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Original article

Neonatal encephalopathy beyond hypoxic-ischemic etiology: experience of a Level III Neonatal Intensive Care Unit in the last decade

Rita Gomes[1], Bebiana Sousa[1], Liliana Teixeira[2], Liliana Pinho[2], Ana Novo[2], Carmen Carvalho[2], Elisa Proença[2]

[1]Department of Pediatrics, Centro Materno-Infantil do Norte, Centro Hospitalar Universitário do Porto (CHUPorto), Porto, Portugal

[2]Neonatal Intensive Care Unit, Department of Neonatology and Pediatric Intensive Care, Centro Materno-Infantil do Norte, Centro Hospitalar Universitário do Porto (CHUPorto), Porto, Portugal

Abstract

Neonatal encephalopathy (NE) is a condition of neurologic dysfunction with heterogeneous severity. The terms hypoxic-ischemic encephalopathy (HIE) and NE are often used interchangeably, although the differential diagnosis is vast. We aimed to evaluate the etiologies behind NE in newborns (NB) treated with therapeutic hypothermia (TH) for a presumed diagnosis of HIE.

A retrospective analysis between January 2012 and July 2020 was conducted. Demographic data, information regarding pre- and perinatal factors, systemic dysfunction parameters, neuroimaging and neurologic sequelae were collected. A comparative analysis between the group considered with hypoxic-ischemic versus non-hypoxic-ischemic NE was performed.

Forty-six NB were included. HIE was confirmed in 29 (63.0%) patients (group 1). There was no evidence of perinatal asphyxia in 17 (37.0%) patients (group 2). In the latter group, intracranial hemorrhage was the most frequent etiology (7; 15.2%), followed by infection (5; 10.9%). In group 1, there was a higher prevalence of emergency cesarean section ($p = 0.013$), clinical seizures at admission ($p = 0.048$) and a higher encephalopathy severity ($p = 0.027$). In this group, amplitude-integrated electroencephalogram improvement at 48 hours of TH was less frequent ($p = 0.027$) and major neurologic sequelae were more prevalent at 12 ($p = 0.006$) and 24 months ($p = 0.041$).

HIE was the main cause of NE. Despite the clinical overlap, clinicians should recognize other etiologic factors beyond anoxic events. Our findings might help to prospectively differentiate between HIE and NE from different etiologies early after birth, ideally prior to initiation of TH, in the future.

Keywords

Infant, newborn, encephalopathy, therapeutic hypothermia, hypoxic-ischemic encephalopathy.

Corresponding author

Rita Gomes, Department of Pediatrics, Centro Materno-Infantil do Norte, Centro Hospitalar Universitário do Porto (CHUPorto), Largo do Professor Abel Salazar, 4099-001, Porto, Portugal; tel.: +351914723308; email: ritagomesmoreira02@gmail.com.

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Introduction

Neonatal encephalopathy (NE) is a heterogenous condition of neurologic dysfunction occurring in the first days of life, with an estimated incidence of 2 to 6 per 1,000 live births [1, 2]. The clinical manifestations range from mild irritability and feeding difficulties to altered level of consciousness, tone and reflexes, seizures, respiratory insufficiency and multiorgan failure [3]. NE can be reversible or indicative of permanent cerebral dysfunction and is a major predictor of death and long-term disability [1].

The terminology NE is not specific to the underlying condition. The etiology is variable and clinical overlap may occur [3]. NE that is caused by an intrapartum event leading to perinatal asphyxia has historically been called hypoxic-ischemic encephalopathy (HIE) [1]. Other causes include vascular, infectious, toxic-related, genetic/congenital, metabolic and epileptic conditions. However, the etiology remains unexplained in approximately half of the cases [1, 3, 4]. HIE is the most common cause, accounting for 15% to 35% of cases and occurring in approximately 1.5 per 1,000 term births [2, 4-6].

Evaluation should be tailored based on the clinical scenario, but it includes laboratory workup, neuroimaging and neurophysiologic monitoring to help determine both etiology and prognosis [3]. Brain monitoring using continuous video-electroencephalogram (EEG) or, if not available, amplitude-integrated EEG (aEEG) is important to evaluate electrocortical activity as well as the presence of seizures, since clinical evaluation alone is unreliable [7]. Magnetic resonance imaging (MRI) is the imaging modality of choice [1, 8]. A distinctive pattern of injury can be seen for HIE compared to other causes of NE, but there are no specific alterations and it is crucial to consider the timing of image acquisition relative to the presumed injury [3]. The pattern of injury in HIE depends on the severity, duration, and repetitiveness of the hypoxia-ischemia and can lead to basal ganglia, thalami, brain stem, and/or cerebral white matter involvement in different combinations [9]. An MRI performed between 24 and 96 hours of life provides the most useful guide on the potential timing of a cerebral insult, but cerebral abnormalities will become most evident after 7 days from a cerebral injury. Ideally, 2 MRI scans should be performed: the first on day 2 to 4 of life to assist in clinical management and evaluation of the timing of cerebral injury, and a second on day 10 or later to assist with full delineation of the nature and extent of cerebral injury. However, cranial ultrasonography may be the only neuroimaging modality able to be obtained in the first hours of life of an unstable infant [3, 8].

Neonates with encephalopathy should be cared for by experienced professionals at a Neonatal Intensive Care Unit (NICU) of a tertiary hospital. At the moment, in addition to supportive intensive care, therapeutic hypothermia (TH) is the only validated treatment and the standard of care for term or late preterm newborns (NB) with HIE [1, 10, 11]. Multiple trials have demonstrated its safety and efficacy in improving outcomes if initiated within the first 6 hours of life and maintained for 72 hours, being associated with reduced death and disability [1, 12]. A few clinical trials support the hypothesis that early postnatal allopurinol may improve outcome in infants with evolving HIE [13-15]. More recent investigations that have examined adjuvant therapies, such as erythropoietin and stem cells, are showing promising results, though the results of larger multicenter trials are still pending [16-21].

The terms NE and HIE have been used interchangeably. Some authors state that when an

asphyxia etiology is not apparent the diagnosis of HIE is not justified and the more general term NE should be used, allowing the investigation and treatment of other conditions not to be hindered [10, 22, 23]. The use of the terms "presumed HIE" or "apparent HIE" has been proposed for those NB that have clinical features and brain injury patterns on MRI suggestive of an anoxic mechanism, since there are no specific biomarkers or imaging alterations for HIE and the exact pathogenesis is often unknown [1, 10, 23].

All neonates included in this study underwent treatment with TH for a presumed HIE diagnosis within the immediate postnatal period. We tried to retrospectively confirm the initial diagnosis of HIE or realize if there was a more accurate alternative diagnosis, based on the perinatal factors, clinical course and complementary exams. The aims were to evaluate the prevalence of the different etiologies of NE in this sample and to perform a comparative analysis between the group of neonates with confirmed hypoxic-ischemic versus non-hypoxic-ischemic NE.

Methods

Study design and sample

We conducted an observational retrospective study by analyzing patients' clinical records. All NB treated with TH for a presumed HIE diagnosis, between January 2012 and July 2020, at our tertiary NICU were included. Patients in whom an alternative diagnosis was found were excluded from this study.

Data collection and variable definition

Demographic data (neonate's age and sex, mother's age), maternal medical history (diseases and medications) and obstetrics background (gestational age, single or multiple pregnancy, fetal anomalies, suspected chorioamnionitis) and prenatal conditions (threatened preterm delivery, oligohydramnios, gestational diabetes, premature or prolonged rupture of membranes, hypertension, bleeding, anemia, decreased fetal movements, fetal bradycardia/tachycardia) were collected. Type of delivery, anatomopathological exam of the placenta and peripartum factors (placental rupture, anterior placenta, uterine rupture, cardiotocographic changes including sustained fetal bradycardia, decelerations and low variability, meconium-stained amniotic fluid and meconium aspiration, umbilical cord prolapse, umbilical cord knot, shoulder dystocia, maternal shock) were also reviewed. Data relative to the immediate postnatal period was also analyzed, namely birth weight, Apgar scores at 1st, 5th and 10th minutes and need for advanced resuscitation for more than 10 minutes.

Blood acid-base balance, rectal temperature and clinical seizures at admission to NICU were reviewed. Both clinical seizures and aEEG features suggestive of seizures were considered during TH. The severity of encephalopathy was based on clinical assessment at admission using the Thompson score (mild 0-10, moderate 11-14, severe ≥ 15) [24]. Analytical evidence of infection (leukocytosis/leukopenia, thrombocytopenia, C-reactive protein elevation and positive blood cultures) was reviewed. Abnormal findings detected on cranial ultrasound were considered at admission and after TH. Changes in aEEG pattern were evaluated at admission, at 48 hours and after TH. Imaging findings from the first MRI performed were also considered. Systemic dysfunction parameters during TH (persistent pulmonary hypertension, bradycardia, hypotension, need for inotropic support and ventricular dysfunction, kidney injury, hepatic dysfunction, thrombocytopenia and coagulation alterations or hemorrhagic dyscrasia) were also reviewed. Multiorgan dysfunction was considered when at least two organ systems were involved. Length of hospital stay and number of deaths was also recorded. The presence of major neurologic sequelae (motor dysfunction including cerebral palsy, global developmental delay, severe visual and hearing impairment and epilepsy) was evaluated at 12 and 24 months of follow-up. When an MRI was performed at 12 and 24 months of follow-up, imaging alterations were reviewed.

To categorize the etiology as hypoxic-ischemic we looked for any of the following: neonatal signs consistent with an acute peripartum or intrapartum event (Apgar score ≤ 5 at 5 and 10 minutes, fetal umbilical artery pH < 7.0, base deficit ≥ 12 mmol/L, multisystem organ failure consistent with HIE); a sentinel event occurring immediately before or during labor and delivery associated with consistent fetal heart rate monitor patterns; suggestive neuroimaging alterations on brain MRI. Sentinel event was defined as a serious pathologic event, including the following: ruptured uterus, placental abruption, umbilical cord prolapse, amniotic fluid embolus, maternal cardiovascular collapse and fetal exsanguination [8].

We divided the total sample into two subgroups: group 1, which includes neonates that displayed anoxic lesions on MRI or who presented a clinical course suggestive of HIE and had no evidence of an alternative diagnosis; group 2, which encompasses neonates in whom we considered a cause for encephalopathy other than hypoxic-ischemic.

Therapeutic hypothermia protocol

According to the Portuguese neonatal recommendations, all neonates born at ≥ 36 week's gestation who revealed at least 1 criterion suggestive of asphyxia (Apgar score ≤ 5 at 10 minutes; need for advanced resuscitation at 10 minutes; pH < 7.0 in the first hour of life; base deficit ≥ 16 mmol/L in the first hour of life) and presented with seizures or moderate to severe encephalopathy (defined as altered level of consciousness, tonus, reflexes or respiratory autonomy) were eligible for TH. All neonates were monitored with aEEG during treatment with TH and during rewarming. Cranial ultrasound was performed at admission, within the first 24 hours of life, on the 3rd-4th day of life and on the day of the brain MRI (7th-10th day of life). Whenever possible, otoacoustic emissions and ophthalmologic evaluation were performed before discharge. After discharge, follow-up was ensured by a multidisciplinary team (neonatologists, neuropediatricians, developmental-behavioral pediatricians, ophthalmologists, otorhinolaryngologists and physiatrists) [25].

Ethics

This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration. The study was approved by the Ethics Committee of Centro Hospitalar Universitário do Porto and Institute of Biomedical Sciences Abel Salazar. In line with recent normative, the requirement to obtain informed consent was waived for this study [26].

Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics 25.0. Categorical variables were expressed as frequency and percentage, and continuous variables were expressed as median and percentiles 25 and 75. Comparison between groups was established through Pearson's Chi-square and Fisher exact tests, Kruskal Wallis and logistic regression models. A p-value of less than 0.05 was considered as statistically significant.

Results

The sample baseline characterization is described in **Tab. 1**. A total of 50 patients underwent TH during the previously mentioned period and were analyzed. Four were excluded from this study because the alternative diagnosis of sudden unexpected postnatal collapse was considered (full-term NB with Apgar scores of at least 8 that suddenly collapsed during the first hours of life due to cardiorespiratory arrest).

After reviewing clinical files, we assumed the diagnosis of HIE in 29 (63.0%) patients (group 1). There was no evidence of perinatal asphyxia in 17 (37.0%) patients (group 2). In the latter group, intracranial hemorrhage was the most frequent finding (7; 15.2%), followed by infection (5; 10.9%) and hypovolemic shock (2; 4.3%). One patient was diagnosed with a metabolic disease, 1 had a stroke and 1 remained idiopathic.

A first brain MRI was performed in 44 patients (95.7%) on average on the 7th day of life (SD 2.37; minimum 3, maximum 16 days). There was evidence of hypoxic-ischemic lesions in 20 (45.5%) and 12 (27.3%) were normal. All 29 patients from group 1 had performed a brain MRI, 6 of them being normal. Regarding imaging reevaluation at 12 months of follow-up, a brain MRI was performed in 12 out of 36 (33.3%) and 3 revealed alterations suggestive of a prior hypoxic-ischemic lesion (2 of them had evidence of hypoxic-ischemic lesions on the initial MRI and 1 showed a small peak of lactates on spectroscopy). At 24 months, a brain MRI was performed in 2 out of 29 (6.9%), 1 being normal and the other showing periventricular leukomalacia.

The results of the comparative analysis between NB from groups 1 and 2 are displayed in **Tab. 2**. Eight patients (27.6%) from group 1 died, whilst only 2 neonates (11.8%) from group 2 had this outcome. In group 1 there was a higher prevalence of emergency cesarean section (p = 0.013) and clinical seizures at admission (p = 0.048). A higher Thompson score at admission was also found in this group (OR = 1.2; p = 0.019). With regards to severity, there was a significant difference between the groups, with the majority of patients from group 1 having moderate or severe encephalopathy (31.0% and 48.3%, respectively), whilst most patients from group 2 had mild encephalopathy.

Table 1. Sample baseline characterization (n = 46) (continues on the next page).

Male		26 (56.5%)
Maternal age, years		30 (26-34)
Maternal diseases		17 (37.0%)
Fetal anomalies (n = 44)		8 (18.2%)
Twin pregnancy (n = 44)		2 (4.5%)
Suspected chorioamnionitis		17 (37.0%)
Anatomopathological placental exam (n = 22)	**Normal**	9 (40.9%)
	Chorioamnionitis	8 (36.4%)
	Funisitis	7 (31.8%)
	Other alterations	4 (18.2%)
Gestational age, weeks		39 (38, 40)
Type of birth (n = 44)	**Vaginal delivery**	5 (11.4%)
	Vacuum delivery	10 (21.7%)
	Forceps delivery	2 (4.5%)
	Cesarean section	6 (13.6%)
	Emergency cesarean section	23 (50.0%)
Prenatal conditions		17 (37.0%)
Peripartum factors		37 (80.4%)
Birth weight, grams		3,152.5 (2,895, 3,503)
Apgar scores	**1st minute**	2 (0, 3)
	5th minute	4 (2, 5)
	10th minute	5 (4, 6)
Advanced resuscitation > 10 minutes		9 (22.0%)
Acid-base balance during the 1st hour of life	**pH**	6.90 (6.80-6.99)
	Base excess	-21.00 (-24.20, -18.00)
Rectal temperature at admission		33.8 (33.2, 34.4)
Clinical seizures at admission		31 (67.4%)
Thompson score at admission		12.5 (8.8, 17.0)
Hours of life at the beginning of TH hours		5.5 (4.5, 6.5)
Encephalopathy severity	**Mild**	16 (34.8%)
	Moderate	13 (28.3%)
	Severe	17 (37.0%)
aEEG at admission (n = 45)	**Normal**	5 (11.1%)
	Epileptic activity with normal baseline	2 (4.4%)
	Burst suppression	27 (60.0%)
	Moderately abnormal	10 (22.2%)
	Suppressed	1 (2.2%)
aEEG at 48 hours of TH	**Normal**	24 (52.2%)
	Epileptic activity with normal baseline	1 (2.2%)
	Burst suppression	6 (13.0%)
	Moderately abnormal	8 (17.4%)
	Suppressed	4 (8.7%)
	Status epilepticus	1 (2.2%)
Cranial ultrasound at admission (n = 43)	**Normal**	2 (4.7%)
	Signs of cerebral edema	37 (86.1%)
	Brain parenchyma alterations	36 (83.7%)
	Blood flow alterations	7 (16.3%)
Seizures (n = 44)	**Clinical**	25 (56.8%)
	Electrical	28 (63.6%)
Thompson score after TH		8.0 (5.5, 14.0)
aEEG or EEG after TH (n = 44)	**Normal**	12 (27.3%)
	Burst suppression	8 (18.2%)
	Focal paroxysmal activity	6 (13.6%)
	Multifocal paroxysmal activity	17 (38.6%)
	Discontinuities during NREM sleep	4 (9.1%)

Table 1. Sample baseline characterization (n = 46) (continues from the previous page).

Cranial ultrasound after TH (n = 41)	**Normal**	7 (17.1%)
	Signs of cerebral edema	23 (56.1%)
	Brain parenchyma alterations	33 (80.5%)
	Blood flow alterations	3 (7.3%)
Organ failure	**Persistent pulmonary hypertension**	7 (15.2%)
	Bradycardia	10 (21.7%)
	Hypotension	20 (43.5%)
	Kidney injury	24 (52.2%)
	Hepatic dysfunction	17 (37.0%)
	Ventricular dysfunction	22 (47.8%)
	Need for inotropic support	28 (60.9%)
	Thrombocytopenia	21 (45.7%)
	Coagulation alterations or hemorrhagic dyscrasia	14 (30.4%)
Analytical evidence of infection		24 (52.2%)
Positive blood culture (n = 45)		2 (4.4%)
MRI (n = 44)	**Normal**	12 (27.3%)
	Hemorrhage	10 (22.7%)
	Ischemia	2 (4.50%)
	Anoxic/hypoxic-ischemic	20 (45.5%)
Length of hospital stay, days		11.0 (8.8, 15.0)
Mortality		10 (21.7%)
Major neurologic sequelae at 12 months of follow-up (n = 36)		15 (41.7%)
Major neurologic sequelae at 24 months of follow-up (n = 29)		14 (48.3%)

Data is presented as number (n), n (percentage; %), median (25^{th}, 75^{th} percentile: P25, P75), as appropriate.
aEEG: amplitude-integrated electroencephalogram; EEG: electroencephalogram; MRI: magnetic resonance imaging; NREM sleep: non-rapid eye movement sleep; TH: therapeutic hypothermia.

Table 2. Comparative analysis between neonates from groups 1 and 2 (n = 46).

Variable		**Group 1: HIE (n = 29 [63.0%])**	**Group 2: non-HIE (n = 17 [37.0%])**	**p-value**
Maternal diseases		11 (37.9%)	6 (35.3%)	0.761
Prenatal conditions		13 (44.8%)	4 (23.5%)	0.499
Peripartum factors		24 (82.8%)	13 (76.5%)	0.140
Suspected chorioamnionitis		10 (34.5%)	7 (41.2%)	0.755
Sentinel events		24 (82.8%)	9 (52.9%)	**0.044**
Delivery mode	**Vaginal delivery**	2 (6.9%)	3 (17.6%)	**0.013**
	Vacuum delivery	4 (13.8%)	6 (35.3%)	
	Forceps delivery	0 (0.0%)	2 (11.8%)	
	Cesarean section	4 (13.8%)	2 (11.8%)	
	Emergency cesarean section	19 (65.5%)	4 (23.5%)	
Clinical seizures at admission		23 (79.3%)	8 (47.1%)	**0.048**
Thompson score at admission		14 (11-17)	9 (7-12.5)	**0.019 OR = 1.2**
Encephalopathy severity	**Mild**	6 (20.7%)	10 (58.9%)	**0.027**
	Moderate	9 (31.0%)	4 (23.5%)	
	Severe	14 (48.3%)	3 (17.6%)	
aEEG normalization at 48 hours of TH (n = 40 [a])		10 (47.6%)	11 (52.4%)	**0.027**
Multiple organ failure		19 (65.5%)	12 (70.5%)	0.520
Mortality		8 (27.6%)	2 (11.8%)	0.282
Major neurologic sequelae at 12 months (n = 36)		13 (61.9%)	2 (13.3%)	**0.006**
Major neurologic sequelae at 24 months (n = 29)		11 (64.7%)	3 (25.0%)	**0.041**

Data is presented as number (n), n (percentage; %) and median (25^{th}-75^{th} percentile, P25-P75).
[a] There was information regarding aEEG at admission in 45 patients and regarding aEEG at 48 hours of TH in all (46) patients; 40 newborns had alterations on aEEG at admission: among these, the analysis regarding aEEG normalization at 48 hours of TH was performed.
aEEG: amplitude-integrated electroencephalogram; HIE: hypoxic-ischemic encephalopathy; OR: odds ratio; TH: therapeutic hypothermia.

All patients from group 2 who presented with severe encephalopathy were diagnosed with infection. Patients from group 1 showed a less frequent aEEG improvement at 48 hours ($p = 0.027$) and a higher prevalence of major neurologic sequelae at 12 ($p = 0.006$) and 24 months ($p = 0.041$). There were no statistically significant differences regarding maternal conditions, risk factors for neonate infection, multiple organ failure and mortality.

Discussion

Few studies have evaluated risk factors for NE other than hypoxia-ischemia, and many of the existing epidemiologic studies lack brain MRI data and information regarding long-term outcomes. We aimed to evaluate the etiologies of NE in NB treated with TH for a presumed diagnosis of HIE. We compiled a constellation of data concerning neonatal status, contributing events and developmental outcomes in order to retrospectively determine if they were consistent with HIE or realize that there was a more accurate alternative diagnosis.

Despite the clinical overlap, clinicians should be aware of the extensive differential diagnosis since it is extremely important to distinguish HIE as a subcategory of NE. If clinicians fail to identify a sentinel event, it is less likely that the aberrant clinical neurologic findings are secondary to HIE and a diligent search for other etiologies is essential [27]. There are still knowledge gaps that preclude a definite test or set of markers that accurately identifies an infant in whom NE is attributable to an acute intrapartum event. Therefore, it is essential to perform a comprehensive evaluation of neonatal status and all potential contributing factors, identify treatable causes and ensure optimal management and better prognostic outcome [8].

As expected, HIE was the main cause of NE in our sample, with a higher prevalence than that described in previous studies [2, 4, 28]. This discrepancy can be explained since only NB who were treated with TH were included in our study. NB with milder forms of encephalopathy who did not undergo treatment with TH and those who presented with altered neurologic status after the first days of life were not included in our study, which may have led to a selection bias.

All NB in whom the diagnosis of HIE was retrospectively confirmed (group 1) had performed an MRI. Despite presenting criteria for HT, no abnormal findings were found in 6, presumably because it was performed precociously (mean of 6 days of life; minimum 5, maximum 8 days) or because timely initiation of HT prevented the onset of brain damage. Retrospectively reviewing the 46 NB treated with TH, there was no evidence of perinatal asphyxia in 17 (37.0%) patients (group 2). In this group, intracranial hemorrhage was the most frequent finding. Of the 7 neonates with intracranial hemorrhage, 6 had an instrumental delivery; 5 had mild encephalopathy, and among these only 1 had in fact a clear indication for TH; the other 2 presented moderate encephalopathy and had clinical seizures, which is the presenting symptom in the majority of neonates with intracranial hemorrhage, and did in fact meet criteria for TH [3].

Infection should always be considered as a cause of NE [3]. An infectious cause was seen in 5 patients, 2 of whom had positive blood cultures for group B *Streptococcus*. All had multiorgan dysfunction, and 2 died within the first 3 days of life. Regarding placental histology, 2 had evidence of both chorioamnionitis and funisitis and 1 was normal. It should be noted that placental examination was performed in only 22 (47.8%) patients. Since it reflects the intrauterine environment, it could help to clarify the underlying etiology and guide clinical management [27]. However, in our experience, the results are only available between day 7 and 10 of life in the majority of cases.

Although hypovolemic shock can be a potential cause of neonatal asphyxia, this diagnosis was considered individually, due to its specific treatment. In this series, one case concerns a twin pregnancy complicated with feto-fetal transfusion. The other was a neonate with a history of delivery complicated by placental abruption who presented with disseminated intravascular coagulation and multisystemic bleeding. Retrospectively, none of them met the criteria for TH. Metabolic disorders and stroke are less frequent causes of NE, which is in line with our results [1, 3]. Only 1 patient remained idiopathic.

As described in the literature, the presence of a sentinel event was associated with a higher probability of HIE. Previous studies that examined risk factors for HIE have shown indirect intrapartum factors associated with HIE, such as abnormal fetal heart tracings, prolonged rupture of membranes, a tight nuchal cord, shoulder dystocia, thick meconium or a failed vacuum delivery [4, 8, 29]. Our results suggest that a

greater impairment of cerebral activity, translated by a higher Thompson score, the presence of seizures and non-recovery of the aEEG pattern at 48 h, was associated with a higher probability of HIE. Additionally, encephalopathy severity, evaluated by the Thompson score at admission, was significantly higher in the HIE group. These findings might be helpful in clinical practice when deciding to pursue additional evaluation and specific management within the first hours and days of life.

NE is associated with high morbidity and mortality rates, and infants with moderate to severe encephalopathy are more likely to develop long-term neurologic morbidity. While prognosis has improved since the widespread use of TH, outcomes remain suboptimal for those who survive and who are at risk for long-term disabilities, including cerebral palsy, epilepsy, cognitive impairment and developmental delay [30-32]. Predictors of unfavorable outcomes include a higher severity of encephalopathy, EEG abnormalities, refractory seizures and evidence of moderate to severe injury on MRI [1, 11, 33]. Possibly as a consequence of the greater impairment of brain electrocortical activity, neonates from group 1 had a higher prevalence of major neurologic sequelae at 12 and 24 months of follow-up. This finding highlights the importance of the follow-up being undertaken in an experienced tertiary center by a multidisciplinary team for at least the first 24 months.

We acknowledge some limitations in our study, including the small sample size, the selection bias and the absence of a control group which limits drawing inferences from our results. Some strengths should also be noted: to our knowledge, there are only a few studies that tried to categorize the different etiologies of NE; we used a precise definition of NE and a standardized approach that did not change throughout the study period; this study was performed at a NICU of a tertiary reference center; we reviewed information regarding an 8-year experience and a 2-year follow-up period, which is a considerable period of time; finally, unlike other studies, brain MRI information was taken into account in the diagnostic classification.

In conclusion, NE with indication for TH is relatively frequent in NICU. Etiologic categorization has been remarkably under-investigated, although it could allow the development of targeted adjunctive therapies and preventive strategies. The terms NE and HIE should not be used interchangeably. Our findings might help to prospectively differentiate between HIE and NE from different etiologies early after birth, ideally prior to initiation of TH, in the future. However, more studies are needed to evaluate clinical, analytical and imaging markers of HIE. Given the risk of long-term disability, follow-up in an experienced center is essential. Long-term large prospective multicenter studies of infants with NE stratified by etiology are necessary to fully understand pathogenic mechanisms, to compare the response to hypothermia and long-term outcomes, in order to allow the establishment of recommendations.

Abbreviations

aEEG: amplitude-integrated electroencephalogram
EEG: electroencephalogram
HIE: hypoxic-ischemic encephalopathy
MRI: magnetic resonance imaging
NB: newborns
NE: neonatal encephalopathy
NICU: Neonatal Intensive Care Unit
NREM sleep: non-rapid eye movement sleep
OR: odds ratio
TH: therapeutic hypothermia

Declaration of interest

The Authors have no conflict of interest to declare.

References

1. Glass HC. Hypoxic-Ischemic Encephalopathy and Other Neonatal Encephalopathies. Contin Lifelong Learn Neurol. 2018;24:57-71.
2. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev. 2010;86:329-38.
3. Russ JB, Simmons R, Glass HC. Neonatal Encephalopathy: Beyond Hypoxic-Ischemic Encephalopathy. Neoreviews. 2021;22:e148-62.
4. Nelson KB, Bingham P, Edwards EM, Horbar JD, Kenny MJ, Inder T, Pfister RH, Raju T, Soll RF. Antecedents of neonatal encephalopathy in the Vermont Oxford Network Encephalopathy Registry. Pediatrics. 2012;130:878-86.
5. Thornberg E, Thiringer K, Odeback A, Milsom I. Birth asphyxia: incidence, clinical course and outcome in a Swedish population. Acta Pædiatr. 1995;84:927-32.
6. Smith J, Wells L, Dodd K. The continuing fall in incidence of hypoxic-ischaemic encephalopathy in term infants. BJOG. 2000;107: 461-6.
7. Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello JJ, Abend NS, Nguyen S, Wusthoff CJ, Clancy RR. The American clinical neurophysiology society's guideline on continuous

electroencephalography monitoring in neonates. J Clin Neurophysiol. 2011;28:611-7.
8. American Academy of Pediatrics. Statement of Endorsement. Neonatal Encephalopathy and Neurologic Outcome, Second Edition. Pediatrics. 2014;133(5):e1482-8.
9. Volpe JJ. Neonatal encephalopathy: An inadequate term for hypoxic-ischemic encephalopathy. Ann Neurol. 2012;72:156-66.
10. Molloy EJ, Bearer C. Neonatal encephalopathy versus Hypoxic-Ischemic Encephalopathy. Pediatr Res. 2018;84:574.
11. Martinello K, Hart AR, Yap S, Mitra S, Robertson NJ. Management and investigation of neonatal encephalopathy: 2017 update. Arch Dis Child Fetal Neonatal Ed. 2017;102: F346-58.
12. Gunn AJ, Thoresen M. Neonatal encephalopathy and hypoxic-ischemic encephalopathy. Handb Clin Neurol. 2019;162:217-37.
13. Benders MJ, Bos AF, Rademaker CM, Rijken M, Torrance HL, Groenendaal F, van Bel F. Early postnatal allopurinol does not improve short term outcome after severe birth asphyxia. Arch Dis Child Fetal Neonatal Ed. 2006;91(3):F163-5.
14. Van Bel F, Shadid M, Moison RM, Dorrepaal CA, Fontijn J, Monteiro L, Van De Bor M, Berger HM. Effect of allopurinol on postasphyxial free radical formation, cerebral hemodynamics, and electrical brain activity. Pediatrics. 1998;101:185-93.
15. Gunes T, Ozturk MA, Koklu E, Kose K, Gunes I. Effect of Allopurinol Supplementation on Nitric Oxide Levels in Asphyxiated Newborns. Pediatr Neurol. 2007;36(1):17-24.
16. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013;2013(1):CD003311.
17. Lee CYZ, Chakranon P, Lee SWH. Comparative Efficacy and Safety of Neuroprotective Therapies for Neonates With Hypoxic Ischemic Encephalopathy: A Network Meta-Analysis. Front Pharmacol. 2019;10:1221.
18. Wu YW, Mathur AM, Chang T, McKinstry RC, Mulkey SB, Mayock DE, Van Meurs KP, Rogers EE, Gonzalez FF, Comstock BA, Juul SE, Msall ME, Bonifacio SL, Glass HC, Massaro AN, Dong L, Tan KW, Heagerty PJ, Ballard RA. High-dose erythropoietin and hypothermia for hypoxic-Ischemic encephalopathy: A phase II trial. Pediatrics. 2016;137(6):e20160191.
19. Juul SE, Comstock BA, Heagerty PJ, Mayock DE, Goodman AM, Hauge S, Gonzalez F, Wu YW. High-Dose Erythropoietin for Asphyxia and Encephalopathy (HEAL): A Randomized Controlled Trial-Background, Aims, and Study Protocol. Neonatology. 2018;113:331-8.
20. Serrenho I, Rosado M, Dinis A, Cardoso CM, Grãos M, Manadas B, Baltazar G. Stem cell therapy for neonatal hypoxic-ischemic encephalopathy: A systematic review of preclinical studies. Int J Mol Sci. 2021;22(6):3142.
21. Perrone S, Lembo C, Gironi F, Petrolini C, Catalucci T, Corbo G, Buonocore G, Gitto E, Esposito SMR. Erythropoietin as a Neuroprotective Drug for Newborn Infants: Ten Years after the First Use. Antioxidants. 2022;11(4):652.
22. Nelson KB. Is it HIE? And why that matters. Acta Paediatr. 2007;96:1113-4.
23. Dammann O, Ferriero D, Gressens P. Neonatal encephalopathy or hypoxic-ischemic encephalopathy? Appropriate terminology matters. Pediatr Res. 2011;70:1-2.
24. Thompson CM, Puterman AS, Linley LL, Hann FM, van der Elst CW, Molteno CD, Malan AF. The value of a scoring system for hypoxic ischaemic encephalopathy in predicting neurodevelopmental outcome. Acta Paediatr. 1997;86:757-61.
25. Graça AM, Pinto F, Vilan A, Dinis A, Sampaio I, Matos C, Rodrigues M, Neves F. Consenso nacional – Hipotermia induzida no tratamento da encefalopatia hipóxico-isquémica neonatal. Available at: https://www.spneonatologia.pt/wp-content/uploads/2016/11/2012-Hipotermia.pdf, date of publication: 2012, last access: 2022.
26. Manti S, Licari A. How to obtain informed consent for research. Breathe. 2018;14:145-52.
27. Wiswell TE. Evaluation for the etiology of neonatal encephalopathy and the diagnosis of FIRS. Semin Fetal Neonatal Med. 2020;25:101140.
28. Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, Pemberton PJ, Stanley FJ. Antepartum risk factors for newborn encephalopathy: The Western Australian case-control study. Br Med J. 1998;317:1549-53.
29. Martinez-Biarge M, Diez-Sebastian J, Wusthoff CJ, Mercuri E, Cowan FM. Antepartum and intrapartum factors preceding neonatal hypoxic-ischemic encephalopathy. Pediatrics. 2013;132(4):e952-9.
30. Finer NN, Robertson CM, Richards RT, Pinnell LE, Peters KL. Hypoxic-ischemic encephalopathy in term neonates: Perinatal factors and outcome. J Pediatr. 1981;98:112-7.
31. Levene ML, Kornberg J, Williams THC. The incidence and severity of post-asphyxial encephalopathy in full-term infants. Early Hum Dev. 1985;11:21-6.
32. Van Handel M, Swaab H, De Vries LS, Jongmans MJ. Long-term cognitive and behavioral consequences of neonatal encephalopathy following perinatal asphyxia: A review. Eur J Pediatr. 2007;166:645-54.
33. Committee on Fetus and Newborn; Papile LA, Baley JE, Benitz W, Cummings J, Carlo WA, Eichenwald E, Kumar P, Polin RA, Tan RC, Wang KS. Hypothermia and neonatal encephalopathy. Pediatrics. 2014;133:1146-50.