A BRIEF REVIEW ON MCARDLE DISEASE (GLYCOGEN STORAGE DISEASE TYPE V)

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ABSTRACT
McArdle disease is also referred as glycogen storage disease type V is a myopathy caused by an inherited deficiency of myophosphorylase, an enzyme responsible for the breakdown of glycogen and it is a disease of childhood or adolescence. The disease is most common muscle glycogenosis in which patients experience reversible exercise intolerance, acute crises (fatigue and contractures), myoglobinuria and rhabdomyolysis due to static muscle contractions like weightlifting or dynamic exercise like climbing stairs or running. This review emphasizes on the main features of McArdle disease including etiology, epidemiology, sign and symptoms, pathophysiology, diagnostic parameters and management with pharmacological treatments and nutritional supplement for improving exercise performance and quality of life in McArdle disease.

KEYWORDS: McArdle disease, myophosphorylase, fatigue, myoglobinuria, exercise, nutritional supplement.

INTRODUCTION
McArdle disease or glycogen storage disease type V (GSD-V) also known as Glycogenosis type V is an uncommon hereditary metabolic disease and is characterized by muscle phosphorylase deficiency.[1] Myophosphorylase is an important enzyme of carbohydrate metabolism that converts glycogen to glucose-1-phosphate.[2] McArdle disease is a disorder of muscle metabolism caused by the absence of the glycolytic enzyme, muscle phosphorylase. Deficiency of myophosphorylase in muscle reduces adenosine triphosphate (ATP) formation by glycogenolysis which results in accumulation of glycogen.[3] A person suffering from McArdle syndrome suffers from the inability to break down glycogen. Myophosphorylase deficiency is transmitted as a recessive autosomal trait with symptoms usually starting in childhood or adolescence.[4] Patients experience exercise intolerance with premature fatigue, myalgia, and cramps (contractures) during exercise.[1, 5] Myoglobinuria occurs in some of the patients while some suffer from acute renal failure.[4, 6-8] Brian McArdle presented first patient with exercise induced myalgia and failed to produce rise in blood lactate during ischaemic forearm exercise.[9]
In 1959 muscle phosphorylase was discovered and its deficiency was associated in McArdle disease.\textsuperscript{[10, 11]} The muscle glycogen phosphorylase activity in the majority of affected individuals is absent and in a few patients 20\% to 30\%enzyme levels are reduced.\textsuperscript{[12]} In McArdle disease oxidative phosphorylation is impaired due to low substrate flux through the tricarboxylic acid (TCA) cycle because of absence of pyruvate from glycolysis and reduces the rate of formation of acetylCoenzyme and affects the TCA cycle. Due to decrease in oxidative phosphorylation oxygen consumption reduced to 35\% to 40\% of that observed in normal muscle. It may lead to partial ischaemia and increase in heart rate and ventilation rate.\textsuperscript{[13, 14]}

**ETIOLOGY**

McArdle syndrome is caused by mutations in a \textit{PYGM} gene, which encodes myophosphorylase and it result in lack of functional mature protein and the gene is responsible for making the enzyme glycogen phosphorylase so the body cannot break down glycogen in the muscles.\textsuperscript{[15]} This disease is an autosomal recessive genetic disorder that means one must get a copy of the nonworking gene from both parents but person who gets a nonworking gene from only one parent usually does not develop this syndrome and family history of McArdle syndrome increases the risk of the disease.\textsuperscript{[16]} Myophosphorylase is the form of the glycogen phosphorylase found in muscle and failure of this enzyme impairs the operation of ATPases. This is due to the lack of normal pH fall during exercise which impairs the creatine kinase equilibrium and exaggerates the rise of adenosine diphosphate (ADP). The enzyme phosphorylase is needed to catalyse reactions to convert stored glycogen to glucose for anaerobic muscle work. Muscle work performed at 50\% of maximal oxygen consumption is anaerobic and hence oxygen is not used. In McArdle’s disease, persons lack the enzyme hence glycogen accumulates in muscle tissue. Alternative fuel sources include fat and energy rich phosphates (adenosine triphosphate, phosphocreatine). Fat is mainly used in low intensive exercise and at rest while phosphates supply energy for short duration muscle work up to 30 seconds. Exercise intensity should be moderate otherwise intensive muscle work may result in muscle cell energy crisis and muscle cell degeneration. Damaged muscle cells may leak substances into the blood such as electrolytes like potassium, enzymes like myoglobin and phosphocreatine. The gene coding for the enzyme myophosphorylase is located on chromosome 11 (11q13) and is known as \textit{PYGM}. Two mutations in this gene explain more than 50\% of all cases of McArdle’s disease, but several other PYGM mutations also cause complete or partial myophosphorylase deficiency. There is considerable heterogeneity in the severity of symptoms even in individuals having the same genetic mutation. It includes modifying genes such as the angiotensin converting enzyme gene.
(ACE) and alpha actinin 3 (ACTN3) genes, differences in lifestyle, diet, fitness and aerobic capability. [17]

Heredity

McArdle’s disease is a hereditary autosomal recessive disorder as shown in figure 1. That means that both the parents of a child with the syndrome are healthy carriers of the mutated gene. If both parents are healthy carriers then 25% risk that child will inherit the disease. In 25% of the cases the child will not inherit the disease and not become carrier of mutated gene. In 50% of the cases the child will inherit one recessive mutant gene and like the parents he or she will be a healthy carrier. If one parent is not a carrier but the other has an inherited autosomal recessive disorder (two defective genes) the children will be carriers of the defective gene but the condition will not affect them. If an individual with an inherited autosomal recessive disorder has a child with someone who has one copy of the defective gene, there is a 50% risk that the child will develop the condition, while in 50% of the cases the child will be a healthy carrier. [18]

![Autosomal recessive inheritance of McArdle syndrome](image)

**Figure 1. Autosomal recessive inheritance of McArdle syndrome**

**EPIDEMIOLOGY**

There is variability in the clinical manifestation of the disease in individuals even between the affected relative subjects. The time of onset of the symptoms and the degree of exercise intolerance will vary between the patients in early or late childhood and in adulthood. Patients are oligosymptomatic in rare cases and are correctly diagnosed because of having an affected relative while the disease is profoundly incapacitating in other patients. [19] The first patient
reported with the disease was a 30-year-old male in 1951 by the British physician Brian McArdle. 
\[20\] Incidence of the disease is approximately 1 in 100,000 as same as glycogen storage disease type I. \[21\] A few hundred cases have been reported but the disorder is under-diagnosed because of the mild symptoms in many patients. \[22\] The incidence of all glycogen storage diseases is about 2.3 children per 1,00,000 births per year. \[23\]

**SIGNS AND SYMPTOMS**

The onset of the disease is usually noticed in the childhood but not diagnosed until the third or fourth decades of life and it is difficult to distinguish these symptoms from childhood. \[24\] McArdle syndrome symptoms include early fatigue, painful cramps, exercise intolerance with myalgia, exercise intolerance and myoglobinuria. Myoglobinuria results from rhabdomyolysis; a condition characterized by breakdown of muscle cells and leakage of contents into the bloodstream. The patients may exhibit a symptom known as second wind phenomenon which is characterized by the patient’s better tolerance for aerobic exercise including walking and cycling after approximately 10 minutes and that leads to increased blood flow and the body ability to find alternative sources of energy like proteins and fatty acids. \[25\] After a long time, patients may exhibit renal failure due to the myoglobinuria and with increasing age, weakness and muscle loss increases. Patients with muscles contractures and pain require assessment for rhabdomyolysis as it leads to acute renal failure in about 30% of the cases and if left untreated can be life threatening. While in some cases compartment syndrome may develop which require quick surgical referral. Symptoms of McArdle syndrome includes Exercise intolerance with poor stamina, Muscle cramps and muscle pain, Muscle stiffness, Muscle weakness, Muscle contractures, Fatigue, Myoglobinuria (urine appears Burgundy-colored), Second wind phenomenon, Compartment syndrome and Acute renal failure. \[16\]

**PATHOPHYSIOLOGY**

Myophosphorylase is an enzyme involved in the breakdown of glycogen to glucose in muscle and removes 1, 4-glycosyl residues from the outer branches of glycogen and adds inorganic phosphate to form glucose-1-phosphate. After phosphorylation myophosphorylase is in the active form. During glycogen breakdown, cells form glucose-1-phosphate instead of glucose because the glucose which is polar and phosphorylated cannot cross the cell membrane and is marked for intracellular catabolism. In normal persons, glucose-1-phosphate is converted into glucose-6-phosphate which undergoes glycolysis and results in pyruvate production. Muscle pyruvate can be converted to lactate in hypoxic conditions and then released to the blood at a similar rate to its production. Most of the pyruvate crosses the mitochondrial membrane and
converted into acetyl-CoA and enters into the citric acid. But patients with McArdle syndrome are unable to obtain energy from their muscle glycogen stores due to myophosphorylase deficiency. However, only upstream glycolysis is blocked and still the skeletal muscle fibers can take up glucose from the blood and convert it into glucose-6-phosphate, which then enters the downstream steps of glycolysis. Hence, glycolysis is not totally impaired in patients and carbohydrates ingestion before exercise can improve exercise tolerance.

**DIAGONOSIS**

The following laboratory tests are used in the diagnosis of GSD-V:

1. **Muscle biopsy**- It indicates the absence of myophosphorylase in muscle fibers while in some cases microscopy shows the presence of acid-schiff stained glycogen.

2. **Genetic sequencing**- Genetic sequencing of the PYGM gene which codes for the muscle isoform of glycogen phosphorylase is done to determine the presence of gene mutations and it indicates whether disease is present or not. This test is less invasive than a muscle biopsy and involves bidirectional sequencing of the coding regions of all 20 PYGM exons and add about 50 Bpof non-coding flanking DNA on each side. The test has two tiers and since the disease consists of two gene mutations, carriers of the disease are also identified. Tier 1 involves sequencing of exons 1 and 5 and if two likely causative mutations are detected in patients in Tier 1 or one mutation carriers in Tier 1, then the testing stops. Otherwise, testing is continued with Tier 2 involving sequencing the remaining 18 exons.

3. **Ischemic forearm exercise test**

4. **No ischemic test**- It involves no reduction of the blood flow to the exercising arm while the failure of lactate in venous blood and exaggeration of ammonia levels are found in the disease which indicates a severe muscle glycolytic block.

5. **Creatine kinase (CK)** - CK levels are increased in 90% of the patients. Normal range of CK is about 60 to 400IU/L while patient with McArdle syndrome has CK level about 5,000 IU/L at rest and with muscle exertion increased up to 35,000 IU/L. Hence, it distinguishes McArdle’s syndrome from carnitine palmitoyltransferase II deficiency (lipid based metabolic disorder which prevents fatty acids transported into mitochondria for use as an energy source).

6. **Serum electrolytes and endocrine studies**- Studies such as growth hormone level, thyroid function and parathyroid function can be tested to check the presence of disease.

7. **Urine studies**- Urine studies are required if rhabdomyolysis is suspected then urine volume, urine sediment and myoglobin levels are measured. And if rhabdomyolysis is present then
creatine kinase, lactate dehydrogenase, serum myoglobin, electrolytes and renal function are measured. Some other tests are also performed like Electromyography, Magnetic resonance imaging (MRI) and Lactic acid in blood.\[16]\n
The definitive diagnosis is made by muscle histochemistry and the finding of absent functional muscle phosphorylase. In some cases DNA analysis for the common mutations can give an unambiguous diagnosis.

**TREATMENT**

There is no specific therapy for McArdle disease but mainly aerobic exercise and high protein diets are preferred. Benefit from specific nutritional or pharmacological treatment still needed to be found.

**Pharmacological treatment**

Various placebo controlled trials has been conducted with more than 5 patients. Pharmacological interventions include ACE inhibitors and dantrolene sodium.\[32, 33\] Dantrolene sodium has produced positive effect in reducing exertional myalgia in one McArdle patient.\[34\] The efficiency of muscle adaptation is may be due to ACEpolymorphic variants. Polymorphisms leading to insertions or deletions can alter muscle performance after exercise. The I allele is associated with reduced ACE activity shows improved performance after aerobic exercise. ACE polymorphism insertions or deletions could affect phenotypic severity.\[35\] The ACE inhibitors might improve efficiency in McArdle disease. In McArdle disease, the primary genetic abnormality is a missense mutation in the PYGM gene leading to a stop codon and aminoglycoside may allow the potential to read through stop codons and may induce the synthesis of a fulllength protein.\[36\] This novel therapeutic strategy may be explored with new pharmacological compounds for McArdle disease.

**Nutritional treatment**\[37-54\]

Nutritional treatment includes Vitamin B6 (pyridoxine)supplementation, D-ribose supplementation or creatine supplementation and carbohydrate rich diet, oral administration of branched chain amino acids or sucrose or intravenous glucose infusion before exercise. Low dose creatine supplementation about 60 mg/kg/day for 4 weeks can increase tolerance to ischemic exercise in McArdle diseasepatients but higher doses 150mg/kg/day may worsen myalgia. A high protein diet improves the exercise capacity in patients. The most beneficial intervention is achieved by diet with 65% of complex carbohydrates (pasta, vegetables, cereals, fruits, bread and rice) and 20% of fat and 30-40g of glucose, fructose or sucrose ingestion in adults. Research is going on to increase the availability of these substrates through
supplementation or dietary modification. At least 80% of vitamin B6 (pyridoxine) in skeletal muscle is bound to phosphorylase and in McArdle disease vitamin B6 is less. For amino acid metabolism, a number of enzymes require the active form of vitamin B6 as an co-factor. Creatine supplementation may increase the availability of ATP from ADP and increase the exercise capacity and strength in people with mitochondrial myopathies. Magnetic resonance spectroscopy studies showed reduction in phosphocreatine level with exercise so creatine supplement might be useful. Facilitation of oxidative metabolism with exercise, diet or drugs might increase the availability of a second wind. An intravenous glucose infusion during exercise enables glycolysis which will regulate oxidative phosphorylation.

**Advice to patients**

Avoid anaerobic or sustained exercise like pushing and lifting and take regular mild exercise such as walking or cycling.\[^{55,56}\] Patients should not exercise in severe pain as it may leads to myoglobinuria and acute renal failure and for treatment drink plenty of fluids and monitor urine excretion. Maintain weight to normal level and maintain physical fitness to control the symptoms and improvement of quality of life. Anesthetists should be aware about diagnosis of McArdle's disease and avoid some anaesthetic agents. Tourniquets should not be used during surgeries in McArdle's disease patients.\[^{57}\]

**CONCLUSION**

McArdle disease or glycogen storage disease type V is an uncommon hereditary metabolic disease and is characterized by muscle phosphorylase deficiency and person is unable to break down glycogen. Myophosphorylase deficiency is transmitted as a recessive autosomal trait. The mutation in gene coding for the enzyme myophosphorylase is located on chromosome 11 (11q13) and is known as *PYGM*. Two mutations in this gene explain more than 50% of all cases of McArdle’s disease. Diagnosis tests includes Muscle biopsy, Genetic sequencing, Ischemic forearm exercise test, No ischemic test, Creatine kinase, Serum electrolytes, endocrine studies and Urine studies. There is no specific therapy for McArdle disease but mainly aerobic exercise and high protein diets are preferred. Benefit from specific nutritional or pharmacological treatment still needed to be found. Nutritional treatment includes Vitamin B6, D-ribose or creatine supplementation and carbohydrate rich diet, oral administration of branched chain amino acids or sucrose or intravenous glucose infusion before exercise.
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