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AN ATYPICAL INFANTILE-ONSET POMPE DISEASE WITH GOOD PROGNOSIS FROM MAINLAND CHINA: A CASE REPORT

Infantile-onset Pompe disease and atypical symptoms and prognosis

Abstract

BACKGROUND

Pompe disease has a broad disease spectrum, including infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD) forms. It is a type of glycogen storage disorder belonging to autosomal recessive genetic disease, for an estimated incidence of 1/40,000 among the neonatal population. In severe cases, the natural course is characterized by death due to cardiopulmonary failure in the first year after birth. However, the clinical outcomes have improved since the emergence of enzyme replacement therapy (ERT) was widely used.

CASE SUMMARY

The reported female case in China was an atypical infantile-onset Pompe disease (IOPD) , which demonstrates an unusual presentation of glycogen accumulation syndrome type II without obvious skeletal muscle involvement, and reviewed physical examination, biochemical examinations, chest radiograph, and acid α-glucosidase (GAA) mutation analysis. After 4-month specific enzyme replacement therapy, the case received 12-month follow-up. Moreover, the patient has obtained a very good prognosis under enzyme replacement therapy.

CONCLUSION

For the atypical infantile-onset Pompe disease (IOPD) patients, early diagnosis and treatment may contribute to good prognosis.

Key Words: Pompe disease; rare genetic disease; enzyme replacement therapy (ERT); Case report

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Core Tip: Infantile-onset Pompe disease, a form of Pompe disease, is a rare autosomal recessive genetic disease occurred in infants, who represent hypertrophic cardiomyopathy, because of unusual accumulation of glycogen or acid maltase deficiency. More than 90% patients died before 1 year old. In this manuscript, we report a female case which is an atypical IOPD with novel inherited pathogenic heterozygous variants for GAA gene have not been reported before, and the patient has obtained a good prognosis under the enzyme replacement therapy.

INTRODUCTION

Pompe disease has a broad disease spectrum, including infantile-onset type (IOPD) and late-onset type (LOPD). Its typical symptoms are proximal muscle weakness and respiratory insufficiency in childhood or late adulthood. And the disease is also known as glycogen storage disease type II (GSD II) or acid maltase deficiency with a rare type of acid α-glucosidase (GAA) deficiency in the lysosome. It is a type of glycogen storage disorders which belongs to autosomal recessive (AR) genetic disease in neonatal period with an estimated incidence of 1/40,000, Apart from African Americans, the population with a higher incidence is located in southern China. In severe cases with an infantile onset or an early onset, the natural course is characterized by death due to cardiopulmonary failure in the first year after birth. However, the clinical outcomes

have improved significantly since the rise of the emergence of enzyme replacement therapy (ERT) .

The case in this manuscript focuses on a girl born in northern China, which is an atypical IOPD case. The case shows an unusual presentation of glycogen accumulation syndrome Type II without obvious skeletal muscle involvement, and with two novel inherited pathogenic heterozygous variants for GAA gene. Moreover, the patient has obtained a very ideal prognosis under the enzyme replacement therapy.

CASE PRESENTATION

Chief complaints

Jaundice, without muscle weakness nor hypotonia.

History of present illness

The case was first hospitalized for jaundice, without more accompanying symptoms at the age of 25 days, no muscle weakness nor hypotonia. While the classical IOPD occurs, early manifestations of muscle weaknesses are often seen, together with cardiomyopathy or cardiac hypertrophy.

Apart from the special features above, the patient is an atypical IOPD. This female patient is Han nationality, native of Shandong China, and 25 days after birth. The current weight of the patient when given the diagnosis is 4.09 kg, normal growth and development, breathing 32 times/min, regular rhythm, no cyanosis, normal crying, normal mental and breastfeeding status, stool yellow paste 2-3 times a day, urine yellow and clear. And the identification of IOPD was only after examinations.

History of past illness

None.

Personal and family history

The patient's mother was with a background of G4P2, 40+6 wk gestation, normal delivery, birth weight 3.45 kg, the family denied the history of asphyxia rescue, denied amniotic fluid, umbilical cord and placenta abnormalities. Newborns are normal after birth, breastfed. The father is 43 years old and the mother is 32 years old, both in good health and not in close marriage. The mother had previously voluntarily induced two abortions. G1P1 was a 14-year-old boy, healthy, and denied history of gestational diabetes and genetic diseases.

Physical examination

The current weight of the patient when given the diagnosis is 4.09 kg, normal growth and development, breathing 32 times/min, regular rhythm, no cyanosis, normal crying, normal mental and breastfeeding status, stool yellow paste 2-3 times a day, urine yellow and clear. Yellowish skin, visual bilirubin 10～15 mg/dL, and no skin rash. Moreover, bregma 1.5 cm × 1.5 cm, flat and soft, no positive signs on cardiopulmonary abdominal examination, 1.0 cm below the right rib of the liver, sharp soft edges, free movement of limbs, normal muscle tension, primitive reflexes can be elicited, and peripheral circulation is normal also.

Laboratory examinations

Biochemical examinations: direct bilirubin (DB): 12.2 μmol/L (0～6.8 μmol/L), indirect bilirubin (IB): 128.2 μmol/L (1.7～10.2 μmol/L), total bile acid (TBA): 17 μmol/L (0.1～10.0 μmol/L), creatine kinase (CK): 833U/L (18.0～198.0 U/L), creatine kinase myocardial band (CKMB): 19 U/L (0～ 18U/L), alanine transaminasen (ALT): 67 U/L (0 ～ 40 U/L), aspartate transaminase (AST): 153 U/L (0 ～ 37 U/L), lactate dehydrogenase (LDH): 673 U/L (135.0～215.0 U/L), and γ-gγlutamyl transpeptidase (γ-GT): 83 U/L (3.0～50.0 U/L). Electrolytes, and blood sugar level are all normal. There is no abnormality in thyroid function. No specific fatty acid abnormalities were found in the screening of hematuria metabolic disease. There was no obvious abnormality shown

by electromyography. GAA mutation analysis is "c.859-2A>T" and "c.1861T>G p.Trp621Gly".

Imaging examinations

B-mode ultrasound images on the liver, gallbladder, spleen and brain showed no abnormalities. The chest radiograph shows that the left heart margin is full. Echocardiography suggests left and right ventricular hypertrophy (LVPW left ventricular posterior wall 8 mm ～ 12 mm, RVAW right ventricular anterior wall 6 mm ～ 7 mm, IVS interventricular septum 12 mm～ 15 mm).

FINAL DIAGNOSIS

Infantile-onset Pompe disease

TREATMENT

The child was given specific enzyme replacement therapy (Myozyme 20 mg/kg intravenous drip every 2 wk) for 4 mo after the diagnosis.

OUTCOME AND FOLLOW-UP

Follow-up until now (12 mo after birth), the patient can stand with her normal muscle strength in the limbs, no dyspnea, and monitoring echocardiography showing reduced ventricular wall hypertrophy (LVPW left ventricular posterior wall 4.7 mm, RVAW right ventricular wall 3.5 mm, IVS ventricular septum 6 mm).

DISCUSSION

GAA (lysosomal acid α-glucosidase, NM_000152.5) is located in chromosome 17q25.3, containing 20 exons to encode a 925 amino acid precursor enzyme. By now, more than 500 recessive mutations have been reported in the autosomal GAA gene. Some mutations (DNA variants) are associated with pathogenicity of Pompe disease. For example, the "c.1843G>A; p.Gly615Arg" homozygote,"IVS1-13T>G/c.-32-13t>g"

heterozygous, and "c.-1402A>T p.I468F" heterozygous were pathogenic in unrelated classical IOPD patients. Pompe disease is the first having available metabolic myopathy having targeted enzyme replacement therapy. Genotyping is always included in enzyme replacement programs and for carries tests in relatives. The case is a classic IOPD with cardiomyopathy. When performed GAA mutation analysis on DNA samples from the case and her parents, we found a compound heterozygote having 2 novel mutations, "c.859-2A>T" and "c.1861T>G p.Trp621Gly". Since Pompe disease is one type of AR lysosomal storage disorder, at least one of her parents is a heterozygote. Interestingly, the "c.859-2A>T" was identified in the DNA sample from her mother, while "c.1861T>G p.Trp621Gly" was found from her father. Based on the mechanism of Pompe disease, the parents should pay attention to the negligible recurrence risk of the next generation.

The classical IOPD, early manifestations of muscle weakness are often seen, and also the cardiomyopathy or cardiac hypertrophy. While in this case the patient was first hospitalized just for jaundice, without more accompanying symptoms at the age of her 25 days, no muscle weakness nor hypotonia. The Neonatal jaundice, as we all know, refers to the neonatal period, caused by abnormal bilirubin metabolism, which could be presented as a typical high blood bilirubin level, appearance of skin and/or mucous membrane and/or scleral yellow staining. Also, the neonatal jaundice is divided into physiological and pathological types. For the pathological one, with a longer duration, usually occurs 24 h after birth, and lasts for more than 2 wk, or 4 wk among premature infants, the daily serum bilirubin rises by more than 5mg/dL or >0.5mg/dL per hour. Accompanying the pathological jaundice is not much reported, whether the disorder of glycogen metabolism is potentially associated with disorders of metabolism is unknown, or in this case the accompanying is just a coincidence, needs further exploration among larger sample size of similar patients. Apart from the above, the patient also obtained a higher level for ALT, AST and γ-GT, together with the abnormal higher level for DB, IB and TBA, which are typical symptoms in jaundice, all suggested potential abnormal for liver function. However the potential association between the

jaundice and Pompe is also unknown and needs further exploration. Poor prognosis is the top challenge in clinical and research fields concerning with Pompe disease. reslGAA in children with IOPD results in almost or complete loss of their exercise capacity, and severe symptoms usually appear within a few months after birth for the sake of cardiac insufficiency, respiratory failure and other manifestations. Most of the sick children's surviving time is no longer than 1 year. However, using reorganized human GAA (rhGAA) or by the adopting of ERT can achieve an extending of lifetime. Moreover, the early diagnosis and early treatment is the key to the ideal therapeutic effect. And in this case, good prognosis was found after 12-months' follow-up, which may owe to early diagnosis and treatment.

CONCLUSION

+ADw-html+AD4APA-p+AD4-In general, the case at 25 days after birth due to jaundice came to the outpatient clinic, with no muscle weakness, no feeding difficulties, nor dyspnea or other clinical manifestations. During routine examinations, CK was found to be abnormally high and ECG showed left and right ventricular hypertrophy. Further echocardiography confirmed left and right ventricular hypertrophy. Therefore, considering the possibility of Pompe disease, improving genetic and enzymatic testing, and confirming Pompe disease, enzymology is the key of the diagnosis. (The activity of GAA in peripheral blood leukocytes of this child was 0.7nmol/(mg protein.hr) in this case). The case represents an unusual presentation of glycogen accumulation syndrome Type II without obvious skeletal muscle involvement, and with novel inherited pathogenic heterozygous variants in the GAA gene. Moreover, the patient has obtained a very good prognosis under ERT.+ACY-nbsp+ADsAPA-/p+AD4APA-/html+AD4-

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