THE BARE ESSENTIALS

Muscle disease

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Muscle diseases impair mobility and frequently have cardiorespiratory complications. Their age of onset is extremely wide; patients may die young, or there may be lifelong motor disability with cardiorespiratory complications, or late onset muscle weakness.

About 50 000 people in the UK population of 60.5 million have one of the diverse group of genetic and acquired conditions which make up the primary muscle diseases; many more have muscle symptoms due to drugs or systemic diseases such as cancer. The important acquired muscle diseases include the inflammatory myopathies which are treatable and so the diagnosis must not be missed (or overdiagnosed and some other disorder treated inappropriately), as well as the drug-induced myopathies. Neurologists are also often asked to assess patients with secondary muscle dysfunction due to aging, immobility, critical illness and cancer.

DIAGNOSIS

Distinguishing myopathies from peripheral neuropathies, anterior horn cell diseases (eg, motor neuron disease) and neuromuscular junction disorders (eg, myasthenic syndromes) requires careful clinical evaluation supplemented by investigations, which may include peripheral neurophysiology, imaging, muscle biopsy and genetic testing.

Clues from the history

Age of onset

- Duchenne muscular dystrophy presents at <5 years, inclusion body myositis in middle life, while mitochondrial diseases at any age.
- Dermatomyositis is far commoner than polymyositis in childhood.
- Many dystrophies, such as facioscapulohumeral, myotonic and limb girdle, typically present in adolescence or early adult life, but late onset and very young onset are recognised.

Childhood features

- Reduced fetal movements in pregnancy, "floppy baby" at birth, feeding/breathing problems, delayed motor milestones and limited sporting achievements all point to a congenital or childhood onset muscle disorder. These features alone may not differentiate from neuromuscular junction or peripheral nerve disorders.

Family history

- May reveal autosomal, X-linked or mitochondrial DNA (maternal) inheritance.
- Systemic features in other family members; eg, cataracts may be the only manifestation of myotonic dystrophy in a preceding generation.

Rate of progression and temporal pattern of weakness

- May be minimal or absent (eg, some congential myopathies)
- May be slowly progressive over years (eg, some dystrophies) or acute/subacute (eg, polymyositis).
- Symptoms may be episodic with or without inter-attack decline in muscle function (eg, channelopathies, mitochondrial and metabolic disorders).
- Although some fatigue may occur, marked fatiguability suggests a defect in neuromuscular junction transmission.

Pattern of muscle involvement

The distribution of muscle weakness can be an important clue to the diagnosis:

- If facial involvement consider facioscapulohumeral, myotonic, oculopharyngeal dystrophies and sometimes inflammatory myositis and mitochondrial myopathy.
- If ophthalmoplegia check for variability or fatiguability to exclude myasthenia. If no fatiguability the commonest causes are mitochondrial disease, oculopharyngeal muscular dystrophy and myotubular myopathy (ptosis may also be evident in these conditions and some congenital myopathies).
- Proximal limb girdle without facial weakness or ophthalmoplegia is the commonest pattern and has a large number of causes; commonly polymyositis, dermatomyositis, limb girdle muscular dystrophy, metabolic myopathies.
- Inclusion body myositis tends to affect the forearm finger and wrist flexor muscles along with the quadriceps.
- Isolated distal weakness is usually neurogenic (ie, peripheral neuropathy) but can occur in myotonic dystrophy, Welander myopathy and myofibrillar myopathy (eg, desmin myopathy).
- Bulbar weakness with dysphagia/dysarthria: consider oculopharyngeal muscular dystrophy, myotonic dystrophy, inflammatory

2009;9:54–65. doi:10.1136/jnnp.2008.167171

Table 1 Drugs causing muscle problems

Rhabdomyolysis	Painful myopathy	Inflammatory myopathy	Cramp
Alcohol	Amiodarone	Hydralazine	Anticholinesterases
Amphetamines	Cimetidine	L-tryptophan	Caffeine
Cocaine	Clofibrate	Penicillamine	Clofibrate
Cyclosporin	Cyclosporin	Procainamide	Cyclosporin
Fibrates	D-penicillamine		Diuretics
Isoniazid	Gemfibrozil		Labetalol/beta blockers
Lithium	Gold		Lithium
Propofol	Heroin		Nifedipine
Quetiapine	Labetatol		Terbutaline
Statins	Lovastatin		Theophylline
Zidovudine	L-tryptophan		Statins
	Nifedipine		
	Procainamide		
	Salbutamol		
	Vincristine		
	Zidovudine		

myopathies, mitochondrial disease and thyroid myopathy.

Weakness

- May include difficulty with activities above shoulder height, grip, negotiating stairs, rising from seated/squat/supine, falls, and foot drop.
- Facial weakness is usually bilateral and symmetrical (and so is often not noticed), and leads to difficulty whistling, blowing up balloons, using a straw and dysarthria; patients may sleep with "their eyes open" reflecting the facial muscle weakness.

Myalgia

- A common complaint but often not due to muscle disease; it can occur in the inflammatory myopathies (although many patients do not report pain), myotonic dystrophy, hypothyroidism, vitamin D deficiency and drug-induced myopathies (table 1).

Table 2 Muscle diseases associated with respiratory failure

	Causes respiratory failure	Respiratory failure an uncommon complication
Dystrophies	Duchenne muscular dystrophy	Becker muscular dystrophy
	Myotonic dystrophy*	Facioscapulohumeral muscular dystrophy
	Limb girdle 2A, 2I*	
	Scapuloperoneal muscular dystrophy	
Congenital	X-linked myotubular myopathy*	
	Nemaline myopathy*	
	Myofibrillar myopathy*	
Metabolic	Acid maltase deficiency*	
	Primary carnitine deficiency*	
	Debrancher enzyme deficiency*	
Mitochondrial	Generalised myopathy	Chronic progressive external ophthalmoplegia
	Leigh's disease	
Endocrine/electrolyte	Hypokalaemia*	
	Hypophosphataemia*	
	Hypermagnesiumaemia*	
	Barium intoxication*	
	Hyperthyroidism*	
Inflammatory		Polymyositis
		Dermatomyositis

*May present de novo with respiratory failure.

- Myalgia without myoglobinuria or weakness on examination, and with a normal plasma creatine kinase (CK) and electromyography, is unlikely to be due to muscle disease.
- Commonly transient and secondary to systemic infections, eg, viral.
- Myalgia precipitated by exercise occurs in metabolic myopathies, mitochondrial myopathies, dystrophinopathies, myotonic dystrophy (especially type 2) and sometimes in polymyositis/dermatomyositis.

Wasting and enlargement

- Wasting is common in many muscle diseases.
- Some muscle diseases exhibit true hypertrophy: myotonia congenita and neuromyotonia (due to repetitive activity).
- Duchenne and Becker muscular dystrophy, some limb girdle muscular dystrophies and debrancher enzyme deficiency are associated with pseudohypertrophy.

Muscle stiffness

- Although a mild degree of muscle stiffness is a common complaint in many muscle disorders, very marked stiffness and difficulty with muscle relaxation suggests myotonia.
- In myotonia congenita there is worsening with rest and reduced myotonia with exercise—the "warm-up phenomenon". In paramyotonia congenita there is exacerbation with exercise and with low temperature—"paradoxical myotonia".
- Some drugs may exacerbate myotonia, eg, beta blockers.

Cramps

- More commonly seen in neurogenic disorders.
- If very prominent consider drugs (table 1), metabolic muscle disease, mitochondrial myopathies, hypothyroidism.

Respiratory and cardiac muscle involvement

- Respiratory and/or cardiac muscle (tables 2 and 3) may be affected to differing degrees and at different stages.

- Respiratory symptoms are due to diaphragmatic and respiratory muscle weakness, and hypercapnia: dyspnoea, orthopnoea, morning headache, excessive daytime sleepiness.
- Cardiac symptoms are due to dysrrhythmias and cardiac failure: syncope, palpitations, dyspnoea, peripheral oedema.

Myoglobinuria

- Myoglobin released from damaged muscle discolours urine brown-black—"like cola".

Table 3 Muscle diseases associated with cardiac complications

Condition	Cardiac complications
Duchenne muscular dystrophy	Hypertrophic cardiomyopathy (early), dilated cardiomyopathy (late), arrythmias (atrial & ventricular tachycardia), sudden death
Becker muscular dystrophy	Arrhythmias, 30% cardiomyopathy, sudden death
Emery-Dreifuss muscular dystrophy	Arrhythmias: sinus bradycardia (early), atrial tachycardia, AV conduction block (late), cardiomyopathy, sudden death 50%
Myotonic dystrophy	Arrhythmias (brady- & tachyarrhythmias), cardiomyopathy uncommon, sudden death
LGMD1A (myotilin)	Cardiomyopathy, arrhythmias
LGMD1B (laminin A/C)	Arrhythmias, cardiomyopathy
LGMD 2C-F (sarcoglycanopathies)	Cardiomyopathy
LGMD 2I (fukutin-related protein)	Cardiomyopathy
X-linked scapuloperoneal muscular dystrophy	Hypertrophic cardiomyopathy
Primary inflammatory myopathies	Arrhythmias & cardiomyopathy (uncommon)
Andersen-Tawil syndrome	Arrhythmias: prolonged QT (early), bidirectional ventricular tachycardia, bigeminy, conduction block (late); valvular abnormalities; sudden death
Kearns-Sayre syndrome	Arrhythmias (bradycardia), dilated cardiomyopathy (late), sudden death
Carnitine deficiency	Cardiomyopathy
Acid maltase deficiency	Cardiomyopathy
Debrancher enzyme deficiency	Cardiomyopathy

LGMD, limb girdle muscular dystrophy.

- Causes include: disorders of glycogen-glucose metabolism, fat β-oxidation defects, mitochondrial respiratory chain disorders, malignant hyperthermia, Duchenne and Becker dystrophies, inflammatory myopathies, infection, ischaemia, trauma, alcohol and drugs (table 1).

General anaesthesia

- Some myopathies are associated with malignant hyperthermia (eg, central core disease) or similar reactions (eg, periodic paralysis).
- Anaesthesia may unmask previously unrecognised cardiorespiratory insufficiency (eg, myotonic dystrophy).

Examination

Inspection

- Wasting, hypertrophy, pseudohypertrophy, fasciculation, rippling, myokymia, neuromyotonia, skeletal deformity (pes cavus, kyphoscoliosis) and contractures.

Weakness

- Many but not all primary muscle diseases have a proximal symmetrical limb girdle pattern. Other patterns include distal (myotonic dystrophy, inclusion body myositis, Welander distal myopathy, desmin myopathy); combined distal and proximal lower limb (myotonic dystrophy, inclusion body myositis); selective quadriceps weakness (inclusion body myositis).
- Document MRC (Medical Research Council) scores for weak muscles, and vital capacity (not forced expiratory volume).
- Walking on heels and tiptoe, standing from sitting and squatting, running, stairs, timed walk, lifting head from supine, sitting from supine all rapidly assess specific muscle groups.
- Facial and ocular muscle weakness: assess eye movements, ptosis, facial (failure to bury the eyelashes), palatal and tongue muscles, neck flexion/extension and shoulder shrugging.
- Facial weakness without extraocular muscle involvement: myotonic dystrophy, facioscapulohumeral dystrophy, some inflammatory myopathies
- Neck flexion weakness: myotonic dystrophy, myasthenia gravis, inflammatory myopathies, motor neuron disease.

Reflexes

- Preserved in pure myopathy but may be lost when there is advanced wasting and weakness.
- Lost in mitochondrial disease when there is neuropathy as well as myopathy.

Myotonia

- Delayed relaxation of muscle after voluntary contraction due to abnormally increased muscle membrane excitability: myotonic dystrophy, myotonia congenita.
- Percussion myotonia: tap the muscle belly, eg, thenar eminence with a tendon hammer.

Contractures

- Early and prominent in Emery-Dreifuss dystrophy, Bethlem myopathy, rigid spine syndrome, limb girdle dystrophy 1B and 2A.
- Fixed contractures (fibrotic shortening of limb and spinal muscles) can be a late feature in most myopathies.

Non-myopathic features

- Central nervous system: encephalopathy, stroke-like episodes, epilepsy, myoclonus, dementia, ataxia, movement disorders and headache (mitochondrial disorders).
- Eyes: pigmentary retinopathy and optic atrophy (mitochondrial disorders); cataracts (myotonic dystrophy, αβ-crystallinopathies, mitochondrial disorders).
- Ears: sensorineural deafness (mitochondrial disorders, occasionally in facioscapulohumeral dystrophy).
- Gastrointestinal: dysmotility (due to smooth muscle involvement) problems may coexist in mitochondrial disorders, eg, MNGIE (mitochondrial myopathy, peripheral neuropathy, gastrointestinal disease and encephalopathy).
- Liver: hypoglycaemia (debranching enzyme deficiency), hepatomegaly (branching and debranching enzyme deficiency), hepatic impairment (metabolic and mitochondrial disorders).

2009;**9**:54–65. doi:10.1136/jnnp.2008.167171

- Endocrine: mitochondrial myopathies have been linked with endocrine abnormalities (diabetes mellitus, thyroid dysfunction). Several endocrine disorders cause myopathy: hypo- and hyperthyroidism, Cushing's, Addison's, hypo- and hyperparathyroidism, hypopituitarism, acromegaly, hyperaldosteronism, adrenal failure and phaeochromocytoma.
- Kidney: chronic renal failure, dialysis and renal tubular acidosis cause secondary myopathy.
- Blood: haemolytic anaemia (phosphofructokinase deficiency).
- Skin: dermatomyositis causes heliotrope (blue-purple discoloration of eyelids, face and upper trunk) and Gottron's rash (raised violaceous scaly eruption on the knuckles). Lipomatosis may occur in mitochondrial disease.

Investigations

Plasma creatine kinase

- Non-specific marker of muscle damage but may be higher than the "normal" reference range (50–150 IU/l) in Afro-Carribeans, following exercise, trauma, sepsis, hypothermia and cardiac injury (cardiac isoenzyme).
- Normal in some myopathies where no active muscle necrosis or ongoing damage, eg, indolent congenital myopathies, or when an inflammatory muscle disease "burns out".
- Denervating disorders usually do not cause creatine kinase (CK) above 1000 IU/l in adults.
- The level is not a reliable clue to the type of primary muscle disease.
- The higher the CK the more active the muscle damage (necrosis) so can be useful to assess treatment response in inflammatory muscle disease, but only alongside clinical assessment.
- Take more notice of the patient and the degree of weakness than any small changes in CK. Sometimes in polymyositis and dermatomoysitis the patient responds well clinically but the CK does not normalise; this is acceptable provided CK has fallen substantially, the patient is well, and the CK below 1000 IU/l.
- Some patients have florid myositis clinically and on muscle biopsy but the CK is normal or only minimally raised.
- Never rely solely on the CK when assessing a patient with muscle disease.

Tests for metabolic muscle disease

- Specific enzyme assays on muscle, blood, urine, fibroblast and liver specimens.
- Lactate levels (serum and CSF) may be raised in mitochondrial disorders.
- Carnitine (serum and urine), acylcarnitine (serum); urinary organic acid levels; and phosphorus magnetic resonance spectroscopy may be helpful.
- Specific exercise protocols are sometimes used for diagnosis of respiratory chain and glycogen storage disorders.

Genetic analysis

- The first-line investigation for many genetic muscle diseases and may avoid the need for muscle biopsy, eg, myotonic, facioscapulohumeral, Duchenne, Becker, Emery-Dreifuss, oculopharyngeal and certain limb girdle dystrophies, some mitochondrial disorders and muscle channelopathies.
- A precise genetic diagnosis is important for genetic counselling, screening for gene specific cardiorespiratory complications, for certain treatments, and for entry into treatment trials.

Neurophysiology

- Nerve conduction studies and electromyography help exclude neurogenic and neuromuscular junction disorders and may (or may not) show specific myopathic features, eg, small, short duration, polyphasic motor unit potentials and early complex interference (recruitment) pattern.
- Myotonic discharges (trains of waxing and waning frequency) in myotonia, chronic denervation, Pompe's disease, and hypothyroidism.

Muscle biopsy

- Key investigation but requires careful interpretation in the context of the clinical picture; talk to the muscle pathologist—accurate interpretation of a biopsy is always facilitated by detailed clinical information.
- Open (large sample, direct visualisation, more invasive) or needle biopsies can be performed under local anaesthetic.
- Selecting the appropriate muscle to biopsy is important. In a long-standing disease better to biopsy a moderately weak rather than a very weak muscle (the latter may only reveal fibrous tissue and fat). In a disease of short duration the weakest muscle is most likely to reveal diagnostic pathology.
- Pathological changes may be focal and patchy and so sometimes missed on a single biopsy.

Magnetic resonance imaging

- Detects subclinical changes (particularly in deeper muscles), and pattern of muscle involvement which may help diagnostically.
- May be useful in site selection for biopsy, especially if an initial biopsy has not been diagnostic and yet muscle disease is still strongly suspected.

THE ACQUIRED MYOPATHIES

Idiopathic inflammatory myopathies

These are very important to consider in the differential diagnosis in all patients with muscle weakness because they are treatable.

- They occur in isolation or with systemic autoimmune and connective tissue diseases; dermatomyositis (DM) (20–30%) and polymyositis (PM) (5–10%). Also in association with malignancy (risk probably higher in DM than PM, and age over 40.).
- Proximal, usually symmetrical, muscle weakness (with wasting if severe), with or without myalgia, dysphagia and neck flexion weakness. Extraocular muscles normal but facial weakness is seen. Respiratory muscle involvement in severe cases.
- Interstitial lung disease develops in 10% of patients with PM or DM (sometimes preceding the myopathy).
- Cardiac involvement relatively uncommon—atrioventricular conduction defects, arrhythmias and dilated cardiomyopathy.
- Plasma CK may be normal, or up to 100× normal (usually <50× in DM and PM, and <10× in inclusion body myositis).
- Other clinical differential diagnoses include McArdle's disease, phosphofructokinase deficiency, acid maltase deficiency, mitochondrial, endocrine and drug-induced myopathies.
- Inflammatory infiltrates can be missed on biopsy because the disease is often patchy and altered by steroid use; take care because endomysial inflammation is also seen in Duchenne, Becker, fascioscapulohumeral, some limb girdle dystrophies and merosin-deficient congenital muscular dystrophy.
- Infections, connective tissue disease, vasculitis and graft-versus-host disease may all cause clinical and biopsy features of polymyositis which may respond to immunosuppression.
- A tissue diagnosis (ie, a muscle biopsy) is mandatory before starting potentially harmful immunosuppressive medication; there are important histopathologial differences which allow separation of DM, PM and inclusion body myositis.

Dermatomyositis

- Characterised by perivascular and interfascicular inflammation, muscle fibre ischaemia and perifascicular necrosis. B cell mediated.
- Presents subacutely in adults and children, with female preponderance.
- Skin changes (preceding or accompanying weakness) include: heliotrope rash (blue-purple) with eyelid oedema; photosensitive erythematous macular rash on exposed areas; knuckle erythema with Gottron's rash (raised violaceous, scaly lesions), tough palmar skin, thickened cuticles, dilated nailbed capillary loops.
- Contractures and marked subcutaneous calcification sometimes seen in children.
- Screen over the age of 40 for malignancy, or if treatment resistant.
- Responds to immunosuppression and intravenous immunoglobulin.

Polymyositis

- Characterised by intrafascicular endomysial cellular infiltration and muscle fibre necrosis due to cytotoxic T-cell-mediated attack.
- Tends to present after the second decade, more commonly in women, usually subacutely and rarely acutely.
- Screen for malignancy if treatment resistant.
- Usually responds to immunosuppression but not intravenous immunoglobulin (IVIg).

Inclusion body myositis

- The most common acquired muscle disease over the age of 50 years, three times more frequent in men than women.
- There is endomysial cellular infiltration and muscle fibre necrosis due to cytotoxic T-cell-mediated attack but the degree of inflammation is not in keeping with disease severity, and it is generally unresponsive to immunosuppressants. There is also evidence of muscle fibre degeneration with abnormal protein accumulation, eg, amyloid.
- Early involvement of deep finger flexors, foot extensors and quadriceps is an important clue to the diagnosis. Note that in DM and PM shoulder abduction and hip flexion are typically the weakest muscles. In addition, in inclusion body myositis, iliopsoas, triceps and biceps may be selectively impaired. 60% have dysphagia and a similar proportion facial weakness.
- The weakness may be asymmetrical.
- Relentlessly progressive and disabling, progression tends to be slow but constant; most patients require a walking aid after five years.
- Differential diagnoses include: PM, Nonaka distal myopathy, Welander distal myopathy and tibial muscular dystrophy.

Drug-induced myopathies

- A large number of drugs as well as alcohol and other toxins may produce muscular symptoms; always consider this possibility if a patient is on drug therapy (table 1).
- Often the symptoms are reversible if the medication is stopped but failure to recognise the problem can lead to progressive weakness, rhabdomyolsis and even death.

Drug induced muscle problems include:

- Asymptomatic raised plasma CK (statins)
- Myalgia and cramps (statins, diuretics)
- Myotonia (chloroquine, beta 2 adrenergic blockers)
- Necrotising myopathy/rhabdomyolysis (statins, cocaine)
- Chronic progressive myopathy (corticosteroids)
- Rarely mitochondrial myopathy (AZT treatment in HIV) or inflammatory myopathy (D-penicillamine) may be drug-induced.

2009;**9**:54–65. doi:10.1136/jnnp.2008.167171

Table 4 The muscular dystrophies

Muscular dystrophy	Prevalence/ 100 000	Protein	Genetics	Age of onset (years)	CK × upper limit of normal	Cardiac problems	Respiratory problems
Duchenne	7 (males)	Dystrophin	X-linked recessive Xp21	<5	10–100×	Arrhythmia, conduction block, cardiomyopathy 50% (late), mitral leaflet prolapse	100% respiratory failure, late teens ventilator-dependent
Becker	2.4	Dystrophin	X-linked recessive, Xp21	5–15 (up to 40)	10–100×	Arrhythmia, cardiomyopathy	Uncommon
Myotonic	1/8000 lifetime incidence	Myotonin protein kinase	Dominant ↑ CTG chromosone 13	Any	Normal, mild ↑	Arrhythmia, conduction block, mitral leaflet prolapse, rarely cardiomyopathy	Uncommon but can present de novo with respiratory failure
Myotonic type II (proximal myotonic myopathy)	Not known	Unknown function	Dominant 3q21 ↑ CCTG	8–50	Normal, mild ↑	Arrhythmia, conduction block	Uncommon
Facioscapulohumeral	1.5–3	Not identified	Dominant 4q35 [truncated repeat sequence]	7–30 95% signs by 20	Often normal, 10×	Not usually associated	Uncommon
Scapuloperoneal	?	?	Dominant 12q13.3–15	10–30	1.5–10×	Not usually associated	Uncommon
Emery-Dreifuss	0.5	Emerin	X-linked recessive (dominant) Xq28	4–5 (up to 20)	1.5–10×	Arrhythmia, conduction block, 40% sudden death	Uncommon
Oculopharyngeal	1	Polyadenylate-binding protein-2	Dominant, recessive, ↑ GCG 14q11.2–q13	30–60	Normal, mild ↑	Not usually associated	Aspiration pneumonia

Statin-induced muscle symptoms

This is an increasing problem as more and more patients receive these drugs, but the mechanism is not understood. There are four clinical presentations:

- Asymptomatic rise in CK (less than 5x normal) does not require any action.
- Significant myalgia and cramps with rise in CK; often withdrawal of the statin is needed.
- Rhabdomyolysis requires immediate withdrawal of the statin and supportive measures; avoid re-challenge, and use other cholesterol lowering strategies.
- Acute myositis is a rarely described complication requiring cessation of the statin.

Our experience suggests caution in using statins in patients with significant primary or acquired muscle disease.

Corticosteroid myopathy

This is the commonest chronic progressive drug induced myopathy. It is more likely with prednisolone >40 mg per day for prolonged periods. Proximal muscle weakness (especially quadriceps) develops gradually without a rise in CK and can result in significant disability. Biopsy shows type II atrophy. It is usually reversible; physical activity may be protective, as is an alternate day steroid regime if possible.

GENETIC MYOPATHIES

For many genetic myopathies there is a clear clinical phenotype and the diagnosis can be confirmed by a combination of muscle biopsy and/or genetic testing.

Muscular dystrophies

These are inherited, progressive disorders characterised by muscle destruction and often eventual replacement by fibrous tissue and fat (table 4). Many dystrophies also involve the respiratory and cardiac systems (tables 2 and 3) and some have additional non-myopathic features.

Duchenne muscular dystrophy

Duchenne and Becker muscular dystrophies are caused by mutations in the dystrophin gene, which codes for a large sarcolemmal protein essential for muscle membrane structural and functional integrity.

- Presents with progressive symmetrical weakness and wasting of predominantly proximal muscles, spreading distally, delayed motor milestones and usually wheelchair-dependent by 13 years.
- Weakness of hip and knee extension leads to Gower's manoeuvre (rising from a crouched position by walking the hands up the legs), hip abductors to a waddling gait, and hip extensors to accentuated lumbar lordosis.
- Calf pseudohypertrophy and Achilles tendon contractures are common.
- Brain and cardiac dystrophin deficiency may cause cognitive impairment (20% have IQ <70) and dilated cardiomyopathy.
- Respiratory failure is due to respiratory muscle weakness and kyphoscoliosis.
- One third are new mutations, 10% of female carriers manifest symptoms due to skewed X-chromosome inactivation, eg, mild exercise intolerance.

Becker's muscular dystrophy

Milder than Duchenne, most patients are able to walk through teenage years and early adult life, sometimes for much longer. The pattern of muscle involvement is similar to Duchenne but contractures are less common. Dilated cardiomyopathy can occur even in patients with mild weakness.

Limb girdle muscular dystrophies

A group of conditions with dystrophic histology and predominant shoulder and pelvic girdle involvement (table 5) classified as autosomal dominant (type 1A–C) and autosomal recessive (type 2A–K).

- Heterogenous presentation (even within the same genotype) is common.
- Differential diagnosis: Becker muscular dystrophy, late-onset spinal muscular atrophy, myotonic dystrophy type 2, Bethlem myopathy, acid maltase deficiency and polymyositis
- Patients with high CK and proximal weakness may be erroneously considered to have polymyositis on clinical grounds [without a biopsy] and started on immunosuppression which does not work (some so-called steroid resistant myositis cases fall into this category). Always check if patient has ever had a biopsy (sometimes they have not) and if so was a dystrophy considered and was appropriate immunostaining undertaken? If necessary and possible review the biopsy.
- EMG may identify myotonic dystrophy type 2, and muscle biopsy may exclude acid maltase deficiency and other metabolic myopathies.
- The type of limb girdle dystrophy is established by careful clinical assessment and muscle biopsy with detailed Western blotting, immunohistochemistry and genetic testing.

Facioscapulohumeral muscular dystrophy

- Predominantly affects the face, anterior tibial, serratus anterior, periscapular and perihumeral muscles (often in that order) with notable deltoid-sparing. Failure of eye lid closure, transverse smile, inability to whistle, scapular winging and instability resulting in impaired shoulder abduction and foot drop are typical. Later, proximal lower limb muscles may be involved. Myalgia is frequent and some patients may present with severe shoulder girdle pain before any weakness is evident.
- 65% of patients present with asymmetric weakness and up to 20% without facial weakness.
- Severity is very variable, even within families; 20% require a wheelchair by the age of 40 years.
- Complications: sensorineural deafness and retinal vasculopathy, but seldom symptomatic.
- Differential diagnosis includes polymyositis, myotonic dystrophy, limb girdle muscular dystrophies, centronuclear and nemaline myopathy and other scapuloperoneal syndromes.

Emery-Dreifuss muscular dystrophy

- X-linked recessive, autosomal dominant or autosomal recessive.
- All patients present with contractures (elbows, posterior neck and Achilles tendon), scapulohumeroperoneal weakness, later involving proximal muscles; and cardiac involvement (even with mild muscular weakness) with high risk of sudden death due to conduction block.
- Muscle and skin biopsies confirm the diagnosis.

Myotonic dystrophy type 1

Typically presents with distal muscle weakness (out of proportion to wasting) and myotonia. Weakness of grip, facial muscles, ptosis and neck muscles (particularly sternocleidomastoid) along with foot drop are common. The disease progresses proximally but usually maintains a distal predominance. Myotonia is seen after voluntary contraction and on percussion in the hands/forearms.

Table 5 Limb girdle muscular dystrophies (LGMD): classification and clinical features

Type of LGMD	Protein/gene	Age of onset	Clinical features	CK × upper limit of normal	Cardiac involvement	Respiratory failure
LGMD1A	Myotilin	Usually adulthood	Dysarthria, dysphagia, may be distal involvement	<5×	Cardiomyopathy, arrhythmia	Yes
LGMD1B	Lamin A/C	Any age	Contractures, rigid spine, family history of sudden death	<5×	Arrhythmia, cardiomyopathy	Yes
LGMD1C	Caveolin 3	Any age	Myalgia, muscle rippling, hypertrophy	5–10×	Not reported	Not reported
LGMD2A	Calpain 3	2–15 years	Contractures, toe walking, scapular winging, atrophy	5–10×	Infrequent	Infrequent
LGMD2B	Dysferlin	17–25 years	Inability to walk on tiptoe; 10% calf pain & swelling, calf & biceps wasting, upper limb usually later than lower limb (proximal & distal) involvement	>10×	Infrequent	Infrequent
LGMD2C-F	Alpha, beta, gamma, delta sarcoglycan	Any age, usually childhood	May resemble Duchenne/Becker, muscle hypertrophy, secondary contractures	5–10×>10×	Cardiomyopathy	Yes, after confinement to wheelchair
LGMD2G	Telethonin	2nd decade	May be distal weakness	Few cases	Not reported	Not reported
LGMD2H	TRIM32	2nd decade	Limb girdle pattern	Few cases	Not reported	Not reported
LGMD2I	Fukutin-related protein FKRP	Any age	May resemble Duchenne/Becker, muscle hypertrophy	5–10×>10×	Cardiomyopathy	Yes, diaphragm involved, even when ambulant
LGMD2J	Titin	1st decade	Distal in heterozygotes	Few cases	Not reported	Yes, late
LGMD2K	POMT1	1st decade	Learning difficulties, microcephaly, upper limb weakness worse than lower limb	>10×	Not reported	Not reported

2009;**9**:54–65. doi:10.1136/jnnp.2008.167171

Table 6 Skeletal muscle channelopathies

Channel	Muscle disease	Genes
Sodium	Hypokalaemic periodic paralysis	SCN4A
	Hyperkalaemic periodic paralysis (75% of cases)	SCN4A
	Paramyotonia congenital	SCN4A
	Potassium aggravated myotonia	SCN4A
Chloride	Myotonia congenita	CLCN1
	Thomsen's	CLCN1
	Becker's	CLCN1
Calcium	Hypokalaemic periodic paralysis (70% of cases)	CACNA1S
	Malignant hyperthermia	CACNA1S, CACNL2A
Potassium	Andersen-Tawil syndrome (80% of cases)	KCNJ2
Ryanodine receptor	Malignant hyperthermia	RYR1
	Central core & multicore disease	RYR1

Importantly, there are several non-skeletal muscle abnormalities:

- Cardiac involvement, particularly arrhythmias.
- Respiratory compromise may occur and occasionally patients present with respiratory failure.
- Early lens opacities and subsequent cataract are almost universal; retinal pigmentary changes are rare.
- 40% of patients have cognitive impairment and many are lethargic, apathetic and hypersomnolent due to varying combinations of subcortical frontal lobe dysfunction (often white matter hyperintensities on brain MRI), central and peripheral sleep apnoea. As a result the patients may be poor clinic attenders, yet they are at risk of significant cardiorespiratory morbidity and monitoring reduces this morbidity. It is an important challenge to engage myotonic dystrophy patients for follow-up and screening.
- Smooth muscle involvement may lead to dysphagia, gastrointestinal dysmotility, biliary tract dysfunction and impaired uterine contraction during labour.

Table 7 Non-dystrophic myotonias

	Paramyotonia congenita	Thomsen's disease	Becker's disease
Genetics	Dominant	Dominant	Recessive (male preponderance)
Age of onset	Neonatal to infancy	Early childhood	1st decade
Distribution	Face, tongue, neck, arms	Face, arms > legs; distal	Legs > arms, face
Exacerbating factors	Cold, exertion (paradoxical myotonia), spontaneous	Cold, rest (warm-up phenomenon), hunger, fatigue, stress	Cold, rest (warm-up phenomenon), hunger, fatigue, stress
Severity of myotonia	Less severe than Becker's but may be disabling during exercise	Mild, constant or intermittent; 50% percussion myotonia	Often severe
Weakness	Cold-induced weakness, duration: usually minutes, rarely days	Usually normal at rest; some have proximal weakness	Transient (after rest or with short period of exercise), some progressive, mild distal
Muscle hypertrophy	Absent	Present	Present (gluteal)
Electromyography	Compound muscle action potential amplitude decrement on cooling, myotonic changes less prominent	No decrement, 90% myotonia	No decrement, frequent myotonic discharges, myopathic potentials

- Impaired glucose tolerance and increased insulin response to glucose and glucagon, but diabetes mellitus uncommon.
- Atrophy of seminiferous tubules (with testicular atrophy).

It is an autosomal dominant trinucleotide repeat disorder that exhibits anticipation—ie, greater clinical severity in successive generations. Females, but not males, are at risk of having offspring with a severe and sometimes fatal form of congenital myotonic dystrophy. It is important to check there are no sisters of affected patients who might be mildly affected themselves but at risk of a having a severely affected child.

Myotonic dystrophy type 2, also known as proximal myotonic myopathy (PROMM)

This has dominant inheritance and is characterised by myotonia, weakness and multisystem involvement similar to myotonic dystrophy type 1 but without chromosome 19 abnormalities. It is caused by a CCTG expansion in the ZNF9 gene on chromosome 3, and genetic testing is available. The weakness and myotonia are predominantly proximal and myalgia is prominent. Facial and neck weakness tends to be less prominent.

Oculopharyngeal muscular dystrophy

A late onset progressive oculobulbar disorder with ptosis as the presenting feature in two thirds of patients, often asymmetrical; incomplete ophthalmoplegia; and later dysphagia and tongue weakness. Most patients develop proximal muscle weakness, usually in the lower limbs. It is an autosomal dominant (sometimes autosomal recessive) triplet repeat condition which is stable between generations.

Collagen VI disorders

Bethlem myopathy is due to mutations in collagen VI and characterised by proximal weakness and contractures of fingers, wrists, elbows and ankles. Onset is in the first two decades of life, most before age 2. Weakness may improve around puberty but progresses in the third to fifth decades, leaving patients wheelchair-bound in their 50s and 60s.

Distal myopathies/dystrophies

These are a diverse group of inherited primary muscle disorders characterised by progressive muscle weakness that (at least initially) is predominantly distal in distribution. Many are muscular dystrophies, others are myofibrillar myopathies (see below).

- Some of these conditions are found in particular ethnic groups—Udd's myopathy in the Finnish population and Miyoshi myopathy in the Japanese.
- Onset is usually in the distal lower limbs, often in the anterior compartment.
- The hands are the first site of involvement in Welander myopathy and distal caveolinopathy;

Table 8 The periodic paralyses

	Hyperkalaemic periodic paralysis	Hypokalaemic periodic paralysis	Anderson-Tawil syndrome
Prevalence	1:200 000	1:100 000	? Not determined
Genetics	Dominant	Dominant (1/3 new mutations)	Dominant
Age of onset	1st decade	2nd decade	2–18 years
Exacerbating factors	Rest after exercise, cold, potassium, glucocorticoids, fasting (early morning), alcohol, pregnancy, stress	Rest after exercise, cold, carbohydrate loading, menstruation	Potassium, exercise
Relieving factors	Carbohydrate intake, mild exercise	Cautious potassium ingestion	Usually hypokalaemic attacks-cautious K ingestion
Distribution of weakness	Proximal, symmetrical, flaccid; rarely distal & asymmetric in exercised muscles; can be focal; older patients may develop chronic permanent weakness (usually proximal)	Paraparesis or tetraparesis	Rarely permanent weakness, proximal (often) or distal
Duration of attack	Minutes to hours	Hours to days	1 hour–2 days
Attack frequency	More frequent than hypokalaemic form; increased until decline at age 50	Maximal frequency age 15–35 years, decline thereafter	Similar to hypokalaemic form
Severity of attack	Mild/moderate weakness usually	Moderate/severe	Moderate to severe
Other features	Depressed/absent reflexes during paralysis; paraesthesia pre-paralysis; 50% have myotonia or paramyotonia; CK up to 300 IU	Some mutations predispose to rhabdomyolysis; CK increased during attacks	*Cardiac*: prolonged QT (early), arrhythmia, bidirectional ventricular tachycardia, bigeminy, conduction block, valvular abnormalities; *Skeletal*: short stature, clinodactyly, syndactyly, scoliosis; *Face*: hypertelorism, high-arched palate, mandibular hypoplasia, low set ears, malar hypoplasia; *Kidney*: hypoplasia
Serum potassium between attacks	High, can be normal	Low, rarely normal	Variable
Electromyography	Myotonic discharges, compound muscle action potentials (CMAPs) ↓ during attack	No myotonia, CMAPs ↓ during attack	No myotonia, CMAPs ↓ during attack

the hands may also be involved in a number of the other myofibrillar myopathies.

- Weakness may progress to proximal muscles, particularly in Miyoshi myopathy.
- Cardiorespiratory complications are uncommon.
- Diagnosis depends on clinical assessment, CK level and muscle biopsy. Genetic testing is not yet routinely available, other than for dysferlin mutations causing Miyoshi myopathy.

SKELETAL MUSCLE CHANNELOPATHIES

Several disorders of muscle membrane excitability are linked to mutations in calcium, sodium and chloride channel genes and are now known as muscle channelopathies (table 6). Genetic testing is available.

Myotonia congenita

There are autosomal dominant (Thomsen's disease) and recessive forms (Becker's disease) due to mutations in the skeletal muscle chloride channel CLCN1 gene on chromosome 7q35 (table 7). There can be marked phenotypic variation with the same mutation (even within families). Patients typically have a pure myotonic disorder ranging from severe and disabling to mild with little or no weakness. Muscle hypertrophy is common.

Paramyotonia congenita

This is a dominant condition caused by mutations in the muscle sodium channel SCN4A gene on chromosome 17q35. The myotonia is worse with exercise and very significantly exacerbated by cold, when weakness (paralysis) may supervene.

Potassium aggravated myotonias

A group of conditions caused by mutations in SCN4A with pure myotonia (of variable severity) which can be particularly sensitive to potassium ingestion, with no associated weakness.

The periodic paralyses

These are inherited disorders of skeletal muscle excitability characterised by episodic weakness, often with disturbances in serum potassium (table 8). A disabling fixed myopathy often develops. Hyperkalaemic and hypokalaemic periodic paralysis are caused by mutations in ion channels that are not expressed in cardiac muscle, unlike Andersen-Tawil syndrome where patients have periodic paralysis and are at risk of sudden cardiac death due to ventricular arrhythmias or conduction block.

Central core disease

An inherited myopathy defined histologically by cores running through muscle fibres. Most cases are autosomal dominant and have ryanodine receptor mutations. Patients present in infancy with hypotonia and delayed motor milestones, but asymptomatic adult cases are also recognised. Weakness is usually mild and slowly progressive involving the face and proximal lower limbs. It may be associated with scoliosis, foot deformities, joint laxity and contractures. Respiratory failure is uncommon and CK usually normal.

MALIGNANT HYPERTHERMIA

The commonest cause of death during general anaesthesia, with a frequency of 1:7000–50 000 anaesthetics given, 50% occurring before the age of 15 years. Suxamethonium and halogenated inhalation agents are the most common precipitants.

Activation of mutant ryanodine receptors (RyR1) causes calcium release from sarcoplasmic reticulum stores and impaired calcium reuptake, leading to excessive muscle contraction, hypermetabolism, rhabdomyolysis and fever. Mutations in RyR1 on chromosome 19q13 are found in 50% of families and 20% of patients with malignant hyperthermia.

Other conditions may predispose patients to malignant hyperthermia-like like reactions: myotonia congenita, periodic paralysis, myotonic

2009;**9**:54–65. doi:10.1136/jnnp.2008.167171

dystrophy, Duchenne and Becker dystrophies, mitochondrial disorders, carnitine palmitoyltransferase deficiency and Brody's syndrome.

Susceptibility tests (halothane or caffeine are applied to a fresh muscle sample and maximal contraction measured) can be used for patients and family members. Genetic testing is available.

METABOLIC MYOPATHIES

Mitochondrial disorders

Mitochondrial disorders may be confined to muscle (eg, chronic progressive external ophthalmoplegia, progressive proximal myopathy) or form part of a multisystem disease. They are maternally inherited (mitochondrial DNA) or autosomal recessive, dominant or X-linked due to nuclear genome influence.

Non-specific myopathic symptoms include myalgia, fatigue, exercise-intolerance, exercise-induced cramps, myoglobinuria and rhabdomyolysis. Most patients have relatively mild weakness and remain ambulant. Some patients present with episodic weakness (sometimes associated with headache, nausea, vomiting and metabolic acidosis) which may be precipitated by infection, alcohol or exercise. Presentation occurs at any age.

- Chronic progressive external ophthalmoplegia is the commonest mitochondrial myopathy, frequently associated with limb (often proximal) muscle weakness. Impairment of eye movements may be severe but patients rarely have diplopia. Ptosis may be asymmetrical. Associated features include cerebellar ataxia, pigmentary retinopathy, sensorineural deafness, cardiac conduction defects, short stature, delayed sexual maturation, endocrine abnormalities and cranial or peripheral neuropathies.
- Kearns-Sayre syndrome is a subset of chronic progressive external ophthalmoplegia defined by onset before age 20 years, ptosis, ophthalmoplegia and pigmentary retinopathy; with one of three other features: heart block, CSF protein >100 mg/dl and cerebellar ataxia.
- Other mitochondrial syndromes sometimes associated with myopathy include mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS); myoclonic epilepsy with ragged red fibres (MERRF); neurogenic weakness, ataxia and retinitis pigmentosa (NARP); Leber's hereditary optic neuropathy; and Leigh's syndrome.

The plasma CK is usually normal but blood, urine and CSF lactate levels may be raised (abnormally raised lactate on aerobic exercise may be helpful in diagnosis). Muscle biopsy (ragged red fibres and or cytochorome oxidase negative fibres) is usually required to make the diagnosis, but is occasionally normal. Analysis of respiratory chain enzyme activities on muscle biopsy may also be helpful. These tests and the clinical findings guide genetic screening; some mutations can be detected in peripheral blood and urine but muscle is more reliable. Whole mtDNA genome screening is available in selected cases.

Disorders of β-oxidation

β-oxidation is a process of aerobic energy production, conducted by mitochondria, converting long chain fatty acids to acetyl-CoA which is then used to generate ATP via the respiratory chain. Active transport of long chain fatty acids into mitochondria requires carnitine as a carrier, carnitine palmitoyl transferase (CPT) 1 and 2, and carnitine-acyl-carnitine transferase. Defective β-oxidation leads to inadequate energy supply, accumulation of toxic intermediates, and carnitine and coenzyme-A depletion. The general features of these myopathies are:

- In adults, episodic exercise-induced myalgia, myoglobinuria and weakness or a progressive lipid storage myopathy. The myalgia may particularly occur after exercise (cf glycogen storage disorders where myalgia tends to occur during exercise).
- CK is often normal between attacks.
- In childhood, hepatic encephalopathy, fasting hypoglycaemia, hypoketonaemia, hyperammonaemia, raised transaminases and free fatty acids and dilated cardiomyopathy can occur.
- Muscle biopsy may (or may not) show lipid accumulation.
- Urinary organic acids may be elevated especially after an overnight fast, serum carnitine and CPT levels may aid diagnosis. Specific enzyme assays are available.

Disorders of carbohydrate metabolism

Muscle and liver are major sites for glycogen metabolism so both may be involved in these disorders, although isoenzyme differences can result in an isolated myopathy.

Acid maltase deficiency (Pompe's disease, glycogen storage disease type II)

This is an autosomal recessive (chromosome 17q23–25) disorder of glycogen metabolism. Acid maltase is a lysosomal enzyme involved in the conversion of glycogen to glucose.

- Most patients with the infantile form die in the first two years of life, but the childhood form is an important differential for muscular dystrophy; most succumb to cardiorespiratory failure in the second or third decade of life.
- Onset of the adult form occurs at any time after the age of 20 years with a slowly progressive proximal myopathy with muscle atrophy out of proportion to weakness. Respiratory compromise (due to respiratory muscle or isolated diaphragmatic weakness) is a common complication and patients may present de novo in respiratory failure. Non-myopathic features are rare.

Table 9 Specific treatments for muscle disease

Condition	Specific treatments
Duchenne muscular dystrophy	Corticoteroids (trial underway to establish regimen), respiratory support prolongs life, cardiac evaluation and ACE inhibitors
Myotonic dystrophy	Phenytoin, procainamide, quinine, clomipramine, imipramine for myotonia
Polymyositis/dermatomyositis	Prednisolone 1 mg/kg (60–80 mg/day) for 3–4 weeks, following 1 g iv for 3–5 days if severe, taper to 60–80 mg alternate days over 10 days and then by 5–10 mg per week; methotrexate 7.5 mg/week, increase by 2.5 mg/week to 25 mg/week; azathioprine 1–3 mg/kg per day (check MPTP levels)
Paramyotonia congenita	Mexilitine (150 mg BD), acetazolamide, hydrochlorthiazide, tocainide
Myotonia congenita	Mexilitine (150 mg BD, up to 300 mg TDS), phenytoin, quinine, procainamide, tocainide, carbamazepine
Hyperkalaemic periodic paralysis	Acute: salbutamol; Preventative: acetazolamide, thiazide diuretics
Hypokalaemic periodic paralysis	Acute: K+ supplementation; Preventative: low Na+/high K+ diet, dichlorphenamide, acetazolamide, spironolactone
Andersen-Tawil syndrome	K+ management, acetazolamide, implantable defibrillator
Malignant hyperthermia	Dantrolene 1 mg/kg up to 10 mg/kg, treat hyperkalaemia & arrhythmias, sodium bicarbonate for acidosis
Mitochondrial disease	Coenzyme Q10
β-oxidation defects (general)	Avoid fasting, use a low fat diet with sufficient carbohydrate
Primary carnitine deficiency	Carnitine supplements
Long chain acyl dehydrogenase deficiency	Diet containing carbohydrate, medium chain triglycerides and reduced long chain fatty acids
Multiple acyl-CoA dehydrogenase deficiency/riboflavin deficiency	Riboflavin supplements
Acid maltase deficiency	Enzyme replacement therapy: glucosidase-α; (bone marrow transplantation)

Analysis of blood lymphocytes, showing evidence of glycogen granules, is a sensitive and specific test. Muscle biopsy may show vacuoles containing glycogen and increased acid phosphatase activity. Enzyme assay on muscle, liver or fibroblasts confirms the diagnosis.

Myophosphorylase deficiency (McArdle's disease, glycogen storage disease type V)

This is autosomal recessive. Myophosphorylase is involved in glycogenolysis and is found only in skeletal and cardiac muscle. Age of onset is typically before 20 years, and it is more commonly expressed in males. Exercise precipitates myalgia, stiffness and weakness but there is second-wind phenomenon when aerobic fatty acid oxidation becomes the principle energy source. Muscle damage occurs during exercise causing myoglobinuria and sometimes renal failure. A few patients become wheelchair-bound but most are not significantly disabled if strenuous exercise is avoided. About one third of patients develop progressive proximal weakness with mild wasting. Usually, CK is raised and the ischaemic forearm exercise test positive. Diagnosis is made on clinical grounds with muscle biopsy support and enzyme assay.

MYOPATHIES WITH PROTEIN ACCUMULATION—MYOFIBRILLAR MYOPATHIES

These myopathies are characterised by myofibrillar destruction and accumulation of abnormal protein aggregates (usually desmin-positive). The most common mutations are found in desmin (2q35) and myotilin (5q31) but others include αβ-crystallin, ZASP and γ-filamin. These conditions are usually autosomal recessive and present in adults with progressive distal and proximal weakness. Common additional features include stiffness, myalgia, cramps, wasting, ankle contractures, neck flexion weakness, nasal speech and dysphagia. Respiratory failure and cardiomyopathy are relatively common in desminopathies. Myotilinopathies may be associated with peripheral neuropathy and αβ-crystallinopathies with cataracts. CK is usually moderately raised.

CONGENITAL MYOPATHIES

There are a number of uncommon congenital myopathies originally characterised by specific histology but now also defined genetically.

Nemaline myopathy is one example which is characterised by rod-shaped (thread-like) structures within muscle fibres, containing actin and other proteins. There are autosomal dominant, recessive and sporadic forms. Most present in childhood. Weakness and mild wasting occur first in proximal muscles and includes facial, neck flexors, tongue and pharyngeal muscles. Myalgia may be a feature. Respiratory failure (including diaphragmatic weakness) is relatively common.

MANAGEMENT

Management requires a well-integrated multidisciplinary team to ensure all aspects of a patient's needs and potential complications are addressed. This team will often need to include adult and paediatric neurologists, geneticists, cardiac and respiratory physicians, rehabilitationists, palliative care physicians, anaesthetists, spinal surgeons, obstetricians, pathologists, neurophysiologists, occupational therapists, speech and language therapists, physiotherapists, orthotic specialists, and social and care workers.

There are several specific treatments and interventions for certain muscle diseases (table 9).

Inflammatory muscle disease

- Corticosteroids are first line along with steroid sparing immunosuppressive agents.
- Methotrexate may be preferred to azathioprine for steroid sparing because it can provide more rapid benefit, but it can cause pulmonary fibrosis.
- Intravenous immunoglobulin may help in dermato- but not polymyositis
- It is uncertain if immunosuppression helps inclusion body myositis

Dystrophies

- Many patients with Duchenne now receive steroids but there is no consensus on regime or the timing of initiation.

2009;**9**:54–65. doi:10.1136/jnnp.2008.167171

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- With ventilatory support Duchenne patients are surviving into adulthood with improved quality of life; assisted cough techniques, chest physiotherapy and appropriate antibiotic use have greatly contributed to reduced mortality; directed cardiac intervention including early use of ACE inhibitors has also improved survival.
- Regular respiratory and cardiac assessment is essential for patients recognised to have cardiorespiratory involvement (eg limb girdle, Emery-Dreifuss); regular ECG and forced vital capacity (and/or sniff nasal inspiratory pressure) as well as selective use of blood gas analysis, polysomnography and echocardiograms.
- Simple interventions such as exercise, adequate nutritional support and pain management play major roles.
- Surgery for kyphoscoliosis and contractures may preserve mobility and respiratory function.
- Scapular fixation can provide functional benefit for some patients with facioscapulohumeral dystrophy.

Channelopathies

- Periodic paralysis attacks can often be effectively treated acutely with potassium normalisation, and the attacks prevented with acetazolamide. It is uncertain but suspected that the attack prevention strategies reduce the likelihood of a fixed myopathy.
- Mexilitene for myotonia in patients with myotonia congenita.

Malignant hyperthermia

- Dantrolene inhibits release of calcium from the sarcoplasmic reticulum; early administration reduces mortality from 70% to around 10%. All at risk patient groups should be aware of this risk and be supplied with appropriate documentation (eg, medic-alert).

Glycogen storage diseases

- Enzyme replacement (glucosidase-α) licensed for infantile Pompe's and is suggested in adult disease although this needs further evaluation.

Mitochondrial disease

- Coenzyme Q10 is widely used but with limited trial evidence. There may be a role for exercise programmes.

CONCLUSIONS

- An accurate diagnosis in every patient with muscle disease is important for optimum management and improves quality and quantity of life.
- Careful clinical evaluation combined with electrophysiology, muscle biopsy and/or selected genetic and metabolic testing will allow an accurate diagnosis in most patients.
- Genetic and molecular advances are revealing new therapeutic targets in muscle disease; the effectiveness of possible new treatment options is being assessed in an increasing number of clinical trials.
- Optimum patient care and the option for patients to enter trials rely on a precise histological and/or genetic diagnosis.

Acknowledgements: MGH is supported by a centre grant from the MRC, MRC Centre for Neuromuscular Diseases [G0601943] Information about neuromuscular clinical trials available at http://www.cnmd.ac.uk/

Competing interests: None declared.