



ORIGINAL ARTICLE

Etiology and Outcome of Hydrops Fetalis: Report of 62 Cases



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Key Words

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Aim: We aimed to define the etiologic and prognostic factors in live-born infants with hydrops fetalis (HF) in our tertiary neonatal intensive care unit over a 10-year period.

Methods: Medical records of newborn infants with HF during 2002–2011 were reviewed retrospectively. Demographic data, prenatal interventions, clinical and laboratory findings, outcomes, and the results of postmortem examinations were analyzed.

Results: During the study period, 62 newborn infants with HF were identified from 16,200 live-born deliveries and the incidence of HF was 3.8/1000 live births in our hospital. Twenty-eight infants (45.2%) had immune HF, whereas 34 (54.8%) had nonimmune HF. An etiologic factor could be identified in 24 (70.5%) infants with nonimmune HF. Lymphatic dysplasias comprised the majority (23.5%) of the infants with nonimmune HF. Mortality rate was 50%. The presence of two or more serous cavity effusions and gestational age were independently associated with the risk of mortality. **Conclusion:** Despite the improvements in neonatal care, mortality rate in infants with HF is still high. Gestational age and the extent of serous cavity determine the risk of mortality. Timely and advanced prenatal or postnatal new therapeutic strategies may alter this fatal outcome in appropriate patients.

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1. Introduction

Hydrops fetalis (HF) is excessive fluid accumulation in fetal extravascular compartments and body cavities leading to

edema, ascites, pleural and pericardial effusions, and anasarca. HF can be mainly categorized as of immune and nonimmune causes, but with the decline of rhesus immunization, most cases have nonimmune etiology. It is estimated that approximately 76–87% of all cases of HF are of nonimmune origin.¹

Nonimmune HF (NIHF) has a multifactorial cause, consisting of maternal, placental, and fetal pathologies. The

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main pathophysiological mechanism of NIHF is related to abnormal fluid transportation between plasma and tissues. The primary causes of the modification of the distribution of body fluids are an increase in hydrostatic capillary pressure and capillary permeability and a reduction of the plasma osmotic pressure or lymphatic flow.²

The diagnosis and management of HF have improved in recent years with advances in prenatal diagnostic and therapeutic interventions together with the advances in neonatal intensive care. However, HF is still associated with a high mortality rate.^{3,4} In the literature, there are limited data about prognostic factors in newborn infants with HF and these include some perinatal interventions and some demographic and clinical features.^{5–8}

In this study we aimed to define the etiologic factors, and short-term outcome of newborn infants with HF and identify predictors of mortality in a single tertiary unit over a 10-year period.

2. Materials and Methods

We performed a retrospective hospital chart review of all live-born cases with HF delivered at Hacettepe University Hospital and admitted to the Neonatal Intensive Care Unit (NICU) of Hacettepe University Ihsan Dogramaci Children's Hospital (Ankara, Turkey) during the 2002–2011 period. The study was approved by the Institutional Ethics Committee. Live-born infants who died in the first minutes of life in the delivery room despite neonatal resuscitation were not included in the study. HF was defined as generalized skin edema with serous effusion in one or more fetal body cavity. The diagnosis of immune HF (IHF) was based on clinical and laboratory findings (maternal and fetal blood group, direct and indirect Coombs test). Maternal and obstetric diseases, prenatal diagnostic and therapeutic interventions, gestational age, birth weight, mode of delivery, Apgar score at fifth minute, delivery room interventions, postnatal therapies including mechanical ventilation and surfactant therapy, the etiology of HF, and mortality were recorded in each infant. If available, post-mortem examination results were also recorded.

Amniocentesis is needed to perform fetal karyotyping, amniotic fluid culturing, testing for CMV infections, assessment of α -fetoprotein levels, testing for thalassemia, and determination of the lecithin-sphingomyelin ratio. Prenatal hydrops signs and fetal anemia (hematocrit <30%) constitute an indication for intrauterine blood transfusion. Middle cerebral artery peak velocity is also used to assess fetal anemia (cut-off level 1.5 multiples of the median). Repeated transfusions were performed considering the need for fetus within every 3–5 weeks. Pleural effusions were managed with fetal thoracentesis. Fetal ascites was treated with *in-utero* paracentesis and peritoneal-amniotic shunting. The severity, duration, and persistence of the pathology determined the procedures used. The indication of maternal digitalization was fetal supraventricular tachycardia.

All infants with HF underwent a diagnostic flow chart according to our NICU protocol. Prenatal and postnatal ultrasonographic examinations were performed on all infants. All infants with HF received echocardiography. Fetal or neonatal karyotyping was offered in all cases of NIHF.

The presence of lymphatic dysplasia was evaluated by microscopic and biochemical investigation (lipid profile) of ascites, pleural, or pericardial fluids. In addition, magnetic resonance imaging or computerized tomography was performed to establish lymphatic malformations in selected cases. Hematologic disorders were evaluated by complete blood count, peripheral blood or bone marrow smear, Coombs test, blood group, hemoglobin electrophoresis, and Kleihauer–Betke stain. Inherited metabolic diseases were evaluated with blood and urine amino acid analysis, urine organic acid analysis, lysosomal enzyme activities, bone marrow aspiration and, if necessary, specific enzyme activity or genetic analysis. Macroscopic and microscopic (standard or immunohistochemical staining) examinations were performed for placental anomalies. All infants were screened for intrauterine infections such as toxoplasmosis, rubella, cytomegalovirus, herpes simplex, parvovirus, and syphilis. Complete and partial postmortem examinations were offered where relevant.

Statistical data were analyzed by using SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA) on a personal computer. Data was expressed as percentage or mean \pm standard deviation. Continuous variables were compared by two-tailed *t* test for parametrically distributed data or Mann–Whitney test for nonparametrically distributed data. Categorical variables were analyzed by χ^2 test or Fisher exact test. All the variables significantly associated with mortality were included in the stepwise multiple logistic regression models to determine the independent prognostic study variables. The results are presented by odds ratio and 95% confidence intervals. A *p*-value of <0.05 was accepted as statistically significant.

3. Results

During the study period, 62 cases of HF from 16,200 live born infants were identified in our hospital and the incidence of HF was 3.8/1000 live births, whereas the incidence of NIHF was 2/1000 live births. Mean gestational age was 33.1 ± 2.9 weeks (27.0–39.0 weeks) whereas mean birth weight was 2350 ± 640 g (940–3370 g). Prenatal diagnoses were available in 35 (56.5%) infants and the most frequent (25, 40.3%) prenatal diagnostic and therapeutic intervention was cordocentesis + blood transfusion. The mean number of intrauterine transfusions was 2.2 ± 1.8 (1–5). Forty-five (72.6%) infants had aggressive resuscitation at birth and 31 (50.0%) received urgent thoracentesis or paracentesis at birth. Fifty-five (88.7%) infants needed mechanical ventilation during NICU stay. Mortality rate was 50.0%. Demographic and clinical characteristics of infants with HF are shown in Table 1.

Twenty-eight (45.2%) infants had IHF, whereas 34 (54.8%) had NIHF. Rh isoimmunization was diagnosed based on maternal and fetal–neonatal Rh status and positive maternal, neonatal coombs tests within the presence of hemolysis. Of 28 infants with IHF, only one infant was diagnosed with Kell isoimmunization whose Kell antigen was positive and whose mother was negative within the positive maternal indirect Coombs test.

Among the infants with NIHF a plausible cause could be found in 24 (70.5%) infants. Lymphatic dysplasia was the most common (12.9%) identifiable underlying cause in all

Table 1 Demographic and clinical characteristics of infants with hydrops fetalis ($n = 62$).

Demographic and clinical characteristics	
Sex (M/F)	33/29 (53.2/46.8)
Gestational age (wk)	33.1 \pm 2.9 (27.0–39.0)
Birth weight (g)	2350 \pm 640 (940–3370)
Consanguineous parents	15 (24.2)
Prenatal steroids	25 (40.3)
Prenatal diagnosis	35 (56.5)
Prenatal diagnostic and therapeutic procedures	
Amniocentesis	9 (14.5)
Chorionic villus sampling	—
Cordocentesis + blood transfusion	25 (40.3)
Cordocentesis	2 (3.2)
Thoracentesis	4 (6.5)
Paracentesis	4 (6.5)
Maternal digitalization	1 (1.6)
Mode of birth (vaginal/CS)	9/53 (14.5/85.5)
Apgar score (5 min)	5.7 \pm 2.3 (2–10)
Aggressive resuscitation at birth (PPV \pm CC \pm Drug)	45 (72.6)
Affected compartments in hydrops fetalis*	62 (100.0)
Skin and subcutaneous tissue	34 (54.8)
Pleural effusion	12 (19.4)
Pericardial effusion	54 (87.1)
Ascites	30 (48.4)
Two or more serous cavity effusions	
Thoracentesis and/or paracentesis at birth	31 (50.0)
Hypoxic respiratory failure (OI >14)	24 (38.7)
Need for mechanical ventilation	55 (88.7)
Need for HFOV treatment	17 (27.1)
Need for surfactant therapy	28 (45.2)
Need for inhaled NO therapy	3 (4.8)
Pneumothorax	13 (21.0)
Duration of mechanical ventilation (day)	3.0 (0–38)
Duration of hospitalization (day)	8.5 (0.5–80)
Mortality	31 (50.0)
Postmortem examination (partial or whole autopsy)	14 (45.2)

Data are presented as n (%), mean \pm SD (range), or median (range).

CC = cardiac compression; CS = cesarean section; HFOV = high frequency oscillatory ventilation; NO = nitric oxide; OI = oxygenation index; PPV = positive pressure ventilation; SD = standard deviation.

* More than one compartment can be affected in each infant.

infants with HF (Table 2). The survival rates were comparable between infants with IHF and NIHF (42.9% vs. 55.9% respectively, $p > 0.05$). In the infants with lymphatic dysplasia ($n = 8$) only one infant died, with a mortality rate of 12.5%.

In comparing infants who survived and died, mean gestational age and birth weight of infants who died were

Table 2 Type and etiology of hydrops fetalis ($n = 62$).

	n (%)
<i>Immune</i>	
Rh-isoimmunization	27 (43.5)
Anti-Kell isoimmunization	1 (1.6)
<i>Nonimmune</i>	
<i>Cardiovascular diseases</i>	
Hypertrophic cardiomyopathy	1 (1.6)
Non-compaction cardiomyopathy	1 (1.6)
Ebstein anomaly	1 (1.6)
Supraventricular tachycardia	1 (1.6)
<i>Lymphatic dysplasia</i>	
Chylothorax	3 (4.8)
Chylous ascites	3 (4.8)
Lymphangioma	2 (3.2)
<i>Hematologic diseases</i>	
Congenital dyserythropoietic anemia	2 (3.2)
Hereditary spherocytosis + hemophagocytosis	1 (1.6)
<i>Inborn errors of metabolism</i>	
Nieman Pick Type C disease	1 (1.6)
Gangliosidosis	1 (1.6)
Zellweger syndrome	1 (1.6)
<i>Placental disorders</i>	
Twin-to-twin transfusion syndrome	1 (1.6)
Placental hemangioma	1 (1.6)
Placental thrombosis and chorioangioma	1 (1.6)
<i>Infections</i>	
Congenital CMV infection	1 (1.6)
<i>Others</i>	
Trisomy 21 + myelodysplastic syndrome	1 (1.6)
Sacrococcygeal teratoma	1 (1.6)
<i>Undefined etiology</i>	10 (16.1)

CMV = cytomegalovirus; Rh = rhesus.

significantly lower than infants who survived ($p < 0.01$ and $p < 0.05$ respectively) and they needed more neonatal resuscitation at birth ($p < 0.001$), as expected. In accordance with this, the frequency of two or more serous cavity effusions was significantly higher in infants who died ($p < 0.001$). Infants who died needed more surfactant therapy during NICU stay ($p < 0.001$; Table 3).

Type of delivery, sex, prenatal steroids, and presence of pericardial effusions and pneumothorax during follow-up did not influence the outcome ($p > 0.05$). Factors associated with mortality were younger gestational age, lower birth weight, lower Apgar score at 5 minutes, aggressive resuscitation at birth, presence of pleural effusions, ascites, presence of two or more serious cavity effusions, the need for surfactant treatment, and mechanical ventilation (Table 3). However, by stepwise multiple logistic regression analysis, gestational age and the presence of two or more serous cavity effusions was associated independently with mortality (Table 4).

The median average duration of follow-up was 8.5 days (range, 0.5–80 days) in all HF cases whereas it was 3 days (range, 0.5–35 days) in nonsurvivors and 20 days (range, 8–80 days) in survivors up to discharge. Postmortem examinations were performed in 11 of 16 non-surviving infants with NIHF. This led to exact diagnosis in three cases

Table 3 Comparison of the clinical and demographic characteristics of infants with hydrops fetalis who died or survived.

Demographic and clinical characteristics	Infants who survived (<i>n</i> = 31)	Infants who died (<i>n</i> = 31)	<i>p</i>
Gestational age (wk)	34.2 ± 2.8 (27.0–39.0)	32.1 ± 2.8 (27.4–38.0)	0.005
Birth weight (g)	2543 ± 511 (1670–3300)	2156 ± 702 (940–3370)	0.016
Apgar score (5 min)	7.1 ± 1.9 (3–10)	4.4 ± 1.7 (2–8)	0.000
Aggressive resuscitation at birth	16 (51.6)	29 (93.5)	0.000
Type of hydrops fetalis			
Immune	12 (38.7)	16 (51.6)	0.307
Nonimmune	19 (61.3)	15 (48.4)	0.444
Affected compartments in hydrops fetalis			
Skin and subcutaneous tissue	31 (100.0)	31 (100.0)	1.000
Pleural effusion	12 (38.7)	22 (71.0)	0.011
Pericardial effusion	3 (9.7)	9 (29.0)	0.106
Ascites	23 (74.2)	31 (100.0)	0.005
Two or more serous cavity effusions	6 (19.3)	24 (77.4)	0.000
Prenatal diagnostic and therapeutic procedures			
Amniocentesis	6 (19.4)	3 (9.7)	0.473
Cordocentesis + blood transfusion	13 (41.9)	12 (38.7)	0.710
Cordocentesis	1 (3.2)	1 (3.2)	1.000
Thoracentesis	2 (6.5)	2 (6.5)	1.000
Paracentesis	1 (3.2)	2 (6.5)	0.550
Maternal digitalization	1 (3.2)	0 (0)	—
Thoraparacentesis and/or blood transfusion at birth	8 (25.8)	23 (74.2)	0.000
Hypoxic respiratory failure (OI >14)	11 (35.5)	13 (41.9)	0.602
Need for mechanical ventilation	24 (77.4)	31 (100.0)	0.011
Need for HFOV treatment	11 (35)	6 (19.4)	0.255
Need for surfactant therapy	6 (19.4)	22 (71.0)	0.000
Pneumothorax	4 (12.9)	9 (29.0)	0.211

Data are presented as *n* (%) or mean ± SD (range).

HFOV = high frequency oscillatory ventilation; OI = oxygenation index; SD = standard deviation.

(noncompaction cardiomyopathy, Niemann–Pick type C disease, congenital CMV infection) and the confirmation of the diagnoses in three cases (Down syndrome-associated myelodysplastic syndrome and congenital dyserythropoietic anemia in two cases).

4. Discussion

In recent years, most newborn infants with HF were classified as NIHF as the proportion of infants with IHF decreased to 10% due to the use of anti-D immunoglobulin prophylaxis, intrauterine transfusions, and close follow-up of the pregnancies with Rh-isoimmunization in developed countries.³ However, in developing countries the incidence of IHF is still high, as also reflected by our results.⁹ In our

study, nearly half of the cases (45.2%) had IHF. Our hospital is a tertiary level perinatal center for high-risk pregnancies and many pregnancies with Rh isoimmunization are referred from rural regions of Turkey. Unfortunately, most of these patients are usually referred in the advanced periods of pregnancy, which makes therapeutic interventions less effective. In the literature, the incidence of NIHF varies widely from 0.3/1000 to 2.4/1000 live births.^{10,11} In this study, we found a high incidence of NIHF (2/1000) in our hospital as it is a referral center for high-risk pregnancies.

The most common diagnosis associated with NIHF was lymphatic dysplasia in this study. The prognosis was favorable in eight infants in this group of etiology because there was only one death. Of the eight infants, seven were diagnosed with chylothorax and chylous ascites. The symptoms rapidly resolved with the drainage of the accumulated fluid by thoracentesis or paracentesis, enteral nutrition with medium chained triglycerides, and somatostatin analogues after birth. In the literature, in a large multicenter study by Abrams et al,³ the lowest mortality rate was found among infants with congenital chylothorax (5.9%).

In our study population, congenital heart diseases constituted the second most common cause of NIHF. In a systemic review of 5437 NIHF cases, congenital cardiovascular diseases were reported as the most frequent etiologic factor by a ratio of 21.7%.¹

Table 4 Stepwise multiple logistic regression analysis of predictive factors for poor outcome in hydrops fetalis.

	Adjusted odds ratio	95% confidence interval	<i>p</i>
Gestational age	0.63	0.44–0.89	0.009
Two or more serous cavity effusions	12.9	2.4–70.9	0.003
Need for surfactant	0.22	0.04–1.12	0.069

Inborn errors of metabolism have been estimated to account for 1–2% of all NIHF cases.¹ However, in our study 9% of infants with NIHF had inborn errors of metabolism and we think this was the result of a high incidence of consanguineous marriages in Turkey.

The percentage of idiopathic cases in NIHF reported in the literature is 4–60%, depending primarily on the diagnostic methods available in each service.^{3,12,13} In our study, the ratio of infants with idiopathic NIHF was approximately 30%. Besides limited sophisticated diagnostic procedures, one of the explanations for this high incidence of idiopathic cases may be that it is the result of the limited time for the establishment of the exact diagnosis as most of the infants with NIHF died in the first week of life. Also, performing postmortem examinations is important for the establishment of an exact diagnosis.¹⁴ In the study by Rodríguez et al¹² the cause of HF was confirmed at a rate of 92% in 51 still-born fetuses. In our study, the diagnosis of six infants (55%) was achieved with a postmortem examination.

Various antenatal and postnatal indicators of prognosis have been described in infants with HF.^{4–8,15} These are prenatal diagnosis of HF, gestational age at delivery, 1st minute and 5th minute Apgar scores, intubation and chest compression in the delivery room, low serum albumin concentration, two or more serous cavity effusions, the presence of pleural effusion, and need for thoracentesis.

Gestational age at delivery was found to be a prognostic factor in a number of recently published studies.^{15,16} About 30 years ago, early delivery was suggested to be a favorable factor for the survival of the fetus with HF.¹⁷ However, in a large multicenter study, association between prematurity and poor outcome has been shown clearly.³ We think that preterm delivery reflects the severity of HF and that prematurity brings an additional burden by its complications such as respiratory distress syndrome to the management of HF. Tocolytic therapy and close monitoring to prolong pregnancy in selected patients might improve the survival. However, administration of antenatal steroids did not influence survival in the present study, which is in line with previous reports.^{4,18}

Poor response to neonatal resuscitation at birth has been shown to be associated with mortality in previous reports.^{4,15} In our study, fatal cases required significantly more aggressive resuscitation at birth and they had lower Apgar scores.

In our study, by stepwise multivariate analysis of all risk factors, gestational age, and presence of two or more serous cavity effusions was found to be the strongest predictor of mortality. This result was similar to previous reports.^{8,18} Pleural effusion develops with a compression of the heart and obstruction of the venous return and causes pulmonary hypoplasia leading to respiratory distress soon after birth. It has been shown that *in utero* decompression of hydrothorax may reverse fetal distress and this procedure could give time for the delivery of uncompromised infants.¹⁹ Also, a detailed review of the literature indicates that pleural drainage *in utero* may improve outcome in fetuses with persistent effusions.²⁰ These prenatal interventions include thoracentesis, thoracoamniotic shunting, and pleurodesis. It was suggested that thoracentesis is of limited value and pleural fluid accumulates 1–7 days after the procedure. Therefore, it was concluded that

thoracoamniotic shunting may improve the survival rate especially in fetuses whose effusion rapidly reaccumulates.⁷ We did not perform thoracoamniotic shunting in any of the infants. Of four infants who required thoracentesis, two died. We feel that it is not accurate to the judge outcome of thoracentesis due to the small case series.

In our study, outcome was not satisfactory in infants who were treated with surfactant and mechanical ventilation. Surfactant was used in infants whose clinical pictures were complicated with respiratory distress syndrome or who were thought to have pulmonary hypoplasia.

In conclusion, there is strong association between gestational age, the presence of two or more serous cavity effusions, and poor outcome in infants with HF. Therefore, severity of hydrops is the main predictor for mortality. Despite improvements in postnatal care such as advanced mechanical ventilation, surfactant treatment, and inhaled nitric oxide, mortality rates are still high in infants with HF.

Conflicts of Interest

The authors have no conflicts of interest relevant to this article.

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