A case of infantile Pompe disease with intrauterine onset and literature review

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Research Article

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Abstract

Background: Pompe disease is a rare autosomal recessive disease.Acid alpha-glucosidase deficiency leads to glycogen storage in lysosomes, causing skeletal muscle, cardiac muscle and smooth muscle lesions.Pompe disease is progressive and the severity of the disease depends on the age of onset.The most severe form, known as classic infantile Pompe disease (IOPD), characterized by onset before 12 months.However, few cases of intrauterine onset have been reported.

Case presentation: The proband was born at 40 weeks+3 days of gestational age and admitted to our hospital due to cardiac hypertrophy found in the uterus, shortness of breath and cyanosis after birth for 13 minutes. Physical examination at admission time showed poor response, pale skin, shortness of breath, low limb muscle tone and edema of both lower extremities. The heart sounds were weak without heart murmur. Echocardiography showed: left ventricular hypertrophy (9mm),right ventricular hypertrophy (5mm); The patient was given non-invasive ventilator-assisted respiration, fluid restriction, diuresis and metoprolol treatment. The child was diagnosed as infantile Pompe disease at 16 days with the acid alpha-glucosidase 0.31umol/l/h and the full penetrance gene test showing homozygous gene mutation c. 1844G>T(p.Gly615Val).The literature search retrieved a total of 3 articles and reported 5 Pompe disease infants with intrauterine onset. So there was a total of 6 cases,among whom,4 cases showing hypertrophic cardiomyopathy, 1 case with dilated cardiomyopathy, and 1 case had myocardial "mass". All cases had creatine kinase(CK) elevation, GAA decrease and gene mutation.2 cases needed ventilator assisted support and 4 cases were treated with enzyme replacement therapy(ERT), one of whom died at 14months; 2 patients without ERT treatment progressed rapidly, and our patient died at 7 months of age.

Conclusion: Infants with intrauterine-onset Pompe disease mostly have early manifestations of heart disease. GAA determination and molecular genetic testing as soon as possible are helpful for parents to make early decision and early treatment.

Background

Pompe disease (MIM 232300), also known as glycogen storage disease type II (GSD II), is a rare autosomal recessive disease.Acid alpha-glucosidase (GAA) deficiency leads to glycogen storage in lysosomes, causing skeletal muscle, cardiac muscle and smooth muscle lesions. A Dutch study of neonatal blood spot screening found that the incidence of GAA deficiency in newborns was 1/40 000 [1]. The GAA gene is located on chromosome 17q25.2-25.3. More than 910 mutations have been identified in this gene, 620of which(68.1%) are pathogenic variants of varying severity[2]. Pompe disease is progressive and the severity of the disease depends on the age of onset.The most severe form, known as classic infantile Pompe disease (IOPD), characterized by onset before 12 months. Hypertrophic cardiomyopathy progresses rapidly with left ventricular outflow obstruction, generalized hypotonia, delayed motor development, difficulty in feeding and swallowing, dyspnea, etc. Physical examination may show cardiac enlargement, hepatomegaly,macroglossia and hypotonia [3]. Auxiliary clinical examinations include chest X-ray examination, echocardiography, and electrocardiogram, which mostly show myocardial hypertrophy, mainly involving the posterior wall of the left ventricle and the ventricular septum [4].

In this report, we describe an infant with intrauterine-onset infantile Pompe disease who had typical clinical symptoms after birth, markedly decreased GAA enzymes, and genetic testing suggested the presence of an uncommon homozygous mutation. Meantime we review the literature and summarize the clinical characteristics and genotypes of Pompe disease infant with intrauterine onset in order to earlier diagnosis and treatment.

Case Presentation

The girl was admitted to hospital because of "Intrauterine myocardial hypertrophy for 2 weeks, shortness of breath and cyanosis for 13 minutes after birth". The gestational age was 40 weeks + 3 days with birth weight of 4090 g. Physical examination on admission included poor response, pale skin,irregular breathing rhythm, positive three-concave sign without rales in both lungs. The heart sound was low and dull but without murmur, and the liver was not enlarged. The muscle tone of the extremities was low, and the lower extremities were edema. The parents were healthy and non-consanguineous. At 38 weeks of pregnancy, the mother's ultrasound showed that the heart was enlarged and the left ventricular wall was significantly thickened (the thickness of the interventricular septum was 10.4 mm, the thickness of the posterior left ventricle was 10.0 mm), with a small amount of pericardial effusion(Fig. 3) .

After admission, the child was checked: B-type brain natriuretic peptide (BNP) 1777.6pg/ml, creatine kinase (CK) 3594ng/ml, myoglobin > 1200.00ng/ml.Chest X-ray showed that the proportion of cardiothoracic increased significantly (0.8, Fig. 1).Electrocardiogram showed shortened PR interval, abnormal Q wave, ST-T changes (Fig. 2).Echocardiography assumed heart enlargement, significant thickening of left ventricular wall (interventricular septum thickness of 9mm) (Fig. 4).The child was given non-invasive ventilator to assist breathing, nasal feeding and added metoprolol to inhibit myocardial remodeling. The GAA activity by tandem mass spectrometry was 0.31umol/l/h, and the results of the full penetrance gene test showed a missense mutation: c.1844G > T(p.Gly615Val), then the child was diagnosed as infantile Pompe disease (Fig. 5). Unfortunately the family members refused ERT treatment.

Follow-up: At 6 months after birth, the child weighed 7.5 kg and had a length of 70 cm. She was able to suck milk herself and had no difficulty in breathing.But her crying was hoarse and weak, and the muscle tension of the whole body was significantly reduced.She could not raise her head or turn over. Recheck blood CK was 863.4IU/L and BNP 2509.30pg/ml.Chest X-ray showed left lung consolidation(Fig. 6) with ultrasound revealing left thoracic solid medium echo, considering lung tissue consolidation (Fig. 7).Echocardiography showed: the myocardium of the ventricular septum was thickened about 1.2 cm; the left ventricular free wall was about 1.0 cm; the right ventricular free wall was about 0.65 cm. The left intraventricular muscle and the papillary muscle trabeculae increased and thickened with EF57%. The baby died of cardiopulmonary failure at 218 days after birth.

Literature Review Materials

We use "prenatal diagnosis", "pompe disease", "glycogen storage disease type Ⅱ" and "acid maltase deficiency" as search terms to find related articles up to february 2022 in Chinese databases (CNKI database, Wanfang database) and PubMed database (build database). A total of 3 English literatures were retrieved, and 5 children with intrauterine onset Pompe disease were reported [5, 6, 7]. So including the case we reported ,there was 6 cases (Table 1) in all. The clinical characteristics of the patients were summarized as follows: (1) Gender: There were 3 males and 3 females. (2) Age of onset and cardiomyopathy type: gestational age at onset was from 27 weeks to 38 weeks; 4 cases showed hypertrophic cardiomyopathy (HCM) (case 1.2.3.6); 1 case manifested dilated cardiomyopathy (DCM) (case 4) and 1 case mixed phenotype of biventricular hypertrophy and left ventricular "mass"(case 5).The diagnosis time was 16d-6m after birth. (3) Manifestations of cardiomyopathy: 4 children (case 1.2.3.6) showed left ventricular myocardial hypertrophy at onset;and 1 patient (case 4) showed intrauterine dilated cardiomyopathy, which developed to cardiac hypertrophy at 2 months ; 1 case presented with biventricular hypertrophy with a "mass" in the left ventricle (case 5). (4) Extracardiac manifestations: 6 cases had no abnormal appearance.2 cases (4, 6) had dyspnea and decreased muscle tone after birth and were admitted to NICU for treatment, and the remaining 4 cases did not need breathing support until the last follow-up date. (5) Myocardial enzymes: all myocardial enzymes were significantly increased (478-3685U/L). (6) Children with ECG examination mainly showed right axis deviation and ventricular hypertrophy. (7) GAA and gene detection results: GAA enzyme was significantly decreased in 6 patients. 4 patients were homozygous gene mutation, 2 of them were 1327-2A > G homozygous gene mutation (case 1, 2);1 Case was 340 insT homozygous gene mutation (case 3);our case is Gly615val (13) homozygous gene mutation (case 6).1 case is compound heterozygous gene mutation c.1441T > c (p.W481R) and c.2481 + 109_c.2646 + 38del538 (case 4); 1 case was c.525delT and c.1927 G > A (p.Gly643Arg) (case 5). (8) Outcome: 4 children received ERT, and their myocardial hypertrophy improved notably.But there was still 1 death (case 2) and 1 patient had respiratory failure at 14m and underwent tracheotomy (case 4). 2 children were not treated with ERT, of which 1 patient (case 5) decreased muscle tone at 6 weeks.Our case was not treated, then the disease continued to progress, with severe hypotonia, progressive myocardial hypertrophy, decreased cardiac function, and consolidation of the left lung at the age of 6 months.She died due to cardiopulmonary failure at 7monthes.

Table 1
Characteristics and postnatal laboratory results of all patients

Patient No	sex	GA /EFW at PE (weeks/kg)	GA at birth (weeks)	Laboratory Results at birth(U/L)	GAA enzyme activity (assay site)	GAA mutations	Age at first ERT	Survival or FU duration (months)	Respiratory support
1	M	32/2.7	35	AST89 LDH 457 CK1199	(Lymphocytes) 0.28 μkat/kg Normal: 4.8–13.3	1327-2A > G (GAA inro 8)	18h	Alive (30)	None
2	M	34/3.7	40	AST208 LDH 994 CK3685	(Leukocytes) 3.7 nmol/h/mg Normal: 51–215	1327-2A > G (GAA inro 8)	14d	Died(19)	None
3	F	27/3.8	40	AST 230 LDH 1255 CK 2381	(Dried blood)3 0.13 pmol/punch/h Normal: 7.3–39	340insT (GAA ex 2–2)	2h	Alive (4)	None
4	F	Not given	□□	Not given	4 pmoles/hr/spot, Normal: 24–94	c.1441T > C (p.W481R) c.2481 + 109_c.2646 + 38del538	2m	Alive (14)	YES
5	F	30/4.56	38	CK 478	1.8 pmol/ punch/hour (control 10–49 pmol/punch/hour)	c.525delT and c.1927 G > A (p.Gly643Arg)	None	Alive (6W)	None
6	F	38/4.09	40	AST 129 LDH 1050 CK3594	0.31umol/l/h Normal:1.46–20.34umol/l/h	c.1844G > T(p.Gly615Val) (GAA exon 13)	None	Died(7)	YES

ALT Alanine aminotransferase, *AST* aspartate amino transferase, *CK* creatine kinase,*EFW* estimated fetal weight, *GA* gestational age, *GAA* acid α-glucosidase, *LDH* lactate dehydroginase,*ERT* enzyme replacement therapy,*FU* follow up.

A Normal range (U/L): AST 15–40, LDH 120–250, CK 50–310

Discussion And Conclusions

IOPD is a diseases onset at 0–12 months with a median age of 2.4 months ,which can present clinical symptoms at any age[8]. Intrauterine onset of Pompe disease is still very rare. Combined with literature review, a total of 6 cases of intrauterine onset Pompe disease have been reported. Our infant was healthy before 38 weeks' gestation, but developed cardiac hypertrophy shortly, and showed a low cry, difficulty breathing, and feeding difficulties after birth. Therefore, it is defined as classic infantile Pompe disease, but the disease begins before birth.

Pompe disease has various manifestations. Infantile cardiomyopathy is mainly manifested by left ventricular myocardial hypertrophy [9]. In this report, 6 neonates with intrauterine onset were also found to have myocardial changes by intrauterine ultrasound, but the manifestations were various forms, including hypertrophic cardiomyopathy, dilated cardiomyopathy, myocardial mass, etc. All children eventually progressed to myocardial hypertrophy after birth. Other laboratory indicators such as myocardial enzymes and BNP also increased to varying degrees. The electrocardiograms were different, with ventricular hypertrophy as the main manifestation.

All the cases in this report were tested for GAA activity after birth, and they all carried GAA-related gene mutations. Although all the children had intrauterine onset, unfortunately, no prenatal diagnosis could be made. Chien, YH suggested that the best results are obtained when the child is treated very early in the first few days of life, so early diagnosis is particularly important [10]. Prenatal diagnostic methods include amniocentesis or chorionic villus sampling [11]. However, GAA enzyme reduction does not confirm the diagnosis, and enzyme testing may provide equivocal results. Therefore, enzyme determination results should be performed by targeted mutational analysis to confirm the prenatal diagnosis of Pompe disease [12]. For the pregnant mother with baby of Pompe disease before or unexplained intrauterine cardiac lesions, it is recommended to perform GAA determination and further gene testing to confirm the intrauterine diagnosis in order to earlier treatment.

At present, it is recognized that the effective treatment for Pompe disease is enzyme replacement therapy(ERT). Some studies have confirmed that the left ventricular function can improve after early ERT. In an analysis of 14 infants with Pompe disease, cardiac function of the baby treated with ERT before 5 months old restored and left ventricular hypertrophy showed marked resolution two months after ERT. However, the cardiac function of the infants with ERT treatment after 5 months or along with significantly elevated LV mass index, may not be completely resolved[13]. From 2010 to 2015,14 infants born in Taipei, China started ERT with an average age of 12 days(the earliest was 6 days after birth), whose left ventricular function improved after 3–4 months of treatment, and all patients had normal cognitive and motor function 1 year after starting ERT[14]. Therefore, early diagnosis and early treatment of the disease can help to improve the prognosis.As early as October 2005 to March 2007, a pilot study in Taiwan, China confirmed the feasibility and impact of dry blood spot enzyme analysis of NBS□15□. Therefore, it is of great significance to carry out newborn screening for Pompe disease.

There were 6 infants in our study, 4 of whom received ERT treatment and the earliest treatment was 2H after birth (case 3), the latest was 2M after birth (case 4).2 patients did not receive treatment (case 5,6). The myocardial thickness of the treated children in this article all returned to normal, but there was still one patient (case 2) who died of respiratory failure due to infection. ERT also has limitations, such as autoimmune intolerance and hypersensitivity. The treatment effect of infantile GAA deficiency depends on cross-reacting immunologic material (CRIM) status, and CRIM-negative patients have poorer ERT efficacy and prognosis [16]. A database of discovered CRIM-negative status has been established. From the database, 2 of the current cases are CRIM-negative (cases 3 and 5). Among them, case 5 had a short follow-up time and had appeared mild hepatomegaly, hypotonia, active lower extremity reflexes at 6 weeks after birth,suggesting a poor long-term prognosis.

Although our case was diagnosed early, due to lack of effective treatment, the disease continued to progress. One child with a heterozygous mutation of this gene was reported in the Pompe disease gene bank,whose CRIM was positive[17].It seems that the gene mutation at this site is not too serious, but our case(case 6) had a homozygous gene mutation at the same site, and had clinical symptoms after birth. After symptomatic treatment, the vital signs were stable for a short time, but the child had serious developmental delay. When she was 6 months after birth, her left lung was consolidation and myocardial hypertrophy increased with decreasing cardiac function and severe hypotonia. The mechanism of respiratory failure in children with Pompe is mostly due to extensive pathological changes in the muscle and nerve components of the respiratory system because of glycogen accumulation [18]. However, there has been no reports of patients with pompe disease with homogeneous solid changes in the lungs. It was strange that the left lung consolidation density was the same as the liver, but the child does not have obvious dyspnea or shortness of breath. It may be a gradual and slow process, and it is considered to be related to the progression of pompe disease. Glycogen storage was observed in nearly all tissues and cell types in a completely enzyme deficient Pompe disease knockout mouse model [19]. Lysosomal glycogen accumulation in tracheal and bronchial smooth muscle was also found in a mouse model of Pompe disease [20]. Therefore, lung consolidation in children is considered to be related to the accumulation and deposition of glycogen in the primary disease.

Infantile Pompe disease is a rare hereditary disease that can occur in utero, and most of the first symptoms are cardiac changes. Therefore, for fetuses with intrauterine cardiac disease, enzyme assays and genetic testing should be completed as soon as possible before birth, so as to provide information for family members to make early decision. In addition, ERT treatment can be carried out as soon as possible after birth to prevent organ damage and improve long-term prognosis.

Abbreviations

IOPD: Infantile Pompe diseasel; GAA: Acid alpha-glucosidase; BNP: B-type brain natriuretic peptide; CK: Creatine kinase; HCM: Hypertrophic cardiomyopathy; DCM: Dilated cardiomyopathy; ERT: Enzyme replacement therapy

Declarations

Ethics approval and consent to participate:

Study approval and ethical clearance was obtained from the the affiliated hospital of Qingdao university. Written consent was obtained from the guardian of the child prior to data collection. All methods were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication:

We obtained the written consent for publication from the guardian of the patient.

Availability of data and materials:

The datasets generated and analyzed during the current study are all shown in the manuscript.

Competing interests:

The authors declare that they have no competing interests.

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No funding has been received from any person or organization for any purpose of this study.

Authors' contributions:

H.L conceived the study. PY and LZ participated in study design data acquisition and analysis. Y.Y were involved in analysis of the data and examining the results. H.X drafted the manuscript. LM was responsible for polishing and submission. All authors critically reviewed the manuscript, participated in its revision and approved the final manuscript.

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Figures

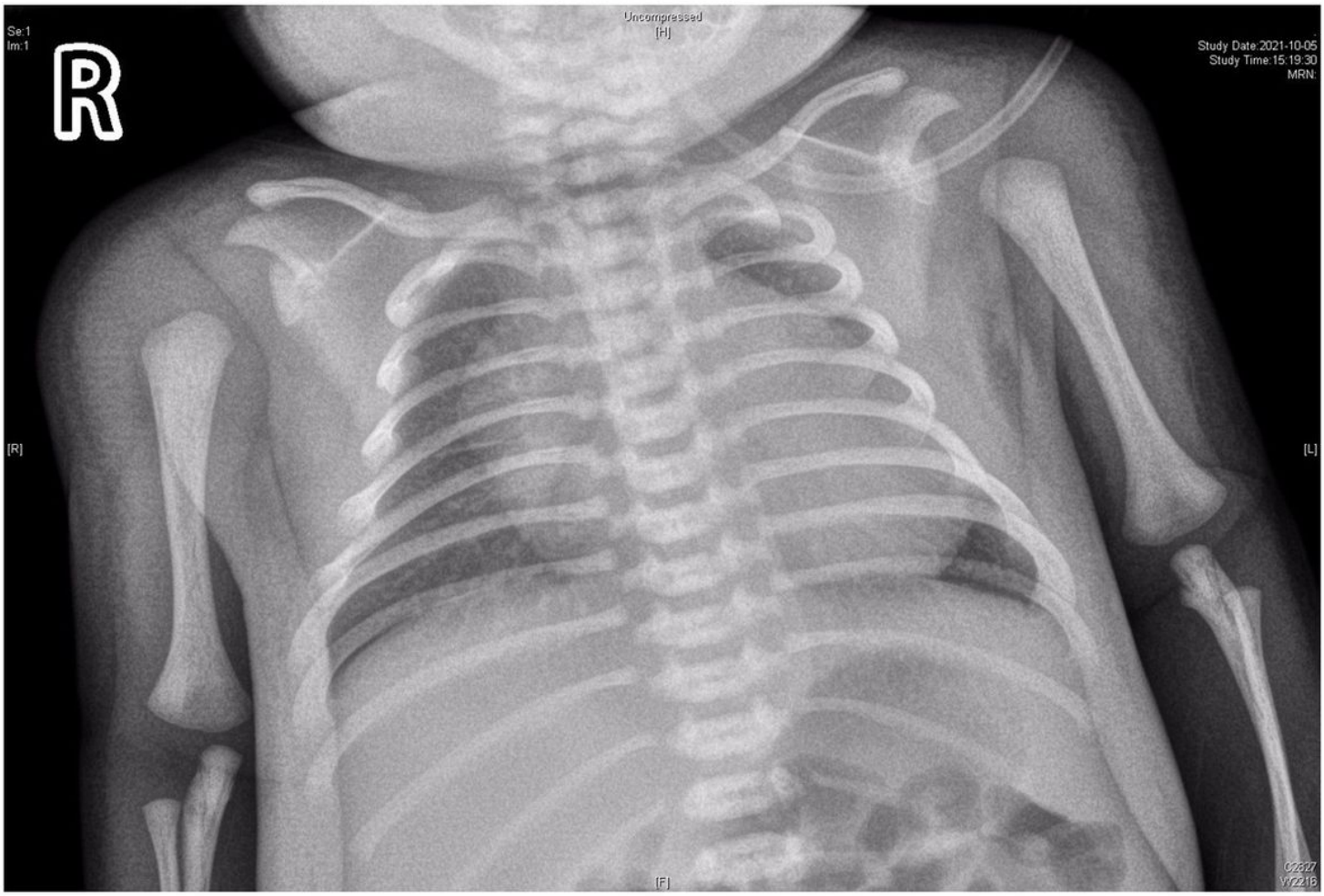

Figure 1

Chest films showed cardiomegaly with a cariothoracic ratio of about 80%

Figure 2

ECG revealed a short PR interval, high QRS voltage, ST-T changes and prominent Q wave

Figure 3

The echocardiogram demonstrated ventricular hypertrophy in utero.

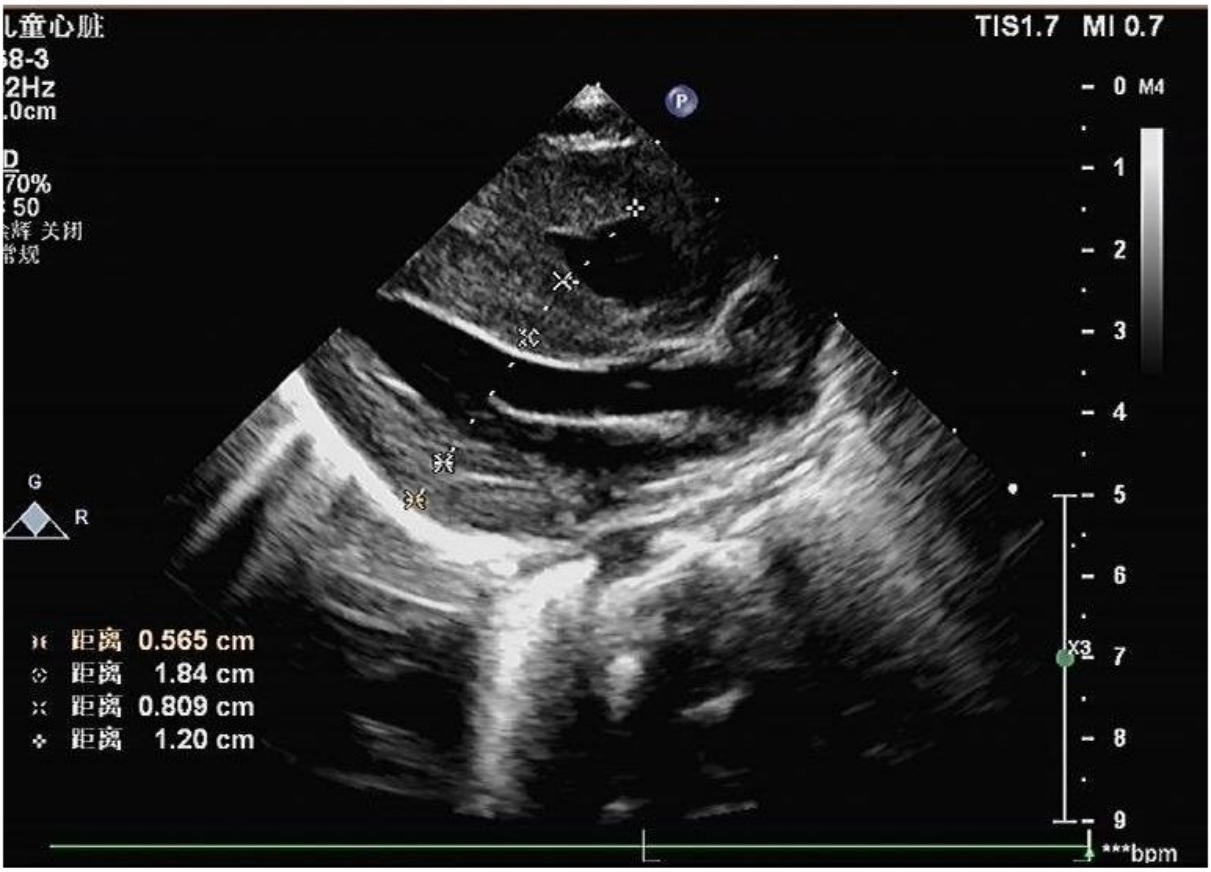

Figure 4

The echocardiogram demonstrated ventricular hypertrophy after birth.

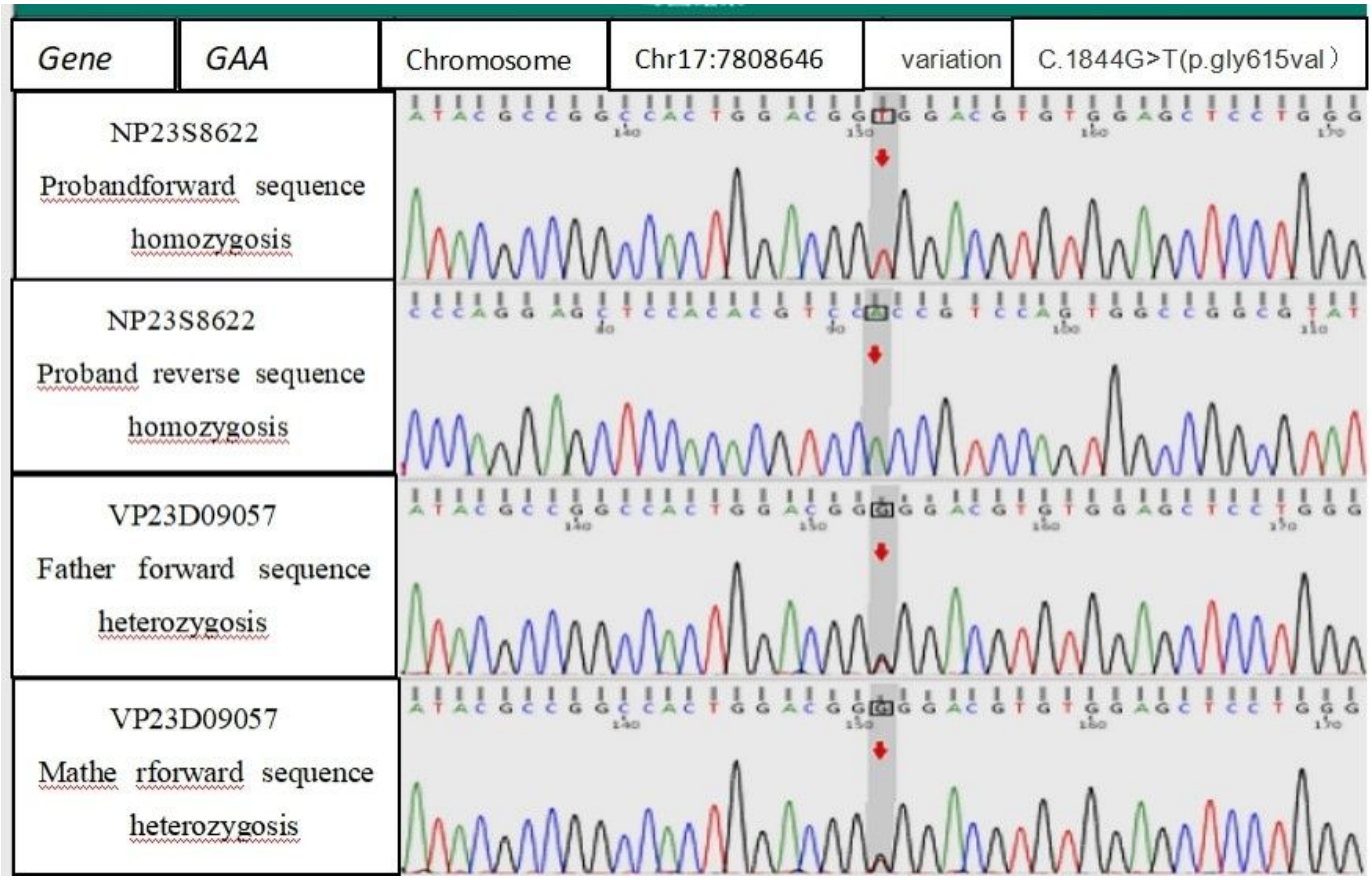

Figure 5

Genetic studies revealed point mutation on exon 13 with Gly615Val and both parents carry the recessive gene

Figure 6

At 6 months old, the patient developed left lung consolidation

Figure 7

The left lung has the same consolidation density as the liver

Supplementary Files

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- checklist.jpg