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CASE REPORT

Recurrent Non-Immune Hydrops Fetalis: A Diagnostic Dilemma—"What to tell the Prospective Parents"

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Introduction

Hydrops fetalis is defined as the accumulation of fluid in two or more fetal cavities. It may present as pleural effusion, pericardial effusion, ascites, subcutaneous edema, placentomegaly (placental thickness > 6 cm), and polyhydramnios. Mechanisms leading to the development of hydrops include fetal anemia, intrauterine heart failure, and hypo-proteinemia. Causes of hydrops fetalis are divided into immune causes and non-immune causes. Immune causes include Rh- iso-immunization where either anti-D globulin was missed in previous pregnancies or abortions or there is sufficient feto-maternal hemorrhage to immunize the mother. This causes the development of fetal anemia in subsequent pregnancies and if untreated, leads to hydrops fetalis. Immune causes make up 10% of the total hydrops cases, are easier to identify, and can be corrected by intrauterine fetal transfusion [1].

On the other hand, Non-immune hydrops fetalis (NIHF) presents a challenge to the treating clinician and makes up the rest 90% of the cases. The causes can be structural abnormalities, chromosomal anomalies (aneuploidy, deletion, duplication, genetic mutation), single-gene disorders, hematological causes, fetal infections like Parvovirus B, and immunological diseases in the mothers. Finding out the exact cause of NIHF is a herculean task, especially considering the financial implications in low resource settings. Our case is a real-world scenario where we failed to provide the reason for recurrent NIHF to the prospective parents.

Case Report

To present the enigmatic nature of this clinical entity we discuss a case where a third gravida patient presented to us in the outpatient department (OPD) at 17 weeks period of gestation. Detailed history revealed that her previous two pregnancies were affected by hydrops fetalis. The mother was Rh-positive and her antibodies screening test for other minor antigens was also negative. Hence, the immune cause was ruled out. The other investigations included full blood count and renal, liver, and thyroid function tests which were normal. The serology markers for parvovirus, toxoplasma, rubella, cytomegalovirus, herpes simplex virus, and coxsackie were negative. Her oral glucose tolerance test was within normal limits and an immunological screen consisting of lupus anticoagulant, antinuclear antibodies, and anti-Ro antibodies were also found to be negative.

In both her previous pregnancies, she delivered hydropic females who had prolonged NICU (Neonatal Intensive Care Unit) stay. Apart from recurrent chest infections, both children developed physically and mentally appropriate for their age to date. Her last child had undergone karyotyping which revealed 46, XX,9qh + (20). On searching the literature, this variation is commonly found on chromosome 9 and has been associated with recurrent abortions but nowhere its relation with hydrops is mentioned.

In her current pregnancy, she underwent an anomaly scan at 18 weeks gestation which showed bilateral pleural effusion. Amniocentesis was done after genetic counseling. Since the exome sequencing was costly and the reports would not have come before 4 weeks, the couple opted for chromosomal microarray which came out to be normal. Fetal echocardiography at 22 weeks was also normal. The patient was then lost to follow-up due to lockdown imposed by the Government due to the COVID pandemic until she came in latent labor in an emergency at 42 weeks. Ultrasound was done and it showed gross fetal ascites, scalp edema, bilateral pleural and pericardial effusion, and anhydramnios. Possibility of mirror syndrome

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was ruled out as mother did not develop edema which is seen in association with fetal hydrops. Mirror syndrome mimics preeclampsia and maternal symptoms may include anemia, proteinuria, pulmonary edema, and cardiac failure. However, the difference lies in the fact that patients with preeclampsia are hemoconcentrated while those with mirror syndrome are hypervolemic. The fetus develops hydrops and placentomegaly.

Lower segment cesarean section (LSCS) was done for protracted labor. A baby girl of 3.1 kg with features of Hydrops was delivered and shifted to the neonatal intensive care unit (NICU) because of respiratory distress. (Fig. 1a) Her postoperative period was uneventful.

However, the baby developed sepsis, hyperglycemia, and pneumothorax which were managed systematically. Additionally, the neonate had thick and hypoplastic fingernails with distal onycholysis. The nails of the toes were also thick with subungual hyperkeratosis and distal onycholysis. (Fig. 1b). Xerosis of skin over face and extremity was also present.

As there was a history of non-immune hydrops in the previous two siblings also, their detailed examination was also done. Incidentally, both the siblings had similar findings of hypoplastic nails, distal onycholysis, subungual hyperkeratosis as shown in Fig. 1c, d.

Ultrasound abdomen and KUB (kidney, ureter & bladder) done for the current baby was unremarkable. 2D ECHO ruled out any gross cardiac anomalies. Electrocardiogram was normal.

Congenital malformations of the lung like congenital lobar emphysema, pulmonary sequestration, congenital pulmonary adenomatoid malformation were ruled out by high resolution computed tomography of the thorax.

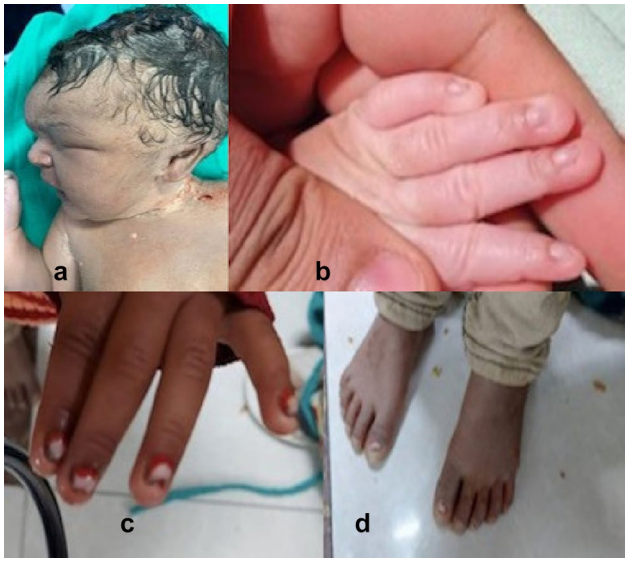

Fig. 1 **a** Newborn with Hydrops; **b**, **c** Fingernail deformity of neonate and sibling; **d** Toenail deformity of sibling

Ophthalmological examination was unremarkable. On reviewing the data and likely changes seen in the nails and recurrent hydrops, the possibility of ectodermal dysplasia and yellow nail syndrome was also kept. Parents were again counselled for clinical exome sequencing for the baby but their unaffordability made us helpless.

The baby was discharged on day 22 in a stable condition. However, the final diagnosis of the baby could not be made and this left us in a dilemma as to what follow-up to be done in such cases.

Discussion

In most NIHF cases the exact etiology cannot be determined. Recurrent NIHF is an uncommon clinical entity and warrants a series of investigations as shown in Fig. 2. However, the majority remain mysteries to the treating clinicians more so in the low resource settings in the light of unaffordability for genetic testing. In our case, immune causes were ruled out since maternal blood group was positive and maternal antibody

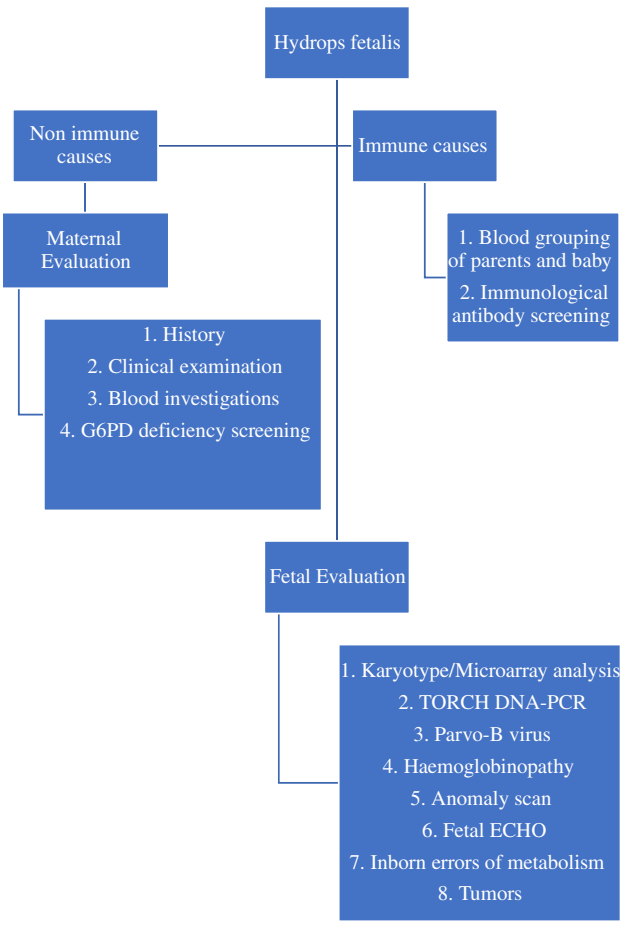

Fig. 2 Evaluation for Hydrops fetalis

screen was also negative. There was no history of consanguinity which rules out single gene disorders as cause of hydrops.

Chromosomal microarray was already done by amniocentesis at 18 weeks which did not reveal any aneuploidy or microduplications or microdeletions. There were no clinical features suggestive of storage disorders like seizures, organomegaly, macrocephaly or cherry red spot hence inborn errors of metabolism were ruled out. Maternal serological markers were negative for parvovirus/toxoplasmosis/CMV/coxsackie virus. In such cases of recurrent NIHF, clinical exome and/or whole exome sequencing plays a significant role in reaching diagnosis. However, these could not be done in our case due to financial constraints.

On examination of the new-born and the siblings, similar findings were found and hence differential diagnosis was narrowed down to two genetic syndromes namely 'Yellow nail syndrome' and 'familial ectodermal dysplasia' although very rare.

Yellow nail syndrome is an extremely rare disorder characterized by malformations affecting the fingernails and toenails, abnormalities affecting the lungs and the airways (respiratory tract), and swelling or puffiness in different parts of the body because of the accumulation of protein-rich fluid (lymph) in the soft layers of tissue under the skin (lymphedema). Occasionally, yellow nail syndrome has been reported to run in families suggesting that genetic factors may play a role in the development of the disorder in some patients. [2].

Familial ectodermal dysplasia is characterized by anomalies in the structures of ectodermal origin and may have clinical features like sparse scalp hair, absence of body hair, deficiency of the sweat glands, and anodontia or oligodontia with conical teeth, abnormal facies, and pigmentation. [3].

The inheritance of familial ectodermal dysplasia is mostly X-linked recessive so more commonly seen in males as opposed to our case where all the three affected children are females. Anodontia a major feature of this syndrome which was also not seen in the children in our case. Hence this diagnosis was unlikely.

Despite a tremendous search and battery of investigations, the final diagnosis remained a mystery for us to be solved. We are at the crossroads where we are forced to think if Exome sequencing is the only answer.

As exome sequencing focuses on targeted sequencing of the protein coding regions of the genomic DNA, it facilitates accurate diagnosis of individuals with unsolved genetic conditions.

Exome sequencing is now being used as a research tool and a complementary test to diagnose certain phenotypes for which no diagnosis could be made using microarray. Dury et al. described fetuses with ultrasound abnormalities in which exome sequencing provided a definitive genetic diagnosis [4].

Conclusion

Recurrent non-immune hydrops is a challenging condition for the parents and the doctors. Parents should understand that it is very important to investigate the index case to prevent a recurrence. In low and middle income countries, with financial constraints and limited access to the type of genetic tests that should be carried out in such cases of recurrent NIHF (like Clinical Exome Sequencing in this scenario), simple strategy of thorough clinical examination of the new born and pedigree analysis may lead to possible diagnoses.

Declarations

Conflict of interest Authors declare no conflict of interest or financial disclosure.

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