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Challenging Mild Hypoxic-Ischemic Encephalopathy: Insights Into Neurological Outcomes

Mustafa Canbeldek*[1], Coşkun Armağan*[2], Hüseyin Bahadır Şenol[3], Hüseyin Burak Baykara[4], Ayşen Bahar Baykara[5], Handan Güleryüz Uçar[6], Uluç Yiş[3], Funda Tüzün Erdoğan[2], Nuray Duman[2], Hasan Özkan[2]

[1]Department of Pediatrics, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye
[2]Division of Neonatology, Department of Pediatrics, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye
[3]Division of Pediatric Neurology, Department of Pediatric, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye
[4]Department of Child and Adolescent Mental Health and Diseases, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye
[5]Department of Psychology, İzmir Economy University Faculty of Science and Letters, İzmir, Türkiye
[6]Department of Radiology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye

What is already known on this topic?

- *Hypoxic-ischemic encephalopathy is a major cause of neonatal mortality and long-term neurological impairment.*
- *Therapeutic hypothermia is effective in moderate and severe HIE but is not currently recommended for mild HIE.*
- *Mild HIE has traditionally been considered to have a favorable prognosis, yet emerging evidence suggests that it may still be associated with subtle but significant neurodevelopmental impairments.*

What this study adds on this topic?

- *This study demonstrates that a substantial proportion of infants with mild HIE exhibit neurological abnormalities, challenging the notion that mild HIE is benign.*

ABSTRACT

Objective: This study aims to evaluate the long-term neurological outcomes of neonates diagnosed with mild hypoxic-ischemic encephalopathy (HIE) and compare them with moderate/severe cases, hypothesizing that a significant proportion of mild HIE cases may experience adverse neurodevelopmental sequelae.

Materials and Methods: This was a cross-sectional observational study evaluating the neurodevelopmental outcomes of neonates with mild versus moderate/severe HIE. Maternal, perinatal, and neonatal characteristics along with treatments were documented. Neurological outcomes were assessed via brain MRI, the Ankara Developmental Screening Inventory (ADSI), and developmental milestones.

Results: The study included 42 infants, 20 (47.6%) were classified as having mild HIE and 22 (52.4%) as moderate/severe HIE. Baseline characteristics were similar except that moderate/severe cases had lower 1-minute Apgar scores (median 4 vs. 6; $P = .02$) and more frequent need for advanced resuscitation (68% vs. 25%; $P = .006$). All moderate/severe infants received TH vs. none in the mild group. Invasive mechanical ventilation and adjuvant neuroprotective agents were also more frequently used in the moderate/severe group. Magnetic resonance imaging abnormalities consistent with HIE were present in 2/12 mild cases (16.7%) vs. 8/19 (42.1) in moderate/severe cases. There were no significant differences in HIE injury pattern between the 2 groups ($P = .197$). On ADSI screening, 8/12 (66.7%) mild HIE survivors showed gross motor delay compared with 5/7 (71.4%) moderate/severe survivors.

Conclusion: Even infants with mild HIE are at risk of adverse neurological outcomes. The development of more sensitive diagnostic tools could improve treatment strategies and early interventions, ultimately impacting prognosis. With proper recognition, tailored follow-up, and appropriate therapeutic approaches, potential neurodevelopmental impairments in mild HIE cases could be mitigated.

Keywords: Hypoxic-ischemic encephalopathy, neurodevelopment, neonatal encephalopathy, follow-up, brain injury

*These authors contributed equally to this work and share first authorship.

Corresponding author:
Funda Tüzün Erdoğan
✉ funda.tuzun@deu.edu.tr

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- *Abnormal MRI findings and developmental delays were present even in mild cases, indicating the need for refined diagnostic tools and close follow-up.*
- *A Thompson score ≥4 was significantly associated with poor neurological outcomes, suggesting its potential role as an early prognostic marker even in mild cases.*
- *The findings underscore the importance of enhanced neurodevelopmental surveillance and the need for consensus on management strategies for mild HIE.*

INTRODUCTION

Neonatal hypoxic-ischemic encephalopathy (HIE) remains a leading cause of neonatal mortality and long-term neurological impairment worldwide with an incidence of 2-9 per 1000 live births and accounting for up to 9% of neonatal deaths.[1,2] Pathophysiologically, HIE triggers energy failure, excitotoxicity, and oxidative injury, culminating in neuronal death and evolving brain damage.[3,4]

Clinical staging—most commonly via the Sarnat classification and Thompson scoring—guides early management and prognostication, while amplitude-integrated electroencephalogram (aEEG) provides supplementary neurophysiological insights.[5] Therapeutic hypothermia has not been tested in mild HIE since infants with mild encephalopathy were excluded from most clinical trials. Recently, its efficacy and indications in this subgroup have become a topic of growing debate.[6-8]

Traditionally, the prognosis for infants diagnosed with mild HIE was considered uniformly favorable, leading to a longstanding clinical focus on moderate and severe cases while comparatively neglecting those with milder presentations. However, emerging studies employing diffusion-weighted magnetic resonance imaging (MRI) and long-term developmental surveillance have revealed that a subset of infants with mild HIE may exhibit clinically significant alterations in brain structure and function.[7,9-14] These findings suggest that mild HIE may not be as harmless as previously thought, and the risk of brain injury and long-term neurodevelopmental problems in these infants has likely been underestimated.

In this study, we hypothesized that a subset of neonates clinically classified as mild HIE will manifest adverse neurodevelopmental outcomes. Specifically, the aims were to (i) compare long-term neurological and developmental profiles between mild and moderate/severe HIE groups and (ii) evaluate the predictive value of early clinical and biochemical markers for later impairment. To address these objectives, a cross-sectional observational study was conducted at a tertiary neonatal intesive care unit (NICU), integrating detailed perinatal data, standardized neurological assessments, neuroimaging, and structured developmental screening.

MATERIALS AND METHODS

Study Design

This was a cross-sectional observational study evaluating neurodevelopmental outcomes in neonates with mild and moderate/severe HIE. The study population included infants diagnosed with HIE admitted to the NICU between January 1, 2018, and June 30, 2023. Ethical approval for the study was obtained from the Dokuz Eylül University Non-Interventional Local Research Ethics Committee (Approval No: 2023/25-08; Date: August 2, 2023). Written informed consent was obtained from the patients' families who agreed to take part in the study.

Study Population and Classification of Hypoxic-Ischemic Encephalopathy

The study population consisted of infants with a gestational age of 34 weeks or more who were clinically diagnosed with HIE. Exclusion criteria included the presence of metabolic, genetic, or congenital cardiac diseases.

Hypoxic-ischemic encephalopathy diagnosis and severity was determined according to institution's standardized protocol, employing a 3-tiered assessment: (i) Perinatal risk indicators, including acute obstetric events (such as late or variable fetal heart rate decelerations, umbilical cord prolapse or rupture, uterine rupture, maternal trauma, maternal hemorrhage, or maternal cardiorespiratory arrest), as well as a 10-minute Apgar score of ≤5, requirement for assisted ventilation for ≥10 minutes after birth, and/or severe metabolic acidosis (defined as a pH <7.0 or base excess ≤−16 mmol/L within the first hour of life). For infants with borderline metabolic acidosis (pH 7.01-7.15 or base excess between −10 and −15.9 mmol/L) or when immediate blood gas results were unavailable, a combination of acute obstetric events with either a 10-minute Apgar score ≤5 or the necessity of assisted ventilation lasting ≥10 minutes, were considered. (ii) A structured neurological examination performed by experienced neonatologists using the modified Sarnat staging system. (iii) Amplitude-integrated electroencephalogram monitoring was used to assess cerebral background activity and detect moderate/severe suppression or seizures. This structured assessment aligns with national and international guidelines.[2,15,16]

Modified Sarnat staging system covered 6 clinical domains: level of consciousness, spontaneous activity, posture, muscle tone, primitive reflexes (sucking and Moro), and autonomic function (pupils, heart rate, and respiration).[16] Mild HIE was defined as 1-2 mild abnormalities across the 6 domains without any moderate or severe features, and with normal amplitude activity on aEEG. Moderate/severe HIE was defined as the presence of ≥3 moderate or severe abnormalities on examination and/or abnormal aEEG background. These definitions are in line with those used in recent large-scale cohort studies.[7,17] Clinical decisions like intubation or passive cooling were center specific and not part of classification.

Data Collection

Data were collected from patient files, the hospital database, and through interviews or telephone calls with the families of the patients. The collected data included maternal and antenatal characteristics, perinatal and neonatal clinical data, initial blood gas parameters (pH, base excess, lactate, bicarbonate), therapeutic hypothermia administration, adjunctive neuroprotective therapies (such as erythropoietin, allopurinol, melatonin, magnesium sulfate, and topiramate), and supportive therapies (such as invasive mechanical ventilation, vasoactive drug use, respiratory support, and nutritional support at discharge). Additionally, neurological assessment data, including cranial MRI, EEG, aEEG, and neurological examination findings at discharge, were also collected.

Magnetic Resonance Imaging Protocol

Cranial MRI examinations were carried out using a 1.5 Tesla scanner (Gyroscan Achieva, Release 8.1; Philips Medical Systems, The Netherlands), incorporating T1-weighted, T2-weighted, and diffusion-weighted sequences. Scans were ideally scheduled between the fourth and seventh days of life, with adjustments based on the infant's clinical condition. While MRI was routinely performed in neonates with moderate or severe HIE, its use in mild cases was determined individually by the attending consultant. Indications for imaging in mild HIE included prolonged resuscitation at birth—particularly in infants transferred from other facilities—previous exposure to passive cooling, persistent or evolving neurological concerns, and the need for individualized neurodevelopmental risk assessment during extended NICU care.

Magnetic resonance imaging findings were evaluated by a pediatric neuroradiologist. Magnetic resonance imaging findings were classified using a previously established scoring system that evaluates the extent and location of hypoxic-ischemic brain injury. Based on this system, a score of 0 indicates no detectable abnormalities. Score 1A reflects focal injury confined to the frontal and parietal subcortical white matter, while Score 1B represents more widespread subcortical involvement including the frontal, parietal, and occipital regions. Score 2A corresponds to signal abnormalities in the deep gray matter structures such as the basal ganglia and thalami, as well as the posterior limb of the internal capsule. Score 2B indicates injury involving both the deep gray nuclei and cortical regions. The most severe category, Score 3, denotes extensive damage across the cerebral hemispheres.[18]

Neurological Prognosis Assessment

Families of the infants included in the study were contacted and invited for follow-up evaluations. Written consent was obtained from the families before data collection. The prospective data focused on the current neurological status of the patients, including assessments of neurodevelopmental milestones, antiepileptic use, visual and hearing impairments, the use of hearing aids, the presence of cerebral palsy, and the need for special education. These evaluations were conducted through direct interviews with the families or through telephone interviews. Delays defined as not achieving the milestone by the CDC "Learn the Signs. Act Early." red flag age thresholds. These thresholds represent the age by which most children (typically ≥75%) are expected to have achieved the milestone.[19]

During the study period, patients who were available were evaluated at the Department of Pediatric Neurology and the Department of Child Psychiatry. The Ankara Developmental Screening Inventory (ADSI) is a comprehensive tool designed to assess cognitive, motor, and mental development in infants aged 3-18 months similar to the Bayley Scales of Infant Development. The inventory is highly effective in identifying developmental risks by evaluating a range of abilities, including fine and gross motor skills, language, and cognitive functions.[20] Its criterion validity has been demonstrated, making it a reliable instrument for both clinical settings and routine infant check-ups, ensuring early detection of developmental delays across various domains.[21] Additionally, a neurological examination was performed by pediatric neurologists to assess the overall neurological condition of the patients.

In alignment with the criteria used in previous neonatal HIE outcome studies,[11,13] patients were categorized into 3 severity groups based on clinical assessments:

Severe: Death, use of antiepileptic drugs, diagnosis of cerebral palsy, vision loss, or hearing impairment not responsive to amplification.

Moderate: Hearing impairment responsive to amplification, use of hearing aids, or abnormal neurological findings.

None/Mild: Patients who did not meet any of the above criteria.

Statistical Analysis

Statistical analyses were performed using SPSS version 21.0 for Windows (IBM SPSS Corp.; Armonk, NY, USA). Normality of continuous variables was assessed using the Shapiro-Wilk test, and histograms. Normally distributed variables are reported as mean ± SD; non-normally distributed variables are presented as median (minimum–maximum). Comparisons were made using the student's *t*-test or Mann–Whitney *U*-test, and categorical variables were compared using chi-square or Fisher's exact test. Fisher's exact test with Monte Carlo simulation was used for multi-level categorical comparisons. Correlations were evaluated using Spearman's rank correlation coefficient and interpreted according to standard thresholds: $\rho < .25$ was considered no or very weak correlation; $\rho = 0.25$-0.50 as low correlation; $\rho = 0.50$-0.70 as moderate correlation; $\rho = 0.70$-0.90 as high correlation; and $\rho > .90$ as very high correlation. A *P*-value of <.05 was considered statistically significant.

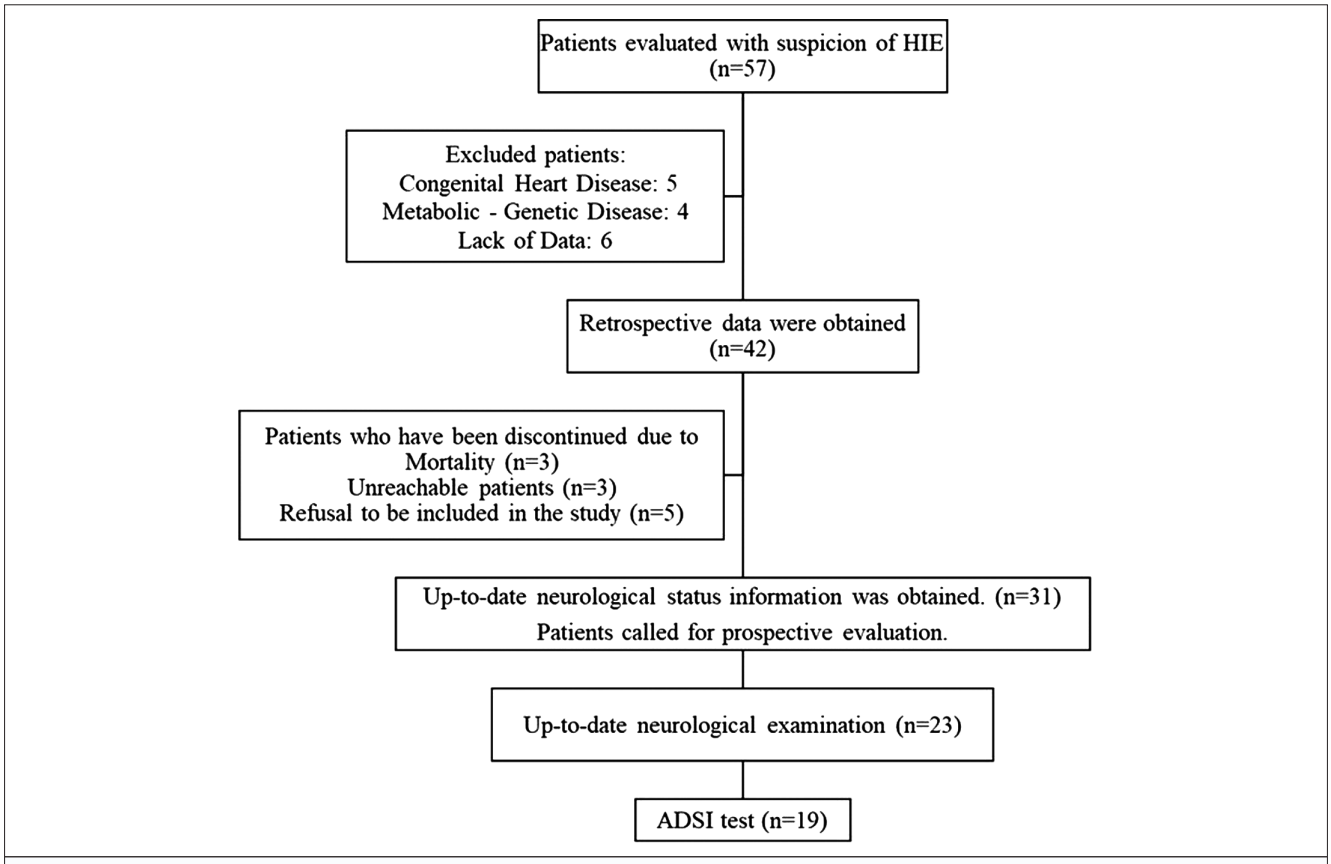

Figure 1 Flowchart of patient inclusion, data collection, and neurological evaluation.

RESULTS

Study Population

Initially, 57 infants were identified with a diagnosis of HIE during the study period. However, 15 infants were excluded based on the exclusion criteria, leaving a final study population of 42 infants (Figure 1).

Perinatal and Neonatal Characteristics

Of the 42 patients, 29 (69.1%) were male, and 13 (30.9%) were female. Based on the severity of HIE, 20 (47.6%) were classified as having mild HIE, while 22 (52.4%) were classified as having moderate/severe HIE. In the mild HIE group, 7 out of 20 infants (35%) were female, while in the moderate/severe HIE group, 6 out of 22 infants (27.3%) were female. There was no statistically significant difference in sex distribution between the 2 groups (P = 0.588). The analysis of perinatal and neonatal characteristics, such as Apgar scores, initial blood gas parameters, and the need for resuscitation, revealed significant differences between the mild and moderate/severe HIE groups as shown in Table 1. The median 1-minute Apgar score was significantly lower in the moderate/severe HIE group compared to the mild HIE group (3 vs. 5, P = .009). In addition, the moderate/severe HIE group showed higher mean lactate levels (12.4 vs. 9.4 mmol/L, P = .009) and greater base excess (–19.3 vs. –14.9 mmol/L, P = .003).

Cranial MRI was available for 12 out of 20 patients in the mild HIE group and for 19 patients in the moderate/severe HIE group. Magnetic resonance imaging abnormalities consistent with HIE were observed in 2 of 12 mild cases (16.7%) and in 8 of 19 moderate/severe cases (42.1%) (P = .214). No significant differences were found in the distribution of injury patterns between the 2 groups (P = .197) (Table 2).

All infants underwent aEEG monitoring, initiated within the first 6 hours of life in accordance with the unit's institutional encephalopathy protocol. None of the infants in the mild HIE group showed abnormal aEEG patterns, whereas 8 out of 22 infants (36.4%) in the moderate/severe HIE group exhibited abnormal findings (Table 2).

Invasive mechanical ventilation was required significantly more often in the moderate/severe HIE group (20/22; 90.9%) than in the mild HIE group (8/20; 40%) (P < .001). Furthermore, the median duration of mechanical ventilation was notably longer in the moderate/severe group (96 hours vs. 4 hours; P < .001) (Table 2). The use of adjunctive treatments (erythropoietin, magnesium sulfate, allopurinol, and topiramate), administered on a case-by-case basis, was significantly more frequent in the moderate/severe HIE group (22 out of 22, 100%) compared to the mild HIE group (5 out of 20, 25%) (P = .001).

Neurological Prognosis

According to the severity groups based on clinical assessments, among the infants with mild HIE (n = 20), all (20/20, 100%)

Table 1. Comparison of Maternal, Perinatal, and Early Neonatal Characteristics Between Mild and Moderate/Severe Hypoxic-Ischemic Encephalopathy Groups

	Mild HIE N = 20	Moderate/ Severe HIE N = 22	*P*
Maternal age	27 (26-33)	28 (25-32)	.655
Gestational week	38 (36-39)	38 (36-39)	.410
Sex (female)	7 (35%)	6 (27.3%)	.588
Place of birth (referral)	11 (55%)	16 (72.7%)	.231
Mode of delivery (vaginal delivery)	11 (55%)	10 (45.4%)	.131
Need for resuscitation	6 (30%)	16 (72.7%)	**.006**
Apgar score at 1 minute*	5 (4-6)	3 (1-5)	**.009**
Thompson score (within the first hour)	3.0 (2.0-3.0)	11.5 (8.25-14.0)	**<.001**
pH in initial blood gas	7.0 ± 0.1	6.94 ± 0.1	.156
Lactate in initial blood Gas (mmol/L)	9.4 ± 3.5	12.4 ± 5.2	**.009**
Base excess in initial blood gas (mmol/L)	−14.9 ± 2.4	−19.3 ± 6	**.003**

Categorical variables are presented as n (%). Continuous variables are expressed as mean ± SD for normally distributed data, or as median with interquartile range [25th–75th percentile] for non-normally distributed data. Comparisons were made using chi-square or Fisher's exact test for categorical variables and the Mann–Whitney U-test or independent samples t-test for continuous variables, depending on normality. HIE, hypoxic-ischemic encephalopathy. Bold values indicate statistically significant differences between groups ($P < 0.05$). *The fifth- and tenth-minute Apgar scores were excluded from analysis due to incomplete numerical documentation in several cases labeled only as "intubated."

had no or mild neurological impairment, with no moderate or severe impairments observed. In the moderate/severe HIE group (n = 22), 18 infants (81.8%) were classified as having no or mild neurological impairment, while severe impairment was present in 4 infants (18.2%). No infants were categorized with moderate impairment in either group based on available data.

According to the achievement of developmental milestones, patients were classified as delayed or non-delayed. No statistically significant differences were observed between the groups ($P > .05$ for all comparisons) (Table 3). The median ages at which developmental milestones were achieved did not significantly differ between the 2 groups, except for head control, which was attained later in the moderate/severe HIE group ($P = .03$) (Supplementary Table 1).

Developmental screening using the ADSI was completed in 19 infants (12 mild, 7 moderate/severe). Specifically, among infants with mild HIE, gross motor abnormalities were identified in 4 out of the 12 evaluated cases (33.3%) (Table 4). Due to the limited subgroup size and limited heterogeneity, these findings were reported descriptively and not subjected to statistical comparison.

There was a statistically significant moderate correlation between the 72-hour Thompson scores and neurological prognosis, with higher scores indicating a worse prognosis ($P = 0.58$, $P = .002$).

Given the exploratory nature of this study and the rarity of mild HIE cases with long-term follow-up setting, a priori power analysis was not feasible. However,ü a post hoc power analysis was conducted using G*Power, based on the observed outcome rates—poor neurological prognosis in 35% of mild HIE vs. 64% in moderate/severe cases. With alpha = 0.05, the study achieved a power of 61%, indicating a moderate probability of detecting a true difference.[22,23]

DISCUSSION

This study aimed to evaluate the long-term neurological prognosis of infants diagnosed with HIE in the NICU, with a particular focus on comparing the outcomes of mild HIE cases with those of moderate and severe HIE. The findings indicate that even infants with mild HIE are at risk for adverse neurological outcomes, a result that aligns with emerging literature suggesting that mild HIE should not be considered a universally benign condition.

Recent studies have highlighted that infants with mild HIE may develop cognitive and behavioral impairments comparable to those seen in moderate HIE cases.[7,13,24-27] These findings underscore the importance of structured long-term follow-up and early intervention programs for all infants diagnosed with HIE, regardless of initial clinical severity. In agreement with recent literature, the data also challenge the traditional assumption that mild HIE carries a uniformly favorable prognosis. While a therapeutic paradigm shift is emerging—with some centers offering hypothermia treatment in selected mild HIE cases—the evidence remains inconclusive, and current studies do not endorse its routine use in this group.[14] However, beyond this debate, this study is not capable of recommending or discouraging therapeutic hypothermia to mild HIE cases.

Although clear criteria exist for HIE diagnosis, distinguishing between mild and moderate/severe HIE remains challenging.[28] The diagnosis of mild HIE is particularly complex, especially within the limited treatment window of the first 6 hours after birth. This complexity stems from the dynamic progression of neonatal encephalopathy during the early postnatal period, as well as variability in the onset and severity of the hypoxic-ischemic event. Clinical signs can fluctuate or evolve and may resemble both normal neonatal transitional behaviors and features of more advanced HIE, making early classification prone to error. Adding to the challenge is the lack of a universally accepted definition of mild HIE during the critical early hours when treatment decisions, such as the initiation of therapeutic hypothermia, must be considered. Notably, the modified Sarnat score—while widely used for staging—did not initially distinguish mild cases from normal neurological findings, further limiting diagnostic precision. These challenges may result in inconsistent management practices and contribute to variability in the reported outcomes across different clinical settings and studies.[29] This underscores the importance of accurate early assessment through serial neurological examinations, validated scoring systems, and continuous monitoring. In the cohort, none of the infants diagnosed with mild HIE developed seizures or clinical worsening in the early neonatal period, and no cases showed findings suggestive of progression to moderate encephalopathy.

Table 2. Comparison of Diagnostic and Therapeutic Characteristics Between Mild and Moderate/Severe Hypoxic-Ischemic Encephalopathy Groups

Diagnostic Tests/Treatments	Mild HIE n/N (%)*	Moderate/Severe HIE n/N (%)	P**
Hypothermia	0/20 (0%)	22/22 (100%)	–
Passive hypothermia (during transport)***	14/20 (70%)	21/22 (95.5%)	**.04**
Transportation duration (hour)	4 (2-6)	5 (2-7)	.852
Invasive mechanical ventilation (IMV)	8/20 (40%)	20/22 (90.9%)	**<.001**
Duration of IMV (hour)	4 (0-4)	96 (4-144)	**<.001**
Use of vasoactive agents	2/20 (10%)	7/22 (31.9%)	.085
Adjuvant therapies	5/20 (25%)	22/22 (100%)	**.001**
Cranial MRI (HI injury score)#			
Score 0	10/12	11/19	.197
Score 1	2/12	4/19	
Score 2	0/12	2/19	
Score 3	0/12	2/19	
aEEG (within first 6 hours, ≥24-hour record)	20/20 (100%)	14/22 (63.6%)	**<.001**
EEG (normal)	12/12 (100%)	12/21 (57.1%)	**.011**

*Categorical variables are presented as n/N (%), and continuous variables are expressed as median (25th-75th percentile). **Statistical comparisons were performed using Fisher's exact test for categorical variables and the Mann–Whitney U-test for continuous variables. Fisher's exact test (with Monte Carlo simulation) was used for multi-level Cranial MRI comparison. ***Passive hypothermia was initiated during transport at referring centers before full classification was available. Bold values indicate statistically significant differences between groups ($p < 0.05$).#MRI scoring was applied according to established criteria.[18]

Supporting these observations, a systematic review by Conway et al[30] reported that up to 22% of infants diagnosed with mild HIE exhibited abnormal neurological outcomes, further questioning the adequacy of current classification systems. A recent national multicenter cohort study from Türkiye by Okulu et al[31] also highlights the need for closer attention to mild HIE cases. Including over 900 neonates, this large-scale prospective study reported considerable variability in the application of therapeutic hypothermia, particularly among infants with mild HIE. The findings reflect ongoing uncertainty in clinical decision-making and emphasize the lack of standardized criteria for managing this subgroup. Additionally, the study underscored the potential role of early brain imaging in predicting outcomes.[31] The recent therapeutic paradigm shift toward offering hypothermia even in mild HIE cases reflects a growing recognition of the complexity and potential deviations in the accuracy of the classification.

Table 3. Delayed Developmental Milestones in Mild and Moderate-Severe Hypoxic-Ischemic Encephalopathy Groups*

Examination Finding	Mild HIE (N = 12) n (%)	Moderate/Severe HIE (N = 7) n (%)	P
Head control >3 months	2 (16.7)	3 (42.9)	.305
Sitting without support >9 months	1 (8.3)	2 (28.6)	.523
Crawling >12 months	1 (8.3)	1 (14.3)	1.000
Walking >18 months	0 (0.0)	1 (14.3)	.368
Conscious smiling >4 months	0 (0.0)	1 (14.3)	.368
Tracking people >6 months	1 (8.3)	1 (14.3)	1.000
Speaking (first words) >15 months	1 (8.3)	1 (14.3)	1.000
Forming sentences >30 months	0 (0.0)	1 (14.3)	.368

The table reports the number of infants (n) in each group who failed to achieve the milestone. Statistical comparisons were performed by Fisher's exact test. *Delays were identified according to thresholds derived from developmental surveillance guidelines, in which 75% of children would be expected to achieve a milestone at a given age.[19] HIE, hypoxic-ischemic encephalopathy.

In this study, although the proportion of MRI abnormalities was higher in the moderate/severe HIE group compared to the mild group (42.1% vs. 16.7%), the difference did not reach statistical significance. This may reflect both the limited sample size—particularly within the mild HIE subgroup—and the relatively low frequency of severe events, which together reduce the statistical power to detect group-level differences. Nonetheless, the presence of MRI abnormalities in 16.7% of mild cases and gross motor developmental delays in over 30% of this group challenges the notion that mild HIE is uniformly benign. The findings are consistent with earlier prospective data such as the PRIME study, in which 17% of mild HIE infants exhibited MRI abnormalities, mostly classified as Score 1 injury patterns.[7] However, it is important to note that all infants in that pilot study underwent therapeutic hypothermia. In more recent studies, the frequency of MRI-detected abnormalities in mild HIE has been reported to be as high as 70%.[32] This wide variability is likely influenced by several factors, including differences in study design, MRI scoring criteria, and the timing of imaging.

Limitations

Several limitations must be acknowledged. First, the retrospective nature of data collection could introduce biases related to incomplete records or recall bias from families. Second, the comparison between mild HIE (without therapeutic hypothermia) and moderate/severe HIE (with therapeutic hypothermia) should be interpreted with caution, as the groups differed in

Table 4. Ankara Developmental Screening Inventory Test Results in Mild and Moderate-Severe Hypoxic-Ischemic Encephalopathy Groups*

Test Category	Mild HIE (n = 12)	Moderate/ Severe HIE (n = 7)
Overall	12/12 (100%)	6/7 (85.7%)
Language development	12/12 (100%)	6/7 (85.7%)
Fine motor development	10/12 (83.3%)	6/7 (85.7%)
Gross motor development	8/12 (66.6%)	5/7 (71.4%)
Social skills and self-care development	12/12 (100%)	6/7 (85.7%)

*ADSI findings were reported descriptively. Categorical data are presented as n (%). Statistical comparisons were not performed due to small subgroup size and distribution homogeneity. HIE, hypoxic-ischemic encephalopathy.

terms of treatment. Moreover, the absence of a healthy control group further limited the ability to assess neurodevelopmental outcomes in relation to normal developmental trajectories. Thirdly, the relatively small sample size, especially for follow-up ADSI assessments, restricts the generalizability of the findings. Additionally, neurodevelopmental outcomes relied partially on parental reporting, introducing potential bias despite clinical confirmation efforts. Lastly, variability in the timing and application of neurodevelopmental assessments may have influenced the findings, limiting inferential conclusions.

Conclusion

Although infants diagnosed with mild HIE are typically managed less intensively, emerging evidence—including the findings—indicates that this classification may underestimate the risk of long-term neurological impairment. The potential for residual brain injury, developmental delays, and limitations in early diagnostic tools challenges the assumption that mild HIE always follows a benign course. While structured neurological examination remains central to initial assessment, the integration of more sensitive and objective tools—such as prolonged aEEG and neuroimaging—is increasingly warranted. Until results from larger, prospective multicenter studies become available, the most prudent approach is to adopt vigilant and continuous neurodevelopmental surveillance. Crucially, structured follow-up should be provided to all infants with mild HIE, regardless of their eligibility for therapeutic hypothermia, to enable timely identification and intervention for those at highest risk.

Take-Home Messages

- Mild HIE may not always follow a benign course.
- Early identification of high-risk infants and structured follow-up are essential, even in cases not meeting criteria for therapeutic hypothermia.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics **Committee Approval:** Ethical committee approval was received from the Ethics Committee of Dokuz Eylül University (Approval No: 2023/25-08, Date: August 2, 2023).

Informed Consent: Written informed consent was obtained from the patients' families who agreed to take part in the study.

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Supplementary Table 1. Comparison of Developmental Outcomes Between Mild and Moderate/Severe HIE Groups

Examination Finding		Mild	Moderate/Severe	p-value
Developmental Milestones	Head Control	2 (2–4)	3 (2–3)	**0.041**
	Sitting Without Support	6 (5–7)	6 (5–9)	0.779
	Crawling	8 (6–11)	8.5 (7–11)	0.099
	Walking	12 (11–15)	12 (11–17)	0.333
	Conscious Smiling	2.5 (2–4)	3 (2–5)	0.626
	Tracking People	4 (3–6)	5 (3–6)	0.417
	Speaking (First Words)	12 (9–15)	12 (10–15)	0.799
	Forming Sentences	18 (12–23)	18 (17–24)	0.304

Values are presented as median (min–max). Statistical comparisons were made using the Mann–Whitney U test. This table complements Table 3 by providing continuous milestone timing data.