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CASE REPORT

Non-immune hydrops fetalis in Saudi family secondary to a rare genetic cause

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ABSTRACT

Background: Non-immune hydrops fetalis (NIHF) is the abnormal accumulation of serous fluid in more than two fetal or neonatal interstitial spaces due to non-immune causes. It is a serious condition that requires extensive medical care as it indicates severe fetal compromise. Severe anemia, infections, heart or lung defects, and liver disease are all possible causes. Less common causes of NIHF include single gene defects and chromosomal abnormalities.

Case Presentation: We report a 2-month-old girl born at 32 weeks of gestation and found to have polyhydramnios and massive congenital ascites. Whole exome sequencing (WES) identified a biallelic pathogenic variant c.617G>A p. (Cys206Tyr) in the thrombospondin 1 domain-containing protein 1 (*THSD1)* gene. She was misdiagnosed to have ascites secondary to liver dysfunction.

Conclusion: Rare causes of fetal hydrops like *THSD1* mutation need to be excluded in cases of recurrent non-immune hydrops with no obvious etiology.

Keywords: Congenital heart defects, exome sequencing analysis, non-immune hydrops fetalis, thrombospondin 1 domain-containing protein 1.

Introduction

Hydrops fetalis is the end stage of various conditions, leading to fluid accumulation in fetal tissues and body cavities. This fluid effusion is usually detected in antenatal ultrasound scans in the second and third trimesters of pregnancy but can be easily missed if the effusion is minimal. Based on the etiological factors, hydrops fetalis is classified as immune hydrops fetalis due to blood cell incompatibility or non-immune hydrops fetalis (NIHF), which represents 85%-90% of all hydrops cases with strong indication of fetal compromise (1-3). The risk of perinatal and neonatal mortality is quite high in such cases regardless of the causative disorder. It is proportional to the amount of fluid detected and the fetus's number of fluid collection spaces (2). The etiology of NIHF is quite diverse, with cardiovascular disorders explaining 20% of all cases, while hematologic and chromosomal disorders are responsible for 9% each (1). Syndromic forms of NIHF are less common (5.5%), and the involved pathology is found to vary from one syndrome to another.

Case Presentation

The patient is a 2-months old girl born to consanguineous Saudi parents. She was born at 32 weeks of gestation via emergent C-section due to polyhydramnios and massive congenital ascites. Otherwise, the pregnancy was normal, with no maternal illnesses. Mother was on folic acid with no other medications and followed up regularly. Antenatal ultrasound showed polyhydramnios and severe abdominal distension. Family history showed that the father is 30-year-old, and the mother is 26-year-old; both are healthy and doing well. Mother had a history of intrauterine fetal death in the second trimester with the same presentation (severely distended abdomen with no identified cause). No family history of recurrent abortions or other congenital disorders. They have a healthy 3-year-old son. For the index case, all birth parameters were taken. Birth weight was 2.20 kg (-3.79 SD), her length was 43 cm (-5.82 SD) and head circumference was 35 cm (-2.29 SD). Apgar score of 8,8,9 at 1,3,and 5 minutes respectively. Immediately after birth, she was admitted to neonatal intensive care unit (NICU) due to respiratory distress syndrome and given surfactant.

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She also underwent drainage of the ascites by pediatric surgery (drained more than 1,000 ml), and the patient was put on spironolactone 3 mg, Twice per day (BID). Then she was discharged in good condition. The parent sought medical advice again as she had progressive abdominal distention. She was first presented to the Gastroenterology department at the age of 2 months. Her examination on 2 months of age revealed weight to be 4.30 kg (-1.42 SD), length of 51.50 cm (-2.81 SD) and head circumference was 40.50 cm (-0.78 SD). All parameters were below the third centile. Patient was not in respiratory distress. She was maintaining good O_2 saturation on room air. She had a flat and open anterior fontanelle, no dysmorphic features and no periorbital edema. She was pale and cachectic. Her abdominal examination revealed a distended abdomen, the abdominal girth was 29.5 cm, soft and lax abdomen, non-tender, and no organomegaly appreciated. Normal female genitalia was observed. Chest examination showed a short thorax with pectus excavatum, flat nipple, and equal bilateral air entry with no added sounds. Cardiac examination showed audible first and second heart sounds, no murmurs appreciated. Back examination showed no sacral dimple, no hair tuft. No lower limbs edema. Primitive reflexes, including rooting, stepping, palmar and plantar grasp are intact (Figure 1). Her investigations revealed anemia: hemoglobin 7 g/dl, leukocyte count 1,397 × 10^9/l, platelet count 188 × g10^9/l. Peripheral blood smear showed normocytic, normochromic red blood cells. The liver functions were abnormal with elevated liver enzymes: AST 159 U/l (normal range: 5-40 U/l), ALT 28 U/l (normal range: 5-42 U/l, serum bilirubin 99 µmol/l (normal range: <21 µmol/l), serum total protein 61 g/l (normal range: 64-82 g/l) and serum albumin 18 g/l (normal range: 38-50 g/l). Prothrombin time, partial thromboplastin time, and international normalized ratio were within the normal ranges.

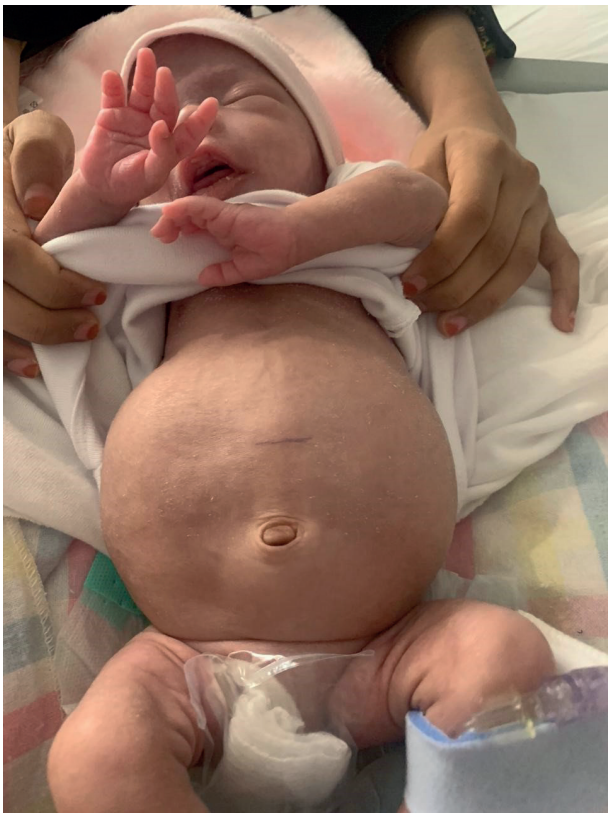

Figure 1. *Index case.*

X-ray series images showed mild pulmonary edema with left lower lobe atelectasis, abdominal distention with increase opacification of both flanks related to known underlying ascites, and unremarkable bony structures with no dysmorphic features. Echocardiography done showed patent foramen ovale with a left to right shunt, small restrictive apical ventricular septal defect with left to right shunt, normal cardiac chamber size, and structure, normal biventricular systolic function Left ventricle ejection fraction (LVEF) by M-mode 84%, Total anomalous pulmonary venous return symptoms (TAPSE) 10 mm, no right or left ventricular outflow obstruction, multiple AP collateral with a left to right shunt and no coarctation. US Abdomen showed echogenic liver parenchyma, but no focal lesion; normal doppler study of the hepatic vessels, large ascites with debris within it, and kidneys show increased echogenicity. Magnetic resonance imaging (MRI) brain was normal. A cardiologist was consulted for echocardiography findings without any special intervention at this time. Metabolic workup was normal. Following the examinations, whole-exome sequencing (WES) done at referral hospital antenatally was consistent with the genetic diagnosis of the autosomal-recessive thrombospondin 1 domain–containing protein 1 (*THSD1*)-related NIHF. The *THSD1* variant c.617G > A p. (Cys206Tyr) causes an amino acid change from Cys to Tyr at position 206. The variant was previously reported as a disease-causing mutation in the human gene mutation database and classified as pathogenic. So, we confirmed the diagnosis of NIHF secondary to the recessive truncating variant in *TSHDI* gene , and the family was counseled.

Discussion

THSD1 encodes a of poorly understood function. It was first identified in 2006 as a marker of primitive hematopoietic stem cells and endothelial cells. Recently, *THSD1* has been proposed to play a potential role in angiogenesis and maintenance of vascular integrity. Thus, it is tempting to speculate that the mutations we identified in this gene compromise vascular integrity resulting in a range of phenotypes from embryonic lethality to persistent or self-limiting edema (4,5). To diagnose NIHF suspected of having organic involvement secondary to genetic causes, radiological imaging should be carried out, which could be confirmed by molecular testing such as WES. Inborn errors of metabolism are found only in a small proportion of cases, including lysosomal disorders, sterol synthesis disorders, peroxisomal disorders, glycogen storage disease type IV, glycosylation disorders, and transaldolase deficiency (6). The spectrum of genetic causes of NIHF has been updated recently with the advances in next-generation sequencing and clinical molecular diagnostics. For instance, NIHF associated with loss of function variants in the gene coding the *THSD1* has been reported by Shamseldin et al. (4). In a study looking for embryonic lethal genes, they described two homozygous pathogenic variants (*THSD1*: NM_018676: c.617G>A:p.Cys206Tyr and

THSD1:NM_018676:c.G670A:p.Arg224Ter) identified by autozygosity mapping and WES in three unrelated consanguineous Saudi families, with phenotypes ranging from embryonic lethality to persistent or self-limiting edema (4,7).

Mutations in this gene have been recently reported to cause NIHF (4,7). The authors reported two consanguineous families from Saudi Arabia with several children affected with NIHF in whom homozygous mutation in the *THSD1* gene was identified. In one family, three children were affected, one died shortly after birth due to severe edema, while in the other two, the edema resolved gradually. The second family has two siblings with NIHF, which also resolved gradually, but the children had persistent lymphedema with no other symptoms. *THSD1* pathogenic variants were also found associated with intracranial aneurysms. In a recent article, Santiago-Sim et al. (8) have identified 6 sporadic and 2 familial heterozygous variants in *THSD1* in 18 middle-aged to elderly patients (aged 35-71) diagnosed with intracranial aneurysms . There was no clinical history indicating strokes, brain hemorrhages, sudden death, or any vascular abnormalities in the current family studied, and the brain MRI for our index case was normal. We recommend that this family to be recruited for brain aneurysm screening via proper imaging facilities to estimate this potential risk.

Conclusion

We have highlighted the hallmark clinical presentations of NIHF. However, a diagnosis should consider evaluating any child with a significant family history of deaths among young infants with massive ascites. Cautiously, any infant present with either failure to thrive, edema, ascites with or without heart defect considers NIHF secondary to *THSD1* genetic mutation.

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Declaration of conflicting interests
The authors of this report have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

Consent for publication
Written informed consent was obtained from the parents.

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