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CASE REPORT

Late Onset Pompe Disease in Children: Report of the First Patient with Two New Variants in Colombian Population

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Abstract

Here we report a 5-year-old male with a history of hypotonia, developmental delay and mildly increased creatine kinase from 4 months of age. Echocardiogram was normal. Dried blood spot and leukocytes alpha glucosidase activity was reduced, and diagnosis of Pompe disease was made. Next generation sequencing test made at 9 months of age detected a heterozygous c.1780C>T; p.Arg594Cys variant, classified at that time as a variant of uncertain significance. A multiplex ligation-dependent probe amplification test showed an exon 18 deletion, confirming the diagnosis. Enzyme replacement therapy with alglucosidase alpha was started, with improvement of the hypotonia. We report the first case of late-onset Pompe disease from ? area caused by two variants not previously described in Colombian population and review the genotype-phenotype correlation of the variants found in this patient.

Keywords: Late onset Pompe disease; Glycogen storage disease type II, acid alpha glucosidase, exon 18 deletion

Introduction

Pompe disease (OMIM #232300) is a severe progressive myopathy caused by a deficiency of acid alpha glucosidase, secondary to pathogenic or likely pathogenic variants in *GAA* gene. This enzyme catalyzes the hydrolysis of glycogen to glucose in lysosomes, and its deficiency leads to glycogen accumulation in skeletal and cardiac muscle, liver, and other tissues, causing cellular damage and, in consequence, multiple clinical manifestations [1-3]. Its frequency is as low as 1:40.000 in the infantile onset and 1:57.000 in the adult form.

Although Pompe Disease is a wide spectrum condition, two phenotypes have been described according to the onset of symptoms and the presence of cardiomyopathy [4]. The infantile onset Pompe Disease (IOPD) phenotype has its first manifestations at birth or in the first months of life, a severe course, and the presence of cardiomyopathy. Without treatment, mortality rate is 74% at 12 months and 88% at 18 months of age [3]. In 1973 Beratis et al. [5] reported several patients with Pompe disease of adult onset in which a residual enzyme activity was detected (5-20% of the normal control levels), concluding that the complete deficiency of the enzyme is responsible for the infantile and severe phenotype of Pompe disease. The late onset Pompe disease (LOPD) include all the patients without cardiomyopathy and those with onset of disease after 12 months of age, and its course is slower than the IOPD [6]. The main feature of LOPD is the skeletal muscle compromise that leads to progressive weakness, and respiratory insufficiency which derives in reduced life expectancy [7]. Enzyme replacement therapy (ERT) for Pompe disease was approved by the Food and Drug administrationin 2006. Since then, several authors have reported its positive effect in IOPD and LOPD especially when it is started early in life, showing improvement of cardiomyopathy and muscular weakness, and even improvement in cognitive outcomes in IOPD [8].

The information of *GAA* variants in Colombian population is scarce, and the prevalence of Pompe disease in Colombia is unknown [9]. Here we describe a patient with LOPD with onset before 12 months of age, with a newly described pathogenic variant in conjunction with a deletion of exon 18 of *GAA* gene. Both variants have never been described in Colombian population.

Case Description

A four-month male was referred to Pediatric Neurology clinic due to developmental delay. He is the only child of non-consanguineous parents, both of Colombian ancestry. The pregnancy was uneventful. The vaginal delivery was normal, with normal height and length for gestational age. The family history was negative for neuromuscular disorders.

The physical examination at four months showed normal weight, length, and head circumference for age. Generalized, axial-predominant hypotonia, poor head control and myopathic facies were present (Figure 1). The patient did not roll over. Alertness, visual and auditory tracking, smiling, blabbing, bilateral grip and sensitivity were normal. There were no dysmorphic features or organ enlargement.

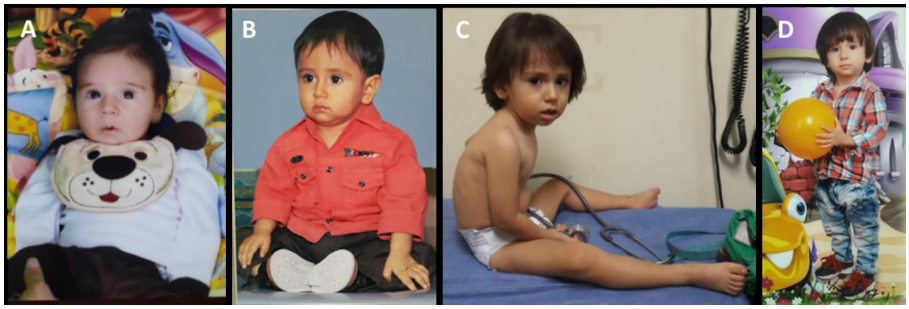

Figure 1: The patient at 4 months (A), 18 months (B), 4 years (C) and 5 years of age (D). Hypotonic facies, generalized hypotrophy and absence of dysmorphic features are evident. In C winging scapulae and trunk weakness are observed.

Laboratory tests including complete blood count, thyroid function, electrolytes, creatin kinase, plasma amino acids and urine organic acids were normal. Imaging studies including thoracic x ray, abdominal echography and echocardiogram were also normal. Electromyography showed a myopathic pattern. Enzyme activity of alpha glucosidase in dried blood spot was low (0.25 umol/L/h; reference values: >4.46 Umol/L/h. University of Miami). Sanger sequencing of *GAA* gene showed the missense variant c.1780C>T, p.Arg594Cys, in heterozygous state, initially classified as a variant of uncertain significance (VUS), and the variant c.2065G>A, p.Glu689Lys, that has been previously classified as a pseudodeficiency allele. The *in-silico* prediction of the variant was evaluated with three software that classified it as deleterious (Mutation Taster: disease causing; Polyphen: Probably damaging; SIFT: not tolerated).

Alpha glucosidase enzyme activity in leukocytes was done, showing very low activity (0.03 nmol/mg-prot/h; reference value 0.4-1.43 nmol/mg-prot/h). With this result, the diagnosis of late-onset Pompe disease was confirmed.

ERT started at 9 months of age. The motor development improved: the patient rolled over at 9 months, sat at 12 months, and walked at 18 months. However, hypotonia was persistent, especially of the paravertebral muscles and pelvic girdle, and postural kyphosis and unstable gait were present. The patient was evaluated at 5 years of age by Genetics; the neurological findings revealed mild hypotonia, hyporeflexia, difficult at one foot jumping, and impaired fine motor skills (pencil grasp and writing). He also had language delay and was not able to identify letters and numbers. At physical examination, tongue fasciculations and gastrocnemius pseudohypertrophy were not seen. Blood test showed creatine kinase in 306 U/L, AST 118 U/L, ALT 59.2 U/L, all of them elevated. Gamma glutamyl transferase was normal (10.16 U/L).

Given the uncertainty of the genetic findings, the p.Arg594Cys variant was reviewed, and it was reclassified in 2018 as likely pathogenic (http://www.pompevariantdatabase.nl). However, since there was only one variant, a multiplex ligation-dependent probe amplification (MLPA) test was requested, showing a c.(2481+1_2482-1)_(2646+1_2647-1) deletion in heterozygous state, compatible with the exon 18 deletion. Both variants were confirmed as being in trans state: the p.Arg594Cys variant was detected in the mother and the exon 18 deletion was found in the father, confirming the diagnosis of LOPD.

Discussion

Pompe disease is an autosomal recessive disease that, although is considered a glycogenosis, is classified as a lysosomal storage disease (LSD). *GAA* gene is localized in 17q25.2-25.3, has 3,6 kb and spans 20 exon with 2859 bp in its codifying sequence. Around 550 variants have been reported in The Pompe Disease Mutation Database (http://www.pompecenter.nl), 75% have been identified as pathogenic or likely pathogenic and 10% as VUS [2, 10]. Genotype-phenotype association in Pompe disease has been described by multiple authors [1,10]. Some variants confer severe clinical manifestations (e.g., IVS1) and different levels of residual enzyme activity, as well as cross reactive immunological material (CRIM) status. CRIM status of a variant is a predictor of antibody generation against ERT and, therefore, it is associated with a potential adverse reaction to ERT [2, 11–13].

The Arg594Cys variant and exon 18 deletion of *GAA* gene have not been previously described in Colombian population with Pompe disease [9]. The exon 18 deletion is considered one of the most frequent pathogenic variants in Caucasian population [14], and it is possible that its presence in Colombian population is a consequence of a founder effect. Exon 18 deletion has a positive CRIM status, and it is associated to a severe phenotype in homozygous state, and a LOPD phenotype in compound heterozygosis [15]. The variant Arg594Cys has been reported in a Chinese patient with LOPD (onset at 13 years old), in compound heterozygous state with the Arg600Pro variant [16]. The latter variant has been classified as pathogenic in the ClinVar database (National Center for Biotechnology Information. ClinVar; [VCV000370130.6], https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000370130.6. Accessed April 20, 2021). The laboratory tests described in this patient showed high creatin kinase levels (586.2 U/L), and muscle biopsy showed vacuolar myopathy, however, alpha-glucosidase activity was not reported. Arg594Cys and Arg600Pro variants have been reported as mild severity and positive CRIM status (Pompe database). This finding explains the clinical presentation of the patient, since his phenotype is not IOPD given

the absence of cardiomyopathy, but it is not the typical juvenile or adult LOPD because the onset was before 12 months of age [12]. Also, at the moment of this publication, the patient has had good response to ERT and has not had any adverse reaction, which is concordant with his positive CRIM status.

Hypotonia is the cardinal symptom of Pompe disease, therefore is paramount the evaluation of muscular tone in all ages, especially on the first year of age. In this context, Pompe disease is one of the causes of floppy baby syndrome in newborns and infants. Hypotonia in Pompe disease is peripheral, which causes motor developmental delay with normal adaptive and social responses [17]. In Pompe disease the cervical muscle compromise is a common feature associated with poor head control as described in the patient. However, the proportion of the patients with Pompe disease without cardiomyopathy that have symptoms before 12 months of age is approximately 12% [12]. The principal cause of pediatric consultation in IOPD is the cardiomyopathy; in LOPD with onset before the year of age is developmental delay, and hypotonia is the most frequent cause of referral to pediatric neurology [1]. Given the low incidence of children with LOPD and the absence of cardiomyopathy, other common causes of hypotonia at this age are considered, for example spinal muscular atrophy, hereditary dystrophies or Prader Willi syndrome. Other atypical manifestations of Pompe disease in infants are neck flexor muscles weakness, unexplained fatigue of persistent diarrhea [1].

Although the main feature of Pompe disease is the skeletal muscle compromise, recent publications have reported glycogen deposits in the central nervous system, and this finding could explain the low scholar performance in some patients with Pompe disease. Even some patients have borderline cognition or mild intellectual disability, and others have specific learning difficulties in reading, writing and language [11,18]. Speech deficiency is also related to hearing loss secondary to cochlear or conductive alterations, along with compromise of brainstem nuclei and motor neurons from the medulla [8, 9, 18]. Our patient has learning difficulties but does not have auditory impairment.

The amount and velocity of accumulation of glycogen in muscle and other organs determine the clinical manifestations in Pompe disease, therefore the individual prognosis depends on an opportune diagnosis and early onset of ERT [12, 13]. One strategy to detect Pompe disease in an early stage is the newborn screening. The main hindrance is the pseudodeficiency variants which have a high incidence in Asian population [10]. Unfortunately, in Colombia there is not a newborn screening program for LSD, therefore there is not registry of pseudodeficiency variants in Colombian population

Pompe disease should be considered as a differential diagnosis in a child with floppy baby, even without the presence of cardiomyopathy since the early detection of this disease and the early onset of ERT changes the short- and long-term prognosis of the patients.

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Conflict of Interests

The authors declare no conflict of interests.

Informed Consent

An informed consent was requested to the mother of the patient, and the authorization of photographs publication was signed.

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