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Predictive Value of N-Terminal Pro-Brain Natriuretic Peptide as Prognostic Biomarker in Assessment of Myocardial Ischemic Injury in Neonates with Hypoxic Ischemic Encephalopathy (HIE): Review article

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ABSTRACT

Background: Any illness that disrupts the central nervous system in the first few days of life can induce encephalopathy among neonates. This ailment can have a variety of causes. Hypoxic-ischemic encephalopathy (HIE) is a significant risk factor in neonates, with cardiac dysfunction leading to higher mortality and severe brain injury. Myocardial dysfunction is directly linked to birth asphyxia severity, worsening clinical outcomes. Factors like low Apgar scores and inotropic therapy are linked to acute kidney injury and cardiac dysfunction in HIE patients. In the majority of cases, the B-type natriuretic peptides are produced and released in a constitutive manner by the ventricular cardiac myocytes. A classic name for neonatal encephalopathy that results from an intrapartum incident that causes perinatal hypoxia-ischemia is hypoxic-ischemic encephalopathy.

Objective: This article aimed to examine the diagnostic relevance of the N-terminal pro-brain natriuretic peptide biomarker in the evaluation of myocardial ischemia injury in infants who have hypoxic ischemic encephalopathy.

Methods: In our search for information on N-Terminal Pro-Brain Natriuretic Peptide and its role as biomarker in myocardial ischemic injury among neonates with HIE, we used Google Scholar, Science Direct, PubMed, and other internet databases. Additionally, the writers combed through relevant literature for references, however they only included researches covering the years from 2010 to 2024. Due of lack of translation-related sources, documents in languages other than English were excluded. Also, works in progress, unpublished publications, abstracts from conferences, and dissertations that did not form part of broader scientific investigations were excluded.

Conclusion: Neonates with HIE may have higher NT-proBNP levels than controls. Neonates with myocardial ischemia injury have higher levels of NT-proBNP than those without.

Keywords: NT-proBNP, Hypoxic-ischemic encephalopathy, HIE, BNP.

INTRODUCTION

As known that HIE is a major systemic disease, which affects different body organs. In this article we will look for the cardiac affection in this disease, how to detect and manage it as well. A variety of conditions can cause neonatal encephalopathy, which is an illness that affects the central nervous system during the first few days of life. Affected mental status (such as agitation, coma, and reduced responsiveness) hypotonia, seizures, aberrant primitive reflexes, feeding difficulties, apnea, and unusual crying are the hallmark symptoms of newborn encephalopathy. According to **Glass [1],** neonatal encephalopathy may be reversible and temporary, or it may be the initial indication of a brain injury, or brain abnormality that results in permanent disability.

The exact pathophysiology is often unknown, so the term neonatal encephalopathy was preferred over hypoxic-ischemic encephalopathy to describe neonatal encephalopathy. This type of encephalopathy occurs when an event occurs during intrapartum life that causes perinatal hypoxia-ischemia (HI), also called perinatal asphyxia. A kind of brain damage called hypoxic-ischemic encephalopathy (HIE) occurs when there is a protracted reduction in blood flow to the brain and oxygen levels drop too low [2].

Birth encephalopathy is caused by more than only hypoxia and ischemia. One of the most evident and frequent signs of encephalopathy is seizures, which can be utilized to diagnose encephalopathy cases. It is noteworthy that preterm infants frequently experience seizures and neonatal encephalopathy, however, the seizures are typically asymptomatic [3].

In the industrialized world, the prevalence of newborn encephalopathy is estimated to be between 2 and 6 per 1000 live-term infants, with HIE occurring in about 1.5 of those cases. Perinatal HIE was found in the US with a population frequency of 1.7 per 1000 [2].

About 40% of new consultations in the newborn intensive care unit are related to neonatal encephalopathy, which is caused by confirmed or suspected HIE. It is one of the most prevalent diagnoses made by a neurologist [4]. In Egypt, 16% of the newborns at the Neonatal Intensive Care Unit in Sharqia Governorate had hypoxic-ischemic encephalopathy [5].

Pathophysiology:

The fetal brain needs a steady stream of ATP to be able to metabolize glucose, ketone bodies, and lactate. Because the prenatal brain may store energy for use when needed, it is more able to withstand hypoxia-ischemia (HI) than older brain. But the fetal brain is susceptible in equal manner to damage in the event of a severe ATP shortage [6].

Cellular and systemic responses result from lack of blood with oxygen reaching to the cerebellum of the

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fetus as it leads to depletion of ATP, which is caused by significant hypoxia, that resulted from different conditions (e.g., pre-eclampsia, chronic maternal hypoxia, shoulder dystocia, umbilical cord knotting, placental abruption, and umbilical cord prolapse). Brain damage occurred at various levels [7].

The ischemic problem, causing neuronal cells disruption at the mitochondrial and cytoplasmic levels, affect the blood brain barrier (BBB) (peroxidation degree of membrane is positively correlated with the ATP exploitation severity), and initiates a critical inflammatory reaction, starts when the 1^{ry} vital energy failure happens. This uncontrollably releases excitatory neurotransmitters [8]. These lead to excitotoxic buildup, cytotoxic edema, and failure of oxidative metabolism. Following restoring the circulation in the cerebrum, a latent phase that lasts for about six hours is followed by a 2^{ry} failure of energy, which could linger for days and occurs six to fifteen hours after HI. Seizures, recurrent cytotoxic edema, poor metabolism of oxidative energy, excitotoxin release, and ultimately death of neurons are characteristic of this phase [6]. The five primary processes that comprise the pathophysiology of HIE are oxidative stress, intracellular Ca^{2+} buildup, mitochondrial dysfunction, excitotoxicity, and inflammation. Each of these events is interconnected with the others [9].

Clinical presentation:

Seizures, unconsciousness, weakened primitive reflexes and impaired tone are among the clinical indicators of encephalopathy. Severe encephalopathy was shown on repeated exams, and the encephalopathy degree in the context of suspected HIE was categorized as severe, moderate, or mild. Crucially, death and the encephalopathy degree are related [7].

While children with less severe encephalopathy endure and moderate encephalopathy degrees have in between odds of survival, severe cases have increased odds of mortality rate also, patients have a very strong likelihood of lasting neurological abnormality [10].

Evaluation of the neonate with encephalopathy:

A thorough assessment is necessary due to the wide range of encephalopathy's etiology, particularly in situations where there is little chance of prenatal asphyxia or in which there has been no sentinel episode.

Examination and taking a history:

A review of the mother's medical history, her use of drugs or alcohol, her obstetric history, the results of fetal US and pre-natal screening, her intra-partum experiences, including monitoring of the fetal heart rate, and her placental pathology, which will be examined to rule out placental abruption, vascular lesions, thrombosis of umbilical cord or infections. All should be considered as potential antecedents of neonatal encephalopathy. A diagnosis other than HIE may be suggested by a family history of congenital neurological diseases, convulsions, and neuromuscular diseases [11].

The history of the child must describe the encephalopathy and seizures, including their beginning, timing, and course. A hypoxic event and HIE can be supported by the existence of low urine output, low blood pressure, coagulopathy, or transaminitis, all of which indicate multiorgan failure [12].

Neonates should have a thorough neurologic examination as well as a meticulous assessment for indications of aberrant fetal development, such as birthmarks, dysmorphic facial features, and congenital abnormalities of the skeleton and internal organs. Persistence of reduction in fetal movements may be indicated by a palmar crease absence, joint contractures, and micrognathia, which may indicate the prenatal beginning of encephalopathy [13].

Assessment of a Laboratory:

The pH of the base and the umbilical artery both offer essential information considering the way in which the fetus is being perfused. In addition to newborn lactate levels and blood gas, a full CBC, calcitonin, blood cultures and C-reactive protein, to check for indicators of infection. An extensive laboratory evaluation also includes tests for blood urea nitrogen (BUN), liver enzymes, creatinine, bilirubin, coagulation profile, glucose, and electrolyte panel. These tests are performed to check for signs of infection. In the event that an infection of the CNS is suspected, lumbar punctures should be done in order to do cell counts, cultures, and viral tests concerning viruses such as herpes simplex virus, parovirus, and rota-virus, amongst others [12].

The testing of urine organic acids, blood ammonia, and serum amino acids, which may be required in locations that do not have a comprehensive newborn screening program in order to check for inborn metabolic errors or in circumstances where a newborn metabolic error is thought to be. In order to ascertain the reason of congenital abnormalities and possible syndromic disorders, it is essential to conduct genetic evaluations, which may include single-nucleotide polymorphism array analysis [11].

Neuroimaging:

For all infants with encephalopathy or seizures, magnetic resonance imaging (MRI) is advised in order to help determine the cause of the encephalopathy and to aid in the prognosis. Although, head ultrasonography is helpful at the bedside to identify hemorrhage or ventriculomegaly, it is frequently normal in the acute phase following a hypoxic-ischemic event [12]. Because significant radiation doses are required to obtain good resolution of the brain parenchyma, computed tomography (CT) is rarely employed in babies [14].

When properly supervised and trained, MRI can be safely performed on severely ill children many times

without the need for sedation. Magnetic resonance spectroscopy and diffusion-weighted imaging (DWI) are crucial for identifying acute impairment and conventional imaging whereas susceptibility-weighted imaging (SWI) can help identify small regions of bleeding [10].

In addition to predisposing to additional hypoxic-ischemic injury during birth, structural-developmental abnormalities shown on conventional T1 and T2 scans may lead to seizures or early encephalopathy. During the acute period, which is the first seven to ten days following an accident, DWI can be utilized to identify anatomic sites of harm. Low N-acetyl aspartate (NAA), which denotes compromised neuronal integrity, or a lactate peak, which is indicative of aberrant metabolism most frequently brought on by acute damage, can both be seen using magnetic resonance spectroscopy [10].

Due to its ability to anticipate future deficits based on the severity and pattern of injury, MRI is a valuable prognostic tool. The load of injury visible on MRI is reduced in newborns receiving therapeutic hypothermia, especially in the thalamus and basal ganglia, but also in the watershed regions and white matter [14].

Management:

A neonatal intensive care center is the best place to care for infants with encephalopathy, as it offers neuromonitoring, neuroimaging, and specialized neurologic care. Systemic support is crucial for newborns with HIE, restoring cerebral blood flow and preventing secondary damage [12]. Hypoxic insults can cause metabolic alterations in infants, reducing carbon dioxide synthesis and reducing oxygen production. Hypocapnia, a risk for poor neurodevelopmental outcomes and death, can also have negative effects on newborns with HIE. Adequate oxygenation and normocapnia can help prevent further damage. Blood pressure should be kept within the critical range of 40 to 60 mm Hg, with organ-specific regional oximetry helping personalize care [13]. Echocardiography is helpful in individuals with HIE, as clinical or historical evidence of hypovolemia may require extra volume [10]. Neonatal fluid restriction is recommended due to the high glucose consumption in the developing brain, which accounts for 70% of total glucose consumption [8]. The developing brain can use alternative substrates like lactate or ketones as energy sources, but the availability of these is not consistently high. High newborn Sarnat stages are correlated with lower serum glucose values, and hypoglycemia is a significant risk factor for perinatal brain damage [13]. Careful glucose monitoring is required to prevent and cure hypoglycemia. Therapeutic hypothermia should be initiated within 6 hours of birth to reduce the risk of mortality or moderate to severe impairment. Passive cooling and servo-controlled devices can be used to maintain consistent temperatures and prevent overcooling [15]. Continuous brain monitoring is recommended for all neonates experiencing hypothermia, with a preference for video-EEG [16]. Seizures are experienced by approximately 50% of hypothermic neonates and should be promptly addressed with antiseizure medications. Phenobarbital and phenytoin are both effective, but approximately half of children experience recurring seizures following the first bolus of either medication [17].

Myocardial ischemic in neonates:

Myocardial ischemic injury in neonates, particularly in the context of hypoxic-ischemic encephalopathy (HIE), is a significant concern, as it is associated with high morbidity and mortality rates. Research indicates that myocardial damage occurs in 28%–73% of asphyxiated neonates, with elevated cardiac troponin I (cTnI) levels serving as a reliable biomarker for myocardial injury and correlating with the severity of HIE and adverse outcomes [18]. In a cohort study, higher cTnI levels were observed in neonates with more severe stages of HIE, suggesting its potential as a prognostic indicator [19]. Furthermore, cardiac dysfunction in neonates with HIE has been linked to increased mortality and brain injury, emphasizing the need for comprehensive cardiac assessment in these patients [5]. Interventions like subhypothermia have shown promise in mitigating myocardial damage and improving outcomes in affected neonates [20]. Thus, understanding the interplay between myocardial injury and HIE is crucial for improving neonatal care.

N-Terminal Pro-Brain Natriuretic Peptide:

In 1988, the B-type natriuretic peptide was discovered. **Hunt and colleagues** [21] were the first to demonstrate evidence of the presence of amino-terminal pro–B-type natriuretic peptide (NT-proBNP) in human circulation and its association with heart function. In 1995, it was discovered that ventricular cardiac myocytes generate and discharge the preponderance of B-type natriuretic peptides, which are frequently referred to as BNP [21].

The atrial myocytes of the heart include perinuclear granules that secrete some proBNP 108. Atrial natriuretic peptide (ANP) secretion and this happen at the same time. The main cause for the generation and release of BNP is the elongation of myocytes caused by transmural distending pressure. The release of NT-proBNP 1-76 and its carboxy-terminal congener, BNP 1-32, is a 1:1 ratio that occurs upon cleavage of proBNP 108 [22].

Given their biological activities, cardiac natriuretic peptides (NP) may be a component of an endogenous compensatory system that helps to reduce the negative consequences of overexertion of the muscles and volume expansion. Natriuresis, diuresis, vasodilation, and lusitropism are some of these effects, along with the direct inhibition of systems that retain volume and constrict blood vessels, like the renin-angiotensin-aldosterone and sympathetic nervous systems [22]. In addition, NP have trophic effects that counteract the

effects of heart fibrosis and hypertrophy. The association between intracardiac pressures and plasma concentrations of BNP and NT-proBNP is the principal factor that **D'Souza *et al.*** [23] found to contribute to the efficacy of these biomarkers in the context of heart failure.

The stress on the wall of the cardiac chamber, which is the primary element responsible for the synthesis and release of NP, is directly related to the pressure within the chamber and the chamber radius, and it is inversely related to the wall thickness, as per the law of Laplace. Concentrically hypertrophied hearts exhibit reduced unit wall stress, a common observation in patients with heart failure (HF) and preserved ejection fraction (HFpEF). This is in stark contrast to the circumstances of patients with HF, who exhibit dilated left ventricles and a reduced ejection fraction (HFrEF) [21]. As a result, HFpEF, or heart failure with preserved ejection fraction, had lower plasma NP levels in ADHF compared to HFrEF, or heart failure with reduced ejection fraction. There is a correlation between NT-proBNP and a number of echocardiographic markers of heart anatomy and function. The following parameters are included in these indications: pressures in the right ventricle, ejection fraction in the left ventricle, left atrial dimensions, longitudinal strain in the left ventricle, circumferential strain in the left ventricle, and end-diastolic wall stress in the left ventricle [24].

A variety of echocardiographically derived measurements of cardiac anatomy are associated with the concentrations of NT-proBNP in plasma, as has been discovered. **Wu *et al.*** [11] research in 2021 indicated that individuals who have experienced an acute myocardial infarction have elevated levels of brain-type natriuretic peptide (BNP) or N-terminal fragment of the prohormone (NT-proBNP) in their circulation. These levels are capable of precisely predicting the mortality of these patients.

Potential mechanisms of role of N-Terminal Pro-Brain Natriuretic Peptide in myocardial injury:

Ventricular BNP gene expression and BNP production were rapidly increased in the initial animal investigations of experimental infarction in rats. This was observed in the nonischemic myocardium that surrounded the infarct region, as well as in the infarct site and the ischemic periinfarct region. The alterations in gene expression were observed as early as four hours after the infarction, and they reached their peak one day after the infarction. The myocardial cells were identified as the primary source of BNP synthesis in the research conducted by **Ji *et al.*** [25] and **Elgendy *et al.*** [26]**.** Furthermore, hypoxia induces cell death in isolated rat ventricular myocytes, despite the fact that it elevates BNP expression and release. This discovery supports the hypothesis that ischemia may serve as an inducer of BNP expression. BNP may directly limit the extent of infarcts by activating an ATP-sensitive potassium channel, in addition to the hormonal counter-regulatory actions of natriuretic peptides that have been well-documented for a long time, according to an intriguing series of discoveries from isolated rat hearts [27].

Predictive Value of N-Terminal Pro-Brain Natriuretic Peptide as Prognostic Biomarker in Assessment of Myocardial Ischemic:

N-terminal pro-brain natriuretic peptide (NT-proBNP) has emerged as a significant prognostic biomarker in assessing myocardial ischemia, particularly in the context of ST-elevation myocardial infarction (STEMI). Research indicates that elevated NT-proBNP levels prior to primary percutaneous intervention (PCI) correlate with poorer myocardial reperfusion outcomes, such as reduced ST resolution and lower TIMI flow grades, suggesting its utility in risk stratification for STEMI patients [28]. Additionally, NT-proBNP levels have been shown to predict the success of fibrinolytic therapy, with higher concentrations associated with increased in-hospital mortality and adverse cardiovascular events [29]. Furthermore, NT-proBNP has demonstrated independent prognostic value in predicting major adverse cardiovascular events in healthy individuals, enhancing risk assessment beyond traditional factors [30]. Collectively, these findings underscore NT-proBNP's role as a reliable biomarker for evaluating myocardial ischemia and guiding treatment strategies in various clinical scenarios [31-32].

CONCLUSION

NT-proBNP level increases in neonates with HIE than in controls and increases with severity of HIE. NT-proBNP level increases in neonates with myocardial ischemic injury than in those without myocardial ischemic injury.

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