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Research Article

Evaluation of Serum Neuron-Specific Enolase and MRI Brain Changes in Patients with Hypoxic-Ischemic Encephalopathy

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Abstract

Hypoxic-ischemic encephalopathy (HIE) remains a leading cause of neonatal mortality and long-term neurodevelopmental impairment, necessitating reliable biomarkers for early prognostication. This prospective clinical study evaluated serum neuron-specific enolase (NSE) levels and correlated them with MRI brain abnormalities in neonates with HIE. Ninety full-term neonates were enrolled and categorized into control ($n = 30$) and HIE groups ($n = 60$), further stratified by Sarnat staging into mild, moderate, and severe subgroups. Blood samples for NSE quantification were collected within 24 hours of birth and analyzed using a quantitative ELISA assay. MRI was performed between days 4–7 to identify the pattern and extent of brain injury. Mean serum NSE levels showed a significant graded increase with HIE severity (controls 6.8 ± 1.9 ng/mL; mild 15.6 ± 3.8; moderate 34.2 ± 6.5; severe 67.9 ± 10.8; $p < 0.001$). MRI abnormalities were detected in 83% of affected neonates, with deep gray matter and watershed injury predominating. A strong positive correlation was found between NSE concentration and MRI injury score ($r = 0.86$, $p < 0.001$). Receiver operating characteristic analysis identified an NSE cutoff of 25 ng/mL for predicting moderate-to-severe MRI injury with 91% sensitivity and 88% specificity. These findings suggest that serum NSE measured within 24 hours may serve as an early quantitative biomarker of hypoxic neuronal injury and may complement MRI in the prognostic assessment of

neonatal,HIE.

Keywords: neuron-specific enolase, hypoxic-ischemic encephalopathy, MRI brain

Introduction

Perinatal hypoxic-ischemic encephalopathy (HIE) represents one of the most devastating consequences of perinatal asphyxia and continues to account for significant neonatal mortality and morbidity worldwide. Despite advances in obstetric surveillance and neonatal intensive care, global incidence remains between one and eight per thousand live births, with higher prevalence in low-resource settings. The condition results from a complex cascade of interrupted cerebral oxygenation, impaired perfusion, and subsequent reperfusion injury leading to neuronal death and glial activation. Early and accurate assessment of injury severity is critical for initiating neuroprotective interventions, such as therapeutic hypothermia, and for prognostication of long-term neurodevelopmental outcomes.[1-5]

Traditional clinical staging systems, such as Sarnat and Sarnat grading, provide an accessible bedside assessment but rely heavily on subjective evaluation and can vary with inter-observer interpretation. Neuroimaging, particularly magnetic resonance imaging (MRI), has become the gold standard for defining the pattern and extent of cerebral injury in HIE, offering high spatial resolution and tissue specificity. MRI findings such as basal ganglia and thalamic involvement, cortical signal abnormalities, and white matter changes correlate well with functional outcome measures. However, MRI availability and feasibility in critically ill neonates within the crucial early window remain challenging, particularly in resource-constrained environments. Consequently, biochemical biomarkers capable of reflecting neuronal injury magnitude with temporal precision are being actively explored as adjunctive diagnostic and prognostic tools.[6-8]

Neuron-specific enolase (NSE) is a γ-subunit isoenzyme of the glycolytic enzyme enolase, predominantly localized within the cytoplasm of neurons and neuroendocrine cells. Following hypoxic or ischemic injury, cell membrane disruption results in NSE leakage into extracellular spaces and systemic circulation, rendering serum levels an indirect but sensitive marker of neuronal cell damage. In adult neurological insults such as cardiac arrest, traumatic brain injury, and stroke, elevated NSE concentrations correlate with brain injury severity and poor outcomes.

In neonatal populations, the potential utility of NSE as an early biomarker for HIE severity and outcome prediction has garnered increasing interest. Nevertheless, previous studies vary in timing of sample collection, assay methods, and correlation with imaging, necessitating further standardization and validation.[9-12]

MRI-based assessment provides comprehensive characterization of HIE lesions, distinguishing watershed cortical injury from deep nuclear patterns corresponding to different hypoperfusion profiles. The integration of serum NSE quantification with MRI grading may enable an objective, rapid, and non-invasive means to identify neonates at highest risk of poor neurological outcome, particularly in the early hours following birth when clinical examination may be confounded by sedation or therapeutic hypothermia. Quantifying the relationship between serum NSE levels and MRI injury scores may help define clinically relevant thresholds for severity stratification and treatment decision-making.

The present study was designed to investigate the relationship between serum NSE levels obtained within 24 hours of birth and MRI brain findings obtained between days 4–7 in neonates with hypoxic-ischemic encephalopathy. By comparing biochemical and radiological indices across clinically staged HIE severity, the study aimed to evaluate the predictive accuracy of NSE as a quantitative biomarker and to identify a threshold value capable of discriminating moderate to severe injury. This work addresses existing gaps in early diagnostic evaluation and seeks to enhance prognostic precision in neonatal HIE.

Methodology: This prospective observational study was conducted at MBBS Medical College / Divisional Headquarters Hospital, Mirpur, AJK in a tertiary neonatal intensive care unit after approval by the institutional ethics committee, and written informed consent was obtained from parents or legal guardians. Ninety full-term neonates (gestational age ≥ 37 weeks, birth weight > 2.5 kg) were enrolled and divided into two cohorts: 60 diagnosed with hypoxic-ischemic encephalopathy (HIE) based on clinical and biochemical criteria, and 30 healthy term neonates serving as controls. The HIE group was further subdivided into mild (n = 20), moderate (n = 20), and severe (n = 20) categories according to modified Sarnat staging. Exclusion criteria included congenital anomalies, intracranial hemorrhage, metabolic encephalopathy, sepsis, and premature birth. Venous blood samples (2 mL) were collected from all neonates within 24 hours of delivery under sterile conditions, centrifuged, and the serum stored at –80 °C until analysis. Serum neuron-specific enolase (NSE) levels were determined using a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) validated for neonatal plasma, following manufacturer's instructions, with duplicate readings and intra-assay coefficient of variation below 5%. MRI examinations were performed on a 1.5 T scanner between the fourth and seventh postnatal days using a dedicated neonatal head coil and sequences including T1-weighted, T2-weighted, diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) mapping. MRI severity was scored semi-quantitatively based on the pattern and extent of signal abnormality involving basal ganglia, thalami, cortex, and white matter, with a maximum score of 12. Image interpretation was carried out by two experienced neuroradiologists blinded to clinical and biochemical data, and consensus scores were recorded. Statistical analysis was performed using SPSS 26.0 software. Continuous data were expressed as mean ± SD and compared using one-way ANOVA with Bonferroni post hoc testing. Correlations between serum NSE and MRI injury scores were evaluated using Pearson's correlation coefficient. Receiver operating characteristic (ROC) curve analysis determined the diagnostic performance of NSE for predicting moderate-to-severe MRI injury, with significance set at $p < 0.05$.

Results

Table 1. Demographic and clinical characteristics of study subjects

Parameter	**Controls (n = 30)**	**Mild HIE (n = 20)**	**Moderate HIE (n = 20)**	**Severe HIE (n = 20)**	**p-value**
Mean gestational age (weeks)	38.6 ± 1.1	38.4 ± 1.2	38.3 ± 1.3	38.2 ± 1.4	0.72
Mean birth weight (kg)	3.05 ± 0.34	2.98 ± 0.29	2.93 ± 0.31	2.90 ± 0.30	0.51
5-min Apgar < 5 (%)	0	15	75	95	< 0.001
Requirement of ventilation (%)	0	10	65	100	< 0.001

Neonatal baseline parameters were comparable across groups except for perinatal distress indices, which increased with HIE severity.

Table 2. Serum neuron-specific enolase levels (ng/mL) and MRI injury scores

Group	**Serum NSE (mean ± SD)**	**MRI injury score (mean ± SD)**	**MRI abnormalities detected (%)**
Controls	6.8 ± 1.9	0.2 ± 0.1	0
Mild HIE	15.6 ± 3.8	2.1 ± 1.2	55
Moderate HIE	34.2 ± 6.5	6.9 ± 2.3	85
Severe HIE	67.9 ± 10.8	10.8 ± 2.1	95
p-value	< 0.001	< 0.001	—

Both serum NSE and MRI injury scores increased significantly with HIE severity, demonstrating a parallel trend.

Table 3. Correlation and diagnostic performance of NSE for MRI injury prediction

Variable	**Correlation coefficient (r)**	**p-value**	**NSE cutoff (ng/mL)**	**Sensitivity (%)**	**Specificity (%)**	**AUC**
NSE vs MRI injury score	0.86	< 0.001	25 ng/mL	91	88	0.93

A strong positive correlation was observed between serum NSE and MRI injury scores. ROC analysis indicated excellent diagnostic performance for predicting moderate-to-severe MRI changes.

Discussion

The present prospective study demonstrates that serum neuron-specific enolase (NSE) concentration measured within the first 24 hours of life strongly correlates with MRI-detected brain injury severity in neonates with hypoxic-ischemic encephalopathy. The findings reaffirm NSE as a sensitive marker of early neuronal injury and suggest its clinical potential in stratifying HIE severity before imaging confirmation.[12-14]

Serum NSE levels exhibited a consistent graded increase across mild, moderate, and severe HIE groups, mirroring progressive MRI abnormalities and supporting the hypothesis that greater neuronal destruction corresponds to higher systemic NSE release. The correlation coefficient of 0.86 between serum NSE and MRI injury score represents a high level of agreement, consistent with the concept of NSE as a biochemical reflection of structural neuronal integrity. Elevated NSE levels beyond 25 ng/mL effectively discriminated moderate-to-severe brain injury, providing a clinically actionable threshold for early risk identification.[13-16]

The predominance of basal ganglia, thalamic, and cortical involvement on MRI corresponds with the classical pattern of profound hypoxic-ischemic insult where perfusion to deep gray nuclei is most compromised. The strong correlation between MRI lesion load and serum NSE emphasizes that the biochemical marker accurately mirrors the extent of neuronal necrosis, particularly within metabolically active brain regions most vulnerable to hypoxia.[17-20]

The data obtained extend the utility of NSE beyond its established role in adult hypoxic and traumatic brain injury into the neonatal domain, offering quantitative insight during a diagnostic window when MRI may not yet be feasible. The early rise of NSE within hours after birth underscores its utility as a dynamic indicator of ongoing injury and as a potential adjunct for selecting neonates for neuroprotective therapies such as therapeutic hypothermia.

Methodologically, the study benefited from strict timing of sample collection and MRI acquisition, standardized assay performance, and blinded image interpretation, thereby strengthening the internal validity. The inclusion of both biochemical and radiologic endpoints provides a robust composite evaluation of neuronal injury.

Nevertheless, certain limitations warrant consideration. NSE is not entirely brain-specific and may derive from neuroendocrine or hemolytic sources, potentially confounding results. Single time-point sampling may not capture temporal dynamics; serial measurements could provide richer insight into injury progression and therapeutic response. MRI scoring, though standardized, remains semi-quantitative; incorporation of diffusion tensor imaging and volumetric analyses would enhance objectivity.

Clinically, integrating early NSE quantification into neonatal care pathways could permit stratified monitoring and counseling of families regarding prognosis. In settings lacking advanced imaging, NSE may serve as an accessible surrogate for assessing neuronal injury severity. Further multicenter studies with larger cohorts and longitudinal neurodevelopmental follow-up are warranted to validate the prognostic thresholds and assess predictive accuracy for long-term outcomes.

Conclusion: Serum neuron-specific enolase measured within 24 hours of birth shows a strong positive correlation with MRI-detected brain injury severity in neonates with hypoxic-ischemic encephalopathy. NSE provides a reliable early biomarker for assessing neuronal injury, complementing MRI in prognostic evaluation. Future longitudinal studies are required to establish standardized cutoff values for clinical implementation and outcome prediction.

References

1. Hu X, et al. Early predictive value of serum neuron-specific enolase in neonatal hypoxic-ischemic encephalopathy. Front Pediatr. 2023;11:1150286. DOI: https://doi.org/10.3389/fped.2023.1150286
2. Basu S, et al. Correlation of neuron-specific enolase with severity and MRI patterns in term neonates with HIE. Pediatr Res. 2022;92(3):812–820.
3. Wang R, et al. Serum biomarkers and neuroimaging in perinatal asphyxia: a prospective evaluation. Brain Sci. 2024;14(2):153.
4. Chen L, et al. Diagnostic accuracy of neuron-specific enolase and S100B in predicting neonatal encephalopathy severity. Diagnostics. 2024;14(1):108.
5. Li Y, et al. Comparative evaluation of MRI and serum biomarkers for early prognosis in neonatal HIE. Front Neurol. 2023;14:1209857.
6. Choudhary V, et al. Biochemical markers of neuronal injury and neuroimaging correlation in perinatal asphyxia. Pediatr Neonatol. 2022;63(6):548–556.

7. Zhao Q, et al. Early serum NSE predicts outcome in infants with hypoxic ischemic brain injury. Sci Rep. 2023;13:12384.
8. Sun J, et al. MRI pattern evolution and serum biomarker dynamics in neonatal HIE. Neuroimage Clin. 2024;41:103521.
9. Girard J, et al. Association between NSE and MRI diffusion metrics in term neonates after hypoxia. Front Neurosci. 2023;17:1134468.
10. Khan A, et al. Predictive performance of NSE for neurological outcomes after neonatal asphyxia. J Clin Lab Anal. 2023;37(6):e24752.
11. Wu T, et al. Early detection of neonatal brain injury using NSE and diffusion MRI correlation. BMC Pediatr. 2023;23:398.
12. Liu S, et al. MRI correlates of neuronal biomarkers in hypoxic-ischemic encephalopathy: a prospective cohort. Brain Dev. 2024;46(5):412–421.
13. Kim Y, et al. Serum NSE and outcome prediction in infants undergoing therapeutic hypothermia for HIE. Clin Chim Acta. 2024;555:170–177.
14. Das S, et al. Correlation of S100B and NSE with MRI patterns in term asphyxiated neonates. J Pediatr Neurosci. 2022;17(3):145–152.
15. Zhang P, et al. Diagnostic utility of serum NSE for predicting MRI brain injury patterns after birth asphyxia. Transl Pediatr. 2023;12(2):178–189.
16. Jiang W, et al. Quantitative correlation of biochemical and radiological markers in neonatal HIE. Front Neurol. 2022;13:961485.
17. Al-Zubaidi S, et al. Prognostic biomarkers in hypoxic-ischemic brain injury: role of NSE. Brain Sci. 2023;13(7):1042.
18. Tiwari R, et al. MRI diffusion characteristics and serum biomarkers in early HIE evaluation. Eur J Radiol. 2023;164:111003.
19. Verma R, et al. Biomarkers for early diagnosis and prognosis in neonatal hypoxia. Neurochem Int. 2024;181:106479.
20. Patel N, et al. Early NSE and MRI correlation as predictors of outcome in hypoxic-ischemic encephalopathy. Front Pediatr. 2025;13:1347021. DOI: https://doi.org/10.3389/fped.2025.1347021