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McArdle Disease Misdiagnosed as Meningitis

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Conflict of interest: None declared

Patient: Female, 44
Final Diagnosis: McArdle disease
Symptoms: Exercise intolerance • muscle contracture • myalgia • myoglobinuria • recurrent rhabdomyolysis
Medication: —
Clinical Procedure: —
Specialty: Neurology

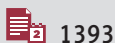
Objective: Rare disease
Background: McArdle disease is a glycogen storage disorder mainly characterized by exercise intolerance. Prolonged muscle contracture is also a feature of this condition and may lead to rhabdomyolysis (RM), which is a serious event characterized by acute skeletal muscle damage.

Case Report: A 44-year-old female patient presented with an acute contracture of the posterior neck muscles, causing severe nuchal rigidity. The contracture was induced during a dental extraction as she held her mouth open for a prolonged period, with her neck in a rigid position. She presented with severe pain in her ear and head, as well as fever, vomiting, and confusion. Based on her symptoms, she was initially misdiagnosed with bacterial meningitis and experienced an acute allergic reaction to the systemic penicillin she was subsequently administered. Lumbar puncture results were normal. High serum creatine kinase (CK) levels, recurrent exercise-related muscle symptoms, and a previous history of recurrent myoglobinuria raised the suspicion of an underlying neuromuscular condition. McArdle disease was confirmed by muscle biopsy and a genetic test, which revealed that the patient was homozygous for the R50X mutation in the *PYGM* gene.

Conclusions: This case illustrates that even seemingly innocuous movements, if rapid isotonic or prolonged isometric in nature, can elicit a muscle contracture in McArdle disease patients. Here, we highlight the need for careful management in this patient population even during routine healthcare procedures. The allergic reaction to antibiotics emphasises that misdiagnoses may result in iatrogenic harm.

MeSH Keywords: Diagnostic Errors • Glycogen Storage Disease Type V • Meningism • Rhabdomyolysis

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Background

Rhabdomyolysis (RM) is a potentially life-threatening event characterized by muscle breakdown. Symptoms vary and may include muscle pain/weakness, flu-like symptoms, nausea, vomiting, confusion, and dark urine (myoglobinuria). Several inherited disorders may be associated with RM [1], including McArdle disease (GSDV). This is an autosomal recessive metabolic myopathy caused by skeletal muscle glycogen phosphorylase (myophosphorylase) deficiency. Absence of this enzyme due to a mutation in the *PYGM* gene prevents conversion of skeletal muscle glycogen to glucose-1-phosphate, blocking the production of ATP via glycolysis [2]. In those without pathology, muscle glycogen fuels energy in early exercise and during high intensity work [3]. Thus, common symptoms of McArdle disease include exercise intolerance and muscle pain within minutes of starting physical activity, and/or isometric muscle contraction. Sustained muscle contractures may also occur. Early fatigue and exercise intolerance are apparent in childhood, yet are often misinterpreted until an acute event such as RM triggers further investigation. A diagnosis of McArdle disease is usually made between the second and third decade of life, or later. A study of 45 patients showed that 38 (84%) remembered experiencing symptoms before the age of 10, yet the greatest proportion of diagnoses were made between 30 and 39 years of age [2].

McArdle disease is a very rare condition with a prevalence of approximately 1 in 167 000 live births [4]. The frequency of misdiagnosis in this population is high (approximately 88%) [5], and the correct diagnosis is usually identified after several years of investigations. Early diagnosis and symptom management are important to prevent severe complications such as recurrent RM episodes.

This case report presents a patient with undiagnosed McArdle disease who, after suffering an acute contracture of the posterior neck muscles and RM, was misdiagnosed with bacterial meningitis. The importance of careful management during healthcare procedures in this group of patients is emphasised.

Case Report

A 44-year-old white woman developed severe acute pain in her ear and head immediately following a dental extraction. Symptoms rapidly progressed to include fever, vomiting, and confusion. Physical examination at an emergency unit revealed contracture of the posterior neck muscles. Based on her symptoms, particularly “nuchal rigidity”, she was diagnosed with bacterial meningitis and immediately given systemic penicillin. She experienced a subsequent allergic reaction, including a whole-body rash and swollen face, following antibiotic

treatment. Cerebrospinal fluid (CSF) results were within normal limits, but dark urine and high serum creatine kinase (CK) levels were noted upon hospital admission, confirming acute RM. A previous history of recurrent myoglobinuria suggested an underlying neuromuscular disease. She made a full recovery and was discharged for outpatient investigations.

The patient experienced a similar occurrence of flu-like symptoms and dark urine following a second dental appointment for root canal treatment. She reported being very tense during the procedure, which appears to have been the cause of her posterior neck muscle contracture on both occasions.

The patient was referred for neuromuscular evaluation to investigate the recurrent RM. She had been aware of muscle problems from a young age. A thorough history revealed that her physical activity and exercise capacity had always been limited, and she described several episodes of muscle contracture, flu-like symptoms, and dark urine in the past. Upon referral to a specialist neuromuscular clinic, she reported at least 3 episodes of RM in the last 4 years. Physical examination results were normal, with no muscle weakness or wasting. In the clinic, she walked a distance of 700 metres during the 12-Minute Walk Test (12MWT), [6,7] and demonstrated a “second wind”. This phenomenon is characterized by an initial increase in both muscle pain and heart rate after approximately 1–3 minutes of commencing physical activity. This is due to an inability to convert glycogen into glucose. However, a minor reduction in the level of physical activity can ameliorate symptoms within 8–10 minutes. This “second wind” phenomenon is believed to be a result of increased blood flow, an increase in fatty acid oxidation, and increased use of liver glycogen. Even prior to her diagnosis, the patient had been able to manage her physical activity-related pain, despite no conscious awareness of the “second wind”. Since her initial admission to hospital, her baseline CK levels have been more moderately raised (around 600 IU/L). A muscle biopsy was performed, revealing a vacuolar myopathy with absence of muscle glycogen phosphorylase. Genetic evaluation revealed homozygous mutations at R50X in the *PYGM* gene, confirming a diagnosis of McArdle disease.

The patient was seen by a specialist multi-disciplinary team comprising a physician, physiotherapist, clinical nurse specialist, clinical psychologist, dietitian, exercise physiologist, and patient support group representative. She has been known to the team for 4 years, and has been given advice on appropriate exercise regimens for McArdle disease, which she performs regularly on a cycle ergometer. She has not had any further episodes of myoglobinuria or emergency hospitalization since her referral for multi-disciplinary care.

Discussion

This report describes a patient with McArdle disease who was misdiagnosed with meningitis, resulting in iatrogenic harm. The patient's neck contracture was induced by having to hold her mouth open and neck rigid for a prolonged period of time to facilitate a dental extraction. The resultant flu-like symptoms were related to the RM episode. Although this patient had experienced symptoms of McArdle disease from early childhood, it was not until she had severe RM that an underlying neuromuscular disorder was considered.

Neck stiffness, fever, headache, and a change in mental status are considered classic symptoms of acute bacterial meningitis [8], a neurological emergency with a high risk of morbidity and mortality. The patient presented at an emergency unit with these symptoms, supporting the prompt use of antibiotics while awaiting CSF results. She also had myoglobinuria and raised serum CK levels upon presentation. The patient's medical history, including exercise intolerance, repeated muscle contracture, and episodes of myoglobinuria, had been an issue since childhood. These signs and symptoms should raise the suspicion of a genetic cause for recurrent RM, supporting further investigation for presence of an inherited metabolic myopathy [1]. In general, onset of symptoms after just a few minutes of physical activity suggests a disorder of glycogen metabolism, whereas those occurring after several hours would suggest a disorder of fatty acid metabolism. The differential diagnosis with other types of glycogen storage disorders was easily identified from the medical history and physical examinations such as the 12MWT, which revealed the "second wind" phenomenon, the hallmark of McArdle disease.

This case illustrates that contracture in McArdle disease does not necessarily follow exercise *per se*. A case-series published in 2014 [9] suggests even emotionally-intense situations can cause sustained muscle contractures, triggering acute RM. Such cases emphasise the importance of taking a detailed medical history to determine the triggers of muscle symptoms. This can aid identification of inherited neuromuscular disorders in patients presenting with recurrent RM [1].

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Antibiotics should be administered promptly when there is suspicion of bacterial meningitis, which was the correct initial medical treatment in this case. However, the allergic reaction to the first dose of antibiotics emphasises that misdiagnosis may cause iatrogenic complications.

Despite the rarity of McArdle disease, it is important for doctors to be familiar with this condition and it should be a differential diagnosis whenever high CK levels and recurrent myoglobinuria are involved. Additionally, patients with McArdle disease might need careful management during medical procedures, including dental treatments. Currently, there is no cure for McArdle disease, but early diagnosis and appropriate exercise may improve functional capacity and help prevent severe long-term complications [10,11]. Exercise prescription with this patient population requires specialized knowledge. Walking courses led by experienced patients have helped others understand exercise principles, learn self-management techniques, increase aerobic fitness, and make activity part of their daily routine [12,13].

Conclusions

This is the first time life-threatening iatrogenic damage has been reported as arising from misdiagnosis of rhabdomyolysis (RM) in undiagnosed McArdle disease. This highlights the importance of early diagnosis and correct management. A detailed medical history of RM triggers, occurrence of a "second wind" phenomenon, and raised baseline CK levels should provide a strong clinical suggestion of McArdle disease. Furthermore, McArdle disease should be considered in patients presenting with acute RM symptoms. Muscle contracture in McArdle disease is triggered by sustained muscle contraction, which may be initiated by everyday activities, including simple medical procedures. For this reason, people with McArdle disease may require careful management even during routine dental procedures.

Competing interests

None declared.

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