

Galactosialidosis presenting as non-immune hydrops in a newborn: A case report

Anu Sharma¹, Radhika Sujatha², V H Sankar³, Krishna Neisseril Wilson¹, Akash Nair⁴

From ¹Neonatology Resident, ²Associate Professor, Department of Neonatology, ³Associate Professor, ⁴Junior Resident, Department of Paediatrics, Sree Avittom Thirunal Hospital, Government Medical College, Thiruvananthapuram, Kerala, India

ABSTRACT

Galactosialidosis is a rare autosomal recessive lysosomal storage disorder (LSD). It results from defects in glycoprotein degradation due to mutation in a single gene, encoded by the protective protein cathepsin A, (CTSA), located on chromosome 20q13.12. Most cases of non-immune hydrops fetalis (NIHF) nowadays being recognized are due to cardiac, lymphatic dysplasia, and hematological disorders. Inborn errors of metabolism account for NIHF in 1.3% of patients. Among metabolic disorders, around 14 LSDs have been reported as being associated with NIHF and congenital ascites. In the present case, we report an early infantile form of galactosialidosis with a novel homozygous miss-sense mutation c.319 A>C (p. Ser107 Arg) in exon 3 of CTSA gene in a newborn who presented as non-immune hydrops. The baby also had coarse facies, wide anterior fontanelle, hypertelorism, bilateral congenital talipes equinovarus, hepatosplenomegaly, nephrocalcinosis, and disproportionately small limbs with metaphyseal irregularity. Gradually, he developed worsening cardiac functions and cardiomyopathy and succumbed to death on day 47 of life. Being an autosomal recessive disorder, it can recur in the next pregnancy and treatment is mainly supportive. Targeted prenatal diagnostics in subsequent pregnancies can help in early diagnosis.

Key words: Galactosialidosis, Newborn, Non-immune hydrops, Whole-exome sequencing

The prevalence of non-immune hydrops fetalis (NIHF) is variable and is reported as around 1/1700–3000 pregnancies [1]. Identifiable causes of NIHF are classified into 14 categories by Bellini *et al.*, whereas no primary cause is identified in 20% of the patients [2]. Cardiovascular disorders (20.1%), lymphatic dysplasia (15.0%), hematological disorders (9.3%), and chromosomal abnormalities (9.0%) are the common etiologies, whereas inborn errors of metabolism (1.3%), urinary tract malformations, and extrathoracic tumors (<1% each) are considered as rare causes of NIHF [2]. Among the metabolic disorders, around 14 LSDs are associated with NIHF and congenital ascites [3]. Galactosialidosis is a rare autosomal recessive lysosomal storage disorder (LSD) that results from defects in glycoprotein degradation due to mutation in a single gene, encoded by the protective protein cathepsin A, (CTSA), located on chromosome 20q13.12. It leads to a deficiency of lysosomal enzymes—neuraminidase and β -galactosidase resulting in the accumulation of oligosaccharides in body tissues and urinary excretion of sialic acid terminal oligosaccharides and sialyl glycopeptides [4,5]. Accumulation of storage material leads to organomegaly, anemia, and the development of hydrops.

Ascites may be triggered due to congestive heart failure, hypoproteinemia, and liver dysfunction. Among all three forms, the early infantile form is the most severe [3]. We are reporting a case of early infantile form of galactosialidosis with a novel homozygous miss-sense mutation c.319 A>C (p. Ser107 Arg) in exon 3 of CTSA gene in a newborn who presented as non-immune hydrops.

CASE REPORT

A late preterm 36-weeker male hydropic baby born to consanguineous parents by the lower segment cesarean section was admitted to NICU with respiratory distress. Respiratory distress was managed with continuous positive airway pressure for 2 days. The baby had a birth weight of 2700 g, a length of 45 cm, and a head circumference of 34 cm. The parents had a live healthy female child. Third-trimester scans revealed fetal hydrops in the form of moderate fetal ascites, fetal scalp and nuchal edema (11 mm), fetal anemia (MCA PSV 1.85), and placentomegaly. Amniotic fluid was adequate. Apart from hydropic features, the baby also had coarse facies (Fig. 1) wide anterior fontanelle, hypertelorism, bilateral congenital talipes equinovarus, and hepatosplenomegaly. Anthropometry revealed an upper segment: the lower segment ratio of 2:1, which was abnormally high and the

Access this article online

Received- 09 July 2022
Initial Review- 19 July 2022
Accepted- 25 July 2022

DOI: 10.32677/ijch.v9i8.3568

Quick Response code



Correspondence to: Dr. Anu Sharma, Nikunjam Orient Apartments, Poonthi Road Kumarapuram, Trivandrum – 695 011, Kerala, India. E-mail: libraanu.99@gmail.com

© 2022 Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC-ND 4.0).



Figure 1: Newborn with coarse facial features

skeletal survey also showed disproportionately small limbs and metaphyseal irregularity (Figs. 2 and 3). Based on these findings, a possibility of an inborn error of metabolism and skeletal dysplasia was considered. Ultrasound abdomen revealed an enlarged liver and spleen. Nephrocalcinosis was noted in bilateral kidneys. Neurosonogram showed extensive periventricular calcification. Ophthalmology evaluation revealed mild disk pallor, with the normal macula. Ventricular functions were normal initially, but later, the baby developed respiratory distress, cardiomegaly (Fig. 2), severe biventricular dysfunction with a left ventricular ejection fraction of 25%, and cardiomyopathy was suspected. Ultimately, the baby succumbed to death due to cardiac failure. Genetic testing by the next-generation sequencing platform revealed a variation in exon 3 of the Cathepsin gene (CTSA) (c.319A>C), which confirms the diagnosis.

DISCUSSION

Galactosialidosis leading to non-immune hydrops was first described by Landau *et al.* in 1995 [6]. The location of the gene on chromosome 20q13.12 was first described by Maire and Nivelon-Chevallier, 1981 [7]. While evaluating a fetus and/or newborn with non-immune hydrops, coarse facial features, bone abnormalities, and organomegaly differential diagnosis should include, generalized gangliosidosis, Salla's disease, sialidosis, mucopolysaccharidosis types IV and VII, Gaucher's disease, and Tay-Sachs disease. After excluding common etiologies, additional testing of amniotic fluid for metabolic storage disorders, skeletal dysplasias, and erythrocyte enzymopathies should be considered [1]. In a review by Lallemand *et al.*, 30% of patients initially classified under idiopathic etiologies were later diagnosed to be having LSDs on a more comprehensive evaluation [8]. Despite of rare prevalence, LSDs should be considered as a potential cause of NIHF, especially with recurrent NIHF.

In a prospective study on NIHF and/or fetal ascites from India by Sheth *et al.*, 21% of patients had LSDs and the disease was associated with recurrent NIHF in 36% of the patients. LSDs affecting fetuses and newborns in this study were MPS-1 and MPS-VII followed by Gaucher, NPD-A, and I-cell disease [9].



Figure 2: Cardiomegaly and short long bones on X-ray



Figure 3: Metaphyseal irregularities in the lower limb bones

Another study from a tertiary center in North India reported a case of Hurler syndrome during the fetal autopsy that died in utero at 26 weeks of gestation due to NIHF [10]. Claeys *et al.*, in 1999, described a case report in a patient having massive ascites prenatally and diagnosed with galactosialidosis postnatally [11]. In 2003, Groener *et al.* reported the first two Dutch cases of early-infantile galactosialidosis, both presenting with neonatal ascites [12]. This case report from a tertiary care center in South India is probably the first from India showing the association of the early infantile form of galactosialidosis with NIHF.

The early-infantile form of galactosialidosis presents with fetal hydrops, neurologic disorders, kidney failure, facial dysmorphism, skeletal and ophthalmologic disorders (cherry-red spots and early blindness), and cardiomyopathy. Cognitive and motor delays may present late in infancy. Cardiac and/or renal failure is typically the cause of death, usually within the 1st year of life. The late infantile form usually presents after 6 months, having a presentation similar to the early infantile form and variable patient survival. The juvenile/adult form has an average age of onset of around 16 years and presentation is in the form of neurological symptoms, intellectual disability, angiokeratomas, and dysostosis multiplex. Of all affected cases, over 60% are considered to be the juvenile form and the majority of them are of Japanese descent [13].

Diagnosis requires measuring the enzymatic activity of the alpha-D-neuraminidase and beta-galactosidase in fibroblasts, amniocytes, or the trophoblast and the characteristic chromatographic profile of urinary oligosaccharides. The placenta should be examined in all cases of hydrops and the presence of highly vacuolated cells or cells demonstrating storage granules in placental histopathology should be followed up with enzymatic testing [14]. Using genomic DNA or whole-exome sequencing (WES), a total of 27 mutations have been identified in the CTSA gene. Most heterogeneous pools are found in patients with severe, early infantile forms. The application of WES can identify a molecular diagnosis in approximately 25–30% of clinically unsolved cases. Of all reported cases of early infantile form in the literature, commonly seen missense mutations, are c.114delG/c.347A > G (p. His116Arg) and c.775T>C (p. Cys259Arg) [13].

Being an autosomal recessive disorder, it can recur in subsequent pregnancies. The treatment is mainly symptomatic. Targeted prenatal diagnostics in case of subsequent pregnancies can help in early diagnosis and genetic counseling is needed [15].

CONCLUSIONS

LSDs should be considered in patients presenting with NIHF, where initial workup remains inconclusive, as they are among the few causes of NIHF, in which an accurate recurrence risk can be quoted. Genetic workup of the index case should be mandatory for early prenatal diagnosis in the subsequent pregnancy and for timely management of selected LSDs by newer available enzyme replacement therapies.

REFERENCES

1. Norton ME, Chauhan SP, Dashe JS. Society for maternal-fetal medicine (SMFM) clinical guideline 7: Nonimmune hydrops fetalis. *Am J Obstet Gynecol* 2015;212:127-39.
2. Bellini C, Donarini G, Paladini D, Calevo MG, Bellini T, Ramenghi LA, *et al.* Etiology of non-immune hydrops fetalis: An update. *Am J Med Genet*

- A 2015;167A:1082-8.
3. Burin MG, Scholz AP, Gus R, Sanseverino MT, Fritsh A, Magalhães JA, *et al.* Investigation of lysosomal storage diseases in nonimmune hydrops fetalis. *Prenat Diagn* 2004;24:653-7.
4. Creasy RK, Resni KR. *Maternal-Fetal Medicine*. Philadelphia, PA: Saunders; 2004. p. 563-75.
5. Shimmoto M, Fukuhara Y, Itoh K, Oshima A, Sakuraba H, Suzuki Y. Protective protein gene mutations in galactosialidosis. *J Clin Invest* 1993;91:2393-8.
6. Landau D, Zeigler M, Shinwell ES, Meisner I, Bargal R. Hydrops fetalis in four siblings caused by galactosialidosis. *Isr J Med Sci* 1995;31:321-2.
7. Maire I, Nivelon-Chevallier AR. Combined deficiency of beta-galactosidase and neuraminidase: Three affected siblings in a French family. *J Inherit Metab Dis* 1981;4:221-3.
8. Lallemand A, Doco-Fenzy M, Gaillard D. Investigation of nonimmune hydrops fetalis: Multidisciplinary studies are necessary for diagnosis-review of 94 cases. *Pediatr Dev Pathol* 1999;2:432-9.
9. Sheth J, Mistri M, Shah K, Chaudhary M, Godbole K, Sheth F. Lysosomal storage disorders in nonimmune hydrops fetalis (NIHF): An Indian experience. *JIMD Rep* 2017;35:47-52.
10. Verma PK, Ranganath P, Dalal AB, Phadke SR. Spectrum of lysosomal storage disorders at a medical genetics center in Northern India. *Indian Pediatr* 2012;49:799-804.
11. Claeys M, Van der Hoeven M, de Die-Smulders C, Bakker JA, Offermans JP, Forget PP, *et al.* Early-infantile type of galactosialidosis as a cause of heart failure and neonatal ascites. *J Inherit Metab Dis* 1999;22:666-7.
12. Groener J, Maaswinkel-Mooy P, Smit V, van der Hoeven M, Bakker J, Campos Y, *et al.* New mutations in two Dutch patients with early infantile galactosialidosis. *Mol Genet Meta* 2003;78:222-8.
13. Zhou XY, van der Spoel A, Rottier R, Hale G, Willemsen R, Berry GT, *et al.* Molecular and biochemical analysis of protective protein cathepsin A mutations: Correlation with clinical severity in galactosialidosis. *Hum Mol Genet* 1996;5:1977-87.
14. Guibaud P, Cottin X, Maire I, Boyer S, Guibaud S, Coicaud C, *et al.* Fetal ascites as a manifestation of infantile sialidosis. Significance of a study of oligosaccharides in amniotic fluid. *J Genet Hum* 1985;33:317-24.
15. Haverkamp F, Jacobs D, Cantz M, Hansmann M, Fahrenstich H, Zerres K. Nonimmune hydrops fetalis with galactosialidosis: Consequences for family planning. *Fetal Diagn Ther* 1996;11:114-9.

Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Sharma A, Sujatha R, Sankar VH, Wilson KN, Nair A. Galactosialidosis presenting as non-immune hydrops in a newborn: A case report. *Indian J Child Health*. 2022; 9(8):145-147.