

Exercise induced muscle weakness in a young adult: McArdle's disease unusual presentation

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Abstract

McArdle's disease (Glycogen storage disease type V) is a rare inherited autosomal recessive disease involving defect in enzyme, glycogen phosphorylase (PYGM) which results in accumulation of glycogen mainly affecting skeletal muscles. It commonly presents in childhood and rarely in adults with symptoms like exercise intolerance, muscle weakness, cramps and fatigue. Herein, we report an unusual case of a 22 years old male in Pakistan with probable McArdle's Disease presenting with repeated episodes of generalized cramping muscle pain, exercise intolerance and haematuria. The diagnostic approach to identifying this disease as well as the differentials of other rare types of skeletal muscle disorders that should be kept in mind while dealing with a similar clinical picture, irrespective of the age of presentation, have been discussed.

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Introduction

In 1951, Dr. Brian McArdle reported a rare condition in which the patient complained of 'exercise intolerance' that primarily affects skeletal muscles¹. This disease, which came to be known as McArdle's disease, is now recognized as the most common muscle glycogen storage disorder (GSD Type V). Latest insight into the mechanism of McArdle's disease has shown that it results from a deficiency in the muscle isoform of the enzyme glycogen phosphorylase (myophosphorylase)². Clinically, McArdle's disease is characterized by exercise intolerance, at least one episode of rhabdomyolysis, second wind phenomenon, cramping muscle pain and spasms, and sometimes permanent muscle weakness^{3,4}.

Here we discuss a probable case of McArdle's disease. A young patient experiencing exercise intolerance and dark

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coloured urine. Along with that, the diagnostic approach as well as the possible differentials shall also be discussed.

Despite our extensive literature review, we were not able to find any other case report about McArdle's disease, specifically, in Pakistan.

Case Report

In April 2021, a 22-year-old male, who worked as an army sepoy, presented to CMH Lahore with complaints of generalized cramping muscle pain upon exertion for the past one day. The pain was sudden in onset, occurred after carrying a heavy weight on his back and was relieved with rest. It was unrelated to food intake. There was no history of any drug or alcohol abuse. No one in his family had ever had a similar complaint. His parents have a consanguineous marriage. The general physical exam findings were unremarkable. His ALT/AST levels were in normal limits, but serum CK (creatin kinase) levels were elevated that was 478units/L (Normal range in males: 55-170 units/L)

The patient had experienced similar episodes in the past. Initially in April 2019, he was admitted to CMH Malir, Karachi after experiencing generalized body aches, flank pain and haematuria following strenuous exercise. The patient had run 2 miles as part of his military exercise. It was not associated with fever, rash or arthralgias and there was no history of trauma, crush injury or long-term drug or alcohol use. The creatinine and CK levels were deranged, and he was diagnosed as a case of acute kidney injury secondary to rhabdomyolysis for which he received 5 sessions of haemodialysis. The patient was prescribed Tramadol HCl, Paracetamol and Tizanidine during his hospital stay before being discharged. He remained well for a year.

A year later, in July 2020, he came to CMH Quetta for a dental procedure where his baseline investigations were done and incidentally showed raised CK levels. Set of investigations done to reach the diagnosis is given in Table

Based on the High creatine kinase levels and forearm ischaemic test (FIET), he was diagnosed with Glycogen Storage disease type V. There was no follow-up.

Table: Investigations done to reach the correct diagnosis of McArdle's disease (July 2020).

Investigations	Findings
Creatine Kinase (CK)	20468units/L (Normal 55-170 units/L)
Ischaemic forearm test	serial decrease in the lactate level (2.2 to 2.0mmol/l) and a serial increase in the ammonia level (64.6to 110µmol/l)
Muscle biopsy	Unremarkable
Electromyography and Nerve Conduction Studies	Myopathy/myositis
Liver function test	Normal
Uric Acid	8.14mg/dl (Normal 3.4-7mg/dl)
Rheumatoid factor	Positive
Other Autoimmune Myopathy profile (ASMA ¹ , ANA ² , AntiSSA/Ro ³ , Anti-La/SSB ⁴ , AntiTG ⁵ , AntiSm ⁶ , AntiRNP ⁷ , AntiSCL ⁸ , AntiMi2 ⁹ , AntiNXP2 ¹⁰ , AntiTIF1 _v ¹¹ , ASAs ¹² , MAAs ¹³)	Negative
Aldolase	11.5units/L (Normal 1-7.5units/L)
IgG to Cytomegalovirus and Epstein bar virus	Positive
MRI shoulder joint and pelvic girdle	Normal

¹Anti-smooth muscle antibody (ASMA)²Antinuclear Antibody (ANA)³Anti-Sjögren's-syndrome-related antigen A (anti-SSA)⁴Anti-Sjögren's-syndrome-related antigen B(anti-SSB)⁵Anti-Tissue Transglutaminase Antibody (Anti-tTG)⁶Anti-Smith antibodies (AntiSm)⁷Antinuclear ribonucleoprotein antibody (AntiRNP)⁸Antiscleroma 70-kD Antibodies (Anti SCL)⁹Anti-Nucleosome-remodeling deacetylase complex antibody (Anti Mi2)¹⁰Anti-Nuclear matrix protein antibody (Anti NXP2)¹¹Anti-Transcription intermediary factor 1_v antibody (AntiTIF1_v)¹²Antisynthetase antibodies (ASAs)¹³Myositis-associated antibodies (MAAs)

Discussion

Our patient showed signs of a metabolic muscle disorder. Along with Glycogen storage diseases, other possible differentials include mitochondrial myopathy, myoadenylate deaminase deficiency, and non-metabolic conditions such as muscular dystrophies.

The forearm ischaemic test (FIET) was employed since it is quite characteristic for a metabolic muscle disorder. The elevated serum ammonia and normal serum lactate were strongly suggestive of a muscle glycogen storage disease⁵.

Along with an abnormal EMG and FIET and raised serum CK levels, this was rather a clinical diagnosis with a history of cramps, fatigue and an episode of rhabdomyolysis complicated by acute kidney injury. Other possible glycogen storage diseases are type II, VII, X and XI. Of particular importance is GSD type VII (Tarui disease) which is the most identical to our provisional diagnosis where both affect skeletal muscles, and present with similar

signs and symptoms. The difference is absence of second wind phenomena, normal CK levels and presence of haemolytic anaemia in GSD VII1.

There were a few peculiarities regarding our case. The patient had a relatively late onset of symptoms occurring in the third decade of his life. The second wind phenomenon (rapid recovery following an initial transient period of progressive fatigue of exercised muscle), which is a very common occurrence in this disease, was found to be absent when inquired about^{3,6}.

A study into the incidence of different manifestations in McArdle's disease patients showed that about 84% of patients recall experiencing symptoms before the age of 10 years and the rest go unnoticed until later in life. The late onset may be due to the patient and/or the family simply attributing the symptoms to "growing pains" of childhood⁷.

The second wind phenomenon was noted to be absent in 22% of the cases possibly due to failure to recognize, although it was always seen with exercise assessment⁷.

More essentially, the muscle biopsy taken from the gastrocnemius muscle came out to be completely normal in our study, contradictory to the diagnosis. Usually, marked subsarcolemmal glycogen deposition in Periodic acid-Schiff (PAS) staining is observed on biopsy of GSD type V3. This may possibly be due to faulty muscle biopsy. Moreover, a study has noted that chances of missing positive results on biopsy may perhaps be due to undertaking the biopsy too soon after an episode of rhabdomyolysis⁷.

Another observation was an elevated serum uric acid level in this patient on investigation. This correlates with the findings of other studies which demonstrate hyperuricaemia and even development of gout in patients with McArdle's disease^{4,8}.

For further evaluation, a repeat muscle biopsy should be undertaken to rule out any systematic error in the previous one. This should preferably be done at least a month after any possible episode of future rhabdomyolysis⁷. Also, other modalities should be employed such as genetic analysis of the PYGM gene. The ischaemic forearm test has been replaced by the non-ischaemic forearm test lately thus it should also be considered in the armamentarium of investigations⁹.

Conclusion

This study shows how McArdle's disease can have atypical clinical as well as positive lab findings. We want to emphasize that rare types of skeletal muscle disorders

should also be considered as differentials in adults presenting with a relevant clinical picture. Together with adequate clinical suspicion and appropriate work up, such pathologies can be diagnosed and managed on a timely basis.

Consent for publication: Consent of the patient was taken for publishing this case report.

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