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ORIGINAL ARTICLE

Prevalence of late-onset pompe disease in Portuguese patients with diaphragmatic paralysis – DIPPER study

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Abstract Pompe disease is a rare autosomal recessive neuromuscular disorder caused by acid α-glucosidase enzyme (GAA) deficiency and divided into two distinct variants, infantile- and late-onset. The late-onset variant is characterized by a spectrum of phenotypic variation that may range from asymptomatic, to reduced muscle strength and/or diaphragmatic paralysis. Since muscle strength loss is characteristic of several different conditions, which may also cause diaphragmatic paralysis, a protocol was created to search for the diagnosis of Pompe disease and exclude other possible causes.

Methods: We collected a sample size of 18 patients (10 females, 8 males) with a median age of 60 years and diagnosis of diaphragmatic paralysis of unknown etiology, followed in the Pulmonology outpatient consultation of 9 centers in Portugal, over a 24-month study period. We evaluated data from patient's clinical and demographic characteristics as well as complementary diagnostic tests including blood tests, imaging, neurophysiologic and respiratory function evaluation. All patients were evaluated for GAA activity with DBS (dried blood test) or serum quantification and positive results confirmed by serum quantification and sequencing.

Results: Three patients were diagnosed with Pompe's disease and recommended for enzyme replacement therapy. The prevalence of Pompe, a rare disease, in our diaphragmatic paralysis patient sample was 16.8%.

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Conclusion: We conclude that DBS test for GAA activity should be recommended for all patients with diaphragmatic paralysis which, despite looking at all the most common causes, remains of unknown etiology; this would improve both the timing and accuracy of diagnosis for Pompe disease in this patient population. Accurate diagnosis will lead to improved care for this rare, progressively debilitating but treatable neuromuscular disease.

Introduction

Pompe disease is a rare autosomal recessive neuromuscular disorder caused by acid α-glucosidase enzyme (GAA) deficiency, resulting in the accumulation of glycogen in the lysosomes of numerous, but primarily muscular, tissues.[1] It is often termed glycogen storage disease type II (GSDII) or acid maltase deficiency.[2,3]

Depending on the age of onset, Pompe is divided into infantile and late-onset[4] disease. Infantile onset Pompe disease represents the most severe form and almost invariably leads to death, due to cardio-respiratory failure, within one year. The late-onset variant presents at any time after the age of one year, and is characterized by a spectrum of phenotypic variation. It may range from asymptomatic patients with increased creatine kinase (CK) to muscle cramps and pain syndrome or rigid-spine syndrome.[5–7] The lower limbs and paraspinal muscles are frequently affected first, followed by the respiratory muscles, particularly the diaphragm, intercostal and accessory muscles. Respiratory failure is the main cause of increased morbidity and mortality[8,9] and the main cause of respiratory failure is diaphragmatic weakness.[10]

The diaphragm is the major muscle of ventilation constituted by a dome-shaped structure of tendons and muscle innervated by the phrenic nerves which provide sensory, sympathetic and motor function. Diaphragm contraction expands the chest increasing pleural negative pressure and promoting air flow into the lungs. Whenever there is diaphragmatic weakness the diaphragm fails to contract appropriately, causing reduced inspiratory volume and possible dyspnea. An extreme form of diaphragmatic weakness is unilateral or bilateral diaphragmatic paralysis.[11] Several different conditions may present with respiratory failure and distinguishing among them is important to determine the correct therapeutic options.[12] Pompe disease is in the differential diagnosis of a wide variety of myopathies, and therefore accurate diagnostic tools are needed for an effective screening of this condition. Particularly when the progressive involvement and weakness of respiratory muscles and diaphragm, characteristic of the disease, are closely related to respiratory dysfunction which affects sleep, daily life activities, and overall quality of life.

The prevalence of this condition in the general population is unknown, and varies according to clinical presentation and ethnicity. The late-onset form has an estimated incidence of 1/57 000.[13] In Portugal, there is no accurate data on the prevalence of Pompe disease, but it is estimated that there are 27 cases of patients under enzyme replacement therapy (ERT).[14–16]

Therefore, the primary objective of this study was to estimate the prevalence of this disorder in patients with a diagnosis of diaphragmatic paralysis of unknown etiology followed in the outpatient setting of a Pulmonology clinic, and to characterize the clinical and socio-demographic profile of these patients. A secondary objective was to create an algorithm for the accurate diagnosis of late-onset Pompe disease in patients with diaphragmatic paralysis of unknown etiology, which will lead to better management and treatment of patients with this neuromuscular disease.

Materials and methods

This was a national, multicenter, epidemiological study of patients with a diagnosis of diaphragmatic paralysis of unknown etiology. The study population was identified from the Pulmonology outpatient consultations of 9 centers in Portugal over a 24-month study period. Patients were consecutively enrolled if they were ≥18 years of age, gave informed consent to participation, and fulfilled one of the following inclusion criteria: diagnosis of (unilateral or bilateral) diaphragmatic paralysis of unknown cause; diagnosis of restrictive lung disease (both FVC [forced vital capacity] and TLC [total lung capacity] < 80% of predicted, or ≥12% decrease in VC [vital capacity] in the supine position), decreased maximal inspiratory pressure (IPmax) or sniff nasal inspiratory pressure (SNIP) (at least −10 cm of H_2O than predicted) of unknown origin; diagnosis of progressive chronic myopathy with respiratory involvement, particularly of the diaphragm, with either inconclusive muscle biopsy or a diagnosis based on the generic definition of inclusion body myositis.

Patients were excluded from the study if they were unable or unwilling to provide informed consent, were tracheostomized or pregnant, required invasive mechanical ventilation, or suffered from one of the following conditions: neuromuscular junction diseases (Eaton–Lambert syndrome, myasthenia gravis), myopathies (polymyositis and other mixed connective tissue diseases, dystrophy mitochondrial myopathies, amyloidosis), spinal cord myelopathy (cervical spine injury, sarcoidosis, syringomyelia, polyomyelitis, amyotrophic lateral sclerosis), peripheral neuropathy [cervical spine injury, mediastinal tumor, Guillain–Barré syndrome, nutritional neuropathies (vitamin B12 deficiency) and lead neuropathy] or active neoplastic disease.

Information retrieved from patients included socio-demographic and clinical history, as well as physical exams

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