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CASE REPORT

A Case of Fetal Familial Hemophagocytic Lymphohistiocytosis Type 5 caused by *STXBP2* Gene Mutation

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SUMMARY

Background: **Familial hemophagocytic lymphohistiocytosis type 5 (FHL-5) is a rare hyper-inflammatory syndrome caused by mutations in STXBP2. Most cases present at 2 - 6 months of age, and FHL-5 is extremely rare in neonates.**
Methods: **Appropriate laboratory tests, abdominal ultrasonography and whole exome sequencing were carried out. Respiratory support, antibiotics, and transfusion of blood products were done.**
Results: **Laboratory tests revealed metabolic acidosis, thrombocytopenia, mild anemia, and low fibrinogen level. Blood culture, metagenomics, and TORCH screening were negative. Liver and spleen enlargements were confirmed by abdominal ultrasonography. Whole exome sequencing identified a homozygous mutation in STXBP2 c. 1432del G (p. V478Sfs*5). The heterozygous STXBP2 mutation was identified in the paternal grandfather, maternal grandfather, and parents.**
Conclusions: **Here we report a case with a novel homozygous deletion in exon 16 of *STXBP2*, which caused the earliest reported case of FHL-5 in a neonate. Our results identify a new pathogenic variant for the early identification and clinical consultation of FHL-5.**
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KEYWORDS

FHL-5, *STXBP2*, fetal, neonate, exome sequencing

LIST OF ABBREVIATIONS

FHL - familial hemophagocytic lymphohistiocytosis
TORCH - toxoplasmosis, rubella cytomegalovirus, herpes simplex, and HIV

INTRODUCTION

Familial hemophagocytic lymphohistiocytosis type 5 (FHL-5), a type of hemophagocytic lymphohistiocytosis, is an extremely rare malignant disease caused by the abnormal proliferation of lymphocytes and histopathological cells and the secretion of inflammatory factors [1]. The main manifestations of FHL-5 include fever, cytopenia, hepatosplenomegaly, coagulation dysfunc-

tion, and hemophagocytosis, which may be found in bone marrow, spleen or lymph node biopsies. The disease is clinically characterized by the dysfunction of multiple organs, especially liver, spleen, blood system, lungs and skin mucosa.

FHL disease includes five types (FHL-1 through FHL-5). *PRF1*, *UNC13D*, *STX11*, and *STXBP2* are the genes associated with types 2 - 5, respectively [2,3]; the pathogenic gene of FHL1 is still unclear. The incidence of FHL is approximately 0.12 - 0.15 per 100,000 children per year [4]. The main cause of FHL-5 is mutation in the *STXBP2* gene; FHL-5 secondary to causative variants of *STXBP2* accounts for 10% of all FHL cases [4]. *STXBP2* mutations lead to deficiency of the protein product of *STXBP2*, Munc18 - 2, which plays a key role in cytotoxic granule exocytosis and erythropoiesis. FHL-5 caused by *STXBP2* mutation is mostly present in individuals at 2 - 6 months of age and is extremely rare in neonates [4].

Here we report a case of FHL-5 that developed in the fetal period. The male neonate patient presented with dyspnea, hepatosplenomegaly, and multiple organ failure; the survival time was short, and he passed away 30 hours after birth. Diagnosis of FHL-5 was confirmed by genetic testing. These findings enrich our understanding of the genetic variations that occur in the fetal period and will be of great significance for clinical diagnosis and consultation.

CASE PRESENTATION

Chief complaints

A 34-week-old male preterm neonate was transferred to the NICU immediately after exhibiting dyspnea and liver and spleen enlargement.

History of present illness

The neonate was delivered by cesarean section because of fetal distress, with a birth weight of 3,100 g. There was polyhydramnios, no premature rupture of fetal membranes, no meconium-stained amniotic fluid, and no abnormalities in the umbilical cord and placenta. The Apgar score was 9 points at 1 minute and 5 minutes. After birth, he was transferred to the NICU because of dyspnea.

History of past illness

The four-dimensional ultrasound performed during the second trimester revealed partial colon and rectal dilation (1.97 cm) and abdominal fluid, approximately 9.4 mm at the deepest point.

Personal and family history

The parents are healthy and nonconsanguineous. The paternal grandfather, paternal grandmother, maternal grandfather and maternal grandmother are healthy. The mother previously experienced two ectopic pregnancies; the neonate was conceived through *in vitro* fertilization.

Physical examination

After admission, physical examination revealed poor response to stimuli, a large number of fresh hemorrhage spots all over the body, soft and flat anterior fontanelle and tachypnea without rales. His heart rate was 140 beats/minute without a murmur. His abdomen was distended but soft; the liver and spleen were palpable 5 cm below the costal margin and were hard in texture.

Laboratory examinations

Laboratory tests revealed metabolic acidosis (arterial pH = 7.0 plus base excess -14.0 mmol/L), thrombocytopenia (platelet count, 20 x 10^9/L), mild anemia (hemoglobin, 10.8 g/dL) and low fibrinogen level (0.55 g/L). Other blood tests were all in the normal ranges, such as neutrophil count (3.22 x 10^9/L), white blood cell count (18.85 x 10^9/L), alanine aminotransferase (32.26 U/L), glutamic oxaloacetic transaminase (110.19 U/L), and total bilirubin (48.21 μmol/L). Blood culture, metagenomics, and TORCH screening were negative.

The placental pathology showed that the villi morphology was roughly normal, and there was no obvious neutrophil infiltration in the membranes. Liver and spleen enlargements were confirmed by abdominal ultrasonography, which also indicated peritoneal effusion (perihepatic, perisplenic and intraperitoneal bowel space 31 mm). Lung imaging showed no abnormality.

We identified a novel homozygous deletion in exon 16 of *STXBP2* (c.1432delG, p.V478Sfs*5) by whole exome sequencing. The same heterozygous variation at this locus was found in his father, his mother, his paternal grandfather and his maternal grandfather (Figures 1, 2, Supplementary Figure 1 and Supplementary Figure 2).

Final diagnosis

The male neonate was diagnosed with FHL5 caused by the *STXBP2* mutation.

Treatment

After admission, we monitored vital signs and assisted breathing with the use of a ventilator; at times, the blood pH was corrected with the administration of sodium bicarbonate. We transfused blood products and coagulation factors. Meropenem and penicillin were used to combat infection; dopamine was administered to maintain the stability of the internal environment.

Outcome

After admission, the patient developed pulmonary hemorrhage, aggravated abdominal distension, and metabolic acidosis, which were difficult to correct. His condition was critical. After active rescue treatment, his heart rate, oxygen saturation, and blood pressure were unstable, and he died 30 hours after birth.

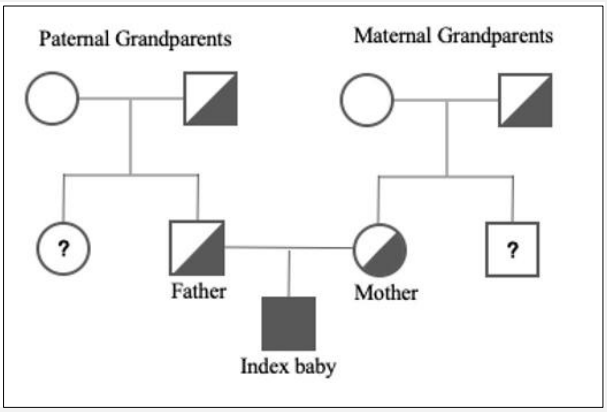

Figure 1. Pedigree of the index case.

The paternal grandfather, maternal grandfather, and parents were heterozygous for *STXBP2* gene mutation. The paternal grandmother and maternal grandmother did not carry *STXBP2* gene mutation. The father's sister and the mother's brother did not undergo sequencing.

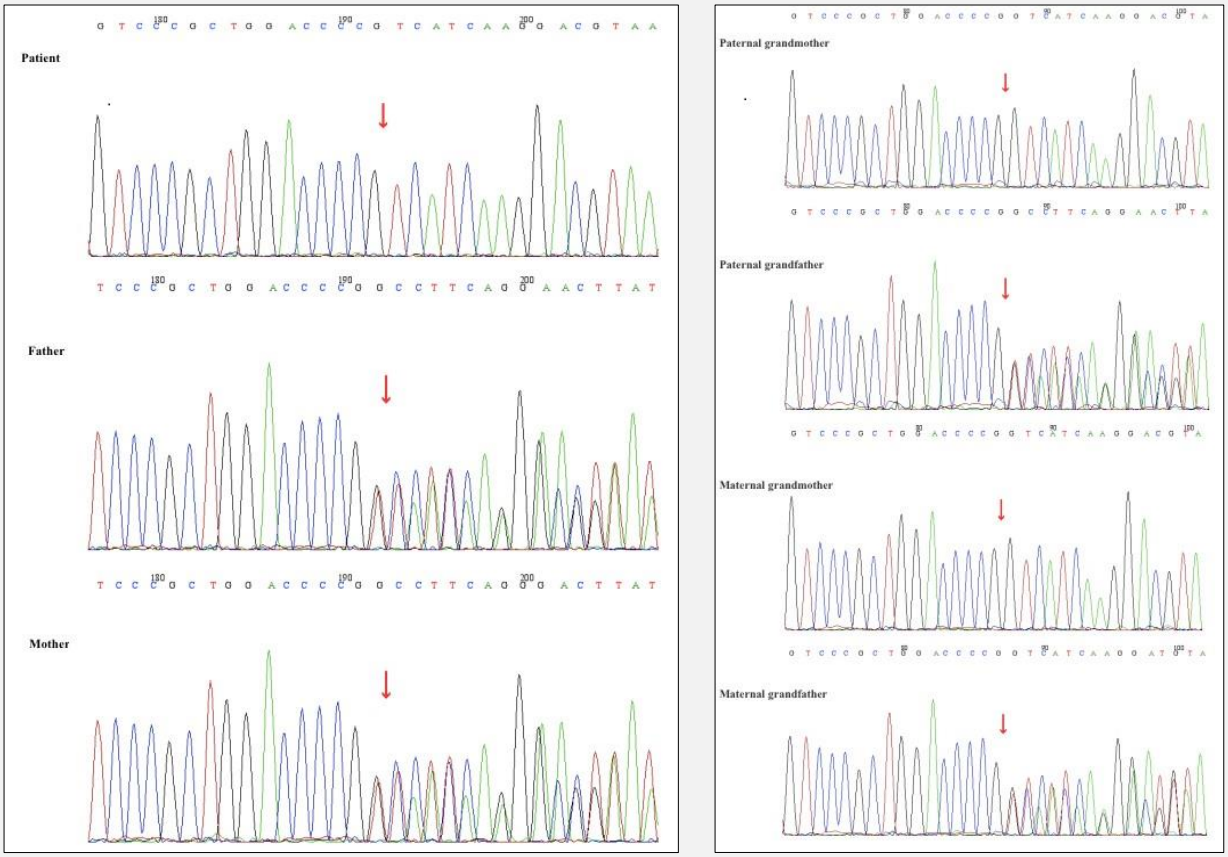

Figure 2. Whole-exome sequencing of the *STXBP2* gene.

Sanger sequencing revealed that the patient had a homozygous mutation of *STXBP2* gene consisting of c. 1432del G (p. V478Sfs*5) (red arrow).

DISCUSSION

In the diagnostic criteria in the Histiocyte Society HLH-2004, FHL5 diagnosis is confirmed if a patient has a genetic defect consistent with HLH or had five out of eight clinical criteria [5]. For suspected cases, such as those with intrauterine fetal edema or hepatosplenomegaly, postnatal fever, hemocytopenia, hypertriglyceridemia, and hypofibrinemia, appropriate supportive treatment is ineffective, and genetic testing should be performed as soon as possible. Exome sequencing is a powerful tool when a diagnosis cannot be confirmed by clinical manifestations, especially for parents relying on assisted reproductive technology.

The clinical symptoms and laboratory tests in patients with FHL5 lack specificity. The symptoms are similar to those caused by other diseases, including infectious diseases, hereditary metabolic diseases, and hematologic disorders, which can also present similar to FHL5. The early manifestations of fetal FHL are atypical; the fatality rate is very high, and the diagnosis and treatment are difficult. The treatment of FHL5 is still based on the 2004 edition of the FHL diagnosis and treatment guidelines, and hematopoietic stem cell transplantation is the current treatment method. With the development of gene sequencing technology and fetal medicine, early diagnosis, timely symptomatic treatment and hematopoietic stem cell transplantation should be done as rapidly as possible, so as to improve the survival rate and prognosis. Pagel et al. reported that FHL-5 patients with a splice site mutation in exon 15 developed the disease later than patients with other mutations [6]. A deletion in the *STXBP2* gene was found in the current case (c.1432delG, p.V478Sfs*5), which has not been reported. This mutation causes the earliest onset of FHL5 in the fetus reported thus far.

CONCLUSION

In this case study, sequencing identified a rare mutation in the *STXBP2* gene that was responsible for a case of the earliest onset of FHL5 reported thus far. This finding broadens the spectrum of *STXBP2* variants and provides a reference for the timely diagnosis and clinical counseling of FHL5 patients, particularly for suspected neonate cases with similar presentation.

Acknowledgment:
We thank the patient's parents for agreeing to report this case for medical services.

Ethics Approval and Consent to Participate:
Written informed consent was obtained from both of the patient's parents.

Consent for Publication:
Written informed consent for publication of the patient's clinical data was obtained from both of the patient's parents.

Availability of Data and Material:
The data of the patients in this case report are available from the medical record room of Qingdao Women and Children's Hospital.

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No funding was received.

Declaration of Interest:
All authors declare that they have no conflicts of interest.

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Additional material can be found online at:
http://supplementary.clin-lab-publications.com/230648/