Importance of clinical suspicion in the diagnosis of late-onset Pompe disease

Miguel A. Barba-Romero, Irene García-Cuartero

Internal Medicine Department. Albacete University Hospital. Castilla-La Mancha University. Albacete, Spain.

Corresponding author: Miguel Ángel Barba Romero MD, PhD. Internal Medicine Department. Albacete University Hospital. Hermanos Falcó, 37. E-02006 Albacete (Spain).

E-mail: mabarbar@sescam.jccm.es

Conflict of interest: M.A.B.R. has received honoraria from Genzyme, Shire and Alexion, for conferences and role as an advisor.

Accepted: 21.03.16.

How to cite this article: Barba-Romero MA, García-Cuartero I. Importance of clinical suspicion in the diagnosis of late-onset Pompe disease. Rev Neurol 2016; 63: 236-8.

Versión española disponible en www.neurologia.com

Pompe disease is a recessive autosomal metabolic myopathy caused by a deficiency in the activity of the lysosomal alpha acid glycosidase (GAA) enzyme, which is involved in glycogen breakdown. This deficiency causes glycogen storage in the lysosomes of the muscle cells in the skeletal, smooth and cardiac muscles, leading to progressive muscle weakness [1].

Two forms of presentation have been described: The infantile form, and the late-onset form, starting after the first year of life [2]. The clinical presentation of late-onset Pompe disease (LOPD) is very variable with respect to age of onset, organic presentation, myopathy degree and progression rate [2]. In LOPD, muscle involvement is overall progressive and characterized by proximal weakness, greater in the pelvic girdle muscles, showing difficulty to climb up the stairs, run or stand up [3]. Respiratory insufficiency is the main cause of morbidity and mortality; thus, it is important the early identification of respiratory muscles involvement to initiate support measures [4].

The variability in symptoms onset, as well as, sometimes, their unspecific nature, usually lead to a considerable delay in diagnosis, which in turns delays the possibility to initiate the currently available enzyme replacement treatment (ERT) to slow down and modify the clinical course of the disease [5].

We present the case of the first patient with LOPD in our service who required several complementary tests to be finally diagnosed after eight years since the onset of his symptoms.

Table. Laboratory data.

	1986	1988	1993	1994	1995
Creatine kinase (U/L)			1,088 (≤ 190)	680 (≤ 195)	
Aldolase (U/L)				16.3 (≤ 7.5)	14.3 (≤ 7.5)
Myoglobin (μg/L)				200 (≤ 100)	200 (≤ 100)
Total bilirubin (mg/dL)				1.57 (≤ 1.2)	
Alanine aminotransferase (U/L)	84 (≤ 25)	113 (≤ 37)	137 (≤ 37)	94 (≤ 37)	
Aspartate aminotransferase (U/L)	99 (≤ 29)	122 (≤ 40)		106 (≤ 40)	
Lactate dehydrogenase (U/L)			756 (≤ 460)	534 (≤ 460)	

Data in parenthesis: value considered as normal at that time point.

The patient was a 27-year old male (1991) at the time he was first evaluated at the Internal Medicine department due to constitutional syndrome and discomfort in right hypocondrium. His history included smoking, mild drinking habit, and surgery for right inguinal hernia repair in 1986, showing transaminases increases in the pre-operatory laboratory analyses (Table).

Three years previously (in 1989), he had been evaluated in the Gastroenterologist department due to discomfort in upper hemi-abdomen and back, along with retrosternal pyrosis. Increases in transaminases were already observed (Table). Complementary tests (serology for hepatitis B and hepatitis C virus), abdominal ultrasound, gastroscopy, and liver biopsy were performed with no significant findings. The years that followed, the patient continued complaining from unspecific discomfort in right hypocondrium, and weakness, plus asthenia, anorexia and discrete non-quantified weight loss in the month previous to his visit to the Internal Medicine department.

Due to the increased levels of creatine kinase (CK) found at the internal medicine department in 1991 (Table), a muscle biopsy was performed but showed no evidence of pathology under the optic microscope. During the following three years, the patient kept on reporting limb weakness and shortness of breath. In the analytical studies, the increase in muscle enzymes persisted (Table); thus, an electromyography (EMG) was requested in 1994 showing, on the left tibialis anterior muscle, a normal pattern of maximum strength and motor unit potentials (10% polyphasic potentials) with spontaneous potentials at rest (fibrillation potentials) at two point sites, and on the biceps brachialis, a normal pattern of maximum strength and motor unit potentials (except for 27% polyphasic potentials), and again fibrillation potentials at two point sites; the conclusion was 'exploration within normality'. Likewise, baseline spirometry was reported as normal and maximum inspiratory and maximum expiratory pressure were 80% and 76%, respectively, over the normal value for sex and age.

The controls performed during the following two years showed difficulty to climb up the stairs and to sit down from a laying position, as well as weakness of lower limbs.

Upon suspicion of possible muscle dystrophy, another EMG was performed in 1996 studying the left tenar eminence muscle and the left tibialis anterior muscle, resulting in 'within normality'. Likewise, a new muscle biopsy was performed showing variation in fiber size and dystrophic fiber pattern, irregular distribution of oxidative enzymes, presence of vacuoles and PAS positive deposits, necrosis and phagocytosis images, fibrosis, and absence of inflammatory changes and of inclusion bodies but with presence of a great number of scalloped fibers, and focal alteration of dystrophin 2 and spectrin. At the electron microscopy, glycogen storage was observed in cytosomes membrane coated and polymorphic residual bodies. The conclusion was 'myopathy compatible with type Pompe glycogenesis in the adult'.

In 2003, the enzymatic activity was assessed in fibroblasts, and the result was compatible with

a deficiency of alpha acid glycosidase (40.8 vs. 543 nmol/h per mg of protein, as control value).

In 2007, the genetic analysis of the patient's DNA looking for mutations in the *GAA* gene (Erasmus Centre) did not show any of the known pathogenic Pompe disease-associated mutations. Different polymorphisms in homozygosity were found (exons 3-5, 11, 13, 15, 16, 18), as well as a variant in exon 15, which might worsen the effect of another genetic defect. A study of large gene reorganizations (deletions-insertions) was not conducted.

Finally, in 2014, and with absence of genetic confirmatory Pompe disesase diagnosis, the total activity of acid α-glycosidase was assessed in lymphocytes resulting in 0.02 nmol/min/mg of protein (normal range: 0.15-1.0) and 13.3% intra-lymphocyte residual GAA activity; values, both of them, clearly compatible with the previous diagnosis of LOPD.

Lysosomal storage diseases (LSDs) are a group of disorders characterized by a deficiency in the metabolism of complex molecules inside the lysosome. The deficient activity of a lysosomal enzyme leads to the accumulation of the corresponding non-metabolized substrate in most tissues [6]. LSDs may onset in adolescents or in adults. In the late-onset forms, one may find residual enzyme activity, which together with other genetic, epigenetic and, even, extragenetic factors, is responsible of the high phenotypical variability, different severity of the clinical manifestations and the evolutionary pattern of the organic disorder.

Pompe disease corresponds to the only congenital disorder of the glycogen metabolism within the LSDs [7]. The infantile form includes patients with rapidly progressive disease, mainly characterized by cardiac involvement, and other patients with slower progression and less severe cardiomyopathy, which may show variable presentation in either case [8,9]. The clinical presentation of its late-onset form (either juvenile or adult) is very heterogeneous [2], and similar to that of other more frequent neuromuscular disorders, such as polymyositis, miasthenia gravis or Duchenne type-like muscular dystrophies, which makes more difficult its correct diagnosis [1]. CK is not always increased in adults [10], and histologic studies or EMG may be normal, if they have not been performed on the involved muscle [11]. That is why one third of patients with the disorder suffer from a diagnostic delay ranging between 5 and 30 years [10].

Pompe disease should be suspected when physicians face patients with symptoms such as muscle fatigue, motor disorder, respiratory difficulty or increase in muscle enzymes [11]. In addition, the early diagnosis of the disease is very important, since ERT with human recombinant alpha glycosidase enzyme is available since 2006, and may slow-down the disease progression [5], which should be periodically assessed during the follow-up of the patient undergoing treatment [12].

The case we report reflects, unfortunately, the 'pilgrimage' these patients may endure until obtaining the right diagnosis. The increase in liver enzymes of our patient led to screening for hepatopathy, since at that moment CK was not assessed. When muscular weakness and increase in muscular enzymes were reported, studies were conducted to rule out an underlying myopathy and the complementary tests performed were initially labelled as 'normal', probably due to being performed on muscles not yet involved and because only the optic microscope was used in the first biopsy. A second biopsy, followed by electron microscope and immune-hystochemical analyses, finally correctly guided the diagnosis after 8 years since the onset of symptoms, with later confirmation of GAA deficiency in fibroblasts. Currently, the enzymatic activity of GAA may be determined by means of a blood-dried spot, although genetic confirmation is advisable afterwards [11,13]. The efficacy and reliability of the blood-dried spot test to screen for Pompe disease in patients with suspected myopathy has been recently confirmed [14].

Since specific ERT is available for this disease, it is extremely important that medical professionals may suspect of Pompe disease in cases with the previously described symptoms or with an inexplicable increase in muscular enzymes, which will result in early diagnosis and the possibility for the patient to benefit from early specific treatment.

References

1. Van der Ploeg AT, Reuser AJ. Pompe's disease. Lancet 2008; 372: 1342-53.
2. Kishnani PS, Steiner RD, Bali D, Berger K, Byrne BJ, Case LE, et al. Pompe disease diagnosis and management guideline. Genet Med 2006; 8: 267-88.
3. Dubrovsky A, Corderi J, Karasarides T, Taratuto AL. Pompe disease, the must-not-miss diagnosis: a report of 3 patients. Muscle Nerve 2013; 47: 594-600.
4. Gaeta M, Musumeci O, Mondello S, Ruggeri P, Montagnese F, Cucinotta M, et al. Clinical and pathophysiological clues of respiratory dysfunction in late-onset Pompe disease: new insights from a comparative study by MRI and respiratory function assessment. Neuromuscul Disord 2015; 25: 852-8.
5. Van der Ploeg AT, Clemens PR, Corzo D, Escolar DM, Florence J, Groeneveld GJ, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. N Engl J Med 2010; 362: 1396-406.
6. Parker EI, Xing M, Moreno-De-Luca A, Harmouche E, Terk MR. Radiological and clinical characterization of the lysosomal storage disorders: non-lipid disorders. Br J Radiol 2014; 87: 20130467.
7. Hers HG. Alpha-glucosidase deficiency in generalized glycogenstorage disease (Pompe's disease). Biochem J 1963; 86: 11-6.
8. Moreno-Medinilla E, Berzosa-López R, Mora-Ramírez MD, Blasco-Alonso J, Martínez-Antón J. Variabilidad en la presentación clínica de la enfermedad de Pompe infantil: presentación de dos casos y respuesta al tratamiento con enzima recombinante humana. Rev Neurol 2014; 59: 503-7.
9. Ley-Martos M, Salado-Reyes MJ, Espinosa-Rosso R, Solera-García J, Jiménez-Jiménez L. Variabilidad en la presentación clínica en la enfermedad de Pompe: evolución tras terapia de reemplazo enzimático. Rev Neurol 2015; 61: 416-20.
10. Winkel LP, Hagemans ML, Van Doorn PA, Loonen MC, Hop WJ, Reuser AJ, et al. The natural course of non-classic Pompe's disease; a review of 225 published cases. J Neurol 2005; 252: 875-84.
11. Barba-Romero MA, Barrot E, Bautista-Lorite J, Gutiérrez-Rivas E, Illa I, Jiménez LM, et al. Guía clínica de la enfermedad de Pompe de inicio tardío. Rev Neurol 2012; 54: 497-507.
12. Gutiérrez-Rivas E, Illa I, Pascual-Pascual SI, Pérez-López J, Vílchez-Padilla JJ, Bautista-Lorite J, et al. Guía para el seguimiento de la enfermedad de Pompe de inicio tardío. Rev Neurol 2015; 60: 321-8.
13. Winchester B, Bali D, Bodamer OA, Caillaud C, Christensen E, Cooper A, et al. Methods for a prompt and reliable laboratory diagnosis of Pompe disease: report from an international consensus meeting. Mol Genet Metab 2008; 93: 275-81.
14. Gutiérrez-Rivas E, Bautista J, Vílchez JJ, Muelas N, Díaz-Manera J, Illa I, et al. Targeted screening for the detection of Pompe disease in patients with unclassified limb-girdle muscular dystrophy or asymptomatic hyperCKemia using dried blood: a Spanish cohort. Neuromuscul Disord 2015; 25: 548-53.