

Metabolic myopathies

Metabolic myopathies most often present with either (1) recurrent episodes of acute-onset and reversible muscle dysfunction or (2) progressive muscle weakness (Table 1). In general, episodic abnormalities, such as fatigue, pain, weakness and rhabdomyolysis, correlate well with our knowledge of the underlying defects in energy production (see Box on page 20). The mechanisms by which metabolic abnormalities bring about permanent weakness are poorly understood.

The clinical features of disorders of carbohydrate metabolism (glycogenoses), lipid metabolism (lipidoses) or electron transport chain (mitochondrial) function vary with age at presentation. Defects in cellular energy production in the newborn and infants often give rise to severe multisystem disorders but adult-onset disease is usually restricted to muscle. This review will focus on adult presentations of non-mitochondrial disorders of muscle metabolism.

Presentations of metabolic muscle disease

The most characteristic presentation of metabolic myopathies is episodic muscle dysfunction. Premature fatigue, exertional muscle pain, contractures and rhabdomyolysis are seen in attacks of increasing severity. Those metabolic muscle diseases causing progressive weakness tend to have a more non-specific 'myopathic' phenotype and are less likely to give rise to attacks of rhabdomyolysis.

PREMATURE EXERTIONAL FATIGUE

Defects in carbohydrate metabolism result in an early rise in heart rate, respiratory rate and fatigue within minutes of starting intense exercise while disorders of lipid metabolism only become symptomatic after several hours of sustained submaximal exertion. Muscle disease is clearly not the commonest cause of decreased exercise tolerance which is more likely to be the result of deconditioning or an indicator of primary cardiac or pulmonary disease (Table 2). However, the muscle fatigue in metabolic myopathies has a different and unpleasant quality not reported by normal individuals.

EXERCISE-INDUCED CRAMPS

Individuals with glycogenoses report exertional aching, burning or cramps in muscles which may reach a peak 6 hours after exercise. Continued exercise may result in the muscle 'locking up' due to the development of painful contractures. In contrast to true cramps, a metabolic muscle contracture is hard and tender; the pain is made worse by attempted stretching; the pain lasts for hours rather than minutes; and the EMG is silent.

Muscle pain in lipidoses is characteristically seen during or after sustained exercise but can also be unrelated to exercise, particularly during periods of fasting or dieting, exposure to cold, general anaesthesia and intercurrent infection. Affected individuals may find that the use of glucose tablets or chocolate improves exercise tolerance. In contrast to the glycogenoses, they do not develop painful contractures.

MYALGIA

Muscle pain during exercise is rarely seen in healthy individuals. While a common feature of metabolic muscle disease, it is relatively

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unusual for exercise-related myalgia in isolation to be the dominant symptom: individuals are more likely to report "weak legs" or "jelly legs." Normal muscle characteristically gives rise to pain 24 to 48 hours after unaccustomed exertion, particularly in individuals who lead a sedentary lifestyle.

RHABDOMYOLYSIS

Muscle pain in individuals with a metabolic myopathy is a harbinger of muscle fibre breakdown and is accompanied by a rise in plasma CK, dark urine and a concomitant risk of renal impairment. In between attacks the plasma CK often remains high in glycolytic disorders but usually returns to normal in disorders of lipid metabolism. However, the CK rise during an attack of rhabdomyolysis is often higher in lipidoses and is more likely to lead to renal failure.

Metabolic myopathies causing episodic muscle dysfunction

Individuals with episodic presentations of glycogenoses and lipidoses are clinically normal between attacks although with time they may become mildly weak. Attacks of rhabdomyolysis are treated symptomatically. Further investigations, especially muscle biopsy, are deferred until at least one month after the episode since muscle necrosis interferes with biochemical analyses and necrotic muscle fibres mask other histochemical findings. The main informative investigations in glycogenoses are raised serum CK levels, myopathic EMG findings and subsarcolemmal vacuoles on muscle histology. In contrast, laboratory investigations in the lipidoses are usually normal between attacks and the diagnosis depends on clinical suspicion leading to muscle enzyme estimation in a specialist laboratory. With the notable exception of phosphofructokinase, episodic weakness is a feature of deficiencies in muscle-specific enzymes.

DISORDERS OF CARBOHYDRATE METABOLISM

Myophosphorylase deficiency (McArdle's disease)

Myophosphorylase deficiency is the commonest defect affecting muscle carbohydrate metabolism. Myophosphorylase is responsible for glycogenolysis in the early stages of intense exercise so affected individuals report fatigue and pain within the first few minutes of strenuous activity. Continued exercise results in increasing pain which is initially deep and aching but rapidly

TABLE 1: The clinical presentation and investigation of the major metabolic myopathies

	EPISODIC MUSCLE DYSFUNCTION †	PROGRESSIVE WEAKNESS
DISORDERS OF CARBOHYDRATE METABOLISM	Myophosphorylase deficiency Phosphofructokinase deficiency	Acid maltase deficiency Debranching enzyme deficiency
Presentation	premature exertional fatigue, muscle pain, contractures, rhabdomyolysis early during intense exercise	symmetrical muscle weakness, respiratory failure
Investigations	CK raised EMG myopathic Ih subsarcolemmal vacuoles	CK raised EMG myopathic ± irritable* Ih cytoplasmic vacuoles
DISORDERS OF LIPID METABOLISM	CPT II deficiency VLCAD deficiency	Carnitine deficiency
Presentation	premature exertional fatigue, muscle pain, rhabdomyolysis during/following sustained exercise	symmetrical muscle weakness, cardiomyopathy, encephalopathy
Investigations	CK normal EMG normal Ih normal	CK raised EMG myopathic Ih lipid storage vacuoles

†Investigations should be deferred at least one month after an episode of rhabdomyolysis (see text)

*irritable = fibrillations and positive sharp waves

Abbreviations: CK = serum creatine kinase; Ih = histochemical findings on muscle biopsy

TABLE 2: Differential diagnosis of premature exertional fatigue

Unaccustomed exertion	No pain during exercise Muscle pain occurs 24-48 hrs after exertion
Dystrophinopathies	Fixed weakness Fatigue after exercise is common
Cardiorespiratory problems	Exercise-induced asthma Heart disease
Other disorders	Fibromyalgia Chronic fatigue syndrome

gives way to a painful tightening of the muscle. A second-wind phenomenon is characteristic of the condition: if instead of stopping the subject slows down when they experience fatigue, the symptom will usually subside and the muscle may begin to function more normally allowing prolonged exercise of moderate intensity. Symptoms often improve with a high-carbohydrate meal or glucose.

An absent or blunted rise in serum lactate during exertion is the basis of a forearm exercise test that may confirm a clinical suspicion of a disorder in carbohydrate mechanism. Although performed under standardised laboratory conditions, the traditional ischaemic test has a significant risk of inducing muscle necrosis and is likely to be superseded by a non-ischaemic test. The investigation of choice is the histological demonstration of subsarcolemmal vacuoles (Fig. 1) and absent myophosphorylase staining.

Phosphofructokinase deficiency

Phosphofructokinase (PFK) catalyses the rate-limiting step of glucose breakdown, the conversion of fructose-6-phosphate to fructose-1,6-diphosphate. Symptoms of deficiency are indistinguishable from myophosphorylase deficiency. Descriptions of the second-wind phenomenon are less common while nausea and vomiting are more frequent. Also, the location of the metabolic block means that symptoms are exacerbated rather than ameliorated by a high-carbohydrate meal or glucose: the 'out of wind' phenomenon.

The approach to investigations is similar to myophosphorylase deficiency. The presence of a haemolytic trait (raised serum bilirubin and increased reticulocyte count) is the result of muscle isoforms of PFK normally contributing about 50% of the PFK in red blood cells.

DISORDERS OF LIPID METABOLISM

CPT II and VLCAD deficiency

Carnitine palmitoyltransferase II (CPT II) deficiency is one of the more common biochemical abnormalities in muscle and is the commonest cause of recurrent rhabdomyolysis. Affected individuals have no difficulties with short-lived exercise, which is largely dependent on glycogen, and can even participate in certain competitive sports. Difficulties arise with sustained exercise particularly in the fasting state. Attacks of myoglobinuria tend to be more severe in CPT II deficiency than in the

glycogenoses and are more likely to lead to renal dysfunction. Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is paradigmatic of a growing number of described defects of beta-oxidation whose presentation is clinically indistinguishable from CPT II deficiency. At least 25 chain-length-specific enzymes have been identified and symptomatic deficiencies have been described in almost half of these.

Routine laboratory investigations, including muscle histochemistry, are usually normal in CPT II deficiency and VLCAD. Specialised serum biochemical analyses of fatty acid derivatives can help pinpoint the metabolic defect in suspected cases and CPT II activity can be measured in muscle tissue.

Metabolic myopathies causing progressive weakness

Progressive presentations of metabolic muscle disease are difficult to distinguish on clinical grounds from other myopathies such as the limb-girdle muscular dystrophies or polymyositis. In contrast to metabolic myopathies presenting with episodic dysfunction, rhabdomyolysis is rare but cardiac involvement is more frequent. The serum CK is usually raised and the EMG is myopathic but the most characteristic finding is the histological observation of 'storage' vacuoles containing carbohydrate or lipid. In contrast to metabolic myopathies causing episodic weakness, most of the metabolic defects known to cause progressive muscle weakness are in enzymes that are not specific to muscle. The pathogenic significance of this striking biochemical dichotomy is unclear.

Acid maltase deficiency

Adult-onset acid maltase deficiency presents as mild proximal muscle weakness with characteristic respiratory involvement. Respiratory failure is the presenting symptom in up to 30% of affected individuals.

The serum CK tends to be very high and 'irritable' features (spontaneous activity) are often noted on the EMG. The large cytoplasmic vacuoles seen on muscle sections are characteristic (Fig. 1) and enzyme levels can be measured directly in white blood cells, cultured skin fibroblasts or muscle.

Debranching enzyme deficiency

Given its metabolic proximity in glycogenolysis to myophosphorylase, it is somewhat surprising that debranching enzyme deficiency does not usually cause paroxysmal symptoms except in extremely weak individuals. Instead, it presents in the third or fourth decade with muscle wasting that is often distal more than proximal with occasional respiratory involvement, a pattern which can lead to a diagnosis of motor neuron disease although there is usually a concomitant mild sensory axonal polyneuropathy.

The EMG characteristically displays mixed myopathic and

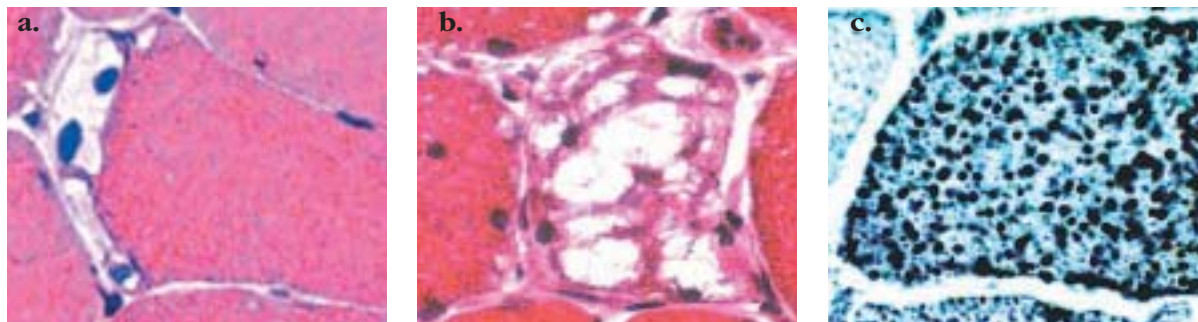


Figure 1: Immunohistochemical characteristics of metabolic muscle disease. a. Myophosphorylase deficiency (McArdle's disease): subsarcolemmal vacuoles (H&E stain); b. Acid maltase deficiency (adult-onset): cytoplasmic and intramyofibrillar vacuoles (H&E stain); c. Carnitine deficiency: lipid storage vacuoles (Sudan black stain).

neuropathic features and nerve conduction studies are often slow. Histochemistry reveals both subsarcolemmal and intermyofibrillar glycogen storage vacuoles.

Carnitine Deficiency

The importance of carnitine in metabolism is in the regulation of levels of acyl-CoA which can cause damage when present in excess. Typically the deficiency of carnitine is secondary to a defect in another enzyme system that results in the overproduction of acyl-CoA or in a deficiency of acyl-CoA clearance. These disorders can present with a progressive myopathy but this is usually associated with cardiomyopathy and encephalopathy, most strikingly coma after a period of starvation. Exacerbations and fluctuations occur but fatigue, exercise-related symptoms and myoglobinuria are usually absent. The diagnosis is supported by the presence of multiple lipid droplets on muscle histology (Fig.1)

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References & further reading

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Overview of energy metabolism in muscle

Muscle contraction and relaxation depend primarily on energy derived from hydrolysis of adenosine triphosphate (ATP). The main substrates used by muscle to generate ATP are glycogen, glucose, and free fatty acids (FFAs). The particular energy sources used depend on whether the muscle is at rest or contracting; the intensity, type and duration of exercise; and on diet and physical conditioning. Glycogen and glucose are metabolised in the cytoplasm to pyruvate which can diffuse into the mitochondrion. Short- and medium-chain fatty acids (less than 10 carbon atoms) freely cross the outer and inner mitochondrial membranes. Longer-chain fatty acids have to be transported into the mitochondrial matrix complexed to carnitine to which they are linked and then unlinked by carnitine palmitoyltransferases (CPTs) I and II respectively.

When the oxygen supply is adequate to meet metabolic needs the main energy substrates of muscle are circulating FFAs (at rest and during sustained low intensity exercise) and blood glucose (low intensity exercise). During high intensity submaximal (ie still aerobic) exercise intracellular stores of glycogen are mobilised. Under these conditions acetyl-coenzyme A (acetyl-CoA) in the mitochondrial matrix, the product of oxidative decarboxylation of pyruvate and beta-oxidation of FFAs, enters the Krebs cycle where carbon dioxide and reducing equivalents are generated. The reducing equivalents drive most of the ATP production through the electron transport chain.

During intense isometric exercise the metabolic demand of muscle outstrips the capacity of oxidative metabolism to synthesize ATP. Most of the additional ATP is provided by anaerobic glycolysis during which pyruvate is metabolised to lactate instead of acetyl-CoA. Additional ATP can also be generated by the phosphocreatine pathway and the purine nucleotide cycle. In the former, creatine kinase (CK) catalyses the reaction of phosphocreatine with adenosine diphosphate (ADP) to produce ATP. In the latter, muscle adenylate kinase catalyses the conversion of two molecules of ADP to one each of ATP and adenosine monophosphate (AMP) which is later deaminated by myoadenylate deaminase with concurrent production of ammonia.

Psycho Social Impact of Epilepsy

**Professional Development Seminar
for specialist medical, educational
and care professionals with an
interest in the field of epilepsy.**

The National Centre For Young People With Epilepsy – NCYPE - is the major provider of specialised services including education, medical treatment and residential care to young people aged 5–19 who have epilepsy and a wide range of learning disabilities.

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This one-day seminar will help provide a greater understanding of the wider implications of the diagnosis of epilepsy. The day will focus on particular areas of difficulty, such as education, employment, social and recreational activities, social integration, behavioural and emotional difficulties, independent living and childhood development

Cost: £75 including lunch and refreshments
Venue: NCYPE, Resource Centre, St Piers Lane,
Lingfield Surrey, RH7 6PW
Time: 9.30 – 3.30
Date: Thursday 17th October 2002

For a booking form please contact Natalie Hopkins on 01342 831 237 or email nhopkins@ncype.org.uk. Alternatively, you can book online through our website at www.ncype.org.uk/resource_centre.htm



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