The Novel Compound Heterozygous Mutations of GAA Gene in Mainland Chinese Patient with Classic Infantile-Onset Pompe Disease
A Case Report and Literature Review

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Summary

Pompe disease (PD) is a rare and fatal neuromuscular disease, which is an autosomal recessive disorder. This is the first study to report a case of the compound heterozygous c.1822C>T and c.2297A>C mutations of the GAA gene in mainland Chinese patient, which led to the classic infantile-onset Pompe disease (IOPD) characterized by hypertrophic cardiomyopathy. This case highlights that the detection of GAA activity in peripheral blood by dried blood spot and GAA gene analysis can clarify the diagnosis of IOPD and provides the genetic counseling to those parents whose children have IOPD for giving birth in the future. Although PD is rare, and universal screening has not yet been established, we suggest that clinicians should consider the possibility of Pompe in the presence of hypertrophic cardiomyopathy.

Key words: Glycogen storage disease II, Hypertrophic cardiomyopathy, Acid alpha-glucosidase

Case Report

A female infant, with an age of 4 months and 14 days, was transferred to our hospital with "cyanosis around the mouth when crying for more than 1 month, cough, and asthmoid dyspnea for 2 days" on August 16, 2017. The patient was a second child with a full-term cesarean section and a birth weight of 3.95 kg. The infant cried loudly without asphyxiation or cyanosis. After birth, the weight of the infant increased slowly, and the head was unstable. And 3 months after birth, cyanosis was around the mouth when crying. Physical examination revealed that the patient's height was 67.0 cm, weight was 6.0 kg, temperature (T) was 39°C, pulse rate (P) was 180 beats per minute, respiratory rate (R) was 52 times per minute, head width was 40.0 cm, blood pressure was 101/45 mmHg, and transcutaneous oxygen saturation (TcSpO2) was 86% without oxygen uptake. Moreover, she presented with fatigue, low crying, flaring of alae nasi, cyanosis of face and lips, megaloglossia, uncontrollable protruding tongue, and three depressions sign positive. The respiratory sounds of both lungs were rough, and phlegm and wheezing sounds could be heard. Dense fine or medium bubbling rales could be heard at the base of the left lung. The heart rate was 180 beats per minute. In addition, there was regular heart rhythm, the cardiac sound was low, and no murmurs were heard in all auscultatory valve areas. The abdomen was soft. The liver took on soft texture 4.0 cm below the right rib and 4.0 cm below the

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178
The patient had low muscle tone in her limbs, and tendon reflex couldn’t be drawn out.

The routine blood examination showed the abnormal values of decrease in neutrophilic granulocyte percentage (27.80%; reference range, 40-75%) and increase in lymphocyte percentage (57.50%; reference range, 20-50%) and platelet (377 × 10^9/L; reference range, 125-350 × 10^9/L). Blood biochemistry showed that the alanine aminotransferase (ALT) level was 174.1 U/L (reference range, 7-40 U/L), aspartate aminotransferase (AST) level was 228 U/L (reference range, 13-35 U/L), creatine kinase level was 1038 U/L (reference range, 25-200 U/L), creatine kinase isoenzyme (CKMB) level was 38 U/L (reference range, 0-25 U/L), lactate dehydrogenase (LDH) level was 1063 U/L (reference range, 90-240 U/L), alpha-hydroxybutyric dehydrogenase (α-HBDH) level was 973 U/L (reference range, 80-220 U/L), and brain natriuretic peptide level was 529 pg/mL.

Three-dimensional (3D) reconstruction of the trachea and bronchus in chest CT showed the following: (1) the left principal bronchus narrowed, and the partial segmental bronchus and lower lobe bronchus were obstructed, (2) there was multiple inflammation in both lungs and atelectasis of the left lung, and (3) there were heart enlargement and hypertrophic ventricular walls, especially in the left ventricle.

Electrocardiogram (ECG) showed sinus tachycardia, left ventricular hypertrophy, and ST-T change (Figure 1).

Cardiac ultrasound showed that the interventricular septum and the left free ventricular wall (LFVW) were thickened, myocardial echoes were rough, intimal hyperplasia with increased echoes was present, motion was still coordinating, and the amplitude of cardiac contraction decreased slightly (Figure 2). Slender tubes were seen between the aorta and the pulmonary artery. Effusion echo could be detected about 3 mm deep in the cavum pericardii, and sound transmission was good.

Color Doppler ultrasonography showed that the fine continuous shunt signals from left to right could be detected in the level of the artery and that a small amount of regurgitation signal could be detected from the mitral valve.

After admission, nasal continuous positive airway pressure (NCPAP)-assisted ventilation, active anti-infection, and cardiac, diuretic, and symptomatic treatment were given to the patient for 1 week. There was no significant relief of the asthmatic dyspnea. Afterward, the patient’s families requested to transfer her to the superior hospital. With the consent of the family, we retained the venous blood of the patient and her parents during the hospitalization period. As a follow-up after discharge, we got to know by phone call that the patient died in a superior hospital 3 days after the transfer.
Investigation showed that the parents of the patient were noninbred, and there were no abnormal manifestations of the heart, skeleton, or muscle, no abnormalities in electrocardiogram or cardiac ultrasound examination, and no family history of disease.

After the death of the patient, with the informed consent of the patient’s families and the approval from the Ethics Committee of the Affiliated Hospital of Jining Medical University, the peripheral blood from the patient was tested for GAA activity, and the coding regions of GAA gene from the patient and her parents were sequenced. It was found that the activity of GAA in patient was 0.18 nM/punch/hour while that in normal control was 11.43 nM/punch/hour (reference range, 8-97.7 nM/punch/hour). In addition, GAA gene sequencing results (Figure 3) showed the mutation of c.1822C>T at exon 13, resulting in the change of normal arginine (R) into termination codon (X), namely, p.r608x (the patient’s and her father’s c.1822C>T mutation). B: The top one is the normal c.2297A sequence. The bottom one is the mutation of c.2297A>C at exon 16 (shown by the arrow), resulting in the change of normal tyrosine (Y) into serine (S), namely, the missense mutation of p.y766s (the patient’s and her mother’s c.2297A>C mutation).

Discussion

PD is a progressive autosomal recessive neuromuscular disorder caused by the deficiency of lysosomal GAA. The clinical features are muscle weakness, dyspnea, myocardial hypertrophy, and cardiac insufficiency. The classic IOPD is the most severe end of the spectrum with rapidly progressive hypertrophic cardiomyopathy, cardiomyopathies, hypotonia, respiratory distress, respiratory infections, feeding difficulties, and failure of survival. 

Enzyme replacement therapy (ERT) with alglucosidase alfa remains the only FDA-approved treatment for PD. Because of the high cost of treatment, ERT was not cost-effective. However, it has a significant effect on most patients with IOPD, significantly prolonging the lifespan of patients. Moreover, the early initiation of treatment results in best outcomes. Therefore, early diagnosis is particularly important. The diagnosis of PD mainly depends on the detection of GAA activity and gene analysis. Dried blood spot (DBS) is a noninvasive, rapid, and effective method for the detection of GAA activity. It is not only suitable for newborn screening but is also the first choice for the diagnosis of PD. Gene analysis is the gold standard for the diagnosis of PD, while the conventional methods such as skin and muscle biopsies have certain limitations for the diagnosis of this disease. Moreover, Adadi et al. demonstrated the use of exome sequencing as a systematic and unbiased diagnostic tool in a pediatric case with hypertrophic cardiomyopathy. Screening in healthy newborns is now possible by demonstrating low GAA activity in DBS complemented by DNA mutation analysis. Newborn screening is the best method for early diagnosis of PD, and at present, newborn screening has been carried out in Taiwan and parts of the United States, which is of great significance for the prognosis of IOPD patients.

In this case, the patient onset was 4-5 months in infancy, manifested by respiratory infection, motor delay, slow increase of body weight, megaloglossia, slight hepatomegaly, hypotonia, and significant increase in creatase. Both an ECG and a color Doppler ultrasonography
showed that interventricular septum and ventricular wall were significantly thicker. The above symptoms are in accordance with the features of IOPD. DBS from the infant were tested to determine the GAA activity, and the result confirmed that the GAA activity was clearly lower than the normal range. Gene analysis revealed that the GAA gene in the patient had the novel compound heterozygous mutations in mainland Chinese patients: c.1822C>T and c.2297A>C. Therefore, on the basis of the clinical signs, laboratory results, and the detection of GAA activity and GAA gene analysis, leading to a diagnosis of IOPD.

The deficiency of GAA results from the mutations in the gene encoding the GAA (GAA gene). The GAA gene is located on the long arm of chromosome 17q25.2-q25.3, approximately 20 kbp long, consisting of 20 exons. At present, more than 500 mutations in the GAA gene have been described in the PD Mutation Database and Human Gene Mutation Database. There are different mutations in different races, and the genotypes and clinical manifestations of mutations are also correlated. In this study, the patient was found to have mutations of c.1822C>T and c.2297A>C. Among them, the mutation of c.1822C>T originated from the patient’s father, whose genotype was heterozygote and had no clinical onset. Moreover, the mutation of c.2297A>C originated from the patient’s mother, whose genotype was heterozygote and had no clinical onset. The compound heterozygous c.1822C>T and c.2297A>C mutations of the GAA gene resulted in classic IOPD characterized by hypertrophic cardiomyopathy. Both mutations have not been detected in patients in mainland China. Homozygous c.1822C>T mutation has been confirmed to have a definite pathogenic effect. Additionally, c.1822C>T was identified as the second-most common mutation considering only IOPD in Japanese patients. The c.2297A>C variant is rare, but ClinVar interprets c.2297A>C as pathogenic. Moreover, Yoon et al. reported that the compound heterozygous c.1309C>T and c.2297A>C mutations of the GAA gene can lead to late-onset Pompe disease (LOPD), and the patients can be manifested as having limb girdle weakness, a loss of GAA enzyme activity, development delay, hepatomegaly, and consanont articulation disorder, but no heart murmur or abnormal respiratory sounds. Bali et al. found c.2297A>C in homozygosity in three IOPD patients. Because the GAA gene is located on an autosome, the heredity of this gene mutation in this family conforms to Mendel’s genetic law, and the hereditary mode conforms to the characteristics of autosomal recessive disorders. In this case, the phenotypic expression occurs when both alleles of the GAA gene harbor a pathogenic mutation.

The disease in this study is an autosomal recessive disorder, and the proband’s parents have a 25% risk of reproductive relapse. Early diagnosis of the disease was delayed due to the lack of adequate knowledge of PD. After the detection of GAA activity and GAA gene analysis, the diagnosis of IOPD was confirmed. It provides genetic counseling for her parents to reproduce in the future, and prenatal diagnosis can be made for their high-risk fetuses. It has important practical significance for patient’s parents to have normal children. Although PD is rare, and universal screening has not been established, we suggest that clinicians should consider the possibility of PD in the presence of hypertrophic cardiomyopathy. At the same time, we suggest that we should further expand the newborn screening of PD and establish a more sensitive, complete, and inexpensive screening system, in order to improve the prognosis of infants with IOPD by early diagnosis or to be able to alert even more parents to the possibility of IOPD in their children.

Conclusion

Compound heterozygous c.1822C>T and c.2297A>C mutations of the GAA gene can lead to classic IOPD characterized by hypertrophic cardiomyopathy. The detection of GAA activity and GAA gene analysis are feasible and effective diagnostic methods.

Disclosure

Conflicts of interest: The authors have no conflicts of interest to declare.

Ethical standard: The subject’s parents have given their written informed consent to publish her case (including publication of images). In addition, the study protocol was approved by the Ethics Committee of the Affiliated Hospital of Jining Medical University.

References