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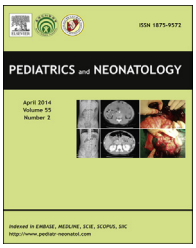

ORIGINAL ARTICLE

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.

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 isoimmunization, 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, postmortem 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 imagining 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 $\pm$ 2.9 weeks (27.0–39.0 weeks) whereas mean birth weight was 2350 $\pm$ 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 $\pm$ 1.8 (1–5). Forty-five (72.6%) infants had aggressive resuscitation at birth and 31 (50.0%) received urgent thoracentesis or paracenthesis 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