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Mcardle’s disease (Glycogen storage disease type V)

Synonyms: McArdle's syndrome, myophosphorylase deficiency, muscle glycogen phosphorylase deficiency, PYGM deficiency

McArdle's disease is caused by myophosphorylase deficiency (glycogen storage disease type V), first described by Brian McArdle in 1951. Most patients with McArdle's disease have undetectable myophosphorylase activity and are therefore unable to release glucose from glycogen in muscle.

See also the article on Glycogen Storage Disorders.

How common is McArdle’s disease? (Epidemiology)

- A rare autosomal recessive disease, with heterozygotes being asymptomatic.
- The gene for myophosphorylase (PYGM) is on chromosome 11.[1] Mutations are spread throughout the gene and there is no clear genotype:phenotype correlation.[2]
- It is now known as one of the most common disorders of muscle metabolism, with an estimated prevalence of approximately 1 per 100,000 people.[3]
- In the UK approximately 1 person in 280,000 is diagnosed, and it is believed that many people remain undiagnosed.[4]

McArdle’s disease symptoms[3]

The majority of patients with McArdle's disease first present in the first decade of life but are only diagnosed in the third or fourth decade of life. One review found that about 4% of cases are diagnosed before 10 years of age and about 50% are diagnosed between 10–30 years of age. The main symptoms are often tiredness, cramping and exercise intolerance.[5]

Presentation

- Clinical presentation and severity are very variable but patients typically experience reversible exercise intolerance, fatigue and acute crises (severe fatigue and painful muscle cramps, sometimes with rhabdomyolysis and myoglobinuria) triggered by static muscle contractions (eg, lifting weights) or dynamic exercise (eg, climbing stairs or running).[6]
- Following a period of careful pacing and/or rests (the initial pain usually subsides within less than one minute), after about 8 minutes most patients achieve a 'second wind' and can then continue exercise with less difficulty.
- Symptoms tend to worsen with age as weight increases and aerobic fitness is reduced.
- Fixed muscle weakness and wasting may occur, particularly in older patients.

Symptoms

- Diagnosis is suggested by the history.
- People with McArdle's disease develop severe muscle cramps and fatigue in the first few minutes of activity.
- Individual presentation can be unique.
- Some adults develop a progressive proximal weakness.
- Some adults develop a fixed motor weakness.
- The so-called 'second wind' phenomenon universal to all patients but some may not recognise it.

- About one half of all patients will have experienced myoglobinuria (dark urine) following intense exercise.

Signs

- Clinical findings may be absent on physical examination. Muscle strength and reflexes may be normal.
- In later adult life, persistent proximal weakness and muscle wasting may be present.

Differential diagnosis

- Glucose intolerance.
- Glucose-6-phosphate dehydrogenase deficiency.
- Other glycogen storage diseases.
- Liver failure.
- Hypoglycaemia.
- Other causes of fatigue.

Investigations

- Creatine kinase levels are elevated in more than 90% of patients with McArdle's disease at rest.
- A history of painful muscle cramps that occur within a few minutes of initiating activity and which subside rapidly with rest, in conjunction with a raised serum CK, is highly suggestive of McArdle's disease.[7]
- Blood urate levels may be raised.
- There is no increase in venous lactic acid levels following exercise testing.
- Urine studies are indicated because myoglobinuria may occur after exercise.
- In the UK, "hot spot" DNA testing for the two most common mutations can be arranged through the national McArdle Service. Up to 85% of patients can be confirmed without muscle biopsy.[4]

- Electromyography: may show nonspecific myopathic changes or increased muscle irritability. Electrical activity may be absent during exercise-induced muscle cramps.
- Diagnosis is by a muscle biopsy, which shows an excess of glycogen and absence of the muscle enzyme phosphorylase.[4]
- DNA testing then provide genetic confirmation.[4]

McArdle's disease treatment and management

- No specific treatment exists. There is no evidence of significant benefit from any specific nutritional or pharmacological treatment in McArdle's disease.[8]
- Anaesthetists should be made aware of the diagnosis of McArdle's disease, and may choose to avoid certain anaesthetic agents.[4]
- Tourniquets should not be used during operative procedures in patients with McArdle's disease.[4]

- Advice to patients:
    - It is important to avoid strenuous (anaerobic or sustained) activity, including lifting or pushing.[4]
    - Patients should not continue to exercise in the presence of pain, as this may increase the risk of rhabdomyolysis with myoglobinuria and subsequent acute kidney injury.[6]
    - However, regular aerobic exercise seems to be beneficial.[8] It is important to take regular gentle exercise, such as walking or cycling. Keeping physically fit is the most effective way of controlling the symptoms of McArdle's disease and improving quality of life.
    - If an episode of myoglobinuria occurs, the patient should drink plenty of fluids.[4]
    - The patient should seek medical attention immediately if they feel unwell or stop producing urine.[4]
    - Excessive weight gain should be avoided, as increased weight lowers the aerobic threshold and increases the effort of exercise.[4]
- Although there is some evidence of benefit with creatine, oral sucrose, ramipril and a carbohydrate-rich diet, there is no strong evidence to indicate significant clinical benefit.[9]
- There are some reports that vitamin B6 may be beneficial.[10]

Complications

- Severe rhabdomyolysis may lead to acute kidney injury.[1] Progression to chronic kidney disease has not been described.
- Seizures may occur but are extremely rare.
- Potential hyperuricaemia; overproduction of adenosine monophosphate (AMP), with accelerated liberation of hypoxanthine and xanthine into the blood, possibly leading to hyperuricaemia.[6]

Prognosis

- McArdle's disease is a chronic but often relatively benign disorder.
- There does not seem to be any adverse effect on pregnancy and childbirth.[4]

Preventing McArdle's disease

- Genetic counselling is appropriate for all individuals with a genetic disorder.

Further reading

- International Association for Muscle Glycogen Storage Disease

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