CASE REPORT

Emotionally-intense situations can result in rhabdomyolysis in McArdle disease

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SUMMARY

Despite the majority of patients with McArdle disease reporting symptoms including fatigue, cramps and episodes of myoglobinuria from early childhood, diagnosis is often delayed by several decades. Additionally, many individuals with rhabdomyolysis remain undiagnosed. The occurrence of symptoms during exercise, particularly isometric muscle contraction such as heavy lifting, is well known in McArdle disease. However, isometric muscle contraction that occurs with emotion is not recognised as exercise and may be missed as a trigger for rhabdomyolysis, potentially leading to a delay in diagnosis. Three patients are presented here, all with symptoms from childhood including episodes of rhabdomyolysis induced by tense emotional situations without physical exertion; two patients reported recurrent episodes while watching rather than playing football. The remaining patient developed rhabdomyolysis during a heated argument. These patients' histories emphasise the risk from sustained isometric muscle contraction that occurs in emotive situations for patients with McArdle disease.

BACKGROUND

Glycogen storage diseases (GSD) represent a range of pathologies affecting the storage, mobilisation and metabolism of glycogen. These conditions are the result of genetic mutation and are inherited as either autosomal recessive or X linked recessive traits. McArdle disease (GSD type V) is an autosomal recessive metabolic myopathy associated with mutations in the *PYGM* gene, which encodes the muscle form of glycogen phosphorylase (myophosphorylase), the enzyme catalysing the breakdown of muscle glycogen. Traditionally, the diagnosis was based on typical symptoms and the inability to produce lactate during a forearm exercise test and absent myophosphorylase staining on muscle biopsy. More recently, genetic analysis of the *PYGM* gene is frequently performed as a first-line investigation. Ninety-five per cent of British Caucasian patients carry the R50X mutation on at least one allele of the *PYGM* gene. There is limited data on the prevalence of McArdle disease in Europe, however, a recent study found the prevalence in Spanish Caucasians to be approximately 1:167 000.[1]

The absence of myophosphorylase results in patients with McArdle disease being unable to mobilise glucose from muscle stores of glycogen. This severely limits physical activity and, therefore, normal functional activity is challenging, making the tasks of daily living difficult and negatively impacting on the patient's quality of life. Typically, patients experience symptoms from early childhood, including painful cramps and fatigue when exercising. These symptoms are relieved by a reduction in the intensity, or with cessation, of exercise.[2] After several minutes of intervening rest or reduced activity patients with McArdle disease are able to continue exercising without difficulty; this phenomenon, referred to as a 'second-wind', is pathognomonic of McArdle disease and is observed on exercise testing. Exercise, in particular anaerobic exercise including isometric muscle contraction such as squats and weight-lifting, can cause painful muscle contractures lasting for several hours, myoglobinuria and, infrequently, acute renal failure. Although exercise is of benefit for patients with McArdle disease, the occurrence of symptoms with exercise leads to anxiety and fear and hence many patients avoid exercise and adopt a sedentary lifestyle—the 'McArdle paradox'.[3]

Three patients with McArdle disease are presented who developed rhabdomyolysis in emotionally tense situations not typically regarded as exercise, namely: watching a football match and during a heated argument, highlighting that isometric muscle contraction rather than 'exercise' per se is a major precipitant for muscle damage and contractures in patients with McArdle disease.

CASE PRESENTATION

Patient 1: A 32-year-old Caucasian man with exercise-related myalgia and fatigue from 4 years of age. He was unable to sprint and avoided school sports. His symptoms in childhood were labelled by medical professionals as 'growing-pains'. He was diagnosed with McArdle disease at 24 years of age; genetic testing revealed homozygous R50X mutations in the *PYGM* gene. Prior to diagnosis, he had an episode of Coca-Cola coloured urine, consistent with myoglobinuria, 4 h after raising and tensing his arms to cheer while watching his favourite football team score a goal. A further episode of myoglobinuria occurred under similar circumstances 4 years later. These episodes were due to isometric muscle contraction in both arms. Physical examination revealed mild symmetrical bilateral scapular winging. The patient was only able to walk 445 m during a 12 min walk test (TMWT)[2] and exhibited a second wind.

Patient 2: A 23-year-old Caucasian man experienced exercise-related myalgia since school age. He was diagnosed with McArdle disease after the diagnosis was performed in his younger brother. Genetic testing confirmed homozygous R50X mutations in the *PYGM* gene. He experienced two episodes of severe myalgia and Coca-Cola coloured

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urine after cheering and tensing his arms when his local football team scored a goal. On these occasions he required admission to hospital where his serum creatine kinase (CK) levels were found to be significantly elevated at 62 000 IU/L and 120 000 IU/L (normal <250 IU/L). Physical examination revealed mild left-sided scapular winging and bilateral calf hypertrophy. The patient was able to walk 720 m during a TMWT and exhibited a second wind.

Patient 3: A 26-year-old Pakistani man first presented with acute bilateral arm and leg contractures that occurred during a heated argument. During the argument he was knocked to the floor; however, he was unable to get up as his arms and legs had gone into spasm. He was admitted to hospital where his CK was found to be grossly elevated at 318 200 IU/L. Despite aggressive fluid resuscitation, he developed acute renal failure requiring admission to the intensive care unit and haemodialysis. A diagnosis of McArdle disease was performed on the basis of an abnormal forearm exercise test and a muscle biopsy taken several weeks later, which revealed absent myophosphorylase. In hindsight, he recalled symptoms from early childhood including recurrent episodes of Coca-Cola coloured urine, a 'second-wind' while exercising and myalgia in any muscles he was exercising, including his jaw when chewing. Physical examination revealed bilateral hypertrophy of the calf, deltoid and bicep muscles. During the TMWT he was able to walk 535 m and exhibited a second wind. Genetic testing revealed homozygous deletions (c.14delT) in the *PYGM* gene confirming the diagnosis of McArdle disease.

TREATMENT

Each patient was given advice on appropriate exercise, including a plan for at least 30 min of aerobic exercise three times a week and carbohydrate supplementation before planned exercise; they were also instructed on how to avoid and manage episodes of rhabdomyolysis.

OUTCOME AND FOLLOW-UP

All three patients remain under follow-up. Patient 1 has increased the distance he is able to walk during a TMWT by 140% to 1090 m over 4 years. Patient 2 has increased the distance he can walk during a TMWT by 52% to 1020 m over 2 years and reduced his body mass index (BMI) from 33 to 28 kg/m^2. Neither patient has experienced any further episodes of rhabdomyolysis. Although the distance that patient 3 is able to walk during the TMWT has not changed, he has had no further episodes of rhabdomyolysis over the past 6 years.

DISCUSSION

Individuals with rhabdomyolysis may present to a number of different medical specialties including general practitioners, rheumatologists, neurologists and musculoskeletal physicians, many of whom are aware that a history of cramps or myalgia in any muscle during exercise should prompt investigation for a metabolic myopathy such as McArdle disease. Sustained isometric exercises such as squats are most likely to trigger contractures and rhabdomyolysis in patients with McArdle disease. The patients described here emphasise that activities not traditionally thought of as exercise, such as an argument or watching a sport, can result in contractures and rhabdomyolysis as individuals may become tense from excitement or fear, contracting their muscles isometrically. Therefore, a careful history in patients presenting with rhabdomyolysis should not only focus on exercise-related symptoms, but also on other activities in which isometric muscle contraction may occur. This is further highlighted by other patients attending our specialist clinic who have developed contractures riding rollercoasters and during sexual intercourse, an important problem not typically raised by patients that should be asked about directly.

Emotional distress triggered rhabdomyolysis has been reported in metabolic myopathies due to disorders of lipid metabolism such as carnitine palmitoyl-transferase II (CPT II) deficiency[4] and very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency.[5] In these disorders, rhabdomyolysis is typically induced by prolonged exercise (more than 45 min), fever, fasting and stress, and there is no history of a 'second wind'. In disorders of carbohydrate metabolism, on the other hand, symptoms related to physical activity will develop within 2–3 min and fever, fasting and stress have not been reported as triggers for rhabdomyolysis. These clinical differences may help in refining the diagnostic approach to patients with rhabdomyolysis.

The occurrence of symptoms with exercise and the delay in diagnosis, often by several decades, results in many patients with McArdle disease avoiding exercise; some may even be advised to do so. In childhood, undiagnosed individuals are often 'stigmatised' as lazy and in our experience, patients' symptoms during childhood are often labelled as 'growing-pains'. A recent review of 45 patients with genetically confirmed McArdle disease revealed that in the majority of patients (84%) onset of symptoms was in childhood, but diagnosis was frequently delayed until after 30 years of age.[2] The association of painful cramps and myalgia with exercise results in many patients adopting a sedentary lifestyle; 72% of patients with McArdle disease were found to be overweight with a median BMI >31 kg/m^2.[2] This is compounded by fear of developing rhabdomyolysis and acute renal failure. However, a number of open-labelled studies have shown that aerobic exercise and training are safe for individuals with McArdle disease.[6]

It is important that patients with McArdle disease be made aware of the potential risk of rhabdomyolysis in highly emotive situations and counselled on how to manage such situations; however, they should also be counselled that aerobic exercise is safe and can have significant functional benefit. With advice on appropriate activity, diet and potential triggers, none of the patients reported here have had further episodes of rhabdomyolysis and two have substantially improved their aerobic fitness and therefore their functional capacity.

Learning points

- Symptoms of McArdle disease occur in the majority of patients during childhood but diagnosis is often delayed by several decades.
- Sustained isometric muscle contraction occurs in everyday situations not recognised as exercise, such as watching football, and may trigger contractures and rhabdomyolysis in patients with McArdle disease.
- Aerobic exercise is safe in McArdle disease and can result in significant functional benefit.
- A good source of practical advice on how to adjust activities to avoid problems for patients with McArdle disease, their families and those not familiar with the condition is '101 Tips for a good life with McArdle Disease' by Andrew Wakelin,[7] which is available from the Association for Glycogen Storage Disease (UK).

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