David Hilton- Jones 24.19.4 Metabolic and endocrin

David Hilton- Jones 24.19.4 Metabolic and endocrine disorders 6334 David Hilton-Jones and Richard Edwards

section 24 Neurological disorders 6334 Myotonic dystrophy type 2 (DM2) Despite the similarity in name, and overlapping clinical features, there should generally be little difficulty distinguishing this condi- tion from DM1. There appears to be remarkable variability in the in- cidence of this disorder between countries, only partly explained by missed or failed diagnosis of the condition. Thus, in Germany DM2 appears to be about as prevalent as DM1; it is common in North America, but only a handful of families have been identified in the United Kingdom. Similar to DM1, the underlying molecular basis is an unstable nucleotide repeat expansion in an untranslated part of a gene, the consequences of which seem to be mediated through disruption of RNA metabolism. Despite the superficial similarities to myotonic dystrophy, there are also differences. Onset, or at least presentation, is usually in mid-adult life. Muscle pain and stiffness, particularly affecting the thighs, are common, and are sometimes the presenting symptoms. The pattern and distribution of myotonia are similar to DM1, but, in contrast to DM1, early proximal weakness is usually evident, but hand weakness may also be prominent. Cataracts may be indistin- guishable from those seen in myotonic dystrophy. Cardiac conduc- tion problems appear to be less common. Male hypogonadism and deafness occur. A congenital form of DM2 has not been described. Cognitive involvement appears to be rare and excessive daytime sleepiness does not appear to be a major feature. FURTHER READING Myotonic dystrophy type 1 Brook JD, et al. (1992). Molecular basis of myotonic dystrophy:
expansion of a trinucleotide (CTG) repeat in the 3′ end of a
transcript encoding a protein kinase family member. Cell, 68, 799–808. Gagnon C, et al. (2010). Health supervision and anticipatory guidance in adult myotonic dystrophy type 1. Neuromuscular

Disorders, 20, 847–51. Harper P (2001). Myotonic dystrophy, 3rd edition. W.B. Saunders, London. Harper P, et al. (2004). Myotonic dystrophy: present management, future therapy. Oxford University Press, Oxford. Reardon W, et al. (1993). The natural history of congenital myotonic dystrophy: mortality and long term clinical aspects. Arch Dis Childh, 68, 177–81. Turner C, Hilton-Jones D (2014). Myotonic dystrophy: diagnosis, management and new therapies. Curr Opin Neurol, 27, 599–606. Myotonic dystrophy type 2 Day JW, et al. (2003). Myotonic dystrophy type 2: molecular, diag- nostic and clinical spectrum. Neurology, 60, 657–64. Meola G, Cardini R (2015). Myotonic dystrophies: an update on clin- ical aspects, genetics, pathology and molecular pathomechanisms. Biochimica et Biophysica Acta, 1852, 594–606. Ranum LPW, et al. (1998). Genetic mapping of a second myotonic dystrophy locus. Nat Genet, 19, 196–8. Molecular basis of myotonic dystrophy Machuca-Tzili L et al. (2005). Clinical and molecular aspects of the myotonic dystrophies: a review. Muscle Nerve, 32, 1–18. Treatment Logigian E, et al. (2010). Mexiletine is an effective antimyotonia treatment in myotonic dystrophy type 1. Neurology, 74, 1441–8. 24.19.4 Metabolic and

endocrine disorders David Hilton-Jones and Richard Edwards† ESSENTIALS Disturbances of the biochemical or ionic balance of muscle re- sulting in impaired muscle function can be caused by a disparate group of conditions, including primary inherited disorders af- fecting enzymes or ion channels, and secondary disorders in which metabolic or endocrine disequilibrium disturbs normal function. Primary metabolic myopathies The primary metabolic myopathies are mostly autosomal recessive disorders in which lack of activity of a specific enzyme impairs ad- enosine triphosphate generation. Clinical presentation is with exer- cised-induced symptoms, but there are fundamental differences in manifestations depending upon whether the enzyme defect affects glycogen/glucose metabolism or fatty acid metabolism, reflecting the very different contributions that these pathways make to energy production depending on the nature of the exercise. Disorders of glycogen and glucose metabolism—these include: (1) Myophosphorylase deficiency (McArdle’s disease)—the most common (but still very rare) glycogenosis; symptoms usually start in childhood, but are often not recognized at that time; cardinal features are pain, weakness, and stiffness of muscles early in exercise, relieved by rest; strenuous exercise may precipitate rhabdomyolysis and acute kidney injury. Diagnosis is established by histochemical demonstra- tion of the absence of phosphorylase staining (or by enzyme assay) on muscle biopsy, or by genetic studies. There is no specific treatment. (2) Acid maltase deficiency—typically presents with a slowly progres- sive, painless, proximal myopathy; diaphragmatic involvement is common and can lead to presentation with respiratory failure; there are no exercise-induced symptoms. Enzyme replacement therapy may benefit some patients. (3) Other conditions—these include debrancher enzyme deficiency and phosphofructokinase deficiency. Disorders of fatty acid metabolism—these include: (1) Carnitine palmitoyltransferase deficiency—symptoms are precipitated by sustained exercise (e.g. long-distance running) or prolonged fasting, and severe episodes may precipitate rhabdomyolysis and acute kidney injury; diagnosis requires enzyme assay; treatment with a high-carbohydrate, low-fat diet may reduce the number of attacks. (2) Other conditions—numerous defects of β-oxidation. † Sadly, Professor Edwards died after completion of the original script.

24.19.4 Metabolic and endocrine disorders 6335 Secondary metabolic and endocrine myopathies Endocrine myopathies—nearly all forms of endocrine disturbance can be associated with weakness, typically relatively mild and involving the proximal muscles. The most common are Cushing’s syndrome (including iatrogenic steroid excess), and hypo- and hyperthyroidism. Weakness resolves when the hormone imbalance is corrected. Disorders of calcium, vitamin D, and parathyroid

hormone metabolism—myopathy is a feature of osteomalacia, primary hyper- parathyroidism, renal osteodystrophy, dialysis osteodystrophy, and ischaemic myopathy. Other conditions—(1) Alcohol excess—alcoholics frequently have muscle weakness, but it is often unclear whether the primary cause is myopathic or neuropathic. Alcoholic rhabdomyolysis typically follows a binge. (2) Drug-induced myopathies—the most common cause seen in clinical practice is statins. Skeletal muscle channelopathies These rare inherited disorders affect muscle membrane ion chan- nels, resulting in altered electrical characteristics: (1) periodic paralysis—underlying mutations affect either the sodium or cal- cium channels; manifest with episodic weakness; (2) myotonic dystrophies—see Chapter 24.19.3; (3) malignant hyperthermia— caused by mutations in the calcium channel associated ryanodine receptor; muscle relaxants and anaesthetic agents may trigger gen- eralized muscle contraction with rapid rise in body temperature that can be fatal if untreated. Introduction This section deals with disorders of voluntary muscle that arise as the result of either a disturbance of muscle metabolism or dis- ordered ion flux. In many cases precise mechanisms have yet to be defined. The term ‘metabolic myopathy’ is applied to those disorders in which there is a primary defect, usually an enzyme deficiency, in the biochemical pathways associated with energy generation (adeno- sine triphosphate or ATP synthesis). This group includes the mito- chondrial disorders, which are some of the most common causes of primary metabolic myopathy seen in clinical practice. Endocrine myopathies and nutritional and toxic myopathies, including those that are drug induced, can be considered as sec- ondary (acquired) metabolic myopathies. Defects in genes coding for subunits of the skeletal muscle so- dium and calcium channels underlie primary hyperkalaemic and hypokalaemic periodic paralysis, respectively. Both autosomal dominant and autosomal recessive myotonia congenita are caused by mutation in the skeletal muscle chloride channel. Mutations affecting two skeletal muscle calcium channels, the dihydropyridine (DHPR) and ryanodine (RYR1) receptors, are associated with malignant hyperthermia (MH). The congenital myopathy cen- tral core disease is allelic to MH and is associated with RYR1
mutations. The cardinal symptoms of myopathy are weakness, fatigue and/ or pain; altered excitability may also occur. It is important that the physician appreciates several points. There are nonspecific effects, such as loss of muscle, which may be far more important as a cause of weakness than the energetic consequences of the biochemical defect. Visual inspection and circumference measurements tend to underestimate the extent of wasting, which may be better docu- mented by quantitative scanning methods (MRI or CT). Not all the biochemical abnormalities cause symptoms. Clinical expression of the underlying defect depends on the habitual de- mands on the muscle for movement and weight lifting. A patient with a metabolic myopathy may have common, non- myopathic, musculoskeletal complaints that have no relation to the inherited or acquired defect. Muscle symptoms may have no physiological connection with the underlying defect and may be consequences of somatization or other psychological processes. The practical assessment of metabolic myopathy should in- clude consideration of the World Health Organization’s (WHO’s) International classification of impairments, disabilities, and handi- caps (ICIDH-2) (2000)—a classification of the functioning and dis- ability criteria of impairment, activities, and participation (revised from the ICIDH of the WHO from 1980). In this generic consid- eration, the relationship between antigravity muscle strength and the body weight to be carried is crucial: performance may be im- proved as much or more by weight reduction as by therapeutic at- tempts to reverse the myopathy, provided that calorie restriction does not aggravate the metabolic defect (e.g. in the case of carnitine palmitoyltransferase deficiency, where carbohydrate starvation may exacerbate the energy supply problem of the underlying enzyme defect). An objective

assessment of a response to treatment requires the measurement of individual muscle strength and/or timing of the performance of tasks relevant to the patient's symptoms, and the everyday life demands placed on the diseased muscles. Metabolic myopathies are unusual or rare conditions that are very variable in presentation. They are not easy to discuss in the light of current, evidence-based healthcare philosophies, which are largely based on the results of randomized controlled trials (RCTs) of therapeutic interventions. The treatments of the metabolic my- opathies tend to fall under the general rubric of 'orphan drugs' and 'orphan diseases', because, as with other rare diseases, a commercial return on the investment in research and development to deliver effective treatments is unlikely. Furthermore, in view of their rarity, there is little or no chance of formal treatment evaluation by RCTs. These conditions are, therefore, still to be evaluated by thoughtful clinical research employing the most relevant modern biochemical and physiological approaches. The patient with a metabolic myopathy is a person and, there- fore, far more important and complex to understand and help than the underlying metabolic diagnosis, difficult though that may be. It is essential to the humane and effective management of such a patient to see the individual as coping in a personal and social sense despite the metabolic impairment. The aim is to determine what is likely to best improve the patient's overall quality of life. Here, as with other disabilities, the constructive analysis and re- commendations of the WHO are useful as a basis for working with the patient to determine an individual management plan (Table 24.19.4.1).

section 24 Neurological disorders 6336 Primary metabolic myopathies The principal energy currency of living cells is ATP. Whereas in most organs the rate of ATP utilization is fairly constant, in volun- tary muscle the change from rest to strenuous activity may increase the demand on ATP generation several thousandfold. If that de- mand is not met, contractile failure (i.e. fatigue or weakness) will develop and may be accompanied by the destruction of muscle fibres. In many of the primary metabolic myopathies it is often as- sumed that exercise-induced symptoms relate to a failure of ATP generation and, although this is probably not always correct, it is a useful generalization. Although exercise-induced symptoms are often a striking feature of this type of metabolic myopathy, they are not always present. Some patients develop a chronic progressive myopathy. The main fuels providing energy for ATP generation in skeletal muscle are glycogen, fatty acids, and glucose (Fig. 24.19.4.1). Their relative contributions depend upon the state of nutrition and, more importantly, the level and duration of exercise. A gross oversimplifi- cation of these pathways aids understanding of the clinical features of the different forms of metabolic myopathy. At rest, the main fuel source is circulating free fatty acids, with a lesser contribution from circulating glucose. Small amounts of ATP may be generated directly from glycolysis, but the production of the energy-rich electron carriers (reduced nicotinamide adenine dinucleotide or NADH and reduced flavin adenine dinucleotide (FADH2) from fatty acid β-oxidation, and the citric acid cycle) is more important. Transfer of electrons to molecular oxygen through the electron transport chain of the mitochondria releases energy for the generation of ATP (oxidative phosphorylation). The increased demand on ATP generation during early strenuous exercise cannot be met by oxidative pathways. The resting blood flow provides an inadequate delivery of oxygen and substrate, and compression of blood vessels by the contracting muscle exacerbates the problem. ATP is therefore generated by the breakdown of muscle fibre stores of glycogen (anaerobic glycolysis). The relative lack of oxygen leads to increasing levels of NADH and pyruvate. NADH accumulation would inhibit glycolysis, and thus ATP generation, and is avoided by the reduction of pyruvate to lactate, explaining the lactic acidosis seen in disorders of oxidative metabolism. Adaptive processes occur as exercise continues; muscle blood flow increases, the

respiratory rate rises, and free fatty acids are mobilized from adipose stores. Glycogen stores in muscle become depleted and circulating free fatty acids become the main energy source, with a very small contribution from circulating glucose. Certain deductions can be made from the aforementioned that are largely borne out in clinical practice. Disorders of glycogen and glucose metabolism are typically asymptomatic at rest, but produce symptoms early in exercise when anaerobic glycolysis is important for energy supply. If low levels of exercise can be sustained, symptoms can improve as fatty acid oxidation increases ('second wind' phe- nomenon in McArdle's disease). Disorders of fatty acid metabolism, Table 24.19.4.1 Key features of disability evaluation and management in metabolic myopathy Body Person Society Impairment Activities (limitations) Participation (restriction) Metabolism/function/structure Severity, localization, duration Difficulties, duration, assistance needed Extent, facilitators, environmental demands of barriers Harmful consequences, e.g. myoglobinuria, falls Physical and mental adaptive responses Positive or negative psychosocial factors Treatment options: modification
of chemistry by diet or drugs? Counselling for exercise behaviour modification; avoidance of excessive weight gain; mechanical solutions, e.g. wheelchair/bicycle Better popular understanding of side effects of prescription drugs and alcohol; positive attitudes to assisting those with locomotor disability, improved access Developed from World Health Organization (2000). International classification of functioning and disability ICIDH-2. Geneva, WHO. Available
at: http://www3.who.int/icf/icftemplate. Glucose Blood Free fatty acids Glycogen Cytosol ATP NADH NAD NADH ATP CoA Fatty acyl-CoA Carnitine CoA CPT I CPT II PDH β-oxidation Acetyl-CoA Fatty acyl-CoA FADH2 NADH TG droplets Mitochondrial matrix NAD FAD ATP H2O NADH FADH2 ADP O2 Pyruvate Lactate Intermembrane space Plasma membrane Outer mm ACAS PT Inner mm C R CoA FAC FADH2 NADH Krebs' cycle Fig. 24.19.4.1 Major pathways associated with energy production in skeletal muscle. ACAS, acyl-CoA synthetase; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CoA, coenzyme A; CPT, carnitine palmitoyl transferase; FAC, fatty acylcarnitine; FAD, flavin adenine dinucleotide; FADH2, reduced FAD; mm, mitochondrial membrane; NAD, nicotinamide adenine dinucleotide; NADH, reduced NAD; PDH, pyruvate dehydrogenase complex; PT, pyruvate translocase; RC, respiratory chain; TG, triglyceride.

24.19.4 Metabolic and endocrine disorders 6337 insufficient to cause symptoms at rest, are likely to be exposed by sustained exercise and fasting. The central role of oxidative phos- phorylation explains why disorders of the respiratory chain may be symptomatic at rest. The clinical presentation will also depend upon whether the enzyme defect is restricted to skeletal muscle or is more generalized, thereby causing dysfunction of other tissues and organs. Systemic features may dominate in disorders of β oxidation and in mitochondrial disorders, but are absent in McArdle's disease because the defective enzyme is muscle specific. Disorders of glycogen and glucose metabolism (See also Chapter 12.3.1.) Several of the glycogenoses show significant skeletal muscle in- volvement. The major pathways of metabolism, and the enzymes associated with these disorders, are shown in Fig. 24.19.4.2. They are autosomal recessive disorders, except for the X-linked reces- sive, phosphoglycerate kinase deficiency. In most of these disorders serum creatine kinase (CK) is elevated at rest, and massively so after exercise-induced muscle damage. Acid maltase deficiency (type II glycogenosis) Acid maltase is a lysosomal enzyme not directly involved in ener- getic pathways, and exercise-induced symptoms are absent. In the infantile form (Pompe's disease) there is widespread organomegaly as well as skeletal muscle involvement, and death occurs by the age of 2 years due to cardiac or respiratory failure. The adult form is of considerable importance and has probably been underdiagnosed. The most obvious feature is a slowly

progressive, painless, proximal myopathy. Diaphragmatic involvement is an important characteristic, and some of these patients first present with respiratory failure. Nocturnal noninvasive ventilation alleviates sleep-disordered breathing and may prolong survival for many years. Serum CK ac- tivity is usually moderately elevated, but can be normal. Muscle bi- opsy typically shows acid phosphatase positive, glycogen-containing vacuoles, but is often normal, or shows only nonspecific changes. If the diagnosis is suspected, it can readily be proven or excluded by a recently developed, cheap, enzyme assay that uses a dried blood spot. DNA analysis is available but is not undertaken routinely in most centres. Enzyme replacement therapy has been shown to be effective in the severe infantile form, substantially prolonging survival. In the late-onset form, the evidence of benefit remains limited, and has to be considered against the enormous cost of treatment. Myophosphorylase deficiency (type V
glycogenosis—McArdle's disease) The onset of symptoms is usually during childhood, although they are often not recognized at that time, and the cardinal features are pain, weakness, and stiffness of muscles early in exercise, relieved by rest. The prevalence is estimated to be around 1 in 100 000 population but many cases are undiagnosed. Strenuous exercise, such as helping to push a car or lift heavy furniture, may induce painful, muscle con- tractures (if electrophysiological studies could be performed, the contractures would be noted to be electrically silent, unlike the con- tractures associated with cramps which are due to high-frequency nerve discharge). Muscle fibre breakdown is reflected in myalgia and myoglobinuria (dark red/black urine), which, if severe, may cause renal failure. Muscle breakdown is accompanied by a large release of CK into the blood, and a failure to see such a rise in serum CK levels should cast doubt on a diagnosis of myoglobinuria. Conversely, if renal failure is present, then no myoglobinuria may be seen and the only evidence of rhabdomyolysis is the raised CK level. Exercise-in- duced symptoms may ease ('second wind' phenomenon) if low levels of activity are maintained, as circulating free fatty acids and glucose become available as alternative fuels. Even when at rest, and asymp- tomatic, the serum CK activity level is usually moderately elevated. GLYCOGEN UDPG Phosphorylase Limit dextrin Debrancher enzyme Glucose 1-phosphate Fructose 6-phosphate Fructose 1,6-diphosphate Phosphofructokinase Glyceraldehyde 3-phosphate 1,3-Diphosphoglycerate Phosphoglycerate kinase 3-Phosphoglycerate Phosphoglycerate mutase 2-Phosphoglycerate Pyruvate Lactate Lactate dehydrogenase Lysosomal acid maltase GLUCOSE Glucose 6-phosphate Fig. 24.19.4.2 Pathways of glycogenolysis and glycolysis. Enzymes known to be associated with particular clinical syndromes are shown.

 Progressive proximal weakness frequently develops in middle age and is sometimes the mode of presentation in late-onset cases. Failure of lactate generation (accompanied by increased blood ammonia and hypoxanthine concentrations) during forearm exer- cise is consistent with the diagnosis. However, this is not specific because it also occurs in other glycogenolysis disorders, and may be seen to some extent in acquired conditions such as alcoholic myop- athy or hypothyroidism. Also, the test may give a misleading ('false-negative') result if the myophosphorylase deficiency is only partial. The definitive diagnosis is established by histochemical demonstra- tion of the absence of phosphorylase staining (or by enzyme assay) on muscle biopsy, or by genetic studies of the coding and expression of muscle phosphorylase. Debrancher enzyme deficiency (type III glycogenosis—Cori– Forbes disease) In infancy and childhood, the main features of this disorder are hepatomegaly, hypoglycaemia, and failure to thrive. During ado- lescence muscle symptoms become more prominent. A small group of patients first present during adult life with muscle symptoms, but may give a history of a

protuberant abdomen in childhood. Both exercise intolerance (although less striking than in McArdle's disease) and a slowly progressive proximal myopathy are present. Some patients develop a potentially fatal cardiomyopathy. The forearm exercise test shows impaired, but not absent, lac- tate generation, muscle biopsy shows glycogen accumulation, and the administration of glucagon fails to produce a hyperglycaemic response. The definitive diagnosis is established by enzyme assay in samples of muscle, liver, erythrocytes, and leucocytes. Phosphofructokinase deficiency (type VII
glycogenosis—Tarui's disease) The clinical picture is very similar to that of myophosphorylase defi- ciency, but a phosphofructokinase (PFK) deficiency in erythrocytes leads to the additional features of haemolytic anaemia and gout. It is very much rarer than myophosphorylase deficiency. Unlike patients with myophosphorylase deficiency, ingested glucose does not im- prove exercise tolerance in those with PFK deficiency because of the position of PFK in the sequence of enzymes in the glycolytic pathway (see Fig. 24.19.4.2), and indeed may worsen symptoms (sometime called the 'out-of-wind' phenomenon). Diagnosis is established by enzyme assay in muscle. Defects of distal glycolysis Deficiencies of phosphoglycerate kinase, phosphoglycerate mutase, and lactate dehydrogenase have been found but are all ex- tremely rare. All three are associated with exercise intolerance and myoglobinuria. It is possible that other defects of glycolysis, causing similar symptoms, remain to be discovered. Treatment With the exception of the recent introduction of enzyme replace- ment therapy for acid maltase deficiency there is, as yet, no specific treatment for any of the disorders described here. Attempts at dietary manipulation have generally proved unsuccessful. Patients must be aware of the risk to renal function from myoglobinuria, and try to avoid intense exercise. There is evidence, in patients with muscle pain due to McArdle's disease and other metabolic myopathies, that maintaining a reasonable level of aerobic fitness is beneficial, by sus- taining sufficient activity of muscle mitochondria to provide energy from oxidative phosphorylation to adapt to the deficiencies in en- ergy availability from glycogenolysis. Disorders of lipid metabolism Unlike glycolysis, lipid metabolism is entirely dependent on oxida- tive processes. Moreover, there is a close relationship between the disorders described next and defects of the mitochondrial respira- tory chain (e.g. lipid accumulation in muscle is a common histo- logical feature in respiratory chain disorders). Free fatty acids, mainly from the blood but also from trigly- ceride droplets stored within muscle fibres, are a major fuel at rest and during sustained exercise (see Fig. 24.19.4.1). They are con- verted to fatty acyl-CoA at the outer mitochondrial membrane which, within the mitochondrial matrix, can undergo β oxi- dation.
A transport system involving carnitine and the enzyme system carnitine palmitoyltransferase is required to enable fatty acyl-CoA to cross the inner mitochondrial membrane. Defects involving carnitine, carnitine palmitoyltransferase, and β oxida- tion are recognized. Carnitine deficiency Secondary carnitine deficiency is common and seen in association with many primary metabolic disorders, including defects of fatty acid oxidation and respiratory chain disorders. Primary carnitine deficiency is very rare and is caused by a defective carnitine trans- porter, OCTN2. It may cause varying combinations of myopathy, hypoketotic hypoglycaemia, and hepatic encephalopathy. Defects of β oxidation Many enzyme deficiencies have been described, but clinical fea- tures are limited. They may present during the neonatal period with hypotonia, hypoglycaemia, cardiomyopathy, failure to thrive, and early death. Such defects may be a cause of some cases of sudden infant death syndrome. Later-onset cases develop Reye's syndrome- like crises, muscle weakness, and cardiomyopathy. Secondary carnitine deficiency is common. A high-carbohydrate and low-fat diet may help. Carnitine palmitoyltransferase deficiency This rare autosomal recessive disorder shows a male predomin- ance. It is the most common of the lipid

disorders to present with myopathic features. Symptoms are precipitated by sustained exer- cise (e.g. a route march) or prolonged fasting, and consist of muscle pain followed by myoglobinuria, which may cause renal failure. The diagnosis may be strongly suggested by tandem mass spec- trometry, looking at the acylcarnitine profile, in a blood sample taken after an overnight fast, but confirmation requires enzyme assay, usually on cultured fibroblasts. A high-carbohydrate, low-fat diet may reduce the number of attacks. Myoadenylate deaminase deficiency Deficiency of myoadenylate deaminase has been suggested as a cause of exercise-induced myalgia, weakness, and cramps but its exact status remains controversial. It has been described as an incidental finding in muscle needle biopsies taken from normal volunteers to study muscle chemistry in sports science research. The enzyme

24.19.4 Metabolic and endocrine disorders 6339 catalyses the reaction adenosine monophosphate (AMP) → inosine monophosphate (IMP) + ammonia (NH_3). Theoretically, this re- action may aid ATP production by removing AMP and increasing flux through the adenylate kinase reaction $2ADP \rightarrow ATP + AMP$. The diagnosis is established from the absence of a rise in the plasma ammonia level during forearm exercise testing and from the histo- chemical demonstration of absent enzyme activity. Endocrine myopathies Although weakness is a common symptom in many endocrine dis- orders, the mechanisms are generally poorly understood. However, the myopathy responds to treatment of the underlying hormonal disorder, and extensive investigation of the myopathic component is rarely required. The most common pattern is limb-girdle weakness. Thyroid disorders (See also Chapter 13.3.1.) Thyrotoxicosis Typically, weakness develops shortly after the onset of other thyrotoxic symptoms, and 80% of patients have demonstrable weak- ness at presentation. The shoulder girdle muscles tend to be involved before the pelvic musculature. Muscle atrophy is usually slight. Asymmetrical and distal weakness, myalgia, cramps, and fascicula- tions are rare findings. The serum CK level is usually normal, but electromyography shows features consistent with muscle disease. The myopathy re- sponds to treatment of the thyrotoxicosis. Thyrotoxic periodic paralysis Most cases have been reported in individuals from the Orient, with a strong male predominance. Clinical features closely mimic those of familial hypokalaemic periodic paralysis. The weakness is dis- proportionate to any muscle wasting. The onset of paralytic attacks usually follows the development of hyperthyroid symptoms and the attacks cease when the patient is rendered euthyroid. A genetic basis has not been established. Thyroid ophthalmopathy (Graves' ophthalmoplegia) The classic features of this condition include eyelid lag, retraction and swelling, as well as progressive swelling of the extraocular muscles and orbital soft tissues, leading to proptosis and diplopia and, in severe cases, corneal ulceration, papilloedema, and optic at- rophy. An extremely important, but often missed, variant is the pa- tient who presents with minimal diplopia only. In mild cases, MRI or CT is useful for detecting extraocular muscle swelling. Simple tests of thyroid function may be normal. Estimation of antithyroglobulin and antimicrosomal antibodies, and the performance of a thyrotropin-releasing hormone stimula- tion test may be required. Thyroid-stimulating immunoglobulins are present in most patients. If thyrotoxic, the patient should be rendered euthyroid. Lid retrac- tion may respond to topical 10% guanethidine. Persisting major eye problems may require high-dose prednisolone, plasma exchange, or orbital decompression. Tarsorrhaphy protects the cornea. Thyroid disease and myasthenia Patients with myasthenia gravis have an increased incidence of thyroid disease, including hyperthyroidism, hypothyroidism, Hashimoto's thyroiditis, and increased antibodies to thyroglobulin or microsomal fractions. Thyroid disease may predate or follow the onset of myasthenia and must be considered as a cause of deteri- oration in an otherwise stable patient with myasthenia. Some 5% of patients

with myasthenia will develop thyroid disease, but only about 0.1% of thyrotoxic patients develop myasthenia. Hypothyroidism Although hypothyroid myopathy may be asymptomatic, mild weak- ness is probably present in most patients. Muscle biopsy charac- teristically shows evidence of type II (fast twitch, glycolytic, high intrinsic force) muscle fibre atrophy with type I fibre dominance. Even in the absence of weakness the serum CK level is often mark- edly raised. Slow relaxation of the tendon jerks may be present in isolation. Muscle pain and cramps are common. In children, the combination of hypothyroidism, weakness, and muscle hypertrophy is referred to as the Kocher–Debré–Semelaigne syndrome. In adults, Hoffman's syndrome describes the combination of hypothyroidism, weakness, muscle hypertrophy, cramps and myoedema (the forma- tion of a localized ridge of muscle following direct percussion). They probably represent variants of the same disorder. All hypothyroid myopathic symptoms respond to thyroxine replacement. Pituitary–adrenal axis disorders Clinically, the most important of these is iatrogenic steroid myop- athy, discussed next under 'Glucocorticoid excess'. Acromegaly Proximal weakness, pelvic more than shoulder girdle, is present in about half of patients. Common complaints include tiredness, weakness, and myalgia; muscle wasting is slight. Serum CK levels are normal or slightly raised. Normalizing growth hormone levels improves the myopathy, but recovery may be incomplete. Hypopituitarism Growth hormone deficiency in childhood impairs muscle and skel- etal development proportionately; weakness is not usually a fea- ture. In adults, panhypopituitarism causes generalized weakness and fatigue, which usually responds to thyroxine and cortisone replacement therapy. Replacement of growth hormone in growth hormone-deficient adults has been associated with varying degrees of improvement in the strength of wasted muscles. Glucocorticoid excess Adrenocorticotropic hormone excess, from either a functioning pi- tuitary adenoma or ectopic production, is usually associated with high glucocorticoid levels, producing pituitary or ectopic Cushing's syndrome. Weakness is common and thought to relate to gluco- corticoid excess. Weakness may occur in Nelson's syndrome, in which there is a high level of adrenocorticotropic hormone, but no glucocorticoid excess. The myopathy associated with Cushing's syndrome is prob- ably related to glucocorticoid excess, and the clinical features are

 essentially the same as those of iatrogenic steroid myopathy. The 9α- fluorinated steroids, including dexamethasone, triamcinolone, and betamethasone, appear to have the greatest myopathic potential. Topical steroids can cause myopathy. The most common picture is of a slowly progressive limb-girdle wasting and weakness, pelvic more than shoulder girdle, often ac- companied by myalgia. The drug-induced form may have a more acute onset. Myopathy without other features of glucocorticoid ex- cess is unusual. The serum CK level is usually normal and muscle biopsy shows nonspecific type II fibre atrophy. Steroid withdrawal is followed by recovery over several months. If steroid therapy for the primary disorder has to be continued, then a nonfluorinated compound such as prednisolone should be used, preferably on an alternate-day basis. Successful treatment of Cushing's syndrome leads to recovery. Conn's syndrome Weakness is present in about 75% of patients and is due to the as- sociated hypokalaemia. Secondary hypokalaemic periodic paralysis may occur. Addison's disease Weakness, fatigue, and myalgia occur in up to half of patients. Rare myopathic presentations include progressive flexion contractures and secondary hyperkalaemic periodic paralysis. The serum CK level is normal or slightly increased. Glucocorticoid replacement therapy is curative. Disorders of calcium, vitamin D, and parathyroid hormone metabolism (See also Chapter 13.4.) There are complex interactions of vitamin D metabolism, calcium and phosphate homeostasis, and parathyroid hormone activity. Myopathy occurs in several clinical situations, but the precise patho-

physiological mechanisms are unclear. Osteomalacia Weakness is the presenting symptom in a third of patients, affecting predominantly the pelvic girdle musculature. Bone pain is prom- inent. The serum CK level is usually normal. Muscle biopsy may show type II fibre atrophy, sometimes severe. The pain responds fairly rapidly to vitamin D treatment, but the weakness recovers more slowly and may be incomplete. Primary hyperparathyroidism Myalgia, stiffness, and complaints of fatigue are common, but overt weakness is rare. Symptoms resolve when the underlying parathy- roid adenoma is removed and serum calcium levels fall. Renal osteodystrophy End-stage renal failure is frequently accompanied by a predomin- antly pelvic girdle myopathy, sometimes with buttock and thigh pain. Symptoms respond to dialysis, transplantation, or vitamin D treatment. Dialysis osteodystrophy Some patients undergoing dialysis develop a severe myopathy with bone pain, fractures, and vitamin D resistance. It probably relates to aluminium toxicity. Fatigue and muscle weakness are common. Objective muscle testing is needed to distinguish true changes in muscle function from the nonspecific causes of fatigue and ill-health seen in patients on dialysis. Ischaemic myopathy Rarely, a painful ischaemic myopathy with arterial narrowing due to calcium deposition complicates renal failure. Skin ulceration and bowel infarction may also occur. Nutritional and toxic myopathies Although malnutrition causes muscle wasting, specific myopathic effects of nutritional deficiencies are uncommon, a notable excep- tion being vitamin D deficiency, discussed next. Myopathies due to ingested toxins are relatively more common than the inherited metabolic myopathies and include those due to alcohol, and thera- peutic drug excess or idiosyncrasy. Alcoholic myopathies People with chronic alcohol problems may develop subacute or slowly progressive, proximal muscle weakness with mild-to- moderate wasting and muscle biopsy evidence of type II fibre at- rophy, mainly affecting the lower limbs. Occasionally the wasting is more generalized, as alcoholism may be associated with neurogenic muscle atrophy secondary to concomitant thiamine deficiency and more generalized malnutrition. It is thus still debated whether the so-called chronic alcoholic myopathy is purely myopathic, neuro- pathic, or both, and whether the cause is a direct toxic effect of alcohol or a secondary phenomenon, perhaps relating to malnutri- tion. Abstinence may lead to some degree of recovery. Much more dramatic is acute alcoholic myopathy (‘alcoholic rhabdomyolysis’), which usually occurs during or shortly after a binge. There may be widespread cramps, pain, and weakness. However, the most striking feature is the development of ex- tremely painful muscle swelling, which may be localized or gen- eralized. Myoglobinuria presents a threat to renal function, and hyperkalaemia may be present in severe cases. The serum CK is ele- vated and muscle biopsy shows acute necrosis. Recovery, which may be incomplete, occurs over several weeks. Vitamin E deficiency Vitamin E deficiency probably causes a myopathy, but interpretation is confused by the presence of additional neurological problems including neuropathy and ataxia. Drug-induced myopathies Drug-induced neuromuscular disorders are common, under recognized and underreported. Numerous drugs have been impli- cated, several mechanisms are responsible (Table 24.19.4.2), and some drugs can affect both muscle and peripheral nerves (e.g. vincristine, d-penicillamine, and perhexiline). Arguably the most important is statin-induced myopathy, because myopathic symptoms are relatively common and the prescription of statins is becoming ever more wide- spread, with over-the-counter preparations being available in some countries. A small percentage of patients develop myalgia, usually with elevation of the serum CK, but without demonstrable weakness.

 The symptoms resolve on drug withdrawal. Much more rarely, statins may induce rhabdomyolysis/myoglobinuria, and deaths have been re- ported. Risk factors include high doses of statins (e.g. >40 mg daily of simvastatin) and, probably in more

than 60% of cases, concomitant use of drugs that interfere with statin metabolism (e.g. ciclosporin). Very recently evidence has emerged that statins may trigger an immune- mediated myopathy, with antibodies against HMGCoA reductase (the enzyme inhibited by statins), that persists on statin withdrawal but responds to immunosuppressant therapy. There remains debate as to whether a pre-existing myopathy, symptomatic or not, or carrying a muscle disease related gene, increases the risk of stain-induced my- opathy. Current expert advice is that statins are not contraindicated in such circumstances, but that the patient should be aware of the debate, serum CK should be measured before starting treatment and again if symptoms develop, and that the drug should be discontinued imme- diately if muscle symptoms develop. Skeletal muscle channelopathies There has been an explosion in the identification of central and per- ipheral nervous system and cardiac disorders caused by ion channel dysfunction. Ion channels may be ligand gated or voltage gated. In the field of muscle diseases, the most important ligand-gated channel is the skeletal muscle nicotinic acetylcholine receptor, at the neuromus- cular junction. Antibody-mediated destruction underlies acquired myasthenia gravis, whereas inherited mutations of genes coding for the subunits of the receptor are the basis of several forms of congenital myasthenic syndrome. Acquired neuromyotonia and Lambert–Eaton myasthenic syndrome are caused by antibody-mediated damage to the voltage-gated potassium and calcium channels, respectively, of the terminal axon, and are discussed, together with myasthenia gravis and the myasthenic syndromes, in Chapter 24.18. The following section is concerned with inherited disorders of skel- etal muscle voltage-gated sodium, calcium, and chloride channels. In passing, it should be noted that channelopathies are not confined to muscle, and note was made earlier of two neuronal channelopathies. Other disorders caused by an inherited channel defect include certain forms of epilepsy (nocturnal frontal lobe epilepsy, benign neonatal convulsions), episodic ataxia, hemiplegic migraine, deafness, night blindness, cardiac long QT syndromes, and nephrolithiasis. Periodic paralyses Marked hypokalaemia and hyperkalaemia from whatever cause may produce weakness or paralysis (secondary periodic paralysis). The primary periodic paralyses are familial, dominantly inherited dis- orders characterized by recurrent attacks of paralysis. These have previously been subdivided into hyperkalaemic, hypokalaemic, and normokalaemic forms on the basis of changes in the serum potas- sium level during attacks. Recent evidence has shown that the pri- mary abnormality in the hyperkalaemic and normokalaemic forms is a mutation affecting the adult skeletal muscle sodium channel, whereas the hypokalaemic form is caused by a mutation affecting the skeletal muscle calcium channel. Hypokalaemic periodic paralysis Attacks usually start during the second decade of life and then vary in frequency from daily to years between episodes. Weakness may be present on waking or develop during the day, typically in response to a heavy carbohydrate meal or during rest after strenuous exer- cise. The weakness involves the legs more than the arms, proximal muscles more than distal, and may be asymmetrical. Bulbar and re- spiratory muscle weakness is rare. Attacks last from hours to sev- eral days. The tendon reflexes may be depressed or lost during an attack. Permanent and progressive proximal weakness often develop by middle age. The serum potassium level typically falls during an attack, but not necessarily outside the normal range. The disorder is caused by a mutation in the CACNA1S gene (on chromosome 1) encoding the DHPR component of the skeletal muscle calcium channel. The DHPR is located within the transverse tubular system, and acts as a voltage sensor for the RYR1 component of the calcium channel, which is located in the sarcoplasmic reticulum and is responsible for triggering calcium release and thus muscle con- traction. Different mutations in the same gene, and mutations in the RYR1 gene, are associated with malignant hyperthermia (see next). Table 24.19.4.2 Drug-induced myopathies Focal

damage/fibrosis Intramuscular Opiates Antibiotics Paraldehyde Necrosis Heroin Clofibrate ε-Aminocaproic acid Myoglobinuria/rhabdomyolysis Heroin Methadone Amphetamines Barbiturates Diazepam Isoniazid Carbenoxolone Phenformin Amphotericin B Statins Inflammatory myopathy Procainamide d-Penicillamine Hypokalaemic weakness Diuretics Carbenoxolone Liquorice Purgatives Subacute or painless proximal myopathy Corticosteroids Chloroquine β-Blockers Myasthenia d-Penicillamine Aminoglycosides Malignant hyperthermia Suxamethonium Cyclopropane Halothane Enflurane Ketamine

section 24 Neurological disorders 6342 Acetazolamide is the treatment of choice to prevent attacks. Acute attacks respond to oral potassium, given as an unsweetened aqueous solution. Apparently identical attacks may occur in association with thyro- toxicosis and resolve when the patient is rendered euthyroid. Hyperkalaemic periodic paralysis Attacks tend to start at an earlier age than in the hypokalaemic form, and do not last as long. Precipitants include cold, fasting, rest after exercise, pregnancy, alcohol intake, and potassium loading. Readily utilized carbohydrate sources, such as a sweet drink, may abort an at- tack. A progressive proximal myopathy may also develop. Myotonia is present in some patients (see next). The serum potassium level may rise during an attack, but the change is often slight. The underlying abnormality is a mutation within the SCNA4 gene (on chromosome 17) encoding the α-subunit of the skeletal muscle sodium channel. Mild attacks respond to carbohydrate ingestion. Kaliuretic diur- etics usually prevent attacks. Paramyotonia congenita Paramyotonia congenita describes a dominantly inherited condition characterized by cold-induced weakness and muscle stiffness (para myotonia), which is sometimes accompanied by periodic paralysis. The relationship between this disorder and primary hyperkalaemic periodic paralysis had been much debated, but recent evidence has shown that hyperkalaemic periodic paralysis, hyperkalaemic periodic paralysis with myotonia, paramyotonia congenita and paramyotonia congenita with periodic paralysis are allelic disorders involving the SCNA4 gene (on chromosome 17) encoding the α-subunit of the skeletal muscle sodium channel. Myotonia congenita Autosomal dominant (Thomsen’s disease) and recessive (Becker- type) forms of this condition are recognized, with the recessive type being much more common. Onset tends to be earlier in the dom- inant form, but both usually become apparent in childhood. There is muscle stiffness, worse after rest and exacerbated by cold, minimal, or no weakness, readily demonstrable percussion myotonia, and muscle hypertrophy, which tends to be more marked in the recessive form. Both the recessive and dominant forms are caused by mutations in the CLCN1 gene (on chromosome 7) encoding the skeletal muscle chloride channel. Malignant hyperthermia The main features of this autosomal dominant disorder are a rapidly rising body temperature and generalized muscular rigidity during anaesthesia. Additional features include skin mottling, cyanosis, tachypnoea, tachycardia, cardiac dysrhythmias, and autonomic instability. Attacks in susceptible individuals may be triggered by suxamethonium and anaesthetic agents (halothane, cyclopropane, enflurane, ketamine). A similar disorder may be associated with heavy exercise in very hot conditions (e.g. recruits undergoing route marches on mountains during a hot summer). Attacks are life-threatening. Treatment consists of withdrawing the offending agent and providing general supportive measures and intravenous dantrolene 2 mg/kg body weight. Disturbed calcium homeostasis underlies the attacks, with ex- cessive Ca^{2+} influx into the sarcoplasmic reticulum. The disorder is genetically heterogeneous. In many families the underlying abnor- mality affects the skeletal muscle calcium channel with a mutation in either the RYR1 gene (on chromosome 19) or the CACNA1S gene (on chromosome 1). RYR1 mutations may also cause central core disease (CCD)—CCD and MH are allelic disorders and may occur together in the same individual or independently. Other CACNA1S gene mutations cause hypokalaemic periodic paralysis. Screening

for MH susceptibility involves muscle biopsy and in vitro testing for a reduced contractile threshold to halothane and caffeine. It is hoped that specific molecular biological tests will be- come available. A significant practical problem is the management of family members who fear that they may be at risk. As with those patients who have suffered hyperpyrexia under anaesthesia (even in those in whom repeated exposure has not led to a consistent re- occurrence), it is advisable for those individuals of proven or sus- pected risk to wear, at all times, some form of bracelet or locket giving details of the risk, in case they are casualties in an emergency such as a road accident. Myoglobinuria This important symptom and sign must be differentiated from haematuria and haemoglobinuria. Red cells are visible on micros- copy in the former but not in the latter. In all three conditions, the haemoperoxidase stick test is positive. Myoglobin is a protein that acts as an oxygen store within skel- etal muscle fibres. Myoglobinuria causes a dark-brown/red dis- coloration of the urine, the main concern being that the protein can cause renal tubular necrosis and thus renal failure. Numerous disorders are known to be associated with myoglobinuria (Table 24.19.4.3). In the metabolic disorders, the presumed mechanism Table 24.19.4.3 Causes of myoglobinuria Metabolic Glycogenoses Carnitine palmitoyl transferase defi ciency Severe electrolyte disturbance Excessive activity/ temperature Marathon running Military training Status epilepticus Malignant hyperthermia Neuroleptic malignant syndrome Drugs and toxins Several drugs (see Table 24.24.4.2) Venoms and animal toxins Infection Viral Toxic shock Clostridial infection/gangrene Ischaemia and trauma Crush Coma Any cause of severe ischaemia Compartment syndrome Electric shock Inflammatory myopathies Dermatomyositis Polymyositis

---

Revision #1
Created 2026-01-22 16:43:44 UTC by Omar Ayman
Updated 2026-01-22 16:43:44 UTC by Omar Ayman