

# McArdle disease: what do neurologists need to know?

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## SUMMARY

McArdle disease (also known as glycogen storage disease type V) is a pure myopathy caused by an inherited deficit of myophosphorylase, the skeletal muscle isoform of the enzyme glycogen phosphorylase. The disease exhibits clinical heterogeneity, but patients typically experience exercise intolerance, that is, reversible, acute crises (early fatigue and contractures, sometimes with rhabdomyolysis and myoglobinuria) triggered by static muscle contractions (e.g. lifting weights) or dynamic exercise (e.g. climbing stairs or running). In this Review, we discuss the main features of McArdle disease, with the aim of providing neurologists with up-to-date, useful information to assist their patients. The topics covered include diagnostic tools—for example, molecular genetic diagnosis, the classic ischemic forearm test and the so-called ‘second wind’ phenomenon—and current therapeutic options—for example, a carbohydrate-rich diet and carbohydrate ingestion shortly before strenuous exercise, in combination with medically supervised aerobic training of low to moderate intensity.

**KEYWORDS** exercise intolerance, glycogen storage disease, glycogenosis, myopathy, myophosphorylase

## REVIEW CRITERIA

Pubmed was searched using Entrez for articles published up to mid-June 2008. Search terms included “McArdle(s)”, “glycogenosis” and “myophosphorylase”. Owing to limitations on the number of references, we cited only those articles that we judged most important and applicable for clinical practice.

## CME

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### Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the organs affected by McArdle's disease.
- 2 Describe the primary inheritance pattern of McArdle's disease.
- 3 Describe the clinical features associated with McArdle's disease.
- 4 List the manifestations of acute crises associated with McArdle's disease.
- 5 List the current treatment modalities for McArdle's disease.

### Competing interests

The authors, the Journal Editor H Wood and the CME questions author D Lie declared no competing interests.

## INTRODUCTION

Glycogenosis type V, also known as glycogen storage disease type V (GSD-V) or myophosphorylase deficiency (Online Mendelian Inheritance in Man® [OMIM®; Johns Hopkins University, Baltimore, MD, USA] number 232600), is the most common disorder of skeletal muscle carbohydrate metabolism and one of most frequent genetic myopathies (estimated prevalence ~1:100,000 in the Dallas Fort Worth area, TX, USA).<sup>1</sup> This disorder is usually known as ‘McArdle disease’, in homage to the British physician Brian McArdle who first described it in 1951.<sup>2</sup>

Patients with McArdle disease have mutations in both alleles of the *PYGM* gene, which encodes myophosphorylase, the skeletal muscle isoform of glycogen phosphorylase. These mutations result in a lack of functional mature protein.<sup>3</sup> As the liver and heart isoforms of glycogen phosphorylase are unaffected, McArdle disease presents as a pure

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myopathy.<sup>4</sup> McArdle disease is approximately equally represented in both sexes and is inherited in an autosomal recessive manner.<sup>3</sup> Heterozygous individuals (~1:158)<sup>5</sup> are usually asymptomatic, but typical symptoms of McArdle disease have been described in some of these individuals because of an unusually low level of myophosphorylase activity (20–40% of the normal level).<sup>3</sup> An apparent dominant (or pseudo-dominant) transmission of the disease has been reported in some families when a 'symptomatic' heterozygous individual has children with a homozygous individual.<sup>5,6</sup>

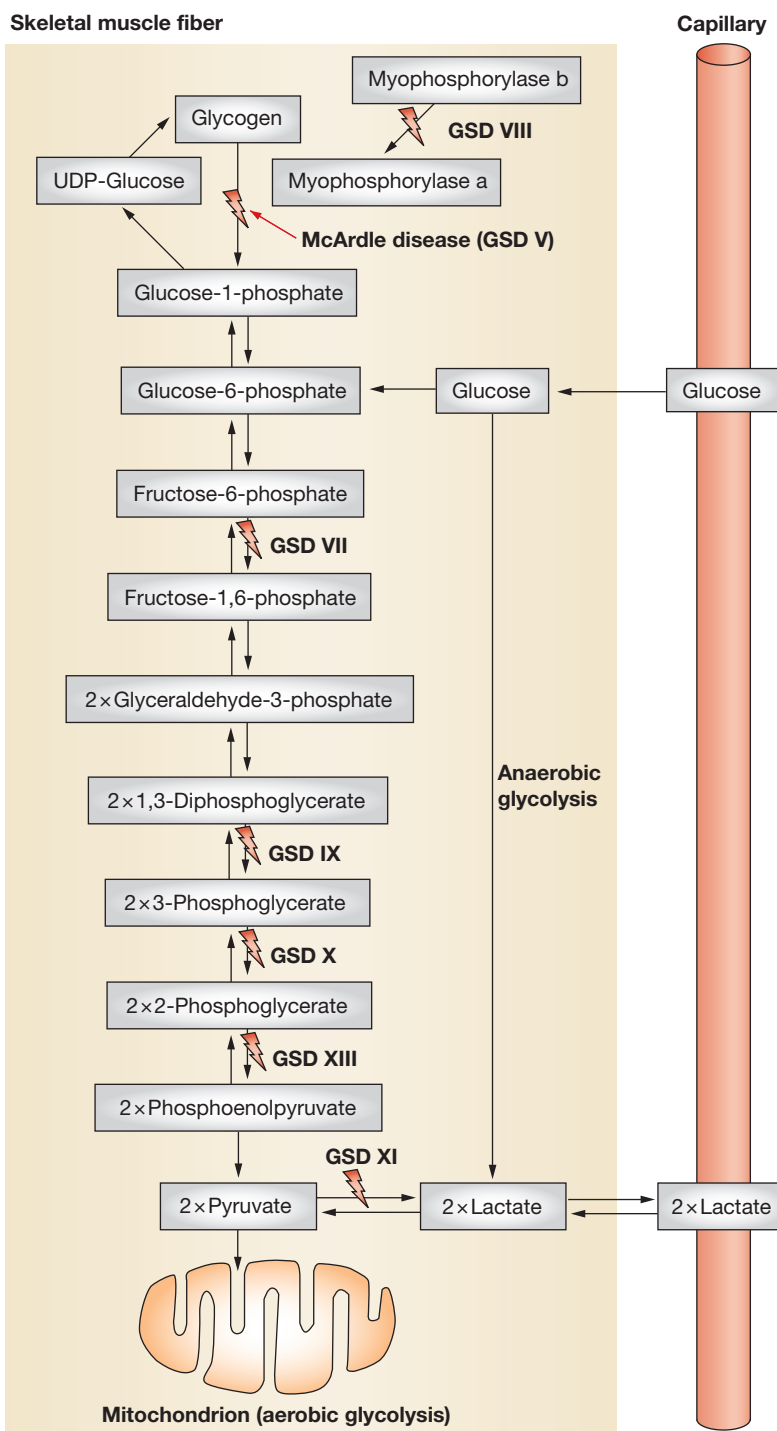
The aim of this Review is to summarize the current body of knowledge regarding the pathophysiology of McArdle disease, as well as the available diagnostic tools and possible therapeutic options. This is intended to provide a practical guide to help neurologists recognize and manage this condition in their patients.

## PATHOPHYSIOLOGY

### Muscle glycogenolysis, but not muscle glucose utilization, is blocked

Myophosphorylase initiates the breakdown of muscle glycogen by removing (1,4)- $\alpha$ -glucosyl units from the outer branches of glycogen, leading to liberation of glucose-1-phosphate (Figure 1). In healthy individuals, glucose-1-phosphate is converted into glucose-6-phosphate, which subsequently undergoes glycolysis, resulting in pyruvate production. Muscle pyruvate can be converted to lactate (e.g. in hypoxic conditions), which is then released to the blood at a rate proportional to its production, but most of the pyruvate crosses the mitochondrial membrane where it is converted into acetyl-CoA, which then enters the citric acid, or Krebs, cycle. As a consequence of deficient myophosphorylase activity, patients with McArdle disease are unable to obtain energy from their muscle glycogen stores.<sup>7</sup>

In view of the fact that glycolysis is blocked upstream, the skeletal muscle fibers of patients with McArdle disease can still take up glucose from the blood and convert it into glucose-6-phosphate, which then enters the downstream steps of glycolysis. Muscle glycolysis is not, therefore, totally impaired in these patients, and pre-exercise ingestion of carbohydrates can markedly improve their exercise tolerance.<sup>8</sup> Some patients exhibit diurnal variations in their degree of exercise intolerance, depending on the timing of their last meal and its carbohydrate content. Fasting periods lasting several hours



**Figure 1** Schematic representation of skeletal muscle glycogen metabolism. The figure indicates the steps in the pathway that are affected in various glycogen storage diseases that cause defects in skeletal muscle function, leading to exercise intolerance. Abbreviation: GSD, glycogen storage disease; UDP, uridine diphosphate.

lead to hypoglycemia and a probable decrement in muscle function in these patients, owing to the low availability of glucose to working muscles.

### Functional consequences of blocked muscle glycogenolysis

Patients with McArdle disease typically exhibit intolerance to static or isometric muscle contractions and also to dynamic exercises. During static or isometric exercise (e.g. lifting a heavy weight, handgrip exercises), high mechanical demands are imposed on a relatively small muscle mass, and the sustained muscular contraction dramatically increases the pressure inside the muscle, causing the supply of oxygenated blood to be transiently cut off.<sup>2</sup> In this situation, muscles rely on an anaerobic energy supply from intracellular glycogen stores.

Dynamic, 'aerobic' exercises involving large muscle mass and smaller mechanical loads (e.g. stair-climbing, running or very brisk walking) can also trigger acute exercise intolerance in patients with McArdle disease. Muscle oxidative capacity in these patients is impaired because their ability to produce pyruvate—a molecule that has an anaplerotic role in the Krebs cycle—is severely reduced. The reduced rate of oxidative phosphorylation in these patients is reflected on phosphorus magnetic resonance spectroscopy (<sup>31</sup>P-MRS) by significantly greater phosphocreatine consumption and lower ATP concentrations than in healthy controls after submaximal isometric calf contractions.<sup>9</sup> The resultant marked decrease in skeletal muscle phosphorylation potential ( $[ATP]/[ADP][\text{phosphate}]$ ) leads to the accumulation of phosphate, and probably also ADP, in patients' muscles, thereby inhibiting myofibrillar ATPase, calcium pump and sodium–potassium pump reactions and leading to premature muscle fatigue and contractures.<sup>10</sup>

Although the pathophysiology of the contractures typically experienced by patients with McArdle disease is not yet fully understood, impaired glycolysis could have an important role. A deficiency in the glycogen-dependent ATP supply to sodium–potassium pumps in skeletal muscle fibers might result in downregulation of these pumps in the cells, leading to exercise-induced hyperkalemia and accelerated loss of membrane excitability.<sup>11</sup>

Finally, the accumulation of potassium, phosphate and ADP in working muscles, due to the reduced muscle phosphorylation potential leads to an excessive release of these substances into the blood, thereby stimulating vascular smooth muscle and metabolically sensitive nerve afferents in skeletal muscle. This might explain, at least partly, the hyperkinetic cardiovascular response exhibited by patients with McArdle disease during

dynamic exercise (i.e. increased cardiac output: oxygen uptake ratio).<sup>10</sup>

### Disorders characterized by exercise intolerance

Irrespective of the specific defect (i.e. whether affecting lipid or carbohydrate metabolism, or the respiratory chain), all genetic disorders that alter energy supply to skeletal muscles essentially result in either muscle weakness (predominantly induced by exercise) or exercise intolerance. In the latter type of disorders, acute exercise can trigger episodes of reversible 'muscle crises'. Acute crises manifest mainly in the form of excessive, premature fatigue and contractures, frequently accompanied by marked muscle breakdown (rhabdomyolysis) and sometimes by myoglobinuria.<sup>4</sup>

Genetic disorders that affect lipid metabolism in skeletal muscles or result in respiratory chain defects are often associated with exercise intolerance, but the syndrome of exertional fatigue, contractures, and rhabdomyolysis and myoglobinuria are most commonly caused by McArdle disease. Nevertheless, it is important for neurologists to rule out several other muscle glycolytic defects when presented with a patient exhibiting these characteristics (Figure 1). Potential differential diagnoses include defects in phosphofructokinase (PFK; GSD VII or Tarui disease), phosphorylase b kinase (GSD VIII), phosphoglycerate kinase (GSD IX), phosphoglyceromutase (GSD X), lactate dehydrogenase (GSD XI) and  $\beta$ -enolase (GSD XIII).<sup>4</sup> Therefore, it is vital to provide neurologists with the necessary information to differentiate the clinical presentation of McArdle disease from that of other disorders associated with exercise intolerance. Fortunately, several aspects of the exercise response in McArdle patients are unique to this condition, as we will discuss below.

### EPIDEMIOLOGY

There is individual variability in the clinical manifestation of McArdle disease, even between affected relatives. The time of onset of the typical disease symptoms (early or late childhood, and sometimes adulthood) and the degree of exercise intolerance both vary between patients. In rare cases, patients are oligosymptomatic and are correctly diagnosed only because they have an affected relative; in other patients, the disease can be profoundly incapacitating.<sup>12</sup> The first reported patient with the disease (in 1951) was a 30-year-old male,<sup>2</sup> and he was a good example of extreme phenotype manifestation.

He reported severe exercise intolerance in almost all types of physical activities and myalgia in any muscle involved in a given task (including, sometimes, masticatory muscles when chewing gum), together with muscle weakness and stiffness.

One reason for clinical heterogeneity might lie in different dietary regimens (e.g. low vs high carbohydrate content, especially before exercise) and lifestyles, with more-physically active individuals exhibiting better functional capacity than those with a more sedentary lifestyle.<sup>4</sup> Another factor that might contribute to phenotypic heterogeneity is the patient's sex, with women generally being more severely affected than men, at least in our experience.<sup>13,14</sup> In some women, peak cardiorespiratory capacity is barely high enough to sustain the metabolic cost of physical activities of daily living.<sup>14</sup> This might explain why we recently observed a higher degree of physical limitation in women than in men during common daily activities, such as housework.<sup>13</sup> Among the middle-aged patients whom we studied, proximal muscle wasting and weakness was more frequent in women than in men; in some cases, the severity was such that the patients had to use an electric toothbrush as they easily became fatigued when brushing their teeth manually. In addition, the few adult patients in whom respiratory muscles have been shown to be affected have all been women.<sup>15,16</sup>

Genetic variants of several candidate genes that modulate human responses to exercise can also have a role in determining the severity of the McArdle disease phenotype. One such example is the insertion–deletion polymorphism of the angiotensin-converting enzyme (*ACE*) gene. The insertion allele, which is associated with reduced enzyme activity, improves cardiovascular function and higher uptake of blood glucose into skeletal muscle fibers<sup>17</sup> and favors a less-severe clinical presentation of the disease;<sup>12,13</sup> in women, this genotype also results in improved exercise capacity.<sup>18</sup> By contrast, the coexistence in the same individual of McArdle disease and homozygous<sup>12,19</sup> or even heterozygous mutations in the gene encoding muscle adenylate deaminase (*AMPD1*), an important regulator of muscle metabolism during intense exercise, might account for a more-severe phenotypic manifestation of the disease.<sup>20</sup>

### NATURAL HISTORY AND PRECAUTIONS

In the past, McArdle disease has rarely been diagnosed before adulthood, possibly because the relevant medical information and diagnostic tools (in

particular, molecular genetics) were not widely available until relatively recently. In our series (currently ~110 patients), however, most individuals remember having had painful symptoms associated with severe exercise since early childhood, during physical education classes for example.<sup>21</sup> It is possible that McArdle disease could have been the cause of (or at least contributed to) severe respiratory insufficiency and death in a 13-year-old girl described in a case report in 1978.<sup>22</sup>

Besides the typical symptom of exercise intolerance, around a third of patients with McArdle disease also develop fixed weakness and wasting (affecting more proximal than distal muscles) with aging.<sup>3,7</sup> In addition to aggravated exercise intolerance over the years, proximal muscle weakness and wasting could be the fate of some patients at an advanced age because of the long-term effects of the disease itself, which is frequently associated with 'chronic' muscle damage even under resting conditions, and a lifetime of sedentary habits. We recently studied an elderly patient (now 81 years old and sedentary since childhood) with marked exercise intolerance and proximal muscle atrophy and fixed weakness.<sup>23</sup>

McArdle disease is not usually a life-threatening condition, although there are some exceptions. Continuing to exercise in the presence of severe pain (which, as well as being an unpleasant symptom, is also a physiological, self-protective mechanism) might increase the risk of myoglobinuria and subsequent acute renal failure. Myoglobinuria occurs in about 50% of patients after intense exercise, and about 50% of these patients also develop acute renal failure, which is almost always reversible but, nevertheless, requires emergency treatment.<sup>24</sup> Patients should, therefore, be advised to refrain from any exercise that induces severe pain, especially if it involves static muscle contractions; however, as further explained below, medically prescribed dynamic exercise of low to moderate intensity is a safe, recommended therapeutic option for these patients. Another potential problem in these patients is myogenic hyperuricemia. Owing to impaired ATP production, muscular exertion can induce overproduction of AMP, with accelerated liberation of the metabolites ammonia, inosine, hypoxanthine and xanthine to the blood.<sup>25,26</sup> These purine metabolites subsequently serve as substrates for the synthesis of uric acid, leading to hyperuricemia.<sup>26</sup>

Although McArdle disease does not seem to cause severe perioperative problems in routine anesthetic care, measures for preventing muscle

**Table 1** Main tools for correct diagnosis of McArdle disease and differential diagnosis with other myopathies.

Diagnostic feature	Prevalence in McArdle disease	Differential diagnosis
<b>Clinical diagnosis</b>		
Exercise intolerance (crises of early fatigue, myalgia, contractures and sometimes myoglobinuria induced by exertion)	Reported by ~100% of patients	GSD associated with fixed muscle weakness (GSD II, III, IV and XII) Some disorders of lipid metabolism (deficiency of carnitin transporter, MCAD, SCAD, GA II, and TG storage disease)
Fixed proximal weakness	Reported by ~33% of patients	Limb-girdle muscular dystrophies and acquired myopathies
Second wind (pathognomonic)	Reported by ~80% of patients <sup>47</sup> Objectively assessable in 100% of patients <sup>33</sup>	All other disorders of muscle metabolism
<b>Laboratory diagnosis</b>		
Increased levels of serum CK at rest	>200 U/l: 100% of patients <sup>14</sup> >1,000 U/l: ~50% of patients <sup>14</sup>	Most disorders of muscle metabolism, notably CPT-II deficiency <sup>a</sup>
Negative histochemical reaction for myophosphorylase and no myophosphorylase activity	100% of patients <sup>13</sup>	All other disorders of muscle metabolism
Pathogenic mutation(s) in both <i>PYGM</i> alleles	100% of patients <sup>b</sup>	All other disorders of muscle metabolism
<sup>a</sup> Patients (especially children) with CPT-II deficiency can show exercise intolerance similar to that seen in McArdle disease, but their CK levels are rarely elevated. <sup>36</sup> <sup>b</sup> It is not always easy to identify these mutations. Abbreviations: CK, creatine kinase; CPT II, carnitine palmitoyltransferase II; GA II, glutaric acidemia type II; GSD, glycogen storage disease; MCAD, medium-chain acyl coenzyme A dehydrogenase deficiency; SCAD, short-chain acyl-coenzyme A dehydrogenase deficiency; TG, triglyceride.		

ischemia and rhabdomyolysis should be kept in mind, as should the potential of patients with this condition to develop postoperative fatigue, myoglobinuria and renal failure.<sup>27</sup> In pregnant patients, we propose that vaginal delivery is probably a better option than cesarean section, so as to prevent any potential problem associated with anesthesia, although more data are required to confirm the validity of this approach. To ensure appropriate and safe management of the patient after delivery, and to avoid partum-induced rhabdomyolysis and myoglobinuria, obstetricians should be well briefed by neurologists on the characteristics of McArdle disease and its potential risks.

The use of statins could exacerbate rhabdomyolysis in patients with McArdle disease; therefore, it is important to exercise caution when prescribing such drugs to these individuals.<sup>28</sup>

## DIAGNOSIS

### Initial suspicion: features indicative of McArdle disease

In view of the fact that McArdle disease is mainly associated with exercise intolerance, in the form of acute episodes of reversible 'muscle

crisis', neurologists must be attentive to their patients' self-reports of exercise intolerance, as well as to the occurrence of dark urine following heavy exertion. Patients typically describe myoglobinuria as urine looking like cola, marsala, or red wine.

The main diagnostic tools for McArdle disease are summarized in Table 1. In particular, four features that are present in the great majority of patients should set the initial basis for a correct diagnosis. The first feature is exercise intolerance, usually since childhood, with or without actual fixed muscle weakness at the moment of evaluation. The patient might also report improved exercise tolerance after ingesting carbohydrates (e.g. pasta, rice, sports drinks). Another classic feature is a high serum level of total creatine kinase (CK) activity, even at rest, that is, in the absence of heavy exercise in the previous hours or days. In one of our series,<sup>14</sup> a mean CK activity of about 3,200 U/l was recorded in 24 men, and a mean of about 1,600 U/l was recorded in 22 women at rest. A third characteristic of the disease is one or more previous episodes of hyper-CK-emia (several thousand U/l, indicating marked

rhabdomyolysis) after intense exercise. The fourth feature, as we will discuss below, is the 'second wind' phenomenon.

### The 'second wind': a unique feature of McArdle disease

The so-called 'second wind' phenomenon is a pathognomonic feature of McArdle disease that many (but not all) patients are able to adequately report during medical interview and that can be easily reproduced in a laboratory in all cases. As first described by Pearson *et al.*,<sup>29</sup> the second wind denotes a sudden, marked improvement in the tolerance to aerobic, dynamic, large muscle mass exercise (walking or cycling) after about 10 min, that is, disappearance of the excessive fatigue, breathlessness and tachycardia that were triggered by the start of exertion. Most patients describe this phenomenon as the ability to resume exercising (e.g. walking, or brisk walking in the more-fit patients) if they take a brief rest at the appearance of premature fatigue early during exercise.<sup>4</sup>

The second wind phenomenon can be attributed to the fact that the first few minutes of exercise act as a warm-up (e.g. inducing muscle vasodilation), after which more circulating glucose is available to working muscle fibers; therefore, the upstream blockade in glycogenolysis is partially bypassed, leading to considerable attenuation of early fatigue.<sup>30</sup> In fact, Haller and Vissing elegantly showed that the second wind phenomenon is abolished by glucose infusion<sup>30</sup> or sucrose ingestion before exercise.<sup>8</sup> Indeed, with pre-exercise carbohydrate ingestion, high amounts of circulating glucose are readily available to be utilized by working muscles from the start of exercise. This measure prevents the early fatigue symptoms associated with the critically low muscle glycolytic flux during the transition from rest to exercise and the subsequent amelioration (second wind).<sup>8</sup>

The second wind distinguishes McArdle disease from—and, therefore, allows differential diagnosis with—muscle PFK deficiency (GSD VII), a disorder with a similar clinical manifestation.<sup>31</sup> These two disorders can also be distinguished by the opposing effects of carbohydrate administration; pre-exercise glucose partially bypasses the metabolic block of McArdle disease, which occurs upstream of blood glucose uptake, whereas carbohydrate-rich meals exacerbate the exercise intolerance of PFK-deficient patients because their metabolic block occurs further downstream in glycolysis (Figure 1), and

increased glycemia decreases the blood levels of alternative muscle fuels, such as free fatty acids.<sup>32</sup> The fact that GSD VII results in a partial defect in PFK activity in erythrocytes, leading to hemolytic anemia and hyperbilirubinemia, can also assist in the differential clinical diagnosis.<sup>4</sup>

The second wind is believed to occur in all patients with McArdle disease and can be reproduced by a 15-minute cycle-ergometer test at low, constant workloads (~40 W).<sup>33</sup> This is considered to be a simple, sensitive and specific diagnostic test, with a heart-rate monitor and a cycle-ergometer being the only equipment required. The second wind, as manifested by a marked decrease in early exertional tachycardia (e.g. a decrease from ~140–150 beats/min to ~120 beats/min) starting after around 7 min of exercise, does not occur in patients with other disorders that are also associated with exercise intolerance, such as GSD VII, GSD VIII,<sup>34</sup> GSD X,<sup>35</sup> mitochondrial myopathies or disorders of lipid metabolism (deficit of carnitine palmitoyltransferase II or very long-chain acyl-CoA dehydrogenase).<sup>36</sup>

### The 'classic' forearm ischemic test

Brian McArdle developed an ingenious forearm ischemic ('anaerobic') test—no increase in pyruvate and lactate levels in venous blood flowing from contracting, ischemic forearm muscles—to define his eponymous disease.<sup>2</sup> This has long been the first diagnostic test used by clinicians, but it can be painful, and it can produce false negative results in the weakest or less-motivated patients, or false positive results in patients with other defects of glycogenolysis or glycolysis.<sup>7</sup> In 2001, a compartment syndrome attributable to ischemia-induced muscle swelling was reported in a patient who underwent this test.<sup>37</sup> A modified, less unpleasant, aerobic version of the classic forearm test has been described and does not require restriction of circulation,<sup>38</sup> but the problem of producing false positive results persists.

### Confirmation of diagnosis: muscle biopsy and molecular genetics

Biopsy of the vastus lateralis or biceps brachialis muscles is commonly conducted in patients with McArdle disease so that histochemical and biochemical analyses can be conducted. We recommend that, if possible, the Bergström's percutaneous needle technique<sup>39</sup> should be used instead of the more-invasive open muscle biopsy. Besides subsarcolemal or intermyofibrillar glycogen deposits, muscle specimens show a

negative histochemical reaction for myophosphorylase and null activity of this enzyme.<sup>40</sup> Although a small percentage of patients can harbor residual myophosphorylase activity, in our series (~50 biopsy specimens), enzyme activity was consistently null.<sup>13</sup>

In centers where the relevant technology is available, diagnosis based on molecular genetics can be very useful.<sup>40</sup> Unfortunately, however, not all patients can be easily diagnosed with this methodology. For instance, Bruno and co-workers were able to diagnose most (~90%), but not all, mutant *PYGM* alleles in a large cohort ( $n = 68$ ) of Italian patients.<sup>41</sup>

The *PYGM* gene was localized to chromosome 11 in 1984,<sup>42</sup> and the first pathogenic mutations were reported in 1993.<sup>6,43</sup> The molecular diagnosis of McArdle disease can be complicated by the high degree of genetic heterogeneity that exists among patients. At our last count, around 100 different mutations had been described in *PYGM*, and there does not seem to be a 'hot spot' region in the gene—mutations can occur in every exon.<sup>40,44,45</sup> Despite this broad mutational spectrum, however, the genetic diagnosis can be relatively focused by considering the geographical origin of the patient. A nonsense mutation located in exon 1, originally known as p.R49X but since renamed p.R50X, is the most frequently found mutation in the white population (allelic frequency ranging from 31% to 72%),<sup>46,47</sup> and it should be the first mutation to be screened for in patients of this origin.<sup>40</sup> This mutation changes an arginine residue to a stop codon, resulting in a truncated, non-active protein. The second most common mutation is a missense mutation in exon 5, known as p.G205S.<sup>6</sup>

There are other mutations that have a high incidence in specific groups; for example, p.F710del in the Japanese population,<sup>48</sup> p.W798R in the Spanish population<sup>46,49</sup> and p.E541X in Finnish people.<sup>50</sup> Numerous mutations are, however, private (found in a single patient or in one family), so we should keep in mind the possibility of finding new mutations while performing genetic analysis for diagnostic purposes. The number of mutations affecting splicing continues to increase,<sup>51</sup> highlighting the importance of complementary DNA-based molecular studies for the diagnosis of McArdle disease. In patients with manifesting heterozygosity—that is, those with only one identified mutant *PYGM* allele—muscle complementary DNA analysis has been shown to be helpful for identifying the second mutant allele.<sup>52</sup>

## TREATMENT

Despite previous, valuable efforts,<sup>53,54</sup> no effective gene therapy is expected to be available in the foreseeable future to replace myophosphorylase deficiency in humans. Adenovirus type V and adeno-associated virus type II can transiently restore myophosphorylase activity in sheep muscle<sup>54</sup>—a promising result given that the corporal mass of the sheep is similar to that of humans—but permanent restoration of enzyme activity is the ultimate goal in patients. More than 90% of patients with McArdle disease have mutations that produce a premature termination codon (PTC). This leads to nonsense-mediated messenger RNA decay, a cellular protective mechanism that eliminates the majority of messenger RNA transcripts containing nonsense and frameshift mutations.<sup>55</sup> An investigational new drug, PTC124, has been shown to translate genes with a PTC into full-length protein in cystic fibrosis and Duchenne muscle dystrophy.<sup>56</sup> In patients with McArdle disease, however, short-term treatment (10 days) with gentamicin, a drug that also has the potential to read through PTCs, failed to normalize <sup>31</sup>P-MRS indicators of myophosphorylase deficiency in muscle.<sup>57</sup>

Several randomized, placebo-controlled trials (each with more than five patients) have been conducted in patients with McArdle disease; both pharmacological interventions (ACE inhibitors<sup>58</sup> or dantrolene sodium,<sup>59</sup> a drug normally used for the prevention of anesthetic-induced rhabdomyolysis) and nutritional interventions (D-ribose<sup>60</sup> or creatine<sup>61,62</sup> supplementation, a carbohydrate-rich diet,<sup>63</sup> pre-exercise oral administration of branched-chain amino acids<sup>64</sup> or sucrose<sup>8,65</sup> or pre-exercise intravenous infusion of glucose<sup>30</sup>) have been investigated. These approaches are reviewed by Quinlivan *et al.*<sup>66</sup> in a recent Cochrane update. Low-dose creatine supplementation (60 mg/kg per day for 4 weeks) can increase tolerance to ischemic exercise in patients with McArdle disease,<sup>61</sup> but higher doses (150 mg/kg per day) might actually exacerbate myalgia.<sup>62</sup> Given the susceptibility of patients to recurrent muscle injury, it is important to ensure a sufficient intake of protein in the diet, as this could theoretically improve the potential for muscle repair. Uncontrolled case studies have suggested an improvement in the exercise capacity of two patients with McArdle disease who were given a high-protein diet,<sup>67,68</sup> but randomized controlled trials investigating the short-term<sup>64</sup> or long-term<sup>69</sup> effects of branched-chain

**Table 2** Exercise therapy in patients with McArdle disease: recommendations and precautions.

	Type of exercise	Example	Frequency	Duration of each session (after gradual build up)	Intensity	Is pre-exercise carbohydrate ingestion necessary? <sup>a</sup>
Recommended exercises	Low to moderate dynamic 'aerobic' (endurance) exercise	Brisk walking, light cycling ( $\leq 50$ W)	$\geq 5$ days per week	$\geq 30$ min	At a level that permits talking in people who are fit	No (although patients might feel more comfortable if ingesting carbohydrates before the initial training sessions)
Exercises recommended only with caution	Vigorous dynamic 'aerobic' (endurance) exercise	Very brisk paced walking ( $>4$ mph), uphill brisk walking, cycling ( $>50$ W), swimming	$\geq 3$ days per week	$\geq 20$ min	Markedly increased heart rate and breathing rate, normal talking not possible	Yes

<sup>a</sup>Ingestion of 30–40 g of simple carbohydrates (sucrose, fructose or glucose) shortly ( $\sim 5$  min) before exercise should not increase the risk of patients with McArdle disease gaining weight or developing insulin resistance, as their working muscles rapidly burn blood-borne glucose. Patients seeking further improvement in their fitness level and health status can (and should) surpass the minimum recommendations for exercise duration (under medical supervision), but not for exercise intensity.

amino acids administered before exercise showed no benefit;<sup>69</sup> in fact, short-term administration resulted in a decrement in performance.<sup>64</sup>

At present (and keeping in mind the need for further research in the field), the most beneficial intervention for patients with McArdle disease, in combination with aerobic conditioning, consists of ensuring that sufficient blood glucose (derived from high hepatic glycogen stores) is constantly made available to patients' working muscles during the daytime. This is achieved by adopting a diet with a high proportion (65%) of complex carbohydrates (such as are found in vegetables, fruits, cereals, bread, pasta and rice) and a low proportion (20%) of fat,<sup>63</sup> and through ingestion of simple carbohydrates (30–40 g of glucose, fructose or sucrose in adults,<sup>14,65</sup> which translates to around 440 ml of most commercially available sport drinks, and 20 g in children<sup>21</sup>) about 5 min before engaging in strenuous exercise, such as brisk walking,<sup>14</sup> or physical education classes in the younger patients.<sup>21</sup>

We have detailed the exercise recommendations for patients with McArdle disease in Table 2 and Box 1. Paradoxically, the main enemy of these patients, acute exercise, can become their ally if carefully prescribed and performed on a regular basis. Aerobic, dynamic exercise involving large muscle mass (e.g. cycling or walking) at low to moderate intensities (i.e. at a level that permits talking after some build up) is a safe and recommended therapeutic option for these patients.<sup>14,70</sup> Notably, this intervention markedly improves (by around 44%) their maximum cardiorespiratory capacity ( $VO_{2peak}$ ), which usually falls well below

**Box 1** Exercises that should be avoided in patients with McArdle disease.

- Static muscle contractions (e.g. handgrip exercises)
- Static muscle contractions or heavy loads on low muscle mass (e.g. weightlifting)
- Dynamic exercises at a high-intensity level (e.g. competitive ball games)
- Exercises with a high involvement of eccentric (lengthening) muscle contractions (e.g. jumps)
- Very dynamic exercises (e.g. running, strenuous swimming, or cycling) except in very fit patients

25 ml  $O_2$ /kg per min (the minimum threshold for optimal health in humans), even after pre-exercise carbohydrate ingestion.<sup>14</sup> This is an important consideration, as  $VO_{2peak}$  reflects peak muscle oxidative capacity and is arguably the best indicator of health and predictor of all-cause mortality in humans. Furthermore, serum CK levels decrease with training, suggesting that the stimulation of muscle growth prompted by exercise training might partially counterbalance muscle damage and wasting in patients with McArdle disease.<sup>14</sup>

In general, vigorous dynamic exercise (i.e. at a level that does not permit normal talking) should be performed only by the more-fit patients (after months of gradual habituation) and should be combined with pre-exercise carbohydrate ingestion. Very intense exercises, particularly those involving high loads on low muscle mass, are strongly discouraged in these patients.

## CONCLUSIONS

McArdle disease, a disorder associated with a block in muscle glycogenolysis caused by an inherited deficiency of myophosphorylase, is arguably the paradigm of the exercise intolerance syndrome in humans. This syndrome is characterized by acute exercise-induced crises, consisting of excessive, premature muscle fatigue and contractures, frequently accompanied by rhabdomyolysis and sometimes myoglobinuria. No effective gene therapy is expected to be available in the short term. Until a definitive cure is found, carefully supervised aerobic, gentle physical activities, combined with 'muscle protection' by pre-exercise ingestion of carbohydrate drinks, can help to improve the functional capacity of patients with McArdle disease. Controlled, randomized therapeutic trials, possibly involving numerous research centers and hospitals in view of the rarity of the disease, will be needed to uncover additional nutritional and/or exercise interventions that might be of benefit to these patients.

## KEY POINTS

- McArdle disease is a pure myopathy caused by an inherited deficit of the skeletal muscle isoform of glycogen phosphorylase
- The main problem in this condition is exercise intolerance, with most patients experiencing acute 'muscle crises' after static or intense dynamic exercise
- Crises appear in the form of early muscle fatigue and contractures, sometimes with marked muscle breakdown (rhabdomyolysis) and myoglobinuria
- Until a definitive cure is found, patients can benefit from adopting a diet rich in complex carbohydrates and ingesting simple carbohydrates before strenuous exercise
- Carefully supervised, regular, aerobic exercise of low to moderate intensity is a safe, recommended therapeutic option, but exercises that involve heavy static contractions or induce severe myalgia should be avoided

## References

- 1 Haller RG (2000) Treatment of McArdle disease. *Arch Neurol* **57**: 923–924
- 2 McArdle B (1951) Myopathy due to a defect in muscle glycogen breakdown. *Clin Sci* **10**: 13–33
- 3 Andreu AL *et al.* (2007) McArdle disease: molecular genetic update. *Acta Myol* **26**: 53–57
- 4 DiMauro S (2007) Muscle glycogenoses: an overview. *Acta Myol* **26**: 35–41
- 5 Isackson PJ *et al.* (2005) A novel mutation in the PYGM gene in a family with pseudo-dominant transmission of McArdle disease. *Mol Genet Metab* **85**: 239–242
- 6 Tsujino S *et al.* (1993) Molecular genetic heterogeneity of myophosphorylase deficiency (McArdle's disease). *N Engl J Med* **329**: 241–245
- 7 DiMauro S *et al.* (2002) Myophosphorylase deficiency (glycogenosis type V; McArdle disease). *Curr Mol Med* **2**: 189–196
- 8 Vissing J and Haller RG (2003) The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. *N Engl J Med* **349**: 2503–2509
- 9 Zange J *et al.* (2003) Breakdown of adenine nucleotide pool in fatiguing skeletal muscle in McArdle's disease: a noninvasive <sup>31</sup>P-MRS and EMG study. *Muscle Nerve* **27**: 728–736
- 10 Lewis SF and Haller RG (1986) The pathophysiology of McArdle's disease: clues to regulation in exercise and fatigue. *J Appl Physiol* **61**: 391–401
- 11 Haller *et al.* (1998) Reduced levels of skeletal muscle Na<sup>+</sup>K<sup>+</sup>-ATPase in McArdle disease. *Neurology* **50**: 37–40
- 12 Martinuzzi A *et al.* (2003) Phenotype modulators in myophosphorylase deficiency. *Ann Neurol* **53**: 497–502
- 13 Rubio JC *et al.* (2007) Genotype modulators of clinical severity in McArdle disease. *Neurosci Lett* **422**: 217–222
- 14 Maté-Muñoz JL *et al.* (2007) Favorable responses to acute and chronic exercise in McArdle patients. *Clin J Sport Med* **17**: 297–303
- 15 Paradas C *et al.* (2005) Variable presentation of the clinical phenotype of McArdle's disease in a kindred harbouring a novel compound genotype in the muscle glycogen phosphorylase gene. *Neurosci Lett* **31**: 28–31
- 16 Voduc N *et al.* (2004) McArdle's disease presenting as unexplained dyspnea in a young woman. *Can Respir J* **11**: 163–167
- 17 Williams AG *et al.* (2000) The ACE gene and muscle performance. *Nature* **403**: 614
- 18 Gómez-Gallego F *et al.* (2008) The I allele of the ACE gene is associated with improved exercise capacity in women with McArdle disease. *Br J Sports Med* **42**: 134–140
- 19 Tsujino S *et al.* (1995) Double trouble: combined myophosphorylase and AMP deaminase deficiency in a child homozygous for nonsense mutations at both loci. *Neuromuscul Disord* **15**: 263–266
- 20 Rubio JC *et al.* (2008) AMPD1 genotypes and exercise capacity in McArdle patients. *Int J Sports Med* **29**: 331–335
- 21 Pérez M *et al.* (2007) Exercise capacity in a child with McArdle disease. *J Child Neurol* **22**: 880–882
- 22 DiMauro S and Hartlage PL (1978) Fatal infantile form of muscle phosphorylase deficiency. *Neurology* **28**: 1124–1129
- 23 Pérez M *et al.* (2006) Exercise capacity in a 78 year old patient with McArdle's disease: it is never too late to start exercising. *Br J Sports Med* **40**: 725–726
- 24 DiMauro S and Tsujino S (1995) Nonlysosomal glycogenoses. In *Myology*, 1554–1556 (Eds Engel AG and Franzini-Armstrong C) New York: McGraw-Hill
- 25 Jinnai K *et al.* (1993) Glycogenosis type V (McArdle's disease) with hyperuricemia: a case report and clinical investigation. *Eur Neurol* **33**: 204–207
- 26 Mineo I *et al.* (1987) Myogenic hyperuricemia: a common pathophysiologic feature of glycogenosis types III, V, and VII. *N Engl J Med* **317**: 75–80
- 27 Bollig G *et al.* (2005) McArdle's disease and anaesthesia: case reports: review of potential problems and association with malignant hyperthermia. *Acta Anaesthesiol Scand* **49**: 1077–1083
- 28 Lorenzoni PJ *et al.* (2007) McArdle disease with rhabdomyolysis induced by rosuvastatin: case report [Portuguese]. *Arq Neuropsiquiatr* **65**: 834–837
- 29 Pearson C *et al.* (1961) A metabolic myopathy due to absence of muscle phosphorylase. *Am J Med* **30**: 502–517

- 30 Haller RG and Vissing J (2002) Spontaneous 'second wind' and glucose-induced second 'second wind' in McArdle disease: oxidative mechanisms. *Arch Neurol* **59**: 1395–1402
- 31 Haller RG and Vissing J (2004) No spontaneous second wind in muscle phosphofructokinase deficiency. *Neurology* **62**: 82–86
- 32 Haller RG and Lewis SF (1991) Glucose-induced exertional fatigue in muscle phosphofructokinase deficiency. *N Engl J Med* **324**: 364–369
- 33 Vissing J and Haller RG (2003) A diagnostic cycle test for McArdle's disease. *Ann Neurol* **54**: 539–542
- 34 Ørngreen MC *et al.* (2008) Is muscle glycogenolysis impaired in X-linked phosphorylase b kinase deficiency? *Neurology* **70**: 1872–1873
- 35 Vissing J *et al.* (2005) Effects of fuels on exercise capacity in muscle phosphoglycerate mutase deficiency. *Arch Neurol* **62**: 1440–1444
- 36 Deschauer M *et al.* (2005) Muscle carnitine palmitoyltransferase II deficiency: clinical and molecular genetic features and diagnostic aspects. *Arch Neurol* **62**: 37–41
- 37 Lindner A *et al.* (2001). Acute compartment syndrome after forearm ischemic work test in a patient with McArdle's disease. *Neurology* **56**: 1779–1780
- 38 Kazemi-Esfarjani P *et al.* (2002) A nonischemic forearm exercise test for McArdle disease. *Ann Neurol* **52**: 153–159
- 39 Bergström J (1975) Percutaneous needle biopsy of skeletal muscle in physiological and clinical research. *Scand J Clin Lab Invest* **35**: 609–616
- 40 Nogales-Gadea G *et al.* (2007) Molecular genetics of McArdle's disease. *Curr Neurol Neurosci Rep* **7**: 84–92
- 41 Bruno C *et al.* (2006) McArdle disease: the mutation spectrum of PYGM in a large Italian cohort. *Hum Mutat* **27**: 718
- 42 Lebo RV *et al.* (1984) High-resolution chromosome sorting and DNA spot-blot analysis assign McArdle's syndrome to chromosome 11. *Science* **225**: 57–59
- 43 Bartram C *et al.* (1993) McArdle's disease: a nonsense mutation in exon 1 of the muscle glycogen phosphorylase gene explains some but not all cases. *Hum Mol Genet* **2**: 1291–1293
- 44 Aquaron R *et al.* (2007) Molecular characterization of myophosphorylase deficiency (McArdle disease) in 34 patients from Southern France: identification of 10 new mutations: absence of genotype-phenotype correlation. *Neuromuscul Disord* **17**: 235–241
- 45 Deschauer M *et al.* (2007) Analysis of spectrum and frequencies of mutations in McArdle disease: identification of 13 novel mutations. *J Neurol* **254**: 797–802
- 46 Martin MA *et al.* (2000) Molecular heterogeneity of myophosphorylase deficiency (McArdle's disease): a genotype-phenotype correlation study. *Ann Neurol* **50**: 574–581
- 47 Rubio JC *et al.* (2006) A proposed molecular diagnostic flowchart for myophosphorylase deficiency (McArdle disease) in blood samples from Spanish patients. *Hum Mutat* **28**: 203–204
- 48 Tsujino S *et al.* (1994) Three new mutations in patients with myophosphorylase deficiency (McArdle disease). *Am J Hum Genet* **54**: 44–52
- 49 Fernandez R *et al.* (2000) A novel missense mutation (W797R) in the myophosphorylase gene in Spanish patients with McArdle disease. *Arch Neurol* **57**: 217–219
- 50 Bruno C *et al.* (1999). Molecular characterization of McArdle's disease in two large Finnish families. *J Neurol Sci* **165**: 121–125
- 51 Fernandez-Cadenas I *et al.* (2003) Splicing mosaic of the myophosphorylase gene due to a silent mutation in McArdle disease. *Neurology* **61**: 1432–1434
- 52 García-Consuegra I *et al.*: Novel mutations in patients with McArdle disease by analysis of skeletal muscle mRNA. *J Med Genet*, in press
- 53 Pari G *et al.* (1999) Myophosphorylase gene transfer in McArdle's disease myoblasts *in vitro*. *Neurology* **53**: 1352–1354
- 54 Howell JM *et al.* (2008) Adenovirus and adeno-associated virus-mediated delivery of human myophosphorylase cDNA and LacZ cDNA to muscle in the ovine model of McArdle's disease: expression and re-expression of glycogen phosphorylase. *Neuromuscul Disord* **18**: 248–258
- 55 Nogales-Gadea G *et al.* (2008) Expression of the muscle glycogen phosphorylase gene in patients with McArdle disease: the role of nonsense-mediated mRNA decay. *Hum Mutat* **29**: 277–283
- 56 Welch EM *et al.* (2007) PTC124 targets genetic disorders caused by nonsense mutations. *Nature* **447**: 87–91
- 57 Schroers A *et al.* (2006). Gentamicin treatment in McArdle disease: failure to correct myophosphorylase deficiency *Neurology* **66**: 285–286
- 58 Martinuzzi A *et al.* (2008) Randomized, placebo-controlled, double-blind pilot trial of ramipril in McArdle's disease. *Muscle Nerve* **37**: 350–357
- 59 Poels PJ *et al.* (1990) Dantrolene sodium does influence the second-wind phenomenon in McArdle's disease: electrophysiological evidence during exercise in a double-blind placebo-controlled, cross-over study in 5 patients. *J Neurol Sci* **100**: 108–112
- 60 Steele IC *et al.* (1996) A double blind, placebo controlled, cross over trial of D-ribose in McArdle disease. *J Neurol Sci* **136**: 174–177
- 61 Vorgerd M *et al.* (2002) Creatine therapy in myophosphorylase deficiency (McArdle disease): a placebo-controlled crossover trial. *Arch Neurol* **57**: 956–963
- 62 Vorgerd M *et al.* (2002) Effect of high-dose creatine therapy on symptoms of exercise intolerance in McArdle disease: double-blind, placebo-controlled crossover study. *Arch Neurol* **59**: 97–101
- 63 Andersen ST and Vissing J (2008) Carbohydrate- and protein-rich diets in McArdle disease: effects on exercise capacity. *J Neurol Neurosurg Psychiatry* [doi:10.1136/jnnp.2008.146548]
- 64 MacLean D *et al.* (1998) Oral branched chain amino acids do not improve exercise capacity in McArdle's disease. *Neurology* **51**: 1456–1459
- 65 Andersen ST *et al.* (2008) Effect of oral sucrose shortly before exercise on work capacity in McArdle disease. *Arch Neurol* **65**: 786–789
- 66 Quinlivan R *et al.* Pharmacological and nutritional treatment for McArdle disease (glycogen storage disease type V). *Cochrane Database Systematic Reviews* 2008, Issue 1. Art. No.: CD003458. doi:10.1002/14651858.CD003458.pub3
- 67 Jensen KE *et al.* (1990) Kinetics following high protein diet in McArdle's syndrome: a 31P magnetic resonance spectroscopy study. *Acta Neurol Scand* **81**: 499–503
- 68 Slonim AE and Goans PJ (1985) Myopathy in McArdle's syndrome: improvement with a high-protein diet. *New Engl J Med* **312**: 355–359
- 69 Kushner RF and Berman SA (1990) Are high protein diets effective in McArdle's disease? *Arch Neurol* **47**: 383–384
- 70 Haller RG *et al.* (2006) Aerobic conditioning: an effective therapy in McArdle's disease. *Ann Neurol* **59**: 922–928

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**Competing interests**

The authors declared no competing interests.