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WHEN FATIGUE HIDES A METABOLIC MYOPATHY: A CASE REPORT OF MCARDLE DISEASE WITH MOLECULAR DIAGNOSIS

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ABSTRACT

McArdle disease, or glycogen storage disease type V, is a rare inherited metabolic myopathy caused by mutations in the *PYGM* gene, resulting in deficiency of the enzyme myophosphorylase. Patients usually present with lifelong exercise-induced fatigue, muscle pain, and sometimes rhabdomyolysis, but the condition is underdiagnosed due to its nonspecific manifestations. This case is distinctive because it documents molecularly confirmed McArdle disease in a woman with persistently elevated creatine kinase and a suggestive family history, underlining the importance of clinical suspicion, timely genetic testing, and appropriate counselling.

A 35-year-old woman reported lifelong myalgia and easy fatigability. Her past history included recurrent migraines and use of a progestogen-only contraceptive. One sister, aged 21, had similar symptoms, while her other sister and parents were healthy. Physical examination was unremarkable. Laboratory tests showed an isolated elevation of creatine kinase (1,504 U/l). Genetic analysis revealed the PYGM c.148C>T, p.(Arg50*) variant in apparent homozygosity, a rare mutation transmitted in heterozygosity. At follow-up she was 30 weeks pregnant and was referred, along with her symptomatic sister, to a genetic consultation. Behavioural guidance focused on regular moderate exercise and symptom management.

McArdle disease is underdiagnosed because its symptoms are often misinterpreted as poor physical fitness. This case highlights that early recognition, and molecular confirmation can avoid unnecessary invasive tests and provide clarity in patients with chronic exertional intolerance. The identification of a rare *PYGM* variant further emphasizes the importance of genetic counselling, which enables family screening and informed reproductive planning. Timely recognition and tailored management are essential for improving patient quality of life.

KEYWORDS

Muscle fatigue, creatine kinase, muscle phosphorylase, glycogen storage disease, McArdle disease

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LEARNING POINTS

- *Early recognition and diagnosis:* McArdle's disease is underdiagnosed due to nonspecific symptoms. This case highlights the importance of maintaining clinical suspicion for timely diagnosis.
- *Impact on quality of life:* Although no curative treatment exists, simple measures such as regular moderate exercise and carbohydrate intake can substantially improve symptoms and daily functioning.
- *Value of genetic counselling:* Genetic confirmation allows family screening, clarifies prognosis, and supports individualized management strategies for patients and their relatives.

INTRODUCTION

McArdle disease, a form of glycogen storage disorder classified as type V, was first recognized in 1951 and results from a deficiency in the muscle enzyme myophosphorylase, which is essential for glycogen breakdown during exertion. Without this enzyme, the muscle's ability to generate adenosine triphosphate is impaired, resulting in glycogen buildup within muscle fibres and diminished tolerance to physical activity. The disease is autosomal recessive, resulting from mutations in the *PYGM* gene located on chromosome 11 and affects both sexes equally, with an estimated prevalence of 1:100,000 individuals[1,2]. Because hepatic and cardiac phosphorylase isoforms are unaffected, McArdle disease manifests as a pure myopathy[3].

Typical symptoms include exercise-induced fatigue, myalgia, and tiredness. Patients show marked elevation of creatine kinase (CK) and may experience rhabdomyolysis with myoglobinuria, which can lead to acute kidney injury[4]. Although McArdle disease is considered a benign condition with no impact on life expectancy, some patients develop more severe forms featuring hypotonia, generalized weakness, or progressive respiratory failure[3,5].

Confirmation of the diagnosis can be achieved either by demonstrating absent myophosphorylase activity on muscle biopsy or, more commonly today, through genetic testing identifying pathogenic *PYGM* mutations[1,2]. There is no specific curative therapy, but symptoms can be managed and quality of life improved with lifestyle interventions such as carbohydrate ingestion before exercise and structured aerobic training[6,7].

CASE DESCRIPTION

We report the case of a 35-year-old woman referred to the Internal Medicine clinic for generalized myalgias and easy fatigability present since childhood, without recent worsening. She reported that symptoms appeared gradually with physical exertion and improved after 15 to 30 minutes. She formerly practiced swimming but had stopped temporarily for reasons unrelated to her symptoms. During childhood she tired more quickly than her peers and, after running, had to stop because of shortness of breath, myalgias and asthenia. She denied respiratory complaints such as cough, wheeze, sputum production, snoring or non-restorative sleep. There were no weight changes, fever or night sweats. She also denied palpitations, chest pain, peripheral oedema and gastrointestinal disturbances. Past medical history included migraine associated with the menstrual cycle with no need of chronic medication and tonsillectomy at the age of 6. Routine medication comprises a progestogen only oral contraceptive. She has a 21-year-old sister with similar symptoms of unknown cause. Physical examination was unremarkable.

Initial laboratory tests showed an elevated CK level of 1 504 U/l. The remaining baseline panel was normal, with no anaemia, thyroid or renal dysfunction, and negative antinuclear antibodies. Myoglobinuria could not be measured because the test was unavailable at our hospital.

At the second visit the patient reported persistent but stable fatigue. She walked 2 to 3 times a week for 45 minutes and swam once weekly, always needing to pause for muscle recovery. Given the clinical picture of a pure myopathy beginning in childhood, persistent isolated CK elevation and a similar family history of unknown aetiology, genetic testing was requested. The analysis identified the c.148C>T, p.(Arg50*) variant in the *PYGM* gene in apparent homozygosity, a variant reported as rare in population databases[8]. This variant is transmitted to offspring in heterozygosity. A diagnosis of McArdle disease/glycogen storage disease type V was therefore established with molecular confirmation.

At the follow up visit the patient was 30 weeks pregnant and was referred to a Medical Genetics clinic. Referral of her sister was likewise recommended. For her offspring, the empirical recurrence risk is <1 % in the absence of consanguinity and if the partner has no similar personal or family history; this risk can be further refined by molecular analysis of the partner's *PYGM* gene. Behavioural measures were advised: muscle gradual warm up before exercise, avoidance of intense exertion, maintenance of regular aerobic activity and adequate hydration.

DISCUSSION

McArdle disease remains underdiagnosed because of its rarity and nonspecific symptoms, which are frequently misattributed to poor physical fitness[1,2]. Symptoms typically manifest in childhood with exertional fatigue, cramps, and intolerance to exercise[3]. A diagnostic hallmark is the "second-wind phenomenon", in which symptoms improve after several minutes of sustained activity as energy metabolism shifts from blocked glycogenolysis to

alternative fuels delivered via increased muscle blood flow[4]. Recognition of this feature is crucial in clinical practice.

Although average life expectancy is generally preserved, complications include recurrent rhabdomyolysis with myoglobinuria and, in some patients, progressive fixed weakness or respiratory involvement[3,5]. These highlight the heterogeneity of disease severity and the need for individualized follow-up.

Our case demonstrates the importance of thorough history-taking and family assessment. Persistent CK elevation with long-standing exertional intolerance raised suspicion, and molecular testing confirmed the diagnosis, avoiding the need for muscle biopsy[2,9]. Identification of a rare *PYGM* variant reinforced the diagnostic value of genetic analysis and supported referral for genetic counselling, especially in the context of pregnancy, enabling reproductive risk assessment and screening of symptomatic relatives[1].

Management remains symptomatic but effective when personalized. Regular aerobic activity, carbohydrate ingestion before exertion, and patient education improve functional tolerance and quality of life[6,7]. Low-dose creatine supplementation may benefit selected patients, though evidence is inconsistent[6]. More recently, structured models of long-term care have been proposed to optimize outcomes and integrate multidisciplinary support[5].

In conclusion, this case reinforces the importance of considering McArdle disease in patients with unexplained lifelong exertional intolerance and CK elevation. Early suspicion, molecular confirmation, and genetic counselling are key to improving outcomes, enabling preventive strategies, and sparing invasive investigations.

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