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Neurological manifestations in late onset pompe disease

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Abstract

Pompe disease is a rare glycogen storage disorder that is caused by a lack of lysosomal enzyme Alpha-Glucosidase (GA), which is responsible for lysosomal glycogen degradation. Pompe disease has an autosomal recessive inheritance. In most cases, Pompe disease is infantile, but rarely it may show in adulthood, called Late-Onset Pompe Disease (LOPD). It is characterized by a wide range of multisystemic manifestations. The diagnosis can be delayed due to the lack of typical features, leading to late implementation of enzyme replacement therapy. In this case report, A 36-year-old African American female, presented with chronic progressive proximal muscle weakness and mild CK elevation for 1 year with no major respiratory compromise and normal electromyography. Genetic testing showed pathogenic homozygous mutation of the GAA gene. The neuromuscular aspects of our case resemble a wide range of disorders and it lacks the typical clinical and electromyographic features. The delayed diagnosis of Pompe disease may lead to irreversible muscle damage and renders enzyme replacement less effective. It is recommended to keep Pompe disease in the differential diagnosis when facing such cases and implement the dry blood spot for screening of idiopathic myopathies or genetic testing for metabolic myopathy.

Keywords

Pompe disease; Late onset pompe disease; LOPD with findings of normal EMG and TPS muscles; Family history of LOPD; Autosomal recessive inheritance; GAA genetic testing.

Abbreviations

GAA: Glucosidase Alpha Acid, also known as acid maltase; LOPD: Late-Onset Pompe's Disease; EMG: Electromyography; NCS: Nerve Conduction Study; CMAP: Compound Motor Action Potential; ERT: Enzyme Replacement Therapy; PT: Physical Therapy.

Introduction

Pompe's disease is an autosomal recessive inherited disorder that occurs due to a mutation in the *GAA gene* located on chromosome 17. The gene codes for a lysosomal enzyme called GAA (glucosidase alpha acid) also known as acid maltase. 1% of tertiary neuromuscular centers patients with proximal weakness, or high CK or neck muscle weakness have acid maltase deficiency [1]. The enzyme breaks a complex sugar known as glycogen. Based on the inheritance pattern of the disorder, [2,3] carriers are not symptomatic since they have adequate functional levels of GAA enzyme [4]. However, when both parents are heterozygous for the trait, the phenotype of the offspring will be 3:1. Which translates to 25% of the off spring are homozygous for the mutation and will be affected. 50% of the offspring will be carriers and 25% will be healthy homozygous off spring [4]. Deficiency in the GAA enzyme leads to tissue damage due to dysfunctional autophagy. The classification of the disease is based on the age of onset and severity of the disease. It is classified into three types, infantile-onset Pompe, Juvenile-onset Pompe, and Late-Onset Pompe's Disease (LOPD). The classical Infantile disease usually occurs within a few months of birth, patients with the disorder have muscle weakness, hypotonia, hepatomegaly, breathing problems, and heart defects [5]. If untreated, it leads to heart failure and death within the first year of life. Juvenile onset appears at 12-21 years of age and presents with musculoskeletal deformities and respiratory failure, Whereas LOPD usually presents between first and sixth decade [6], it has a more functional amount of enzyme but less than normal levels. Individuals with the disorder have progressive muscle weakness in the legs and trunk, as the disorder progress, it can lead to serious problems, like a respiratory failure. The focus of this case study is LOPD, with a varied clinical presentation like myopathies making the diagnosis more complex and delayed.

Case Study

35-year-old, African American female Height: 66 inches (167.64 cm), Weight 285 lbs. (129.28 kg). The patient presented to the clinic with symmetrical, painless, progressive, proximal leg weakness that started at the age of 24 years following childbirth. Initially, 11 years earlier, the patient noticed weakness in lower limbs presented as difficulty in rising from the chair, difficulty in climbing the stairs, and lifting arms for long periods. The symptoms have worsened over time to a situation where she was unable to stand up without the support of her arms. Significant medical history includes uncontrolled diabetes, hypertension, morbid obesity, and non-alcoholic steatohepatitis. The Patient's family history showed no neuromuscular involvement.

On physical examination, she had waddling gait. The distribution of the weakness was predominantly among hip flexors, hip adductors, and knee flexors. The patient denied swallowing or breathing difficulties, she denied any visual symptoms. She didn't complain of muscle atrophy or cramping. No exercise intolerance earlier in age.

Her labs showed Creatinine Kinase 846 U/L (ref 29-143 U/L), and Hemoglobulin A1c 11%. Forced vital capacity is 72% of predicted.

She had normal Electromyography (EMG) needle examination of the arms, legs, and para spinal

muscles. The Nerve Conduction Study (NCS) showed diffuse motor slowing with normal Compound Motor Action Potential (CMAP) configuration and amplitude. Normal sensory responses.

The chronicity and waddling gait suggested a hereditary muscle disease, the Limb-girdle muscular dystrophy gene panel was ordered (it included metabolic myopathy panel) and the genetic test analysis showed homozygous pathogenic mutation of the GAA gene [4].

p. (Arg854Ter) (CGA>TGA): c.2560 C>T in exon 18 of the GAA gene (NM_000152.3) c.-32-13 T>G:p.? in intron 1 of the GAA gene (NM_000152.3). Following genetic testing, acid alpha-glucosidase- blood was checked and was found to be 1.60 p mol/punch/Hr (ref. more than 3.88 p mol/punch/Hr) [3,7]. Enzyme replacement therapy was started. No improvement was noted a year after therapy. It was not clear if the ERT slowed down the progression.

Discussion

The patient presented with mainly neuromuscular symptoms, which was not specific and can be caused by different acquired and hereditary myopathies such as inflammatory myositis, metabolic myopathies, andlimb-girdle muscle dystrophies.

The distribution of weakness which was affecting hip flexors, hip adductors, and knee flexors is not typical for polymyositis and is commonly seen in Limb-Girdle muscular dystrophies such as Calpainopathy (which is also, an autosomal recessive disease). Although, lack of weakness in arms and lack of scapular winging is atypical of Calpainopathy. Motor slowing with normal sensory responses is commonly seen in spinal muscular atrophy and other motor neuron disorders, but there is no denervation by needle exam.

The patient had a history of gradual, painless progressive weakness of both lower limbs with a minimal weakness in upper limbs and not involving respiratory muscles is an atypical presentation for Late-onset Pompe disease. Normal EMG is a common feature in chronic myopathies. The lack of paraspinal spontaneous discharges is atypical for acid maltase deficiency. Due to its nature of autosomal recessive inheritance, negative family history is common in LOPD. Early confirmed diagnosis of adult-onset Pompe's is essential as delayed diagnosis and intervention cause irreversible damage to the point of no functional return [7]. Enzyme Replacement Therapy (ERT) and Physical Therapy (PT) are the treatment options for this condition. The patient was started on Lumizyme and physiotherapy. ERT with alpha-glucosidase alfa is shown to reduce morbidity and improve quality of life [8].

Employing dry blood spotor GAA genetic testing as a part of routine outpatient evaluation of idiopathic myopathies enhances early detection of this condition and thus timely intervention and management of symptoms and complications.

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