ORIGINAL ARTICLE

CHARACTERIZATION OF NEWBORNS WITH NONIMMUNE HYDROPS FETALIS ADMITTED TO A NEONATAL INTENSIVE CARE UNIT

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MASCARETTI RS et al. - Characterization of newborns with nonimmune hydrops fetalis admitted to a neonatal intensive care unit. **Rev. Hosp. Clín. Fac. Med. S. Paulo 58**(3):125-132, 2003.

PURPOSE: To determine the incidence and characteristics of nonimmune hydrops fetalis in the newborn population.

METHOD: A retrospective study of the period between 1996 and 2000, including all newborns with a prenatal or early neonatal diagnosis of nonimmune hydrops fetalis, based on clinical history, physical examination, and laboratory evaluation. The following were analyzed: prenatal follow-up, delivery type, gender, birth weight, gestational age, presence of perinatal asphyxia, nutritional classification, etiopathic diagnosis, length of hospital stay, mortality, and age at death.

RESULTS: A total of 47 newborns with hydrops fetalis (0.42% of live births), 18 (38.3%) with the immune form and 29 (61.7%) with the nonimmune form, were selected for study. The incidence of nonimmune hydrops fetalis was 1 per 414 neonates. Data was obtained from 21 newborns, with the following characteristics: 19 (90.5%) were suspected from prenatal diagnosis, 18 (85.7%) were born by cesarean delivery, 15 (71.4%) were female, and 10 (47.6%) were asphyxiated. The average weight was 2665.9 g, and the average gestational age was 35 3/7 weeks; 14 (66.6%) were preterm; 18 (85.0 %) appropriate delivery time; and 3 (14.3%) were large for gestational age. The etiopathic diagnosis was determined for 62%, which included cardiovascular (19.0%), infectious (9.5%), placental (4.8%), hematologic (4.7%), genitourinary (4.8%), and tumoral causes (4.8%), and there was a combination of causes in 9.5%. The etiology was classified as idiopathic in 38%. The length of hospital stay was 26.6 ± 23.6 days, and the mortality rate was 52.4%.

CONCLUSIONS: The establishment of a suitable etiopathic diagnosis associated with prenatal detection of nonimmune hydrops fetalis can be an important step in reducing the neonatal mortality rate from this condition.

DESCRIPTORS: Hydrops fetalis. Nonimmune hydrops fetalis. Newborn infant. Anasarca. Hydropic.

Hydrops fetalis is defined as the excessive accumulation of fluids in the interstitial compartment[1] including edema, ascites, and pleural and pericardial effusions[2], leading to anasarca.

One of the methods used to classify hydrops fetalis is to categorize it according to immune and nonimmune causes[3], because nowadays, as a consequence of a more precocious detection and a higher control of the immune causes, 75% of the perinatal cases are of nonimmune etiology[4]. The main pathophysiologic mechanism involved in the genesis of nonimmune hydrops fetalis (NHF) is related to abnormal fluid transportation between plasma and tissues**.** In this pathological situation, the primary causes of modification of the distribution of body fluids are the increase of hydrostatic capillary pressure and capillary permeability and reduction of plasma osmotic pressure or lymphatic flow[2,4,5].

Regarding etiology, NHF is differently classified in the literature, without consensus[3,4,6,7]. We have developed a classification system, presented on table 1, in which the main causes are classified as cardiovascular**,** genetic**,** infectious, placental, hematologic, miscellaneous and/or multiple causes, and idiopathic.

Foremost among the main causes of NHF are the cardiovascular, genetic,

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infectious, placental, and hematologic causes, among others (Table 1). Despite the technological advances in the last decades, the cause in 50% of the cases remains undefined, which are classified as idiopathic[2].

The occurrence of NHF is not frequent, occurring in 1 of 3000 live births[2,8,9]. Moreover, a high mortality rate is associated with NHF; 50% of the cases diagnosed in the intrauterine period evolve to death, and 50% of the live newborns who have the disease do not survive the neonatal period[2].

As previously mentioned, the prognosis of the newborn with NHF depends directly on an etiopathic diagnosis and on the prevention of prematurity[10]. In order to have an effective reduction in morbidity and mortality rates, a correct and precocious etiopathic diagnosis becomes fundamental, so that an adequate perinatal approach is possible.

This study aims at determining the incidence and characterization of NHF in newborns admitted to a neonatal risk unit during a 5-year period.

PATIENTS AND METHODS

A retrospective study was performed from January 1996 to December 2000.

Every newborn that was born during this period and had an immediate prenatal or neonatal diagnosis of hydrops was included in the study. Hydrops was characterized by 1 or more clinical signs, such as anasarca**,** peripheral edema, ascites, pericardial and/or pleural effusions, anemia, congestive heart failure, and hypoalbuminemia.

From these newborns, the ones with an immune etiology were excluded, based on clinical history, laboratory evaluation (blood type and Coombs tests of the newborn and the mother), and clinical evolution.

The presence of the clinical presentation and the absence of maternal-fetal blood incompatibility defined NHF.

Among the newborns that fulfilled the inclusion criteria, the following factors were evaluated: occurrence of prenatal diagnosis of hydrops, gender, type of delivery, gestational age, birth weight, nutritional adequacy of birth weight, presence of perinatal asphyxia, etiopathic diagnosis, mortality, age at death, and length of hospital stay.

The gestational age (GA) was based on the last menstruation date and ultrasonographic and postnatal classification methods (Capurro[11], Dubowitz[12], or New Ballard Score[13]). The newborns with a GA greater than or equal to 37 weeks were considered term. For the calculation of the definitive GA, the following criteria were used in descending order of priority, according to the service routine:

- maternal information about the date of the last menstrual period (Naegele's rule, that considers 280 days as the normal gestation time) when this date differs less than 2 weeks from the early fetal ultrasonography;
- early ultrasonography performed during the first 20 weeks of gestation, in cases when the GA was not considered reliable and the difference among the calculated ages by the ultrasonography and postnatal methods was less than 2 weeks;
- calculated postnatal age through the Capurro, Dubowitz, or New Ballard Score methods, when this age differs more than 2 weeks from both the ultrasonographic and GA as determined from maternal information.

Table 1 - Causes of nonimmune hydrops fetalis.

CARDIOVASCULAR
• Arrhythmia
• Myocardiopathy
• Structural malformations (Ebstein anomaly, premature closure of the foramen ovale)
• Vascular obstruction (tumor, structural, fibroelastosis)
• Vascular malformation and hemangioma
GENETIC
• Skeletal dysplasias and myopathies
• Metabolic diseases (Gaucher, GM1 gangliosidosis, mucopolysaccharidosis)
• Autosomic diseases (Nooan, Prune belly, Fanconi)
• Chromosomal abnormalities (trisomy 21, 18, 13, Turner's syndrome)
CONGENITAL INFECTIONS
• Virus (cytomegalovirus, parvovirus B19, rubella, varicella, herpes, sintitial respiratory)
• 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)
• Gastrointestinal (duodenal/jejunal atresia, anal imperforation, peritonitis)
• 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 Phibbs R, 1996.[2]

Ramos' intrauterine growth curve[14], using the 10th and 90th percentiles as limits, was used to assess the nutritional adequacy of the birth weight to GA. The newborn with an inferior birth weight (under the 10th percentile), was classified as small for GA (SGA), the newborn with birth weight between the percentiles 10 and 90 was considered adequate for GA (AGA), and the ones with a birth weight higher than the 90th percentile of the reference curve were considered large for GA (LGA).

An Apgar score of less than or equal to 6 in the 5th minute of life characterized the presence of perinatal asphyxia.

Regarding the etiopathic diagnosis, the cases of NHF were classified in the following categories: cardiovascular, infectious, genetic, hematological, placental, miscellaneous and/or associated causes, and idiopathic.

RESULTS

During the period of study, 11,190 live births occurred in the service. In this population, the diagnosis of hydrops fetalis was made in 47 newborns (0.42% of the live births); 18 (38.3%) of whom presented an immune form and 29 (61.7%) with a nonimmune form, with an incidence of nonimmune hydrops fetalis (NHF) of 1 per 414 live births during this period. The data obtained was derived from 21 newborns, of whom 19 (90.5%) had been diagnosed prenatally (Table 2).

Regarding the characteristics of the newborns (Table 3), 18 (85.7%) were delivered by cesarean, 15 (71.4%) were female, and 10 (47.6%) presented perinatal asphyxia. The average birth weight was 2665.9 g ± 613 (1550 – 3600 g), and the average GA was 35.5 weeks ± 2.4 (30 – 39 3/7 weeks), with 14 of these (66.6%) being born preterm. Regarding the nutritional classification, 18 (85.7%) were adequate and 3 (14.3%) were large for GA. The average length of hospital stay was 26 ± 23.6 days, the mortality rate was 52.4% (11 newborns), and the age at death was 4.55 ± 4.2 days of life.

An etiopathic diagnosis was obtained in 62% of the newborns; 19.0% of these were cardiovascular, 9.5% infectious, 4.8% placental, 4.8% hematologic, 4.8% genitourinary, 4.8% tumoral causes, and in 9.5% there was a combination of causes. The etiology was not identified in 38% of the cases, which were classified as idiopathic NHF (Table 4).

Table 2 - Characterization and etiopathic diagnosis of the study population**.**

Cause	Delivery	Gender	Birth weight (g)	Apgar	Gestational age	Weeks	Classification	Evolution	Diagnosis
Cardiovascular	cesarean	female	1970	2/6/8	33	5/7	preterm, AGA	discharge - 39 days	Myocardiopathy *
	cesarean	female	3150	4/7/9	37	4/7	term, AGA	death - 6 days tachyarrhythmia *	Supra-ventricular
	cesarean	male	3600	2/6/6	38		term, AGA	discharge - 81 days	Ebstein + hydronephrosis *
	cesarean	female	2680	1/6/7	32	1/7	preterm, LGA	transferred	Aortic and pulmonary stenosis *
Genetic	cesarean	female	2460	0/0/2	34	3/7	preterm, AGA	death - 3 days	GM1 Gangliosidosis type 1 *
	cesarean	female	3460	2/2/1	33	3/7	preterm, LGA	death - 1 hour	Thanatophoric dysplasia *
Infectious	cesarean	male	2840	3/9/10	38	1/7	term, AGA	discharge - 18 days	Congenital rubella *
	cesarean	male	2670	8/9/9	36	3/7	preterm, AGA	discharge - 29 days	Toxoplasmosis *
Hematologic	forceps	female	2420	8/9/9	37	4/7	term, AGA	discharge - 7 days	Non hemolytic anemia*
Placental	cesarean	male	2850	8/9/9	35	3/7	preterm, AGA	discharge - 11 days	Twin-twin transfusion syndrome *
Miscellaneous and/or	cesarean	female	1660	3/7/7	33		preterm, AGA	death - 12 days	Congenital nephrotic syndrome + trissomy 21 *
Multiple causes	vaginal	female	2530	3/5/5	34	6/7	preterm, AGA	discharge - 44 days	Ebstein + trissomy 21 *
	cesarean	female	3470	1/1/1	39	3/7	term, AGA	death - 6 hours	Thoracic-abdominal tumors + pulmonary hypoplasia*
Idiopathic	cesarean	female	2015	1/5/7	37	3/7	term, AGA	death - 19 hours	Idiopathic *
	vaginal	male	2680	1/7/8	35	5/7	preterm, AGA	discharge - 26 days	Idiopathic *
	cesarean	male	2790	1/9/10	36	1/7	preterm, AGA	death – 3 days	Idiopathic *
	cesarean	female	3310	9/10/10	38	4/7	term, AGA	discharge - 8 days	Idiopathic *
	cesarean	female	1550	0/6/7	34	5/7	preterm, AGA	death - 2 days	Idiopathic
	cesarean	female	3260	1/1/1	33	1/7	preterm, LGA	death - 2 hours	Idiopathic
	cesarean	female	1700	2/7/7	30		preterm, AGA	death - 10 days	Idiopathic + sepsis *
	cesarean	female	2920	2/7/8	35	5/7	preterm, AGA	death - 10 days	Idiopathic

* Antenatal diagnosis for nonimmune hydrops fetalis, AGA = adequate for gestational age, LGA = large for gestational age, Apgar-1st, 2nd and 5th minute of life.

Table 3 - Characterization of the newborn infants with nonimmune hydrops fetalis.

	n (21)	%		mean ± SD	range
DELIVERY TYPE			**BIRTH WEIGHT**		
Vaginal	3	14.3	**(g)**	2.665.9 ± 613.0	1550 - 3600
Cesarean	18	85.7			
GENDER			**GESTATIONAL AGE**		
Female	15	71.4	**(weeks)**	35.5 ± 2.4	30 – 39 3/7
Male	6	28.6			
PERINATAL ASPHYXIA			**LENGTH OF**		
Yes	10	47.6	**HOSPITAL STAY**	26.6 ± 23.6	3 – 44
No	11	52.4	**(days)**		
CLASSIFICATION			**AGE OF DEATH**		
adequate for gestational age	18	85.7	(days)	4.55 ± 4.2	1 - 12
large for gestational age	3	14.3			

Table 4 - Data from the review of the literature regarding the etiopathic classification of nonimmune hydrops fetalis.

Causes for Nonimmune hydrops fetalis	POESCHAMANN et al# modified 529 cases	PROENÇA et al# 21 cases
Cardiovascular	n=120 **(23%)**	n=4 **(19%)**
· malformations	50 (42%)	2 (50%)
· arrhythmia	37 (31%)	1 (25%)
· other	33 (27%)	1 (25%)
Genetics	n=70 **(14%)**	n=2 (9.5%)
· trisomy 21	16 (23%)	-
· Turner's syndrome	18 (26%)	-
· skeletal	20 (28%)	1 (50%)
· other	18 (25%)	1 (50%)
Infectious	n=17 **(3%)**	n=2 (9.5%)
· CMV	7 (41%)	-
· toxoplasmosis	3 (18%)	1 (50%)
· other	7 (41%)	1 (50%)
Placental	n=38 **(7%)**	n=1 **(4.76%)**
· twin-twin transfusion syndrome	32 (84%)	1 (100%)
· other	6 (16%)	-
Hematologic	n=24**(4.5%)**	n=1 **(4.76%)**
· alpha-thalassemia	12 (50%)	1 (100%)
· nonhemolytic anemia	11 (46%)	-
· other	1 (4%)	-
Miscellaneous	n=107 **(20.5%)**	n=3 **(14.3%)**
· respiratory	30 (28%)	-
· gastrointestinal	26 (24%)	-
· genitourinary	22 (21%)	-
· other	30 (28%)	3 (100%)
Idiopathic	n=150 **(28%)**	n=8 **(38%)**

#Adapted from the work of Poeschamann et al.[4], using literature data gathered by the author between 1967-1987.

DISCUSSION

The first report concerning hydrops fetalis was made by Diamond in 1932, who described a newborn with erythroblastosis fetalis in a terminal stage of generalized edema[2]. The immune etiology was the only known type until 1943, when Potter described 17 hydrops fetalis cases without associated isoimmunization[4]. The most frequently reported etiology of hydrops fetalis until the 1960s was the isoimmunization by the Rh factor[1].

Nowadays, the prenatal treatment of immune hydrops is so efficient that in many situations it can revert the disease course through prophylaxis with anti-D immunoglobulin and the through intrauterine transfusion. Therefore, NHF appears to be the most important cause of perinatal hydrops fetalis, being responsible for 75% of the cases[15]. In this study, the immune etiology occurred in 38% of the newborns, which shows that these rates in our environment still remain high, probably because ours is a reference service for hemolytic disease related to the Rh system, as well as because of a deficiency in prenatal monitoring of those pregnancies at risk for developing immune hydrops.

The reported incidence of NHF is relatively low compared with this study, at approximately 1 per 3000 live births[2]. In this study, 1 case of NHF was observed for every 414 live births, a frequency 7.6 times higher than in the general population. The explanation of this fact is quite simple: since this medical center is a tertiary and quaternary reference in the

health system for risk pregnancy, it therefore selects for a larger number of hydropic fetuses.

As previously mentioned, strict control during the prenatal period of pregnancies involving hydropic fetuses and the precise indication of the type of delivery required to improve the fetal prognosis led to a high frequency of cesarean deliveries (85.7%) and prematurity (67%).

Prenatal diagnosis of NHF was accomplished in more than 90% of the cases, and the etiology was determined in 62%. The better prognosis and a lower morbidity and mortality are related to these facts because follow-up of the pregnancy in a specialized center permits the creation of better delivery conditions.

The analysis of the study population showed that the average birth weight was 2.665 ± 613 g, and regarding the nutritional classification, 18 (85.6%) of the newborns were classified as adequate for GA, 3 (14.3%) as large for GA, and none as small for GA. The presence of fluids in the interstitial space results in newborns with a weight higher than expected for GA because of the increase in the total body fluid, therefore explaining the higher frequency of adequate and large newborns for GA.

This fact deserves to be emphasized because it is very difficult to evaluate nutritional status of hydropic newborns. The anthropometric parameters (weight, length, head and arm circumference, and skinfold thickness) widely used in the neonatal period must be avoided in those children. Additionally, biochemical parameters such as the visceral protein determination do not apply either. The use of the fetal growth curve (birth weight x GA) will tend to result in classifications that are at a higher level than the actual nutritional status, as previously mentioned[16,17].

Imaging methods, such as ultrasonography and sectional computerized tomography of the arm, could have some utility in the nutritional evaluation, since they can be used to estimate the mass. Nevertheless, these methods are not yet well defined for neonatals[18].

Regarding perinatal asphyxia, the frequency found in this population of 52% reinforces the hypothesis that the presence of hydrops is a relevant factor in the worsening of the fetal welfare because, in addition to the unfavorable condition during the intrauterine life, the generalized edema causes a more difficult delivery.

The predominance of females (71.4%) occurring in our study is a finding that is not reported in the literature, because those studies did not focus on gender differences in the incidence. However, some of the etiologies of hydrops are more prevalent in females.

When we compared our etiopathic diagnosis data with that in the literature (Table 4), we found that the main causes of NHF were variable in every studied population. This variation is due to a variety of factors; the two primary ones are 1) the influence of genetics, where an example is the higher frequency of cases due to hematologic causes in southeastern Asian populations where there are higher numbers of alpha-thalassemia carriers[5,19]; and 2) the variation in the occurrence of infectious diseases, where an example is the increase in the diagnosis of hydrops that is secondary to infection by parvovirus B19[5,20,21] in the last decade, due to a real increase in the number of cases or an improvement in the diagnosis of this viral disease.

The primary cause of NHF in this study arose from cardiovascular origin (19%), which is comparable to other studies in which cardiovascular diseases appear in 15% to 27% of the hydropic newborns, mainly due to arrhythmia and structural defects[9,23].

Genetic abnormalities, primarily the chromosomopathies including trisomy 21 and 18 and Turner syndrome[24,25], have been associated with hydropic fetuses in which this chromosomopathy can be the only cause of edema or it can be associated with other pathologies. In this study, genetic causes were responsible for 9.5% of the cases, but when evaluated for association with other causes, an increase of the incidence to 19% was observed. This increased incidence probably occurs because of the combination of the different pathophysiologic mechanisms, causing a fetus with a chromosomal abnormality evolve to hydrops.

The percentage of the idiopathic cases varies in the literature, depending primarily on the diagnostic methods available in each service. In this study, the etiopathic diagnosis of NHF was not achieved in 8 (38%) newborns.

The reported mortality rate for fetal hydrops is very high, around 50% to 100%[10], depending on the etiology[22]. In this study, 11 (52.4%) evolved to death, showing that the mortality rate, although high, was lower than in other major studies. Moreover, the deaths occurred primarily in the first week of life (average of 4.55 ± 4.2 days), arising out of complications associated with hypervolemia, such as cardiac, renal, and respiratory insufficiencies.

It has been reported that just 20% to 25% of the newborns with idiopathic NHF survive in the neonatal period[2]. This study's findings concur, with survival of only 2 (25%) of the 8 newborns with idiopathic etiology. This failure to survive is a consequence of various factors, of which the following stand out: the impossibility of an adequate control, either prenatal or postnatal, of the etiopathic cause that resulted in the generalized edema; a higher frequency of prematurity; and increased severity of hydrops at birth, increasing the difficulty of postnatal treatment.

The newborns that survived remained hospitalized for a long period (average of 26.6 ± 23.6 days), either because of the need for a prolonged treatment or the need to control the etiopathic causes and the secondary complications of prematurity and hydrops.

In summary, when confronted with the possibility of hydrops fetalis during the gestation, all possible effort should be made to achieve an etiopathic diagnosis. First it must be determined whether the hydrops are immune or nonimmune so treatment may be initiated. The establishment of a correct etiopathic diagnosis associated with precocious nonimmune hydrops is fundamental to an adequate selection of the prenatal and neonatal therapeutic approach, reducing as a consequence the morbidity and mortality risks associated with this serious dysfunction.

RESUMO

MASCARETTI RS e col. – Caracterização dos recém-nascidos com hidropisia fetal não imune admitidos em uma unidade neonatal de terapia intensiva. **Rev. Hosp. Clín. Fac. Med. S. Paulo 58**(3):125-132, 2003.

OBJETIVOS: Determinar a incidência e caracterizar a população de recém-nascidos com hidropisia fetal não imune.

MÉTODO: Estudo retrospectivo, referente ao período de 1996 a 2000, incluindo todos os recém-nascidos com diagnóstico antenatal ou neonatal, com base na história clínica, exame físico e avaliação laboratorial. Foram analisados: seguimento pré-natal, tipo de parto, sexo, peso de nascimento, idade gestacional, presença de asfixia perinatal, classificação nutricional, diagnóstico etiopatogênico, tempo de internação, mortalidade, idade do óbito.

RESULTADOS: Foram selecionados 47 recém-nascidos com hidropisia fetal (0,42% dos nascidos vivos), 18 (38,3%) com a forma imune e 29(61,7%) com a não imune. A incidência de hidropisia fetal não imune foi de 1:414 nascidos vivos. Obtiveram-se dados de 21 recém-nascidos destes, 19 (90,5%) apresentavam suspeita diagnostico antenatal, 18 (85,7%) nasceram de parto cesariano; 15 (71,4%) eram do sexo feminino; 10 (47,6%) foram asfixiados. O peso médio foi 2665,9g, e a idade gestacional média de 35 3/7 sem, 14 (66,6%) pré-termo; 18 (85,7%) adequados e 3 (14,3%) grandes para idade gestacional. O diagnóstico etiopatogênico foi realizado em 62% dos recém-nascidos, sendo decorrente de causas cardiovasculares (19%), infecciosas (9,5%), placentária (4,76%), hematológicas (4,76,%), gênito-urinária (4,76%), tumoral (4,76%) e houve associação de causas em 9,5%. A etiologia foi classificada em idiopática em 38%. O tempo de internação foi de 26,6 dias ± 23,6 e

a mortalidade de 52,4%.

CONCLUSÕES: O estabelecimento de um correto diagnóstico etiopatogênico, associado à detecção antenatal da hidropisia fetal não imune, constitui elemento importante para uma redução da mortalidade neonatal decorrente desta grave doença.

DESCRITORES: Hidropisia fetal. Hidropisia fetal não imune. Recém-nascido. Anasarca. Hidrópico.

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