DOI: https://doi.org/10.53350/pjmhs22165996

ORIGINAL ARTICLE

Mcardle's Disease Complicated by Acute Renal Failure

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ABSTRACT

McArdle's disease is a Glycogen storage disease (type V) which is caused due to the inherited deficiency of myophosphorylase enzyme required for the breakdown of muscle glycogen. It typically presents with complaints of exercise intolerance, early fatigability, and muscle aches. The disease can be complicated by rhabdomyolysis in severe cases.

We present the case of a 27 years old male with McArdle's disease who presented with bilateral lower limbs weakness associated with muscle aches and dark colored urine which later turned into anuria. Diagnosis of acute renal failure complicating rhabdomyolysis in background of McArdle's disease was made.

Keywords: Glycogen storage disease, Glycogen phosphorylase, myopathy, rhabdomyolysis

INTRODUCTION

McArdle's Disease, also known as Glycogenosis type V, is a rare inherited disorder. It is transmitted in autosomal recessive pattern. Mutation of gene PYGM leads to decrease levels of muscle myophosphorylase enzyme causing the disease. Muscle myophosphorylase enzyme is responsible for metabolism of glycogen in skeletal muscle. [1]

Typical symptoms of McArdle's disease include; muscle fatigue, stiffness, tiredness and weakness. Strong co-relation with exercise leading to reduce exercise tolerance is pathognomonic feature of this disease.[2] Here we discuss the case of McArdle's disease complicated by rhabdomyolysis leading to acute renal failure.

CASE REPORT

A 27yrs old male, unmarried, student of Master of Business Administration (MBA) presented to Emergency Department with lower limbs pain, weakness, and decreased urine output. He had no pre-morbid and no hospitalization history previously.

The lower limb pain was started three days back. It occurred when he went for hiking. Pain involved entire lower limbs bilaterally. It was dull in character. It increased in intensity as the time passed. As the pain improved with rest the patient attributed it to fatigue and continued hiking. The pain recurred, increased in intensity and became persistent.

Next day the patient was unable to move his lower limbs. According to him it was weaknesss that lead to this, along with pain which did not subside. Passing of dark urine was also noted by him at this instance. Later he was unable to pass urine at all. He attended nearby healthcare facility for symptomatic relief. Despite intravenous analgesics administration and intravenous hydration, he did not improve and was referred to our hospital emergency.

On further probing, the patient gave history of exercise intolerance, easy fatigability, and dark colored urine after moderate to severe physical activity and during fasting since childhood. According to him these complaints did not bother him as much, as they used to occur transiently and improved without any medical intervention. Family history revealed that his parents were being treated for Type II Diabetes Mellitus. His parents, siblings and relatives did not complain of such illness.

On general physical examination, patient had average built and height. He was well oriented in time place and person. His pulse rate was 96/minute, blood pressure 110/70 mm Hg, respiratory rate 20/min, $Sp0_2$ 97% at room air, and temperature 98.6 F. On lower limb examination no skin changes, muscle wasting, deformity or signs of inflammation were noted. No hypotonia or hypertonia was noted. Power was reduced (1/5) in proximal and distal muscles of lower limbs bilaterally. Planter reflex was down going bilaterally. Rest of neurological, cardiac, respiratory and abdominal examination was unremarkable.

He underwent haematological, metabolic, and other laboratory evaluations. Details in this regard are given in Table I. Nerve conduction studies (NCS) and Electromyography (EMG) were suggestive of myopathy. His forearm ischemia test failed to show any rise in lactate level after 1 minute of muscle activity, which was suggestive of Glycogen storage disease. Muscle biopsy was performed and subsarcolemmal glycogen accumulation was highlighted on PAS (Periodic acid-Schiff) staining, which is hallmark of McArdle's disease.

Table I. Details of laboratory investigations

Blood cp and esr			Normal value
	Haemoglobin	13.6 g/dl	13-18 g/dl
	Mcv	84.9 fl	78-98fl
	Tlc	16.5×10^9/l	$4.0\text{-}11.0\times10^9$/l
	Neutrophils	93.3%	48-77%
	Lymphocytes	3.2%	10-40%
	Platelets	159×10^9/l	$150\text{-}350\times10^9$/l
	Esr	40 mm after 1st hour	0-10mm/hr
Liver function test (lfts)			
	Serum total bilirubin	0.6 mg/dl	0.18-1.23mg/dl
	Alt	560 iu/l	10-50 iu/l
	Alp	87 u/l	40-125 u/l
Renal function test (rfts)			
	Urea	137mg/dl	10.2-36.0mg/dl
	Creatinine	7.9mg/dl	0.6-1.1mg/dl
Serum electrolytes			
	Potassium	4.4meq/l	3.5-4.5meq/l
	Sodium	135meq/l	136-146meq/l
	Chloride	104meq/l	96-106meq/l

Urine r/e			
	Blood	+++	Nil
	Proteins	Nil	Nil
	Rbcss	1-2/hpf	0-3/hpf
	Wbcs	2-3/hpf	0-4/hpf
	Casts	Nil	Nil
Viral serology			
	Anti hcv antibodies	Negative	Negative
Creatinine kinase		>90000 u/l	22-198 u/l
Usg abdomen and kub		1-hemangioma right liver lobe 2-bilateral grade ii renal parenchymal disease 3-spleen size upper normal limit.	

Diagnosis of McArdle's disease complicated with rhabdomyolysis leading to acute renal failure (ARF) was made. Patient was managed with hydration and analgesics. Prophylactic Heparin was administered. Fluid input and output monitored. Hemodialysis was performed for acute renal failure. After 3rd sessions of dialysis, his renal function tests and urine output started improving. Seven sessions of hemodialysis were carried out during his hospital stay. Patient was discharged after 1 month of hospitalization. He is currently on regular follow up. His renal function tests are normal 6 months after the presentation. He has been advised to avoid strenuous exercise, keep himself hydrated and counselled regarding dietary modification.

CASE DISCUSSION

McArdle's disease was first described by Mr. Brain in 1951 and it is the most common glycogen storage disease. [1] Internationally its prevalence is 1:100,000 – 167,000.[3]

The genetics involved in McArdle's disease demonstrates that parents of an affected person are heterozygotes carrying one mutant allele. Heterozygotes (carriers) are mostly asymptomatic. One mutation in the PYGM gene has been identified in case of symptomatic heterozygous patient. Relatively decrease activity of myophosphorylse enzyme with presumptive threshold of 20-40 % is the underlying cause. In pseudo-dominant inheritance pattern, an apparent dominant transmission occurs due to the copulation of a heterozygote with a homozygote. However, in our patient no genetic testing was done nor any of his parents had any feature of McArdle's disease. Myophophorylase deficiency is hallmark of McArdle's disease. The phosphorylase enzyme has three isoforms; brain isoform, liver isoform and muscle isoform i.e., myophosphorylase. The fetal muscles contain both liver and brain isoenzymes that are gradually replaced by myophosphorylase during muscle maturation process. Hence, the only form in adult muscle fibers is the myophosphorylase. Myophosphorylase enzyme is responsible for glycogen breakdown and energy provision required for sustained muscular activity. PYGM located on chromosome 11 controls production of myophosphorylase enzyme. The enzyme has two identical subunits of 97,000 Daltons each making it a homodimer. The dimers associate into a tetramer to form the enzymatically active phosphorylase A. The N-terminal domain extends from amino acid residue 1 to 482 ("regulatory" domain) and the C-terminal domain extends from residue 483 to 842 ("catalytic" domain).[4] About 130 mutations in this gene have been documented. Arg50Ter or R50Xnumber of mutations are commonly noted in North American and European populations. PYGM mutation leads to early termination of translation amino acids in PYGM protein. Protein produced by the mutated gene contains less amino acids. The myophosphorylase enzyme is nonfunctional, unstable, and is rapidly degraded.[5]

McArdle's disease has a typical presentation occurring in teenage years. Atypical presentations can occur at birth, infancy, sixth and seventh decade. Sufferers may be asymptomatic but have elevated creatinine kinase levels.[1] Our patient developed symptoms at the age of 10 years.

Common presenting features of McArdle's disease include; muscle stiffness, weakness, fatigue, and muscle pains. Disease affects exercise tolerance ability of patients. At rest and during low intensity aerobic exercise, oxidative phosphorylation of free fatty acids is the source of energy for skeletal muscles. In McArdle's Disease absence of muscle glycogen phosphorylate will alter the utilization of muscle glycogen stores leading to exacerbation of symptoms during anaerobic metabolism.[6] Triggering factors for rhabdomyolysis include exertion, ischemic, temperature, metabolic or inflammatory injuries and other genetic factors.[2]

Second wind phenomenon is an interesting feature of the disease. It is characterized by symptomatic improvement after 7-8minutes of exercise. It is due to utilization of non-muscular energy substrates i.e., glucose and free fatty acids for energy production along with increased blood flow.[7] Rhabdomyolysis and myoglobinuria can complicate McArdle's disease. Myoglobinuria causes tubulointerstitial nephritis.[6] It can be associated with urine discoloration, renal failure, and confusional status. [1]

Persistent rise in creatinine kinase (CK) level is a characteristic of McArdle's disease. For diagnosis of McArdle's disease forearm exercise lactate test, muscle biopsy, and genetic analysis can be done.[8] For patients with suspicion of glycogen storage disease, muscle enzyme function can be evaluated by caring out minimal ischemia test.[9] In this test, baseline venous sample is obtained and then sphygmomanometer cuff is inflated around the arm to occlude brachial artery. It is released after 1 minute of mild to moderate muscle activity and subsequent blood samples are taken at 1, 5, and 10 minutes. Normally there is an increase of three-folds to five-folds in the level of serum lactate after 1 minute of cuff release, after which it falls gradually. In McArdle's disease impaired glycogen breakdown will lead to decreased level of lactate in blood.[10] In muscle biopsy the hallmark finding in favor of McArdle's disease is glycogen deposits along with the deficiency or absence of myophosphorylase enzyme.[8] In our patient soleus muscle biopsy was done. Subsarcolemmal glycogen accumulation was highlighted on PAS staining. Genetic testing demonstrates the type of mutation in PYGM gene differentiating homozygous and heterozygous mutations.[8] However, genetic testing was not done in our patient.

There is no definitive curative therapy for the disease. The essential milestones of treatment include life style modifications like moderate physical activity, intake of rapid absorption sugars prior to exercise initiation, high protein and sucrose diet, vitamin B6 supplementation, and gene replacement therapy. However intense sustained exercise should be avoided.[1,11]

Glycogen storage disease have a drastic effect on the quality of life because of limitation in daily activities but in most of the cases it does not alter life expectancy.[1] In our patient, McArdle's Disease lead to acute renal failure requiring renal replacement therapy.

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