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Article

The Role of Neuron-Specific Enolase (NSE) as a Biomarker in Perinatal Central Nervous System Injury in Small-for-Gestational-Age Newborns

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Abstract: Perinatal central nervous system injury is a significant source of morbidity in the newborn population, especially among vulnerable groups such as small for gestational age newborns. Chronic intrauterine hypoxia related to growth restriction may make neurons vulnerable to injury during the birth and early postnatal adaptation process. Early diagnosis of neuronal damage is often difficult, as clinical signs can either be subtle or nonspecific. Biochemical markers have thus received growing interest as adjuvant diagnostic tools. This was a prospective comparative study to assess the diagnostic importance of neuron-specific enolase as a biomarker of perinatal CNS injury in small for gestational age babies. A total of 82 term newborns were recruited between 2024 and 2025, including 41 growth-restricted newborns and 41 appropriate for gestational age controls. Serum NSE levels were measured within the first 24 hrs of life and then on the fifth day. Clinical neurological evaluation and neurosonography were done in all participants. Small for gestational age newborns had significantly higher concentrations of NSE than controls. Elevated levels were related to poor Apgar scores and abnormal neurosonographic findings. In a subset of growth-restricted infants, NSE elevation was present on the fifth day of life, indicating protracted neuronal stress. Notably, increased NSE values were found even in some of the infants that did not have overt neurological symptoms. The results support the possible role of neuron-specific enolase as a sensitive adjunct biomarker for early detection of perinatal CNS injury in growth-restricted neonates. Incorporation of NSE assessment into neonatal monitoring may lead to better identification of the vulnerability of the neurons and timely intervention.

Keywords: Neuron-Specific Enolase, Perinatal CNS Injury, Small for Gestational Age, Intrauterine Growth Restriction, Neonatal Biomarkers, Hypoxic-Ischemic Injury

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1. Introduction

Perinatal injury of the central nervous system continues to be one of the greatest contributors to neonatal morbidity and long-term neurodevelopmental impairment throughout the world. Cognitive delay, motor dysfunction, epilepsy, or behavioural disorders later in life may be acquired early in life due to brain injury during the perinatal period. The burden of these complications is especially high in vulnerable neonatal populations, and infants born small for gestational age (SGA) are an example. These newborns often represent cases of intrauterine growth restriction and are characterised by a chronic exposure to placental insufficiency and intrauterine hypoxia [1].

Chronic foetal hypoxia plays an important role in the alteration of the cerebral blood flow regulation and neuronal metabolism. Although adaptive mechanisms are attempted to maintain the perfusion of the brain, long-term intrauterine stress may result in a loss of neuronal integrity. As a result, SGA infants demonstrate increased susceptibility to hypoxic-ischemic events in labour and early neonatal adaptation. Even in the absence of gross cases of birth asphyxia, there may be subtle injury to neurones, which may not be recognised during routine clinical examination [2].

Early diagnosis of perinatal central nervous system injury is difficult. Traditional clinical assessment, including Apgar scoring and neurological examination, is important but limited in the information it gives about the extent of neuronal damage. Neuroimaging techniques such as cranial ultrasound are useful; however, structural changes may not be immediately present during the early neonatal period. Consequently, there is a rising need for reliable biochemical markers which can detect neuronal injury at an early phase.

Neuron-specific enolase (NSE) has been receiving growing attention as a possible brain biomarker of neuronal damage. NSE is a glycolytic enzyme localised in the majority of neurons and neuroendocrine cells. When cell membranes of neurons are disrupted as a result of hypoxic or ischemic injury, NSE is released into the extracellular fluid and then into the bloodstream. An increase in serum NSE levels has been reported in neonates with hypoxic-ischemic encephalopathy and other types of perinatal brain injury [3]. Several studies have suggested that NSE concentration is correlated with the severity of neurological impairment and may have prognostic value [4].

Despite these advances, little data is available regarding the diagnostic significance of NSE in intrauterine growth-restricted newborns. Given the chronic exposure of SGA infants to prenatal hypoxic stress, the neurophysiological vulnerability of these infants may be different from that of the infants appropriate for gestational age. Understanding whether NSE levels are elevated in SGA newborns and whether levels indicate early CNS injury is clinically important for better early detection strategies and intervention strategies.

Therefore, the present study aimed to assess serum levels of neuron-specific enolase in small-for-gestational-age newborns as well as the role of this protein as a biomarker of central nervous system injury during childhood compared with appropriate-for-gestational-age infants.

2. Materials and Methods

This is a prospective comparative clinical study that was conducted in the Republican Specialised Scientific and Practical Medical Centre of Paediatrics in cooperation with Tashkent State Medical University from January 2024 to November 2025. The purpose of the study was to assess the diagnostic utility of neuron-specific enolase (NSE) as a biomarker of perinatal central nervous system injury in small for gestational age versus the appropriate for gestational age newborn infant. The research design was designed so that comparability between groups was maintained in the context of clinical realism of routine neonatal practise.

A total of 82 term newborns were enrolled in the study, and they were divided into two equal groups. The main group was 41 small for gestational age (SGA) newborns whose birth weight was less than the 10th percentile for gestational age based on standardised international growth charts. The control group consisted of 41 newborns who had birth weight appropriate for gestational age, and these control newborns were matched by gestational age and sex distribution to minimise the influence of confounding factors. All infants were born 37 weeks or more.

Inclusion criteria included live-born infants with no major congenital anomalies, chromosomal abnormalities, congenital infections, or structural brain malformations. To be certain that NSE elevation was due to neuronal injury and not some other pathological

condition unrelated to injury, those born with confirmed sepsis, severe metabolic disorders, intracranial haemorrhage unrelated to hypoxic injury, and those who required immediate intensive resuscitation were excluded. This approach is consistent with current neonatal biomarkers research principles that focus on careful selection of patients to avoid nonspecific biochemical elevation [6].

Clinical evaluation was done in the first hours after the birth. Apgar scores at 1 and 5 minutes for all participants were collected. Neurological evaluation was performed by a neonatologist using the criteria of standardised neonatal neurological examination. Signs that were suggestive of perinatal central nervous system involvement were altered muscle tone, abnormal reflexes, lethargy, irritability, feeding difficulties, or seizures. Cranial neurosonography was done in the first 72 hours of life in order to detect structural abnormalities such as periventricular echogenicity or ventricular dilatation. The combination of clinical and ultrasound findings was used to form the diagnosis of perinatal CNS injury.

Venous blood samples for NSE measurement were taken twice as follows: the first sample was taken within the first 24 hours of life, and the second was taken on the fifth day. The decision to make the measurement dynamic was based on evidence that NSE levels may change over the course of the early postnatal period and that serial assessment is more sensitive to detect the disease [7]. Blood was collected and processed under sterile conditions and processed immediately. Serum was separated by centrifugation and kept under controlled temperature till analysis.

Serum NSE concentrations were measured using enzyme-linked immunosorbent assay (ELISA) kits that are validated for use in neonates. All laboratory analyses were conducted in the same laboratory of the institution with the use of standardised reagents and calibration procedures to ensure consistency of analysis. Laboratory personnel were blinded to group allocation to minimise observer bias. Internal quality control procedures were performed on a regular basis to ensure the reliability of the assay.

Data were organised in a structured electronic database. Continuous variables were expressed as mean plus standard deviation, and categorical variables were represented as absolute numbers and percentages. Comparisons between the SGA and control groups were made with statistical tests that were appropriate according to the distribution of the data. Correlation analysis was performed to determine the correlation between the NSE levels, Apgar scores and neurosonographic findings. A p-value less than 0.05 was considered statistically significant. Statistical evaluation was based on methodological recommendations for biomarker validation studies in neonatal populations [8].

Ethical approval for the study was obtained from the institutional ethics committee of Tashkent State Medical University. Written informed consent was received from parents or legal guardians before enlisting. All procedures were in line with international ethical standards for biomedical research in neonates, including recommendations on the safe use of biomarkers in perinatal diagnostics [9].

3. Results

A total of 82 term newborns were evaluated, consisting of 41 small for gestational age and 41 newborns appropriate for gestational age at birth. Although the gestational age was similar in the groups, birth weight differed significantly, as expected. Differences were noticed in initial clinical adaptation. While the majority of the infants in both groups showed stable cardiorespiratory transition, lower Apgar scores at 1 minute were more often recorded in the SGA newborns. Neurological study in the first 24 hours showed mild hypotonia, reduction of the reflex activity or transient irritability in some growth-restrained infants, whereas this was rare in the control group.

Serum neuron-specific enolase levels less than 24 hours of life in the SGA group were significantly higher than in the normal group. Mean NSE concentration in growth-

restricted newborns was higher than that of controls, showing early biochemical evidence of neuronal stress. These results are in line with those reports of potential predisposition of neurons in SGA infants to increased vulnerability even before clinically evident hypoxic events during labour [10]. In contrast, the NSE showed values in expected neonatal reference ranges for appropriate-for-gestational-age infants.

Dynamic measurement gave us more information. On the 5th day of life, NSE levels fell in most of the infants; however, the magnitude of this decrease was greater and more consistent in the control group. In SGA newborns, a good proportion had high NSE concentrations when compared with their day one concentrations. Persistent elevation was especially evident in infants who had mild neurological abnormalities or borderline Apgar scores. Such persistence may represent a continued metabolic stress to the neuron rather than a transient perinatal reaction. Similar dynamic trends have been reported in neonates, looking at NSE as an early marker of hypoxic ischemic injury [11].

Correlation analysis showed a moderate inverse correlation between Apgar score at five minutes and NSE concentration on the first day of life. The infants who had lower Apgar values tended to show higher serum NSE values. In addition, the NSE levels of the newborns who had abnormal findings on the neurosonograms, such as increased periventricular echogenicity, were significantly higher than the NSE levels of newborns with normal ultrasound results. This association fosters the biological plausibility of NSE as a marker reflecting membrane disruption of neurons. Previous investigations have highlighted the correlation between NSE elevation and severity of the clinical presentation and imaging abnormalities of neonatal brain injury [12].

Interestingly, even in SGA infants that did not have overt neurological symptoms, NSE concentration was often higher than that of controls. This raises the possibility that biochemical evidence of stress in neurons can come before the clinical manifestations can be seen. The fact that the NSE elevation was absent in the control group enhances the specificity of the results and minimises the chance that the results were due to routine neonatal stress.

Overall, the results show that the serum NSE levels of small for gestational age newborns are higher and more persistent during early neonatal adaptation than those of infants who are appropriate for gestational age. The relationship between NSE concentration, clinical neurological findings and neurosonographic changes provides evidence for the potential diagnostic value of NSE as a biomarker for perinatal central nervous system injury in growth-restricted neonates.

4. Discussion

The present study shows that small-for-gestational-age newborns have significantly higher serum neuron-specific enolase levels during the early neonatal period than the latter group of infants who are appropriate for gestational age. This finding, therefore, suggests that intrauterine growth restriction is not only linked to impaired somatic growth but also to increased neuronal vulnerability. The elevation of NSE within the first 24 hours of life indicates that biochemical evidence of neuronal stress may be present already in the first few hours of life, even in the absence of overt clinical signs.

Chronic intrauterine hypoxia has been suggested as a key process in growth restriction. Prolonged oxygen and nutrient deprivation may have an effect on cerebral autoregulation and may impair metabolic stability in neurons. Although compensatory redistribution of blood flow towards the brain is achieved and is known as the "brain-sparing effect" in order to maintain cerebral perfusion, this mechanism does not fully protect from subtle neuronal injury. Experimental and clinical research suggests that chronic foetal stress may sensitise neurons to excessive vulnerability during the transitional period of birth [13]. The high levels of NSE in the SGA group in this study may reflect such a subclinical neuronal compromise.

An important aspect of the findings is the presence of high NSE levels in a subset of SGA infants even on the fifth day of life. While most appropriate-for-gestational-age newborns showed a decrease in NSE concentrations, infants who were growth-restricted showed slower normalisation of NSE concentrations. This dynamic pattern could represent metabolic instability within the immature brain over a long period of time. Previous neonatal investigations have demonstrated that a persistent elevation in NSE levels is correlated with ongoing disruption of the neuronal membrane and may be linked with a poorer neurologic outcome [14]. Although long-term follow-up was not possible in this study, the biochemical profile in SGA infants would seem to indicate the importance of careful neurodevelopmental follow-up.

The correlation between the NSE levels and lower Apgar scores also supports the biological relevance of this biomarker. Even moderate perinatal stress seemed to increase the release of neuronal enzymes in growth-restricted infants. Notably, higher concentrations of NSE were also found in some SGA newborns with no significant clinical abnormalities. This observation highlights the limitation of using clinical examination alone in the early detection of central nervous system injury. Biochemical markers can show neuron distress before the change can be shown on structural imaging.

Another clinically important finding is the association of high NSE levels and abnormal neurosonographic findings. Infants with elevated periventricular echogenicity had elevated enzyme levels, indicating that NSE must be related to true neuronal membrane disruption and not to nonspecific stress in the body. Similar relationships between NSE and abnormalities in neuroimaging have been found in neonates with hypoxic ischemic encephalopathy and periventricular leukomalacia [15].

Taken together, these findings suggest that neuron-specific enolase may be an adjunct tool for evaluating perinatal CNS injury in growth-restricted newborns with high sensitivity. While NSE should not be considered a substitute for clinical or imaging evaluation, its addition to protocols to detect early neuronal injury could lead to an increased detection of subclinical neuronal injury. Given that SGA infants are a biologically vulnerable population, early identification of central nervous system involvement may enable more individualised strategies to monitor children and to intervene early [16].

Future studies should investigate the prognostic value of serial NSE measurement and its correlation with the long-term outcome of neurodevelopmental status. Nonetheless, the present study adds more evidence to how biochemical assessment can provide meaningful information on neuronal adaptation in newborns exposed to intrauterine growth restriction.

5. Conclusion

The results of this study show that small-for-gestational-age newborns show significantly higher serum neuron-specific enolase levels during the early neonatal period than do infants appropriate for gestational age. This elevation indicates heightened neuronal vulnerability in the growth-restricted infant; this is probably related to the chronic intrauterine hypoxia and poor cerebral metabolic adaptation. Importantly, NSE levels were not only elevated during the first 24 hours of life, but were also still higher in a subset of SGA newborns on the fifth day, suggesting prolonged neuronal stress and not a transient perinatal response. The association between high levels of NSE, low Apgar score and abnormal neurosonographic findings, observed in this study, provides evidence for the clinical value of this biomarker in identifying early central nervous system involvement. Notably, elevated levels of NSE were detected even in some of the SGA infants who did not have noticeable neurological symptoms, highlighting the importance of biochemical methods for detecting subclinical neuronal injury not immediately apparent by routine examination. These results suggest the possible usefulness of neuron-specific enolase as an adjunct in the early evaluation of perinatal CNS injury in growth-restricted neonates. The inclusion of NSE measurement in neonatal monitoring protocols

is potentially valuable for early detection of neuronal compromise and to assist in making timely clinical decisions. Further studies examining long-term neurodevelopmental outcomes are needed to elucidate the prognostic importance of early NSE elevation in this vulnerable population.

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