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Research Paper

Genetic and Congenital Anomalies in Infants With Hypoxic-Ischemic Encephalopathy

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ABSTRACT

Background: Infants with hypoxic ischemic encephalopathy (HIE) may have underlying conditions predisposing them to hypoxic-ischemic injury during labor and delivery. It is unclear how genetic and congenital anomalies impact outcomes of HIE.
Methods: Infants with HIE enrolled in a phase III trial underwent genetic testing when clinically indicated. Infants with known genetic or congenital anomalies were excluded. The primary outcome, i.e., death or neurodevelopmental impairment (NDI), was determined at age two years by a standardized neurological examination, Bayley Scales of Infant Development, Third Edition (BSID-III), and the Gross Motor Function Classification Scales. Secondary outcomes included cerebral palsy and BSID-III motor, cognitive, and language scores at age two years.
Results: Of 500 infants with HIE, 24 (5%, 95% confidence interval 3% to 7%) were diagnosed with a genetic (n = 15) or congenital (n = 14) anomaly. Infants with and without genetic or congenital anomalies had similar rates of severe encephalopathy and findings on brain magnetic resonance imaging. However, infants with genetic or congenital anomalies were more likely to have death or NDI (75% vs 50%, $P = 0.02$). Among survivors, those with a genetic or congenital anomaly were more likely to be diagnosed with cerebral palsy (32% vs 13%, $P = 0.02$), and had lower BSID-III scores in all three domains than HIE survivors without such anomalies.
Conclusions: Among infants with HIE, 5% were diagnosed with a genetic or congenital anomaly. Despite similar clinical markers of HIE severity, infants with HIE and a genetic or congenital anomaly had worse neurodevelopmental outcomes than infants with HIE alone.

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Introduction

Neonatal encephalopathy is a clinical condition with multiple potential causes including hypoxic-ischemic encephalopathy (HIE), structural congenital anomalies, and inborn errors of metabolism or other genetic conditions. HIE, the most common cause of moderate to severe neonatal encephalopathy, is preceded by a recognized intrapartum sentinel event such as a placental abruption or uterine rupture in only the minority of cases.[1,2] The diagnosis of HIE therefore relies on clinical criteria that are nonspecific but suggestive of a hypoxic-ischemic insult, such as low Apgar scores, cord blood acidosis, and the need for prolonged resuscitation after birth.[3]

Infants diagnosed with HIE may have additional underlying conditions that predispose them to sustaining hypoxic-ischemic injury during the labor and delivery process.[4] However, few studies have focused on the role of genetic and congenital anomalies in HIE. In a recent study of 160 infants undergoing therapeutic hypothermia for HIE, eight infants who were diagnosed with a genetic or syndromic diagnosis had worse outcomes than infants without a concomitant genetic or syndromic diagnosis.[5] In another cohort of 210 infants with possible HIE, 10 were found to have specific genetic defects; however, most of these infants either did not meet criteria for therapeutic hypothermia or experienced refractory seizures indicative of a genetic epilepsy.[6] Given the small sizes of these prior studies and the heterogeneous patient populations, it remains unclear how the presence of a genetic or congenital anomaly impacts the clinical presentation and outcomes of HIE. To address this question, we analyzed a large multicenter cohort of infants with HIE to determine the frequency of genetic or congenital anomalies, and to examine how such anomalies correlate with the clinical presentation and neurodevelopmental outcomes of HIE.

Materials and Methods

Five hundred infants with moderate or severe HIE were enrolled at 17 hospitals in a phase III randomized controlled trial called High-Dose Erythropoietin for Asphyxia and Encephalopathy (HEAL). The HEAL study protocol and primary results have been previously published.[7,8] All infants were enrolled by age 26 hours. Infants were eligible if they met the following inclusion criteria for HIE: (1) ≥36 weeks' gestation, (2) perinatal depression (i.e., Apgar score <5 at 10 minutes, cardiorespiratory resuscitation received beyond age 10 minutes, or pH < 7.00, or base deficit ≥15 mmol/L in cord or infant gas within 60 minutes of birth), (3) moderate or severe neonatal encephalopathy present at age one to six hours based on a modified Sarnat examination,[7] and (4) undergoing therapeutic hypothermia. Infants who were known at birth to have a genetic or congenital anomaly that would affect neurodevelopment (e.g., trisomy 21) or that would require multiple surgeries were excluded. Other exclusion criteria included birth weight <1800 g, head circumference less than 30 cm, ongoing discussions regarding redirection to palliative care, encephalopathy attributed to a postnatal event, guardian of diminished cognitive capacity, and patient anticipated to be unavailable for evaluation at age two years.

A congenital anomaly was defined as a structural malformation of a major organ system (e.g., congenital heart disease). All congenital anomalies that were diagnosed by a treating physician or observed on a neonatal brain magnetic resonance imaging (MRI) were recorded. Genetic testing was not performed on all subjects but only performed when clinically indicated. The indications for genetic testing were recorded as follows: presence of a congenital anomaly, dysmorphic features, family history of genetic or congenital anomaly, or other.

A brain MRI was performed at age four to six days when possible, as previously described.[7] Three independent reviewers recorded the MRI injury score, severity of injury, and patterns of injury using a published scoring system,[9,10] with disagreements resolved by consensus. Of note, this MRI classification system only addresses the presence of brain injury and does not take into account the presence of developmental brain anomalies. Two independent reviewers determined the worst electroencephalography (EEG) background pattern and presence or absence of electrographic seizures during the first 24 hours by reviewing clinical EEG reports.

The primary, binary outcome consisted of death or neurodevelopmental impairment (NDI) versus alive and no NDI at age two years (i.e., 22 to 36 months) as previously described.[8] Secondary outcomes determined at age two years included a five-level ordinal outcome (no NDI, mild NDI, moderate NDI, severe NDI, died),[11] cerebral palsy diagnosed on a validated standardized neurological examination,[12] a modified Gross Motor Function Classification System[13] > 1 indicating inability to take 10 steps independently, and Bayley Scales of Infant Development, Third Edition, cognitive, language, and motor scores.

Baseline characteristics and outcomes from infants with and without a genetic or congenital anomaly are presented as frequency (percent) and median (interquartile range). Characteristics were compared using a chi-square test, Fisher exact test, and Wilcoxon rank-sum test, as appropriate for categorical and continuous data. As this was an exploratory, hypothesis-generating analysis, *P* values were not adjusted for multiple comparisons. Analyses were conducted between February and July 2023 using R Statistical Software version 4.2.3 (R foundation for Statistical Computing).

Results

Of 500 infants with moderate or severe HIE who were enrolled in the HEAL trial, 24 (5%, 95% confidence interval 3% to 7%) were diagnosed with a genetic or congenital anomaly. Of these 24 infants, 10 (2%) were found to have only a genetic abnormality, nine (2%) only a congenital anomaly, and five (1%) had both (Table 1). Among the 15 infants who were diagnosed with a genetic abnormality, the clinical indications for genetic testing were as follows: congenital anomaly (five), positive family history (four), dysmorphic features (three), and other (three) including two infants with hematologic abnormalities and one infant with brain tubers observed on MRI.

There were 14 unique genetic mutations identified among 15 infants with a genetic abnormality (Table 1). One infant with bilateral hearing loss and a family history of congenital bilateral hearing loss was considered to have a genetic abnormality despite the lack of genetic testing performed. Among the 14 infants with a congenital anomaly, abnormalities included cerebral dysgenesis (n = 6, Fig), cardiopulmonary anomalies (n = 4), renal anomaly (n = 1), gastrointestinal anomaly (n = 1), severe ear anomaly (n = 1), and multiple (kidney, lung, gastrointestinal) anomalies (n = 1).

Among 500 infants with HIE, those with a genetic or congenital anomaly had a lower median gestational age than infants without a genetic or congenital anomaly (38.4 vs 39.3 weeks, $P = 0.02$, Table 2). Infants with a genetic or congenital anomaly were also less likely to be exposed to maternal chorioamnionitis (0% vs 16%, $P = 0.04$). The two groups were similar with respect to clinical markers of HIE severity such as severity of encephalopathy, Apgar score, and lowest pH (Table 2). The Sarnat examination findings were also similar between the two groups (Supplementary Table 1).

A similar proportion of infants with and without a genetic or congenital anomaly were followed until age two years for primary outcome assessment (100% vs 96%, $P = 0.62$). The primary outcome of death or NDI was more common in infants with a genetic or

TABLE 1.
Genetic and Congenital Anomalies in 24 Infants With Moderate to Severe HIE

Genetic Finding	Congenital Anomaly	Indication for Genetic Testing*
PTPN11 mutation (Noonan syndrome)	Cardiac: left ventricular hypertrophy and outlet obstruction	Congenital anomaly
COL2A1 mutation	Cardiac: right-sided aortic arch, spinal kyphosis	Congenital anomaly and brain hemorrhage
KIAA1109 mutations (Alkuraya-Kučinskas syndrome)	Brain: dysgenesis of corpus collosum	Congenital anomaly
JAG1 mutation (Alagille syndrome)	Pulmonary: bilateral pulmonary stenosis	Congenital anomaly
45, X (Turner syndrome)	Renal: horseshoe kidney	Congenital anomaly
Hemophilia A	None	Hematologic abnormality
Bilateral hearing loss and family history of same	None	Family history of hearing loss
SLC6A5 mutation (hyperekplexia)	None	Family history of hyperekplexia
G6PD deficiency	None	Hematologic abnormality
CYBB c.1335C>A (chronic granulomatous disease)	None	Family history of mutation in mother
Xp22.33 duplication involving SHOX genes	None	Dysmorphisms: single palmar creases, flat nasal bridge, low ears
TSC1 mutation (tuberous sclerosis)	None	Brain MRI with multiple tubers
14q21.2-3 deletions; balanced 7:18 translocation	None	Dysmorphisms: upslanting palpebral fissures, microretrognathia
NF-1 mutation (neurofibromatosis)	None	Family history of neurofibromatosis
8p11.2: 14.8-Mb deletion	None	Dysmorphisms: single palmar creases, sacral dimple, nuchal folds
Normal WES and normal SNP array	Pelvic kidneys, pulmonary hypoplasia, pyloric stenosis, malrotation	Congenital anomaly
Normal SNP array and normal fragile X	Brain: simplified gyral pattern, wide sylvian fissures	Congenital anomaly
Normal SNP array	Brain: hypoplastic cerebellum and dysmorphic brainstem	Congenital anomaly
No genetic testing	Brain: white matter hypoplasia, wide sylvian fissures	Not applicable
No genetic testing	Brain: dysgenesis of corpus callosum	Not applicable
No genetic testing	Cardiac: ASD, VSD, depressed right ventricular function	Not applicable
No genetic testing	GI: ileal atresia	Not applicable
No genetic testing	Ear: Stahl ear and conchal crus	Not applicable
No genetic testing	Brain: white matter hypoplasia, wide sylvian fissures	Not applicable

Abbreviations:
ASD = Auricular septal defect
GI = Gastrointestinal
HIE = Hypoxic-ischemic encephalopathy
SNP = Single nucleotide polymorphism
VSD = Ventricular septal defect
WES = Whole exome sequencing

* Note that information regarding family history of genetic disorders was not collected for all infants in the study but only for those who received genetic testing.

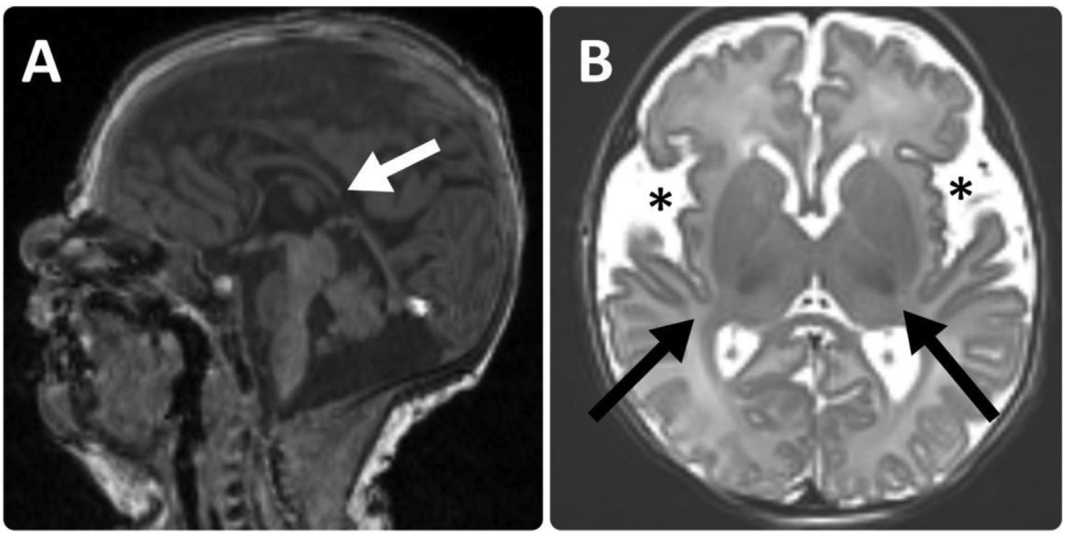

FIGURE. Brain developmental abnormalities in children with moderate to severe hypoxic-ischemic encephalopathy. (A) Sagittal T1-weighted image demonstrates dysgenesis of the corpus callosum, with early termination of the corpus callosum (white arrow) due to absent posterior body and splenium. (B) Axial T2-weighted imaging demonstrates white matter hypoplasia as evidenced by diminished periatrial white matter volume (black arrows) and wide sylvian fissures (black asterisks) in an infant who was born at 40.5 weeks gestational age.

congenital anomaly than those without such a diagnosis (75% vs 50%, $P = 0.02$). Although death rates were similar in the two groups (Table 3), HIE survivors with a genetic or congenital anomaly had a higher rate of cerebral palsy than those without such an anomaly (32% vs 13%, $P = 0.02$), as well as lower Bayley Scales of Infant Development, Third Edition, scores in all domains. In contrast, severity of brain injury on MRI and EEG findings in the first 24 hours were similar between infants with and without a genetic or congenital anomaly (Table 3).

Severe brain injury on MRI was highly predictive of poor outcome (Table 3) as has been previously described in this cohort.[11] All six infants with both severe HIE brain injury and a genetic or congenital anomaly either died or had NDI at age two years. Four infants with a genetic or congenital anomaly had no evidence of HIE injury on MRI; however, all four infants had an abnormal outcome including mild NDI (one), moderate NDI (two), or severe NDI (one), despite the lack of brain injury observed on neuroimaging. Among 100 infants with a normal MRI, an adverse primary outcome of death or NDI was present in four of four (100%) infants who had a genetic or congenital anomaly, compared with 28 of 96 (29.2%) infants without a genetic or congenital anomaly ($P = 0.01$).

Discussion

In a large cohort of infants undergoing therapeutic hypothermia for moderate to severe HIE, 5% were later diagnosed with a genetic or congenital anomaly that had not been suspected within the first hours of birth. The diagnosis of a genetic or congenital anomaly was neither associated with the severity of HIE nor with EEG or neuroimaging biomarkers of brain injury. However, infants with a genetic or congenital anomaly were at higher risk of death or neurodevelopmental impairment at age two years than infants with HIE alone.

The relationship between HIE and coexisting genetic or congenital anomalies is complex and difficult to untangle. In some cases, the underlying genetic defect may predispose the infant to developing HIE during the delivery process. Alternatively, the genetic or congenital anomaly may be the cause of neonatal encephalopathy and therefore may mimic HIE. It is also possible that both scenarios are true, i.e., the genetic or congenital anomaly predisposed the infant to having HIE and is also responsible for neonatal encephalopathy independent of the hypoxic-ischemic process. Finally, in some cases the genetic or congenital anomaly and HIE may be completely unrelated.

Other studies have similarly reported that 5% of infants who were diagnosed with HIE were later found to have a genetic or congenital anomaly.[5,6] The rate of genetic anomalies among infants with neonatal encephalopathy not caused by HIE is even higher, ranging from 12% to 36% in recent cohorts.[14,15] In an Australian population-based case-control study, genetic or congenital anomalies were identified in 27% infants with neonatal encephalopathy compared with 4% of control infants.[16] The genetic or congenital anomaly was considered to be the cause of the neonatal encephalopathy in 37% of cases. After excluding these 37% of cases, the presence of a genetic or congenital anomaly was still associated with a fivefold increased odds of neonatal encephalopathy, presumably by increasing the risk of HIE and other types of perinatal brain insults.

The relationship between cerebral dysgenesis and HIE is not well-studied. We are unable to determine the risk of HIE due to cerebral dysgenesis because our study does not include unaffected controls. However, cerebral dysgenesis was the most common congenital anomaly in our cohort and was present in six of 473 (1.3%) infants. In contrast, a large prospective study of incidental findings on pediatric brain MRIs found that 20 of 11,679 (0.2%) healthy nine- to 10-year-old children had evidence of brain malformation, ventriculomegaly, or cerebellar hypoplasia.[17] A comparison with this historical rate of incidental findings suggests that cerebral dysgenesis may be associated with increased risk of HIE.

In infants diagnosed with HIE, the presence of a genetic or congenital anomaly may not be apparent at birth or even during the first days of life. Our findings suggest that it is important for clinicians caring for infants with HIE to inquire about a family history of genetic disorders and to have a low threshold for performing genetic testing in the setting of dysmorphic features or major organ anomalies. The increasing availability of rapid whole exome and whole genome sequencing may also lead to increased identification of genetic factors impacting neurodevelopment in infants with HIE. A concomitant diagnosis of an underlying genetic or congenital anomaly has important prognostic implications for infants with HIE

TABLE 2.
Comparison of Maternal and Infant Characteristics in Subjects With HIE With and Without a Genetic or Congenital Anomaly

Characteristics	Genetic or Congenital Anomaly Present	No Genetic or Congenital Anomaly	*P* value
	n = 24	n = 476	
Maternal and delivery characteristics			
Age (y), median (IQR)	29 (24, 33)	30 (25, 35)	0.38
Race			
White	11 (46)	174 (37)	0.88
Black	5 (21)	100 (21)	
Asian	6 (25)	172 (36)	
Multiple/other	0 (0)	16 (3)	
Hispanic ethnicity	3 (12)	119 (25)	0.22
Nulliparous (parity = 1)	15 (63)	271 (57)	0.71
Sentinel event	5 (21%)	138 (29%)	0.39
Placenta abruption	4 (17)	67 (14)	0.76
Cord prolapse	1 (4)	22 (5)	0.99
Uterine rupture	0 (0)	24 (5)	0.62
Shoulder dystocia	0 (0)	32 (7)	0.39
Chorioamnionitis	0 (0)	77 (16)	0.04
Delivery mode:			
Spontaneous vaginal delivery	4 (17)	115 (24)	0.83
Vacuum or forceps (vaginal assisted)	3 (13)	49 (10)	
Elective Caesarean	0 (0)	12 (3)	
Emergency or urgent Caesarean delivery	17 (71)	300 (63)	
Infant characteristics			
Female	13 (54)	212 (45)	0.40
Birth weight (g), median (IQR)	3445 (3120, 3539)	3320 (2992, 3750)	0.80
Gestational age (wks), median (S.D.)	38.4 (37.2, 39.5)	39.3 (38.1, 40.3)	0.02
Small for gestational age, <10%	1 (4)	61 (13)	0.34
Large for gestational age, >90%	5 (21)	70 (15)	0.41
Severe HIE	4 (17)	109 (23)	0.62
5-Minute Apgar			
0-3	13 (57)	245 (52)	0.95
4-6	9 (39)	183 (39)	
7-10	1 (4)	39 (8)	
10-Minute Apgar			
0-3	7 (33)	116 (27)	0.22
4-6	12 (57)	205 (47)	
7-10	2 (10)	114 (26)	
Resuscitation measures:			
Positive pressure ventilation	22 (92)	422 (89)	0.99
Intubation	14 (58)	334 (70)	0.22
Cardiac compressions	9 (38)	149 (31)	0.52
Epinephrine	6 (25)	87 (18)	0.41
Lowest pH, mean (S.D.)*	6.9 (6.8,7.0)	6.9 (6.8,7.0)	0.47
Worst base deficit, mean (S.D.)*	−19 (−26,-15)	−18 (−22,-14)	0.32
Assigned to erythropoietin	14 (58)	243 (51)	0.49

Abbreviations:
HIE = Hypoxic-ischemic encephalopathy
IQR = Interquartile range
* Two genetic and 39 nongenetic infants had missing data on lowest pH. Two genetic and 51 nongenetic infants had missing data on worst base deficit.

and neonatal encephalopathy, as they portend a higher rate of adverse outcomes.[16] Thus, although the diagnosis of a genetic or congenital anomaly takes time and may not alter the acute treatment of HIE, it may impact future counseling with regard to neurodevelopmental outcomes.

Strengths of this study include the large sample size, the prospectively applied inclusion criteria for HIE, and the high quality of outcome data collected at age two years. The main limitation of the study is that not all infants underwent genetic testing or imaging studies to detect structural organ anomalies; thus, 5% is likely an underestimate of the true incidence of genetic or congenital anomalies in infants with HIE. Furthermore, infants with a genetic abnormality that was recognized antepartum or within the first day of life, such as trisomy 21, were excluded from the HEAL trial and therefore not captured in this study. Because we did not collect information about the exact nature of the genetic testing that was done (e.g., microarray or whole exome sequencing), our study is unable to provide insights into the yield of specific genetic tests in this population. Finally, we are unable to evaluate risk factors for HIE. Maternal chorioamnionitis, a known risk factor for HIE,[1] was significantly more common (16%) in infants with HIE alone than among infants diagnosed with a genetic or congenital anomaly (0%), suggesting that these two factors lie on separate causal pathways in the pathogenesis of HIE. However, no conclusions can be made regarding risk factors for HIE since our study lacks unaffected control infants.

Conclusions

We found that 5% of infants undergoing therapeutic hypothermia for HIE were diagnosed with a genetic or congenital anomaly that was not apparent during the first day of life. Clinical markers of HIE severity were similar in those with and without a genetic or congenital anomaly. However, the presence of a genetic or congenital anomaly was associated with worse two-year outcomes.

TABLE 3.
Comparison of 2-Year Outcomes and Neonatal EEG and MRI Findings in Infants With and Without a Genetic or Congenital Anomaly

Outcomes	Genetic or Congenital Anomaly Present	No Genetic or Congenital Anomaly	*P* Value
Primary outcome	n = 24	n = 456	
NDI or death	18 (75)	226 (50)	0.02
5-Level secondary outcome	n = 24	n = 456	0.005*
No NDI	6 (25)	230 (50)	
Mild NDI	3 (12)	53 (12)	
Moderate NDI	8 (33)	61 (13)	
Severe NDI	4 (17)	50 (11)	
Died	3 (12)	62 (14)	
Motor outcome among survivors	n = 21	n = 394	
CP	6 (32)	50 (13)	0.02
GMFCS ≥ 1	6 (29)	33 (8)	0.002
Bayley III scores among survivors†	n = 20	n = 376	
Cognitive ≤85	13 (65)	50 (13)	0.02
Language ≤85	13 (65)	50 (13)	0.02
Motor ≤85	14 (70)	50 (13)	<0.001
Cognitive, median (IQR)	83 (69, 90)	90 (80, 100)	0.01
Language, median (IQR)	71 (62, 87)	89 (74, 103)	0.008
Motor, median (IQR)	85 (64, 95)	94 (85, 103)	0.009
EEG in the first 24 hours	n = 23	n = 460	
Electrographic seizure	7 (33)	103 (22)	0.24
Worst background pattern			0.33
Normal	5 (22)	181 (40)	
Excessively discontinuous	10 (43)	161 (35)	
Burst suppression, low voltage, or status epilepticus	8 (35)	113 (25)	
Neonatal brain MRI	n = 22	n = 451	
MRI injury score,[10] median (IQR)	7 (2, 39)	8 (2, 22)	0.78
MRI injury severity			0.92
None (injury score = 0)	4 (18)	96 (21)	
Mild (injury score = 1-11)	8 (36)	169 (37)	
Moderate (injury score = 12-32)	4 (18)	93 (21)	
Severe (injury score = 33-138)	6 (27)	93 (21)	
MRI pattern of injury			0.17‡
No injury	6 (27)	141 (31)	
Any central gray	5 (23)	169 (37)	
Any peripheral watershed	3 (14)	116 (26)	
Global injury	2 (9)	33 (7)	
Cerebral dysgenesis	6 (25)	0 (0)	<0.001

Abbreviations:
CP = Cerebral palsy
EEG = Electroencephalography
GMFCS = Gross Motor Function Classification System
IQR = Interquartile range
MRI = Magnetic resonance imaging
NDI = Neurodevelopmental impairment
* Alive and no NDI versus alive and any NDI.
† No genetic and five nongenetic infants had missing data on Bayley language and motor scores.
‡ Any central gray, peripheral watershed, or global injury versus no injury.

CRediT authorship contribution statement

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Declaration of competing interest

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2024.02.007.

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