Diagnosis of McArdle's disease in an elderly patient: Case report and review of literature

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Citation

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Abstract

McArdle's disease is caused by deficiency of the muscle-specific isoform of phophorylase enzyme. The enzyme splits glucose-1-phosphate from glycogen to fuel the glycolytic pathway needed for muscle activity. McArdle's disease, although being the commonest form of glycogenosis affecting skeletal muscle, is a rare disease. The disease is typically manifested in childhood/adolescence by exercise intolerance, muscle cramps/pain with the classic "second wind" phenomenon (improvement of symptoms after a short period of slowing down or rest). McArdle's disease with late-onset presentation is very rare and clinically more variable in its presentation than the early onset disorder. The disease may escape clinical diagnosis until progressive or persistent muscle weakness or atrophy occurs at advanced age. We report an atypical case of McArdle's disease diagnosed at the age of 65 years in a patient presenting with progressive fixed proximal muscle weakness with no previous history of episodic muscle dysfunction and discuss the clinical-pathological aspects of the disease.

INTRODUCTION

McArdle's disease (glycogenosis type V) is caused by deficiency of the enzyme alpha-1,4-glucan orthophosphate glycosyl transferase (myophosphorylase). The enzyme plays a vital role in the liberation of glucose-1-phosphate from glycogen in skeletal muscles to create energy ([1]). There is currently no reliable data about the frequency of McArdle's disease, however the prevalence of the disease has been estimated to be 1:100,000 ([2]). The disease usually presents in adolescent and young adults with exercise intolerance and muscle cramps that improve after a short period of slowing down or rest, a characteristic feature known as “second wind” phenomenon ([3]). Late presentation of the disease in older age is rare ([4]) and the clinical diagnosis become difficult due to the atypical presenting symptoms ([5]). We report an unusual case of McArdle's disease diagnosed at the age of 65 years in a man presenting with progressive fixed myopathic picture, who did not have obvious episodic muscle dysfunction earlier in his life.

CASE REPORT

The patient was a 65 years old man complaining of weakness, more in proximal arm muscles than in his legs. The exact onset of his symptoms was unclear, as it had been slowly progressive. He had noticed some difficulty getting out of a chair and in raising both arms above the head, fasciculations and loss of muscle mass. He was on Lipitor for 4 years and recently his creatine kinase (CK) was in the 4,000 range which dropped to the mid-300s two months after discontinuation of Lipitor. However, he did not notice improvement in proximal arm strength. He has not had history of myalgias, muscle cramps, any rashes, joint pains, ocular or bulbar abnormalities. There was no family history of neurologic dysfunction. Physical examination revealed questionable atrophy of the proximal muscles with decreased strength in both upper extremities (deltoids 3/3-, biceps 4-/4-, triceps 4/4-). Deep tendon reflexes were trace at the right biceps, absent at the left biceps, trace at the triceps, absent at the brachioradialis bilaterally. In the legs, there was symmetric weakness of the iliopsoas (4+ to 5-) and minimal weakness of the gluteus maximus bilaterally (5-/5), otherwise the other muscles in the legs were normal. His sensory exam and routine labs were unremarkable. There was electrophysiological evidence of myopathic motor units and spontaneous activity in proximal arm and proximal leg muscles.

Biopsy of Left quadriceps was performed. The biopsy showed subsarcolemmal vacuoles in many fibers with no abnormal contents on hematoxylin and eosin (fig. 1A), Masson's trichrome (fig. 1B) or Gomori stains (Fig.1C). Increased glycogen content (Fig. 2A) was present in several fibers on PAS stain (diastase sensitive). Myophosphorylase

activity was absent using enzyme histochemistry (fig. 2B) with a positive control (Fig. 2C). Mild to moderate myopathic features were present including increased fiber size variation and internal nucleation (Fig. 3A) with scattered myofiber hypertrophy and occasional fiber splitting (fig. 3B). Type I fiber smallness was suggested on ATPse stains (fig. 3C). Decreased oxidative enzymes staining with "moth-eaten" appearance was present, mostly in type 1 fibers (fig. 4A) with linearization of the intermyofibrillar architecture in type II fibers (Fig. 4B). Neurogenic atrophy was minimal.

Figure 1

Figure 1: Subsarcolemmal vacuoles with no abnormal contents (A: H&E; B: Masson's trichrome ; and C: Gomori trichrome stains x400).

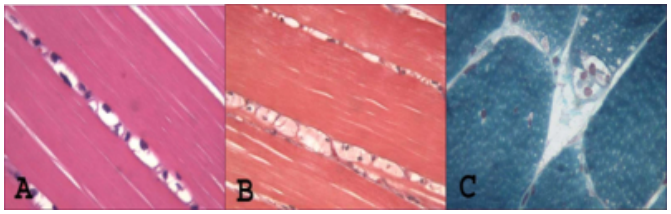


Figure 2

Figure 2: A. Increased glycogen contents (A) and lack of myophosphorylase activity (B) compared to positive control (C) (A: PAS; B &C: myophosphorylase stains, Ax600; B&C x400).

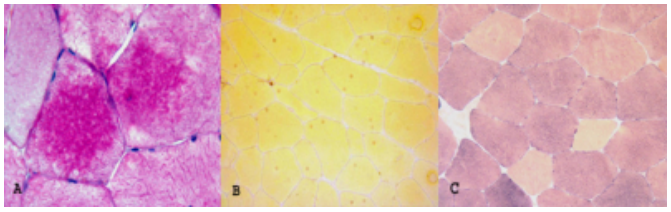


Figure 3

Figure 3: A. Increased fiber size variation and internal nucleation (A); myofiber hypertrophy with splitting (B) and type I fiber smallness/atrophy (C) (A & B: H&E stain x400; C: ATPse stain, pH 4.3; x 200).

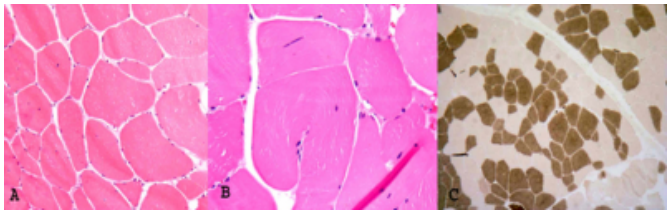
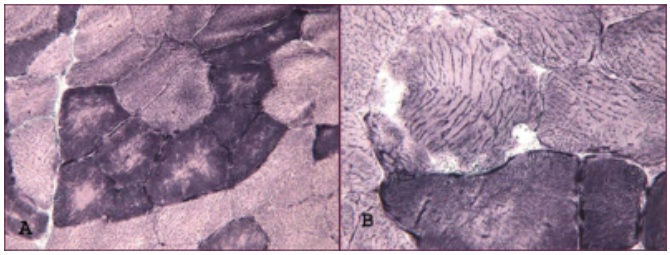


Figure 4

Figure 4: Decreased oxidative staining with "moth-eaten" appearance in type I fibers (A) and linearization of the intermyofibrillar architecture in type II fibers (B) (A&B NADH stain, x 400).



DISCUSSION

McArdle's disease, first described in 1951, is a type V glycogenosis classically restricted to skeletal muscles ([6]). The deficient enzyme was identified, eight years later, as the muscle-specific isoform of phosphorylase enzyme responsible for glycogenolysis in the muscle ([7]).

McArdle's disease is inherited as autosomal recessive disorder. Sporadic non-familial cases are also reported ([2]). The disease has been linked to more than 80 different mutations in the gene coding for myophosphorylase (PYGM gene) located on chromosomes 11q13 ([8]). Mutations are spread throughout the gene and there is no clear genotype/phenotype correlation ([9]) which explains the marked variation in the clinical presentation from one patient to another. Heterozygous individuals are usually asymptomatic ([10]).

During the first 5-10 minutes of exercise, the breakdown of muscle glycogen into glucose is crucial for delivering energy to the contracting muscle ([8]). Blocked glycogen breakdown due to myophosphorylase deficiency results in severe limitation in both aerobic and anaerobic glycolysis in the muscle. The result is a complex pattern of exercise intolerance, in which mild to moderate exercise exhausts oxidative capacity, causing fatigue, tachycardia, and breathlessness, whereas more strenuous activities, which normally would engage anaerobic glycogenolysis ([11]), will elicit highly exaggerated exercise-induced symptoms ([8]).

The clinical features depend of the phase of the disease. In childhood and adolescence the main symptom is easy fatigability. The classical features of the disease are usually manifested in the second or third decade of life by muscle pain, cramps and weakness with tachycardia and breathlessness in the first few minutes of exercise with or without transient myoglobinuria. The patient experiences a

"second wind phenomenon" in which the level of perceived exertion drop after 5-10 minutes of exercise or after a short period of rest or slowing down of exercise allowing significant improvement in exercise tolerance. The second wind phenomenon is a characteristic feature of McArdle disease and is due to increased availability of extramuscular fuels, such as hepatic glucose and fatty acids to partially compensate for the blocked muscle glycogenolysis. However, some patients deny ever experiencing a second wind, but when exercised in a laboratory, the "second wind phenomenon " can be elucidated ([8]). Myoglobinuria from rhabdomyolysis is a serious complication of the disease and, if severe, can cause acute renal failure requiring dialysis ([12]). Fixed muscle weakness become more common with increased age as a consequence of repeated episodic muscle damage ([1]).

The diagnosis is suspected from the classical clinical history and supportive laboratory data including increased serum CK activity and flat lactate response to the forearm ischemic test. Electromyography may show myopathic changes ([13]). The diagnosis is confirmed by biochemical assay or absence of histochemical reaction for the enzyme activity in the muscle biopsy and or by molecular genetic testing. Regarding the wide range of the reported mutations in the PYGM gene, the muscle biopsy is a more practical method for the diagnosis. The histochemical reaction for myophosphorylase used routinely in the muscle biopsy is a valuable diagnostic tool to demonstrate the absence of myophosphorylase activity and establishes the diagnosis. However, a biopsy taken shortly after an episode of rhabdomyolysis may show enzyme activity in the regenerating fibers which contain a fetal isoform of phosphorylase encoded by a different gene expressed transiently during myogenesis ([1,8]).

Atypical cases are rare and include fatal infantile form ([14]), a form associated with congenital myopathy ([15]) and late-onset form as in our case ([13]) . McArdle's disease with late-onset of symptoms is rare and is clinically more variable than the early onset disease. In those patients who do not recall exercise intolerance earlier in life, the diagnosis is obscured due to the atypical symptoms and may need several biopsies to establish the diagnosis ([1,5]). In our case the patient presented with fixed proximal muscle weakness of upper and lower extremities at the age of 65 years. The exact onset of his symptoms was unclear, as it had been slowly progressive with no obvious episodic muscle dysfunction earlier in his life. The atypical clinical picture of the patient and the electrophysiologic studies were not suggestive of the diagnosis. The clinical differential diagnosis was centered around an inflammatory myopathy versus cholesterol lowering agent myopathy. The diagnosis was established from the demonstration of total absence of myophosphorylase activity in two repeat muscle biopsies.

CONCLUSION

McArdle's disease, although the commonest form of glycogenosis, is a rare disease. The clinical picture of exercise intolerance, muscle cramps and "second wind phenomenon" in a young patient is strongly suggestive of the disease. A late onset form of the disease with atypical symptoms, although of rare occurrence, should be considered in the clinical differential diagnosis. The atypical case we present demonstrates that McArdle's disease may present with progressive or fixed proximal muscle weakness at an advanced age without antecedent episodic dysfunction. Due to the spectrum of phenotypic and genetic variations, muscle biopsy plays an important role in establishing the diagnosis by demonstrating the absence of myophosphorylase activity.

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