Journal of Neuromuscular Diseases 1 (2015) S29–30
DOI 10.3233/JND-159027
IOS Press

Poster Abstract: Clinical

A Unique Myopathy Syndrome in a Patient Disclosing Clinical, Laboratory, and Genetic Findings of Late-Onset Pompe Disease, Together with a Lack of Dysferlin on Muscle Biopsy

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BACKGROUND

Autosomal recessive late-onset Pompe disease (LOPD) is caused by compound mutations of the acid-alpha-glucosidase gene (GAA) which lead to deficiency of GAA enzyme activity and accumulation of glycogen within the autophagic vacuoles. Clinical hallmarks are a limb–girdle-like myopathy and ventilator failure due to diaphragm involvement. Dysferlinopathy is an autosomal recessive myopathy due to a mutation in the DYSF gene which causes deficiency of function of the protein dysferlin, involved in muscle repair. Symptoms manifesting in early adulthood primarily affect the limb–girdle skeletal muscles, and leave the heart and diaphragm spared. The unusual case of a patient with a clinicopathologic pattern of both LOPD and dysferlinopathy is described.

MATERIALS AND METHODS

A 39-year-old male came to our observation complaining for 2 years of progressive ventilator insufficiency and fatigability, moderate myalgia, and difficulty walking. Blood muscle enzymes, ventilatory function, electrophysiology, and total body muscle MRI studies were performed. Glycogen storage as well as GAA activity were assessed by peripheral blood smears and muscle biopsy. Genomic DNA was extracted from blood leukocytes.

RESULTS

Mild weakness and atrophy mainly involved the anterior leg muscles; the thighs and hips were involved to a lesser extent; upright posture and gait were only possible with a double support. The upper limbs and shoulders were substantially spared. Serum muscle enzymes were increased by 1.5–2 times the norm; EMG showed a myopathic pattern in the lower limbs and hip muscles and pseudo-myotonic discharges in the paravertebral muscles of the lower back. Forced vital capacity was reduced by 20% of the expected values when standing, and further decreased in the supine position. GAA activity was 2.54 μmol/h/L on DBS, suggesting the diagnosis of LOPD, which was further supported by the finding of numerous glycogen granules within anti-LC3II-positive autophagosomes in lymphocytes on blood smears. Mutation analysis of the entire gene disclosed only a very rare c.2276G>C genetic variant in exon 16 on one allele of GAA, which was confirmed by cDNA studies. Muscles microscopy revealed a mild dystrophic pattern without any evidence of PAS and acid phosphatase-positive vacuoles in the muscle fibers, and a rather markedly reduced expression of dysferlin confirmed by Western-blot.

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ISSN 2214-3599/15/$27.50

DISCUSSION

Our data reinforce the advice that diagnostic protocols should be as complete as possible in LOPD, and stimulate discussion on the criteria for enzyme replacement therapy in heterozygous patients.