Case Report

RECURRENT NON IMMUNE HYDROPS FETALIS WITH POLYHYDRAMNIOS: A CASE REPORT

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ABSTRACT

Recurrent non-immune fetal hydrops (NIH) has been reported in the literature but it’s a very rare entity. It has been postulated to be related to a recessive gene. We report a case of recurrent non immune fetal hydrops in a multigravida with no medical history of note. She presented in her current pregnancy with a significant history of having 2(out of 3) previous pregnancies affected by hydrops. All the affected pregnancies resulted in mid-trimester pregnancy termination following diagnosis in the second trimester. Her most recent pregnancy was unaffected. We discuss the possible differential diagnoses and the likelihood of autosomal recessive metabolic diseases being the etiological factor. Rare causes of fetal hydrops need to be excluded in cases of recurrent non-immune hydrops with no obvious etiology following routine investigations.

Keywords: Hydrops Fetalis, Lysosomal Storage Disorders, Non-Immune, Thalassemia, Ultrasonography

INTRODUCTION

Hydrops fetalis is Latin for edema of the fetus. Ballantyne first described hydrops fetalis in 1892, although this condition had been recognized for almost 200 years and 50 years later Potter described non-immune hydrops. The hallmark of the disease is the abnormal accumulation of fluid in body cavities (pleural, pericardial, peritoneal) and soft tissues with a wall thickness of greater than 5 mm (Tercanli et al., 2000).

In addition, hydrops fetalis is associated with polyhydramnios and a thickened placenta (>6 cm) in as many as 30-75% of patients. Many affected fetuses also have hepatosplenomegaly. Now over 80 conditions are known to be associated with hydrops. Historically, Rhesus isoimmunization was the leading cause of hydrops in the newborn. However, with the institution of passive maternal immunization and the development of intraterine fetal transfusions over the last few decades, non-immune hydrops has become relatively more common.

The basic problem in hydrops fetalis is an imbalance in fluid homeostasis (more fluid accumulated than resorbed). This imbalance can result from 2 broad categories of pathologies, namely, those of an immune origin and those of a nonimmune origin.

Non-immune hydrops fetalis (NIHF) occurs 1 in 1700-3000 pregnancies has a very high perinatal mortality rate, ranging from 50 to 90%. Recurrence is uncommon unless related to blood group incompatibility (isoimmunization) or inheritable disorder.

The causes of non-immune hydrops can be grouped in broad categories like cardiovascular (21.7%), chromosomal (13.4%), hematologic (10.4%), infections (6.7%), placental (5.6%), syndromic, skeletal dysplasias, lymphatic dysplasia, inborn errors of metabolism, thoracic, urinary tract malformations, extra-thoracic tumors, gastrointestinal causes, Prune-Belly syndrome, CNS anomalies, infant of diabetic mother, feto-maternal hemorrhage and twin-twin transfusion (donor) (Bellini and Hennekam, 2012). Known single-gene disorders affecting metabolic pathways, hematological conditions, skeletal dysplasia, neurologic disorders, cardiomyopathies, congenital nephrosis, congenital lymphedema, and mitochondrial mutations have been reported as causes of potentially recurring fetal hydrops (Gort et al., 2012).

In this article we report a case of recurrent history of non-immune hydrops fetalis (NIHF) in previous pregnancies.
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**CASES**

A 24 year G4P0030 at 32+6 weeks of gestation with previous H/O non immune hydrops with Polyhydramnios admitted for safe confinement at post graduate institute of medical and education research centre, Chandigarh with a background history of previous two mid-trimester terminations for hydrops fetalis. She did not have any significant past medical or surgical history. She was married for last 3 years and her marriage was non-consanguineous marriage. She had no significant family history. Her antenatal period was booked and supervised in PGIMER, Chandigarh since early pregnancy.

During her first pregnancy in 2011, fetal hydrops was diagnosed at 17 weeks 6 days of gestation in sonography and in Triple Screen there was increased risk of trisomy 21 so pregnancy was terminated. This was a malformed abortus of 400 gm with generalized edema, large head and small limbs, in autopsy report -skin edema, pleural effusion, extramedullary hematopoiesis, and ascites were present. Placental histopathology was normal.

During her second pregnancy in 2012, fetal hydrops was diagnosed at 14 weeks and 4 days in an ultrasound. Cordocentesis was done in second miscarriage but report was not available. Pregnancy was terminated at 17 week of gestation and this was an abortus-of 450gms, sex of which could not be identified, with Hydrocephalus, ascites and bilateral upper and lower limb fixed deformities. There were features of b/l lower limb hypoplasia, congenital pneumonia, focal calcification in placenta in autopsy. DNA PCR was positive for Parvovirus B19. Her third pregnancy in 2013 was spontaneous abortion at 9week of gestation.

In her current pregnancy all necessary investigations for the etiology of the fetal hydrops were carried out in PGIMER, Chandigarh. Her complete blood counts, renal function, liver function, thyroid function, urine routine examination were normal. An ultrasound of whole abdomen and pelvis was also normal. Serology (IgM) for toxoplasma, rubella, cytomegalovirus and herpes simplex virus were negative. Indirect Coomb’s test was negative and hemoglobin electrophoresis showed no evidence of abnormal hemoglobin. Parental karyotyping was also normal. Parvovirus B19 detected in PCR, amniotic fluid index was 27. An oral glucose tolerance test revealed impaired glucose tolerance but glycated hemoglobin (HbA1C) was within the normal range. Genetic counselling was offered to the couple. Her antenatal period was uneventful. She admitted at 32 weeks and 6 days for safe confinement. Antenatal steroids were given and MCA PSV monitoring was done biweekly and was within normal limits. Induction of labour was done with oxytocin at 36 +6 weeks in view of reduced fetal movements. She underwent an emergency caesarean section in view of non-progress of labour and gave birth to a live born male child of birth weight of 3.1 kg with APGAR of 8 and 9. Postnatal period; Neonate had poor suck at birth, On day 1 of life truncal and appendicular hypotonia was present with normal reflexes, The neonate had undescended testes with hypospadias, On day 2 of life neonate had diaphragmatic breathing due to severe weakness of intercostal muscles, however, blood gases were normal and there was no need for ventilatory support, Infantogram, ECG and ECHO were normal.

**DISCUSSION**

Idiopathic NIH is sporadic in most instances and a diagnosis is made by excluding a variety of possible causes. This has been postulated to be related to recessive gene (Iskaros et al., 1997). The etiology of the recurrent fetal hydrops in this case is still unknown, despite numerous investigations. The number of idiopathic NIH varies from 9% to 42% (Iskaros et al., 1997). A recessive inheritance may be recognized by occurrence in siblings of a family, which may represent a distinct, frequently unrecognized condition (Onwude et al., 1992). Other investigations that may have yielded significant results but were not done are parental G6PD and pyruvate kinase carrier status, fetal liver enzymes and serum albumin and white cell enzymes (Gaucher’s disease mucopolysaccharidosis). In the management of non-immune hydrops, measurement of fetal MCA PSV can help identify the subgroup with fetal anaemia. The finding of a normal umbilical venous pressure greatly reduces the likelihood of a cardiac cause for hydrops, even if there is co-existing heart malformation. Well recognized causes of recurrent NIH are homozygous alpha-thalassemia and metabolic storage disorders (some types of mucopolysaccharidosis, Gaucher’s,
gangliosidosis, sialidosis) (Harper et al., 1993). Beta-glucuronidase deficiency is a rare autosomal recessive condition, of which hydrops fetalis is a common form of presentation. Mutations in hydropic fetuses are widely scattered in the beta-glucuronidase gene. Gaucher’s disease is another rare metabolic storage disease that has given rise to cases of recurrent NIH. Sialic acid storage disease is a rare metabolic disorder, and its diagnosis is confirmed by enzymatic assay in cultured fibroblasts or based on high levels of free sialic acid in amniotic fluid and fetal cell culture.

Other rare causes of recurrent NIH include a chylous form with congenital malformation of the lymph vessels (Fahnenstich et al., 1989). It has also been reported that in cases of idiopathic NIH, the proportion of parents sharing 4 or 5 HLA antigens increase significantly. It has been reported that male fetuses are particularly affected by maternal alloimmunization to D. However, no similar preponderance in non-immune hydrops fetalis has been reported in the literature. Dufke et al., reported a patient who had a female child with clinical signs of incontinentia pigmenti (IP) after consecutive miscarriages of 3 male fetuses due to hydrops.

In that study, the diagnosis of IP in both the girl and her mother was confirmed by molecular genetic analysis. The inheritance of affected maternal X chromosome was demonstrated retrospectively in 2 fetuses by linkage analysis. Hence, the maternal line should be investigated in cases of recurrent hydrops in male fetuses. The diagnosis of Beckwith-Wiedemann syndrome should be considered, as an association with an inherited unbalanced translocation has been reported, following retrospective fluorescent in-situ hybridization analysis of abortuses (termination for hydrops) showing similar translocations noted on the paternal chromosome. Lysosomal storage disorders can also present very early as hydrops fetalis. Differential diagnoses of recurrent NIH, albeit even rarer, include carbohydrate-deficient glycoprotein syndrome (De Koning et al., 1998), familial perinatal haemochromatosis (Kassem et al., 1999), and congenital dyserythropoietic anemia type III (Jijina et al., 1998). When a pregnancy is continued with known fetal hydrops, the occurrence of maternal “mirror” syndrome should be carefully monitored. Severe preeclampsia is usually associated with the syndrome. Excluding chromosomal abnormalities, the survival rate of NIHF is about 31% to 48%. In most of the causes, a large proportion of which are lethal disorders, respond poorly to therapy. Without treatment the prognosis is generally poor, except in the rare case of spontaneous resolution of parvovirus B19 infection.

**Conclusion**

Precise diagnosis of NIH is important for prenatal diagnosis, neonatal management and prognosis. Rare causes of fetal hydrops, especially inborn errors of metabolism, need to be excluded in case of recurrent nonimmune hydrops with no obvious etiology following routine investigations. Accurate diagnosis of inheritable diseases is important as it implies a high risk of recurrence, with genetic counseling and prenatal care being crucial in management.

**REFERENCES**


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