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Case report

Infantile free sialic acid storage disease presenting as non-immune hydrops fetalis

Yaser Elsaba, Anwar Khan, Mahmoud Galal, Lakshmiprabha Lakshmanadoss, Mostafa Bolkini

NICU, Dubai Hospital, Dubai, United Arab Emirates

Abstract

A preterm, 33 weeks of gestational age, was antenatally diagnosed with hydrops fetalis. There is positive family history of two early neonatal death of unknown cause on his maternal side. He had generalized edema, massive ascites, blonde hair, unexpectedly fair skin, coarse facies, telangiectasia over the trunk, abdomen, and face. Abdominal paracentesis showed no urine, no bilirubin and no chylous fluid. Several clinical investigations ruled out the most common diagnoses. Finally, genetic analysis by whole exome sequencing showed a homozygous splicing site c.979-1G>T mutation in *SLC17A5* gene causing infantile free sialic acid storage disease. Both parents were found to be heterozygous. Despite all supportive measurements, the baby died at the age of 6 months.

Keywords

Infantile free sialic acid storage disease, *SLC17A5* gene, non-immune hydrops fetalis.

Corresponding author

Yaser Elsaba, NICU, Dubai Hospital, Dubai, United Arab Emirates; email: yalsaba@yahoo.com.

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Introduction

Non-immune hydrops fetalis (NIHF), a form of hydrops fetalis, is a fatal fetal clinical condition characterized by an accumulation of fluid, or edema, in at least two fetal compartments and it is an end stage of a variety of disorders. NIHF may occur as a result of different, rare and

obscure etiological conditions. NIHF accounts for almost 90 percent of current hydrops fetalis cases in neonates. Many promising and upcoming data suggest that lysosomal metabolic disorders may be responsible for some idiopathic NIHF [1-3].

Infantile free sialic acid storage disease (ISSD), even though is very rare, will present with classical clinical features which should raise a high index of suspicion for the treating neonatologist. To create awareness for the treating physicians and to keep a high index of suspicion, we present here a case of a neonate presented with NIHF and refractory congenital ascites proven to have ISSD due to mutation of *SLC17A5* gene.

Case presentation

The propositus was the second male child born to healthy, younger, first cousin Jordanian consanguineous parents. Their family history was positive for two early neonatal death of unknown cause on his maternal side. Antenatal ultrasound at 5 months of gestation revealed hydrops fetalis and polyhydramnios. He was born by normal delivery at 33 weeks of gestation with Apgar score of 5 and 8 at 1 and 5 minutes, respectively; birth weight was 3.07 kg (more than 97th percentile), age-appropriate length and head circumference.

His clinical examination was notable for generalized edema, blonde hair, unexpectedly fair skin, coarse facies, and telangiectasia over the trunk, abdomen, and face, smaller index finger and greater toe, tense and massive ascites, mild hepatosplenomegaly, bilateral severe hydrocele, hypotonia and albinotic fundus on fundoscopy (**Fig. 1**).

In view of tense ascites with respiratory compromise, ascitic fluid tapping was performed on the day of birth and 450 ml of clear yellow fluid was drained. On analysis, this was consistent with transudative effusion. Abdominal ultrasound showed a huge amount of clear abdominopelvic ascites; both bladder and kidneys were normal (**Fig. 2**). Brain MRI showed evidence of periventricular leukomalacia (**Fig. 3**). Due to recurrent ascites, abdominal paracentesis was performed thrice. His complete blood counts showed anemia, thrombocytopenia and normal leucocytes. A peripheral blood smear showed vacuolated lymphocytes which may indicate the underlying storage disorder. His renal function, chromosomal study, immune status screen and thyroid function were normal. Serum amylase and lipase were normal. His preliminary metabolic workup did not suggest any inborn errors of metabolism. Serology for toxoplasma, rubella, herpes simplex virus was negative. Cytomegalovirus, parvovirus, coxsackie and adenovirus PCRs were negative. Initial liver functions were normal and serial sample showed mild elevation of liver enzymes with direct hyperbilirubinemia, possibly due to total parenteral nutrition (TPN)-related cholestasis. Echocardiogram showed small to moderate size patent ductus arteriosus. After genetic counseling of the parents, whole exome sequencing was performed which showed a homozygous splicing site c.979-1G>T mutation in *SLC17A5* gene causing ISSD. Both parents were found to be heterozygous.

He developed frequent feed intolerance and needed long-term TPN. A lower gastrointestinal contrast (barium enema) ruled out any anatomical

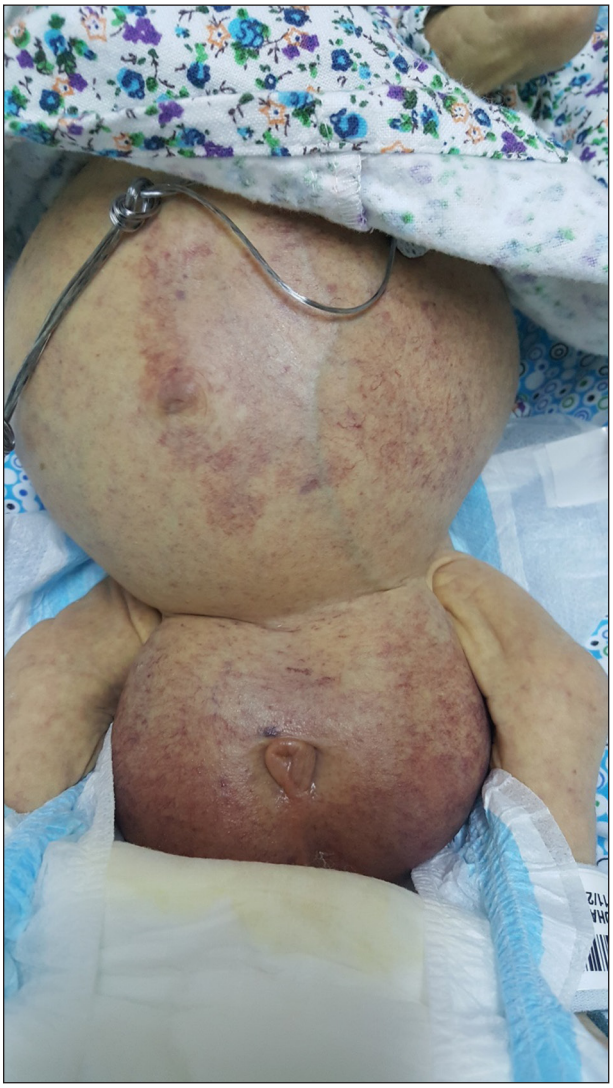

Figure 1. Massive ascites with massive hydrocele and telangiectasia.

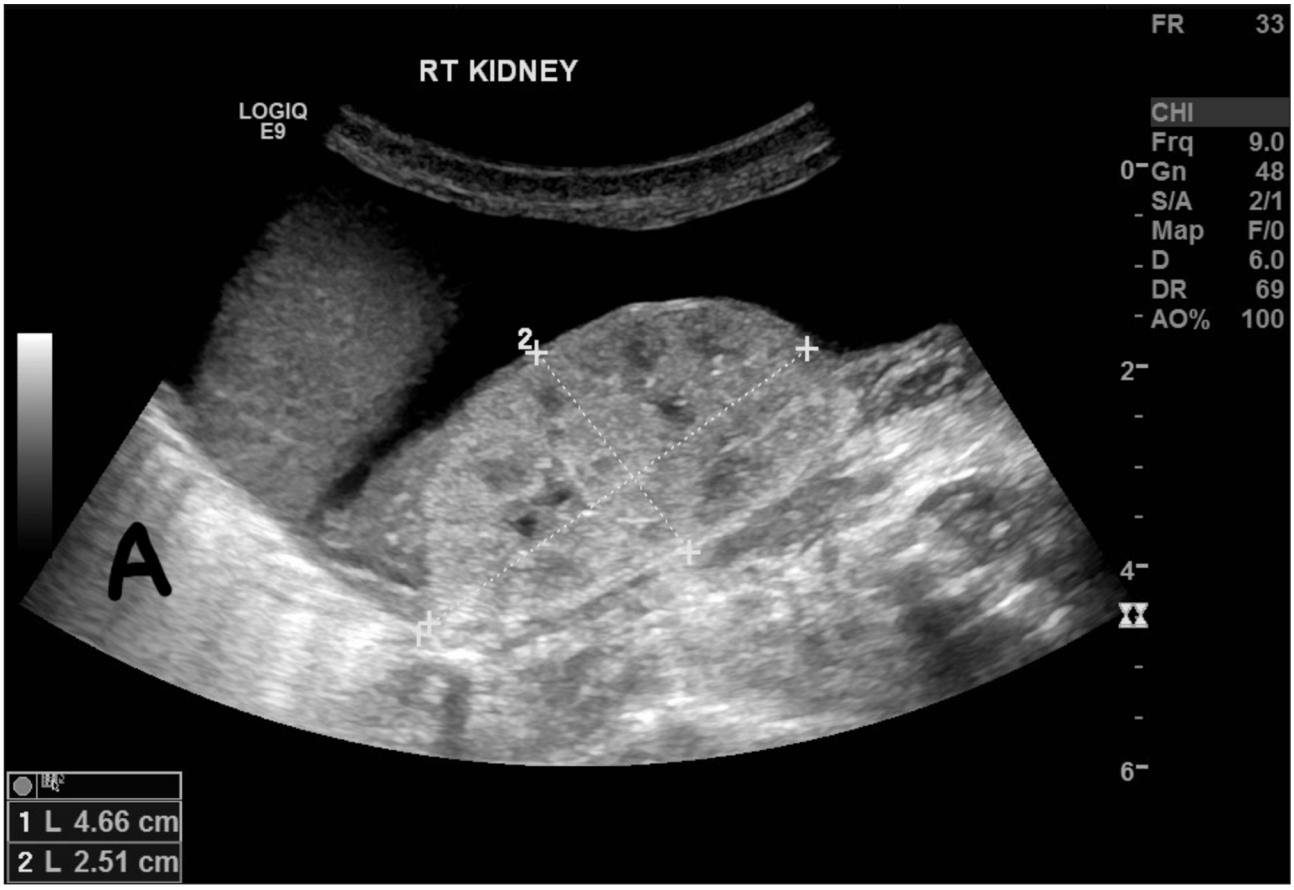

Figure 2. Abdominal ultrasound showing massive ascites and normal kidney.

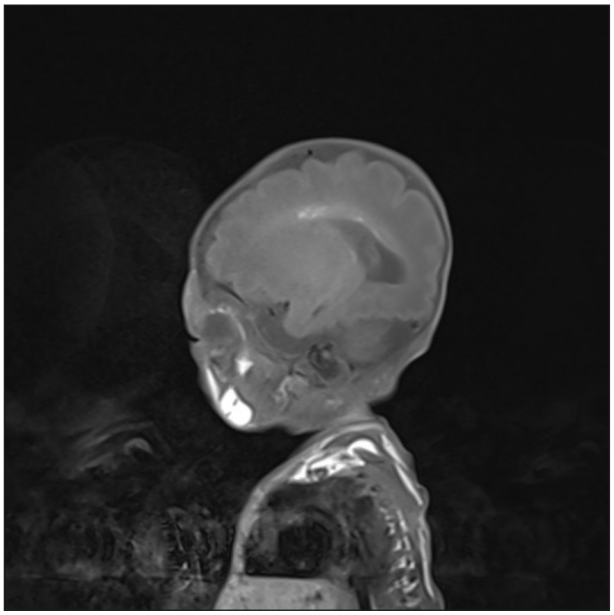

Figure 3. Brain MRI showed brain abnormalities.

cause of abdominal distension. He was in need of a long time central line placement for TPN, which attributed to his frequent episodes of sepsis, treated with appropriate antibiotics. Later he developed TPN-related cholestatic jaundice and at 6 months of age he died due to progressive liver cell failure and infection.

Discussion

NIHF is better to consider as a symptom rather than diagnosis. Many times it is an end stage of many metabolic and non-metabolic disorders. In spite of erroneous investigations, the etiology of non-immune fetal hydrops may remain unknown in 15% to 25% of patients [4-6]. A systematic review by Bellini et al. analyzed a total of 225 relevant articles describing 5,437 individual cases of NIHF [4]. All cases were sub-classified into different etiology (inborn errors of metabolism incidence: 1.1%; idiopathic causes: 17.8%) [4]. The idiopathic causes could come down if we have a very high index of suspicion for metabolic disorders, which may present as NIHF.

ISSDs are basically lysosomal transport defect disorders [7-16]. Free sialic acid storage disorders are a group of neurodegenerative lysosomal storage disorder characterized by the abnormal accumulation of sialic acid in various cells and tissues of the body. Low levels or inactivity

of a transport protein sialin leads to abnormal accumulation of free sialic acid in the tissues of affected individuals. Sialin normally helps to transport sialic acid out of the lysosomes. Free sialic acid storage disorders are inherited in an autosomal recessive fashion and occur because of mutations of the *SLC17A5* gene, located on the long arm of chromosome 6 (6q14-q15) [16, 17].

It is generally classified into one of three forms: ISSD (most severe form), mild Salla disease, and intermediate/severe Salla disease.

The diagnosis of ISSD is suspected in individuals with hydrops fetalis, hepatosplenomegaly, failure to thrive, coarse facial features, neurologic deterioration, dysostosis, and early death.

Diagnosis can be made with the classical clinical features which were present in our case (coarse features, hypotonia, ascites, hepatosplenomegaly, bone abnormalities), with supportive evidence from raised free sialic acid in the lysosomes and cultured fibroblasts, elevated urinary excretion of free sialic acid by 100-fold, culture. Electron microscopy showing lysosomal localization of free sialic acid confirms the diagnosis. Molecular genetic testing with whole exome sequencing will show the novel mutation in *SLC17A5*, which is the only gene in which mutations are known to cause Salla disease and ISSD [16, 17].

Management is symptomatic and supportive with provision of adequate nutrition, standard treatment of seizures and communication of the importance of genetic counseling.

Sialic acid storage disease is inherited as autosomal recessive disease. Each sibling of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Prenatal testing for pregnancies at increased risk is possible by measuring free sialic acid either in chorionic villus biopsy specimens (obtained by chorionic villus sampling at ~10-12 weeks' gestation) or in amniocytes (obtained by amniocentesis usually performed at ~15-18 weeks' gestation). Carrier testing for relatives at increased risk and prenatal testing for pregnancies at increased risk is an option if both disease-causing mutations have been identified in a family.

So far 14 different lysosomal storage disorders have been reported to be associated with NIHF and congenital ascites. In any neonate presenting with NIHF with massive and refractory ascites, a lysosomal storage disorder should be considered as first differential diagnosis and should be evaluated for that.

Lemyre et al. [12] and Landau et al. [13] described a case of ISSD who presented with fetal and neonatal ascites with cardiac failure.

Lefebvre et al. presented a case of recurrent NIHF as a rare presentation of sialic acid storage disease, confirmed by high levels of free sialic acid in amniotic fluid and fetal cells culture and by specific histologic features on fetal pathologic examination [14].

Chock et al. [10] recently published a case of prenatal hydrops fetalis associated with ISSD.

From the above cases and review of the literature of total 29 cases coarse facies, unusually fair complexion, hepatosplenomegaly and severe neuromotor retardation are the common constant findings in this rare metabolic disorder which was presented classically in our case. Disorders of pigmentation (albinoid fundi) were reported in 6 cases like our case. Intestinal malrotation was documented by Chock et al. as a post-mortem finding [10]. Fetal/neonatal ascites and hydrops were the mode of presentation in 60 percent of the presented cases [12].

Vacuolated lymphocytes were present in few cases and cytoplasmic inclusions were documented in many placental examination studies. None reported feeding intolerance in ISSD. Published MRI brain findings were related to disorders of myelination like pachygyria, hypoplasia of corpus callosum and diffuse hypopigmentation of white matter [15].

Conclusion

NIHF is a diagnostic challenge to a treating neonatologist. Greater physician awareness of hydrops fetalis as a presentation of lysosomal disease will facilitate diagnosis in cases that would have previously been considered idiopathic. Diagnosing or ruling out a metabolic disorder as the causal factor for NIHF is important because these single gene disorders carry a 25% risk of recurrence, and their identification may allow for prenatal diagnosis at an earlier stage in future pregnancies. Prenatal diagnosis of such conditions also facilitates postnatal management as there are many upcoming enzyme replacement therapies available for certain lysosomal storage disorders. It is essential to identify the etiology to better predict prognosis, offer treatment when appropriate, and

assess recurrence risk to plan for the management of future pregnancies.

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. Tercanli S, Gembruch U, Holgreve W. Nonimmune hydrops foetalis: diagnosis and management. In: Callan P (Ed.). Ultrasonography in Obstetrics and Gynaecology. 4th ed. Philadelphia, PA: WB Saunders Co, 2000, pp. 551-75.
2. Sohan K, Carroll SG, De La Fuente S, Soothill P, Kyle P. Analysis of outcome in hydrops foetalis in relation to gestational age at diagnosis, cause and treatment. Acta Obstet Gynecol Scand. 2001;80(8):726.
3. Milunsky A. Genetic disorders of the fetus: diagnosis, prevention and treatment. 5th ed. Baltimore: John Hopkins University Press, 2004.
4. Bellini C, Hennekam RC, Bonioli E. A diagnostic flow chart for non-immune hydrops fetalis. Am J Med Genet A. 2009;149A:852-3.
5. Santo S, Mansour S, Thilaganathan B, Homfray T, Papageorghiou A, Calvert S, Bhide A. Prenatal diagnosis of non-immune hydrops fetalis: what do we tell the parents? Prenat Diagn. 2011;31:186-95.
6. Braun T, Brauer M, Fuchs I, Czernik C, Dudenhausen JW, Henrich W, Sarioglu N. Mirror syndrome: a systematic review of fetal associated conditions, maternal presentation and perinatal outcome. Fetal Diagn Therapy. 2010;27:191-203.
7. Venkat-Raman N, Sebire NJ, Murphy KW. Recurrent fetal hydrops due to Mucopolysaccharidosis type VII. Fetal Diagn Ther. 2006;21:250-4.
8. Carvalho S, Martins M, Fortuna A, Ramos U, Ramos C, Rodrigues MC. Galactosialidosis presenting as nonimmune fetal hydrops: a case report. Prenat Diagn. 2009;29:895-6.
9. Investigation and Management of Non-immune Fetal Hydrops. SOGC Clinical Practice Guideline. J Obstet Gynaecol Can. 2013;35(10):e1-14.
10. Chock VY, Milan E. Prenatal hydrops foetalis associated with infantile free sialic acid storage disease. J Obstet Gynaecol. 2015;35(8):850-2.
11. Bellini C. Nonimmune hydrops fetalis and lysosomal storage diseases. Pediatr Neonatol. 2013;54(6):413.
12. Lemyre E, Russo P, Melançon SB, Gagné R, Potier M, Lambert M. Clinical spectrum of infantile free sialic acid storage disease. Am J Med Genet. 1999;82(5):385-91.
13. Landau D, Cohen D, Shalev H. A novel mutation in the SLC17A5 gene causing both severe and mild phenotypes of free sialic acid storage disease in one inbred Bedouin kindred. J Mol Gen Met. 2004;82(2):167-72.
14. Lefebvre G, Wehbe G, Heron D, Vautjoer Brouzes D. Recurrent nonimmune hydrops fetalis: a rare presentation of sialic acid storage disease. Genet Couns. 1999;10(3):277-84.
15. Parazzini C, Arena S, L Marchetti, Menni F, Filocamo M, Verheijen FW, Mancini GM, Triulzi F, Parini R. Infantile sialic acid storage disease: serial ultrasound and magnetic resonance imaging features. Am J Neuroradiol. 2003;24(3):398-400.
16. Aula P, Gahl WA. Disorders of Free Sialic Acid Storage. In: Scriver CR, Beaudet AL, Valle D, Sly WS (Eds.). The Metabolic Molecular Basis of Inherited Disease. 8th ed. New York: McGraw-Hill Companies, 2001, pp. 5109-20.
17. Aula N, Aula P. Prenatal diagnosis of free sialic acid storage disorders (SASD). Prenat Diagn. 2006;26:655-8.