IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Original Article

Follow-up of Neonates with Hypoxic Ischemic Encephalopathy in First Year of Life

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ABSTRACT

Background: Hypoxic-ischemic encephalopathy (HIE) is a significant cause of developmental delays in infants, carrying profound long-term implications. Early detection of developmental impairments is crucial for improving outcomes. This study aimed to evaluate the developmental status of infants diagnosed with HIE using the Denver II test at one year of age.

Methods: This prospective cohort study was conducted at Qaim Hospital and Imam Reza Hospital from October 2019 to August 2020. A total of 39 full-term infants diagnosed with HIE were included. The severity of HIE was classified according to the Sarnat clinical staging system (grade 1: mild, grade 2: moderate, grade 3: severe). Developmental outcomes were assessed at one year using the Denver II test, evaluating four domains: gross motor, fine motor, personal-social, and speech development. Developmental delays were classified based on the number and severity of failures in the test.

Results: Of the 39 infants, 87.2% showed normal developmental outcomes at one year, 7.7% were suspected of having developmental delays, 2.6% exhibited mild developmental delays, and 2.6% demonstrated moderate developmental delays. There was no significant association between developmental outcomes and variables such as gestational age, maternal age, parity, or severity of HIE (all $p > 0.05$). However, the majority of infants with mild and moderate HIE performed normally on the Denver II test, while a smaller proportion of those with severe HIE showed developmental delays.

Conclusion: This study highlights that most infants with HIE, particularly those with mild to moderate forms, achieve normal developmental outcomes by one year of age. However, the presence of developmental delays in a minority of infants with more severe HIE suggests the need for ongoing monitoring. Larger, multi-center studies with longer follow-up are required to better understand the long-term neurodevelopmental trajectories of infants with HIE.

Keywords: Developmental delays, Denver II test, Hypoxic-ischemic encephalopathy, Neonatal care, Perinatal asphyxia

Introduction

Asphyxia and hypoxic-ischemic encephalopathy (HIE) are significant contributors to developmental disorders in infants, carrying profound long-term implications for affected individuals and their families, both mentally and economically. Early detection of developmental delays is crucial for improving outcomes. This follow-up study aims to assess the developmental status of infants diagnosed with HIE using the Denver II test, a widely recognized tool for the

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Please cite this paper as:
Rafinezhad R, Loghmani T, Khodashenas E, Farhat AS, Mohamadzadeh A, Boskabadi H, Maamouri Gh, Faramarzi R, Bakhtiari E. Follow-up of Neonates with Hypoxic Ischemic Encephalopathy in First Year of Life. Iranian Journal of Neonatology. 2025 Oct: 16(4). DOI: 10.22038/ijn.2025.78016.2510

early identification of developmental disorders (1). The study includes 39 infants diagnosed with HIE, categorized according to the Sarnat clinical staging system. Infants presenting with hypervigilance, irritability, hyperreflexia, inattention, and seizures were classified as having mild HIE (grade 1). Those exhibiting lethargy, hypotonia, decreased reflexes, myotonic pupils, and seizures were classified as moderate HIE (grade 2), while severe manifestations such as apnea, severe seizures, or coma were categorized as severe HIE (grade 3). The Denver II test, conducted at one year of age under the supervision of pediatric neurologists, evaluates the infant's performance in four domains: gross motor, fine motor, personal-social, and speech development. Delays were defined by the inability to perform an action that 75-90% of children at the same chronological age could complete. Two or more warnings were considered failures, and these were further classified as suspected, mild, moderate, or severe developmental delays based on the number and type of failures (2).

The perinatal period is critical for human development, marking the transition from maternal dependence to independent life. This separation, however, does not always occur without complications, and the risk of infant mortality is higher during this period than at any other stage, except in older adults (3). The impact of perinatal insults, particularly to the brain, can result in lifelong disabilities. Fetal brain development begins in the first trimester of pregnancy, notably around the fourth week, and continues throughout gestation, with brain development persisting into early childhood and adolescence (4-6).

Developmental delays are characterized by discrepancies in a child's performance across various domains, including motor skills, communication, and cognitive abilities, when compared to age-matched peers. Globally, 5-10% of children experience developmental delays, with gross motor delays being the most common (7). Multiple etiologies contribute to developmental delays, encompassing genetic, environmental, and psychosocial factors. Environmental causes are further divided into antenatal, perinatal, and postnatal factors, with asphyxia and HIE during the perinatal period being significant contributors (8).

Asphyxia is characterized by a reduction in arterial oxygen levels (hypoxemia), leading to cellular hypoxia and ischemia. In newborns, inadequate oxygenation can result in widespread organ damage, particularly to the brain, potentially leading to HIE, which is associated with seizures, intracranial hemorrhage, infarctions, and other neurological sequelae (9). The cardiovascular, respiratory, and renal systems are also affected, contributing to further morbidity (10). Hypoxic-ischemic events can lead to disturbances in electrolytes, such as hyponatremia, hypocalcemia, and hyperkalemia, and affect metabolic parameters, including increased urea and creatinine levels (11). The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics provide guidelines for diagnosing asphyxia in neonates, which include criteria such as an umbilical arterial pH <7, an Apgar score <3 for more than five minutes, and neurological manifestations like seizures or coma (12).

In developed countries, advances in obstetric and neonatal care have reduced the incidence of perinatal asphyxia, with a reported mortality rate of less than 0.1%. However, in developing nations, the prevalence of perinatal asphyxia remains high, with mortality rates ranging from 21.6% to 32% (17). The World Health Organization (WHO) estimates that 4 to 9 infants per 1,000 live births are affected by asphyxia each year, with approximately 1.2 million neonatal deaths attributed to asphyxia globally (13).

Maternal factors, including age, education, socioeconomic status, and health conditions such as hypertension or diabetes, can contribute to the risk of asphyxia during the perinatal period. Perinatal factors such as fetal distress, prolonged labor, and abnormal presentations further exacerbate this risk (14).

Neonatal encephalopathy resulting from ischemic-hypoxic injury follows a multi-phase progression, starting with an acute phase characterized by anaerobic metabolism and neuronal cell death. The latent phase, occurring from 6 to 15 hours post-injury, is followed by a secondary energy failure, and the late phase may involve brain regeneration and long-term neurological impairments (15). Imaging techniques, including ultrasound, CT scans, and MRI, play an essential role in diagnosing brain lesions associated with HIE, although their sensitivity and negative predictive value remain limited (16).

Interventions aimed at preventing and treating HIE include precise control of body temperature, correction of metabolic imbalances, and adequate oxygenation. Emerging therapies such as melatonin, erythropoietin, stem cell therapy, and neuroprotective agents like allopurinol and xenon

have shown promise in mitigating the effects of ischemic injury (17-19).

Methods

This prospective cohort study was conducted to assess the developmental outcomes of infants diagnosed with hypoxic-ischemic encephalopathy (HIE) following their admission to the neonatal intensive care units (NICUs) of Qaem Hospital and Imam Reza Hospital. The study included 39 newborns diagnosed with HIE during their NICU stay. The study period spanned from October 2019 to August 2020.

Inclusion criteria were as follows: a 1-minute Apgar score of less than 3 or a 5-minute Apgar score of less than 5, an umbilical cord pH of less than 7.2, a base excess (BE) of less than -12, and the presence of clinical signs of HIE, including hypotonia, seizures, and impaired consciousness.

Exclusion criteria included congenital abnormalities (e.g., birth defects, neural tube defects) and metabolic diseases (e.g., urea cycle disorders, galactosemia).

For each infant, relevant data regarding the newborn and mother were recorded. The degree of HIE in each infant was classified according to the Sarnat clinical staging system. Infants exhibiting hypervigilance, irritability, hyperreflexia, inattention, and seizures were categorized as having mild HIE (grade 1). Those with lethargy, hypotonia, reduced reflexes, myotonic pupils, and seizures were categorized as moderate HIE (grade 2). Infants presenting with apnea, severe seizures, or coma were classified as having severe HIE (grade 3).

At the age of 12 months, all infants underwent developmental assessment using the Denver II test. This developmental screening tool evaluates four domains: gross motor skills, fine motor skills, personal-social development, and speech/ language development, with performance compared to age-appropriate functional expectations. In the Denver II test, performance below the 75-90% threshold for age-appropriate milestones was considered a "warning," while performance below 75% was considered a "failure." Two or more warnings were classified as a failure, and the number of failures was used to determine the degree of developmental delay: one failure was classified as suspected developmental delay, two failures as mild developmental delay, three failures (with two failures in the same domain) as moderate developmental delay, and four failures as severe developmental delay.

Descriptive statistics were used to summarize the characteristics of the participants, including measures of central tendency, dispersion, and frequency distribution, which were presented in appropriate tables and graphs. For comparisons between two groups, an independent t-test was used. The chi-square test was employed to assess the potential relationships between background variables and the primary outcome. Comparisons of developmental outcomes between baseline and one-year follow-up were analyzed using a paired t-test. Statistical significance was set at a p-value of <0.05.

Ethical approval

This study was approved by the Research deputy and Ethics committee of the Mashhad university Of Medical Science. The ethics approval code is IR.MUMS.MEDICAL.REC.1397.612. We obtained a written informed consent signed by parents of all of our patients at the beginning of admission to the hospital.

Results

Among the 39 newborns studied, 61.5% were male, and 38.5% were female. The mean birth weight was 3191.24 ± 497.05 grams, with a length of 50.72 ± 1.99 cm and head circumference of 36.64 ± 1.13 cm. The mean gestational age was 38.9 ± 1.23 weeks (Table 1).

Table 1. Neonatal Characteristics and Clinical Findings

Variable	Frequency (%)/Mean±SD
Gender	
Male	24 (61.5%)
Female	15 (38.5%)
Birth weight (grams)	3191.24 ± 497.05
Height (cm)	50.72 ± 1.99
Head circumference (cm)	36.64 ± 1.13
Gestational age (weeks)	38.9 ± 1.23
Apgar score (1st minute)	4.75 ± 2.33
Apgar score (5th minute)	7.54 ± 1.77
Tone	
Normal	29 (74.4%)
Loose tone	2 (5%)
Hypotony	8 (20%)
Respiratory issues	
Respiratory distress	20 (51.3%)
Bradycardia	2 (5.1%)
Both conditions	4 (10.3%)
None	13 (33.3%)
HIE Severity	
Grade 1 (mild)	29 (74.4%)
Grade 2 (moderate)	8 (20.5%)
Grade 3 (severe)	2 (5.1%)
Ventilation requirement	
No ventilation	22 (56.4%)
Oxygen hood	2 (5.1%)
Nasal CPAP	8 (20.5%)
Nasal SIMV	1 (2.6%)
Intubation	6 (15.4%)
Resuscitation method	
No resuscitation	27 (69.2%)
Positive pressure	9 (23.1%)

ventilation (PPV)	
Heart massage	3 (7.7%)
Table 1. Continued	
Umbilical cord pH	
< 7.2	30 (85.7%)
≥ 7.2	5 (14.3%)
Thrombocytopenia	5 (13.2%)
Coagulation tests	
Impaired	8 (20.5%)
Normal	4 (10.3%)
Not performed	27 (69.2%)

Apgar scores at the first minute averaged 4.75 ± 2.33, improving to 7.54 ± 1.77 at the fifth minute. Hypotonia was observed in 20% of newborns, while 74.4% had normal muscle tone. Respiratory distress was noted in 51.3% of cases, while 5.1% had bradycardia, and 10.3% exhibited both conditions. Regarding hypoxic-ischemic encephalopathy (HIE), 74.4% of infants had mild HIE, 20.5% had moderate HIE, and 5.1% were classified as severe (Table 1).

Ventilatory support was not required for 56.4% of newborns, while 20.5% needed nasal CPAP, 5.1% required an oxygen hood, 2.6% received nasal SIMV, and 15.4% were intubated. Positive pressure ventilation was administered to 23.1% of infants, while 7.7% required heart massage. Umbilical cord pH was below 7.2 in 85.7% of cases. Thrombocytopenia was present in 13.2%, and 20.5% of newborns had impaired coagulation test results. Cerebral imaging revealed periventricular leukomalacia in one case and suspected subarachnoid hemorrhage in another (Table 1).

The mean maternal age was 30.14 ± 6.44 years, ranging from 18 to 44 years. Half of the mothers were primiparous. Cesarean section was the predominant mode of delivery (66.7%). Delivery complications occurred in 23.1% of cases, including difficult delivery (12.8%) and instrumental delivery (10.3%). Maternal comorbidities included gestational diabetes (23%), hypertension (10.2%), and hypothyroidism (10.2%) (Table 2).

At discharge, 66.7% of newborns showed partial recovery, while 33.3% were discharged at parental request (Table 2).

For all infants, at the age of one year, the Denver 2 test was performed. If the child's performance in 75-90% of the test was lower than expected for their age, it was considered a warning. If the infant's performance was below the 75th percentile for their age, it was considered a failure. Two or more warnings were classified as a failure. In the interpretation of the test results, one failure was classified as suspected developmental delay, two failures as mild developmental delay, three failures (with two failures in the same domain) as moderate developmental delay, and four failures as severe developmental delay. According to the results of the Denver 2 test performed at one year of age, 34 cases (87.2%) were normal, three cases (7.7%) were suspicious, one case (2.6%) had developmental delay, and one case (2.6%) had moderate developmental delay.

Table 2. Maternal Characteristics and Birth Information

Variable	Frequency (%)/Mean ± SD
Maternal age (years)	30.14 ± 6.44
First birth	18 (50%)
Second birth	7 (19.4%)
Third birth	7 (19.4%)
Fourth birth	1 (2.8%)
Fifth birth	2 (5.6%)
Sixth birth	1 (2.8%)
Mode of delivery	
Vaginal	13 (33.3%)
Cesarean section	26 (66.7%)
Delivery complications	
Difficult delivery	5 (12.8%)
Instrumental delivery	4 (10.3%)
No complications	30 (76.9%)
Maternal health conditions	
No conditions	13 (33.3%)
Water sac rupture	8 (20.5%)
Gestational diabetes	9 (23%)
Hypertension	4 (10.2%)
Hypothyroidism	4 (10.2%)
Epilepsy	3 (7.7%)
Heart disease	3 (7.7%)
Asthma	2 (5%)
Other conditions	5 (2.5%)
Discharge status	
Partial recovery	26 (66.7%)
Parental consent discharge	13 (33.3%)

The t-test results show that gestational age (p=0.853), mother's age (p=0.598), mother's parity (p=0.412), Apgar at one minute (p=0.752), Apgar at five minutes (p=0.619), birth weight (p=0.729), birth length (p=0.385), and birth head circumference (p=0.436) were not significantly different in newborns who had a normal Denver test result compared to newborns whose test result was abnormal (Table 3).

Fisher's exact test was used to check the relationship between qualitative variables and Denver test results. The results of this test show that the gender of the newborn (p>0.99), the parity of the mother (p=0.891), the type of delivery (p=0.648), difficult delivery (p=0.752), the muscle tone of the newborn (p=0.286), the initial complaint (p=0.333), the severity of HIE

(p=0.286), history of maternal diseases (p=0.620), type of ventilation (p=0.770), resuscitation

Table 3. Comparison of quantitative variables in newborns with normal and abnormal tests

Variable	Newborn with normal test	Newborn with abnormal test	P value*
Gestational age	38.91± 1.21	38.80 ± 1.48	0.853
Mother's age	30.33 ± 6.21	28.50± 9.03	0.598
Parity	2.09 ±1.37	1.50 ± 1.00	0.891
Apgar 1	4.79 ± 2.32	4.33± 2.88	0.752
Apgar 5	7.45 ± 1.83	8.00 ± 1.00	0.619
Birth weight	3202.33± 470.07	3118.00± 714.08	0.729
birth height	50.53 ± 2.13	51.67± 0.57	0.385
Birth Head circumference	34.56± 1.18	35.25 ± 0.35	0.436

* t-test

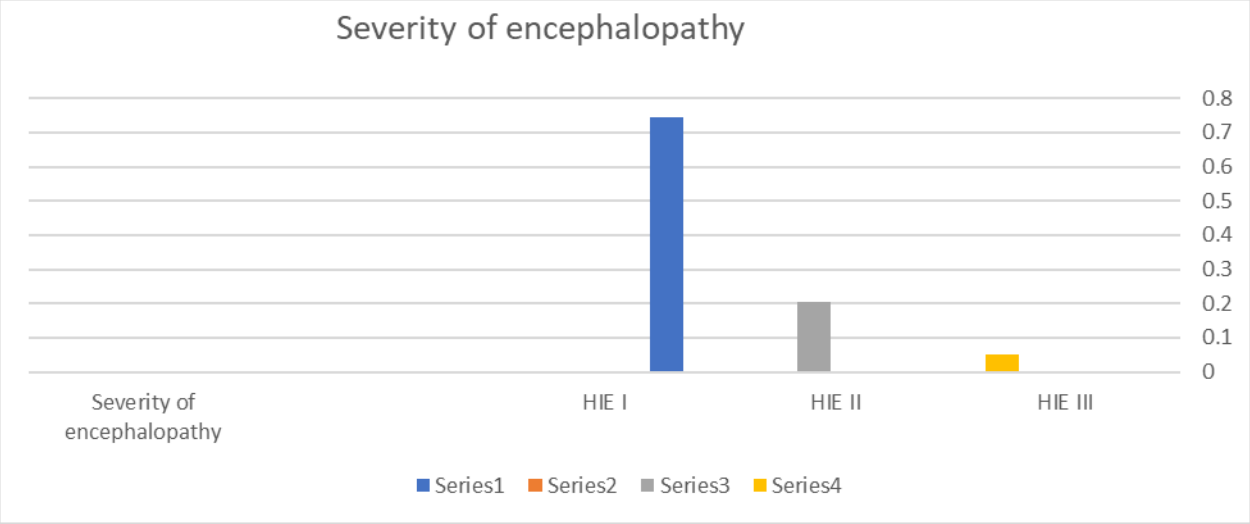

Figure 1. Number of Neonates with Hypoxic-ischimic Encephalopathy By Severrity in The first Year

(p=0.57), test results (thrombocytopenia p=0.527, umbilical cord pH p=0.380, coagulation status p>0.99), brain imaging result (p=0.77), and discharge method (p=0.648) showed no significant relationship with the Denver test result. Newborns with HIE I (86.7%), HIE II (87.5%), and HIE III (50%) had normal results on the Denver test (Table 4).

Table 4. Relationship of qualitative variables with Denver test result

variables		Denver tests 'result		P-value
		normal	abnormal	
Sex	Female Male	13 (86.7%) 21 (87.5 %)	2 (13.3%) 3 (12.5%)	P>0.99
Mode of delivery	NVD CS	12 (92.3%) 22 (84.6%)	1 (7.7%) 4(15.4%)	P=0.648
Difficult or instrumental delivery	hard with tools none	4 (80%) 4 (100%) 26 (86.7%)	1 (20%) 0 4 (13.3%)	P = 0.752
Newborn Tone	normal loos hypo tone	26 (89.7%) 1 (50%) 7 (87.5%)	3 (10.3%) 1 (50%) 1 (12.5%)	P= 0.286
Initial complaint	respiratory distress Bradycardia	19 (95%) 2 (100%)	1 (5%) 0	P= 0.333

	Both	3 (75%)	1 (25%)	
	none	10 (76.9%)	3 (23.1%)	

Table 4. Continued

HIE	I	26(89.7%)	3 (10.3%)	P= 0.286
	II	7 (87.5%)	1 (12.5%)	
	II	1 (50%)	1 (50%)	
Ventilation	No ventilation	18 (81.8%)	4 (18.2%)	P = 770
	Nasal CPAP	8 (100%)	0	
	Intubation	5 (83.3%)	1 (16.7%)	
	Oxyhood	2 (100%)	0	
	Nasal SIMV	1 (100%)	0	
Resuscitation	No resuscitation	25 (92.6%)	2 (7.4%)	P= 0.057
	Heart massage	1 (33.3%)	2 (66.7%)	
	PPV	8 (88.9%)	1 (11.1%)	
Thrombocytopenia	Yes	4 (80%)	1 (20%)	P= 0.527
	no	29 (87.9%)	4 (12.1%)	
coagulation status	Normal	4 (100%)	0	p> 0.99
	disturbed	7 (87.5%)	1 (12.5%)	
	No test	23 (85.2%)	4 (14.8%)	
Brain imaging	Sonography	6 (100%)	0	P= 0.077
	PVL in sonography	0	1 (100%)	
	CSVT in MRI	1 (100%)	0	
	SAH in CT	1 (100%)	0	
	Diffuse periventricular ischemia	0	1(100%)	
	No imaging	26(89.7%)	3 (10.3%)	
discharge	Personal satisfaction	12 (92.3%)	1 (7.7%)	P=0.648
	Partial recovery	22 (84.6%)	4(15.4%)	

* Fisher's Exact Test

Discussion

The present study aimed to evaluate the developmental outcomes of infants diagnosed with hypoxic-ischemic encephalopathy (HIE) using the Denver II test at one year of age. Our findings indicate that a significant proportion of these infants exhibit normal developmental trajectories, with 87.2% classified as normal, 7.7% as suspicious, 2.6% with developmental delay, and 2.6% with moderate developmental delay. These results underscore the potential for favorable developmental outcomes in infants with HIE, particularly those with milder forms of the condition.

Comparatively, previous research has reported varying outcomes based on the severity of HIE and the assessment tools employed. For instance, a study utilizing the Denver Developmental Screening Test II (DDST-II) at six months of age found that 42.6% of infants had severe adverse outcomes, highlighting the importance of early assessment in predicting long-term neurological deficits (20). Another study reported that 52.2% of infants with HIE had normal neurodevelopmental outcomes, while 47.8% exhibited delays, with fine motor skills being the most affected domain (21). These discrepancies may be attributed to differences in assessment timing, the severity distribution of HIE, and intervention strategies.

The Denver II test has demonstrated utility in the early identification of developmental delays among infants with HIE. Its application at six months of age has been shown to predict severe neurological outcomes effectively (20). However, the sensitivity and specificity of the test may vary depending on the timing of administration and the population studied. In our cohort, the use of the Denver II test at one year of age provided valuable insights into the developmental status of infants post-HIE, aligning with findings that emphasize the importance of early and repeated developmental assessments.

Notably, the severity of HIE plays a critical role in determining developmental outcomes. Our study observed that infants with mild HIE had a higher likelihood of normal developmental outcomes compared to those with moderate or severe HIE. This observation is consistent with existing literature, which indicates that increased severity of HIE correlates with a higher incidence of developmental delays (22). In contrast, a study

by Shukla et al. (2018) evaluating 38 infants diagnosed with grade 2 and 3 HIE using the Peabody Development Motor Scales-2 test at 12 to 14 months found that grade 3 HIE cases (p=0.01) were significantly more related to developmental delay compared to grade 2 HIE (23). Our findings show that while the rate of developmental delays was lower than in Shukla et al.'s study, this may be due to differences in diagnostic criteria or the tools used for developmental assessment.

In another study conducted in 2018, 50 infants with asphyxia were evaluated using the Denver II test. The study found that all newborns with HIE I and 72.4% of HIE II cases had normal results, while 100% of HIE III cases exhibited abnormal results (5). In our study, 89.7% of HIE I, 87.5% of HIE II, and 50% of HIE III infants had normal Denver test results, showing a somewhat higher proportion of normal outcomes compared to that study. This discrepancy may be attributed to differences in sample size, inclusion criteria, or variations in neonatal care and interventions.

Additional insights come from Wang et al. (2020), who evaluated 195 infants with perinatal problems, including asphyxia, using the brainstem auditory evoked potential (BAEP) at six months. They subsequently assessed neurodevelopmental status at two years using the Brain Development Index (MDI), a form of the Bailey test. The study concluded that BAEP is capable of predicting neurodevelopmental outcomes and suggested earlier interventions for cases with abnormal BAEP values. Notably, gestational age (p=0.000) and asphyxia (p=0.048) significantly affected developmental disorders (24). In contrast, our study found no significant impact of gestational age on developmental disorders. This difference may be because our study included only term infants, whereas Wang's study included both term (n=100) and preterm (n=95) newborns. Furthermore, variations in assessment tools may contribute to these discrepancies.

Further support for the association between HIE and long-term developmental impairment comes from Lee et al. (2020), who evaluated 29 children aged 6 to 8 years with a history of HIE-related hypothermia using the Wechsler Intelligence Scale for Children (WISC-IV), the Children's Movement Assessment Battery (MABC-2), and the Strengths and Difficulties Questionnaire (SDQ). Their findings revealed that these children exhibited poorer developmental outcomes compared to their age-matched peers without a history of HIE. The study also suggested that therapeutic hypothermia was associated with improved developmental outcomes (25). This aligns with existing evidence indicating that early therapeutic interventions can mitigate some of the neurodevelopmental consequences of HIE.

Adhikari et al. (2017) assessed infants with a history of HIE at 3, 6, 9, 12, 18, and 24 months using the Denver II test. At one year of age, they found that 8.6% had speech disorders, 9.9% had social disorders, 22.9% had gross motor delays, and 8.6% had fine motor delays (26). Additionally, Mah et al. observed that 79.5% of infants with a history of HIE exhibited developmental problems, with 74.4% classified as HIE II and 25.6% as HIE III (1). In contrast, our study found that 12.8% of infants had abnormal Denver II test results. The lower prevalence of developmental delays in our cohort may be due to differences in the severity of HIE among participants, as only 1.5% of our cases were HIE III, compared to higher proportions in the Adhikari and Mah studies.

While this study provides valuable insights into the developmental outcomes of infants diagnosed with hypoxic-ischemic enceph-alopathy (HIE), several limitations must be considered when interpreting the findings. The study included 39 infants, which is a relatively small sample size. This limits the statistical power and generalizability of the results to larger populations. Additionally, the study was conducted at two hospitals, which may limit the generalizability of the findings to different healthcare settings, particularly in regions with varying levels of neonatal care. The developmental assessment was performed at one year of age, which provides a snapshot of early neurodevelopmental status. However, neurodevelopmental delays may become more apparent with age, and longer-term follow-up beyond one year could have provided a more comprehensive understanding of the long-term impact of HIE on development. Further longitudinal studies are needed to assess the persistence and progression of developmental delays over time. While the Denver II test is widely used for developmental screening, it primarily focuses on assessing milestones in four domains: gross motor, fine motor, personal-social, and speech development. The test may not capture all aspects of cognitive, emotional, or behavioral development, which could provide a more complete picture of an infant's developmental status. Additionally, develop-mental milestones assessed by the Denver II may not fully reflect the impact of more subtle neurological impairments that could affect social,

cognitive, or emotional development.

Despite these limitations, our study provides important insights into the early neurodevelopmental outcomes of infants with HIE and highlights the potential for favorable outcomes in infants with milder forms of the condition. However, further research with larger sample sizes, longer follow-up periods, and consideration of additional confounding factors is necessary to better understand the full spectrum of developmental outcomes in this population.

Conclusion

In conclusion, our study reinforces the significance of early developmental assessment using tools like the Denver II test in infants with HIE. The findings suggest that a substantial proportion of these infants, especially those with mild HIE, may achieve normal developmental milestones by one year of age. Nonetheless, continuous monitoring and a multidisciplinary approach remain essential to identify and support infants at risk for developmental delays, optimizing their long-term neurodevelopmental outcomes.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflict of interest.

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