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Liliana Carvalho Teixeira

Perinatal hypoxic-ischemic encephalopathy: severity determinants and outcomes

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Área: Pediatria

Trabalho efetuado sob a Orientação de:
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E sob a Coorientação de:
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Perinatal hypoxic-ischemic encephalopathy: severity determinants and outcomes

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ABSTRACT

Perinatal hypoxic-ischemic encephalopathy (HIE) after perinatal asphyxia is one of the most critical pathologic conditions in neonatal medicine due to the potential for neurological sequelae in later life. The aim of our study is to identify the factors that are associated with a higher degree of severity in HIE and evaluate the outcomes. We performed a retrospective study of all newborns with HIE treated at our neonatal intensive care unit (NICU) from January 2010 to December 2013. Data collected include information about prenatal period, peripartum period, demographic characteristics, admission and evolution during NICU stay and outcomes (assessed in three different times: at discharge, at 6-9 months and 18 months). Forty seven newborns were enrolled in our study, 11 (23.4%) with mild HIE, 21 (44.7%) with moderate HIE and 15 (31.9%) with severe HIE. Prenatal, perinatal and demographic data showed no statistically significant differences between groups. Statistically significant differences were found in values of Thompson score ($p<0.0001$), abnormal aEEG/EEG at admission ($p=0.025$) and at 48 hours ($p=0.018$), need of mechanical ventilation ($p=0.004$), acute renal failure ($p=0.002$) and length of stay ($p=0.038$) with high rates in the moderate and severe HIE groups. Regarding the outcomes, statistically significant differences were found in the prevalence of death ($p=0.010$); need of antiepileptic drugs at discharge ($p=0.001$); motor deficits requiring physiotherapy ($p=0.046$), abnormal deep tendon reflex ($p=0.006$) and need of antiepileptic drugs ($p=0.001$) at 6-9 months follow-up; and cerebral palsy with cognitive impairment at 18 months ($p=0.041$) with high rates in the severe HIE group. These results suggest that Thompson score, abnormal aEEG/EEG at admission and at 48 hours, mechanical ventilation, acute renal failure and length of stay are associated with more severe HIE. We also concluded that more severe HIE reflect worse outcomes whereas mild HIE is associated with normal outcome in the majority of patients at 18 months.

Keywords: hypoxic-ischemic encephalopathy, perinatal asphyxia, newborn, follow-up, outcome, neurodevelopment

INTRODUCTION

Perinatal hypoxic-ischemic encephalopathy (HIE) is a syndrome of disturbed neurological function in the earliest days of life characterized by clinical and laboratory evidence of acute or subacute brain injury [1].

The most frequent cause of HIE in the neonatal period is perinatal asphyxia. All pathological conditions that lead to prenatal, perinatal, or postnatal hypoxia and tissue hypoperfusion are etiologic factors of HIE [2].

Perinatal HIE is associated with high morbidity and mortality rates worldwide, despite the improvements in perinatal care [3].

This condition occurs in 2-6/1000 live full-term births, reaching larger rates in developing countries [3, 4]. Approximately, 15%–20% of affected newborns will die in the postnatal period, and an additional 25% will develop severe and permanent neuropsychological sequelae, including cerebral palsy, mental retardation, learning difficulties, visual motor or visual perceptive dysfunction and epilepsy [5-7].

Brain injury associated with HIE involves a complex cascade of pathophysiologic mechanisms that occur in two energy failure phases. The interval between primary and secondary energy failure represents a latent phase that corresponds to a therapeutic window [5-10]. Therefore, to improve the care in perinatal HIE, it is necessary to focus on the period of time following the hypoxic-ischemic event, when the therapeutic strategies could be critical in the reduction of secondary neuron damage [8, 10].

Currently, the treatment options for HIE were largely supportive with prompt recognition and treatment of seizures, normalization of blood glucose levels, optimizing blood gases and blood pressure [11]. Recently, experimental and clinical studies have shown that treatment with prolonged moderate hypothermia reduces cerebral injury and thereby improves neurological outcomes [9, 12-20]. Despite the unequivocal therapeutic benefit of hypothermia, there is evidence that infants with the most severe forms of HIE will maintain a poor prognosis [17-19]. Other neuroprotective therapies used concurrently with hypothermia or even alternatively are then required. There are many potential treatments under investigation including biological mediators such as erythropoietin and melatonin, N-acetylcysteine, allopurinol, alpha-2 agonists and xenon gas [21].

As with any condition, identifying the factors that are associated with a high degree of severity in HIE is the key to developing preventive strategies.

The aim of our study is to identify the factors that are associated with a higher degree of severity in HIE and evaluate the outcomes according to the degree of severity of HIE.

METHODS

Authors performed a retrospective study of all newborns with HIE admitted at our center, a level III neonatal intensive care unit (NICU) between January 2010 and December 2013.
The inclusion criteria were clinical diagnosis of hypoxic-ischemic encephalopathy and gestational age ≥ 36 weeks.
The newborns included in this study were divided into three different groups according to the classification of Sarnat and Sarnat - mild, moderate and severe [22] done at admission in our NICU.
Data was collected from medical records and included information about individual characteristics of the mother and prenatal period (mother's age, complications during pregnancy such as diabetes mellitus, preeclampsia and cholestasis), peripartum period (rupture of membranes, cardiotocography tracing, acute intrapartum events, delivery method, Apgar score at first and fifth minute, reanimation and pH during first hour of life), demographic characteristics (gestational age, sex, birth weight, born inside/outside of our hospital) and admission and evolution during NICU stay (Thompson score [23] at admission in NICU, clinical or electric seizures during NICU stay, antiepileptic drugs, need of mechanical ventilation, inotropic support, antibiotics, complications like intracranial hemorrhage and acute renal failure – diagnosed as an increase of serum creatinine concentration (≥1.5 mg/dL,) and/or reduce of urine output (<0.5 mL/kg per hour), induced hypothermia protocol, length of stay and death). Since the induced hypothermia protocol was introduced in our NICU in October 2011, only newborns born after this date underwent to this treatment (if fulfill eligibility criteria).
Information about aEEG/EEG (admission and at 48 hours), cranial ultrasound (during the first five days of life with resistive index at admission) and MRI (second week of life) were also collected.
The aEEG/EEG background pattern was classified (in increasing severity) as described previously [24]: continuous normal voltage (CNV), discontinuous normal voltage (DNV), burst suppression (BS), low voltage (LV), and flat trace (FT). Seizures on aEEG were defined by an abrupt rise in the minimum and maximum amplitude, confirmed on raw EEG showing repetitive spikes or sharp wave activity with duration of at least 10 seconds.
Traces with CNV background and EEG seizures absent were classified as "normal." When EEG seizures were present or background activity was DNV, BS, LV, or FT the traces were classified as "abnormal" [25].
Cranial ultrasound performed in the first days of life was classified in: normal, general increase in echodensity of cerebral parenchyma (edema), increased periventricular echodensity and increased basal ganglia and/or thalami echodensity [26]. A color Doppler ultrasound was used to calculate resistive index. MRI scanner (T1, T2 and diffusion-weighted) was performed to document abnormal signal intensities within the basal ganglia and thalami, white matter, posterior limb of internal capsule, cortex, brainstem, and cerebellum. MRI was classified as: no lesions, mild lesions, moderate lesions and severe lesions [27].
The outcomes were assessed in three different times: at discharge, at 6-9 months and 18 months. Outcomes were evaluated by a multidisciplinary team using neurodevelopmental assessment tools and/or via medical interviews and physical examination. At discharge, the following aspects were evaluated: neurological examination, need of oxygen therapy, feeding skills and need of antiepileptic drugs. The assessment of 6-9 months has focused on neurological examination findings – motor deficits requiring physiotherapy and abnormal deep tendon reflex, need of antiepileptic drugs, ophthalmological examination, brainstem auditory evoked response (BAER) and presence or not of renal failure. At 18 months, a formal developmental assessment was performed using Mary Sheridan's developmental evaluation scale and Griffiths mental development scales in some infants. Based on the results of these scales the infants were divided into three groups: cerebral palsy with cognitive impairment, other neurodevelopmental disabilities (such as developmental delays in language skills and in controlling muscle movement - motor skills) and survival without neurological abnormality.
This study was approved by our institutional ethics committee and access to medical records was authorized by the office designated for this function. Data collection and statistical analysis

were performed with *IBM SPSS Statistics v.21* ®. Continuous variables were characterized by mean (± standard deviation) and median (medium-maximum) if they had symmetric or asymmetric distribution respectively and categorical variables by absolute and relative frequencies. To compare continuous variables we used parametric (One-way ANOVA test) or non-parametric (Kruskal Wallis test) tests if they had symmetric or asymmetric distribution respectively, and Mont Carlo test to compare categorical variables. A multivariate analysis by logistic regression (categorical variables) was performed. A p value less than 0.05 was considered statistically significant.

RESULTS

From 2010 to 2013, 47 newborns with the diagnosis of HIE and gestational age ≥ 36 weeks were admitted in our NICU and are enrolled in this study. Newborns were divided into three different groups: mild HIE (n=11, 23.4%), moderate HIE (n=21, 44.7%) and severe HIE (n=15, 31.9%). As newborns included in this study were born between 2010 and 2013, not all reached the minimum age for the assessment of 6-9 months and 18 months and some were lost during follow-up. Thus, 33 of the 47 newborns were evaluated at 6-9 months and 18 at 18 months.

The analysis of the prenatal, perinatal and demographic data showed no statistically significant differences between groups except for the mode of delivery (Table 1 and 2). In the mild HIE group, 45.5% of deliveries were vacuum assisted and 45.5% were C-section whereas in the severe HIE group 73.3% were C-section (p=0.041). Noteworthy that 65.5% of CTG tracing were suspicious (Table 2). Almost every newborns admitted to NICU showed an Apgar score at the first minute less than 6 (95.7%) and most remained with an Apgar score less than 6 at the fifth minute in moderate and severe HIE groups (71.4% and 80%, respectively (Table 2)). The mean pH measured during the first hour of life was less than 7 in all groups with no significant differences between them as well the type of reanimation techniques required (Table 2).

During the study period, 70.2% of the newborns underwent induced hypothermia protocol in the NICU (Table 3).

Thompson score on admission was evaluated in 34 newborns. The median for Thompson score was 4 for the mild HIE group, 8 for the moderate HIE group and 13.5 for the severe HIE group (p<0.0001) (Table 3).

Statistically significant differences were found in both the aEEG/EEG on admission and at 48 hours (Table 3). At admission aEEG/EEG was abnormal in 73.3% of the newborns in the moderate HIE group and in 66.7% in the severe HIE group (p=0.025), at 48 hours aEEG/EEG was abnormal mainly in severe HIE group (70%, p=0.018). When adjusted to induced hypothermia therapeutics, the newborns with severe HIE have a higher probability of exhibiting an abnormal aEEG/EEG at 48 hours (OR= 14, p=0.01). The presence of clinical or electrical seizures during NICU stay was higher in moderate and severe HIE groups (66.7% and 53.3%, respectively; p=n.s) (Table 3).

Cranial ultrasound performed in the first days of life revealed high intragroup variability concerning the different findings such as edema, increased echodensity of periventricular zone, thalamus and/or basal ganglia and no statistical differences were found. Nevertheless, in the severe HIE group all newborns had an abnormal cranial ultrasound (Table 3). The median of resistive index was similar between groups (Table 3). The MRI findings showed a high variability between groups**.** In severe HIE group, 75% of newborns had some kind of lesion on MRI, and severe lesions were mainly found in these newborns (Table 3). The prevalence of acute renal failure during the NICU stay was 46.7% in the severe HIE group vs 4.8% in the moderate HIE group (p=0.002) (Table 3). When adjusted to induced hypothermia therapeutics, the chance of acute renal failure occurrence during NICU stay in severe HIE group was higher (OR=17.33, p=0.013). Statistical differences were also found in the need of mechanical ventilation and length of stay with higher rates in moderate and severe HIE groups (p=0.004 and p=0.002, respectively) (Table 3).

The prevalence of death was 26.7% in the severe HIE group vs 0% in mild and moderate HIE groups (p=0.010) (Table 3). The other variables studied during evolution in NICU are summarized in Table 3.

In the short-term outcome (discharge), there were statistically significant differences between groups for the need of antiepileptic drugs and 45.5% of the newborns in the severe HIE group were discharged treated with antiepileptic drugs (p=0.001). There were no statistically significant differences between groups for the other outcomes at discharge (Table 4 – section discharge).

Assessment of the 6-9 months, differences were found between groups for motor deficits requiring physiotherapy (p=0.046), abnormal deep tendon reflex (p=0.006) and need of antiepileptic drugs (p=0.001) (Table 4 – section 6-9 months). When adjusted to induced

hypothermia therapeutics, the severe HIE group have a higher probability of having motor deficits requiring physiotherapy at 6-9 months (OR=14.34, p=0.027).

Regarding the outcomes assessed at 18 months, cerebral palsy with cognitive impairment was present only in the severe HIE group (50%, p=0.041) (Table 4 – section 18 months). The prevalence of other neurodevelopmental disabilities in mild HIE group was 14.3% and in moderate HIE group was 47.3% (p=0.381) (Table 4 – section 18 months). Most of infants in mild HIE group survived without neurological abnormalities (85.7%), although there were no significant differences between groups for this outcome (Table 4 – section 18 months).

DISCUSSION

Several risk factors have been associated with HIE such as: older maternal age, severe pre-eclampsia, peripartum fever, acute intrapartum event, meconium staining of amniotic fluid, non-spontaneous vaginal modes of delivery and male sex [28-32]. Indeed, most of these risk factors were found in our study population. However, the aim of our study was to determine the factors associated with the severity of HIE.

Our data showed statistically significant differences in the mode of delivery between the groups. In the mild HIE group most deliveries were C-section or vacuum assisted and in the severe HIE group most were C-section, whereas in the moderate HIE group one third were vaginal deliveries. The final mode of delivery is determined by the delivery plan and response to intrapartum events. Although there is a significant difference between the groups regarding the type of delivery, this doesn't mean that a particular type of delivery is associated with more severe HIE. In our study, prenatal, perinatal and demographic data showed no differences between groups (except mode of delivery as mentioned previously), which demonstrated that all these variables are not associated with more severe HIE. Regardless of the severity of HIE, Apgar scores at 1st and 5th minutes are similar between the groups as well as the pH in the 1st hour of life and reanimation techniques required during the first minutes of life. The severity was associated with abnormalities found on neurological examination, demonstrated by values of the Thompson score progressively higher as the severity increases (mild group – 4, moderate group – 8, severe group – 13.5; $p<0.0001$). This could be explained based on fact that Thompson score contains many of the features included in the three stages of Sarnat and Sarnat [23].

In term infants, aEEG/EEG is a good method for evaluating cerebral function and cerebral recovery after hypoxic-ischemic event such as perinatal asphyxia [33]. In our study, abnormal aEEG/EEG at admission was mainly found in moderate and severe HIE groups and at 48 hours most of newborns with moderate HIE had a normal aEEG/EEG. This possibly means that these newborns had a cerebral recovery during the first 48 hours of life. In the other hand, newborns with severe HIE remained with an abnormal aEEG/EEG at 48 hours of life.

Other factor associated with severe HIE, in this study, was acute renal failure. In fact, several studies have shown that severity of renal function abnormality correlates well with degree of asphyxia [34, 35]. The need of mechanical ventilation and longer length of stay were also associated with more severe HIE.

A recent systematic review shows that alterations on MRI performed at the end of the first week or the beginning of the second week of life are evident in 75%–100% of patients with HIE [36]. However, in our study, most of the newborns with severe HIE had alterations on MRI (75%) and severe lesions were mainly found in these newborns.

Regarding outcomes, adverse outcomes are particularly associated with the severe HIE group and this association remains when adjusted for induced hypothermia. All deaths in our study occurred during NICU stay and all in the severe HIE group. Cerebral palsy with cognitive impairment at 18 months was also found only in the severe HIE group. At 18 months, 47.3% of infants in moderate HIE group have some degree of neurodevelopmental disability but none developed cerebral palsy with cognitive impairment, in mild HIE group almost of infants survived without neurological abnormalities. Our results are similar to those found in the literature, i.e. more severe HIE reflect worse outcomes and mild HIE is associated with normal outcome in the majority of patients at 18 months [37]. The short follow-up period is a limitation of this and many other studies of outcomes after HIE. There is emerging evidence that confirm a high prevalence of subtle impairment in children who escape severe disabling conditions after HIE, which only becomes apparent at school age [38]. There is a need for longer-term follow up of infants in order to collect more accurate information on more minor degrees of neurological dysfunction.

HIE continues to be a significant source of morbidity and mortality among newborn infants, and the effects of this injury are broad. Actually, induced hypothermia is the standard of care in HIE. Nevertheless, an adjunctive therapy or therapies to use along with hypothermia are an immensely attractive area of study and could potentially benefit infants.

The major limitation of our study consists in its design. As it is a retrospective study, it mainly relies on information from medical records, with possible inaccuracies and loss of data**.** Another limitation is related to the fact that not all newborns were evaluated at 6-9 months and at 18 months because not all reached the minimum age for the assessment and some were lost during follow-up.

CONCLUSION

In this study, none of prenatal, perinatal and demographic data showed association with severe HIE. The severity of HIE was determined mainly by abnormalities found on neurological examination, demonstrated by values of the Thompson score progressively higher as the severity increases. Abnormal aEEG/EEG at admission and at 48 hours, acute renal failure, need of mechanical ventilation and longer length of stay were also associated with more severe HIE. Regarding outcomes, our results are similar to those found in the literature, i.e. more severe HIE reflect worse outcomes whereas mild HIE is associated with normal outcome in the majority of patients at 18 months.

DECLARATION OF INTEREST

The authors declare that there is no conflict of interest

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Table 1 – Demographic data

	Total (n = 47)	Mild HIE (n = 11)	Moderate HIE (n = 21)	Severe HIE (n = 15)	p
Male sex, n (%)	27 (57.4)	5 (45.5)	11 (52.4)	11 (73.3)	0.363*
Gestational age (wk), mean ± SD	39.36 ± 1.32	39.09 ± 1.30	39.48 ± 1.25	39.40 ± 1.50	0.616§
Birth weight (g), median (min-max)	3310 (1896-4320)	3300 (2250-4320)	3400 (2360-4020)	3230 (1896-4020)	0.521¥
Outborn, n (%)	27 (57.4)	4 (36.4)	11 (52.4)	12 (80)	0.080*

* Monte Carlo test, § One Way ANOVA test, ¥ Kruskal Wallis test

Table 2 – Prenatal and perinatal data

	Total (n = 47)	Mild HIE (n = 11)	Moderate HIE (n = 21)	Severe HIE (n = 15)	p
Maternal age (years), median (min-max)	32 (18-42)	32 (18-40)	33 (21-42)	29 (18-41)	0.476[¥]
Pregnancy complications, n (%)	1 (2.1)	0 (0)	0 (0)	1 (6.7)	
Pre-eclampsia	4 (8.5)	0 (0)	3 (14.3)	1 (6.7)	0.684[*]
Gestational diabetes	1 (2.1)	0 (0)	1 (4.8)	0 (0)	
Cholestasis					
ROM > 18h, n (%)	7 (14.9)	1 (10)	6 (31.6)	0 (0)	0.051[*]
CTG, n (%)					
Normal	6 (20.7)	3 (42.9)	2 (16.7)	1 (10)	
Suspicious	19 (65.5)	5 (57.1)	8 (66.7)	7 (70)	0.620[*]
Pathological	4 (13.8)	0 (0)	2 (16.7)	2 (20)	
Acute intrapartum events, n (%)					
Peripartum fever	6 (12.8)	1 (9.1)	3 (14.3)	2 (13.3)	0.908[*]
Meconium staining of AF	16 (34)	2 (18.2)	10 (47.6)	4 (26.7)	0.240[*]
Nuchal cord	8 (17)	2 (18.2)	5 (23.8)	1 (6.7)	0.482[*]
Placental abruption	6 (12.8)	2 (18.2)	1 (4.8)	3 (20)	0.345[*]
Uterine rupture	2 (4.3)	0 (0)	1 (4.8)	1 (6.7)	0.700[*]
Delivery, n (%)					
Vaginal	9 (19.1)	0 (0)	7 (33.3)	2 (13.3)	
Vacuum assisted	14 (29.8)	5 (45.5)	7 (33.3)	2 (13.3)	**0.041[*]**
Forceps assisted	1 (2.1)	1 (9.1)	0 (0)	0 (0)	
C-section	23 (48.9)	5 (45.5)	7 (33.3)	11 (73.3)	
Apgar score 1st min, n (%)					
0-6	45 (95.7)	11 (100)	19 (90.5)	15 (100)	0.495[*]
7-10	2 (4.3)	0 (0)	2 (9.5)	0 (0)	
Apgar score 5th min, n (%)					
0-6	33 (70.2)	6 (54.5)	15 (71.4)	12 (80)	0.387[*]
7-10	14 (29.8)	5 (45.5)	6 (28.6)	3 (20)	
pH – 1st hour, mean ± SD	6.94 ± 0.15	6.95 ± 0.15	6.99 ± 0.12	6.88 ± 0.17	0.132[§]
Reanimation					
PPV	41 (89.1)	9 (81.8)	18 (90)	14 (93.3)	0.706[*]
ETI	32 (69.6)	5 (45.5)	15 (75)	12 (80)	0.163[*]
Chest compressions	8 (17.4)	2 (18.2)	2 (10)	4 (26.7)	0.477[*]
Drugs	6 (13)	1 (9.1)	1 (5)	4 (26.7)	0.213[*]

ROM: rupture of membranes; CTG: cardiotocography; AF: amniotic fluid; PPV: positive pressure ventilation; ETI: endotracheal intubation

[*] Monte Carlo test, [§] One Way ANOVA test, [¥] Kruskal Wallis test

Table 3 – Admission and evolution in NICU

	Total (n = 47)	Mild HIE (n = 11)	Moderate HIE (n = 21)	Severe HIE (n = 15)	p
Thompson score, median (min-max)	9 (2-16)	4 (2-15)	8 (4-13)	13.5 (10-16)	**<0.0001**[¥]
aEEG/EEG abnormal – admission, n (%)	23 (69.7)	2 (28.6)	11 (73.3)	10 (66.7)	**0.025**[*]
aEEG/EEG abnormal – 48h, n (%)	10 (33.3)	1 (16.7)	2 (14.3)	7 (70)	**0.018**[*]
Seizures, n (%)	25 (53.2)	3 (27.3)	14 (66.7)	8 (53.3)	0.102[*]
Antiepileptic drugs, n (%)	24 (51.1)	3 (27.3)	13 (61.9)	8 (53.3)	0.186[*]
Cranial ultrasound, n (%)					
Normal	7 (17.1)	4 (36.4)	3 (16.7)	0 (0)	
Edema	16 (39)	2 (18.2)	8 (44.4)	6 (50)	
Increased echodensity of periventricular zone	7 (17.1)	4 (36.4)	2 (11.1)	1 (8.3)	0.069[*]
Increased echodensity of thalamus and/or basal ganglia	11 (26.8)	1 (9.1)	5 (27.8)	5 (41.7)	
Resistive index , median (min-max)	0.65 (0.40-0.80)	0.62 (0.56-0.79)	0.66 (0.52-0.80)	0.66 (0.40-0.80)	0.992[¥]
MRI, n (%)					
Normal	16 (44)	2 (40)	11 (57.9)	3 (25)	
Mild lesions	7 (19.4)	1 (20)	4 (21.1)	2 (16.7)	0.377[*]
Moderate lesions	7 (19.4)	1 (20)	3 (15.8)	3 (25)	
Severe lesions	6 (16.7)	1 (20)	1 (5.3)	4 (33.3)	
MV, n (%)	35 (74.5)	4 (36.49)	17 (81)	14 (93.3)	**0.004**[*]
TPN, n (%)	38 (80.9)	8 (72.7)	18 (85.7)	12 (80)	0.648[*]
Inotropic support, n (%)	18 (38.3)	2 (18.2)	7 (33.3)	9 (60)	0.090[*]
Antibiotics, n (%)	46 (97.8)	10 (90.9)	21 (100)	15 (100)	0.228[*]
Induced hypothermia, n (%)	33 (70.2)	3 (27.3)	17 (81)	13 (86.7)	**0.003**[*]
Sepsis, n (%)	3 (6.4)	0 (0)	2 (9.5)	1 (6.7)	0.742[*]
Intracranial hemorrhage, n (%)	4 (8.5)	0 (0)	3 (14.3)	1 (6.7)	0.542[*]
Acute renal failure, n (%)	8 (17)	0 (0)	1 (4.8)	7 (46.7)	**0.002**[*]
Length of stay, median (min-max)	9 (1-39)	5 (1-12)	10 (3-26)	9 (1-39)	**0.038**[¥]
Death, n (%)	4 (8.5)	0 (0)	0 (0)	4 (26.7)	**0.010**[*]

MRI: magnetic resonance imaging; MV: mechanical ventilation; TPN: total parental nutrition
[*] Monte Carlo test, [¥] Kruskal Wallis test

Table 4 – Outcomes assessed at discharge, at 6-9 months and at 18 months

OUTCOME	Total (n = 43)	Mild HIE (n = 11)	Moderate HIE (n = 21)	Severe HIE (n = 11)	p
DISCHARGE					
Abnormal neurological examination, n (%)	10 (23.3)	1 (9.1)	4 (19.0)	5 (45.5)	0.159*
Oxygen need, n (%)	1 (2.1)	0 (0)	1 (4.8)	0 (0)	0.870*
Without feeding skills, n (%)	10 (23.3)	2 (18.2)	3 (14.3)	5 (45.5)	0.193*
Antiepileptic drugs, n (%)	6 (14)	1 (9.1)	0 (0)	5 (45.5)	**0.001***
	Total (n = 33)	**Mild HIE (n = 9)**	**Moderate HIE (n = 17)**	**Severe HIE (n = 7)**	**p**
6-9 MONTHS					
Motor deficits requiring physiotherapy, n (%)	14 (42.5)	3 (33.3)	5 (29.4)	6 (85.7)	**0.046***
Abnormal deep tendon reflex, n (%)	3 (10)	0	0	3 (50)	**0.006***
Seizures, n (%)	3 (9.1)	1 (11.1)	0 (0)	2 (28.7)	0.058*
Antiepileptic drugs, n (%)	5 (15.2)	1 (11.1)	0 (0)	4 (57.1)	**0.001***
Abnormal BAER, n (%)	2 (10.5)	1 (16.7)	1 (11)	0 (0)	0.417*
Abnormal ophthalmological examination, n (%)	1 (5.3)	0 (0)	0 (0)	1 (50)	0.108*
Renal failure, n (%)	1 (6.3)	0 (0)	1 (5.6)	1 (14.3)	0.440*
	Total (n = 18)	**Mild HIE (n = 7)**	**Moderate HIE (n = 7)**	**Severe HIE (n = 4)**	**p**
18 MONTHS					
Cerebral palsy with cognitive impairment, n (%)	2 (11.1)	0 (0)	0 (0)	2 (50)	**0.041***
Other neurodevelopmental disabilities, n (%)	4 (22.2)	1 (14.3)	3 (47.3)	0 (0)	0.381*
Survival without neurological abnormality, (%)	12 (66.7)	6 (85.7)	4 (57.1)	2 (50)	0.539*

BAER: brainstem auditory evoked response
* Monte Carlo test

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ANEXOS

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