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Filipa Batschelet Barros

Non-immune Hydrops Fetalis - Experience of a level III Neonatal Intensive Care Unit

Hidrópsia Fetal Não Imune – Experiência de uma Unidade de Cuidados Intensivos Neonatal terciária

Março, 2017

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TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Non-Immune Hydrops Fetalis – Experience of a level III Neonatal Intensive Care Unit

ORIENTADOR

Prof. Doutora Maria Hercília Ferreira Guimarães Pereira Areias

COORIENTADOR (se aplicável)

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☒

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Aos meus pais, irmãos e Ricardo

Non-immune Hydrops Fetalis – Experience of a level III Neonatal Intensive Care Unit

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Abstract

BACKGROUND: The aim of this study was to evaluate the experience of our level III Neonatal Intensive Care Unit (NICU) with Non-Immune Hydrops Fetalis (NIHF), and thus contribute to the improvement of our practice in prenatal diagnosis and postnatal clinical management of neonates.

METHODS: We analysed the clinical records of neonates admitted to NICU of Centro Hospitalar de São João do Porto between 1 January 1997 and 31 December 2016, with diagnosis of NIHF. Demographic data and information regarding gestation, delivery and neonatal period were examined.

RESULTS: We found 23 patients with NIHF, out of which 12 (52.2 %) died and 11 (47.8 %) survived. The mean gestational age at birth was significantly lower among the deceased patients (30.6 ± 2.2 weeks). Concerning the morbidity, all the disorders evaluated were more frequently found in the deceased group, except for necrotizing enterocolitis; however, the only statistically significant difference was the frequency of anemia, which was higher in the deceased group. The commonest etiology of NIHF was congenital heart disease (52.2%), which was significantly more frequent among the survivors. Specific treatment and antiarrhytmics were administered significantly more frequently among the survivors. Amines, thoracocentesis, paracentesis were significantly more used in the deceased.

CONCLUSIONS: Despite improvements in healthcare, mortality rates of NIHF are high. Some causes of NIHF are responsive to therapy, such as cardiac diseases, which confers a lower mortality. The cornerstone of management of NIHF is based on the underlying etiology, which determines prognosis, appropriate treatment and recurrence risk of future pregnancies.

Introduction

Hydrops fetalis is characterized by pathological fluid accumulation in fetal soft tissues and serous cavities. The features are usually detected by ultrasound, and are defined as the presence of two or more abnormal fluid collections, such as ascites, pleural effusions, pericardial effusion, and generalized skin edema (skin thickness >5 mm). [1] Although polyhydramnios and placental thickening are frequently associated with hydrops fetalis [2], they are not used as diagnostic criteria.

This disease is classified in immune or non-immune hydrops. Non-immune hydrops fetalis (NIHF) refers specifically to cases not caused by red cell alloimmunization. With advances in prenatal diagnosis and routine use of Rh(D) immune globulin in rhesus-negative mothers, alloimmunization and associated immune hydrops has dramatically decreased. [1, 3] Therefore, actually most cases (90%) have a non-immune etiology, with prevalence in studies reported as 1:1700-3000

pregnancies.[1, 3, 4]

The differential diagnosis is extensive, as it can result from a large number of underlying pathologies, including those affecting lymphatic, cardiovascular, pulmonary, renal, hematologic or gastrointestinal systems, and also chromosomal abnormalities, infections and metabolic diseases.[5-7] Overall, chromosomal abnormalities, cardiovascular and hematologic diseases are the most common causes of NIHF.[1, 6] Despite exhaustive investigations, the etiology may remain idiopathic in 15% to 25% of patients.[2]

The prognosis of NIHF differs markedly between different etiological groups, but overall mortality rates are high. [5, 6, 8] More recently, earlier and advanced pre natal diagnosis and interventions, and developed post-natal management had shown to improve survival in selected cases. However, this disease still represents a challenge for physicians all over the world, so all the studies and information are valuable and useful to understand the best way to deal with it.

The aim of this study was to evaluate the experience of our level III Neonatal Intensive Care Unit (NICU) with NIHF, and thus contribute to the improvement of our practice in prenatal diagnosis and postnatal clinical management of these neonates; and to add some useful information to the current literature.

Material and methods

We conducted an observational retrospective study. The study population included all neonates admitted to the level III NICU of Centro Hospitalar São João do Porto (Portugal) between 1 January 1997 and 31 December 2016, with a diagnosis of NIHF. Cases diagnosed with immune hydrops fetalis were excluded from the study. Demographic data and information regarding gestation, delivery and neonatal period were extracted from the medical records (appendix 1). Autopsy study was assessed in 10 of the 12 deceased children (one was not available and the other was refused by the parents).

NIHF was defined as an abnormal fluid collection in two or more areas of the fetal body (ascites, pleural effusion, pericardial effusion, or skin edema), not caused by red cell alloimmunization.

Anemia was defined by a concentration of hemoglobin or a hematocrit less than two standard deviation than the mean of a normal population with the same age and sex. [9] Intraventricular haemorrhage (IVH) was classified according to Papile et al – in our study we just considered grade 3 (transfontanellar ultrasound demonstrating intraventricular bleeding with ventricular dilation) and grade 4 (transfontanellar ultrasound demonstrating intraventricular bleeding with parenchymal involvement.[10] The diagnosis of bronchopulmonary dysplasia (BPD) was based on the National Institute of Child Health and Human.[11] Hyaline membrane disease (HMD) was defined based on the european guidelines.[12] Diagnosis of hemodynamically significant patent ductus arteriosus (PDA) was based on bidimensional heart ultrasound, using Doppler to analyze the blood flow and show the presence of shunt.[13, 14] Proven neonatal sepsis was defined as any systemic bacterial or fungal infection documented by a positive blood culture. Diagnosis of necrotizing enterocolitis (NEC) was established by the criteria of Bell.[15] Congenital anomalies, also known as birth defects, congenital disorders or congenital malformations, were defined as structural or functional anomalies that occur during intrauterine life and can be identified prenatally, at birth, or sometimes may only be detected later in infancy.[16]

We classified the NIHF into 8 categories: congenital heart disease, chromosomal abnormality, congenital infection, urinary tract abnormality, lymphatic dysplasia, fetal tumors, inborn errors of metabolism and idiopathic. Congenital heart disease includes arrhythmias and structural defects.

Prenatal invasive diagnostic testing was considered if amniocentesis or cordocentesis was realized during the pregnancy. Fetal intervention was performed in selected patients, either by pharmacological agents or thoracentesis. Specific treatment was defined as any treatment (pharmacological or not) directed to the underlying etiology of NIHF.

The statistical analysis was performed using SPSS® for Windows®, version 20. Continuous variables with symmetric distribution were characterized by mean (± standard deviation), whereas continuous variables with asymmetric distribution were described by median (medium-maximum). Categorical variables were characterized by absolute and relative frequencies. Parametric testes (independent t test) or non-parametric tests (Mann-Whitney U test) were used to compare symmetric or asymmetric continuous variables, respectively. To compare categorical variables, Chi-Squared or Fisher's exact test were used, the latter for expected values less than 5. A multivariate analysis by logistic regression was performed to evaluate predictive factors for death. A p-value less than 0.05 was considered statistically significant.

The study was approved by the Ethics Committee of the Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto.

Results

There were 57,773 births registered at the hospital, during the period of the study and a total of 23 (0.04%) newborns diagnosed with NIHF were admitted to the NICU during the same period, out of which 12 (52.2 %) died and 11 (47.8 %) survived.

Maternal and perinatal data of all cases of NIHF are shown in table 1 and in table 2 we can observe maternal, perinatal and neonatal morbidity of NIHF patients, comparing deceased and survivors.

The most common cause of NIHF was congenital heart disease (52.2%), which was significantly more frequent among the survivors (p=0.001). The second most common etiologies were congenital TORCH infections (8.7%) and lymphatic dysplasia (8.7%), followed by chromosomal abnormalities (4.3%), congenital nephrotic syndrome (4.3%), cardiac rhabdomyoma (4.3%) and inborn errors of metabolism (4.3%). With respect to congenital heart diseases, three different arrhythmias (supraventricular tachycardia, Wolff-Parkinson-White syndrome (WPW), Atrial Flutter) and two types of structural defects (Atrial Septal Defect and Right-ventricle Hypoplasia) were diagnosed. Tetrasomy 9p was the only chromosomal abnormality detected (Tables 3 and 4).

A total of 11 (47.8%) neonates received specific treatment, and the frequency was significantly greater among the survivors (72.7% survivors, 25.0% deceased; p=0.039). Antiarrhythmics were also administered significantly more frequently among the survivors (p=0.001). Amines and thoracocentesis or paracentesis were significantly more used in the deceased patients (p<0.001 and p=0.012, respectively). Other treatments carried out included diuretics (43.5%), antibiotics (69.5%), surfactant (52.2%), blood transfusions (65.2%), mechanical ventilation (78.3%) and oxygen therapy (73.9%), without significant differences between the two groups (Tables 3 and 5).

A low gestational age at birth and the need to perform thoracocentesis or

paracentesis were identified as the predictive factors of mortality in the multivariate analysis (Table 6).

Discussion

In our study, we reviewed the clinical characteristics, the treatment performed and the outcome (death/survived) of newborns with non-immune hydrops fetalis in a tertiary-referral center, during a 20 year period.

Our data shows that the prevalence of NIHF at our centre is approximately 1: 2500, which is in agreement with other studies.[1, 4, 17]

We notice that the mean birth weight and the mean gestational age at birth were lower in the fetal death than the live birth cases; and the reverse happened with maternal age, which was higher in the deceased patients. These three factors are generally associated with higher risk pregnancies, so it's easy to understand that neonates with these characteristics tend to die more. Just like our study, lower gestational age at birth has been identified as a risk factor for mortality in NIHF in several other recent studies [8, 18, 19] and association between prematurity and poor outcome has been shown undoubtedly.[19, 20] We interpret this as a result of the additional morbidity conferred by the prematurity and by its complications. Besides, the need to perform a preterm delivery may reflect a greater severity of NIHF.[19]

Prenatal fetal intervention, namely pharmacological therapy and thoracocentesis, was more frequently observed in the survivors, although without statistically significant difference. This is consistent with other studies [1, 6, 7, 17], and highlights the importance of the selection of the patients in which fetal therapy is effective. This usually requires evaluation at a specialized center, in which a careful consideration of risks and benefits is carried out.

A prenatal NIHF diagnosis was made in 82.6%, a satisfactory number of patients. However, the main difficulty is not to identify the presence of a hydropic fetus on the ultrasound, but to recognize the underlying etiology. It has been reported that the cause of hydrops can be determined in about 60-85% of cases.[1, 21] The identification of the cause of hydrops is essential. First, because the prognosis of the neonate is directly dependent on the underlying condition.[17, 20] Second, it enables the institution of management strategies and the treatment of potentially treatable conditions, such as arrhythmias. Finally, it allows to rule out genetic and inherited metabolic disorders that have a greater risk of recurrence in future pregnancies.[1] In our study, one-quarter of all cases had no identified etiology (idiopathic cause), which is consistent with the literature.[2, 17, 22, 23]

The etiology of NIHF varies widely among different places and populations.[24] In most series, congenital heart diseases are the most common cause of NIHF, accounting for about 20% of cases.[1, 2, 7, 21, 25] These results are similar to the results in our study, in which the cardiac etiologies, especially arrhythmias, assumed the majority of the cases. However, in our study, they were responsible for a higher amount of cases, namely 52.2% (versus 20% reported in literature). When we analyzed this finding, we discovered that 75% of these NIHF caused by congenital heart disease occurred after 2007, the year when the pregnancy interruption law was approved in our country. Therefore, this may due to a better selection of neonates more able to survive, i.e. since the overall prognosis of cardiac NIHF is better than non-cardiac NIHF, pregnancy termination was more frequent among the latter, leading to the higher prevalence of congenital heart disease in our study. Also, our hospital is the only

referral center for congenital cardiac diseases in the north of the country. The most commonly found arrhythmias were supraventricular tachycardia and atrial flutter, which is in agreement with other series.[1, 26] Notably, one of the most important findings of our study was the significantly higher frequency of congenital heart diseases among the survivors. This is probably due to two reasons: first, the prenatal fetal therapy with transplacentary antiarrhythmics is very effective for these tachycardias [1, 20, 26, 27]; second, they have been shown to be the most treatable of the cardiac causes of NIHF [2, 6, 7], a consequence of the excellent response to postnatal antiarrhythmics and cardioversion. This finding is supported by other studies that showed a lower mortality rate when the cause of NIHF was supraventricular tachycardia that responded to maternal treatment.[25, 27, 28] Apart from cardiac disorders, chromosomal abnormalities and hematologic diseases are reported as part of the most frequent etiologies, with frequencies between 7-16% and 4-12%, respectively.[1, 6, 19, 29] However, in our study, these conditions were not very often diagnosed. Concerning chromosomal abnormalities (4.3%), it was most likely due to a high rate of pregnancy termination of chromosomally abnormal pregnancies. With respect to hematologic diseases (0%), this may be related to the very low prevalence of thalassaemia in our local population. This disease is very common in Southeast Asian populations, accounting for 55% of NIHF in Southern China [1, 2, 30], but not in Western Europe. Other frequently reported etiologies include infections and lymphatic dysplasia, which were the second most common etiologies in our study. Infections were present in 8.7% patients, consistent with other series, in which such infections account for 5-10% of NIHF.[1, 2, 6, 31, 32] Lymphatic dysplasia was also responsible for 8.7% of NIHF, similar to other reports.[1] Finally, the remaining etiologies were congenital nephrotic syndrome, cardiac rhabdomyoma and inborn errors of metabolism, each accounting for 4.3% of the cases, which is in agreement with other series.[1, 6, 7, 25, 33] In the last few years, inborn errors of metabolism have been drawing the attention of physicians. Although they are an uncommon cause of NIHF, they entail a high risk of recurrence. Consequently, the identification of such disorder should prompt specific screening in future pregnancies, to allow an earlier prenatal diagnosis and adequate management.[7, 34, 35]

Concerning the morbidity of the neonates with NIHF, all the disorders were more frequently found in the deceased group, except for NEC. Despite the fact that the only statistically significant difference between deceased and live neonates was the frequency of anemia, these results reflect a worst baseline clinical picture, which contributes to a higher mortality.

A large number of postnatal interventions, including pharmacological or invasive ones, treatment directed to the underlying condition or supportive measures, are available and must be used when necessary. Another important and statistically significant result in our study was that survivors received more frequently a specific treatment for the underlying disorder than the deceased patients. This means that the response to this kind of therapy can revert the hydrops and improve the survival, which is extremely encouraging, given the overall poor prognosis associated with NIHF. Conversely, thoracocentesis, paracentesis and amines were statistically more frequently used in the case of neonatal death compared to the survivors. Likewise, the use of mechanical ventilation, oxygen therapy, blood transfusion and antibiotics was also more frequently found in the case of deceased patients, although the difference was not statistically significant. This probably indicates that these neonates had a

baseline condition more critical and severe, which justifies the need to use these therapies.

Our study struggle with some limitations. It is a retrospective study, realized in a single centre and with a relatively small sample, impairing the generalization of conclusions. Another drawback is that our study only included the cases that were delivered as NIHF, not including prenatal spontaneous resolution cases, which can underestimate the prevalence of NIHF and overestimate the percentage of deaths. Larger and prospective studies are needed, in order to obtain statically significant conclusions about the best approach in the prenatal period, as well as the best management, treatment and follow-up strategy. Long-term outcomes and morbidity of NIHF patients are also information of great interest.

The results of this series may add some useful information to the current literature on NIHF, a very rare clinical condition of the newborn.

Conclusion

The diagnosis and management of NIHF remains a challenge for obstetricians and neonatologists. Despite improvements in pre and postnatal healthcare, overall mortality rates are high. However, some causes of NIHF are responsive to therapy, such as cardiac diseases, which determines a lower mortality and morbidity. Furthermore, the prognosis of NIHF varies clearly between different etiological groups. For these reasons, we can conclude that the cornerstone of management of NIHF is based on the underlying etiology, which allows a better prediction of prognosis, selection of pre and postnatal appropriate treatment and assessment of the recurrence risk of future pregnancies.

Findings of this study, along with review of the literature, are essential for a better understanding of this complex pathology, thereby allowing individual pre and postnatal management and appropriate parental counselling. It is particularly important to exclude potentially treatable conditions, such as arrhythmias, as well as genetic disorders that have a higher risk of recurrence in future pregnancies. This implies timely referral to a specialized centre.

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Table 1. Maternal and perinatal data of all cases of Non-Immune Hydrops Fetalis.

Case nº	Year	Maternal age (years)	Gestational age at birth (weeks)	Gender	Birth weight (g)	Type of gestation	Type of delivery	Antenatal corticosteroids therapy	Prenatal diagnostic testing	Prenatal NIHF diagnosis	Fetal intervention
1	1997	20	29	Male	1870	Single	C-section	Yes	Cordocentesis	Yes	None
2	1998	28	27	Female	890	Single	C-section	Yes	None	Yes	None
3	1998	29	34	Female	3260	Single	C-section	Yes	None	No	None
4	1999	31	30	Male	2045	Single	C-section	Yes	Amniocentesis	Yes	None
5	2000	43	31	Female	1810	Single	C-section	Yes	None	Yes	None
6	2001	33	29	Female	1500	Multiple	C-section	Yes	None	Yes	None
7	2001	30	36	Male	4270	Single	C-section	No	None	Yes	None
8	2002	27	30	Male	2240	Single	C-section	Yes	None	Yes	None
9	2002	31	32	Female	2228	Single	C-section	Yes	None	No	None
10	2003	26	39	Female	3052	Single	Vaginal	No	None	Yes	Digoxin
11	2005	26	31	Female	1320	Single	Vaginal	Yes	Amniocentesis	Yes	Hydroxyzine, Nifedipine
12	2006	38	34	Male	2800	Single	C-section	No	None	No	None
13	2007	34	32	Male	3100	Single	C-section	Yes	Amniocentesis	Yes	Digoxin, Sotalol
14	2007	40	39	Male	3240	Single	C-section	No	Amniocentesis	Yes	Digoxin, Flecainide
15	2007	28	34	Female	3320	Single	C-section	Yes	None	No	None
16	2008	28	31	Female	3342	Single	C-section	Yes	Amniocentesis	Yes	None
17	2009	21	31	Male	2435	Single	C-section	No	None	Yes	Digoxin
18	2009	32	30	Female	1900	Single	C-section	No	None	Yes	None
19	2010	26	34	Female	2605	Single	C-section	Yes	None	Yes	None
20	2013	24	37	Male	3045	Single	C-section	No	None	Yes	None
21	2014	28	30	Male	1530	Single	C-section	Yes	Amniocentesis	Yes	Thoracocentesis
22	2015	34	36	Male	2675	Single	Vaginal	Yes	None	Yes	Digoxin, Flecainide
23	2016	29	31	Male	2220	Single	C-section	Yes	None	Yes	Digoxin

Table 2. Maternal, perinatal data and neonatal morbidity of Non-Immune Hydrops Fetalis cases, comparing deceased and survivors

	Total (n=23)	Deceased (n=12)	Survivors (n=11)	p
Gender, n (%)				
Male	12 (52.2)	6 (50)	6 (54.5)	0.827*
Female	11 (47.8)	6 (50)	5 (45.5)	
Birth weight (g), mean ± SD	2465.1 ± 806.1	2178.8 ± 958.7	2777.4 ± 461.2	0.074§
Maternal age (years), mean ± SD	29.8 ± 5.5	29.9 ± 5.5	29.7 ± 5.8	0.937§
Gestational age (weeks), mean ± SD	32.5 ± 3.2	30.6 ± 2.2	34.4 ± 3.1	**0.003**§
Prenatal NIHF diagnosis, n (%)	19 (82.6)	11 (91.7)	8 (72)	0.317**
Prenatal invasive diagnostic testing, n (%)	7 (30.4)	6 (50)	1 (9.1)	0.069**
Fetal intervention, n (%)	8 (34.8)	3 (25.0)	5 (45.5)	0.400**
Pharmacological	7 (30.4)	2 (16.7)	5 (45.5)	0.999**
Thoracocentesis	1 (4.3)	1 (8.3)	0	0.193**
C-section delivery, n (%)	20 (86.9)	11 (91.7)	9 (81.8)	0.999**
1^{sit} minute APGAR <7, n (%)	18 (78.3)	11 (91.7)	7 (63.6)	0.155**
5th minute APGAR <7, n (%)	10 (43.5)	6 (50.0)	4 (36.4)	0.414**
Reanimation, n (%)	13 (56.5)	9 (75.0)	4 (36.4)	0.100**
Endotracheal tube, n (%)	14 (60.9)	9 (75.0)	5 (45.5)	0.214**
Intraventricular haemorrhage (≥ grade 3), n (%)	1 (4.3)	1 (8.3)	0	0.999**
Patent ductus arteriosus, n (%)	10 (43.5)	6 (50.0)	4 (36.4)	0.680**
Hyaline membrane disease, n (%)	7 (30.4)	4 (33.3)	3 (27.3)	0.999**
Bronchopulmonary dysplasia, n (%)	3 (13.0)	3 (25.0)	0	0.217**
Major congenital malformation, n (%)	3 (13.0)	2 (16.7)	1 (9.1)	0.999**
Anemia, n (%)	14 (60.9)	10 (83.3)	4 (36.4)	**0.036****
Necrotizing enterocolitis, n (%)	1 (4.3)	0	1 (9.1)	0.478**
Sepsis, n (%)	10 (43.5)	6 (50.0)	4 (36.4)	0.680**
Days of hospitalization, median (min-max)	15 (0-56)	9.5 (0-41)	15 (2-56)	0.288¥

*Chi-square test; ** Fisher's exact test; § Independent t test; ¥ Mann Whitney U test

Table 3. Etiology, treatment, and outcome during hospitalization of all cases of Non-immune Hydrops Fetalis.

Case nº	Year	Etiology of NIHF	Specific Treatment	Amines	Diuretics	Antibiotics	Surfactant	Blood transfusion	Thoracocentesis and/ or Paracentesis	Mechanical ventilation	Outcome
1	1997	Toxoplasmosis Infection	None	Yes	Yes	Yes	Yes	Yes	No	Yes	Dead
2	1998	Idiopathic	None	Yes	No	Yes	No	Yes	No	Yes	Dead
3	1998	Lymphatic Dysplasia	None	No	No	Yes	No	No	Thoracocentesis	Yes	Survived
4	1999	Atrial Septal Defect	None	Yes	No	Yes	No	Yes	Thoracocentesis	Yes	Dead
5	2000	Tetrasomy 9p	None	Yes	No	Yes	Yes	Yes	Both	Yes	Dead
6	2001	Right-ventricle hypoplasia	None	Yes	No	No	No	No	No	No	Dead
7	2001	Idiopathic	None	Yes	No	No	No	No	Both	Yes	Dead
8	2002	Idiopathic	None	Yes	No	No	No	Yes	Both	Yes	Dead
9	2002	Sifilis Infection	Penicillin	Yes	No	Yes	Yes	Yes	Paracentesis	Yes	Dead
10	2003	Wolff-Parkinson-White	Propanolol, Flecainide	No	No	No	No	No	No	No	Survived
11	2005	Inborn error of metabolism	None	Yes	No	Yes	No	Yes	Paracentesis	Yes	Dead
12	2006	Atrial Flutter	Adenosine, Cardioversion. Digoxin, Propanolol, Flecainide.	Yes	Yes	Yes	Yes	Yes	No	Yes	Survived
13	2007	Atrial Flutter	Atropine, cardioversion	Yes	Yes	Yes	Yes	Yes	Both	Yes	Dead
14	2007	Supraventricular Tachycardia	None	No	No	No	No	No	No	No	Survived
15	2007	Supraventricular Tachycardia	Adenosine, amiodarone. Digoxin.	No	Yes	Yes	Yes	Yes	No	Yes	Survived
16	2008	Congenital Nephrotic Syndrome	Peritoneal dialysis	Yes	Yes	Yes	Yes	Yes	Thoracocentesis	Yes	Dead
17	2009	Supraventricular Tachycardia	Adenosine. Propanolol, Flecainide	No	No	No	Yes	No	Thoracocentesis	Yes	Survived
18	2009	Supraventricular Tachycardia	Adenosine, Cardioversion. Propanolol, Flecainide.	No	No	Yes	No	Yes	No	No	Survived
19	2010	Wolff-Parkinson-White	Propanolol, Flecainide	No	Yes	Yes	Yes	Yes	No	Yes	Survived
20	2013	Cardiac Rhabdomyoma	None	No	Yes	Yes	Yes	No	No	Yes	Survived
21	2014	Lymphatic Dysplasia	None	Yes	Yes	Yes	Yes	Yes	Thoracocentesis	Yes	Dead
22	2015	Supraventricular Tachycardia	Propanolol	No	Yes	No	No	No	No	No	Survived
23	2016	Supraventricular Tachycardia	Adenosine, Amiodarone, Cardioversion. Propanolol, Flecainide	No	Yes	Yes	Yes	Yes	No	Yes	Survived

Table 4. Etiology of Non-immune Hydrops Fetalis, comparing deceased and survivors.

	Total (n=23)	Deceased (n=12)	Survivors (n=11)	p
Congenital heart disease (structural defect or arrhythmia), n (%)	12 (52.2)	3 (25.0)	9 (81.8)	**0.001**[**]
Idiopathic, n (%)	3 (25.0)	0	3 (13.0)	0.217[**]
Congenital TORCH infection, n (%)	2 (8.7)	2 (16.7)	0	0.478[**]
Lymphatic dysplasia, n (%)	2 (8.7)	1 (8.3)	1 (9.1)	0.999[**]
Chromosomal abnormality, n (%)	1 (4.3)	1 (8.3)	0	0.999[**]
Congenital nephrotic syndrome, n (%)	1 (4.3)	1 (8.3)	0	0.999[**]
Cardiac rhabdomyoma, n (%)	1 (4.3)	0	1 (9.1)	0.478[**]
Inborn errors of metabolism, n (%)	1 (8.3)	0	1 (4.3)	0.999[**]

[**] Fisher's exact test

Table 5. Treatment of Non-immune Hydrops Fetalis patients during hospitalization, comparing deceased and survivors.

	Total (n=23)	Deceased (n=12)	Survivors (n=11)	p
Specific treatment, n (%)	11 (47.8)	3 (25.0)	8 (72.7)	**0.039**[**]
Thoracocentesis and/ or Paracentesis, n (%)	11 (47.8)	9 (75.0)	2 (18.2)	**0.012**[**]
Amines, n (%)	14 (60.9)	12 (100.0)	2 (18.2)	**<0.001**[**]
Antiarrhythmics, n (%)	10 (43.5)	1 (8.3)	9 (81.8)	**0.001**[**]
Diuretics, n (%)	10 (43.5)	4 (33.3)	6 (54.5)	0.414[**]
Antibiotics, n (%)	16 (69.5)	9 (75.0)	7 (63,6)	0.667[**]
Surfactant, n (%)	12 (52.2)	6 (50.0)	6 (54.5)	0.827[*]
Parenteral nutrition, n (%)	16 (69.5)	8 (66.7)	8 (72.7)	0.999[**]
Blood transfusion, n (%)	15 (65.2)	10 (83.3)	5 (45.4)	0.089[**]
Mechanical Ventilation, n (%)	18 (78.3)	11 (91.7)	7 (63.6)	0.155[**]
Mechanical Ventilation (days), median (min-max)	5 (0-41)	9.5 (0-41)	5 (0-23)	0.235[¥]
Oxygen therapy, n (%)	17 (73.9)	11 (91.7)	6 (54.5)	0.069[**]
Oxygen therapy (days), median (min-max)	2 (0-41)	9.5 (0-41)	1 (0-41)	0.151[¥]

[*]Chi-square test; [**] Fisher's exact test; [¥] Mann Whitney U test

Table 6. Multivariate analysis – predictive factors of mortality.

	OR	95% CI	p
Thoracocentesis or paracentesis	25.24	1.27-503.26	0.034
Gestational age at birth	0.5	0.29-0.95	0.034

Authors' contribution statement: Filipa Barros executed the data collection and wrote the article. Gustavo Rocha participated in the design of the study. Filipa Flor-de-Lima performed the statistical analyze of the study. Henrique Soares reviewed the article. Hercília Guimarães was responsible for designing the study and revision.

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– ANEXOS –

Anexo 1.

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Anexo 2.

Comissão de Ética para a Saúde do C.H.S.João e da FMUP

Parecer

Título do Projecto: Non-immune hydrops fetalis – experience of a level III Neonatal Intensive Care

Nome do Investigador Principal: Filipa Batschelet Barros

Promotor do Estudo: NA

Serviço onde decorrerá o Estudo: Serviço de Neonatalogia do Centro Hospitalar de S. João

Objectivo e Pertinência do Estudo:

O estudo que é proposto avaliar visa identificar todos os 23 casos de Hidrópsia Fetal Não Imune internados na UCIN entre 1997 e 2016 e, neles, avaliar a morbilidade e mortalidade, comparar a evolução clínica e o tratamento efectuado em duas décadas distintas (1997-2006 e 2006-2016), e analisar retrospectivamente algumas variáveis de interesse verificadas nos processos clínicos. Serão assim recolhidas dos processos clínicos variáveis demográficas, gestacionais, relativas ao parto, e ao período neonatal, sobre o tratamento efectuado e *outcome*'s.

Esta investigação visa a elaboração de uma Tese de Mestrado Integrado em Medici8na, sob a orientação da Sr.ª Prof.ª Doutora Hercília Guimarães, Directora também do serviço em que se realizará o estudo.

Benefício/risco: NA, dada a natureza do estudo

Respeito pela liberdade e autonomia do sujeito de ensaio: NA, dada a natureza do estudo

Confidencialidade dos dados: Questionada a investigadora, a confidencialidade dos dados a recolher dos processos clínicos será assegurada pela anonimização dos registos e a codificação dos processos.

Elo de ligação: Prof.ª Doutora Hercília Guimarães.

Indemnização por danos: NA

Continuação do tratamento: NA

Propriedade dos dados: Não serão da exclusiva propriedade intelectual do Investigador e estão-lhe referidos critérios de publicação.

Curriculum do investigador: Adequado ao perfil da investigação.

Data previsível da conclusão do estudo: Março 2017

Conclusão: Considerados os objectivos e a natureza da investigação, e tendo sido esclarecida satisfatoriamente a questão elencada no parecer inicial, o parecer da CES é favorável à realização deste projecto de investigação.

Porto e H.S.João, 2017-03-18

O Presidente da CES CHSJ/FMUP

Doutor Filipe Almeida

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)
NÃO ☐
NÃO APLICÁVEL ☒

8. TERMO DE RESPONSABILIDADE

Eu, Filipa Batschelet Barros,
abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 15 / Janeiro / 2017

...missão de Ética para a Saúde tendo ...ado o parecer do Relator, aguarda ... Investigador/Promotor esclareça as ...ões nele enunciadas para que possa ...ir parecer definitivo.

Filipa Barros
O Investigador Principal

2017-02-17

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO/FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

emitido na reunião plenária da CES de ___/___/___

Centro Hospitalar **São João**

CONSIDERADOS QUE FORAM COMO SATISFATÓRIOS OS ESCLARECIMENTOS PRESTADOS PELO(A) INVESTIGADOR(A), A CES APROVA POR UNANIMIDADE O PARECER DO RELATOR, PELO QUE NADA TEM A OPOR À REALIZAÇÃO DESTE PROJETO DE INVESTIGAÇÃO.

2017/02/18

Prof. Doutor Filipe Alv...
Presidente da Comissão de...

– APÊNDICES –

Apêndice 1.

Prenatal, perinatal and neonatal data

1. Demographics

Birth Date: __/__/____
Sex: ❒ F ❒ M
Gestacional age: _____ weeks
Birth weight: ____ g

2. Gestation

Maternal age: ____ years
Multiple gestation: ❒ no ❒ yes
Vigilance: ❒ no ❒ yes
Prenatal Corticosteroids: ❒ no ❒ yes
Smoking during pregnancy: ❒ no ❒ yes
Drugs during pregnancy: ❒ no ❒ yes
Gestational Diabetes: ❒ no ❒ yes
Chronic maternal hypertension: ❒ no ❒ yes
Pre-eclampsia: ❒ no ❒ yes
Eclampsia: ❒ no ❒ yes
HELLP Syndrome: ❒ no ❒ yes
Streptococcus agalactiae (group B): ❒ no ❒ yes
Prenatal invasive diagnostic testing: ❒ no ❒ yes
TORCH screening: ❒ no ❒ yes
Fetal karyotyping: ❒ no ❒ yes
Thoracoamniotic shunting: ❒ no ❒ yes
Intrauterine transfusion: ❒ no ❒ yes
Pharmacological treatment: ❒ no ❒ yes
Thoracocentesis: ❒ no ❒ yes
Prenatal NIHF diagnosis: ❒ no ❒ yes

3. Delivery

C-section: ❒ no ❒ yes
Premature Rupture of Membranes: ❒ no ❒ yes
Intrapartum antibiotics: ❒ no ❒ yes
APGAR (1st and 5th minutes): ___/___
Resuscitation: ❒ no ❒ yes
Endotracheal Tube: ❒ no ❒ yes

4. Neonatal Period

TORCH group infection: ❒ no ❒ yes
Congenital heart disease: ❒ no ❒ yes
    Structural defect: ❒ no ❒ yes _____
    Arrhythmia: ❒ no ❒ yes _____
Lymphatic Dysplasia: ❒ no ❒ yes
Congenital Nephrotic syndrome: ❒ no ❒ yes
Chromosomal abnormality: ❒ no ❒ yes
Inherited Metabolic disease: ❒ no ❒ yes
Fetal tumor: ❒ no ❒ yes

Congenital hemodiaphragmatic hernia: ❒ no ❒ yes
Pulmonary Hipertension: ❒ no ❒ Non Severe ❒ Severe
Cause: _____
Pneumonia: ❒ no ❒ yes
Bronchopulmonary dysplasia: ❒ no ❒ yes
Hyaline membrane disease: ❒ no ❒ yes
Sepsis: ❒ no ❒ yes
Patent ductus arteriosus: ❒ no ❒ yes
Major Congenital Malformation: ❒ no ❒ yes
Twin-to-twin transfusion syndrome: ❒ no ❒ yes
Feto-maternal transfusion: ❒ no ❒ yes
Anemia: ❒ no ❒ yes
Necrotizing enterocolitis (grade ≥ 2A Bell): ❒ no ❒ yes
Intraventricular hemorrhage (grade ≥ 3): ❒ no ❒ yes

Fetal karyotyping: ❒ no ❒ yes
Thoracocentesis: ❒ no ❒ yes
Transfusion: ❒ no ❒ yes
Inhaled Nitric Oxid: ❒ no ❒ yes
Sildenafil: ❒ no ❒ yes
Prostagladins: ❒ no ❒ yes
Amines: ❒ no ❒ yes
Antiarrhythmic: ❒ no ❒ yes
Diuretics: ❒ no ❒ yes
Surfactant: ❒ no ❒ yes
Antibiotics: ❒ no ❒ yes
Specific treatment: ❒ no ❒ yes
Extracorporeal Membrane Oxygenation: ❒ no ❒ yes
Parenteral Feeding: ❒ no ❒ yes
Conventional mechanical ventilation (>12h): ❒ no ❒ yes (duration ___ days)
Oxygen supplementation: ❒ no ❒ yes (duration ___ days)

Days at NICU: ____
Deceased: ❒ no ❒ yes
Autopsy: ❒ no ❒ yes