

## McArdle Disease and Pregnancy

### Doença de McArdle e Gravidez

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#### Abstract

McArdle disease is a hereditary skeletal muscle disorder caused by myophosphorylase deficiency. This syndrome is characterized by exercise intolerance, fatigue, myalgias, cramps, and weakness. It is a rare disease, with few reported cases of pregnancy in women with this condition. Despite not having specific treatment, adequate physical activity can improve patient symptoms and prevent acute rhabdomyolysis. We present a case of a pregnant woman with McArdle disease. During pregnancy there was an improvement of exercise tolerance and creatine kinase levels. This case report illustrates our experience regarding the management of pregnancy and labour in women with McArdle disease.

**Keywords:** Pregnancy; McArdle; Glycogen.

#### INTRODUCTION

McArdle disease is a rare hereditary type V glycogen storage disease characterized by myophosphorylase deficiency. Patients with McArdle disease typically exhibit exercise intolerance, fatigue, myalgias, cramps, and weakness since childhood. There are very few published case reports of pregnant women with McArdle disease. This case report contributes to the improvement of medical knowledge regarding the impact of McArdle disease in pregnancy and delivery. It also helps understanding the behaviour of this disorder during pregnancy, allowing us to plan the adequate surveillance and approach.

#### CLINICAL CASE

A 35-year-old, Caucasian woman, primigravida, at the fourteenth week of gestation was referred to the Maternal-Fetal Medicine Unit. The patient had McArdle disease, a hereditary glycogen storage disorder. She complained of fatigue, muscle cramps, weakness and poor exercise tolerance during sport activities. Al-

though she experienced these symptoms since childhood, the diagnosis was only confirmed in early adulthood. The diagnosis was suspected after an acute episode of rhabdomyolysis and myoglobinuria following intense physical activity. An extensive investigation was conducted, which included a muscle biopsy that revealed increased glycogen and absent myophosphorylase enzyme. Subsequently, a genetic test was performed confirming the diagnosis of McArdle disease.

The patient also reported other pathologic antecedents, such as recurrent tonsillitis and allergic rhinitis. No other cases of McArdle disease were known in the family.

Throughout the pregnancy, the patient had regular appointments at the Maternal-Fetal and Neurology units. The patient reported increased tolerance to exercise, improvement of muscle cramps and had no further episodes of myoglobinuria and rhabdomyolysis. She managed to stay physically active until the end of pregnancy. The patient was advised that aerobic exercise was important since it would help her to remain physically active and keep weight under control. She was informed that she should avoid anaerobic activity, such as lifting heavy weights or sprinting, because it could cause muscle breakdown and pain.

First trimester combined screening revealed low risk for aneuploidy. Blood tests carried out during the first

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trimester showed elevated CK levels (1097 UI/L) (the normal values are 29-168 UI/L), lower than pre-conception values. CK levels normalized and remained low after 24 weeks of pregnancy. An echocardiogram and respiratory functional tests were conducted, but no alterations were evident. The remaining pregnancy ultrasounds and blood tests were normal.

At 38 weeks of pregnancy, she was admitted to the Obstetric Department with the diagnosis of non-reassuring fetal heart rate on the cardiotocography and breech presentation. Thus, the delivery was by caesarean section with loco-regional anaesthesia. The procedure occurred without complications. The newborn was a male infant weighing 3180 g with Apgar score of 9 at 1<sup>st</sup> minute, 10 at 5<sup>th</sup> minute. After delivery, the patient remained asymptomatic, but CK levels started rising, reaching 1352 UI/L at the fourth week postpartum. At the postpartum appointment the patient reported muscle weakness and exercise intolerance, so we recommended an increase in carbohydrate ingestion and hydration to improve tolerance to everyday activities and prevent exercise-induced episodes of muscle injury. She also had follow-up appointments for McArdle disease at the neurology department.

## DISCUSSION

McArdle disease, also known as type V glycogen storage disease, is a hereditary myopathy first described in 1951 by Brian McArdle<sup>1,2</sup>. Although one of the most common glycogen storage disorders, it is a rare disease with a worldwide prevalence of 1/100000.<sup>3</sup>

McArdle disease is an autosomal recessive disorder caused by mutation of both alleles of PYGM gene, located at chromosome 11q13 that encodes for the muscular isoform of myophosphorylase enzyme. Heterozygous individuals, with mutation in one of the alleles, are often asymptomatic, despite a slight reduction of the level of enzyme function. The cardiac and hepatic enzyme isoforms are not affected, and the clinical manifestations are restricted to pure myopathy<sup>1,2,4</sup>.

Myophosphorylase is an enzyme that plays a key role in glycogen degradation at the muscle cell. Glycogen is converted by myophosphorylase in glucose 1-phosphate and later into pyruvate that is used for energy generation through aerobic or anaerobic metabolism depending on the oxygen supply. As consequence of myophosphorylase deficiency, muscle cells are unable to use glycogen storage as an energy source

during exercise. This explains why McArdle patients develop stiffness, tiredness and muscle pain after exercise. However, skeletal muscle cells maintain the ability to use blood glucose, therefore daily activities are easily done by these patients<sup>1-5</sup>.

There is a great phenotypic heterogeneity in McArdle disease. The age of presentation and severity of the symptoms are variable. It usually presents during adolescence or early adulthood<sup>1,4,6</sup>.

Symptoms include exercise intolerance, fatigue, myalgia, cramps, muscle swelling, and weakness since childhood. Patients with McArdle disease typically exhibit intolerance to intense isometric and dynamic exercise<sup>1,4,6</sup>. Severe acute disease can be incapacitating and patients may present acute renal failure due to rhabdomyolysis after intense exercise<sup>1,4,5</sup>. As mentioned previously, the patient was diagnosed during early adulthood following an acute episode of rhabdomyolysis.

The “second wind” phenomenon is a pathognomonic manifestation of McArdle disease. This phenomenon consists of an improvement of exercise tolerance after a rest phase, which can be explained by an increase in muscle vascularization and glucose and fatty acids supply, becoming less dependent on glycogen use. These patients may improve exercise tolerance if there is a previous ingestion of carbohydrates<sup>1,2,5</sup>. Although “second wind” phenomenon is a specific finding of McArdle disease, our patient did not mention it. Our finding is concordant with previous reports found in the literature<sup>2</sup>.

McArdle disease diagnosis includes clinical, laboratory and genetic findings. Common laboratory findings include myoglobinuria and elevated CK. Even at rest, 99% of the patients have elevated CK levels<sup>1,2,6</sup>. When clinical history is suggestive of McArdle disease, the diagnosis may be confirmed with a non-invasive test, the non-ischemic forearm muscle exercise testing, or an invasive approach such as muscle biopsy. If these exams show alterations, genetic testing of PYGM should be performed to confirm the diagnosis. Molecular diagnosis of McArdle disease can be difficult, since there are more than 100 different mutations described in the literature<sup>1,2,4,6</sup>.

There are no specific therapeutic approaches for McArdle disease patients. Rich-carbohydrate diet before aerobic exercise improves exercise tolerance. Some studies have shown the benefits of low intensity aerobic exercise. There are other treatments such as creatinine supplementation, angiotensin-converting en-

zyme (ACE) inhibitors and vitamin B6 supplementation. Nevertheless, their benefits are yet to be proven<sup>1,2,5,10</sup>.

McArdle disease is very uncommon in pregnant women. The number of reported cases is very limited due to the rarity of this disease in the overall population<sup>8,9</sup>. In 1973, Cochrane and Alderman presented the first report of this condition in pregnant women<sup>7</sup>.

During pregnancy our patient reported an improvement of exercise tolerance and other symptoms, such as muscle cramps and weakness. Furthermore, no acute episodes of rhabdomyolysis or signs of pregnancy complications were observed. The majority of cases described in the literature corroborate this improvement of exercise tolerance and rhabdomyolysis, but there is not enough data to explain these findings<sup>5,7-11</sup>. In a prospective clinical study published in 2010, where 14 pregnant women were studied, only 2 reported worsening of the symptoms<sup>10</sup>. Many studies have shown that McArdle disease is not a risk factor for pregnancy and delivery complications<sup>5,7-10</sup>. We could not find in literature specific protocols for pregnancy surveillance, CK level measurement or other control tests in women with McArdle disease. Currently, there is no scientific evidence that recommends prenatal genetic testing to determine if the newborn will be affected. McArdle disease is a rare autosomal recessive condition, without debilitating or severe symptoms, therefore it has no indication for prenatal diagnosis<sup>4</sup>.

Women with this condition do not have an increased risk of caesarean and may have a vaginal delivery. Several case reports describe women with normal uterine contractility during labour<sup>5,7,9,10</sup>. Literature recommends intravenous glucose administration during labour to prevent an acute episode of rhabdomyolysis<sup>11</sup>.

McArdle patients have an increased risk of malignant hyperthermia after the administration of some anaesthetics that cause neuromuscular blockade. Other anaesthesiologic problems include rhabdomyolysis, myoglobinuria and acute renal failure. When a caesarean is needed, loco-regional anaesthesia is desirable. Our patient was submitted to a caesarean section under regional anaesthesia, in order to prevent these anaesthetic complications<sup>12</sup>.

Available medical literature describes a very limited amount of cases of pregnant women suffering from McArdle disease, thus stressing the relevance of this report as an essential contribution to the overall knowledge of this condition. It reinforces the importance of

close surveillance during pregnancy and labour of women with McArdle disease so as to prevent complications.

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