Severe Axial Myopathy in McArdle Disease

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**CONCLUSIONS AND RELEVANCE** This is a highly atypical presentation of McArdle disease with severe paraspinal wasting and weakness. We suspect that this is related to the unusual amount of glycogen vacuoles and stress the importance of including McArdle disease in the differential diagnosis of axial myopathy.

**IMPORTANCE** McArdle disease is a nonlysosomal glycogenosis that classically manifests with exercise-induced pain from childhood. Fixed weakness may occur from the fifth decade and is typically mild and located around the shoulder girdle.

**OBSERVATIONS** We describe a 61-year-old man with exercise-induced pain from a young age and a 3-year history of weight loss and an elevated creatine kinase level up to 4000 U/L. On examination, he was severely atrophic and weak in his shoulder girdle and the entire paraspinal musculature. Magnetic resonance imaging confirmed that the paraspinal musculature was completely converted to fat. A muscle biopsy specimen was myopathic with a lack of myophosphorylase and multiple large vacuoles with glycogen. A nonischemic forearm test demonstrated a lack of increase in lactate together with an exaggerated ammonium elevation. Genetic testing verified the suspicion of McArdle disease.

**Report of a Case**

We describe a 61-year-old man who was referred to our neuromuscular center on suspicion of a muscular dystrophy with a 5-year history of weight loss, muscle weakness, and creatine kinase levels of 2000 to 4000 U/L (to convert to microkatal per liter, multiply by 0.0167) (reference range, <280 U/L). On questioning, it became clear that he had been symptomatic since childhood, with myalgia evoked by seconds to minutes of physical activity. While serving in the military, he had to make up excuses for not participating in strenuous activities, because he was unable to perform these exercises. He did not report myoglobinuria but had a second-wind–like phenomenon that he experienced where if he paused shortly after an initial few minutes of work, he would be able to continue on a higher workload for a long time.

On examination, he was underweight and exhibited a bended posture (Figure, A). The shoulder girdle and paraspinal musculature from the neck to the pelvis was severely wasted (Figure, B). Gluteal and mild thigh atrophy was also noted. There was weakness: Medical Research Council grade 4 around the shoulder girdle and 4+ in the hip and knee flexors. Lying down on his stomach, he could not lift his torso from the couch. Vital capacity was normal.

In accordance with the wasting and profound weakness of the paraspinal musculature, magnetic resonance imaging showed a complete fatty transformation of what should be the paraspinal musculature (Figure, C), corresponding to a Mercury score of 4.

Because of pronounced axial involvement, Pompe disease was suspected, but α-glucosidase activity in leukocytes was normal.

A muscle biopsy specimen from the lateral vastus muscle was myopathic with multiple large vacuoles that appeared empty in all stains, except in the periodic acid-Schiff stain,

**McArdle disease** (glycogen storage disease type V) is the most prevalent nonlysosomal glycogenosis affecting skeletal muscle. It is caused by mutations in the gene *PYGM* encoding the enzyme myophosphorylase, which breaks down muscle glycogen. As a result, patients are in great energy deficiency at the onset of exercise and during continued high-intensity exercise. This results in pain and cramps during intense physical activity, which may cause muscle damage, rhabdomyolysis, and myoglobinuria.

The dynamic exercise-related symptoms of pain and cramps typically start in the first or second decade of life and for the majority remain the only symptoms later in life as well.1 Fixed weakness or wasting in McArdle disease is extremely rare before age 40 years but may occur in about one-third of cases after age 40 years.2 If present, wasting is usually located in the shoulder girdle,3 with only mild decreases in strength. Cases with more widespread involvement, including distal axial involvement of paraspinal muscles, have not been reported.

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where glycogen was demonstrated (Figure, D and E). The myophosphorylase stain demonstrated total lack of myophosphorylase.

A nonischemic lactate forearm test induced a slight decrease in lactate and an exaggerated 10-fold increase in ammonium.

Genetic testing for McArdle disease revealed 2 previously reported pathogenic mutations in PYGM, the very common c.148C>T (p.Arg50*) and c.1948C>T (p.Arg650*), which has been reported only twice in the literature. Both were present in a heterozygous state.

Because of the unusual phenotype for McArdle disease with severe affection of the entire paraspinal musculature and more pronounced glycogen deposits in muscle than usually seen in the condition, we performed investigations to evaluate possible double trouble in muscle carbohydrate metabolism. Anaerobic glycogenolysis and glycolysis in vitro muscle studies revealed a metabolic blockage in digesting glycogen, thus confirming phosphorylase deficiency (myophosphorylase activity, 3 μmol/g/30 min [reference range, 120-170 μmol/g/30 min]). No other blockage was observed in the functionality of glycolysis, indicating that all the involved enzymes...
function normally. Normal enzyme activities were also measured for amylo-1,6-glucosidase and branching enzyme. Muscle glycogen was 5.3 g% (reference range, 0.8-1.6). The mean (SD) glycogen muscle content in McArdle disease is 4.0 (1.1) g%.

Discussion

In this study, we describe a patient with McArdle disease who is unusual in 2 respects. First, our patient resembles a patient with axial muscular dystrophy, with pronounced weakness and fatty replacement of his entire paraspinal musculature, which, to our knowledge, has not been described in McArdle disease before. Second, the muscle biopsy specimen of the patient displayed remarkably many vacuoles filled with glycogen, more prominently than usually found in McArdle disease.

The PYGM mutations of the patient have both been described previously. The p.Arg50* is the most prevalent mutation in PYGM, accounting for approximately 75% of mutant alleles in northern Europe.1,6 The second mutation of the patient, p.Arg650*, has been described on 2 occasions,5,7 one of these, like the present case, combined with the p.Arg50X mutation. The phenotypes of these cases, however, were not described in detail and it is therefore not clear to what extent this mutation contributes to the phenotype. Most likely though, the mutations are not essential for the phenotype, since both of them are nonsense mutations, likely leading to nonsense-mediated messenger RNA decay resulting in the absence of corresponding protein. This is compatible with the complete block of myophosphorylase activity found in the patient on histochemical and biochemical examination of muscle tissue.

It is an enigma why fixed weakness develops in McArdle disease. Repeated episodes of exercise-induced muscle damage could be envisioned to play a role, but the preferential localization of shoulder girdle weakness, which rarely is involved in episodes of muscle injury of patients with McArdle disease, seems to contradict this notion. Clearly, the weakness is an age-related phenomenon, because fixed weakness is almost nonexistent before age 40 years in McArdle disease.2 Glycogenoses with severe muscle weakness, such as Pompe disease and debrancher and brancher deficiencies, are all characterized by large blebs of accumulated glycogen in muscle, which may cause structural abnormalities and interfere with normal muscle contraction. In the described patient, glycogen accumulation was more severe and vacuolar than normally found in McArdle disease and suggests that the weakness could be related to this unusually high regional accumulation.

The present case extends the previously described spectrum of phenotypes for McArdle disease and suggests that McArdle disease should be included in the differential diagnosis of axial myopathies.