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The frequency of late-onset Pompe disease in pediatric patients with limb-girdle muscle weakness and nonspecific hyperCKemia: A multicenter study

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Abstract

The aim of this multicenter study was to screen for late-onset Pompe disease in high-risk children with limb-girdle muscle weakness and nonspecific hyperCKemia using the dried blood spot (DBS) test. Seventy-two children from four pediatric neurology departments in Turkey were enrolled in the study: 37 with limb-girdle muscle weakness and 35 with nonspecific hyperCKemia. Acid α-glucosidase (GAA) activity was measured on DBS by tandem mass spectrometry. Six patients tested positively for Pompe disease. In three patients, one with the limb-girdle muscle weakness and two with nonspecific hyperCKemia, this was confirmed by genetic analysis. The overall frequency of late-onset Pompe disease in the study population was 4.2%. The c.1784C>T mutation found in one patient is a new mutation whereas the c.1655T>C mutation detected in the other two patients is not novel. In conclusion, Pompe disease should be suspected in patients with limb-girdle muscle weakness and nonspecific hyperCKemia. The DBS test is a safe and reliable method of diagnosis but must be confirmed by genetic analysis. In patients with a positive DBS test and negative genetic analysis, tissue assay of GAA should be considered.

Keywords: Late-onset Pompe disease; Limb-girdle muscle weakness; HyperCKemia; Dried blood spots; Enzyme replacement therapy

1. Introduction

Pompe disease (glycogen storage disease type II) is a rare autosomal recessive metabolic myopathy caused by deficiency of acid α-glycosidase (GAA) that degrades lysosomal glycogen [1]. The result is accumulation of glycogen in various tissues, mainly skeletal, muscle, and heart, leading to a wide spectrum of clinical phenotypes of the disease [2]. In the most widely known classical infantile form, glycogen is accumulated mainly in the heart, and infants present with generalized hypotonia and hypertrophic cardiomyopathy soon after birth [1]. The natural course of the disease is devastating and death usually occurs before the age of 1 year if left untreated [1]. In the last 30 years, a late-onset form of the disease with muscle weakness mostly confined to axial and limb-girdle muscles and prominent respiratory muscle involvement in the absence of cardiomyopathy have been described [3–5]. The disease can manifest at any age leading to respiratory insufficiency and eventual death with a slowly progressive course [6]. The diagnosis of the late-onset form is especially challenging and often delayed because the disease is rare with a wide clinical spectrum mimicking other neuromuscular disorders [6]. The estimated incidence of Pompe disease is 1 in 40,000; however, the real incidence is thought to be as high as 1 in 9000 according to prospective trials [7–9].

In 2006, the approval of enzyme replacement therapy (ERT) brought in a new era for the treatment of Pompe disease [10,11]. Clinical trials suggest that early replacement of the deficient enzyme leads to definite improvement of the clinical condition,

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increased survival in the classical infantile form, and a substantial increase in either pulmonary or motor functions in the late-onset form [10–14].

The aim of this multicenter study was to look for the frequency of late-onset Pompe disease in the high-risk children such as nonspecific hyperCKemia, either asymptomatic or paucisymptomatic, and limb-girdle muscle weakness and initiate therapy as soon as possible. We thereby intend to increase the awareness of Pompe disease.

2. Materials and methods

We looked for patients with nonspecific hyperCKemia, either asymptomatic or paucisymptomatic (early fatigue or muscle cramps without weakness), or limb-girdle muscle weakness in the databases of 4 pediatric neurology centers in Turkey. All patients who had been screened over the 1-year period from December 2014 to December 2015 were enrolled in the study and the remaining patients in the database were contacted by telephone and invited to the hospital for screening.

Inclusion criteria were (1) age <18 years, (2) hyperCKemia was defined as serum CK >300 U/L at least two determinations at rest within the last 6 months, and (3) muscle weakness confined to limb-girdle muscles.

Children with identifiable causes of CK elevation including hypothyroidism and electrolyte imbalance were excluded from the study.

Informed consent was obtained from all parents.

All patient information about demographic characteristics, family history of neuromuscular diseases and various laboratory data was recorded on a patient's follow-up form.

Blood samples were immediately spotted on filter paper and dried at room temperature. Patients' dried blood spot (DBS) specimens were analyzed for α-galactosidase activity by electrospray ionization tandem mass spectrometry (ESI-MS). Use of ESI-MS enabled the identification of several disorders by simultaneous measurement of amino acids and acylcarnitines for the first time [9].

Genetic mutation analyses were performed by GAA gene sequencing in samples with suspected enzyme deficiency.

The local ethics committee approved the study.

3. Results

3.1. Demographics

Of the 98 children identified in the databases of 4 pediatric neurology centers, 72 whose parents agreed in screening were enrolled in the study. Among them 52 (72.2%) were male and 20 (27.8%) female. The study included 37 (51.4%) children with limb-girdle muscle weakness and 35 (48.6%) with nonspecific hyperCKemia. The mean age was 8.18 (±5.22) years, ranging from 3 months to 17 years and 9 months. The demographic characteristics of the participants are presented in Table 1.

Table 1
Demographic and clinical characteristics of the participants.

	Patients (n = 72)
Age, years, mean (SD)	8.18 ± 5.22
Gender n (%)	
Female	20 (27.8%)
Male	52 (72.2%)
Clinical presentation n (%)	
Asymptomatic with nonspecific hyperCKemia	35 (48.6%)
Limb-girdle myopathy	37 (51.4%)

3.2. Characteristics of patients with late-onset Pompe disease

Of the 6 children who had decreased enzyme levels in DBS results, Pompe disease was confirmed in 3 (4.2%) by genetic analysis: 1 from limb-girdle muscle weakness, the remaining 2 from hyperCKemia group. The clinical and demographic characteristics, test results and results of genetic mutation analysis of the children with confirmed Pompe disease are presented in Table 2.

Blood CK levels showed a moderate increase ranging from 730 to 1710 U/L (mean 1095.6).

The following mutations were detected in homozygous state. The missense mutation c.1784C>T(p.595L) detected in patient no. 1 with myopathy is a new mutation. Patient nos. 2 and 3 had the same well-known missense mutation c.1655T>C. Both patients were referred to our pediatric neurology clinic with nonspecific hyperCKemia; however, when examined carefully they both had myopathic facies. Parents of patient nos. 1 and 3 are healthy heterozygous carriers of the disease. We were not able to take DBS samples from the parents of patient no. 2. All of the patients were placed on ERT.

Patient no. 1 was a 12-year-old girl with severe scoliosis who showed respiratory involvement and required nocturnal non-invasive ventilation. The remaining patients were 2 males aged 1 and 3 years, respectively. They were referred from pediatric gastroenterology clinics after being evaluated for nonspecific elevation of liver enzymes. Although the parents of these children did not have any neuromuscular complaints they both had myopathic facies when carefully examined.

4. Discussion

Since the approval of acid α-glycosidase ERT of Pompe disease in 2006, early diagnosis has become more important

Table 2
Demographic and clinical characteristics of patients with late-onset Pompe disease.

Patient no.	1	2	3
Gender	Female	Male	Male
Age at screening (years)	12	2	1
Clinical presentation	Myopathy	Asymptomatic	Asymptomatic
Age at onset of symptoms (years)	3	–	–
Delay in diagnosis (years)	9	–	–
CK (U/L)	730	1710	847
EMG	Normal	Normal	–
Heart	Normal	Normal	Normal
Respiratory insufficiency	Yes	No	No
Muscle biopsy	–	–	–
GAA activity (μmol/L/h)	0	0.1	0
Genotype	c.1784C>T	c.1655T>C	c.1655T>C