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Case report

Skeletal alterations, developmental delay and new mutations in juvenile-onset Pompe disease

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Abstract

Pompe disease is an autosomal recessive disorder caused by a deficiency of acid α-glucosidase. In addition to the severe infantile form with cardiac involvement, late-onset variants can affect older children, adolescents (aged >1 year old) or adults. Patients with juvenile (a subgroup of late-onset type) Pompe disease typically do not have cardiac alterations e.g. hypertrophic cardiomyopathy, and the diagnosis is often difficult because it can clinically resemble myriad other neuromuscular disorders. A high level of clinical suspicion is necessary for a timely and accurate diagnosis. We describe 3 interesting cases of patients with juvenile-onset Pompe disease who presented some uncommon clinical features e.g. skeletal alterations and developmental delay, and describe a new genetic variant. Juvenile-onset Pompe disease may be accompanied by uncommon clinical signs that could delay the diagnosis of Pompe disease due to the global pictures resembling other metabolic disorders.

Keywords: Pompe disease; Genetic variants; Juvenile-onset; Skeletal alterations; Developmental disability.

1. Introduction

Pompe disease (OMIM #232300), known as glycogen storage disease type II or acid maltase deficiency, is a progressive myopathy with an autosomal recessive mode of inheritance [1,2]. The combined incidence of Pompe disease is generally 1 in 40,000 and a higher incidence in certain populations such as African Americans (1/14,000), Northern Europeans of Dutch origin and South East Asians. Pompe disease is a lysosomal disorder characterized by a deficiency of acid a-glucosidase (GAA, EC 3.2.1.20) an enzyme that cleaves alpha-1-4 and alpha-1-6 glycosidic bonds of glycogen, maltose and intermediate oligosaccharides within the lysosome. The deficiency of such enzyme causes intralysosomal accumulation of glycogen in all tissues, most notably in skeletal muscles [2]. Pompe disease has two common forms (early-onset/classic and late-onset/non-classic) with differences in degree of disease severity, age of onset and organ involvement [3]. The patients present a broad spectrum of clinical variability such as cardiomyopathy, hypotonia and respiratory insufficiency [2]. Mutations of the gene arise as a result of various deleterious variants in GAA with reduced or absent enzymatic activity. Genotype-phenotype correlation studies among patients with the same mutation in GAA have revealed different clinical manifestations [4]. It seems that this diversity may be a result of interaction of other genetic and non-genetic factors.

Here, we report the interesting cases of three patients with juvenile-onset Pompe disease, a subgroup of patients within the late-onset Pompe disease. These cases have some unusual clinical features which would not normally lead to suspicion of Pompe disease.

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2. Case report

2.1. Patient 1

A 14-year-old male adolescent was referred to the neuropediatrician because of progressive, generalized fatigue, difficulty performing activities of daily life, such as running and sports. He presented with cramps and weakness and reduced muscle strength mainly in his limbs. The symptoms started gradually from age 12 onwards. He was born full-term, the third pregnancy (preceded by a spontaneous miscarriage), to non-consanguineous parents. His birth weight was 3.2 kg (25th percentile) and height was 52 cm (50th percentile), he had normal immunization and had an Apgar score of 9.

Head support was achieved at 7 months, with stable sitting and autonomous position attained at 13 months; he started to walk autonomously at 16 months, and spoke his first words at 10 months with normal language development. There was no family history of metabolic or neurological disease. Upon physical examination, his weight was 45 kg (10th percentile), height was 175 cm (90th percentile), head circumference was 58 cm (percentile >2 standard deviation), and his general condition was normal except for generalized hypotrophy and loss of strength in his lower limbs but with normal deep tendon I/IV reflexes. No dysmorphic features, skin blemishes, or cardiopulmonary alterations were observed. He had pectus excavatum, expansible, and normal breath sounds. Analysis of respiratory function by spirometry revealed a restrictive disorder of ventilation. Cardiac auscultation with unique R1 with mesosystolic murmur grade I/IV at the level of the tricuspid region of the chest, R2 was normal with physiological splitting. Blood pressure was normal (120/80 mm Hg). Echocardiogram showed no structural alterations. His abdomen had no masses or organomegaly. Neurological examination revealed normal cranial nerves, positive Gowers' sign. Muscle strength was reduced in both arms and limbs (III/V) with normal osteotendinous reflexes. Superficial and deep sensitivity were normal.

2.2. Patient 2

A 7-year-old boy was referred to the neuropediatrician owing to quick fatigue while walking and climbing stairs. He fell several times without apparent reason, he had general clumsiness while performing the basic activities of daily life. He presented with weakness and reduced muscle strength and pain in limbs. The symptoms started gradually over the course of a year (at age 6). He was born full-term, a second pregnancy, to non-consanguineous parents. His birth weight was 3.1 kg (25th percentile) and height was 52 cm (50th percentile), he had normal immunization and had an Apgar score of 10.

Head support was achieved at 6 months, with stable sitting and autonomous position attained at 10 months; he started to walk autonomously at 11 months, and spoke his first words at 10 months with normal language development. There was no family history of metabolic or neurological disease. Upon physical examination, his weight was 21 kg (50th percentile), height was 120 cm (50th percentile), head circumference was 54 cm (normal). No dysmorphic features, skin blemishes, or cardiopulmonary alterations in auscultation. He had winged scapulae. Blood pressure was normal (110/70 mm Hg). His abdomen had no masses or organomegaly. Neurological examination revealed normal cranial nerves and focal signs, negative Gowers' sign. Muscle strength was reduced in limbs (III/V) with normal osteotendinous reflexes. Superficial and deep sensitivity were normal.

2.3. Patient 3

A 6-year-old boy was referred to the neuropediatrician with generalized fatigue, difficulty with running and sports at the beginning of the symptomatology and then fatigue when performing basic activities of daily life. He presented weakness and pain in limbs. The symptoms started gradually two years before (at age of 4). He was born full-term, a fifth pregnancy, to non-consanguineous parents. His birth weight was 3.2 kg (25 th percentile) and height was 51 cm (50th percentile), he had normal immunization and had an Apgar score of 9. Head support was achieved at 4 months, with stable siting and autonomous position attained at 12 months; he started to walk autonomously at 13 months, and spoke his first words at 10 months with delayed language development and stereotyped behavior (mainly repeated hand flapping). There was no family history of metabolic or neurological disease. Upon physical examination, his weight was 22 kg (25–50th percentile), height was 114 cm (50–75th percentile), head circumference was 52 cm (normal). No dysmorphic features, skin blemishes, or cardiopulmonary alterations in auscultation. Blood pressure was normal (110/70 mmHg). His abdomen had no masses or organomegaly. Neurological examination revealed normal cranial nerves and no focal signs, with negative Gowers' sign and subtle white-matter abnormalities in T2-weighted MR images (Fig. 1). Muscle strength was reduced in limbs (III/V) with normal osteotendinous reflexes. Superficial and deep sensitivity were normal.

3. Blood and muscle laboratory tests

Blood laboratory test results were normal for haemoglobin, hematocrit, leukocytes, platelets, glucose, lactate, urea, creatinine, serum electrolytes, alkaline phosphatase, alanine and aspartate transaminases (AST and ALT respectively), total bilirubin concentration, cholesterol (above 145 mg/dL), ammonia, thyroid hormones, and thyrotropin for all three patients. The concentration of organic acids in urine, biotinidase, and cystine/homocysteine, acylcarnitine panel as well as all amino acids (including alanine) were also within the normal range. In contrast there were alterations in the blood concentration of lactate dehydrogenase (LDH), creatine kinase (CPK) and the muscle isoform of creatine kinase (M-CPK) (Table 1).

Due to clinical presentations and analytical data dried blood spot (DBS) test was used to analyze the activity of

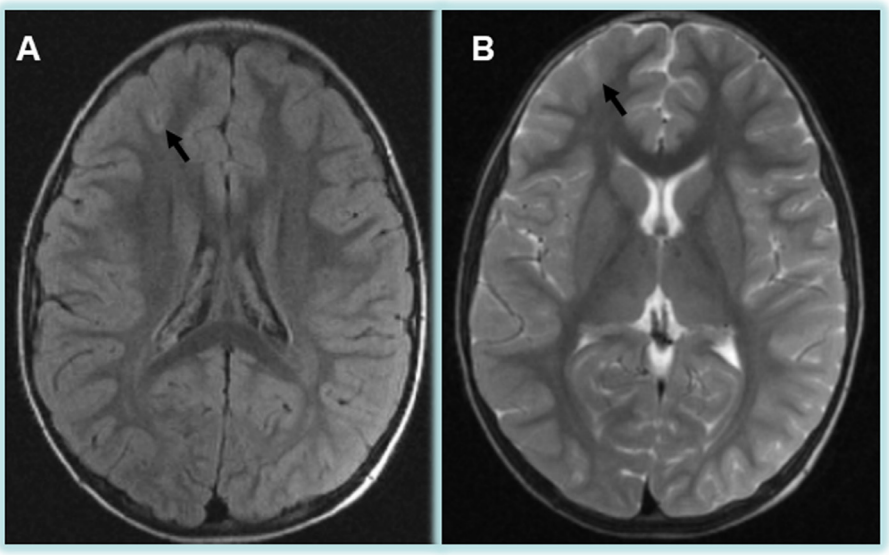

Fig. 1. Axial magnetic resonance T2-weighted images (A) and (B) of patient 3 showing subtle white-matter abnormalities in the right middle frontal gyrus/frontal cortex (indicated by arrows).

Table 1
Summary of the clinical features of the three patients described in this case study.

	Patient 1	Patient 2	Patient 3
Age at diagnosis (males)	14	7	6
Lactate dehydrogenase (LDH) Normal values:100–190 U/L	407 U/L	364	244
creatine kinase (CK) normal values:26–174 U/L	2779 U/L	2680	1511
creatine kinase, muscle isoform (M-CK) normal values:0–25 U/L	93 U/L	88	265
alpha-glucosidase (acid maltase, GAA) valor de referencia <15 mmol/L/h	14.10	5.28	11.09
Muscular symptomatology	YES	YES	YES
Skeletal alterations	YES	YES	NO
Psychodevelopmental delay	NO	NO	YES
Cardiac alteration	YES	NO	NO
Lung function alteration	YES	NO	NO

the enzyme alpha- glucosidase that demonstrated a decreases in Patients 2 and 3 and low limit level in Patient 1 (Table 1).

Due to persistent alterations in CPK (analysis was repeated three times on different days) and the clinical phenotypes of all three patients, femoral muscle biopsies were taken to evaluate any metabolic or histological alterations suggestive of muscular disorders. The histological examination of the muscle biopsy of the right rectus femoral muscle, with the staining of periodic acid Schiff (PAS), showed the existence of vacuoles, with positive PAS material inside the muscle fibers, in a central and sub-sarcolemal position. Electromyography and nerve conduction studies were normal in all three patients.

4. Genetic analysis

We proceed to the molecular genetic study for Pompe disease by automated sequencing by capillary electrophoresis with ABI 3130 xl Genetic Analyzer equipment (Applied Biosystems) and the alignment of the electropherogram produced against the reference sequence of the GAA gene deposited in GenBank (access number NG_009822). Molecular genetic analysis of Patient 1 revealed two new mutations homozygosity in the GAA gene (chromosome 17) e.g., c.547–67C > G and c.547–39T > G, in intron 2 which are not described in the literature or in the data record of mutations in the human genome. The 19 coding exons of the GAA gene, their flanking regions and binding sites were analyzed and the results of molecular study of GAA gene in patient 1 are reported in Table 2. The existence of two mutations in intron 2 and the concordance of clinical and biochemical data allow to affirm that these mutations in the GAA gene are responsible for the alterations found in the patient. In patient 2, c.1064T > C mutation in exon 6 (amino acid change p.Leu355Pro) and 380 G > T (amino acid change p.Gly127Asp) mutation in exon 2 of GAA gene were found. In patient 3 we observed the common mutation c.32–13T > G (old name IVS1-13T > G, (a T to G transversion in the intron 1 that causes a mistake in the splicing out of exon 2 in such a way that correct splicing occurs in approximately 10% of the events).

Table 2
Results of molecular study of GAA gene in patient 1.

Known pathogenic variants
Not Found
Common variants (polimorphisms)
Intron 2 c.547–4C > G homozygosity
Exon 3 p.His199Arg homozygosity
Exon 3 p.Arg223His homozygosity
Intron 4 c.858 + 5ins7 homozygosity
Intron 4 c.858 + 30T > C homozygosity
Intron 5 c.955 + 12G > A homozygosity
Intron 8 c.1327–18A > G homozygosity
Intron 9 c.1438–19G > C homozygosity
Intron 10 c.1551 + 49C > A homozygosity
Intron 14 c.2040 + 20A > G homozygosity
Intron 16 c.2331 + 20G > A homozygosity
Exon 17 p.Val780Ile homozygosity
Unknown variants
Intron 2 c.547–67C > G homozygosity
Intron 2 c.547–39T > G homozygosity

5. Discussion

We presented three clinical cases of juvenile-onset Pompe disease with uncommon clinical (skeletal alterations and developmental delay) and/or molecular features (new mutations) in order to offer clinicians an additional background to suspect Pompe disease when the clinical picture of patients does not fully match with classical presentation of this type of Pompe disease such as loss of strength in his lower-limbs.

The cases reported showed skeletal alterations reported in primary myopathy [5] such as macrocephaly and pectus excavatum (Patient 1), winged scapulae (Patient 2). Pectus excavatum is a posterior depression of the sternum and adjacent costal cartilages that accounts for >90% of congenital chest wall deformities. Patients with these skeletal alterations are often dismissed by physicians as having an inconsequential problem; however, it can be more than a cosmetic deformity in some cases and a deeper analysis should be carried out [6]. In patients 1 this abnormality even not common in Pompe disease may have led to deleterious consequence to treat a ventilation disorder due to failure of respiratory muscles in the future and needs to be constantly checked and evaluated during the patient's follow-up. A previous published case report of late-onset (as adult) Pompe disease with atypical presentation showed lean habitus, high palate, pectus excavatum, joint laxity, and cutaneous fragility being all features suspicious for connective tissue disorders [7] and this offers a challenge for clinicians for the differential diagnosis of Pompe disease. The winged scapula, defined as a clearly visible protrusion of the scapula when the patient was in a resting position or was lifting the arms anteriorly or side wards, has been described previously in adults with Pompe disease [8–11] but not in children with juvenile-onset Pompe disease. This skeletal alteration can be a consequence of weakening of shoulder girdle muscles which is not common in this form of Pompe disease. The muscles particularly involved are the fixators of the scapula (lower trapezius, rhomboid, and subscapularis), and the neck flexors (sternocleidomastoid) and this explains features such as winging scapula and difficulty of the patient in lifting his head while lying in the supine position.

Relative to patients without scapular winging, patients with scapular winging had more severe involvement of the shoulder girdle musculature. The 'limb-girdle' and trunk muscles were affected early in the course of the disease, while the distal muscle groups—if they were involved at all—were affected late in the course of the disease [11]. Confirming this issue, those Pompe disease patients with scapular winging had significantly lower forced vital capacity than those without scapular winging [11]. Since orthopaedic problems can substantially influence the ability to perform the activities of daily live, they represent a major issue in the management of these patients and should be managed by appropriated multidisciplinary team. Macrocephaly as observed in patient 1 has been described in mucopolysaccharidoses, a group of diseases of lysosomal storage diseases [12] but it is not common in Pompe disease [13] and this issue may have led to misdiagnosis or delay diagnosis of Pompe disease and should be taken into account when considering differential diagnosis.

The clinical picture in these patients is that of a proximal myopathy, the severity of which varies from patient to patient being mainly related to the duration of the disease at the time of the observation. Pelvic girdle muscles and proximal muscles of lower limbs are often involved earlier and more severely affected than those of the shoulder girdle and upper limbs. In particular, in this disorder there is a preferential involvement of glutei, adductors of the thigh, and paraspinal muscles. This explains the waddling gait, the lumbar hyperlordosis sometimes accompanied with scoliosis, and the Gower's sign, which usually occurs in these patients but a negative Gower's signs was observed in Patients 2 and 3 suggesting that in the early infancy of late-onset variant of Pompe disease, it is not always present. In contrast, at older ages as observed in patient 1, this clinical sign appears as it occurs in classical Pompe disease and other proximal myopathies [3].

Although accumulation of glycogen has also been seen in the nervous system in patients, the significance of brain involvement in infantile-onset Pompe disease is not clear. The patient 3 described here, showed delay language development and stereotyped behavior which associates with several forms of intellectual disabilities. Recent case-report and observational studies showed also impaired intellectual functions in late-onset of Pompe disease [14–16]. Cognitive development of children with Pompe disease has been shown to vary from stable and normal to declines, up to intellectual disabilities [14,16] evaluated the long-term cognitive and academic outcomes of 11 individuals with infantile onset Pompe disease treated with enzyme replacement therapy from an early age. The IQ scores of children with Pompe disease fall at the lower end of the average range compared to same-aged peers in several studies, but they scored lower in tasks involving visual-motor integration, visual perception and motor coordination compared to same-aged peers were

below average [16,17]. Two distinct subgroups emerged based on participants' average or below average performance on the majority of academic subtests. Those participants with below average academic skills demonstrated average nonverbal cognitive abilities, but had weaknesses in speech and language skills and greater medical involvement. Their profiles were more consistent with a learning disability diagnosis than an intellectual disability. Participants with average academic skills demonstrated average cognitive abilities (verbal and nonverbal) on the Wechsler scale and less medical involvement. Their speech and language skills appeared to be more intact. This study highlights the importance of using appropriate tests to capture both verbal and nonverbal abilities, considering each individual's motor skills, speech and language abilities, hearing status and native language. Changes in the speech and language domain may account for the decline in IQ observed in some Pompe disease children long-term survivors, reflecting a learning disability rather than a decline in overall cognition or an intellectual disability. A recent study showed brain white-matter abnormalities in a subgroup of patients with Pompe disease as shown in patient 3. From approximately age 2 years onwards, brain MRI white-matter abnormalities showed involvement of the periventricular white matter and centrum semiovale, corpus callosum, internal and external capsule, and subcortical areas. From 11 years of age, white-matter abnormalities were also found in the brainstem [14]. Although there seemed to be a characteristic pattern of involvement over time, there were considerable variations between patients, reflected by variations in neuropsychological development.

Regarding the genetic cause of Pompe disease, more than 450 mutations in GAA gene have been reported in individuals with Pompe disease [18], and new variants are continuously described [19]. Here we reported two new mutations in homozygosity at the level in the GAA gene (chromosome 17) e.g., c.547–67C > G and c.547–39T > G, both located in intron 2 (Patient 1). The existence of these mutations in the GAA gene intron 2, which are not reported in the database of mutations related to Pompe disease, and the concordance of clinical and biochemical data suggest that these are responsible for the alterations found in the patient. These findings highlights the importance and obligatory nature of the molecular genetic study in a suspicious patient.

The most frequent mutation found in Pompe disease patients in western countries is those found in patient e.g., 3 (–13T > G) [4]. Regarding the GAA enzyme activity we found a reduction in activity rather an absence, which is consistent with Nascimbeni et al. [20] that described the complete absence of GAA enzyme activity is seen more commonly in individuals with infantile-onset disease, whereas those combinations that allow partial enzyme activity typically have a juvenile- or late-onset presentation as reported here. Other biochemical abnormalities included rise in blood lactate dehydrogenase, total creatine kinase and its muscle isoform, likely reflecting muscle tissue damage [21]. Biopsies of muscular tissue revealed a myopathy characterized by enlarged vacuoles with positive staining with periodic acid–Schiff suggesting glycogen storage, and although these histological alterations are not pathognomonic for Pompe disease, they are quite common [22,23].

Our case series adds new clinical evidence regarding symptoms, signs and genetic variants in juvenile-onset Pompe disease which may vary considerably among patients [10] and could mimic a spectrum of other neuromuscular disorders and because it is a rare disease, arriving at the diagnosis is often delayed many years until severe myopathy and/or cardiac alterations appear. A high level of clinical suspicion is necessary for a timely and accurate diagnosis. All patients were treated with the enzyme replacement therapy with recombinant human GAA (Myozyme®) [24,25], with clinical significant improvement of their symptoms.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2018.11.013.

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