NEUROLOGICAL RARITIES

McArdle's disease

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INTRODUCTION

McArdle's disease (McArdle 1951) (myophosphorylase deficiency, glycogen storage disease type V, OMIM 232600) is undoubtedly rare. No accurate incidence figures are available. Even large specialist muscle clinics are unlikely to see more than one new case a year. In the United Kingdom (population ~55 million), 55 patients are known to the Association for Glycogen Storage Disease (http://www.agsd.org.uk/). Despite its rarity, it is worth having some knowledge about it for two main reasons. Firstly, it is a diagnosis often considered in patients presenting with exercise induced myalgia or myoglobinuria, and it is important to know how to exclude it. Secondly, an understanding of the biochemical basis of the disease provides insight into other metabolic myopathies.

It is an autosomal recessive disorder, but in reported cases there is a higher frequency of males. The myophosphorylase gene is on chromosome 11. Many mutations have been reported, and compound heterozygotes are common (Tsujino *et al.* 1993). The most frequently encountered mutation is a C-to-G in codon 49 of exon 1, changing an arginine to a stop codon (R49X).

PATHOPHYSIOLOGY

In skeletal muscle, as in other tissues, ATP (adenosine triphosphate) is the major immediate source of energy. During vigorous contraction, the demand for ATP generation increases enormously, and that demand is met by two very distinct metabolic processes (Fig. 1). At rest, glucose entering muscle from the blood is mostly converted to the polymer glycogen, and very little is used to generate ATP. The primary source of ATP is fatty acid oxidation, which is an aerobic process. Some fatty acids are stored within muscle as triglyceride.

During early exercise, particularly vigorous exercise, the demand for more ATP cannot be met by fatty acid oxidation because of inadequate delivery of substrate to the muscle – in other words, there is inadequate perfusion and delivery of fatty acids and oxygen. The ATP is then derived from the anaerobic breakdown of glycogen (glycogenolysis) stored within muscle fibres. As exercise continues, perfusion of muscle increases, fatty acids are mobilized from the body's lipid stores, the respiratory rate increases, and muscle gradually switches back to the oxidative metabolism of circulating free fatty acids.

In summary, at rest and during sustained exercise, muscle is dependent on oxidative metabolism of circulating free fatty acids, but in early (particularly during intense) exercise anaerobic breakdown of stored glycogen is pre-eminent. Thus, metabolic defects of glycogen metabolism are likely to present with symptoms early in exercise, whereas disorders of lipid metabolism are likely to present during sustained exercise. The latter is exemplified by myoglobinuria developing during

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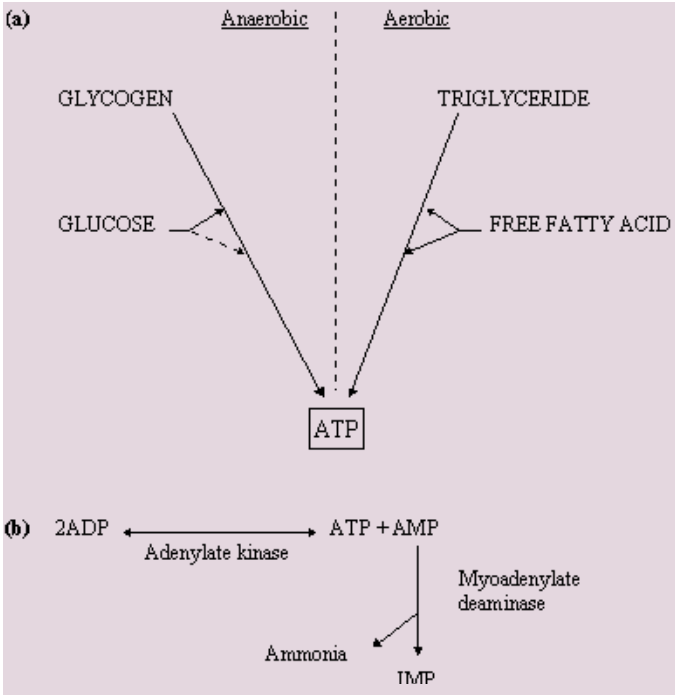


Figure 1 (a) A greatly simplified overview of aspects of muscle metabolism. (b) The purine degradation pathway.

a route march in patients with carnitine palmitoyltransferase deficiency.

Glycogen is a multibranched polymer of glucose. The muscle-specific isoenzyme myophosphorylase cleaves the distal glucose residues, and so in McArdle's disease glycogen is synthesized and accumulates, but cannot be utilized. ATP production during early exercise is compromised, resulting in the characteristic symptoms described below, although there remains some uncertainty as to the exact pathophysiological mechanism. Accumulation of glycogen and myofibrillar disruption may explain the permanent weakness that develops in some patients.

The 'second-wind' phenomenon is common in patients with McArdle's disease. If, after developing symptoms, they reduce their level of activity their symptoms decrease and exercise tolerance increases. The biochemical explanation of this is two-fold. As muscle perfusion increases in response to exercise the muscle can use circulating blood glucose. More importantly, the switch to fatty acid oxidation, described above, starts to take place.

Two final biochemical points are worth mentioning because of their diagnostic value. The end-product of glycogenolysis is pyruvate. In the absence of an adequate oxygen supply, in early exercise, it is converted to lactate rather than entering the tricarboxylic acid cycle. The adenylate kinase and myoadenylate deaminase reactions result in the production of ammonia. When ATP generation is impaired, as in McArdle's disease, other pathways of ATP production are enhanced. These observations form the basis of the forearm exercise test – in glycogenolytic disorders lactate generation is impaired and ammonia production enhanced (Hilton-Jones *et al*. 1995).

CLINICAL FEATURES

The cardinal feature is exercise intolerance. McArdle's Disease does NOT cause rest pain or the type of widespread nonspecific myalgia seen in the chronic fatigue syndrome or fibromyalgia. In early childhood the child may not complain of pain, but is noted to have difficulty keeping up with physical activity. Characteristic symptoms usually become established by the end of the second decade. Exercise induces pain, stiffness and weakness in the exercising muscle. The speed of onset is proportional to the intensity of exercise and may be within 30–60 s. If the patient continues to exercise at the same level, the pain worsens and muscle contracture may develop – the muscle feels hard and is resistant to passive stretching. Pain and swelling may persist for several hours. Contracture is associated with muscle fibre breakdown and if this is extensive (rhabdomyolysis) myoglobinuria may precipitate renal failure. Myoglobinuria is uncommon in childhood, but overall is eventually seen in about one-half of patients, of whom about one-half develop renal failure (DiMauro *et al*. 1994).

Although typical symptoms are established by late-adolescence in most patients, their significance is often not appreciated and diagnosis is frequently delayed. The last three patients seen in my department were all over 50 years of age at the time of first referral.

About one-third of patients develop permanent proximal weakness. This may appear to be the presenting feature but usually there is a history of exercise intolerance. Rare atypical presentations include a fatal infantile form, congenital weakness progressing throughout adult life but without exercise intolerance, and first onset of exercise intolerance over the age of 50 years.

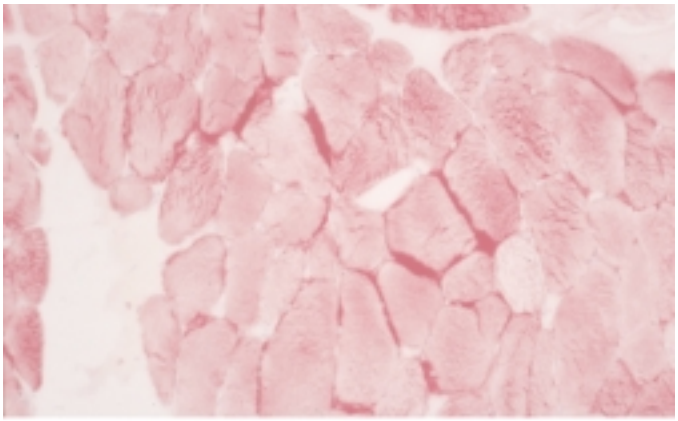
DIAGNOSIS

A specific diagnosis can be achieved in one of three ways: (a) histochemical demonstration of absence of muscle fibre phosphorylase staining; (b) enzyme assay on a muscle biopsy specimen; or (c) DNA analysis. The last is not yet widely

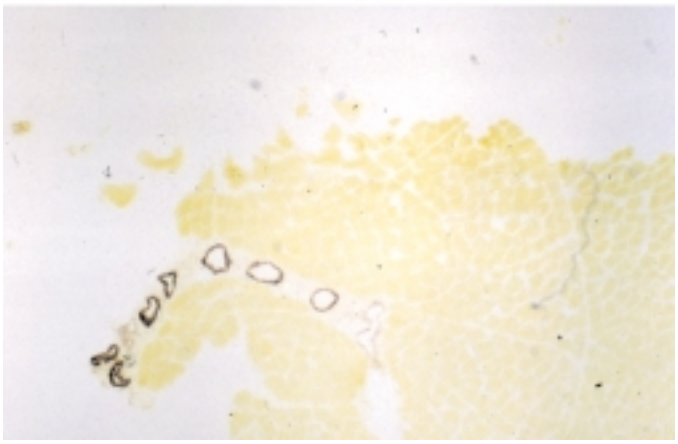
available. In most patients the diagnosis is strongly suggested by histochemistry, but is confirmed by enzyme assay.

Non-specific tests may point towards the diagnosis. In the vast majority of patients (93% in one series) the serum creatine kinase is elevated at rest (DiMauro *et al*. 1994). Electromyography is much less sensitive and is normal in about one-half.

In the forearm exercise test, the forearm flexor muscles are vigorously exercised by getting the patient to squeeze repeatedly a sphygmomanometer bulb, and sequential blood samples are taken from an antecubital vein. Traditionally the test was performed anaerobically by occluding the blood supply with a cuff on the upper arm. This is unnecessary, because circulating substrates contribute little during early vigorous exercise, and it increases the hazard of inducing contracture. A failure of lactate generation and enhanced ammonia production (see above) indicate a defect of glycogenolysis.



(a)



(b)

Figure 2 (a) Muscle biopsy – periodic acid Schiff (PAS) stain showing marked glycogen excess. (b) Muscle biopsy – phosphorylase staining. Note absence of staining of all muscle fibres, but positive staining of blood vessel smooth muscle.

Phosphorus magnetic resonance spectroscopy is a more elegant and informative test, but is not widely available (Hilton-Jones *et al*. 1995). Impaired lactate production is evidenced by absence of the normal fall in intramuscular pH during exercise.

Muscle biopsy is needed in most patients. The periodic acid Schiff (PAS) stain shows accumulation of glycogen (Fig. 2a). Phosphorylase staining is absent (Fig. 2b) – it is important to run a control sample at the same time to show that the procedure is working correctly. However, muscle provides its own internal control, in that blood vessel smooth muscle contains a different phosphorylase isoenzyme, which can be seen to stain normally (Fig. 2b).

MANAGEMENT

There is no specific treatment. Patients typically identify the second-wind phenomenon for themselves. Its nature should be explained to them so that they can capitalise on it. They should be advised to take regular exercise, within limits that do not precipitate substantial pain or contracture. Dietary supplements, attempting to ameliorate the effects of the metabolic block, are generally unsuccessful. Although branched-chain amino acid supplements coupled with an exercise programme have been claimed to be helpful (Slonim & Goans 1985), our own experience is that the exercise regime is better.

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