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McArdle's disease: A differential diagnosis of idiopathic toe walking

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ABSTRACT

Idiopathic toe walking (ITW) is a pathological gait pattern in which children walk on their tip toes with no orthopedic or neurological reason. Physiological characteristics of the gastrocnemius muscles, the Achilles tendon, and the foot of toe walkers differ from subjects with a plantigrade walking pattern. McArdle's disease is characterized by the inability to break down muscle glycogen. It is an autosomal-recessive condition, characterized by low exercise tolerance, muscular atrophy at the shoulder girdle, episodes of myoglobinuria after vigorous physical activities and the occurrence of the second wind phenomenon. The aim of this review is to present the case studies of two subjects who were originally diagnosed as idiopathic toe walkers, but were then found to have McArdle's disease. This review will describe some physical characteristics that distinguish McArdle´s disease from Idiopathic toe walkers.

1. Introduction

Idiopathic Toe Walking (ITW) is defined as a walking pattern in which the weight bearing occurs on the forefoot. It is diagnosed in the absence of any neurological or orthopedic condition if the toe walking persists after 2 years of age[1,2]. The etiology of toe walking is still unknown; however, literature suggests a positive family predisposition in about 40% of the cases[1, 3–5], a congenital short Achilles tendon[6,7] or a sensory processing dysfunction (SPD)[2,8,9].

McArdle's disease is a genetic Type V Glycogen storage disease (located on the chromosome 11). As a result of this deficiency, patients with McArdle disease experience muscle cramps, muscle injury, and myoglobinuria induced by vigorous exercise[10]. One of the main characteristics of this medical condition is the second wind phenomenon[10,11].

The second wind phenomenon is characterized by a period of time when pain decreases and exercise efficiency increases after a period of muscle pain. Before the appearance of the second wind, patients experience tiredness and an increase of the heart rate. The second wind phenomenon occurs after 6–8 min of exercise; typically the patients with McArdle have already stopped exercising or have reduced their pace at this point[16].

This review presents two cases of patients who exhibit a toe walking pattern with no signs of neurological or orthopedic conditions. The two subjects were diagnosed as idiopathic toe walkers. Later findings and clinical examination suggest McArdle's disease. The main goal of this review is to point out some clinical characteristics which children affected by ITW and children with McArdle's disease can have in common and also how they differ. It is very likely that some of the children diagnosed with ITW actually have McArdle's syndrome. Describing these clinical characteristics will help health care practitioners find the correct diagnosis in these cases.

2. Review of case studies

We are reporting the cases of a 10-year-old boy and an 18-year-old woman. In both cases the subjects were diagnosed as idiopathic toe walkers, based on the fact that they walked on their toes, their gait pattern was bilateral and symmetric, and there were no signs of a neurological or orthopedic condition.

During the physical examination, they both reported to have been toe walkers since the onset of walking with a normal neurological and motoric development. Both of them reported having recurring pain in different body parts with difficulties localizing a specific area. The

The 10-year-old boy was tested using next-generation sequencing which was positive for the glycogen storage disease type V or McArdle's disease. The genetic finding was as follows:
PYGM, c. 2128_2130delTTC; p.Phe710del (het.), NM_005609.2, rs527236147:
PYGM, c. 1620 + 1G > A; p.? (het.), NM_005609.2:
Of note, c. 1620 + 1G > A has not been described so far. Both mutation are most likely in compound heterozygous state and can be considered pathogenic.

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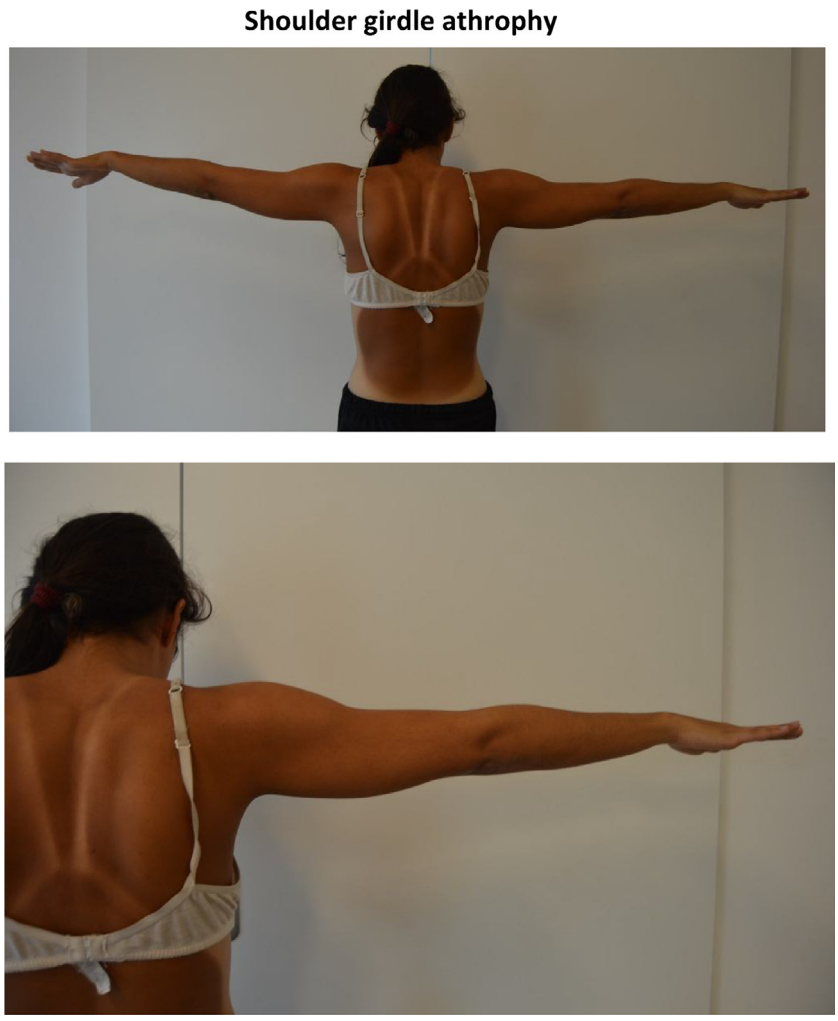

Figs. 1 and 2. Show the shoulder girdle atrophy on the 18 years old young woman. Lateral portion of the triceps brachii muscles and the long head of the biceps brachii muscles show signs of hypotrophy.

intensity of the pain increased with physical exertion.

In the upper extremity the deltoid muscles are apparently normal, but the lateral portion of the triceps brachii muscles and the long head of the biceps brachii muscles show signs of hypotrophy; and there is a general atrophy of the shoulder girdle (Figs. 1–3). Additionally, they presented myoclonus affecting the hands.

In the lower extremity, there is a hypertrophy of the gastrocnemius muscle while the belly of the muscle is more proximal (Fig. 4); the forefoot is wider (Figs. 5, 6), and the ankle's range of motion (ROM) is decreased compared to children with a plantigrade walking pattern.

The "spin" and "walking after spinning" tests were positive for toe walking in both subjects; in the "heel walking test" the young woman was able to heel walk with several compensations (trunk flexion and knee hyperextension). The boy was not able to perform this test. (The tests were taken from "*Idiopathic Toe walking, tests and family predisposition" (1)).*

The 18-year-old woman reported tiredness after activities such as running or walking; however, she actively swims 3–4 h per day, attempting to increase her stamina and speed. She does not report any problems during the training in the water; however, when the training includes weight lifting, she complains about muscular aches and she uses lighter weights and reduces repetitions.

The 18-year-old subject was diagnosed using clinical characteristics of McArdle disease. By recognizing the fatigue, muscle cramping, the atrophy on the shoulder girdle and in particular the second wind phenomena it was possible to diagnose McArdle in the 18-year-old woman

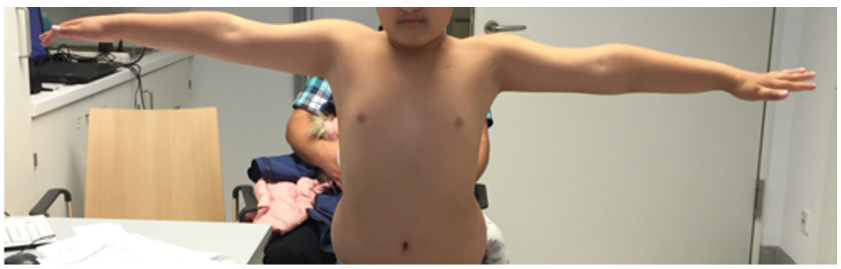

Fig. 3. Shows the shoulder girdle atrophy on the 10 years old boy. Lateral portion of the triceps brachii muscles and the long head of the biceps brachii muscles show signs of hypotrophy.

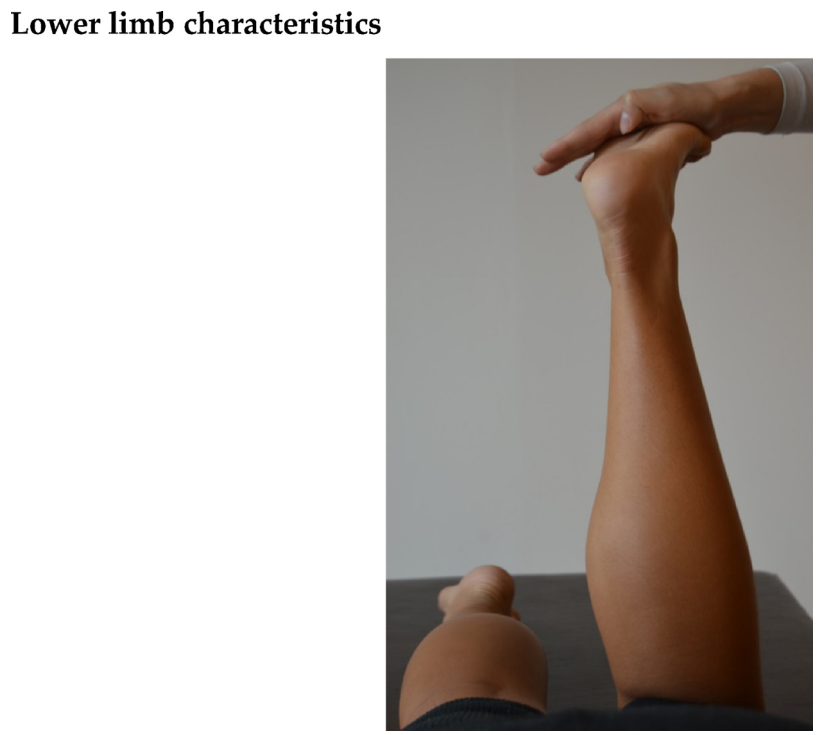

Fig. 4. shows a hypertrophy of the gastrocnemius muscle and the belly of the muscle is more proximal on the 18 years old young woman.

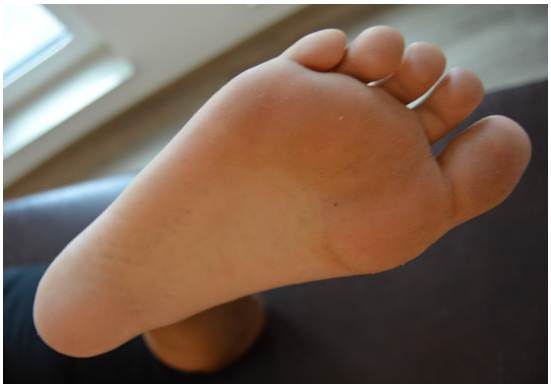

Fig. 5. forefoot of 18 years old young woman. The forefoot is wider.

without genetic testing.

3. Discussion

This case study describes above two subjects diagnosed as idiopathic toe walkers, because they exhibit a symmetric toe walking pattern with no signs of neurological or orthopedic conditions. The patients reported muscle cramping and pain in the lower extremity during the performance of physical activity. One of the subjects experiences exercise intolerance with every physical activity, while the second subject experiences intolerance just with the activities that are not in the water such as walking, running or weight lifting. Sport intolerance and muscle cramping during the performance of activity are some of the main characteristics of McArdle's disease.

McArdle's disease was first described in 1951 as a muscular syndrome or myophosphorylase deficiency glycogenesis type V, placed on the chromosome 11q13[11–13]. This defect is considered an autosomal recessive myopathy; however, there are some families that report the appearance of this condition in several family members, suggesting an autosomal dominant predisposition[12,14,15]. Our two subjects did not report a positive family predisposition.

About 4% of McArdle cases are diagnosed before 10 years of age and about 50% of patients with this condition are diagnosed between 10–30 years of age[12,17]. Both of the cases reported here were diagnosed during this period of time. McArdle has a prevalence of 1:100.000–1:167.000[11,12]. The main symptoms that led to the diagnosis were tiredness, cramping and exercise intolerance. In the 10-year-old subject the Sanger sequencing DNA test was performed in order to confirm the diagnosis. The results were positive for a glycogen storage disease type V.

Some literature describes that the symptoms may only appear in adults, explaining that children can be very active, that their muscles perform better during physical activity and that there are no symptoms of McArdle´s disease[16]. However, there are other reports in which the subjects describe having had muscular tiredness muscle cramping, and low exercise tolerance since childhood[11,12,14,15,17].

The main medical concern for our two subjects was their toe walking pattern. During the analysis of the medical history and the medical examination McArdle´s disease was suspected. Symptoms such as weakness, discomfort, stiffness, muscle pain and exhaustion during the first minutes of physical activity which lead to low exercise tolerance are some of the main signs of a glycogen store disease[11]. The difficulty in processing the enzyme muscle glycogen phosphorylase causes an impairment of physical activity and tiredness.

In addition to the fatigue, weakness and muscle cramping which lead to poor exercise performance, McArdle is determined by the spontaneous manifestation of the second wind phenomenon. The second wind phenomenon occurs in 100% of adult patients with McArdle disease[11,16].

Patients with McArdle disease can normally resume or continue physical activity after the improvement of the symptoms (reduction of the heart rate and decrease of tiredness and fatigue); this usually happens after the 8th minute of activity[10,11,14]. This so-called second wind phenomenon is due to a shift in the metabolic pathway: the body uses fatty acids in order to provide enough energy to continue the physical performance[16]. The 18-year-old-subject reported achieving a high performance level during swim training. The regularity of the training

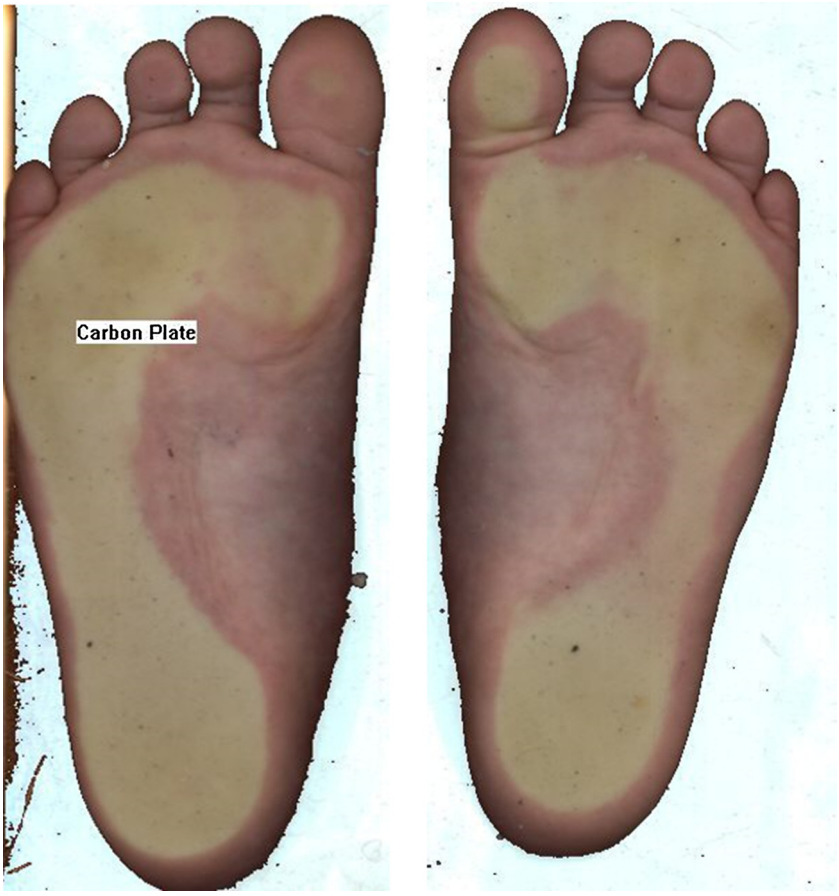

Fig. 6. Left and right foot respectively of 10 years old boy. The forefoot is wider.

and the second wind phenomenon may explain her capability to tolerate the training sessions. Regular trainings can decrease the physical signs of this condition and develop exercise tolerance[10].

There is a large number of patients affected by McArdle disease who decide to avoid physical activity due to these problems. Also there are secondary effects given by the lack of muscle energy during intense exercise. This can result in muscle damage, myoglobinuria, rhabdomyolysis and/or renal failure episodes[11,13,14,17].

In addition to the signs of exercise intolerance, there were other clinical characteristics found in both subjects. In the upper extremity there is atrophy of the girdle muscles and myoclonus affecting the hands. In the lower extremity the belly of the gastrocnemius muscle shows bilateral hypertrophy, the forefoot is wider, and the ROM of the ankle is decreased. These signs are secondary symptoms of McArdle´s disease[20].

There are different ways to make a differential diagnosis of McArdle´s disease:

By measuring the creatine kinase (CK) levels that are significantly elevated[11,12,13,19] in patients affected by McArdle; by doing a lactic acid test after physical activity[14,15]; by biochemical examination of a muscle biopsy, by genetic testing[12], or by the absence of increased lactate during the forearm ischemic exercise test (FIET)[16]. Nevertheless, identifying the second wind phenomenon will help to make a specialized diagnostic in adult patients with McArdle. A 12-minute walking test (12MWT) will help the clinical assessment and the diagnostic process[11]. For more exercises suitable for the diagnosis of McArdle we recommend the following literature: “Cardiovascular and metabolic responses to 5 exercises in a patient with McArdle’s syndrome” and “Unique exercise Lactate profile in Muscle phosphofructokinase deficiency”.[21]

4. Conclusion

There are some patients who are diagnosed as idiopathic toe walkers because they exhibit a toe walking pattern without signs of neurological or orthopedic conditions. However, a more detailed medical examination can help to determine differences between toe walkers and children affected by other medical conditions such as McArdle`s disease. Although the gait is performed on the forefoot, not all children exhibit the same physical characteristics. In these two subjects with McArdle’s disease it was possible to observe different characteristics of the foot, in the form of the gastrocnemios muscle, the shoulder girdle muscle and additionally a low tolerance to physical activity.

Conflict of interest declaration

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