

## McArdle Disease

by Kristen Nowak

Glycogen storage disease type V, glycogenosis type V, or myophosphorylase deficiency is perhaps better known as McArdle Disease, named after the first clinician who described it in 1951, Brian McArdle. McArdle Disease affects skeletal muscles and is disease #232600 in Online Mendelian Inheritance in Man (<http://omim.org/>). McArdle disease patients usually have exercise intolerance to muscle contractions that are static or isometric (such as lifting a heavy weight), and to dynamic exercises (such as running or climbing up stairs). They have crises of early fatigue, contractures, myalgia (muscle pain), and sometimes myoglobinuria (the presence in urine of myoglobin, a breakdown product of muscles, making it brown/red in colour) induced by physical exertion.

The disease severity varies a lot between patients, even those from the same family. The typical age of onset can vary from early or late childhood to adulthood, and whilst some patients exhibit few symptoms, for others their disease can be severely incapacitating. For severely affected patients, even mild activities such as brushing teeth or chewing gum can cause muscle pain, weakness and stiffness.

McArdle Disease is not normally life threatening, with some exceptions. If a patient keeps exercising even despite severe pain, the risk of myoglobinuria and then subsequently acute kidney (renal) failure increases. Despite renal failure being reversible in almost all cases, it still requires emergency intervention. Therefore it is recommended that patients avoid any exercise that causes them severe pain, however some low to medium intensity dynamic exercises are often prescribed therapeutically.

All patients have a “second wind” phenomenon. When they commence aerobic exercise involving large muscles (eg cycling, walking) they experience breathlessness, extreme fatigue and a fast heart beat, but after ~10mins, an obvious improvement is seen in their tolerance to exercise. Thus often if patients have a short break when symptoms occur, they are able to resume the exercise they were performing.

Muscle biopsies of patients show deposits of the energy store glycogen, and are negative for the enzyme myophosphorylase. This is because patients with McArdle disease have defects (mutations) in both copies of their skeletal muscle glycogen phosphorylase gene known as *PYGM*. This gene usually produces the enzyme myophosphorylase (also known as muscle glycogen phosphorylase), but patients with McArdle disease do not produce any functional myophosphorylase enzyme. McArdle disease is a recessive disease, which means that people need both copies of their *PYGM* gene to be defective in order to have the disease. Carriers of the disease (those with only one defective gene) are not usually affected.

The myophosphorylase enzyme is the first enzyme in the process used to breakdown glycogen stores in skeletal muscle. As McArdle patients do not have this enzyme their body cannot perform this step, and thus they are not able to use their muscle glycogen stores to produce energy. However patients are able to uptake glucose from their bloodstream and use that as an energy source instead, and therefore many patients find benefit from ingesting carbohydrates before exercise to increase their tolerance to exercise.

McArdle Disease is one of the most common genetic muscle diseases, affecting both males and females, with a prevalence up to 1 in 100,000 people, and ~1 in 158 people are carriers of the disease. Since the first defects in the *PYGM* gene was described in 1993, more than 100 different defects in this gene have been identified. The commonest defect is known as the p.R50X mutation, with up to 72% of McArdle Disease patients having it in some populations. However, other *PYGM* defects are more frequent in certain populations, such as the Spanish, Japanese and Finnish people. This information is important for genetic testing.

Despite a range of therapeutic approaches investigated and a collection of randomized placebo controlled human clinical trials, not effective treatment for McArdle Disease currently exists. However patients do benefit from carefully designed types of exercise training, and a diet high in complex carbohydrates that provides their muscles with a ready supply of blood glucose to enable them to exercise more effectively.