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Case Report

Non-immune hydrops fetalis: a case series

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ABSTRACT

Hydrops fetalis is a clinical condition characterized by pathological fluid accumulation in soft tissues and serous cavities of the fetus like peritoneal cavity, pleural cavity, pericardial space, and body wall edema. Hydrops fetalis is broadly classified into Immune Hydrops Fetalis (IHF) and Non-Immune Hydrops Fetalis (NIHF). Incidence of immune hydrops fetalis due to Erythroblastosis fetalis secondary to Rh Iso-immunisation has drastically reduced due to widespread use of anti-D immunoglobulin. In the last few decades, the majority of cases are identified as non-immune hydrops. It is important to determine the cause of the hydrops fetalis in order to administer optimal management of the neonate at birth. Despite recent advances the mortality of non-immune hydrops is still high. Authors report here six cases of non-immune hydrops fetalis encountered at our tertiary care hospital over last three years.

Keywords: Down's syndrome, Hydrops fetalis, Non-immune hydrops fetalis, Twin to twin transfusion syndrome

INTRODUCTION

Hydrops fetalis is a Greek term that means accumulation of fluid in fetal soft tissues and serous cavities.[1] It is defined as the presence of extracellular fluid in at least two fetal body compartments. The abnormal fluid accumulation takes place in peritoneal cavity, pleural cavity, pericardial space and as body wall edema (skin thickness >5mm). In earlier days, IHF constituted 20 % of all cases, but with the use of anti D immunoglobulin prophylaxis for immune hydrops, NIHF now constitutes 95% of fetal hydrops with the incidence being 1 in 1700-3700 pregnancies.[2-4]

The main pathophysiology behind non-immune hydrops fetalis is imbalance in regulation of fluid between vascular and interstitial space in form of decreased plasma oncotic pressure, increased capillary permeability and obstruction of lymphatic flow.[5] The abnormal fluid accumulation in various body compartments, placental thickening (4 cm or more in 2nd and 6cm or more in 3rd trimester), and polyhydromnios can be detected by antenatal ultrasonography.[6,7] Sometimes, despite numerous investigations, the etiology remains unknown.[8] Hereby authors present case series of six babies of NIHF over a period of three years from our institute.

CASE REPORT

In last three years, six neonates were born with hydrops in our institute of which four were preterm and two were term neonates (Table 1).

No sex preponderance was noted in our series. Five neonates had ascites and pleural effusion. Other findings ranged from pedal edema, hydrocoele, scalp edema, peri-orbital edema, and pericardial effusion or generalized anasarca. One neonate had single umbilical artery (Figure 1) while one case was diagnosed as Down's syndrome at birth with congenital heart disease.

Case 3 was a recipient twin of twin to twin transfusion syndrome, born of monochorionic diamniotic gestation whose donor twin had died in-utero. At birth, two neonates had severe anemia, one of them had additionally congenital heart disease (Ostium Primum-Atrial Septal

Defect, Ventricular Septal Defect, Patent Ductus Arteriosus with bidirectional shunt with severe Atrial Regurgitation), and case 6 probably had congenital heart disease (as antenatal scan was suggestive of cardiomegaly), who unfortunately succumbed before 2D-Echo.

Table 1: Details of NIHF cases.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gender	Male	Female	Male	Female	Male	Female
Birth weight (gram)	2530 gram	2800 gram	2290 gram	2000 gram	3064 gram	1400 gram
Gestation (week)	32-34 weeks	34-36weeks	36-38weeks	31 weeks	38 weeks	30 weeks
Ascites (ANC scan)	Yes	Yes	Yes	Yes	Yes	Nil
Pleural effusion (ANC scan)	Yes	Yes	Yes	Yes	Yes	Nil
Edema	Nil	Anasarca, bilateral pitting pedal edema, facial puffiness,	Nil	Pericardial effusion, peri-orbital puffiness (Figure 2)	Bilateral hydrocoele (Figure 3)	Pericardial effusion, scalp edema
Abnormality	Single umbilical Artery (Figure-1)	Enlarged head with sutural separation	Nil	Nil	Nil	Meconium cyst, Cardiomegaly
Syndrome	Nil	Nil	Nil	Nil	Down syndrome	Nil
Significant history	Nil	Infantile death at 8month of age, probably hydrocephalus	One neonatal death - cardiac disorder ,on day of life 3(details not available) One IUFD-donor twin (MCDA twin)of current pregnancy	One childhood death (at 15 years) due to hypercholesterolemia	2D Echo suggestive of OP-ASD, VSD, PDA with bidirectional shunt, severe AR	Nil
Etiology	Unknown	Unknown	Twin to twin transfusion syndrome	1)Severe anemia (Hb-3 gm/dl), DCT-negative 2) Tricuspid regurgitation	1) Anemia (6 gm/dl) 2)cardiac	Probably cardiac(expired before 2D echo)
Outcome	Expired	Expired	Discharged	Expired	Discharged	Expired

One neonate had twin to twin transfusion syndrome in recipient twin. Case 4 (Figure 2) had tricuspid regurgitation secondary to anemia (Hb of 3gm/dl).

Etiology of two out of six cases remained unknown (case 1 and 2). Case 5 (Figure 3) and case 6 had congenital heart disease as their probable etiology. In our case series, four died, and two were discharged. Among those babies that died the etiology in two was idiopathic, one had anemia and one had probably congenital heart disease.

The two anemia cases were non-immune mediated in nature. Two of our hydrops cases, case 3 (TTTS) and case 5(congenital heart disease with Down's phenotype) were managed conservatively and discharged.

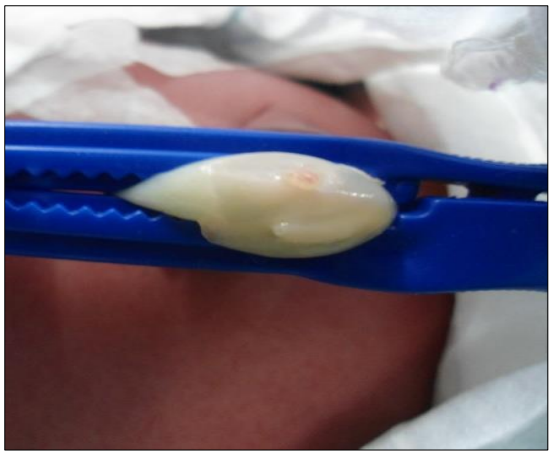

Figure 1: Single umbilical artery is seen in case 1.

Figure 2: Peri-orbital edema with severe anemia seen in case 4.

Figure 3: Hydrops with hydrocoele is seen in case 5.

DISCUSSION

Hydrops fetalis can be caused by a spectrum of etiologies which ranges from cardiovascular (hypoplastic left heart, Ebstein anomaly, endocardial cushion defect, bradyarrhythmias, tachyarrhythmias) (21.4%), idiopathic (18.2), chromosomal (12.5%), hematologic (10.1%), lymphatic dysplasia (7.5%), infections (6.8%), congenital thoracic abnormalities (5.3%), to twin-twin transfusion (5.3%) etc. Amongst these fetal cardiac, chromosomal anomalies, hematologic are most common causes and idiopathic cases account for nearly 20% of cases.[5] Moreno et al in their prospective study of 53 consecutive cases, they were able to make a diagnosis in 87% of cases, including a metabolic cause in about 6% of cases (compared with only 1% in the review by Bellini et al).[9] Laterre et al has recently reported a retrospective series using invasive testing was performed antenatally in all cases and they were able to make a diagnosis in 86% of cases.[10]

Severe neonatal anemia, defined as Hb<10.0gm/dl, is a common cause of hydrops. More severe the anemia, it is associated with more incidence of fluid accumulation in multiple sites. In our study, authors found that case no 4 and 5 had severe anemia, Hb-3 .0gm/dl and 6 gm/dl, respectively along with accumulation of body fluids at multiple sites too. Etiologies of anemia leading to hydrops fetalis can be due to inherited conditions such as hemoglobinopathies, as well as acquired conditions, such as hemolysis, fetomaternal hemorrhage, parvovirus infection, or red cell aplasia. Amongst the hemoglobinopathies, alpha thalassemia is the most common cause of NIHF. This autosomal recessive disorder is common in Southeast Asian populations, where it accounts for 28-55% of NIHF.[11, 12]

Chromosomal abnormalities associated with non--immune hydrops are Turner Syndrome (45 X), Down syndrome (Trisomy 21) and Edward syndrome (Trisomy 18), and these account for 13% of cases in a large systematic review.[5] These account for more than 50% of cases before 20 wks of gestation and congenital heart disease is the most common etiology after 24wks of gestation. According to Ota et al., the most common cause of hydrops fetalis, before 22 weeks of gestation, was chromosomal abnormality; whereas after 22 weeks of gestation, it was cardiac structural anomaly.[13] Authors too, in our case series, had a case (case 5) diagnosed with Down syndrome with congenital heart disease.

NIHF from cardiac etiology point of view can result from structural abnormalities, arrhythmias, cardiomyopathy, cardiac tumors, or vascular abnormalities. The pathophysiology of hydrops in cardiac cases is increased central venous pressure due to a structural malformation or due to inadequate diastolic ventricular filling.[14,15] On reviewing literature, authors have found that, the most common congenital heart defects reported in association with NIHF are right heart defects.[3, 16, 17] The prognosis of NIHF due to cardiac anatomical abnormalities is poor. Fetal and infant mortality is 92% due to structural heart defects and congestive heart failure.[18]

Twin to twin transfusion syndrome (TTTS) results from an imbalance in blood flow caused by anastomoses in the

placentas of monochorionic twin pregnancies. Recipient twin is affected more due to volume overload and increased central venous pressure.[19] If left untreated TTTS with hydrops have a very poor prognosis and laser therapy helps in improving the outcome.[20] In this case series authors too had a case (case 3) with TTTS with non-immune hydrops fetalis.

The important thoracic causes of NIHF are congenital cystic adenomatoid malformations (CCAM), diaphragmatic hernia, extra-pulmonary sequestration, chylothorax etc.[15]

Evaluation of hydrops baby should be done thoroughly. Antenatally detailed ultrasonography of fetus and placenta, middle cerebral artery Doppler, amniotic fluid analysis (karyotyping, fluorescent in-situ hybridization technique, viral PCR), echocardiography and fetal MRI could be performed.[1,5] Postnataly, the first investigation to be done is Indirect Coomb's test to determine if it is non-immune hydrops. A detailed physical examination should be done along with other tests including ultrasonography of head and abdomen, 2D echo, radiographs of chest and abdomen and complete blood count.[1,5] With the help of recent genetic advances like chromosomal microarray and whole genome sequencing authors may be able to identify the underlying genetic basis of NIHF.

Management consists of treating the underlying etiologies.[1] It can be divided in three categories- referral to higher centre on urgent basis for those cases which he can be managed, termination of pregnancy or comfort care for the cases with lethal prognosis and cases with idiopathic etiology, and poor and uncertain prognosis[1]. Prenatal parental counseling about outcome, complication, and prognosis is an important step of management of NIHF.

Parvovirus is associated with profound fetal anemia and intra-uterine transfusion of packed red cells is indicated.[1] Maternal administration of anti-arrhythmics like sotalol or flecainide and use of digoxin is helpful in reverting fetal Brady- or tachy-arrhythmias and improves fetal myocardial function. Unilateral pleural effusions or large congenital cystic adenomatoid malformations (CCAM) are treatable with intra-uterine USG guided thoracoamniotic shunt placement. Solid CCAMs respond to use of maternal steroids. Laser photocoagulation of abnormal placental anastomoses gives promising results in twin to twin transfusion syndrome.[1]

Prognosis of NIHF depends on the etiology, gestational age of onset and presence of large pleural effusion. Earlier the gestational age of onset, poorer the prognosis. Large pleural effusion before 20 weeks of gestation leads to pulmonary hypoplasia and increased incidence of prematurity. Absence of any anatomical anomaly or chromosomal abnormality has a better prognosis.[1] Wonkyung et al. found that the mean gestational age at diagnosis of fetal hydrops was lower in the fetal death cases than the live birth cases.[13] More the sites involved, worse is the prognosis. This is the most important finding; number of fluid collected sites is correlated with neonatal outcome including neonatal death. In this study case 4 had accumulation of body fluids in all four compartments and unfortunately did not survive. Kim et al. in their study of 43 women with non-immune fetal hydrops showed similar type of results. They developed an "Ultrasonographic severity scoring of non-immune hydrops (USNIH)" defined as a total number of abnormal fluid collections.[13] Perinatal mortality rate, defined as stillbirth or neonatal death ≤28 completed days after birth was significantly higher in cases with USNIH of ≥3 than in those with USNIH of 2. These results, suggest that the number of fluid collection sites is one of the most strong antenatal ultrasound risk factors for prediction of poor outcome in fetal hydrops.

CONCLUSION

NIHF is a common cause of abortions, stillbirth, and neonatal mortality. Antenatal ultrasonography, fetal 2D echo, and indirect coombs test, postnatal detailed clinical examination and investigations should be done in all cases. Management of fetal hydrops includes predelivery consultation care delivery room (resuscitation), (based on etiology) and ventilatory management. The prognosis of hydrops fetalis is highly dependent on the underlying etiology, gestational age and presence chromosomal and structural anomalies. Early diagnosis and treatment greatly improves perinatal outcome.

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