Case Report

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A New Mutation of Pompe Disease in a 2-Month-Old Infant

Maryam Taraz[*1,3], **Mojtaba Gorji**[1,3], **Behdad Gharib**[1,3], **Vahid Ziaee**[2,3]

1.Department of pediatric cardiology, Children's Medical Center, Pediatric Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran.

2.Department of pediatric Rheumatology, Children's Medical Center, Pediatric Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran.

3.Children's Medical Center, Pediatric Center of Excellence, Tehran, Iran.

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Running Title A New Mutation of Pompe Disease

ABSTRACT

Pompe disease or type 2 glycogen storage disease (GSD), is an autosomal recessive disorder, occurs by deficiency of an enzyme (acid maltase) which degrades glycogen in lysosomes. It is classified into infantile and late onset types.

Identifying PD presents several challenges due to the wide range of phenotypes and phenotype overlap with other neuromuscular disorder. However, in cases of suspected Pompe disease, performing genetic testing and starting treatment immediately after proving the disease has an effective role in reducing the rate of progression of disease symptoms.

With the progress made in genetic tests, sometimes new mutations are added to the existing genetic bank.

So far, more than 600 mutations are known to cause many signs and symptoms, and some of these mutations are more common in certain breeds and cause more symptoms and more deaths.

In this case report, we introduce a Pompe patient with a new genetic mutation that is of pathogenic types. This patient had presented with sign of severe hypotonia and cardiomegaly, increased cardiac enzymes, and abnormal liver tests. Despite enzyme therapy immediately after diagnosis, she died.

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*** Corresponding Author:**
Maryam Taraz
Address: *Department of Pediatric Cardiology, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran*
E-mail: *maryam.taraz@yahoo.com*

Case presentation

A 2-month-old girl, born to consanguineous parents, was brought to the emergency department due to vomiting, fever, lethargy, and poor feeding from the previous day.

The physical examination was significant for severe hypotonia and decreased deep tendon reflexes. The growth indices were within normal limits. The vital signs were as follows: heart rate of 140 beats/minute, respiratory rate of 32 breaths/minute, blood pressure of 80/50 mmHg, and pulse oxygen saturation of 95 percent without supplemental oxygen.

The patient's past medical history was notable for hospital admission due to pneumonia at 1 month of age.

The laboratory data revealed anemia (hemoglobin = 10.5 grams/deciliter), elevated levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine phosphokinase myocardial band (CK-MB), and creatine phosphokinase (CPK) (Table 1).

Abdominal ultrasonography was performed and found to be normal. A chest X-ray revealed significant cardiomegaly (Figure 1), necessitating further investigation via echocardiography (Figures 2,3). The echocardiography revealed left ventricular hypertrophy as the only abnormal finding, with no evidence of aortic stenosis or coarctation. An electrocardiogram (ECG) (Figure 4) showed tall QRS complexes, high left-sided QRS voltage due to hypertrophy, T wave inversion, ST segment depression, and increased QT dispersion, without short PR intervals. The patient's ammonia and lactate levels were within normal limits, and blood cultures were negative.

The combination of hypotonia, consanguineous parents, and the findings from the echocardiography and ECG led the authors to suspect Pompe disease. They proceeded with molecular genetic testing for Pompe disease, using methods such as DNA extraction, PCR amplification of 19 protein-coding exons and their intron boundaries, and direct Sanger sequencing (the gold standard method).

A novel homozygous frameshift deletion variant was detected in the GBA gene in this patient. Mutations in the Glucosidase Alpha Acid gene, also known as Alpha-glucosidase (GAA, *606800) on chromosome 17q25, a lysosomal enzyme, can cause Glycogen Storage Disease 2. The detected variant (c.527_533del) has not been previously reported. However, based on multiple lines of in silico computational analysis (InterVar, VarSome, Franklin, etc.) and according to the ACMG guideline, this variant can be classified as likely pathogenic.

Enzyme replacement therapy (ERT) was initiated for the patient, but unfortunately, she passed away after

Table 1. The laboratory data

Laboratory item	The measured value	The reference range
Ammonia	68 microgram/deciliter	68-136 microgram/deciliter
lactate	10 milligrams/deciliter	2-20 milligrams/deciliter
White blood cells (WBC)	5.48 x 1000/microliter	4-10 x 1000/microliter
Hemoglobin (Hb)	10.5 gram/deciliter	11-16 gram/deciliter
Platelet	404 x 1000/ microliter	150-450 x 1000/ microliter
Neutrophils	31.7%	
Lymphocytes	5.4%	
Erythrocyte sediment rate (ESR)	9-millimeter/hour	0-10 millimeter/hour
C-reactive protein	3 milligram/Liter	<6 milligram/Liter
Lactate dehydrogenase (LDH)	1042 international unit/liter	5-1100 international unit/liter
CK-MB	66.1 international unit/liter	0-24 international unit/liter
Creatinine phosphokinase (CPK)	445 unit/liter	41-430 unit/liter
Aspartate aminotransferase (AST)	199 unit/liter	10-31 unit/liter
Alanine aminotransferase (ALT)	102 unit/liter	10-31 unit/liter

Table 2. The result of genetic test

Gene (RefSeq)	Variant Location	Variant	Chromosome position (GRCh37)	Zygosity	Inheritance pattern	Variant Classification
GAA NM_000152.5	Exon2	c.527_533del p.Glu176Alafs*43	Chr17:78078912-78078918	Hom	AR	Likely pathogenic

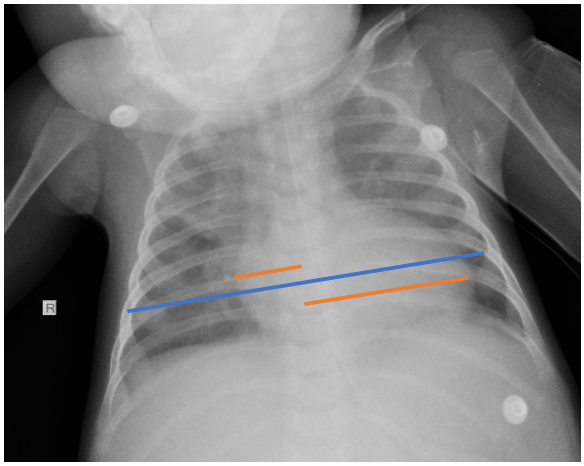

Fig. 1. The chest x ray shows the presence of cardiomegaly. (cardiothoracic ratio =0.64)

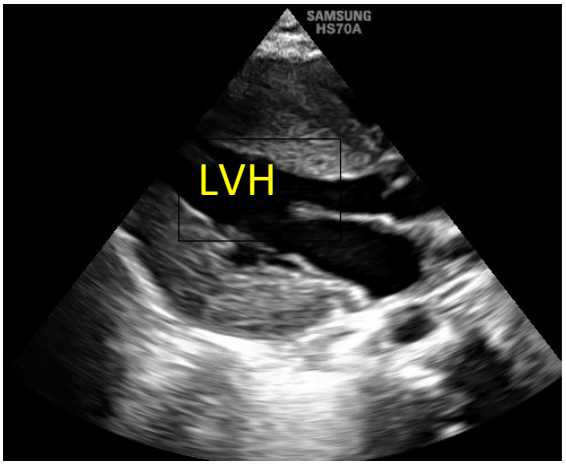

Fig. 2. The echocardiography shows left ventricular hypertrophy. (LVH: Left ventricular hypertrophy)

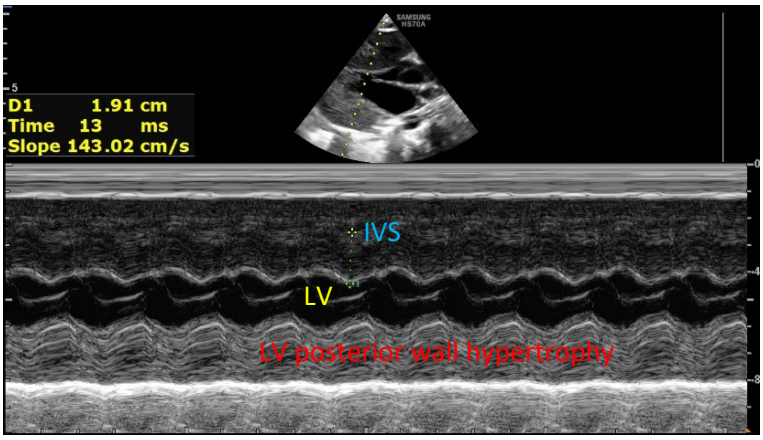

Fig. 3. The echocardiography shows left ventricular hypertrophy. (LVH: Left ventricular hypertrophy, IVS: Inter ventricular septum)

the first dose due to pneumonia and cardiorespiratory failure.

Pompe disease results in the intralysosomal accumulation of glycogen, leading to multisystem manifestations. The infantile form is caused by a complete deficiency of GAA. The disease can present from birth to the first few months of life [7]. The authors' patient was a 2-month-old girl who presented with non-specific symptoms. Hypotonia was one of the presenting signs, and along with consanguineous parents, vomiting, and poor feeding, it led the clinicians to suspect sepsis, metabolic, congenital, and genetic problems [9,10]. The para-clinic findings included elevated levels of lactate dehydrogenase, alanine transaminase, aspartate transaminase, and creatine kinase. Massive cardiomegaly was detected in the chest X-ray, which is usually the first observed symptom. The ECG of this patient showed high voltage QRS, high left-sided QRS voltage due to hypertrophy, T wave inversion, ST segment depression without a short PR interval. Respiratory tract infections due to aspiration pneumonia, swallowing difficulties, and cardiac conduction disturbances manifested as a short PR interval and cardiomegaly due to the accumulation of glycogen within cardiac muscles were notable manifestations of the disease. However, consanguineous parents, the infant's young age, and previous admission for pneumonia indicated the need for further investigation. Echocardiography of this patient included thickening of the left and intraventricular septum and obstruction of the left ventricular outflow tract [1]. The gold standard for diagnosing the disease is the GAA assay implemented on muscle or skin cells [7].

According to the articles that have been published so far about the types of Pompe disease mutations, this patient shows a new mutation. This mutation, occurring in exon 2, has been diagnosed as pathogenic.

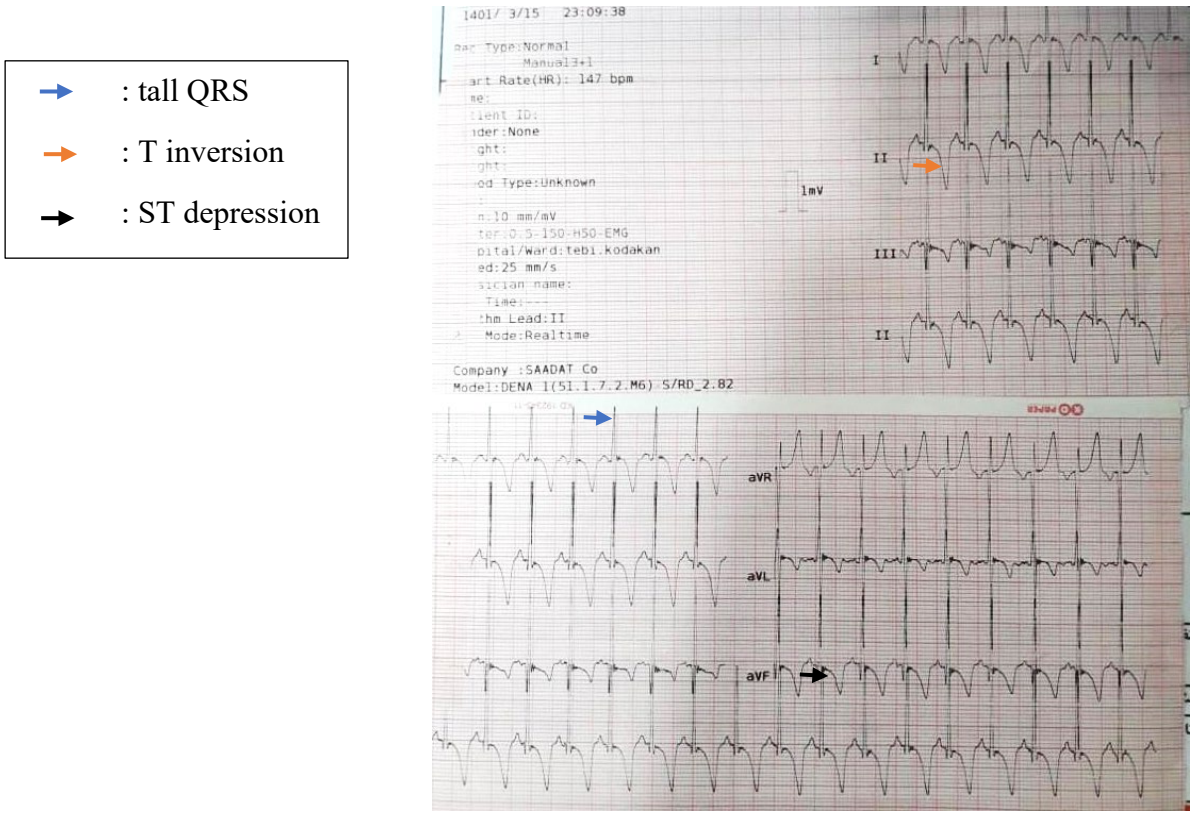

Fig. 4. The ECG shows tall QRS, high left sided QRS voltage due to hypertrophy, T inversion, ST depression

Enzyme replacement therapy (ERT) has been recognized for the treatment of Pompe disease since 2006. It improves cardiac hypertrophy and respiratory capacity. Some countries have started newborn screening for early diagnosis. However, most of the diagnosed newborns have had the late-onset form of the disease, and the timing of ERT for them is not exactly clear [8].

Conclusion

Pompe disease is a rare autosomal recessive genetic disorder, characterized by the accumulation of intralysosomal glycogen in several tissues. The presentation is nonspecific, with symptoms such as lethargy and poor feeding. Precise clinical examination and history taking are the main keys to formulating an appropriate differential diagnosis list. In this case, attention to the nonspecific presentation led to the detection of specific signs, and the diagnosis was confirmed by gene analysis.

Timely and quick diagnosis, prompt initiation of treatment, and providing the necessary information to the family for the necessary care after the diagnosis of the disease are crucial. This includes prevention of pulmonary aspiration caused by lung secretions and nutrition, follow-up of treatment, and regular periodic injection of medicine (ERT). These measures are vital for patients.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

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Conflict of Interests

The authors have no conflict of interest to declare.

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