McArdle’s disease: an underestimated or underdiagnosed myopathy in rheumatologic practice? Cases series and literature review

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OBJECTIVE: McArdle's disease is a metabolic myopathy that manifests with varied clinical conditions and is often confounded with other diagnoses. Herein, the authors report a case series and carry out a literature review.

METHODS: A cross-sectional single-center study evaluating 12 patients with McArdle’s disease was conducted.

RESULTS: Mean age at onset of symptoms was 28.0±17.4 years, while age at disease diagnosis was 39.0±14.8 years. History of intolerance to physical exercises was observed in 10 cases; muscle weakness in 9, second wind phenomenon in only 1 case. The presence of cramps, fatigue and myalgia was observed in 12, 11 and 9 of the cases respectively. The median creatine phosphokinase level was 5951U/L. Most of the patients (83.3%) were initially diagnosed with another condition (polymyositis, inclusion body myositis, fibromyalgia and/or muscular dystrophy), and approximately half had received glucocorticoids and/or immunosuppressants prior to definitive diagnosis. All patients underwent muscular biopsy, which revealed the presence of subsarcolemmal vacuoles characterized by glycogen deposits, and negative histochemical reaction for the myophosphorylase enzyme.

CONCLUSION: The present study reinforces the presence of clinical variability among patients and shows that McArdle's disease should be considered one of the differential diagnoses of inflammatory myopathies and other rheumatic diseases.

KEYWORDS: Fibromyalgia; glycogen storage disease; myopathies; myophosphorylase; myositis.

INTRODUCTION

McArdle’s disease or glycogen storage disease type V is a metabolic myopathy caused by the deficiency of myophosphorylase, an enzyme encoded by the PYGM gene, which catalyzes the degradation of glycogen into glucose in skeletal muscle.1-4

There is scant epidemiological data about McArdle’s disease. The disease has an estimated prevalence of approximately 1 per 100000 - 167000 population,5,6 and affects individuals of both sexes at a mean age of 44 years.6

The symptoms of McArdle’s disease usually commence during adolescence or young adulthood.7 The disease is characterized by exercise intolerance, myalgias and/or muscle cramps.8 The “second-wind” phenomenon is very characteristic of the disease, in which muscle pain may dissipate after a brief rest period and allow the patient to resume exercise at the previous or a slightly reduced level.5 Half of patients have myoglobinuria and 90% of the cases present a considerable increase in creatine phosphokinase (CPK) during periods of disease.

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exacerbation. Muscle biopsy reveals the presence of subsarcolemmal vacuoles, characterized by deposits of glycogen. In addition, histochemistry shows a deficiency in myophosphorylase enzyme activity.

However, the variability of the clinical manifestations and lack of knowledge about the disease can lead to delayed and erroneous diagnosis, such as polymyositis, inclusion myositis, fibromyalgia, among others. Therefore, recognition of McArdle’s disease is of great relevance in rheumatologic practice, especially as one of the differential diagnoses of inflammatory myopathies. Thus, we present a case series of patients with McArdle’s disease, followed by a review of the literature.

### MATERIALS AND METHODS

An inception single-center cohort study describing 12 consecutive patients with McArdle’s disease in the period from 2010 to 2017 was carried out. The study was approved by the Local Ethics Committee (case # 0039/10).

Inclusion criteria: patients presenting with objective skeletal muscle weakness, physical exercise intolerance and/or the presence of a “second wind” phenomenon; elevated serum CPK, without apparent cause; muscle biopsy with evidence of subsarcolemmal vacuoles characterized by glycogen deposits, and negative histochemical reaction for the myophosphorylase enzyme.

Definition of variables: demographic, clinical and laboratory data were obtained through a systematic review of medical records. The following parameters were analyzed: sex; ethnicity; age at onset of muscle symptoms; age at diagnosis of the disease; history of intolerance to exercise, myalgias, fatigue, cramps, objective muscular weakness, presence of the second wind phenomenon; acute renal failure, family history, serum CPK level (basal and maximum); electromyography; findings on magnetic resonance imaging of the thigh muscles of normal amplitude movements but does not overcome the action of gravity; grade 3: integral mobility against action of gravity and some degree of resistance; grade 5: complete mobility against severe resistance and against the action of gravity).

Statistical analysis: The Kolmogorov-Smirnov test was used to evaluate the distribution of each of the continuous variables. The results were presented as mean, standard deviation for continuous variables, and number (%) for categorical variables. The median (minimum - maximum) values were calculated for continuous variables that did not present a normal distribution. All analyzes were performed using SPSS 15.0 software (Chicago, USA).

### RESULTS

The general characteristics of the 12 patients with McArdle’s disease are shown in Table 1. There was a predominance of females and Caucasians. The mean age at the onset of symptoms was 28.0 ± 17.4 years, while the mean age at diagnosis of the disease was 39.0 ± 14.8 years.

A history of intolerance to physical exercise was observed in 10 of the cases, while muscular weakness occurred in 9, and “second wind” phenomenon was described in only 1 case. In addition, the presence of cramps, fatigue and myalgia was observed in 12, 11 and 9 of the cases, respectively. A history of acute renal failure was reported in 2 cases. At admission of the patients to our service, with the exception of 2 patients, all had some degree of muscle weakness of the upper and/or lower limbs. Regarding family history, 2 patients had a history of consanguineous parents.

The mean peak CPK level was 5951 (1162 - 200000) U/L, while the mean baseline CPK serum level was 1341 (110 - 27000) U/L. Only 1 patient had a normal baseline CPK level. Electroneuromyography, performed in half of the cases, revealed a myopathic pattern in about two thirds of the cases. Magnetic resonance imaging of the thigh muscles had been performed in 8 of the 12 patients, four of whom had edema of the muscle compartments.

Ten of the 12 patients were initially treated with the hypothesis of polymyositis, inclusion body myositis, fibromyalgia and/or muscular dystrophy. Half of the patients had received glucocorticoid, immunosuppressants and/or human intravenous immunoglobulin. One patient had a myopathy hypothesis to clarify, and only 1 case was admitted with the initial suspicion of metabolic myopathy.

All of these patients underwent muscle biopsy, which showed the presence of subsarcolemmal vacuoles characterized by glycogen deposits (Figure 1).

### DISCUSSION

In the present study, the demographic, clinical and laboratory profiles of 12 patients with histologically-confirmed McArdle’s disease were described; most of the cases were initially treated as other rheumatic diseases.

Although no molecular analysis was performed to investigate possible mutation in the PYGM gene, the patients included in the study were carefully selected according to the histological findings and with demonstrated deficiency of the myophosphorylase enzyme activity. All had histological analysis of muscle biopsy, the presence...
of subsarcolemmal vacuoles due to the accumulation of glycogen.

The time of onset of symptoms in McArdle’s disease is variable, ranging from early childhood to adulthood, with disease predominance in females. In the present study, this characteristic was confirmed, with the majority of patients presenting the first symptoms in adulthood. In addition, although the onset of symptoms is rare after age 50, there was one case (#8) with initial symptoms at the age of 60.

According to the classification of Vieitz et al., there are three clinically distinguishable groups of patients with McArdle’s disease: 1) with exercise intolerance; 2) with permanent muscular weakness and 3) oligo or asymptomatic. Exercise intolerance is the most common clinical form reported in most studies, as observed in our cohort.

In patients with exercise intolerance, the “second wind” phenomenon, described as an improvement in exercise tolerance after a short period of sustained effort (about 12 minutes) is a classic clinical manifestation. However, in our cohort, the “second wind” phenomenon was observed in only one case.

The most common initial symptoms identified in our patients, besides exercise intolerance, were cramps and myalgias, which corroborates previously described

### Table 1. General characteristics of the 12 patients with McArdle’s disease.

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<th>Cases</th>
<th>1</th>
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<th>3</th>
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AMT: amitriptyline; ENMG: electroneuromyography; F: female; Fibro: fibromyalgia; IS: immunosuppressant; IVIg: human intravenous immunoglobulin; M: male; IBM: inclusion body myositis; LL: lower limbs; UL: upper limbs; mm: muscular; MP: methylprednisolone; MTX: methotrexate; PM: polymyositis; Pred: prednisone; cc: cause to clarify. *: At middle third of the thighs.
Fatigue was also observed in most patients and is usually associated with a hyperkinetic circulation response to exercise.\textsuperscript{21,24}

Although McArdle’s disease is not a potentially fatal condition, rhabdomyolysis can occur and lead to acute renal failure, described in up to 50\% of cases.\textsuperscript{17,21,25} In our series, about one-fifth of cases evolved with rhabdomyolysis without the need for hemodialysis.

The presence of muscle weakness ranges from 16 to 33\%\textsuperscript{14,17} and is generally of proximal predominance. In the present study, the complaint of muscle weakness was observed in 10 of the 12 patients, affecting both upper and lower limbs. Serum levels of muscle enzymes are also variable between the rest period and physical activity.\textsuperscript{16,17,21} Even during rest periods, our patients had elevated levels of CPK.

With regard to electroneuromyography findings these can be normal, nonspecific, neuropathic or, in most cases, myopathic findings.\textsuperscript{18,26} In our series, two thirds of the patients tested had evidence of a pure myopathic pattern.

Ischemic exercise testing is used in the evaluation of patients with suspected McArdle’s Disease. A lack of increase in blood lactate concentration during exercise is indicative of a defect in conversion of glycogen (or glucose) to lactate, consistent with the deficiency of skeletal muscle phosphorylase in this disease. However, this test is unspecific in metabolic myopathies, whereby other glycogen storage diseases, such as phosphofructokinase deficiency and debranching enzyme, also yield an abnormal ischemic exercise response.\textsuperscript{27}

\textbf{Figure 1.} Muscle biopsy of a patient with McArdle’s disease. A) Subsarcolemmal and intracytoplasmic vacuoles in the muscle fiber (Hematoxylin & Eosin) (arrows). B) Schiff’s periodic acid (PAS) showing subsarcolemmal accumulation of glycogen (arrow head). C) Absence of reaction staining for myophosphorylase (negative myophosphorylase reaction). D) myophosphorylase normal reaction in a patient without McArdle’s disease. Black bar = 100 um.
The confirmatory diagnosis of McArdle’s disease can be established by evidence of mutation in the PYGM gene or by muscle biopsy disclosing a deficiency of myophosphorylase activity. Over 100 types of mutations in the PYGM gene have been described to date, the most common being the p.R50X variant (previously known as p.R49X). However, access to genetic testing in Brazil is limited and therefore the diagnosis is typically confirmed by muscle biopsy, usually indicated before the suspicion of myopathy under investigation.

The diagnosis of McArdle’s disease can pose a challenge in clinical practice, since its clinical manifestations can be extremely variable, as shown in the present study, and depends on a high level of suspicion. Patients are often initially diagnosed as having depression, Parkinson’s, chronic fatigue syndrome, fibromyalgia, muscular dystrophy or inflammatory myopathies.

Currently, there is no curative treatment for McArdle’s disease, with no evidence of significant benefit from any specific nutritional or pharmacological treatment, such as ramipril, verapamil, oral ribose, branched chain amino acids, or dantrolene. Similarly, there was no benefit from treatment of the disease with pyridoxine over placebo, except in one study in which one patient was supplemented with vitamin B6 and showed enhanced myophosphorylase activity. Use of low dose creatine produced a slight benefit, but a high dose of creatine caused myalgia in patients with McArdle’s disease.

In general, recommendation for patients with exercise intolerance is primarily the indication of a diet high in carbohydrates (65%) and low in fat (20%), which has been shown to be a beneficial intervention that relieves intolerance and protects against rhabdomyolysis. In addition, supervised aerobic training and self-awareness about the “second wind” phenomenon are considered fundamental in the treatment of McArdle’s disease. Patients may learn to recognize the point at which exercise becomes better tolerated, when glycolytic pathway deviation to lipid beta-oxidation occurs metabolically. This approach has an impact on quality of life and promotes improvement in exercise intolerance.

The limitations of this study were the small number of patients and the lack of genetic analysis, not routinely performed in Brazil.

**Author Contribution**

P A Olivo Pallo: planning, reviewing literature, executing and writing the present article.
E Zanoteli: reviewing literature and writing the present article.
A M S Silva: reviewing literature and writing the present article.
S K Shinjo: planning, reviewing literature, executing and writing the present article.

**Conflict of Interest**

All authors declare no conflict of interest.

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**Summary**

McArdle’s disease has broad clinical variability, often being misdiagnosed as other diseases, leading to costly and unnecessary treatments. Knowing the characteristics of this condition and assuming a high level of suspicion in clinical practice can help establish a faster and more accurate diagnosis.
CONCLUSÕES: O presente estudo reforça a presença de variabilidade clínica entre pacientes e mostra que a doença de McArdle deve ser considerada um dos diagnósticos diferenciais de miopatias inflamatórias e outras doenças reumáticas.

PALAVRAS-CHAVE: Fibromialgia, moléstias de armazenamento de glicogênio, miopatias, monofosforilase, mioesite.

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