Obstetrics; *Maternal-Fetal Medicine and Perinatology*

Management of Severe Non Immune Hydrops Fetalis Cases: The Role of Diagnostic and/or Therapeutic Interventions

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OBJECTIVE: Non-immune hydrops fetalis (NHF) may have a wide variety of etiologies. The prognosis of this condition is generally poor. There are no standard, optimal management strategies and the clinical management presents a dilemma most of the time.

STUDY DESIGN: We retrospectively evaluated 8 NHF cases which several intrauterine interventions are performed. We discuss the role of such interventions in NHF cases.

RESULTS: In these 8 cases, we performed the three interventional methods (FBS, IUT, and intravenous Sandoglobulin) for NHF. 6 patients of them had hydrops fetalis, one had renal agenesia and hydrops and the other had maternal acute CMV infections.

CONCLUSION: These interventions gave us some oppurtunities. For example, the fetus in the first case, could be followed until 35th gestational weeks and was delivered alive. By this way a postnatal diagnosis of galactosialidosis could be possible. Having this information will be useful for the patient when planning the future pregnancies

Key Words: Non-immune hydrops, Fetal blood sampling, Intrauterine transfusion

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Introduction

Hydrops fetalis is defined as the excessive accumulation of fluids in the interstitial compartment including edema, ascites and pleural and pericardial effusions, leading to anasarca.[1,2] NHF comprises the subgroup of cases not caused by an immune mechanism, such as red cell alloimmunisation (eg,Rh (D), Kell). The incidence of NHF ranges from 1/1500 to 1/3800 births and is associated with high perinatal morbidity and mortality at all gestational ages with an overall perinatal mortality rate of 86.6%.[3-8] If the diagnosis is made before 24 weeks' gestation, the perinatal mortality rate is 95%, with 30% having an abnormal karyotype.[9] The main causes of NHF are classified as cardiovascular, genetic, infectious (congenital infections), hematologic, placental, miscellaneous, and idiopathic[10] (Table 1).

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Table 1.Causes of non-immune hydrops fetalis[10]

Cardiovascular	Arrhytmia, Myocardiopathy, Structural malformations (Ebstein anomaly, premature closure of the foramen ovale) Vascular obstruction (tumor, structural, fibroelastosis)
Genetic	Skeletal dysplasia and myopaties Metabolic diseases (Gaucher, GM1 Gangliosidosis, mucopolysaccharidosis, Pyruvate kinase and G6PD deficiency) Autosomal diseases (Noonan, Prune Belly, Fancony) Chromosomal abnormalities (trizomy 21,18,13, Turner's syndrome)
Congenital Infections	Viral infections (cytomegalovirus, parvovirus B19, rubella, varicella, herpes, respiratory sincitial), Toxoplasmosis, Syphilis, Chagas disease
Hematologic	Nonimmune anemia, Alpha-thalassemia, Others (leukemia)
Placental	Twin-twin transfusion syndrome, Causes related to the umbilical cord
Miscellaneous	Respiratory(pulmonary sequestration, adenomatoid disease, chylothorax, tumor) Genitourinary (obstructive uropathy, dysplasia, cysts, thrombosis, nephrotic syndrome) Neurological (encephalocele, intracranial hemorrhage, cerebral aneurysm) Tumoral (sacrococcygeal teratoma, neuroblastoma, hepatoblastoma) Multiple causes (presence of more than one associated etiopathic causes)
Idiopathic	Non-defined cause

Modified from the classification of Mascaretti RS, Falcao MC, Silva AM,Leone R. Characterization of newborns with nonimmune hydrops fetalis admitted to a neonatal intensive care unit.Res. Hosp. Clin.2003; 58:125-132.[10]

Management options of NHF include termination of the pregnancy, therapeutic intervention when possible, and supportive care and monitoring of the mother and fetus in continuing pregnancies.[11-14] Fetal blood sampling (FBS) is an intervention mostly used for the diagnosis of intrauterine infections, severe anemia, choromosomal abnormalities and metabolic diseases. Intrauterine transfusion (IUT) of red blood cells or thrombocyte is another intervention for treatment of severe anemia in preterm fetuses due to any of the following conditions: red cell immunisation, parvovirus infection, chronic fetomaternal hemorrhage, and inherited red cell disorders.[15-16] Administration of hyperimmune globulin for cytomegalovirus and parvovirus B19 infections, and administration of immune globulin for fetal alloimmune thrombocytopenia are other successful interventional therapies in the literature for severe non immune hydrops cases.[17,18] In this study, we aimed to show the role of diagnostic and/or therapeutic interventions in eight severe non immune hydrops fetalis cases.

Material and Method

This study consists of eight singleton pregnancies with severe non immune hydrops fetalis cases. Maternal parameters noted were: maternal age in years, gravidity and parity, gestational age at the time of the intrauterine intervention. Maternal blood investigations (a full blood count and renal, liver and thyroid function tests) were performed. Viral serological tests (parvovirus, toxoplasma, rubella, cytomegalovirus, and herpes simplex virus) were evaluated for acute infection in all pregnancies. An immunological screen consisting of lupus anticoagulant, anti-nuclear, anti-Ro, anti-smooth muscle, anti-parietal and anti-thyroid peroxidase antibodie were performed. All parents were checked for mean corpuscular volume and blood type.

All of the cases were evaluated by a detailed ultrasound examination for the presence or absence of any abnormalities of the fetus, placenta and cord vessels. Fetal echocardiography, pulsed and colour Doppler studies were performed for excluding any fetal arrhytmias or abnormal blood flow patterns.

The placenta localisation and the umbilical cord insertion were determinated by ultrasonography. FBS is planned mainly for diagnostic purposes. FBS procedures were performed by inserting 20 gauge needle under continuous ultrasound guidance into the umbilical vein in all cases. By using these blood samples, fetal choromosome analysis, hemoglobin electrophoresis, blood typing and a direct coombs test were studied. Serology for acute phase-specific IgM, culture, electron microscopy and viral DNA by polymerase chain reaction (PCR) in necessary cases were studied to exclude parvovirus, toxoplasma, rubella, cytomegalovirus and herpes simplex virus infections. Concomitant IUT [blood and/or immune globulin (Sandoglobulin-®)] was performed in necessary cases according to the clinical findings. Suspicion of fetal anemia, severity of hydrops fetalis, diagnostic & delivery strategies, and gestational week were the concerns of the medical team in planning IUT.

Results

In this study, fetal blood sampling was performed in all cases. Choromosomal abnormality was not detected in any of the cases.

In the first case, we have detected doppler examination showed findings of anemia. IUT was performed two times with three weeks intervals. The fetus was delivered at 35 weeks. Upon clinical suspicions, a diagnosis of galactosialidosis was made by enzyme analysis (Table 2).

In the second case, a diagnosis of renal agenesis was suspected by antenatal ultrasonography in addition to presence of hydrops fetalis. The pregnancy was terminated. Postnatal autopsy confirmed the diagnosis.

In the third case, a hyperechogenic fetal intraabdominal mass in addition to fetal ascites were determinated by ultrasonography. As doppler findings were consistent with anemia, IUT was performed. The fetus is died 1 day after IUT. The postnatal autopsy examination showed that the intraabdominal mass was an ileal duplication cyst.

In the fourth case, restrictive cardiomyopathy and restriction of foramen ovale was diagnosed by fetal echocardiograpy. IUT was performed. The fetus died 4 days after IUT. The autopsy examination confirmed the presence of cardiac abnormality.

In the fifth case, the fetus had severe hydrops and IUT plus intravenous sandoglobulin administration were performed. The fetus died 2 weeks after transfusion. There was no congenital abnormality at autopsy examination.

The mother in the sixth case had positive CMV IgG and IgM values, and CMV DNA in the cord blood was found to be positive by polymerase chain reaction. The pregnancy was terminated . The parents did not permit autopsy examination.

In seventh case, the patient was successfully followed for 16 weeks (from 18th to 34th gestational weeks) by three times IUT plus intravenous sandoglobulin administration and delivered by cesarian-section at 34 weeks. The baby had polydactyly, cleft palate and died 3 months after delivery.

Table 2: Some characteristics of the 8 patients

Number of case	Gestational age at diagnosis	Ultrasound findings	Indirect coombs	TORCH studies in fetal blood	Parvovirus PCR in fetal blood	Fetal echo cardiography	Intrauterine transfusion	Outcome	Postnatal or Autopsy Results
1.	26 weeks	Hydrops fetalis	(-)	(-)	(-)	Normal	2 times blood	Delivered alive at 35 weeks.	Postnatally diagnosed as galactosialidosis.
2.	23 weeks	Hydrops fetalis, renal agenesia.	(-)	(-)	(-)	Normal	(-)	Medical Abortion.	Renal Agenesis
3.	27 weeks	Fetal intraabdominal mass, fetal ascites	(-)	(-)	(-)	Normal	160 cc blood	Inrauterine exitus 1 day after transfusion.	Duplication cyst of ileum
4.	34 weeks	Hydrops fetalis	(-)	(-)	(-)	Restrictive cardiomypoathy, Restriction of Foraman ovale	110 cc blood	Intrauterine exitus 4 days after transfusion.	Congenital heart defect
5.	28 weeks	Hydrops fetalis	(-)	(-)	(-)	Normal	60 cc blood+10 cc SG	Intrauterine exitus 2 weeks after transfusion (30weeks).	No congetital malformations.
6.	24 weeks	Maternal serum CMV IgG(+),and IgM (+)	(-)	CMV PCR (+)	(-)	Normal	Not performed	Medical Abortion.	Findings consistent with congenital CMV infection.
7.	18 weeks	Polihydramnios, hydrops fetalis	(-)	(-)	(-)	Normal	3 times blood+iv SG	Delivered by C/S at 34 weeks.	Died three months after birth, had polydactly and cleft palate.
8.	24 weeks	Hydrops fetalis	(-)	(-)	(-)	Normal	70 cc blood	Intrauterine exitus.	No autopsy.

Discussion

Nonimmune hydrops fetalis (NHF) comprises the subgroup of cases not caused by an immune mechanism, such as red cell alloimmunisation (eg, Rh (D), Kell).[3] The incidence of NHF ranges from 1/1500 to 1/3800 births and is associated with high perinatal morbidity and mortality at all gestational ages with an overall perinatal mortality rate of 86.6%. If the diagnosis is made before 24 weeks' gestation, the perinatal mortality rate is 95%, with 30% having an abnormal karyotype.[3-7]

FBS is a useful diagnostic intervention for non immune hydrops cases. Intrauterine infections, fetal blood subgroups, severe anemia, hemoglobin electrophoresis, choromosomal analysis, and metabolic diseases can be detected by FBS.[7-13] In our study, acute CMV infection is determinated by FBS and pregnancy was terminated. All cases were evaluated with choromosomal analyses by FBS.

Intrauterine transfusion is another interventional method for severe immune hydrops fetalis.[19-21] After fetal anemia is determinated by FBS, intrauterine transfusion can be performed periodically until 35 weeks of pregnancy. Fetal anemia accounts for 10 to 27 percent of hydrops cases. It may be due to a variety of causes, including hemorrhage, hemolysis, defective RBC production and production of abnormal hemoglobins. The mechanism for hydrops is thought to be related high output cardiac failure.[3-10] In the literature, there are some cases in which intrauterine transfusion of red blood cells or thrombocyte was performed for treatment of severe anemia in preterm fetuses due to any of the following conditions: red cell immunisation, parvovirus infection, chronic fetomaternal hemorrhage, and inherited red cell disorders.[15-16] Intrauterine transfusion is considered a safe procedure, with a relatively low procedure-related complication rate and a low perinatal loss rate. However, complications do sometimes occur. Transient fetal bradycardia during transfusion is the most common complication, occurring in 8% of procedures.[22] Fetal distress during or after transfusion is the most feared complication and may result in fetal death or emergency delivery with the risk of neonatal asphyxia and death. Fetal distress can occur after cord accidents (rupture, spasm, tamponade from a hematoma), hemorrhage from the puncture site, volume overload, chorioamnionitis, preterm rupture of membranes or preterm labor. Fortunately, all these complications are rare.[21-23]

Fetomaternal alloimmune thrombocytopaenia also presents antenatally as hydrops fetalis. It results from maternal alloimmunisation against fetal platelet antigens inherited from the father and different from those present in the mother, and usually presents as a severe isolated thrombocytopenia in otherwise healthy newborns. Fetal intracranial hemorrhage and severe anemia can also be present. Maternal intravenous immune globulin administration has been shown to be a successfull treatment of this condition.[17] Two of our cases were given sandoglobulin therapy; one of them was successfully followed for 15 weeks and delivered by ceserian/section at 33 weeks.

Treatment of some intrauterine infections by administration of immune globuline is another intervention in NHF cases. The administration of hyperimmune globulin for cytomegalovirus and parvovirus B19 infections have been shown to be successfull therapies in the literature for severe non immune hydrops cases.[17,18]

In these 8 cases, we performed the three interventional methods (FBS, IUT, and intravenous Sandoglobulin) for NHF. These interventions gave us some oppurtunities. For example, the fetus in the first case, could be followed until 35th gestational weeks and was delivered alive. By this way a postnatal diagnosis of galactosialidosis could be possible. Having this information will be useful for the patient when planning the future pregnancies. These interventional therapies also give us a chance to follow the pregnancy, and cervical maturation can occur during this time. It can decrease the ratio of ceserian section.

Ciddi Non İmmün Hidrops Vakalarının Yönetimi: Tanısal ve/veya Terapötik Girişimlerin Rolü

Non-immün hidrops fetalis çok çeşitli etyolojilerden kaynaklanabilmektedir. Bu durumun prognozu genellikle kötüdür. Tüm hastalar için standart, optimum yaklaşım stratejileri mevcut değildir ve bu durumun klinik yönetimi çoğu zaman pek çok çelişkileri beraberinde taşımaktadır. Bu yazıda, çeşitli intrauterin girişimlerin uygulandığı 8 NHF vakası anlatılmaktadır. Bu tür girişimlerin NHF vakalarındaki rolü tartışılmaktadır.

Anahtar Kelimeler: Non-immün hidrops, Fetal kan örmeklemesi, İntrauterin transfüzyon

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