

From exercise intolerance to functional improvement: the *second wind* phenomenon in the identification of McArdle disease

De intolerância ao exercício à melhora funcional: o fenômeno *second wind* na identificação da doença de McArdle

Renata Siciliani Scalco^{1,2,3}, Sherryl Chatfield¹, Richard Godfrey^{1,4}, Jatin Pattni¹, Charlotte Ellerton¹, Andrea Beggs¹, Stefen Brady¹, Andrew Wakelin⁵, Janice L Holton¹, Ros Quinlivan¹

ABSTRACT

McArdle disease is the most common of the glycogen storage diseases. Onset of symptoms is usually in childhood with muscle pain and restricted exercise capacity. Signs and symptoms are often ignored in children or put down to 'growing pains' and thus diagnosis is often delayed. Misdiagnosis is not uncommon because several other conditions such as muscular dystrophy and muscle channelopathies can manifest with similar symptoms. A simple exercise test performed in the clinic can however help to identify patients by revealing the *second wind* phenomenon which is pathognomonic of the condition. Here a patient is reported illustrating the value of using a simple 12 minute walk test.

Keywords: McArdle Disease, glycogen storage disease type V, *second wind* phenomenon, exercise test, 12 minute walk test.

RESUMO

A doença de McArdle é o tipo mais frequente das glicogenoses. A apresentação clínica característica na infância inclui mialgia e intolerância aos esforços/exercício físico. Frequentemente, os sinais e sintomas das crianças não são considerados devidamente, sendo muitas vezes interpretados como "dores do crescimento", retardando o diagnóstico. Erros diagnósticos não são raros uma vez que outras doenças, como distrofia muscular ou canalopatias musculares, podem apresentar sintomas semelhantes. Entretanto, um simples teste de exercício físico realizado no ambulatório/consultório médico pode ajudar a identificar estes pacientes pois evidencia o fenômeno *second wind*, patognômico da doença de McArdle. Aqui é descrito um relato de caso de um paciente ilustrando o valor do simples 12 minutos *walk test*.

Palavras-chave: doença de McArdle, doença de depósito do glicogênio tipo V, fenômeno de *second wind*, teste do exercício, teste 12 minutos de marcha.

McArdle disease or glycogen storage disease type V (muscle phosphorylase deficiency, glycogenosis Type V) is a rare autosomal recessive metabolic myopathy with significant molecular heterogeneity caused by homozygous or compound heterozygous mutations in the muscle glycogen phosphorylase gene (*PYGM*) located at chromosome 11q13^{1,2}. It is the most common glycogen storage disorder affecting muscle, with an estimated prevalence of

1:100,000-1:167,000^{3,4}. The disorder is caused by deficiency of the enzyme muscle glycogen phosphorylase which catalyzes the degradation of glycogen into glucose subunits. Enzyme deficiency can be demonstrated in frozen muscle sections using enzyme histochemistry: muscle fibres show absent phosphorylase activity while the activity is preserved in smooth muscle in the walls of blood vessels due to the expression of the brain isoform, which is expressed by a

¹MRC Centre for Neuromuscular Diseases and Division of Neuropathology, University College London Institute of Neurology, Queen Square London, United Kingdom;

²CAPES Foundation, Ministry of Education of Brazil, Brasilia DF, Brazil;

³Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre RS, Brazil;

⁴Centre for Sports Medicine and Human Performance, Brunel University, London, United Kingdom;

⁵The Association for Glycogen Storage Disease, United Kingdom;

⁶Dubowitz Neuromuscular Centre, Great Ormond Street Hospital, London, United Kingdom.

Correspondence: Renata S. Scalco; Institute of Neurology, First Floor, Queen Square; WC1N 3BG London, UK; E-mail: r.scalco@ucl.ac.uk

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different gene (Figure 1). The inability to metabolise glycogen results in severe impairment of physical activity that is dependent on anaerobic glycolysis. Consequently, people with this condition will experience exercise intolerance during the first minutes of physical activity, represented by fatigue, pain and weakness; and throughout more intense or isometric activity. A contracture, or severe muscle cramp causing rigidity, occurs due to the lack of muscle energy substrate during intense exercise and leads to muscle damage and myoglobinuria.

Despite its rarity, it is important for doctors to be familiar with the condition because early diagnosis and the adoption of an appropriate lifestyle may help in improving quality of life and prevent severe life-threatening complications such as compartment syndrome, acute rhabdomyolysis and acute renal failure. Unfortunately, there is often a delay in diagnosing McArdle disease and affected individuals may be misdiagnosed with other disorders such as polymyositis and chronic fatigue syndrome^{5,6}. The *second wind* phenomenon, as described in a 12 minute walking test and 15 minute cycle test, is known to be pathognomonic for McArdle disease and its identification in the clinic can aid diagnosis.

Here we present a case of a patient with a history of exercise intolerance with immediate increase in exercise capacity and illustration of the *second wind* phenomenon during a 12 minute walk test (12MWT).

CASE REPORT

A 50 year-old-man was referred for neuromuscular evaluation some 20 years after being diagnosed with McArdle disease. From his medical history it was clear that he had problems with exercise since he was a child. He had never been able to run and symptoms such as myalgia and exercise intolerance had always been severe enough to disrupt any physical activity undertaken since the age of 4. Muscle

cramps in his legs were the most common feature. He was reprimanded by his schoolteachers in physical education classes and learnt to avoid sports such as football. He gave up swimming having almost drowned on two occasions. However, despite these early problems, he remained active choosing activities he could do at his own pace including a daily newspaper delivery round. He found that he could even complete day-long hikes and felt better at the end than at the beginning of activities.

Many attempts at diagnosis were rebuffed by family doctors and local specialists. He was resigned to simply having what he called “bad legs”, but at age 16 a canoeing expedition led to bilateral contractures affecting his upper limbs which led to myoglobinuria. He was diagnosed with gout at age 19, despite no obvious risk factors. Over the years he suffered several episodes of rhabdomyolysis but hospital admission resulted only in pain medication and no diagnostic investigation. It was finally a rheumatologist treating his gout 10 years later who listened to his story and carried out a baseline serum creatine kinase (CK) test. The abnormal result (1223 IU/L) led to neurophysiology evaluation, forearm exercise test, urine test for myoglobin and finally a diagnostic muscle biopsy. He received little information about his condition and no follow up until he was referred by his GP to a specialized clinic at age 50. At that time, genetic testing demonstrated homozygous mutations at R50X in the PYGM gene, confirming the diagnosis.

On interview at 50 years of age, it was clear that whilst he had no knowledge of the *second wind* phenomenon he had in fact been using it since childhood. During the 12MWT performed at clinic, an increase in his heart rate (HR) was associated with leg discomfort during the first minutes of activity, with improvement of both symptoms occurred at around 7-8 minutes (Table 1). Thereafter he was able to continue exercise with improvement in his symptoms. The clear demonstration of such *second wind* phenomenon during the 12 MWT, and a discussion of the timings and mechanisms involved, has enabled him to make more confident in his

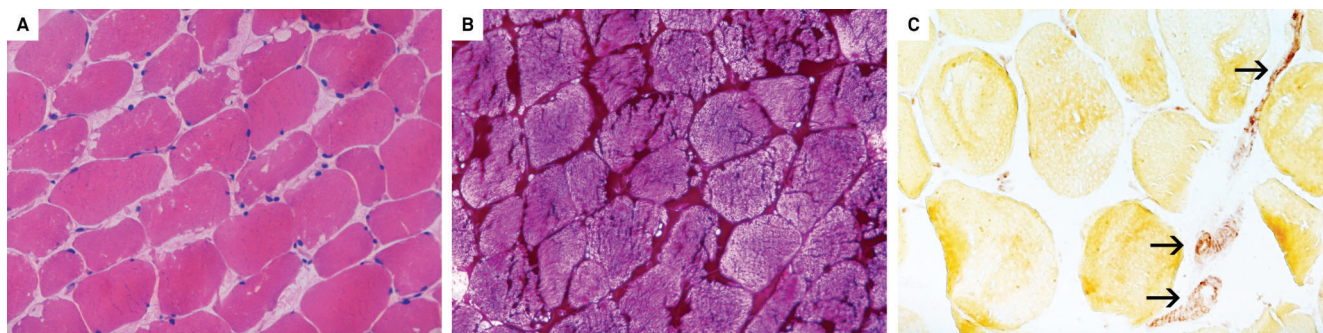


Figure 1. Illustrations of key pathological features. Skeletal muscle shows features of a vacuolar myopathy on H&E (A). There is a marked increase in glycogen content within vacuoles on the PAS preparation (B). Muscle fibres show reduced phosphorylase activity (C) while the activity is preserved in smooth muscle in the walls of blood vessels (arrows). The bar represents 50µm in all panels.

Table 1. 12-minute walk test. During the test, an increase in HR was associated with left leg (thigh more than calf) discomfort during the first 6 minutes of activity, which made him reduce his pace. The patient achieved the *second wind* following 7-8 minutes of activity, when his symptoms and HR reduced without changing the walking speed.

| Time | Walking speed | Distance covered (m) | Heart rate | Borg Pain Rating |
|------|---------------|----------------------|------------|------------------|
| 1 | - | 55 | 90 | 0 |
| 2 | - | 120 | 95 | 1 |
| 3 | Slowed down | 180 | 100 | 2 |
| 4 | - | 240 | 109 | 3 |
| 5 | Slowed down | 290 | 108 | 3 |
| 6 | - | 344 | 113 | 2.5 |
| 7 | - | 404 | 116 | 2 |
| 8 | - | 460 | 111 | 1.5 |
| 9 | - | 530 | 111 | 1.5 |
| 10 | - | 590 | 106 | 1 |
| 11 | - | 664 | 107 | 0.5 |
| 12 | - | 730 | 104 | 0 |

Resting heart rate: 67; Baseline symptoms: none; Distance completed: 730 m.

physical abilities using this phenomenon, thus improving his quality of life substantially.

DISCUSSION

The case reported above describes the typical clinical picture of McArdle disease: exercise intolerance, myalgia, cramps and episodes of myoglobinuria/rhabdomyolysis. A carefully taken history is essential to diagnose this condition. Exercise intolerance usually starts during the first few minutes of physical activity and is described as muscle pain, discomfort, stiffness, cramps, fatigue and/or exhaustion^{2,4,6,7}. It is commonly associated with dyspnoea and tachycardia. Triggers for exercise intolerance include any kind of skeletal muscle activity, particularly anaerobic activity as this is dependent on muscle energy from glycogenolysis⁸. There is an increased risk of myoglobinuria and rhabdomyolysis if activities are continued in the presence of these symptoms. Fixed weakness affecting the paraspinal and upper limb muscles may occur. Muscle hypertrophy can also be seen in a proportion of patients^{4,6,9}.

The finding of a raised serum CK in combination with exercise intolerance should raise suspicion of a metabolic myopathy. Although these features may also be seen in other conditions such as other metabolic myopathies, muscular dystrophies and muscle channelopathies, the “trick of the trade” here is the identification of the *second wind* phenomenon during the walking test. The *second wind* is a period of less painful and more effective exercise after the initial period of muscle cramps. This was first observed and reported by Pearson et al¹¹, and is recognised as a sudden improvement in exercise tolerance associated with a decrease in pain, HR and dyspnoea following an initial abnormal increase in these parameters^{10,11,12}. This phenomenon usually occurs after 6-8 minutes of exercise, during which time exercise is often slowed in pace and/or interrupted by short

rests to manage the pain. Once in the *second wind*, people with McArdle Disease can continue to exercise with amelioration of their symptoms.

The *second wind* phenomenon appears to represent the lag that exists in supplying sufficient energy for physical activity as a result of deficient glycolytic muscle metabolism and the time taken for the release of glucose from liver glycogen stores and fatty acid oxidation to provide the required energy. It is pathognomonic of McArdle disease and is present in 100% of patients with this condition¹³. Consequently, identifying the *second wind* helps with the clinical assessment and diagnostic process.

Although the *second wind* phenomenon is present in all cases of McArdle disease, some patients may have difficulty in recognizing and eliciting the phenomenon in themselves during everyday physical activity^{4,6}. Consequently, they may not volunteer it in the clinical history even if it is specifically asked for. Performing an exercise test to reproduce the phenomenon in a clinic setting may not only help with the diagnostic process for McArdle disease but also be used to demonstrate the phenomenon to patients from a therapeutic perspective. There are two exercise tests that elicit the *second wind* phenomenon in McArdle disease, namely 12 minute walk test (12 MWT)⁶ and cycle test¹³. The 12 MWT is a simple, easy, non-invasive assessment that can be performed in any clinical setting⁶. The test is carried out on a treadmill or in a corridor on a marked 10m length. During this self-paced test the patient completes as many 10m shuttle walks as possible in the 12 minutes. HR and symptoms are monitored each minute during the test, the latter being assessed by the Borg Rating of Perceived Pain (RPP) scale (Table 1)¹⁴. During the test, the HR and symptoms (pain/weakness) initially increase, followed by a reduction in both parameters after 5-10 minutes of physical activity. Likewise, the cycle test demonstrates a similar pattern in HR and symptoms during 15 minutes of cycling at a constant, moderate workload¹³; however, this test requires

Table 2. Learning points of the second wind phenomenon.

Learning Points

The **second wind** is a period of less painful and more effective exercise associated with a decrease in heart rate after the initial period of cramping and/or weakness.

The **second wind** phenomenon is a hallmark for McArdle Disease.

Performing an exercise test during clinic evaluation can confirm the presence of the **second wind** phenomenon.

Some patients may require exercise test and training to help them recognize when they achieve the **second wind**.

Exercise tests can be used to train patients to get into the **second wind** in every-day situations, thus improving quality of life.

a cycle ergometer which may not be available in a clinical setting.

Exercise tests are useful for collecting data which can be used to monitor improvement from one clinic visit to the next. They can also be used to train patients to get into the *second wind* in every-day situations, thus improving quality of life.

In summary, here we report the importance of identifying the *second wind* phenomenon when assessing patients with exercise intolerance (Table 2). This phenomenon is unique to McArdle disease and should guide the diagnostic process. The 12 MWT is easy to perform during the clinical assessment with no significant financial impact and demonstrates the presence of the *second wind* phenomenon. It should be performed as a routine evaluation tool to guide genetic or

histopathology tests for McArdle disease. It also helps both in terms of collecting data, which can be used to monitor improvement from one clinic visit to the next, but also in training patients to recognize their own symptoms.

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