. Currently available antibodies to calpain 3 do not work on tissue sections but need to be used on immunoblotting. Detection of reduced or absent calpain on immunoblotting (see Fig. 24.19.2.7) indicates the need to search for calpain 3 mutations, which are highly variable, are generally non-recurrent, and may involve any part of the large (24 exons) gene. Studies consistently report a level of around 20–25% of nondetection of the second mutation in calpain 3, suggesting the presence of a significant number of mutations missed by current screening technologies. A secondary reduction in calpain 3 may be seen in some cases of dysferlin deficiency. The situation at the muscle biopsy level is also complicated by the fact that patients with mutations, especially in the autocatalytic domain of calpain 3, show normal protein expression on immunoblotting. A multidisciplinary approach to diagnosis in calpainopathy, including the recognition of often a very characteristic phenotype, together with protein and genetic testing, is still required. Interestingly and to add complexity to this field, recent reports suggest rare cases of dominant inherited calpain 3 mutations and further studies are in progress to better understand this new entity.

Dysferlinopathy Here, all other proteins with the possible exception of calpain 3 are within the normal range, and deficiency of dysferlin can be demonstrated on tissue sections or immunoblotting. Decreased or absent dysferlin in muscle is an indication to proceed to mutation detection. The dysferlin gene is very large (55 exons) and, as with the other forms of LGMD, mutations are highly variable. LGMD2I and other forms of LGMD with abnormal glycosylation of a dystroglycan

It is increasingly recognized that mutations in the same genes, which can cause a congenital muscular dystrophy with abnormal glycosylation of α dystroglycan, can also cause a much milder lgmd phenotype. Indeed, mutations in the FKRP gene can give rise to a severe congenital muscular dystrophy (MDC1C) phenotype as well

Box 24.19.2.9 Clinical features of sarcoglycanopathies

- These most frequently present in childhood, but may present at any age. Intrafamilial variability is common.
- These conditions are most closely related clinically to dystrophinopathy which will be the major differential diagnosis and have a similar spectrum of severity.
- Typically motor milestones are less delayed than in dystrophinopathy.
- Muscle hypertrophy is common.
- Intelligence is not affected.
- Cardiomyopathy is an important complication, though not universal, and should be sought through careful surveillance.
- Respiratory failure is an important late complication.
- Scoliosis is seen in the most severely affected individuals.
- Prognosis overall is typically better than dystrophinopathy presenting at a similar age.

Box 24.19.2.10 Clinical features of calpainopathy

- This is the most common form of limb-girdle muscular dystrophy in most populations.
- May present at any age but typically 8–15 years.
- Highly selective muscle involvement: posterior thigh weakness, and wasting; scapular winging common at onset.
- Muscle hypertrophy rare—tends to be predominantly atrophic pattern.
- Preservation of hip abductor muscles even at late stages contributes to characteristic wide-based stance.
- Most have Achilles tendon contractures: a subgroup presents with much more prominent contractures in an Emery–Dreifuss muscular dystrophy-like pattern.
- Progression is variable but never as fast as Duchenne muscular dystrophy.
- Cardiac involvement is not common but respiratory impairment may be seen in late stages.
- Prognosis in all but the most severe and early onset cases is good.

Box 24.19.2.11 Dysferlinopathy: clinical features

- Presentation most commonly in late teens or early twenties.
- Patients often report good muscle

prowess before onset of disease. Serum creatine kinase may not be massively elevated in presymptomatic cases. • Occasional patients present with unilateral calf swelling which may be tender and lead to the clinical diagnosis of myositis. • Primary muscle involvement is always in the lower limbs, with absence of upper girdle involvement at onset. • Lower limb involvement may be of proximal muscles or distal muscles. The distal muscles involved first are typically posterior (leading to difficulty standing on tiptoe as an early feature) but may be anterior. • Progression is typically slow and life expectancy is not reduced. This is the usually mildest type of limb-girdle muscular dystrophy. • Cardiomyopathy is not reported and respiratory involvement is usually mild and at a very late stage only. • The main differential diagnosis, especially in patients presenting with distal weakness, may be an alternative form of distal myopathy. Typically here the creatine kinase is not so high. Patients with ANO5 mutations (LGMD2L) can present in a very similar way, though presentation typically may be later and the pattern of muscle involvement may be more asymmetrical.

24.19.2 Muscular dystrophy 6327 as a much milder and common lgmd phenotype (LGMD2I). The phenotypic spectrum of disease is highly variable, and disease onset can range from the first to the fourth decade of life. This milder phenotype is actually the more common presentation with mutations in FKRP (LGMD2I), which is a relatively common cause of LGMD in northern Europe where there is a founder mutation. Respiratory failure and cardiomyopathy are common features, together with muscle hypertrophy and myalgia. Creatine kinase levels can range from moderately raised to very high levels depending on the subtype. The diagnostic clue in these cases is abnormal α dystroglycan on muscle immunolabelling, sometimes associated with a secondary reduction also in laminin A2 especially on immunoblotting. Other forms of limb-girdle muscular dystrophy Additional rare forms of LGMD have also been described. LGMD2G is mainly seen in Brazil and is due to mutations in telethonin. LGMD2H is restricted mainly to the Hutterite population of Canada and is due to mutations in TRIM32. Homozygous titin mutations in Finland (where a distal myopathy due to titin mutations is relatively common) cause LGMD2J. LGMD2L is due to mutations in ANO5 and mutations in this gene also cause a form of Miyoshi myopathy. The LGMD group is rapidly expanding; at present the LGMD classification is complex and 23 genes have been identified so far in the autosomal recessive group (LGMD2A- LGMD2W). The existence of families with an LGMD phenotype but no detectable mutations to date suggests that novel muscular dystrophy genes remain to be identified and this process is likely to be accelerated by the application of the rapid sequencing technologies that are currently coming on line. With the introduction of next-generation sequencing techniques, patients can now be screened using muscular dystrophy related gene panels, which allows simultaneous testing of multiple known genes causative of muscular dystrophy. Where targeted Sanger sequencing or panel gene screening fail to identify a causative gene, whole exome sequencing (WES) has the potential to identify novel causative genes. WES analysis can be performed as a panel analysis in first instance, screening for known genes first, but offers also the opportunity to widen the screening in order to identify novel genes. These novel and powerful diagnostic techniques will likely reverse the diagnostic workout and approach from what was a phenotype- genotype correlation to a genotype-phenotype correlation. And, if the muscle biopsy and other investigations were so far in most cases preceding the genetic test, this will likely be reversed and used as a tool to prove pathogenicity of variants identified by novel sequencing techniques. Limits of these sequencing methods have to be kept well in mind. Indeed, despite the genome coverage being wide; deletion and duplications, as well as repeat sequences are not always well spotted, and coverage of large genes can represent a challenge. In these cases, standard techniques offer a better diagnostic

approach. Management Once the diagnosis is secure, management should include monitoring and treatment for the specific complications of the various subtypes. Attention needs to be given to the particular prevalence of cardiac or respiratory involvement and appropriate surveillance and treatment initiated. If a clear diagnosis is not possible (e.g. where appropriate samples are not available or where the diagnosis cannot be reached even after exhaustive investigation), the management should, as a minimum, include physiotherapy and regular cardiac and respiratory surveillance.

Oculopharyngeal muscular dystrophy Oculopharyngeal muscular dystrophy is unusual in that it has an exceptionally late presentation. It is another example, like FSHD, where the muscular dystrophy is named for the most characteristic pattern of muscle involvement observed.

Presentation

- Presentation is typically in the sixth decade.
- It commonly presents with ptosis, dysphagia to solids, and dysphonia, which may be as severe as in myotonic dystrophy.
- Other features include ophthalmoparesis, facial weakness, and proximal muscle weakness.

Diagnosis The muscle biopsy in oculopharyngeal muscular dystrophy typically shows the presence of rimmed vacuoles and intranuclear inclusions. DNA analysis confirms the presence of an expanded guanine-cytosine-guanine repeat in the poly(A)-binding protein 2 gene (PABPN1 gene; MIM 602279) on chromosome 14q11.

Prognosis and management Ptosis can be managed surgically, but frequently recurs. Dysphagia may respond, at least partially, to surgical intervention with myotomy of the cricopharyngeal muscle and other annular muscle fibres. Potentially life-threatening complications may include aspiration pneumonia and regurgitation. Progression of the limb muscle weakness is highly variable.

Genetic counselling Oculopharyngeal muscular dystrophy is an autosomal dominant disorder. Genetic analysis offers the potential for presymptomatic testing if this is specifically sought.

Prospects for specific treatment in muscular dystrophy Drug treatments have a limited place in the treatment of muscular dystrophy at present, apart from the use of corticosteroids in DMD and cardiac medications in conditions where cardiomyopathy is a specific risk. Proactive and anticipator treatment for patients and their families based on knowledge on the likely course of specific diseases remains the mainstay of treatment at present, and this is likely to be the case at least for the current generation of patients. This treatment is ideally provided through a specialized multidisciplinary team, bringing together with the 'myologist' the skills of medical and associated colleagues from physiotherapy, occupational therapy, genetics, cardiology, respiratory medicine, and orthopaedics. Treatments to modify the underlying disease are

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