Received: 14 May 2021 | Revised: 20 September 2021 | Accepted: 30 September 2021

DOI: 10.1111/apa.16133

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

REGULAR ARTICLE

Profile of minor neurological findings after perinatal asphyxia

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Funding information
The study was supported by the Foundation for Pediatric Research, Academy of Finland (314450, 335788), the Finnish Brain Foundation, Suomen Aivosäätiö, Helsinki University Central Hospital, the Sigrid Jusélius Foundation and the Finnish Medical Society Duodecim

Abstract

Aim: To characterise the spectrum of findings in sequential neurological examinations, general movements (GM) assessment and magnetic resonance imaging (MRI) of infants with perinatal asphyxia.

Methods: The prospective cohort study of term infants with perinatal asphyxia treated at Helsinki University Hospital's neonatal units in 2016–2020 used Hammersmith Neonatal Neurological Examination (HNNE) and brain MRI at 2 weeks and Hammersmith Infant Neurological Examination (HINE) and GM assessment at 3 months of age.

Results: Analysis included 50 infants: 33 displaying perinatal asphyxia without hypoxic-ischaemic encephalopathy (HIE), seven with HIE1 and 10 with HIE2. Of the infants with atypical HNNE findings, 24/25 perinatal asphyxia without HIE cases, 5/6 HIE1 cases and all 10 HIE2 cases showed atypical findings in the HINE. The HINE identified atypical spontaneous movements significantly more often in infants with white matter T2 hyperintensity.

Conclusion: In this cohort, most infants with perinatal asphyxia, with or without HIE, presented atypical neurological findings in sequential examinations. The profile of neurological findings for children with perinatal asphyxia without HIE resembled that of children with HIE. White matter T2 hyperintensity was associated with atypical spontaneous movements in the HINE and was a frequent MRI finding also in perinatal asphyxia without HIE.

KEYWORDS
general movements, hypoxic-ischaemic encephalopathy, infant neurological examination, minor neurological finding, perinatal asphyxia

Abbreviations: aEEG, amplitude-integrated electroencephalography; BE, base excess; DWI, diffusion-weighted imaging; EEG, electroencephalography; GM, general movements; HIE, hypoxic-ischaemic encephalopathy; HINE, Hammersmith Infant Neurological Examination; HNNE, Hammersmith Neonatal Neurological Examination; IQR, interquartile range; MOS-R, Motor Optimality Score revised; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MRV, magnetic resonance venography; NAA, *N*-acetylaspartate; NPV, negative predictive value; PA, perinatal asphyxia without HIE; PLIC, posterior limb of the internal capsule; PPV, positive predictive value; PWML, punctate white matter lesion; SAH, subarachnoid haemorrhage; SDH, subdural haematoma; SWI, susceptibility-weighted imaging.

1 | INTRODUCTION

Perinatal asphyxia is a serious medical condition that causes 23% of neonatal deaths worldwide.[1] When asphyxia leads to clinical manifestations indicative of brain dysfunction, the resulting medical condition is referred to as hypoxic-ischaemic encephalopathy, or HIE. It is a major cause of neurodevelopmental disabilities in full-term infants and across its three grades of severity[2] has an incidence of 1.5 cases per 1000 live births in high-income countries.[3] If left untreated, 53%–66% of patients with grade HIE2–3 die or develop severe impairments. The positive effect of therapeutic hypothermia on HIE2 mortality and morbidity is apparent, and a significant reduction in HIE3 mortality has also been shown.[4]

However, little is known of the long-term effects of mild-grade HIE (HIE1) and even less about the effects of perinatal asphyxia without apparent neurological symptoms during the neonatal period. It is commonly thought that children with HIE1 or only perinatal asphyxia without HIE (later referred to as PA) develop as their peers do,[5] but recent evidence suggests that, rather than a strict dichotomy between normal and abnormal outcomes, there is a continuum of developmental outcomes from PA to HIE1 and onwards to HIE2–3 at 18–24 months of age.[6-8]

An extensive review from 2018 indicates that HIE1 too is associated with developmental problems, as 25% of affected children ($n = 341$) showed motor or cognitive impairment at 18 months of age.[7] Results of a recent Irish–Swedish cohort study ($n = 471$) suggest that the cognitive composite scores of children with HIE1 at the age of 24 months may be lower than a control group's corresponding scores and may not differ significantly from those of children with HIE2 treated with therapeutic hypothermia.[8] Furthermore, a prospective cohort study reported that 52% of children with HIE1 had abnormal results in neonatal electroencephalography (EEG), brain magnetic resonance imaging (MRI) and/or neurological examination when discharged.[9]

These factors highlight the importance of detailed evaluation of the early signs of developmental risks associated with HIE1 and PA. Accordingly, this study was conducted to describe the profile and continuum of possible clinical findings in sequential standardised neurological examinations at 2 weeks and 3 months, general movements (GM) assessments at 3 months and brain MRI at 2 weeks of age in a cohort of children with perinatal asphyxia with and without HIE. We hypothesised that we would detect signal abnormalities in white matter also in the MRI scans of children in the latter group and that those changes would show an association with atypical findings in sequential neurological examinations.

Key Notes

- Minor neurological findings at 3 months of age in infants with or without mild-to-moderate hypoxic-ischaemic encephalopathy after perinatal asphyxia are common.
- Children with or without mild-to-moderate hypoxic-ischaemic encephalopathy after perinatal asphyxia share similar neurological profile findings.
- White matter T2 sequence hyperintensity in magnetic resonance imaging correlates with atypical spontaneous movements in Hammersmith Infant Neurological Examination.

2 | METHODS

2.1 | Participants

This prospective cohort study included inborn infants who were admitted for treatment of perinatal asphyxia to the Helsinki University Children's Hospital and Jorvi Hospital (Espoo, Finland) neonatal units. Children were recruited prospectively between September 2016 and June 2020.

The study included full-term infants (gestational age: ≥37 + 0 weeks) with clinical signs of perinatal asphyxia (e.g. pathological cardiotocography, signs of placental abruption or umbilical cord complications) and with no other obvious reason for distress at birth (e.g. infection or effects of general anaesthesia). Further inclusion criterion included presentation of at least one of the following: umbilical arterial cord pH below 7.10, a 1-min Apgar score not exceeding 6, need for assisted ventilation at any point in resuscitation and/or cardiopulmonary resuscitation at birth. The exclusion criteria were presence of HIE3, a chromosomal abnormality, congenital anomaly or indication of another neurological condition or apparent infection; participation in another study; and parents with difficulties in communication in Finnish. From clinical point of view, it was in our interest to study which infants need to be recruited to neurological follow-up programme: infants with HIE3 were excluded from our cohort, since they always need intensive follow-up. The sample size took into consideration the limited number of patients meeting the inclusion criteria and the need to maintain a reasonable time frame for recruitment.

Infants meeting the inclusion criteria were defined as having perinatal asphyxia and followed up for the development of HIE. The attending neonatologist ascertained the presence and grade of encephalopathy during the first 6 h by means of a modified Sarnat score and amplitude-integrated electroencephalography (aEEG). Decisions on treatment with therapeutic hypothermia were based on clinical guidelines.[10] For analysis of the findings, the children were categorised into three groups: perinatal asphyxia without HIE (PA), mild HIE with no therapeutic hypothermia (HIE1) and moderate HIE treated with hypothermia (HIE2).

The demographic data of the infants were collected from the electronic patient records. Reduced foetal movements were reported if the mother came to the hospital because of reduced foetal movement count and/or it was seen in an ultrasound that there were no foetal movements. Chorioamnionitis was diagnosed only via pathological examination of the placenta. Time of spontaneous breathing was defined by the attending neonatologist by inspection of breathing movements and auscultation of lungs. If the child

was intubated prior to the start of spontaneous breathing and the neonatologist suspected start of effective spontaneous breathing, ventilation was paused. In a few cases when a child was intubated, the time of spontaneous breathing could not been retrospectively deduced, and these cases were omitted from the analysis of time of spontaneous breathing.

2.2 | Approval and consent

For this study, the hospital district of Helsinki and Uusimaa provided the authorisation (HUS/1331/2016) required under the data protection legislation in force in Finland. Parents of patients gave informed consent for the research and publication of the results.

2.3 | Neurological examinations

A Hammersmith Neonatal Neurological Examination (HNNE) inventory was performed at the age of 2 weeks by one of two clinicians trained in the method, with double-checking from a video recording if performed by the junior clinician. HNNE scoring was done according to Ricci et al.[11] who examined 380 low-risk preterm infants at the postmenstrual age of 38–42 weeks and, proceeding from the findings' frequency distribution, reported that 0–6 deviance-indicating items can be found in children who develop typically.

At the age of 3 months, children were evaluated with the Hammersmith Infant Neurological Examination (HINE) and GM assessment. The HINE instrument was used by one of two clinicians trained in the method, with double-checking from a video recording if performed by the junior clinician.[12] At 3 months of age, HINE global scores ≥62 points indicate typical neurological findings.[13] In addition to checks for fidgety movements, two physical therapists certified for the use of GM assessment (advanced course of GM Trust) assigned qualitative GM scores in conjunction with the revised Motor Optimality Score (MOS-R).[14] Fidgety movements are described as small amplitude, variably accelerating continuous movements in all directions. These movements can be seen in the hips, ankles, shoulders and wrists in typically developing infants at 3–5 months post-term age.[14] Physical therapists worked as a team when assessing GMs. They were unanimous in every video about the fidgety movements. Concerning MOS scoring, interscorer agreement was reached in all cases.

2.4 | Magnetic resonance imaging

Brain MRI followed a routine non-sedated clinical imaging protocol applied via a 3T scanner (Siemens Skyra 3T). The protocol included T1-weighted axial slices; T2-weighted axial, sagittal and coronal slices; diffusion-weighted imaging (DWI), susceptibility-weighted imaging (SWI); magnetic resonance venography (MRV); and single-voxel 1H magnetic resonance spectroscopy (MRS) from the left basal ganglia/thalamus. An experienced paediatric neuroradiologist masked to the clinical condition and previous clinical MRI report classified the MRI results in accordance with the criteria of Weeke et al.[15] Deep grey matter insults, abnormality in the signal for the posterior limb of the internal capsule (PLIC), cortical infarcts, white matter T2 hyperintensity and either punctate white matter lesions (PWMLs) in MRI or MRS findings of lowered *N*-acetylaspartate (NAA)/elevated lactate were regarded as asphyxia-related findings.[16] Findings of subdural haematoma (SDH) and subarachnoid haemorrhage (SAH) were considered birth-related.[16]

2.5 | Outcome categories

The definition for atypical short-term outcomes was MRI findings suggestive of ischaemic injury or atypical neurological findings identified in HNNE scores (≥7 deviant items) or HINE scores (global score <62), or reduced GM MOS-R values (<25).[11,13,14]

2.6 | Statistical methods

The statistical analyses were carried out with IBM SPSS Statistics, version 25 (2017). To assess statistical significance, we employed Fisher's exact test for categorical variables. For continuous variables, the statistical significance was calculated first with multi-group comparison using Kruskal–Wallis and then with pairwise comparisons using Mann–Whitney U and Bonferroni correction. A significance threshold of $p < 0.05$ was set. *p*-values in the tables represent multi-group comparisons and possible statistically significant findings in pairwise comparisons are marked with superscript.

3 | RESULTS

For the study, we recruited 53 term infants with perinatal asphyxia, 51 of whom ultimately participated. One child was excluded from data analysis because in retrospective assessment the child did not meet the criteria for perinatal asphyxia. In total, 96 out of the 100 neurological assessments undertaken were completed, and MRI scans were performed for 49 children and GM assessment for 35 children. Altogether 11 GM videos were missing because of families' unwillingness to make additional visits, misunderstandings about appointments and technical problems. For one patient, MRI data were missing because of a misunderstanding about appointment times. Figure 1 presents a flowchart of participation in the study.

3.1 | Perinatal and infant characteristics

In our cohort, 33 of the 50 infants (66%) had PA and 17 (34%) displayed HIE at birth (HIE1: 7 infants; HIE2: 10). Perinatal and infants' characteristics are presented in Table 1A and Table 1B.

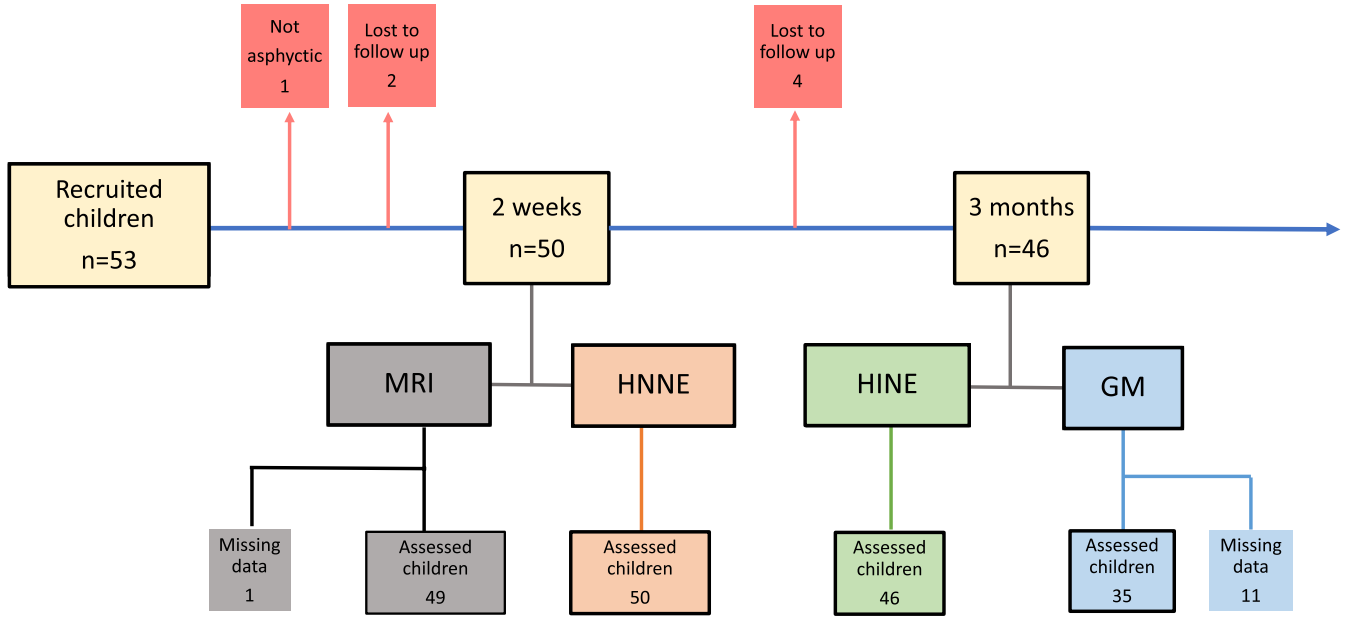

FIGURE 1 Flow chart depicting numbers of patients available at different phases of the study. HNNE, Hammersmith Neonatal Neurological Examination; HINE, Hammersmith Infant Neurological Examination; GM, General Movements

TABLE 1A Perinatal characteristics of the cohort

	PA (*n*=33)	HIE1 (*n*=7)	HIE2 (*n* = 10)	*p* value
Perinatal characteristics				
Birth hospital Helsinki University Hospital	24 (73%)	3 (43%)	3 (30%)	**0.029***
Maternal age, years (median, IQR)	34 (30–36)	32 (30–37)	34 (30–36)	0.988
Primipara	26 (79%)	7 (100%)	6 (60%)	0.153
Breech presentation	6 (18%)	0 (0%)	0 (0%)	0.270
Sentinel event				
Green amniotic fluid	10 (30%)	5 (71%)	3 (30%)	0.137
Abnormal CTG	29 (88%)	7 (100%)	9 (90%)	1.000
Reduced fetal movements	3 (9.1%)	2 (29%)	4 (40%)	**0.045***
Nuchal cord	7 (21%)	1 (14%)	0 (0%)	0.315
Vasa previa	1 (3.0%)	0 (0%)	2 (20%)	0.146
Shoulder dystocia	2 (6.1%)	0 (0%)	2 (20%)	0.259
Uterine rupture	1 (3.0%)	0 (0%)	0 (0%)	1.000
Placental abruption	1 (3.0%)	0 (0%)	3 (30%)	**0.033***
Placental infarction	1 (3.0%)	0 (0%)	2 (20%)	0.146
Chorioamnionitis	0 (0%)	0 (0%)	2 (20%)	0.054
Mode of delivery				
Spontaneous vaginal	10 (30%)	1 (14%)	1 (10%)	0.485
Instrumental vaginal	11 (33%)	4 (57%)	4 (40%)	0.517
Urgent Caesarean	4 (12%)	2 (29%)	2 (20%)	0.451
Emergency Caesarean	8 (24%)	0 (0%)	3 (30%)	0.361

*The statistically significant difference is between PA and HIE2.

We found no statistically significant differences between groups in 1-min Apgar scores, cord arterial pH or BE, but 5- and 10-min Apgar scores were significantly lower in children who later developed HIE ($p = 0.011$ for 5 min and $p = 0.002$ for 10 min). While most infants (76%) in our cohort needed ventilation, those who later developed HIE commenced spontaneous breathing later ($p = 0.001$), were more likely to require ventilation at 10 min of age ($p < 0.001$), and were more likely to be intubated ($p < 0.001$) than children with PA. There were no deaths during the 3-month follow-up.

TABLE 1B Infant characteristics for the cohort

	PA ($n = 33$)	HIE1 ($n = 7$)	HIE2 ($n = 10$)	p value
Infant characteristics				
Male sex	16 (48%)	5(71%)	7 (70%)	0.396
Gestational age, weeks (median, IQR)	40+4 (39+6–41+5)	41+2 (39+1–41+5)	38+6 (38+4–40+2)	**0.013***
Birth weight, grams (median, IQR)	3560 (3300–3790)	3350 (2780–3770)	3260 (2940–3690)	0.325
Apgar (median, IQR)				
1 min	3 (2–5)	3 (2–5)	3 (1–3)	0.154
5 min	6 (4–7)	5 (4–6)	3 (3–4)	**0.011***
10 min	7 (6–8)	6 (6–7)	5 (4–6)	**0.002***
Cord arterial pH (median, IQR)	7.06 (7.00–7.10)	7.04 (6.97–7.10)	7.12 (6.95–7.26)	0.941
Cord arterial BE (median, IQR)	−8.7 (−10.7–(−6.3))	−10.0 (−12.6–(−7.7))	−11.0 (−13.8–(−3.8))	0.546
First postnatal pH (median, IQR)	7.31 (7.26–7.37)	7.25 (7.18–7.30)	7.02 (7.00–7.18)	
First postnatal BE (median, IQR)	−3.3 (−7.3–(−1.4))	−7.1 (−9.4–(−6.0))	−10.5 (−18.8–(−9.1))	
Resuscitation				
Need for ventilation at any point in resuscitation	23 (70%)	6 (86%)	9 (90%)	0.485
Ventilation at the age of 10 min	3 (9.1%)	1 (14%)	7 (70%)	**<0.001***
Onset of spontaneous breathing, minutes (median, IQR)	2 (0–5)	5 (5-7)	11 (5–26)	**0.001***
Intubation	3 (9.1%)	3 (43%)	7 (70%)	**<0.001***
Abnormal neurological status, age <3 h	25 (76%)	7 (100%)	10 (100%)	0.277
Clinical seizures throughout hospital stay	2 (6.1%)	4 (57%)	5 (50%)	**<0.001*[▲]**
Abnormal amplitude EEG	2 (9.5%)[♦]	4 (57%)	8 (80%)	**<0.001*[▲]**
S100 (median, IQR)	2.8 (2.0–4.1)	3.8 (1.6–5.9)	3.7 (1.5–5.9)	0.960
Therapeutic hypothermia	0 (0%)	0 (0%)	10 (100%)	**<0.001*[O]**
Treatment in neonatal ward, days (median, IQR)	2 (1–3)	4 (2–11)	9 (5–11)	**<0.001***

Note: Comparisons between study groups for postnatal pH and BE were not applicable due to different sample timings.

[a] The statistically significant difference is between PA and HIE1.

[b]The statistically significant difference is between HIE1 and HIE2.

[c]aEEG was available for 21 children with PA.

*The statistically significant difference is between PA and HIE2.

3.2 | Neurological examinations

Table 2A shows the HNNE, HINE and GM MOS-R values for the groups PA, HIE1 and HIE2.

All children were assessed with the HNNE, at a median age of 16 days (interquartile range, IQR: 14–19 days). The median number of deviant items in the HNNE was 10 (IQR: 7–13) in children with PA, 9 (8–9) in children with HIE1 and 11 (9–12) in children with HIE2. No significant difference emerged between groups ($p = 0.315$).

The HNNE items for which scores were frequently lower than expected were spontaneous movements (quantity 86%, quality 84%), trunk muscle tone (posture 72%, ventral suspension 70%), head control (head lag 58%, head extensor tone 44%, head flexor tone 46%, prone head-raising 46%), irritability (48%) and Moro reflex (70%). Interestingly, the only differences among the three groups were in tremors, which were found only in children with HIE2 ($p = 0.001$), and plantar grasp, which was atypical more often for those with HIE2 than for those with PA or HIE1 ($p = 0.033$).

At the median calendar age of 14 (IQR: 13–15) weeks, 46 children were assessed with HINE: of the six infants showing typical neurological findings (13%), four were in the PA group and two were in the HIE1 group. The median (IQR) global score in the HINE differed between groups, being 57 (55–61) in PA, 57 (47–62) in HIE1 and 48 (44–52) in HIE2 ($p = 0.004$). Figure 2 shows the group-specific HINE global scores.

Lower-than-expected HINE scores were found most often in the subsections for posture (29/46), spontaneous movements (18/46), and reactions and reflexes (17/46). The only difference between study groups was found for cranial nerve items; the HIE1 group showed deviance more often than the other groups ($p = 0.027$).

At the age of 2 weeks, nine infants (18%) showed typical neurological findings. Eight of these infants had PA and one had HIE1. At 3 months of age, only four of these nine infants had a HINE global score ≥62; the scores of the rest were in the range 51.5–60 (apart from one infant, who did not participate in the HINE examination). Two infants with deviant HNNE results reached the reference

TABLE 2A Neurological status and GM findings for the various groups

	PA	HIE1	HIE2	All	
	Median (IQR) *n* deviant results/*n* evaluated (%)				*p* value
HNNE, 2 weeks	10 (7–13) 25/33 (76%)	9 (8–9) 6/7 (86%)	11 (9–12) 10/10 (100%)	10 (8–12) 41/50 (82%)	0.315
HINE, 3 months	57 (55–61) 25/29 (86%)	57 (47–62) 5/7 (71%)	48 (44–52) 10/10 (100%)	56 (50–60) 40/46 (87%)	**0.004***
MOS-R, 3 months	26 (23–28) 6/22 (27%)	27 (26–28) 0/4 (0%)	25 (22–26) 4/9 (44%)	26 (23–28) 10/35 (29%)	0.137

Note: Comparisons between study groups for MRS metrics were not applicable due to different imaging timings.

* The statistically significant difference is between PA and HIE2.

range in the 3-month HINE assessment. The positive predictive value (PPV) of atypical HNNE results relative to atypical HINE results was 95%.

General movements assessments were completed at the age of 11–20 weeks (median 14, IQR 13–15 weeks). A GM video was available for 35 children, all of whom showed fidgety movements. Our cohort's median MOS-R score total was 26 (IQR: 23–28). In PA, 6/22; in HIE1, 0/4; and in HIE2, 4/9 infants had reduced MOS-R values. Median MOS-R did not differ significantly between groups ($p = 0.137$). In our data, there was no significant correlation between MOS-R and HINE in linear regression analysis R2 = 0.077 ($p = 0.107$).

3.3 | Magnetic resonance imaging

The infants' median age at the time of MRI was 14 (IQR: 6–17) days. An asphyxia-related pattern of brain injury was found in 32 of the 49 infants for whom an MRI scan had been performed (65%). Of the 49 infants scanned, 27 (55%) showed white matter abnormalities and nine (18%) grey matter abnormalities.

Lactate was detectable in 12 spectroscopies, with the median Lac/Naa ratio for these being 0.23 (IQR: 0.20–0.31) and median Lac/Cr being 0.22 (IQR: 0.18–0.28). Twenty-four infants in this cohort (49%) had subdural haematoma or SAH; these were considered birth-related findings. Although the SDH rate was not correlated with the asphyxia's clinical severity, children delivered with instrument assistance showed SDH evidence significantly more often than Caesarean-delivered ones: 14/19 and 3/19, respectively ($p < 0.001$). Table 2B lists the MRI findings for all groups.

3.4 | Associations for neurological findings and MRI

Atypical HNNE findings for eye appearance were more frequent among infants whose MRI showed white matter T2 hyperintensity (13/32 children with PA, 6/7 children with HIE1, and 6/10 children with HIE2; $p = 0.037$). Also, infants with white matter signal abnormalities in MRI tended to have tremors in more cases, were more difficult to console and had more atypical HNNE findings for plantar grasp and spontaneous movement quality, but these differences were not statistically significant.

Significantly more often, HINE results for infants with white matter T2 hyperintensity indicated atypical spontaneous movement quality ($p = 0.007$) and quantity ($p = 0.010$), and their HINE passive shoulder elevation was more atypical ($p = 0.038$). There were more atypical findings for facial appearance, eye movements, auditory response and passive pronation-supination as well, but the differences were not statistically significant. When only infants with atypical findings in both HNNE and HINE assessments were included ($n = 34$), significant associations between white matter T2 hyperintensity and atypical spontaneous movement quality ($p = 0.005$) and quantity ($p = 0.033$) were still detectable.

4 | DISCUSSION

Our study's primary aim was to describe the profile and continuum of detailed neurological findings and MRI findings in children with perinatal asphyxia with and without hypoxic-ischaemic encephalopathy. Belying the general clinical view, the majority of children with PA or with HIE1 in our cohort showed persistent deviant neurological findings in HINE assessment at 3 months of age. This was especially conspicuous for items related to posture, spontaneous movements, and reactions and reflexes.

Strikingly, most PA children had at least seven atypical HNNE items. Such scores in preterm infants have been associated with delayed motor[11] and cognitive[17] performance at age 2 years. Furthermore, for very prematurely born infants, the number of atypical HNNE items shows an association with Touwen test results indicating minor neurological dysfunction at age 11 years.[18]

Previously, 3-month HINE with a cut-off score of 56 has been shown to predict cerebral palsy in a combined cohort of preterm and term infants with both high sensitivity (96%) and specificity (85%).[19] A recent study with a large cohort of preterm children found a link between HINE global scores below 58 at 3 months of age and worse cognitive performance at the developmental age of 24 months.[20] In our cohort, 29 of the 46 infants had 3-month HINE global scores below 58 and 11 infants had scores below 50. Of these 11 infants,

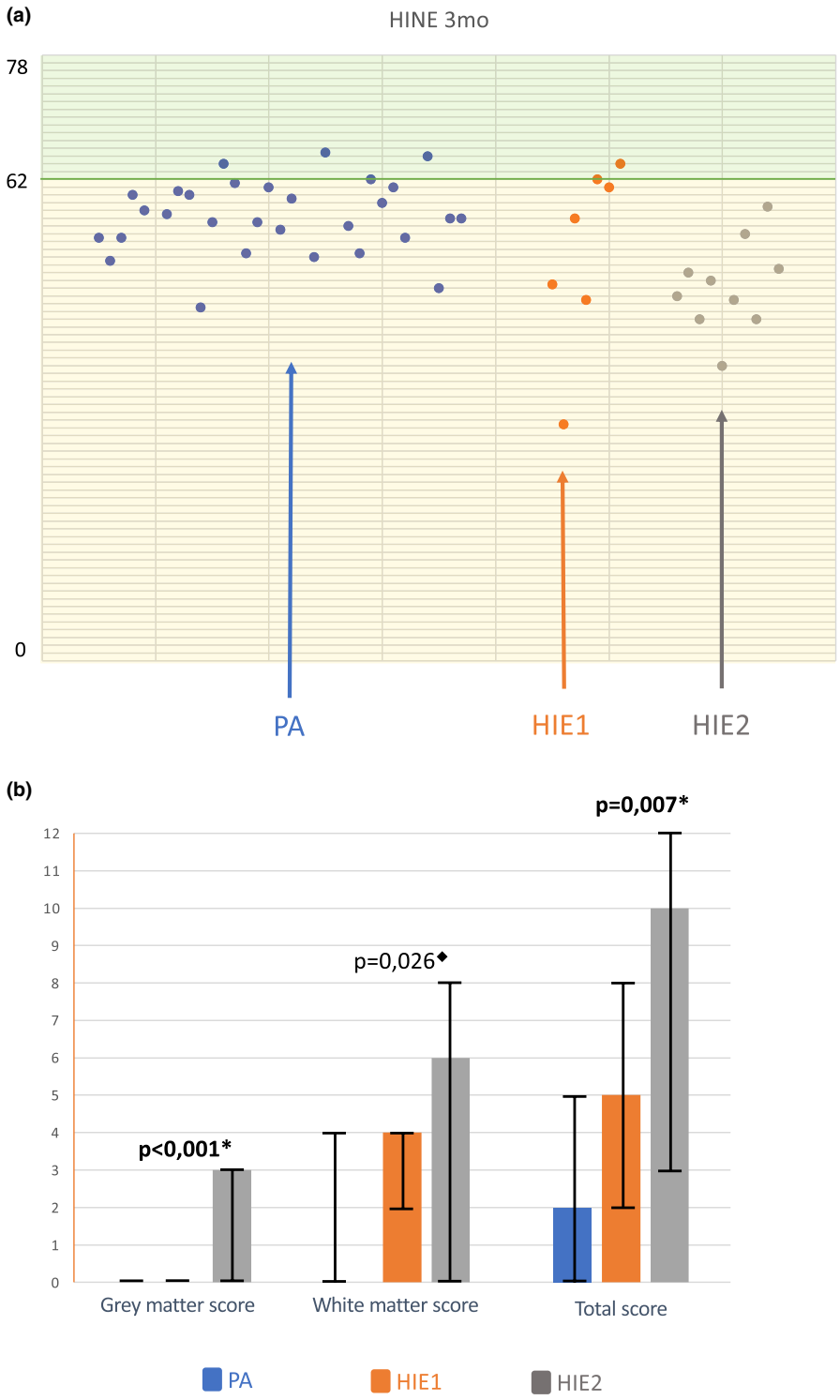

FIGURE 2 (A) HINE global scores at the age of 3 months for individual infants divided into the groups PA, HIE1, and HIE2. HINE global score of 62 points is the cut-off for typical findings at 3 months of age.[13] HINE, Hammersmith Infant Neurological Examination. (B) Median MRI grey matter and white matter subscores and total scores, by group: PA, HIE1, and HIE2. MRI scoring has been made according to Weeke et al.[15] The error bars represent IQRs. *The statistically significant difference is between PA and HIE2. ◆There is no statistically significant difference between two individual groups

six had HIE2, three HIE1 and two PA. To our knowledge, no reports on using HINE cut-off scores at 3 months of age to predict cognitive impairment in full-term infants have yet been published, but scoring below cut-off values of preterm infants can be seen as a plausible risk.

There is a well-documented association between fidgety movements in GM assessment and development of cerebral palsy.[21] Since our work focused on PA, HIE1 and HIE2, cerebral palsy is not an expected outcome. Still, it is not surprising that all children in our cohort had fidgety movements. Results from a recent meta-analysis indicate that general movements at 3–5 months of age can be used to identify children who are at risk of showing cognitive dysfunction at 24 months (PPV: 38%; negative predictive value, NPV: 96%).[22] In our cohort, 27% of the infants with PA and 44% of those with HIE2 had reduced MOS-R results. In our cohort, there was no significant correlation between MOS-R and HINE. To our knowledge, there are no previous publications that would have studied correlation between MOS-R score and HINE. Recently, Harpster et al have recorded a significant but low correlation between GMA and HINE (R2 0.14) comparing fidgety +/- and

TABLE 2B Asphyxia-related findings in MRI and MRS, along with other MRI findings

	PA	HIE1	HIE2	All groups	
	n deviant results/*n* evaluated (%)				*p* value
MRI findings related to asphyxia					
Deep grey-matter insult	1/32 (3%)	0/7 (0%)	3/10 (30%)	4/49 (8%)	**0.035***
PLIC signal abnormality	1/32 (3%)	1/7 (14%)	3/10 (30%)	5/49 (10%)	**0.036***
Cortical infarct	0/32 (0%)	1/7 (14%)	1/10 (10%)	2/49 (4%)	0.116
White-matter T2 hyperintensity	13/32 (41%)	6/7 (86%)	6/10 (60%)	25/49 (51%)	0.078
Punctate white-matter lesions	1/32 (3%)	1/7 (14%)	2/10 (20%)	4/49 (8%)	0.114
MRS findings related to asphyxia					
Elevated lactate	8/21 (38%)	1/4 (25%)	3/7 (43%)	12/32 (38%)	
Lowered NAA	2/21 (10%)	1/4 (25%)	2/7 (29%)	5/32 (16%)	
Other findings in MRI					
Subdural haematoma	14/32 (44%)	4/7 (57%)	4/10 (40%)	22/49 (45%)	0.833
Subarachnoid haemorrhage	2/32 (6%)	0/7 0%)	2/10 (20%)	4/49 (8%)	0.268

Note: p values represent comparisons of median/IQR scores.

*The statistically significant difference is between PA and HIE2.

HINE <56 in very preterm infants. Harpster et al[23] speculated, that the low correlation between GMA and HINE implies that it is unlikely that these tests provide similar prognostic information.

In children with HIE, both mild and moderate basal ganglia or more marked white matter lesions in MRI are associated with developmental delays, especially regarding motor function. Children with watershed injury affecting primarily white matter rarely exhibit severe motor impairment but can still have behaviour problems or delays in developing language skills.[24] A correlation between watershed injury severity and later intelligence quotient (overall and verbal), at age 11 years, has been previously identified.[25] In our cohort, 19 children showed solely white matter signal abnormalities; most of them ($n = 17$) were in the HIE1 or PA group. The development-related significance of purely white matter signal abnormalities for cases of either type is not well established in the literature. A California-based cohort study involving 64 four-year-old children who had suffered perinatal asphyxia with or without neurological symptoms revealed that the severity of watershed injury was associated with the language skills of the children without motor deficits.[26]

The literature suggests that the lactate-to-NAA ratio in MRS offers greater diagnostic accuracy with respect to adverse neurological outcome than conventional MRI for infants with HIE.[27] In our cohort, lactate and NAA changes were detectable in 14/32 spectroscopies. However, only four infants' lactate-to-NAA ratio was above 0.29, the level associated with adverse outcomes[27]; of these infants, one had PA, one had HIE1, and two had HIE2. Given the different timing of MRS performed between the groups (early for HIE2 infants and later for HIE1 and PA infants) and the heavy reliance of MRS on timing, the comparisons between groups for this metric were not applicable.

We hypothesised that an association would be visible between MRI white matter signal abnormalities and atypical findings in neurological examinations even in infants with PA. There have been only a few reports of a correlation between MRI-visible white matter changes and early neurological status; George et al.[28] reported a significant correlation of these changes with HNNE subscore of abnormal signs ($p = 0.03$) and Test of Infant Motor Performance *z*-score figures ($p < 0.01$) in a cohort of 102 preterm infants, and a Japanese cohort of 49 very-low-birthweight infants showed an association between MRI white matter value and general movement optimality score at term.[29] With our cohort, the significant correlation of white matter T2 hyperintensity with spontaneous movements is especially interesting in that the literature hints that spontaneous movements are correlated with later development.[21,22]

The study's prospective design with sequential neurological examinations is among its key strengths. All neurological assessments were done by one of two trained clinicians, with double-checking from a video recording if performed by the junior clinician.

Our work is limited, however, by the absence of GM findings after mild birth asphyxia; technical and logistic factors restricted us to only 35 video recordings. It is worth stressing also that the MRI scans for children with HIE1 or PA in connection with this study were done at 2 weeks, at which point most changes visible in DWI and MRS disappear. In contrast, cooled children with HIE2 had MRI scans, based on clinical indications, significantly earlier—usually when 4 days old.

Long-term outcomes for infants diagnosed with either PA or HIE1 are not entirely clear.[30] Our findings are consistent with recent suggestions that there is a continuum of development outcomes, contingent on the severity of asphyxia and the grade of HIE.[6-8] The findings suggest that this continuum in neurological profile from PA to HIE2 can be observed already between the ages of 2 weeks and 3 months when children are sequentially assessed via a structured neurological examination. We detected a continuous progression

from milder to more severe changes also in the MRI findings. Based on the sequential examinations, we could identify neurological trajectories for individual infants and find a strong association between atypical neurological findings at 2 weeks and the results at 3 months.

Most importantly, our study suggests that atypical early neurological findings are common in infants after PA even in the absence of clinical HIE. This result calls for further studies of these children's long-term neurodevelopmental trajectories.

CONFLICT OF INTEREST

The authors have no financial relationships relevant to this article to disclose. The authors have no potential conflicts of interest to disclose.

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How to cite this article: Tuiskula A, Metsäranta M, Toiviainen-Salo S, Vanhatalo S, Haataja L. Profile of minor neurological findings after perinatal asphyxia. Acta Paediatr. 2022;111:291–299. https://doi.org/10.1111/apa.16133