Acta Myologica • 2013; XXXII: p. 82-84

ORIGINAL ARTICLES

Clinical features of Pompe disease

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Glycogen storage disease type II - also called Pompe disease or acid maltase deficiency - is an autosomal recessive metabolic disorder, caused by an accumulation of glycogen in the lysosome due to deficiency of the lysosomal acid alpha-glucosidase enzyme. Pompe disease is transmitted as an autosomal recessive trait and is caused by mutations in the gene encoding the acid α-glucosidase (GAA), located on chromosome 17q25.2-q25.3. The different disease phenotypes are related to the levels of residual GAA activity in muscles. The clinical spectrum ranging from the classical form with early onset and severe phenotype to not-classical form with later onset and milder phenotype is described.

Key words: Glycogen storage disease type II, Pompe disease, GAA activity

Introduction

Pompe disease, also known as glycogen storage disease type II or acid maltase deficiency, is a rare disorder of the glycogen metabolism with an estimated frequency of 1 in 40,000 in Caucasians. Originally described by, and named after, Dr J. C. Pompe in 1932, the disease is characterized by the lysosomal accumulation of glycogen in numerous tissues of affected individuals. Pompe disease is transmitted as an autosomal recessive trait and is caused by mutations in the gene encoding the acid α-glucosidase (GAA), located on chromosome 17q25.2-q25.3. More than 200 different mutations of the GAA gene have been reported but the most common is the c.-32-13T> G mutation (1). Acidic α-glucosidase is a glycoprotein enzyme which degrades glycogen to glucose within the lysosomes. The altered function of this enzyme hampers the lysosomal degradation of glycogen that progressively accumulates inside the lysosomes, causing swelling and rupture of them with loss of glycogen in the cytoplasm and subsequently cell damage (2). The cellular pathology mainly affects muscle fibers displacing their myofibrils and ultimately leading to skeletal muscle weakness, but also other tissues such as cardiac and smooth muscle cells.

Clinical features

The clinical spectrum ranges from the classical form with early onset and severe phenotype to not-classical form with later onset and milder phenotype. The different disease phenotypes are related to the levels of residual GAA activity in muscles; less than 3% of normal enzyme activity is found in severe infantile cases and residual levels ranging 3-30% of normal are found in less severe late onset forms (1). The classical form occurs soon after birth and is characterized by hypertrophic cardiomyopathy, cardiorespiratory failure and generalized marked muscle weakness with floppy infant syndrome; if not diagnosed and early treated, the infants rarely survive beyond the first year of life. The differential diagnosis includes spinal-muscular atrophy, idiopathic hypertrophic cardiomyopathy or other metabolic disorders (1). The not-classical or late onset form has generally a milder phenotype than classical form and it can present with symptoms any time after age 1 year. Cardiac involvement is very rare and symptoms are dominated by significant involvement of skeletal muscles with a gradually progressing myopathy and respiratory insufficiency leading to varying degrees of disability associated to reduced life expectancy on average. Most patients requires use of a wheelchair and ventilatory assistance (3-5). However, the recent development of a specific treatment, in the form of enzyme replacement therapy is modifying the natural course of the illness.

The clinical presentation of Pompe disease can resemble that of many musculoskeletal disorders, especially muscular dystrophies presenting with limb girdle muscle weakness (LGMW) (3, 4). Pompe disease affects the pelvic muscles more than muscles of the shoulder girdle. Scapular winging is usually prominent. Neck flexors, trunk exten-

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sors, and abdominal muscles are frequently and markedly affected (6). Facial involvement with dysphagia (7) or ptosis (unilateral or bilateral) has also been observed (4). The many phenotypic similarities with other muscle diseases can lead to underdiagnosis and misdiagnosis of Pompe disease. The typical delay from first medical consultation to diagnosis spans approximately 10 years. However, the severity of axial muscle involvement in Pompe disease is usually greater than in other conditions presenting with LGMW and in particular unexplained respiratory insufficiency should raise a suspicion of Pompe disease (8). In fact, differently from other neuromuscular diseases, where respiratory insufficiency occurs after loss of ambulation, respiratory symptoms in Pompe disease can be an early clinical manifestations of the disease, when patients are still ambulant. The respiratory muscles involved are the upper airways, inspiratory muscles of the chest, and the diaphragm. Respiratory failure in patients with Pompe disease can range from insidious to acute onset and respiratory muscle involvement is the most common cause of early death in these patients. Respiratory symptoms increase with Pompe disease progression and include a progressive loss of respiratory muscle function, decrease of vital capacity, sleep disordered breathing, impaired cough, chronic respiratory insufficiency, and finally cor pulmonale and acute respiratory failure (9).

Diagnosis

The diagnosis of the classic form of Pompe disease is made, usually, early and relatively easily because, due to the marked severity of the symptoms of the disease yet at it onset, the patients are immediately admitted to pediatric intensive care centers where physicians are well trained to recognize the disease. Conversely, the diagnosis of late onset forms is complicated by the rarity of the condition and heterogeneity of the clinical manifestations, which vary with respect to organ involvement, age at onset, and severity. Symptoms are often unspecific, especially at onset, and they may remain mild even for decades so that neither the patient nor the doctor consider to deepen diagnostic procedures. The American Association of Neuromuscular and Electrodiagnostic Medicine has developed an algorithm to aid in the diagnosis of Pompe disease (10). In patients presenting with limb-girdle syndrome or symptoms suggestive of respiratory muscle involvement, Pompe disease should be included in the differential diagnosis and patients should undergo further laboratory, electrodiagnostic and pulmonary evaluations, and skeletal muscle Magnetic Resonance Imaging (MRI) studies as appropriate.

Creatine kinase (CK) levels are usually elevated (ranging from 1.5 to 15 times the upper limit of normal in adults) in late onset Pompe disease patients. In some cases, however, CK levels are normal. In asymptomatic or mildly symptomatic individuals, persistent elevations of CK have led to further investigation and the subsequent diagnosis of Pompe disease (11).

In patients with late onset Pompe disease, nerve conduction studies are normal, but needle electromyographic (EMG) findings often indicate myopathy with increased muscle membrane irritability in the form of fibrillation potentials, positive sharp waves, complex repetitive discharges or myotonic discharges in the absence of clinical myotonia. Noteworthy, EMG findings in limb muscles may be normal while abnormalities may be seen only in the paraspinal muscles. In the appropriate clinical setting, myotonic or complex repetitive discharges in the thoracic paraspinal musculature should lead to consider the diagnosis of Pompe disease (12, 13).

Because diaphragm weakness often occurs early in the disease process and muscle weakness may not be evident until later in the disease course, respiratory evaluation is extremely important in patients who may have Pompe disease. Spirometric measurement of forced vital capacity (FVC) in both the seated and supine positions should be made whenever possible. A greater than 10% drop in FVC from the seated to the supine testing position is suggestive of diaphragm weakness and should raise the possibility of Pompe disease. Both measurements should be made regardless of whether respiratory symptoms are present. Because patients may have a normal seated FVC, the presence of diaphragm weakness can be missed if supine FVC is not measured (8, 9).

Results from studies in adult onset Pompe disease patients have demonstrated a correlation between muscle weakness and abnormal findings from magnetic resonance imaging and computed tomography. Although these techniques can identify atrophy and fatty infiltration of specific muscles (i.e. trunk muscles), as well as pattern of muscle involvement, these findings are not unique to Pompe disease and do not specifically aid in establishing a definite diagnosis (14).

The determination of partial or complete deficiency of GAA enzyme activity in blood or fibroblasts is the gold standard for diagnosis in Pompe disease. The currently available GAA enzyme activity assays are both reliable and sensitive. Blood-based assays, performed on whole blood or Dried Blood Spot (DBS) should be employed early in the diagnostic course as a screening tool when Pompe disease is being considered (15). If patient has already undergone muscle biopsy that reveals increased glycogen or vacuolization but no specific diagnosis, blood-based or tissue-based GAA enzyme activity testing is recommended. However, normal muscle biopsy results should not rule out Pompe disease, and a patient's GAA enzyme activity should be analyzed when clini-

cal suspicion of Pompe disease exists (16). If an initial blood-based GAA enzyme assay shows reduced activity, the diagnosis of Pompe disease should be confirmed by a second GAA enzyme activity assay in a separate blood or tissue sample or by GAA gene sequencing. When the results of enzymatic analyses in two different types of tissue samples are discordant, GAA gene sequencing may be particularly useful.

In conclusion the suspicion and recognition of the characteristic symptoms of Pompe disease may improve both the timing and accuracy of the diagnosis of Pompe disease, which will lead to improvement in the care of patients who have this progressively debilitating neuromuscular disease (17, 18).

References

1. van der Ploeg AT, Reuser AJ. Pompe's disease. Lancet 2008;372:1342-53.
2. Raben N, Roberts A, Plotz PH. Role of autophagy in the pathogenesis of Pompe disease. Acta Myol 2007;26:45-8.
3. Hagemans ML, Winkel LP, Van Doorn PA, et al. Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. Brain 2005;128:671-7.
4. van der Beek NA, de Vries JM, Hagemans ML, et al. Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. Orphanet J Rare Dis 2012;7:88.
5. Müller-Felber W, Horvath R, Gempel K, et al. Rate of disease progression during long-term follow-up of patients with late-onset Pompe disease. Neuromuscul Disord 2009;19:113-17.
6. Alejaldre A, Díaz-Manera J, Ravaglia S, et al. Trunk muscle involvement in late-onset Pompe disease: study of thirty patients. Neuromuscul Disord 2012;22 Suppl 2:S148-54.
7. Hobson-Webb LD, Jones HN, Kishnani PS. Oropharyngeal dysphagia may occur in late-onset Pompe disease, implicating bulbar muscle involvement. Neuromuscul Disord 2013;23:319-23.
8. Mellies U, Lofaso F. Pompe disease: a neuromuscular disease with respiratory muscle involvement. Respir Med 2009;103:477-84.
9. van der Beek NA, van Capelle CI, van der Velden-van Etten KI, et al. Rate of progression and predictive factors for pulmonary outcome in children and adults with Pompe disease. Mol Genet Metab 2011;104:129-36.
10. American Association of Neuromuscular & Electrodiagnostic Medicine. Diagnostic criteria for late-onset (childhood and adult) Pompe disease. Muscle Nerve 2009;40:149-60.
11. Spada M, Porta F, Vercelli L, et al. Screening for later-onset Pompe's disease in patients with paucisymptomatic hyperCKemia. Mol Genet Metab 2013;109:171-3.
12. Schlotter-Weigel B, Lochmüller H, Schoser B. Late onset Pompe disease: clinical and neurophysiological spectrum of 38 patients including long-term follow-up in 18 patients. Neuromuscul Disord 2007;17:698-706.
13. Hobson-Webb LD, Dearmey S, Kishnani PS. The clinical and electrodiagnostic characteristics of Pompe disease with post-enzyme replacement therapy findings. Clin Neurophysiol 2011;122:2312-7.
14. Carlier RY, Laforet P, Wary C, et al. Whole-body muscle MRI in 20 patients suffering from late onset Pompe disease: involvement patterns. Neuromuscul Disord 2011;21:791-9.
15. Goldstein JL, Young SP, Changela M, et al. Screening for Pompe disease using a rapid dried blood spot method: experience of a clinical diagnostic laboratory. Muscle Nerve 2009;40:32-6.
16. Vissing J, Lukacs Z, Straub V. Diagnosis of Pompe Disease: muscle biopsy vs blood-based assays. JAMA Neurol 2013;70:923-7.
17. Chien YH, Hwu WL, Lee NC. Pompe disease: early diagnosis and early treatment make a difference. Pediatr Neonatol 2013;54:219-27.
18. Dubrovsky A, Corderi J, Karasarides T, et al. Pompe disease, the must-not-miss diagnosis: a report of 3 patients. Muscle Nerve 2013;47:594-600.