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Prospective Research in Infants with Mild Encephalopathy (PRIME) Identified in the First Six Hours of Life: Neurodevelopmental Outcomes at 18-22 Months

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Abstract

Background: Studies of early childhood outcomes of mild hypoxic-ischemic encephalopathy (HIE) identified in the first 6 hours of life are lacking.

Objective: To evaluate neurodevelopmental outcomes at 18–22 months of PRIME study.

Study design: Multicenter, prospective study of mild HIE defined as ≥1 abnormality using the modified Sarnat within 6h of birth and not meeting cooling criteria. Primary outcome was disability with *Mild*: Bayley III cognitive 70–84 or ≥ 85 **and** either Gross Motor Function Classification System (GMFCS) 1 or 2, seizures, or hearing deficit; *Moderate*: cognitive 70–84 and either GMFCS 2, seizures, or hearing deficit; *Severe:* cognitive < 70, GMFCS 3–5.

Results: Of the 63 infants enrolled, 51 (81%) were evaluated at 19 ± 2 months and 43 (68%) completed Bayley III. Of the 43 infants, 7 (16%) were diagnosed with disability including 1 cerebral palsy and 2 autism. Bayley scores <85 in either cognition, motor, or language were detected in 17 (40%): 14 (32%) language, 7 (16%) cognitive, and 6 (14%) motor domain. Infants with disability had more abnormalities on discharge examination and brain MRI, with longer hospital stay (p<0.001).

Conclusions: In this contemporary untreated cohort of mild HIE, disability occurred in 16% of infants at 18–22 months.

Neonatal hypoxic-ischemic encephalopathy (HIE) remains an important cause of neurodevelopmental impairment and death.[1] While newborns with moderate and severe HIE have been the focus of neuroprotective trials utilizing hypothermia therapy, infants with mild HIE usually have been excluded due to a perceived low risk of death or major disability based on data from the pre-hypothermia era.[2–7] In the original description of the Sarnat scores [8], neonatal encephalopathy following asphyxia was determined based on serial clinical evaluations and electroencephalographic signals during the first week of age. In the current era of therapeutic hypothermia, the assessment of encephalopathy has changed to a more focused neurological examination (i.e. modified Sarnat score) performed within the first six hours of age with or without the use of the amplitude-integrated EEG (aEEG) due to a narrow therapeutic window. This short time window is particularly challenging to identify and define mild HIE. Recent reports suggest that infants with mild HIE may have hypoxic-ischemic injury detected on brain magnetic resonance imaging (MRI) and higher rates of disability at 5 years when compared to historical controls.[9–12] Knowledge gaps remain to be addressed regarding the definition of mild HIE within 6 hours and the need of contemporary prospective studies using current psychometric tools such as the Bayley Scales of Infant and Toddler Development III.[13, 14]

We have reported short-term abnormalities in 52% of infants with mild HIE identified in the first 6 hours after birth and enrolled in the Prospective Research on Infants with Mild

Encephalopathy (PRIME) study.(15) The primary aim of this current study was to describe the neurodevelopmental outcomes of these infants at 18–22 months and associations between neonatal variables and outcomes.

Methods

Study design and population

PRIME was a multicenter, international, observational cohort study conducted from December 2012 to October 2015 (NCT01747863) that started with four and extended to six academic centers (McGill University Health Center, Montreal, Canada; University of Texas Southwestern Medical Center, Dallas, Texas; Brown University, Providence, Rhode Island; Wayne State University, Detroit, Michigan; London Imperial College, London, UK; Mahidol University, Bangkok, Thailand). As previously published (14), newborns were eligible for enrollment in the first 6 hours of age if they were 36 weeks' gestational age, had severe perinatal acidosis or received delivery room resuscitation as defined by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (3), and had abnormalities consistent with mild HIE on the modified Sarnat examination performed by a certified examiner (Table 1).(3)

Mild HIE was defined within 6 hours of age as the presence of any (1) abnormality in any of the six categories of the modified Sarnat scoring system in infants that did not meet the NICHD criteria for cooling, i.e. 3 categories as moderate or severe. Exclusion criteria included the inability to enroll at 6 hours of age, presence of a major congenital abnormality, severe growth restriction (birth weight <1800 g), hypothermia therapy instituted at 6 hours of age, or a completely normal neurological examination. The Institutional Review Board of each center approved the study and written informed consent was obtained from parents.

Study procedures and data collection

All infants enrolled were treated according to the standard of care of each center and none of them received therapeutic hypothermia. As previously published, the short-term outcomes of PRIME were any abnormality on: early aEEG (< 9h of age) or clinical seizures, brain MRI < 30 days of age, or neurological exam at NICU discharge or transfer. The aEEG was recorded for 60 min. aEEG background patterns were classified by two blinded examiners. An abnormal aEEG was defined by the presence of non-continuous background pattern (discontinuous normal voltage = DNV, burst suppression = BS, continuous low voltage = CLV, or flat tracing = FT).(16–18)

MRI studies were obtained without sedation before discharge (T1 and T2 weighted sequences and diffusion weighted images) and were scored by an independent pediatric neuroradiologist blinded to the clinical outcomes and using the NICHD scoring (19, 20): $0 =$ normal MRI; $1a =$ minimal cerebral lesions only with no involvement of basal ganglia and thalami (BGT), anterior limb of the internal capsule (ALIC), posterior limb of the internal capsule (PLIC), or watershed (WS) infarction; $1b =$ more extensive cerebral lesions only with no involvement of BGT, ALIC, PLIC, or WS infarction; $2a =$ any BGT, ALIC, PLIC, or

WS infarction noted without any other cerebral lesions; *2b* = involvement of either BGT, ALIC, PLIC, or area of infarction and additional cerebral lesions; and *3* = cerebral hemispheric devastation.

The standardized neurological exam was performed by certified investigators at   6 h of age, 24 ± 6 h of age, and as close as possible to NICU discharge/transfer. The physical examination at discharge/transfer consisted of an extended exam which included the modified Sarnat and the following items: gag reflex, clonus, fisted hands, abnormal movement, and persistent asymmetric tonic neck reflex (ATNR) which has been reported to be associated with abnormal outcomes in asphyxiated newborns.(21)

Neurodevelopmental outcomes

Infants were evaluated at 18 to 22 months of age with a detailed neurological examination performed by trained examiners to establish the diagnosis of cerebral palsy (CP). The Gross Motor Function Classification System (GMFCS) was used to classify the functional motor impairment (22, 23): a) Level 1 = walk but gait is not fluent; b) Level 2 = unable to walk but can sit on his/her own, creep or crawl and may pull to stand and take steps holding on to furniture; c) Level 3 = require low back support for sitting, can roll and creep and may crawl, d) Level 4 = head control present but requires trunk support for sitting; and e) Level 5 = requires adult assistance to roll. Psychometric testing was performed by one trained psychometrician at each site, blinded to the clinical details of the children, and included the Bayley III cognitive, language, and motor evaluations (mean = 100 [SD 15]; cognitive scale range = 55–155, language range = 45–155, and motor range = 46–154).(23) Additional subscales in language (expressive and receptive) and motor scores (fine and gross) also were done. The English version of the Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®) III was administered at all sites except at McGill University. The French version was administered by one bilingual psychometrician per standard practice at McGill when French was the primary language. Data on growth, vision, and hearing were obtained from history and medical records. Families of those who did not return for follow-up were contacted by telephone with a scripted interview form to screen for neurological problems, seizures, developmental delay, hearing loss, or blindness.

The primary outcome was any disability at 18–22 months of age as defined by the NICHD Neonatal Research Network (24, 25) and determined as: a) <u>Mild</u>: cognitive score of 70–84 alone, or a cognitive score   85 and GMFCS Level 1 or 2, seizure disorder (without antiepileptic medication), or hearing deficit with ability to follow commands without amplification; b) <u>Moderate</u>: cognitive score from 70–84 and GMFCS Level 2, active seizure disorder (receiving anti-epileptic medication), or hearing deficit with the ability to follow commands after amplification; and c) <u>Severe</u>: cognitive score < 70, GMFCS Level 3–5, blindness, or hearing impairment with inability to follow commands in spite of amplification.

Secondary exploratory outcomes included the individual domains of the Bayley III scores (cognitive, language, or motor scores), CP, GMFCS, vision and hearing, as well as exploratory analysis of the associations between early neonatal variables and disability.

Statistical analysis

Data were described as mean ± standard deviation, number (%) or median [interquartile range, IQR] where appropriate. The neurodevelopmental outcomes assessed at 18–22 months of age were further categorized as "no disability" or "any disability," whether the latter was mild, moderate, or severe. Comparisons between these two groups were made with Fisher's Exact or Cochran Armitage trend tests for categorical variables and Student t-tests for continuous variables. Analysis was conducted with SAS 9.4 (SAS Institute, Cary, NC) and a two-sided pvalue of < 0.05 was considered statistically significant.

Results

Of the 63 infants enrolled, 51 (81%) were examined for neurodevelopmental outcomes at a mean age (±SD) of 19 ± 2 months and 43 (68%) completed the Bayley III evaluations (Figure 1). There were no differences in maternal and perinatal characteristics between infants with complete follow-up at 18–22 months and those with limited (n=8) or no follow-up (n=12; Table 2). Of the 8 infants with limited follow-up (Figure 1), 5 had a neurological exam done at the follow-up visit but the Bayley III could not be completed and another 3 had telephone scripted interviews. This allowed exclusion of CP, developmental delays, seizures, hearing loss, or blindness in 81% of the cohort. The remaining 12 infants were lost to follow-up due to relocation.

Primary outcome.

Among the 43 infants who completed the neurodevelopmental assessment, 7 (16%) were diagnosed with disability (Table 3a): 4 (9%) mild and 3 (7%) severe. None of the infants died or had vision or hearing impairments or seizures. Details of the initial neurological examination and outcomes of the infants who developed disability are described in Table 3b. Of the 3 infants with severe disability, one had CP (mixed type) with a GMFCS Level = 4, and 2 others were diagnosed with autism spectrum disorder (ASD). The 2 ASD cases also had a Bayley III composite motor score <70. The diagnosis of ASD was confirmed subsequently by a developmental health care specialist at 36 months of age.

Secondary outcomes.

Bayley scores < 85 occurred in 17 (40%) infants: language = 14 (33%), cognitive = 7 (16%), and motor = 6 (14%) (Table 3a). None of the infants with Bayley scores < 85 had only one abnormal Sarnat category on neurological examination at < 6 hours of age, and none had three moderate or severe categories needed to institute hypothermia therapy. Their neurological examination in the first six hours consisted of a combination of mild and moderate scores (Table 1) involving multiple categories, with a median of 3 abnormal categories (range, 2– 6). Five infants had isolated language scores < 85, and their early examination showed only mild abnormalities in 2 categories. Bayley scores < 70 occurred in 4 infants (9%): 3 (7%) in all domains and 1 (2%) in the language domain only. The remaining 26 infants (60%) had Bayley scores > 85.

The evolution of individual abnormalities on the serial Sarnat scores during the nursery hospitalization in infants with disability and without any disability at 18–22 months is

presented on Figure 2. A higher percentage of abnormalities affecting most categories of the neurological examination were noted on the discharge examination in the group with disability at 18–22 months (highest percentage of abnormalities were in tone, followed by spontaneous activity and level of consciousness).

Infants with disability were therefore significantly more likely to have persistent abnormalities on the neurological exam performed at discharge (5/7, 71%) when compared to infants without disability (6/36, 17%; p=0.01). Of note, the exam trends overall improved after 24 hours, except for 1 infant in the disability group who had clinical seizures diagnosed at 36 h of life but at discharge had a Sarnat score of 1. Other factors associated with disability in the exploratory analyses (Table 4) were lower level of maternal education, abnormal MRI at < 30 days (43% vs. 17%; p=0.04), and longer hospitalization (14 [8–19] vs. 4 [2–6] days; median [IQR], p=0.003). There were no statistically significant differences in Apgar scores at 5 and 10 minutes, blood gas analysis within 1 hour after birth, or outborn status (43% vs. 61%). The median time of MRI performance was 12 days in both groups of infants with or without disability. Also, the time of the initial neurological examination was similar in infants with or without disability (4 ± 1 h). No genetic or metabolic syndromes or other confounding diagnosis were observed in any of the infants diagnosed with disability.

Discussion

This contemporary prospective observational multicenter study reports the 18 to 22 months neurodevelopmental outcomes of infants with mild HIE diagnosed at < 6 hours of age and not treated with therapeutic hypothermia. Key findings were an overall rate of disability of 16%, of which 7% were classified as severe. Any Bayley III cognitive, motor, or language score < 85 was noted in 40% of the infants with the most commonly affected being the language domain, while Bayley motor score < 70 was seen in four (9%) infants. In an exploratory analysis, we observed that infants with disability at 18–22 months were more likely to have abnormal brain MRI findings at < 30 days of age, abnormal neurological examinations at discharge/transfer (mostly an abnormal tone), and longer hospitalization when compared to infants without disability, characterizing a higher risk group of infants within our mild HIE cohort.

The PRIME 18–22 months outcomes are timely, as national and international registries have reported a consistent shift in therapeutic hypothermia practice to include mild HIE. The change in practice is attributed to reports of abnormal short-term outcomes, yet there are no contemporary studies reporting the long-term efficacy of hypothermia in the mild HIE population.(26, 27) Indeed, a recent survey in the United Kingdom demonstrated that 75% of centers are offering hypothermia for infants with mild HIE, with significant variability in cooling practices.(28)

Before therapeutic hypothermia was established as the standard of care, death or major disability were not reported to occur in infants with mild HIE.(2–7) Subsequent follow-up of some of these cohorts at 9–10 years of age revealed that IQ was slightly lower (98.1±12.3) when compared to controls (109.0±12.0).(29) Subtle language and behavioral problems were also noted. However, definitions of mild HIE in these early studies were based on serial

Sarnat examinations during the first week of life. Furthermore, these studies were performed before implementation of Bayley III Scales of Infant Development and used varied definitions of impaired gas exchange precluding direct comparisons with the current investigation. The diagnosis of neonatal encephalopathy requires training and the neurological status might change over time. Despite the above mentioned clinical confounders and the differences in study design, a recent systematic review of mild HIE has reported abnormal neurological outcomes in 25% of infants.(13) Abnormal outcomes were defined as CP or any standardized neurodevelopmental test score > 1 standard deviation below the mean.

To facilitate comparisons with contemporary moderate to severe HIE litterature, we elected to apply the same definition of disability used by recent therapeutic hypothermia trials performed by the NICHD Neonatal Research Network.(24–25) The definition uses solely the cognitive scores of the Bayley III thereby mitigating any possible bias in language scores that could occur in multilingual settings.(30) However, the observed high incidence (33%) of Bayley language scores < 85 in the present study needs further study and follow-up. Evidence of mild disability may be more easily identified at school age or later, further emphasizing the importance of long-term follow-up among infants with mild HIE. Unexpectedly, 2 infants in this cohort were diagnosed with autism spectrum disorder (ASD). Similarly, a large Australian cohort reported 5% of ASD in 239 HIE survivors (31), but a comprehensive meta-analysis demonstrated inconclusive evidence that exposure to perinatal conditions could increase the risk of ASD.(32, 33) These observations if replicated in other HIE cohorts would merit further investigation.

A higher rate of abnormal neurological exam at discharge was observed in the group of infants with disability compared to those without. Interestingly, an abnormal tone was the most commonly affected component of the discharge exam. This study of mild HIE identified in the first 6 hours correlates short-term outcomes such as abnormal brain MRI findings at < 30 days of age, lower level of maternal education, longer length of hospitalization, and abnormal neurological examination at discharge with disability at 18–22 months.

Since this study has a small sample size, associations should be interpreted with caution. Other study limitations include a higher than desired loss to follow-up, despite the academic centers' experience in dealing with follow-up attrition. To mitigate concerns of bias, we compared the neonatal characteristics of infants with and without complete follow-up and performed neurological exam and/or phone interviews in another 8 infants, tracking a total of 51 (81%) of the 63 enrolled patients. Such knowledge of the status of these 51 infants made it unlikely that any had a disability and thus, the overall estimated rate of disability would be 14%. However, it also is posible that the rate of disability was under-estimated due to difficulties in measuring the true cognitive ability at the age of 2 years. Indeed, another cohort study (20032005) that defined mild HIE based on full channel EEG performed at 6 hours also reported normal neurodevelopmental outcomes at 24 months in all infants with mild HIE.(34) However, the same group of investigators reported that when infants were assessed at 5 years of age, lower IQ scores (median, IQR) were seen in infants with mild HIE (99 [94–112]) when compared to historical controls (117 [110–124]).(10) The gap

between intact infants and those with developmental problems may widen over time due to improved detection suggesting that unrecognized disability may be greater than documented at 2 years of age.(35) This discrepancy is likely related to the improved diagnostic ability to detect academic delays and subtle cognitive problems at the older ages.

Given the lack of a uniform consensus on how best to classify mild HIE within the limited 6 hours after birth, the study investigators used the NICHD uniform screening of all infants with an acute perinatal event, fetal acidosis, and any neurological abnormality on the modified Sarnat score that did not qualify for cooling. The mild HIE definition used in this study included a broad spectrum of infants who did not meet evidence-based cooling criteria, and was uniformly applied across all sites in the first six hours after birth by centrally trained examiners. Using this contemporary definition of mild HIE in the first six hours, a mix of mild and moderate scores in multiple Sarnat categories was observed in all infants who had any Bayley score <85. This information, although based on exploratory analysis, could be useful in planning future trials of neuroprotection.

Despite the limitations, the PRIME study fills important knowledge gaps regarding the prospective outcomes of mild HIE infants diagnosed at < 6 h of age with a contemporary followup at 18–22 months of age. Other study strengths include the use of blinded central readers to evaluate the brain MRIs and standardized neurodevelopmental outcomes using Bayley III.

In conclusion, the PRIME multicenter cohort study demonstrated that 16% of infants with mild HIE diagnosed at < 6 hours of age had disability at 18–22 months of age. Furthermore, a Bayley III score < 85 that mostly affected the language component was observed in 40% of the whole cohort, highlighting the need for long-term follow-up of this population. Large multicenter trials will be required to test whether abnormal neurodevelopmental outcomes can be mitigated by neuroprotective strategies in mild HIE infants. Hence, the PRIME prospective contemporary uncooled cohort provides important data needed for planning of these trials which should include larger populations and long-term evaluations of neurodevelopmental outcomes up to 6–7 years of age.

Acknowledgements:

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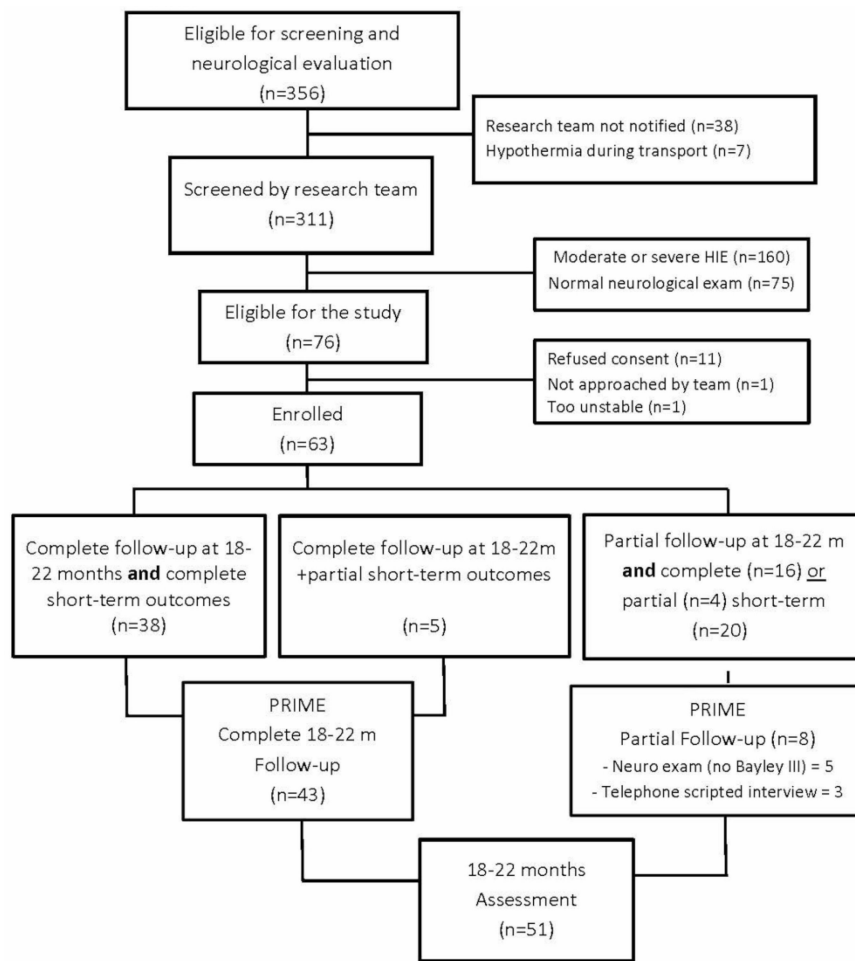
Figure 1.
Flowchart of infants enrolled in PRIME. 5 Infants had incomplete Bayley evaluations and 12 (19%) infants were completely lost to follow up.
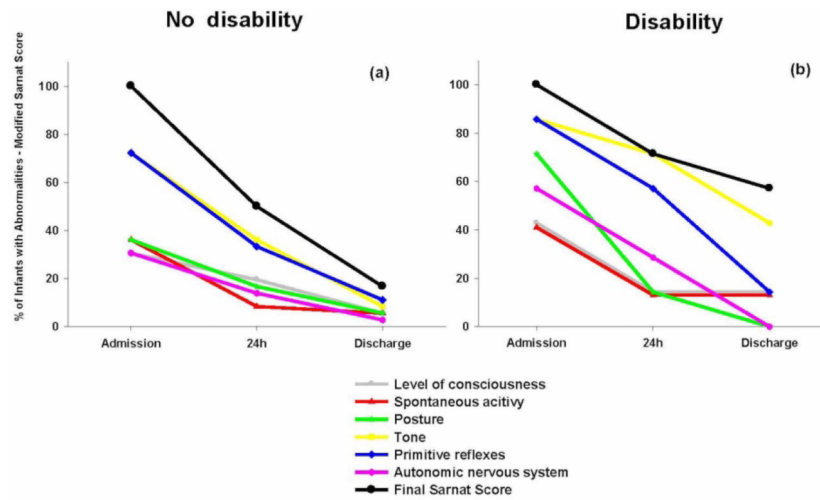
Figure 2.
Evolution of neonatal examination among infants with mild HIE with (2a) and without disability at 18–22 months (2b). The % of infants with Sarnat abnormalities is plotted on the y axis, while serial exams are plotted on x axis: in the first 6 hours, at 24 hours and at discharge.

Table 1.

Modified Sarnat scoring system for categorizing encephalopathy.

Each of the six main categories is assigned a score based on severity (0–3). When findings are common or overlapped in a category (Spontaneous activity and Suck overlap for mild and moderate HIE), the score assigned is one that corresponds to the level of consciousness.

Category	Normal (0)	Mild(1)	Moderate (2)	Severe(3)
Level of consciousness	Alert(responsive to external stimuli)	Hyper-alert (responsive to minimal stimuli)	Lethargic	Stupor/Coma
Spontaneous activity	Normal	Normal or decreased	Decreased	None
Posture	Predominantly flexed	Mild flexion of distal joints	Distal flexion or complete extension	Decerebrate
Tone	Strong flexor tone in all extremities	Normal or slightly increased	a. Hypotonia (focal or general)	Flaccid
			b. Hypertonia	Rigid
Primitive reflexes				
Suck	Strong, easily illicit	Weak or Incomplete	Weak or incomplete and/or bite	Absent
Moro	Complete	Intact (low threshold)	Incomplete	Absent
Autonomic Nervous System (ANS)				
Pupils	Normal	Mydriasis	Myosis	Variable or Nonreactive
Heart rate	100–160 bpm	Tachycardia	Bradycardia	Variable
Respirations	Regular respirations	Hyperventilation	Periodic breath	Apnea or need ventilation

Table 2.

Maternal and perinatal characteristics of the PRIME cohort.

	Complete Follow-up 18–22m (n=43)	Incomplete Follow-up (n=20)
Maternal Characteristics		
Race		
Black	5 (12)	6 (30)
White (non-Hispanic)	19 (44)	4 (20)
Other	19 (44)	10 (50)
High school graduate	36 (84)	14 (70)
Hypertension	1 (2)	2 (10)
PPROM >18 hours	7 (16)	3 (15)
Maternal pyrexia	4 (9)	1 (5)
Chorioamnionitis	4 (9)	3 (15)
Antepartum hemorrhage	4 (9)	3 (15)
Abnormal fetal heart rate	34 (79)	14 (70)
Meconium-stained amniotic fluid	21 (49)	10 (50)
Umbilical cord accidents	2 (5)	0
Shoulder dystocia	2 (5)	0
Cesarean delivery	22 (51)	9 (45)
Perinatal Characteristics		
Gestational age, weeks	39.5 ± 1.4	39.7 ± 1.4
Birth weight, grams	3386 ± 534	3148 ± 667
Male	25 (58)	15 (75)
Delivery room resuscitation		
Intubation	19 (44)	6 (30)
Epinephrine	1 (2)	0
Chest compression	6 (14)	2 (10)
Apgar scores		
1 minute	2 [1–3]	2 [1–4]
5 minutes	6 [3–6]	5 [3–7]
Umbilical cord blood - pH	7.0 ± 0.1	7.0 ± 0.2
Umbilical cord blood - base deficit, mmol/L	13 ± 5	14 ± 7
1st hour blood gas - pH	7.2 ± 0.2	7.2 ± 0.1
1st hour blood gas - base deficit	11 ± 6	11 ± 5

PPROM, prolonged premature rupture of membranes; SGA, small for gestational age. Results are expressed as n (%), mean ± standard deviation or median [IQR]. *p 0.05. Infants are listed as completed all evaluations at 18–22 months (n=43) and incomplete or lost to follow-up (n=20).

*Infants with incomplete follow up had a neurological exam and evaluations performed at 18–22 months (n=5) or scripted phone interviews (n=3) but no Bayley III evaluations.

Table 3.

Neurodevelopmental Outcomes using the Bayley Scales of Infant and Toddler Development (Bayley-III).

a. Cohort Results	(n=43)
Age at evaluation, months	19 [18–22]
Disability	7 (16 %)
Mild	4 (9%)
Moderate	0
Severe	3 (7%)
Cognitive score	95 [90 – 106]
85	36 (84%)
70–84	4 (9 %)
<70	3 (7%)
Language score	89 [79 – 100]
85	29 (67%)
70–84	10 (23%)
<70	4 (10%)
Language subtypes: Receptive communication	9 [7–10]
Expressive communication	8 [7–10]
Motor score [*]	100 [88 – 105]
85	37 (86%)
70–84	3 (7%)
<70	1 (2%)
Motor subtypes: Fine motor	10 [9–12]
Gross motor	9 [8–10]
Cerebral palsy	1 (2%)
Autism	2 (5%)

b. Selected Details of the Seven Mild HIE infants with disability at 18-22 months

Cases with disability	1	2	3	4	5	6	7
Sarnat at admission – abnormal categories (mild=1, moderate=2 and severe=3)	score= 1 For all	Posture=1 Tone=2 Moro=2	Posture= 1 and SA=2	LOC=1 ANS=1, Tone Moro=2	All categories= 1 but ANS=3	Post=1 Tone=1, Suck=2 ANS=3	Posture=1 Suck=1; Tone=2 ANS=3
Total # of abnormal categories	4	3	2	4	6	4	4
Short-term outcomes aEEG at <9h days of age	CNV	CNV	CNV	CNV	CNV	CNV	CNV
Brain MRI at <30d of age	2b	0	0	2b	1b	0	0
Neurological exam at discharge/transfer	All= 1 LOC, activity Tone ATNR	normal	normal	Tone =2b	Abnormal ATNR	Moro =1	Tone =1
Follow-up 18–22 months							
Disability	Severe	Severe	Severe	Mild	Mild	Mild	Mild
Bayley III Score - Cognitive	<70	60	<70	75	80	75	80

b. Selected Details of the Seven Mild HIE infants with disability at 18-22 months

Cases with disability	1	2	3	4	5	6	7
Bayley III Score - Language	<70	56	<47	79	74	97	91
Bayley III Score - Motor	<70	58	<70	88	82	107	88
Cerebral Palsy*	Yes	No	No	No	No	No	No
GMFCS	4[a]	0	0	1	1	0	0
Autism	-	Yes[b]	Yes[b]	-	-	-	-

Disability at 18–22 months of age as defined by the NICHD Neonatal Research Network: a) Mild: cognitive score of 70–84 alone, or a cognitive score 85 and GMFCS Level 1 or 2, seizure disorder (without anti-epileptic medication), or hearing deficit with ability to follow commands without amplification; b) Moderate: cognitive score from 70–84 and GMFCS Level 2, active seizure disorder or hearing deficit; and c) Severe: cognitive score < 70, GMFCS Level 3–5, blindness, or hearing impairment. Results are expressed as n (%), mean ± standard deviation or median [IQR].

[*] Two cases with autism were excluded from the motor scores due to inability to complete testing.

Sarnat at admission included 6 categories that could be scored as Normal 0, mild=1, moderate=2 or severe=3 (Table 1). SA, spontaneous activity; LOC, level of consciousness; ANS, autonomic nervous system (all abnormalities were need of intubation: score 3); aEEG, amplitude integrated electroencephalogram; CNV, continuous normal voltage; MRI, magnetic resonance image; GMFCS, Gross motor function classification score:

[a] mixed cerebral palsy.

[b] Both Cases with a diagnosis of autism were followed beyond 36 months to confirm the diagnosis.

Table 4.

Mild HIE Infants with and without Disability at 18–22 months.

	Disability (n = 7)	No Disability (n = 36)
Maternal age	29 ± 6	30± 5
Maternal Education level*		
Less than High School	1 (14)	6/35 (17)
High School – completed	5 (72)	5/35 (14)
College – incomplete	1 (14)	11/35(32)
College or post-graduation	0	13/35 (37)
Maternal illness		
Diabetes mellitus	1 (14)	2 (6)
Thyroid dysfunction	1 (14)	1(3)
Apgar Scores		
1min	1± 1	3 ± 2
5min	5 ± 2	5 ± 2
10min	7 ± 2	7± 2
Cord blood gas		
pH	6.9±0.1	6.9±0.2
PCO_2	78±20	75±38
Base deficit	13±5	15±7
First hour blood gas		
pH	7.2±0.2	7.2±0.1
Base deficit, mmol/L	13±8	10±6
Age at exam, hours	4.6± 1	4.6± 1
Abnormal exam at discharge*	5(71%)	6(17%)
Abnormal MRI*	3(43%)	6 (17%)
Hospital stay, hours*	229 (101–544)	98(57–171)

Legend: MRI, magnetic resonance image; PCO_2, partial pressure of carbon dioxide.

Results are expressed as n (%), mean ± SD (n), and median [interquartile range]

*
p 0.01