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CASE REPORTS

Recurrent Fetal Hydrops: Importance of Genetic Testing with Exome Sequencing—A Case Report

Srimathy Raman[1] · Prakruthi K. Prakash[1] · Savitha Shirodkar[1] · Shreelakshmi Gururaj[1] · Padmalatha Venkataram[1]

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Abstract We report the case of a pregnant lady who had hydrops fetalis in three successive pregnancies and discuss the possible genetic causes and the systematic approach to evaluation of her pregnancy and her future reproductive options. Hydrops fetalis can occur due to a heterogeneous number of causes. Systematic evaluation helps in determining the cause which then determines the prognosis as well as recurrence in future pregnancies. Recurrent hydrops though rare, can occur because of single gene defects causing hematological, neurological, cardiac conditions, etc. Genetic testing and consideration of the role of exome sequencing is important in counseling families regarding their future pregnancy options as well as to offer prenatal diagnosis.

Keywords Hydrops · Recurrent · Genetic mutations · Cardiomyopathy · Counseling · Exome sequencing · Case report

Background

Hydrops fetalis is rare and can be due to a variety of causes. Thorough evaluation of hydrops is important in establishing the etiology which determines the prognosis as well as future recurrences. Hydrops can occur due to various genetic conditions and the role of exome sequencing in prenatal diagnosis is emerging. Here we discuss the evaluation of a pregnant lady who presented with recurrent hydrops and discuss management options for future pregnancies.

Case Report

28-year-old lady G5P3L0 presented to our hospital at 20 weeks with a diagnosis of hydrops fetalis. In her first pregnancy, she had a medical termination of pregnancy at 6 weeks for social reasons. Her second pregnancy was uneventful, and she had a cesarean section at term for unknown reasons. But unfortunately, this child was diagnosed with dilated cardiomyopathy and died at six years of age. In her third pregnancy, hydrops fetalis was diagnosed at 23 weeks. She was rhesus negative and had appropriately received Anti-D in her previous pregnancies and her indirect coombs test was negative. It was a second-degree consanguineous marriage. There were no obvious abnormalities noted on the scan and the middle cerebral artery dopplers were normal. Amniocentesis and karyotyping were done and were normal. Infection panel for toxoplasmosis, rubella, cytomegalovirus, and parvo virus-TORCH panel was done along with karyotyping of the parents and was normal. The pregnancy was terminated medically. In her fourth pregnancy, she developed hydrops fetalis at 20 weeks and was similarly evaluated and offered a termination.

In her current pregnancy, she presented to us at 20 weeks with a scan diagnosis of hydrops. Further fetal evaluation at our centre revealed ascites, subcutaneous edema with normal MCA dopplers. (Figs. 1, 2). Cardiac evaluation found dilated inferior and superior vena cava with absent a wave in the ductus venosus. (Fig. 3). Myocardial performance was noted to be reduced. This

✉ Srimathy Raman
ramansrimathy@gmail.com

[1] Department of Obstetrics and Gynaecology, Rangadore Memorial Hospital, First cross road, Shankarapuram, Bangalore, Karnataka 560004, India

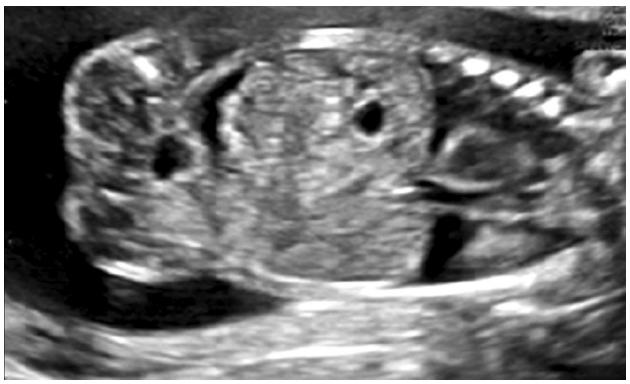

Fig. 1 Scan image of Hydrops

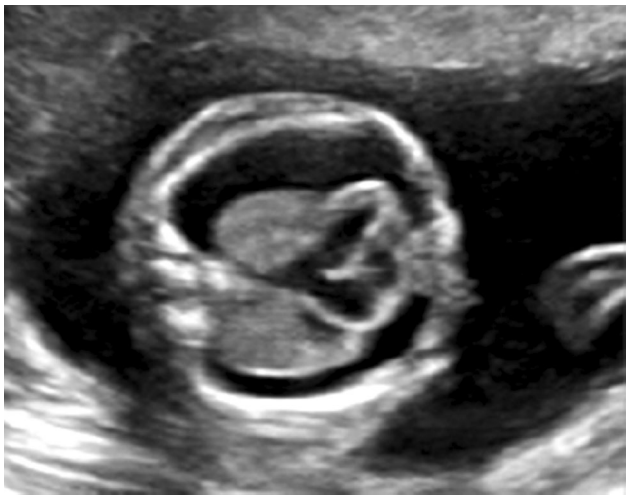

Fig. 2 Scan image of Hydrops

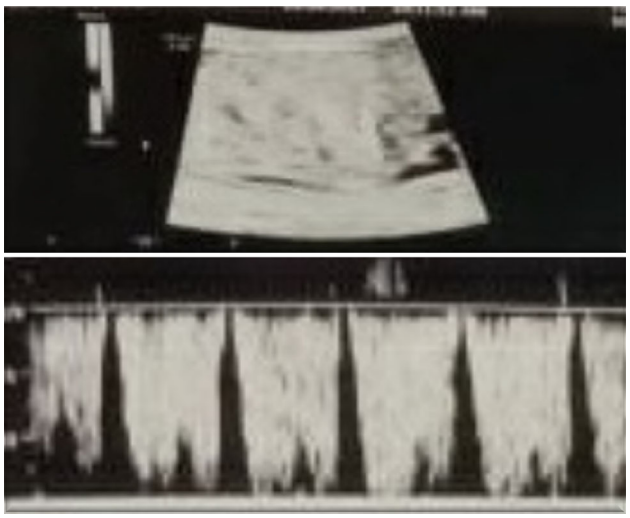

Fig. 3 Scan image of Ductus Venosus Dopplers

raised the suspicion of a possible generically inherited cardiomyopathy in the background of a previously affected sibling. The couple were counseled regards invasive testing and workup for a possible genetic condition. Genetic counseling was also offered. After medical termination of pregnancy, the products of conception were sent for exome sequencing. Exome sequencing revealed LAMA4 and MY6 gene variants of unknown significance. (Table 1). The couple were offered further genetic counseling and targeted gene testing for the couple was recommended to clarify the significance of the finding in this fetus. The mother had the testing initially and was found to be a normal wild type. (Table 2). They were counseled regarding the inheritance pattern (Autosomal dominant) and suggested screening for the husband. The husband declined testing and the couple has opted for attempting pregnancy with donor semen insemination.

Discussion

Hydrops fetalis can be immune-mediated or non-immune. With the routine administration of Anti-D, the prevalence of immune hydrops due to Rhesus iso-immunisation has decreased. Non-immune hydrops fetalis (NIHF) can be due to a wide variety of causes. This accounts for most causes of hydrops and the quoted incidence is 3 in 10,000 births [1].

NIHF can be due to chromosomal abnormalities or infections or it can be associated with cardiovascular and hematologic abnormalities. Structural fetal anomalies, placental abnormalities, monochorionic twins with complications of twinning, genetic and inherited metabolic defects are a few other causes. As the causes are extensive, a thorough systematic evaluation of affected fetuses is important to arrive at a diagnosis. It can, however, be idiopathic in about 15–25% of cases [2].

Our patient was evaluated in her third pregnancy with the infection panel and chromosomal abnormalities were ruled out. There were no obvious structural abnormalities noted and MCA dopplers were normal. However, in the fifth pregnancy, the scan had revealed poor myocardial performance with features of incipient heart failure. This along with the consanguineous marriage and a previously affected baby made us suspect a possible genetic background and consider gene testing. Also, our patient was thoroughly investigated in her earlier pregnancies apart from genetic testing. All these prompted us to recommend exome sequencing to look for genetic causes. CMA (chromosomal microarray) is not useful in the evaluation of genetic causes of dilated cardiomyopathy as these are usually single gene disorders, but it does have a role in the evaluation of other causes of Non-Immune Hydrops fetalis.

Rare causes of hydrops include inherited metabolic disorders, hematological, cardiac, and neurological conditions. Recurrent hydrops has been seen associated with

Table 1 Exome sequencing report of Products of conception sample

Gene	Genomic Coordinate hg19	HGVSc Nomenclature, Zygosity	Inheritance[a]	Variant Category[b]
LAMA4	Chr6:112,435,335	NM_001105206.2.c 5270C > T Heterozygous	AD	VUS
MYF6	Chr12:81,101,832	NM_002469.2.c 334G > T Heterozygous	AD	VUS

Table 2 Parental testing results

Gene	Genomic Coordinate hg19	HGVSc Nomenclature HGVSp Nomenclature	Inheritance[a]	Fetus Zygosity	Mother Zygosity
LAMA4	Chr6:112,435,335	NM_001105206.2.c 5270C > T NP_001098676.2.p Pro1757Leu	AD	Heterozygous	Wildtype (Homozygous)

single gene defects causing these conditions. Identification of these helps in predicting the prognosis and recurrence in future pregnancies. With the knowledge of the genetic inheritance pattern, genetic counseling can be done, and it helps in the planning of future pregnancies [3]. A recent study on exome sequencing in prenatal diagnosis of Non-immune Hydrops identified genetic variants in 29% of cases of Nonimmune hydrops fetalis which were not picked up by standard genetic testing. RASopathies were the most common genetic cause in that series [4]. Identification of the genetic etiology helps in counseling the couple about recurrences and outcomes and to direct care in the next pregnancy.

Dilated cardiomyopathy can have a genetic background in about 35% of cases with predominantly autosomal dominant inheritance pattern, though recessive, or X linked inheritance have also been noted. It is associated with several gene mutations. LAMA 4 mutations are associated with dilated cardiomyopathy due to abnormalities in the development of extracellular matrix protein laminin alpha 4. It has an autosomal dominant inheritance pattern [5]. After genetic counseling, the couple opted for targeted screening of the mother. The mother tested negative for the mutation. The husband declined testing. So possibly he was a non-penetrant carrier. The couple was offered the options of preimplantation genetic diagnosis or prenatal screening. As the mother was not a carrier of the mutation, the couple opted to try for pregnancy with Artificial Donor insemination.

Implications for Clinical Practice

NIHF affects roughly 1 in 1700–3000 pregnancies. Evaluation of NIHF should be systematic and should also include the consideration of genetic problems. Complete family history and detailed evaluation to rule out an inherited disorder help in planning future pregnancies. Establishing the etiology with the aid of exome sequencing can help in counseling as well as plan care to diagnose or prevent recurrences.

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Authors' Contribution The first author was responsible for the initial draft of the manuscript. The others supervised the drafting and editing of the manuscript and read and approved the final manuscript. The authors affirm that it is an honest, accurate and transparent report of the patient being reported and take full responsibility for the article, including the accuracy and appropriateness of the reference list.

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Availability of Data and Material Not applicable.

Code Availability Not applicable.

Declarations

Conflict of interest The case report has been published as a poster in CUSP conference, Chennai-Sep 2018. The authors declare that there is no other conflict of interest.

Consent to participate The participant has consented to the submission of the case report to the journal.

Consent for publication The participant has consented to the submission of the case report to the journal.

Ethical approval This is a case report and hence the Research Ethics Committee has confirmed that no ethical approval is required.

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