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Case report

A case of adult Pompe disease presenting with severe fatigue and selective involvement of type 1 muscle fibers

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Abstract

We present a case of adult Pompe disease (acid maltase deficiency) with an uncommon clinical presentation characterized by severe fatigue and myalgia prior to the onset of limb girdle weakness. Remarkably, the muscle biopsy demonstrated selective involvement of type 1 muscle fibers. The cause and clinical effects of fiber type specific involvement are currently unknown, but the phenomenon might contribute to the clinical heterogeneity in Pompe disease and the variable response to enzyme replacement therapy.

Keywords: Muscle pathology; Muscle fiber type; Fatigue; Lysosomal storage disease; Glycogenosis type II

1. Introduction

Limb-girdle weakness is the most common and prominent presenting sign in adults with Pompe disease, an autosomal recessive metabolic disorder often referred to as acid maltase deficiency or glycogen storage disease type II (OMIM #232300). Pompe disease is a lysosomal storage disorder caused by the deficiency of acid α-glucosidase [1–4]. Expansion and malfunction of the lysosomal system followed by autophagosomal build-up leads to loss of muscle architecture and muscle function [5–9].

The clinical spectrum of Pompe disease is very heterogeneous with regard to the age of onset, disease manifestations and rate of disease progression [3,10]. Light-microscopic examination of skeletal muscle from Pompe disease patients usually reveals a vacuolar myopathy and glycogen storage with nonselective involvement of the different muscle fiber types [4]. However, a limited number of cases have been reported showing preferential involvement of either type 1 [11–13] or type 2 muscle fibers [14]. In all seven cases reported, the selective fiber type involvement was just reported as an unusual observation and it was not questioned whether patients with preferential glycogen storage in one specific fiber type might exhibit a different clinical phenotype.

We present a case of adult-onset Pompe disease with an uncommon clinical presentation characterized by severe fatigue and myalgia prior to the onset of limb girdle weakness. Remarkably, the muscle biopsy demonstrated involvement of only type 1 muscle fibers. This unusual observation is relevant in the context of recent publications suggesting that type 1 muscle fibers might respond better to enzyme replacement therapy than type 2 fibers [15–17].

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2. Case report

In January 2007, a 35-year-old Caucasian woman was referred to our hospital. Since August 2006 she suffered from severe fatigue and myalgia of the muscles of the shoulder girdle and the upper arms and limbs, especially notable when she walked the stairs and combed her hair. A few months later, she had noted minor weakness of the upper arms and legs. Because of these complaints she had abandoned her job as a children day-care worker. There were no clinical signs, such as feeling listless, being without energy, or a lack of motivation, suggesting a vital depression. Physical examination revealed no abnormalities. Neurological examination revealed no muscular atrophy or fasciculations. The muscles were not abnormally tender. Examination of the cranial nerves, sensory functions of the limbs and tendon reflexes were normal. There was symmetrical weakness of the shoulder girdle (m. deltoideus, m. infraspinatus), the gluteal muscles and the proximal muscles of the legs (m. iliopsoas, hamstrings), Medical Research Council (MRC) grade 4. The patient was able to squat, but used her hands to rise from the floor. Pulmonary function tests were normal. She had a mean score of 6.75 (range 0–7) on the fatigue severity scale (FSS), indicating severe fatigue.

Serum creatine kinase (CK) was elevated (1755 U/l; normal value <169 U/l). Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) were slightly elevated. Erythrocyte sedimentation rate (ESR) and thyroid-stimulating hormone (TSH) were normal. Antinuclear antibodies (ANA), anti-SSA, anti-SSB and anti-Jo1, were negative (normal).

Based on the relatively short duration of her complaints, the presence of fatigue, myalgia, and the elevated CK, we considered it most likely that she would have an inflammatory myopathy. A muscle biopsy taken from the quadriceps muscle, however, revealed no signs of inflammation, but rather surprisingly showed a vacuolar myopathy solely affecting type 1 muscle fibers. The vacuoles stained positive for acid phosphatase. Representative pictures are shown in Fig. 1. Glycogen accumulation in some muscle fibers was detected by PAS staining and electron microscopy showed glycogen-filled vacuoles. No abnormalities were found in the NADH (nicotinamide adenine dinucleotide), SDH (succinate dehydrogenase), COX (cytochrome oxidase) and ORO (oil red O) staining. Based on these findings Pompe disease was suspected and subsequently confirmed by demonstrating acid α-glucosidase deficiency in leucocytes and cultured skin fibroblasts. In addition, DNA analysis revealed the presence of two pathogenic mutations in the acid α-glucosidase gene, c.-32-13 T > G and 525delT.

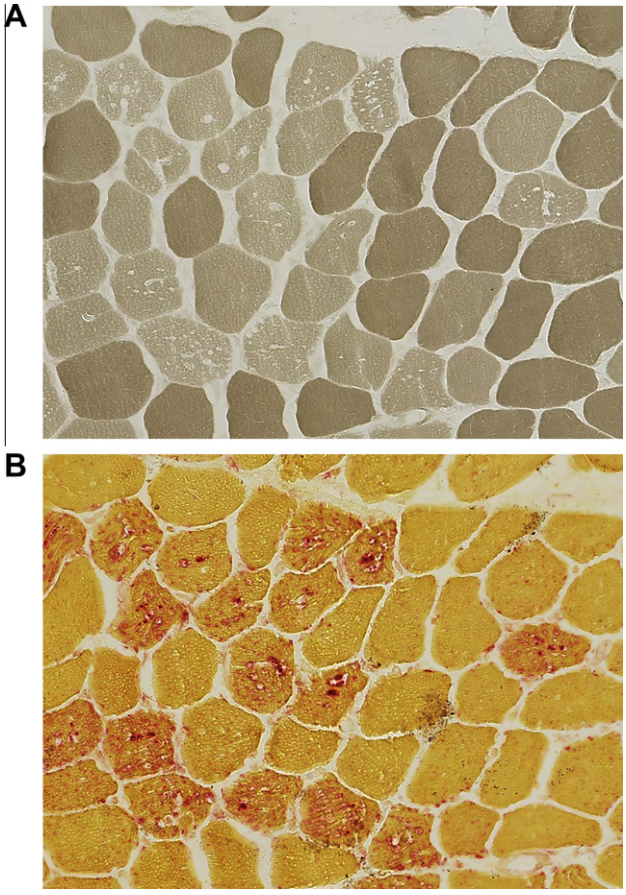

Fig. 1. Biopsy from the m. quadriceps femoralis showing selective involvement of type I muscle fibers. ATPase staining at pH 9.4: Type 1 muscle fibers are lightly stained and are vacuolated (panel A). Acid phosphatase staining (red) of a serial section demonstrates lysosomal pathology in the type I muscle fibers (panel B).

3. Discussion

The case of Pompe disease described here is peculiar in that the patient presented with severe fatigue and myalgia prior to the development of limb-girdle weakness, and because fiber type involvement was restricted to the type 1 muscle fibers. Whether rapid progression, fatigue or pain is related to oxidative type 1 muscle fiber abnormalities in this patient is uncertain and has not been proven.

Although fatigue is prevalent in adults with Pompe disease, it is rarely reported as first symptom [18]. Fatigue can have many different causes [19]. In case of Pompe disease, expansion and dysfunction of the lysosomal system due to glycogen accumulation followed and accompanied by autophagic build-up destroys the muscle architecture and hampers the contraction [20]. Thus, it takes more energy to achieve the same power of contraction resulting in more rapid fatigue [19,21]. Decreased pulmonary function may also contribute to the level of fatigue, but our patient had a normal pulmonary function in both sitting and supine position. Muscle fiber type distribution varies widely within and between muscles depending on their function [22]. Therefore the selective involvement of type 1 muscle fibers in this case can be a chance finding and theoretically can be related to sampling differences, but might be related to the prominent fatigue, rapid progression or pain. Normally, type 1 muscle fibers are fatigue-resistant and well suited for prolonged aerobic exercise [22]. If type

1 fibers are selectively affected in the disease process, type 2 muscle fibers might be challenged to partially compensate for the loss of function while they are not suited for endurance. Whether these mechanisms explain the fatigue in our patient is as yet unknown. Perception of fatigue may also be related to non-physical causes [23].

Selective type 1 muscle fiber involvement with vacuolization has previously been described in a limited number of cases of Pompe disease, but no discussion was devoted to its cause or clinical effects. Three of these five patients suffered from respiratory dysfunction, which is likely to cause fatigue, but pulmonary dysfunction was not found in the case we present. The muscle fiber type specific involvement however could be relevant in clinical practice because it could have an impact on the effect of enzyme replacement therapy.

Research in mice showed that slow-twitch type 1 fibers respond well to ERT in contrast to type 2 fibers. In particular, type 2b fibers seemed much more resistant to therapy. In knockout mice it was shown that the accumulation of autophagic vacuoles in skeletal muscle is limited to type 2 fibers. The combination of increased autophagic activity and inefficient endocytic trafficking in type 2 fibers may contribute to an incomplete therapeutic response [15,24]. However in a single patient with classic infantile Pompe disease it was shown that enzyme replacement therapy can reverse the pathological changes in both type 1 and type 2a muscle fibers [17].

With this case report we want to draw attention to the occurrence of fiber type specific pathology in Pompe disease. It may be relevant for the clinical presentation and for the responsiveness to enzyme therapy, since it has been suggested, that type 1 fibers respond better to enzyme therapy than type 2 fibers [17,24]. Further research is required in adults with Pompe disease to draw further conclusions about the effect of fiber type specific involvement.

Acknowledgments

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