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Short Communication

Highlighting intrafamilial clinical heterogeneity in late-onset Pompe disease ☆

C. Papadopoulos [a,*], G.K. Papadimas [a], H. Michelakakis [b], E. Kararizou [a], P. Manta [a]

[a] Eginition Hospital, University of Athens, School of Medicine, Greece
[b] Department of Enzymology and Cellular Function, Institute of Child Health, Athens, Greece

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ABSTRACT

Background/aims: Pompe disease is a rare metabolic disorder caused by deficiency of the lysosomal enzyme acid alpha-glycosidase (GAA). The late onset form of the disease is characterized by muscle weakness and respiratory involvement of variable severity. The aim of this short communication is to highlight the clinical variability of Pompe disease within siblings suffering from the disease.

Case reports: We report three pairs of siblings with late-onset Pompe disease presenting with different clinical phenotypes within the spectrum of disease phenotypes.

Conclusion: Clinical manifestations in Pompe disease within the same family can be very different. Clinicians should investigate patients' siblings for symptoms throughout the entire spectrum of the disease in order to avoid delays in the diagnosis and to pick-up mildly affected persons as early as possible, when they can benefit the most from enzyme replacement therapy.

1. Introduction

Pompe disease is a rare metabolic disorder caused by deficiency of the lysosomal enzyme acid alpha-glycosidase (GAA) [1]. The late onset form of the disease has a variable age of onset and is characterized by a spectrum of symptoms and phenotypes that largely comprise a slowly progressive myopathy and respiratory muscle involvement [1,2]. Intrafamilial phenotypic variability has been reported in Pompe

* Corresponding author at: 1st department of Neurology, University of Athens, School of Medicine, Eginition Hospital, 74, Vas. Sofias Avenue, GR-115 28 Athens, Greece.
E-mail address: constantinospapadopoulos@yahoo.com (C. Papadopoulos).

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disease, as well as in other glycogen storage diseases even in siblings sharing a similar genetic background [3–5].

With the intention to emphasize the phenotypic variability of Pompe disease within patients sharing the same genetic background, we present three pairs of siblings diagnosed with the disease but presenting with different clinical phenotypes.

2. Methods and results

Three pairs of siblings, that have been previously reported [6,7], are presented. With the exception of the male sibling of pair 3 who was not followed in our center, and to whom clinical details were obtained from his sister, all other patients were analyzed retrospectively. All patients were clinically examined and muscle strength was measured by manual muscle testing according to the MRC (Medical Research Council) scale. Pulmonary function was assessed by spirometry in supine and upright position. The diagnosis of Pompe disease was confirmed by molecular testing.

2.1. Pair 1

The first pair of siblings refers to a woman and her brother diagnosed at the age of 45 and 43 years respectively, harboring heterozygous mutations IVS1-13T>G in one allele and 1293del20 (GAA ex8) on the other. The female patient presented with easy fatigability and difficulties rising from supine position. Laboratory examination showed marginally elevated creatine phosphokinase (CPK) levels (up to 250 IU/lt). Clinical examination revealed mild weakness (5- on MRC scale) of pelvic muscles. Respiratory system evaluation was normal. Muscle biopsy showed a PAS positive vacuolar myopathy. The diagnosis of Pompe disease was confirmed molecularly. Following diagnosis she revealed that her younger brother presented difficulties in climbing stairs. He was examined on the framework of family study. Clinical examination revealed a waddling gait, bilateral scapular winging and proximal weakness of lower and upper extremities (4-/5- on MRC scale). Respiratory system evaluation showed respiratory insufficiency and severe diaphragmatic weakness with a 50% FVC (Forced Vital Capacity) reduction from sitting to supine position. Molecular investigation established the diagnosis of Pompe disease. Both patients over the last four years are on ERT showing no deterioration of their clinical status.

2.2. Pair 2

The second pair refers to two sisters with Pompe disease homozygous for the IVS1-13T>G mutation. The younger sister presented with proximal lower extremities weakness and a waddling gait since her early adolescence. She underwent muscle biopsy that revealed a PAS positive vacuolar myopathy and was diagnosed with Pompe disease at the age of 16. Since her early thirties she started using a walker due to an increase frequency of falls and experienced a slowly progressive deterioration of her respiratory function resulting to the use of mechanical ventilation at the age of 42, despite 58 months of ERT. The diagnosis of the disease on the younger sister at the age of 16 led to the reassessment and diagnosis of her 19 year old sister who was at the time on mechanical ventilation due to a yet unexplained acute respiratory failure following a lower respiratory tract infection. The following years she developed a slowly progressive myopathy of lower extremities that eventually rendered her wheelchair bound at the age of 30. The patient suffered from recurrent respiratory infections and finally deceased at the age of 43 despite three years of ERT.

2.3. Pair 3

The third pair of siblings refers to a 40 year old woman and her 39 year old brother, compound heterozygotes for the IVS1-13T>G in one allele and the c.2066–2070dup on the other. The diagnosis of Pompe disease to the female patient was set at the age of 31 by GAA phenotyping following the discovery of elevated CPK levels on routing laboratory screening (up to 800 IU/lt). She referred to our center at the age of 38. Clinical examination revealed a waddling gait and mild proximal weakness of lower extremities (5- on MRC). Respiratory system evaluation revealed a 28% FVC drop from sitting to supine position.

Cardiac evaluation was unremarkable. The patient received ERT for a period of six months. Her 39 year old brother who is not followed in our center was diagnosed with Pompe disease 6 years before his sister, at the age of 25, and is on mechanical ventilation due to respiratory insufficiency since his late twenties.

3. Discussion

In order to illustrate intrafamilial phenotypic variability in Pompe disease, we report three pairs of siblings with different presenting symptoms within the spectrum of disease phenotypes. Awareness that Pompe disease can present in different ways and follows a variable course even within the same family is essential in order to diagnose siblings of affected persons. Diagnosis of the disease in the female patient in pair 1 and the family framework that followed led to the diagnosis of her younger brother who, unlike his sister, already presented with severe respiratory muscle involvement and proximal weakness that resulted in difficulties with everyday activities. In the second pair the younger sister underwent a muscle biopsy in the context of the evaluation of a proximal myopathy. The diagnosis of Pompe disease led to the assessment under a different point of view of her older sister's symptoms who suffered from severe respiratory insufficiency and no muscle weakness at that time. This wasn't the case in the third pair of siblings where the diagnosis of Pompe disease in the brother, who suffered from severe diaphragmatic weakness, did not resulted to the diagnosis of his asymptomatic at the time sister. Elevated CPK levels on a routine examination 6 years later were required to set the diagnosis.

Intrafamilial variability in Pompe disease, as well as in other glycogen storage diseases, has already been reported in the literature [4,5]. It is probable that additional genes as well as non-genetic factors such as life-style, nutrition or still unknown environmental modifiers influence disease expression in siblings. In the era of enzyme replacement therapy (ERT), delay in the diagnosis of Pompe disease could deprive patients from ERT and its potential benefits which are most important in the early stages of the disease [1]. Presenting disease manifestations and disease course within the same family can be very different. It can range from difficulties in every-day activities and mild hyperCKemia to severe respiratory failure and proximal weakness as in pair 1, from acute respiratory insufficiency progressing to a proximal myopathy in contrast to the typical course of proximal myopathy and late respiratory involvement as in pair 2 and finally from isolated myopathy in contrast to isolated respiratory muscle involvement as in pair 3. We propose that clinical evaluation and laboratory testing with CPK, ASAT and ALAT evaluation should be recommended to siblings of patients diagnosed with Pompe disease. Clinicians should investigate siblings of patients for symptoms throughout the entire spectrum of disease manifestations, comprising muscle strength and pulmonary function evaluation. Moreover, a dried blood spot test, a reliable, rapid and non-invasive test, sensitive to diagnose mildly symptomatic patients [8,9] should be offered in patients' siblings, even if they are asymptomatic, in order to pick-up mildly affected persons early in the course of the disease, where they can benefit the most from ERT [1], and to provide to reproductive-age individuals with prenatal consultation and clinical genetic counseling such as carrier status of the partner in the context of reproductive choices.

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