https://doi.org/ 10.33472/AFJBS.6.9.2024.871-887

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Comparison of Neuron-Specific Enolase (NSE) Levels in Serum and Cerebrospinal Fluid in Patients with Severe Traumatic Brain Injury

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Article Info

Article History

Volume 6,Issue 9, 2024

Received:21 Mar 2024

Accepted : 29 Apr 2024

doi: 10.33472/AFJBS.6.9.2024.871-887

ABSTRACT

Background: Traumatic brain injury (TBI) represents a pressing challenge in emergency medicine due to its high mortality rates and profound impact on patients' lives. Neuron-specific enolase (NSE) levels have emerged as a promising biomarker for assessing TBI severity and prognosis, offering valuable information to guide clinical decision-making in emergency departments.
Aim: The aim of this literature review is to evaluate the comparison of Neuron Specific Enolase (NSE) levels in serum and cerebrospinal fluid in patients with severe traumatic brain injury.
Material and Methods: The research method used involves identifying the research objective to evaluate the difference in NSE levels between serum and cerebrospinal fluid in patients with severe traumatic brain injury, selecting clear inclusion and exclusion criteria, searching the literature using relevant keywords in medical databases, extracting data from studies that meet the inclusion criteria, analyzing the data to identify patterns and differences in NSE levels, preparing a research report that includes an introduction, methods, results, and conclusions based on the findings from the literature review, as well as presenting information systematically and comprehensively according to scientific writing standards.
Results: The results of the literature review discussion indicate a significant difference in NSE levels between serum and cerebrospinal fluid in patients with severe traumatic brain injury, with potential implications for the diagnosis and prognosis of traumatic brain injury.
Conclusion: The comparison of Neuron Specific Enolase (NSE) levels in serum and cerebrospinal fluid among patients with severe traumatic brain injury reveals a significant divergence, suggesting NSE's potential as a diagnostic and prognostic biomarker.

Keywords: Neuron Specific Enolase, Serum, Cerebrospinal Fluid

1. Introduction

Trauma is a daily issue faced in the emergency department of hospitals, and traumatic brain injury is one of the leading causes of death (Abbas, 2020). Traumatic Brain Injury (TBI) is defined as a change in brain function or pathology caused by external force, which includes periods of loss or decreased level of consciousness, loss of memory both anterograde and retrograde, neurological deficits, and changes in mental status. TBI is categorized based on the level of consciousness using the Glasgow Coma Scale (GCS); GCS less than 8 is categorized as severe TBI (Padmaja et al., 2017). The incidence rate of severe TBI varies across different countries worldwide, ranging from 6.64% to 18.02%. Globally, it is estimated that around 69 million people experience TBI each year (95% CI 64.2-73.8), with approximately 5.48 million people suffering from severe TBI, or 73 cases per 100,000 people annually (Centers for Disease Control and Prevention, 2015). Although the incidence or prevalence of severe TBI is not high, the prognosis and mortality rates associated with severe TBI remain high. Several studies have reported high mortality and morbidity rates from TBI, with mortality rates ranging from 31% to 51% and unfavorable outcomes (Glasgow Outcome Scale < 4) ranging from 51% to 66% (Li et al., 2016).

Neurological status measurement frequently performed in TBI is the measurement of GCS in recent years due to its advantages (Padmaja et al., 2017). However, GCS has several conditions where the results shown are not meaningful or the measurement cannot be performed. These conditions include patients who are intoxicated with alcohol, patients who use endotracheal or tracheostomy tubes, patients under the influence of sedative drugs and/or muscle relaxants (Kementerian Kesehatan Republik Indonesia, 2018). The pathophysiology of TBI is essentially divided into primary brain injury and secondary brain injury. Primary brain injury is a disorder caused by direct trauma and often does not respond to therapy, while secondary brain injury results in several cascades such as cerebral blood flow (CBF) disturbances, brain metabolism disorders, the emergence of neurotoxicity and neuronal inflammation. These events will lead to brain tissue death, resulting in decreased prognosis and consciousness (Hutauruk et al., 2020; Han et al., 2017).

In recent years, there has been a growing interest in studying biomarkers for brain injuries as potential tools for evaluating prognosis. One of these biomarkers is neuron-specific enolase (NSE), which is a dimeric isoform of the glycolytic enzyme enolase. It has a size of 78 kDa and is located in the cytoplasm of neurons involved in slow axoplasmic transport. NSE is only produced when axons are damaged, making it a biomarker that directly assesses functional damage to neurons (Isgrò et al., 2015). Several studies have found a correlation between the severity of traumatic brain injury (TBI) and NSE levels in the blood. Patients with severe TBI have the highest average NSE levels (10.60 µg/ml), compared to those with mild TBI (6.69 µg/ml) or moderate TBI (7.44 µg/ml) (Stefanović et al., 2017). Other research has also shown that high NSE levels from 6 to 24 hours after trauma are associated with poor prognosis, while elevated NSE levels 72 hours after injury are associated with increased risk of mortality (Cheng et al., 2014).

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associated with poor prognosis, while elevated NSE levels 72 hours after injury are associated with increased risk of mortality (Cheng et al., 2014).

When an injury occurs to the central nervous system (CNS), NSE is released from cells, leading to an increase in its concentration in the extracellular fluid (cerebrospinal fluid and blood serum). NSE can reach the blood serum through the lymphatic system. The high levels of NSE can be caused by two factors: leakage or upregulation of NSE due to its requirement for cell repair mechanisms and maintenance of homeostasis (Isgrò et al., 2015). NSE levels increase within the first 12 hours after the injury and then decrease over the course of hours to days. The half-life of NSE is 24 to 30 hours (Syafrita & Fitri, 2021). NSE has a peak onset and a relatively long half-life, leading some authors to suggest that the increase in NSE concentration in cerebrospinal fluid (CSF) should be faster and more pronounced, considering the close anatomical and functional relationship between the brain, spinal cord, and cerebrospinal fluid (Hajduková et al., 2015). In summary, the levels of serum and CSF NSE can provide information for assessing traumatic brain injury, with serum NSE offering a systemic perspective on nerve damage, while CSF NSE is more specific to the central nervous system. Based on this background, this literature review aims to compare the levels of NSE in serum and cerebrospinal fluid (CSF) to determine the reliability of serum NSE levels compared to brain damage with a more specific examination (CSF NSE levels) in severe traumatic brain injury patients.

2. Methodology

This literature review seeks to evaluate the comparison of Neuron Specific Enolase (NSE) levels in serum and cerebrospinal fluid in patients with severe traumatic brain injury. The research methodology adopted encompasses several key steps. Initially, the research objective is delineated, focusing on assessing the variance in Neuron Specific Enolase (NSE) levels between serum and cerebrospinal fluid in severe traumatic brain injury patients. Clear inclusion and exclusion criteria are then established to ensure the relevance and reliability of the gathered data. Subsequently, a thorough literature search is conducted utilizing pertinent keywords across medical databases. Data extraction is meticulously performed from studies meeting the predefined inclusion criteria. Analysis of the extracted data follows, aiming to discern trends and disparities in NSE levels. A comprehensive research report is then compiled, comprising sections such as introduction, methods, results, and conclusions derived from the literature review findings. Throughout the process, information is presented systematically and comprehensively in adherence to scientific writing standards, ensuring the rigor and credibility of the research outcomes.

3. Results and Discussion

Changes in Cerebral Blood Flow

Based on several studies, focal or global brain ischemia often occurs even though the total brain ischemia volume is typically less than 10%. The mechanism of ischemia after trauma involves damage to morphology, distortion of blood vessels, autoregulatory failure, and vasospasm due to a deficiency of nitric oxide or cholinergic and potential prostaglandin neurotransmitters causing vasoconstriction.

The decrease in CBF that occurs in the early phase is the main target in therapy. Adverse consequences due to extracranial disturbances in the early phase of injury (hypotension, hypoxemia) worsen secondary damage. Injured brains are at higher risk of further damage because they are unable to provide appropriate vasodilation response during additional disturbances. Brain ischemia events are associated with poor neurological outcomes (death or vegetative state) (Prins et al., 2013).

The frequent association between cerebral hypoperfusion and poor outcomes suggests that traumatic brain injury and ischemic stroke share a common underlying mechanism (although this assumption is true, there are significant differences between the two conditions). In patients with brain injury, the critical threshold of cerebral blood flow (CBF) to cause irreversible tissue damage is 15 ml/100 gram/minute, while in patients with ischemic stroke, it is 5-8.5 ml/100 gram/minute. Brain ischemia predominantly leads to metabolic stress and ion disturbances, while in brain injury, it also exposes brain tissue to frictional forces, resulting in successive morphological injuries to neuronal cell bodies, astrocytes, microglia, damage to microvascular cells and endothelial cells. The mechanism of post-traumatic ischemia occurs due to morphological injuries (blood vessel distortion) as a result of mechanical energy, hypotension due to autoregulatory failure, lack of nitric oxide and cholinergic neurotransmitters, and potentiation of vasoconstriction induced by prostaglandin (Dreixler et al., 2010).

Patients with brain injuries may experience brain hypoperfusion (CBF > 55 ml/100 gram/minute) in the early phase. Hyperemia can also occur immediately after post-traumatic ischemia. This pathological condition is equally detrimental as ischemia in terms of the final outcome because the increased CBF exceeds the metabolic demand associated with paralysis of the cerebral blood vessels, increasing the volume of blood in the brain and ultimately causing an increase in ICP (Intra-Cranial Pressure). It is important to note that the diagnosis of hypoperfusion or hyperperfusion is valid only after measuring CBF, which is related to brain oxygen consumption. Brain ischemia and hyperemia lead to an imbalance between CBF and brain metabolism (Werner & Engelhard, 2007; Prins et al., 2013).

Management of Traumatic Brain Injury (TBI)

Initial management of traumatic brain injury primarily focuses on prevention and supportive therapy, such as monitoring blood pressure and oxygenation, prophylaxis against infection and deep vein thrombosis, analgesia, and determining limits for vital signs such as ICP and CPP (Cerebral Perfusion Pressure). Disturbances in the regulation of metabolism, blood flow, and brain perfusion are early changes that occur after traumatic brain injury. Therapies like Hypothermia and Hyperbaric Oxygen Therapy (HBOT) are options to address these regulatory disturbances.

In the later stage of TBI, neuro-inflammation occurs, leading to increased ICP as the main pathological consequence. Treatment options to prevent this condition include pharmacological therapy such as progesterone administration and hyperosmolar fluids, as well as surgical intervention with decompressive craniotomy. Understanding the inflammatory cascade in TBI and its variability is essential in choosing an effective therapy to manage the damage that occurs.

Long-term complications of TBI include the occurrence of seizures that can become persistent and progressive into epilepsy, however, the Brain Trauma Foundation (BTF) guidelines state that anti-convulsants are not necessary for seizure prophylaxis. Anti-seizure medications such as phenytoin and valproic acid are only given if seizures occur and not for long-term use. Another option for managing post-TBI seizures is the placement of a Vagal Nerve Stimulator (VNS) through a surgical procedure (Algattas & Huang, 2014).

Decompressive Craniotomy

Cerebral edema may arise from a combination of various pathological mechanisms associated with the pattern of primary and secondary injury in traumatic brain injury. With the rising intracranial pressure, brain tissue displacement can cause cerebral herniation, resulting in disability or death.

The surgical procedure known as decompressive craniotomy, which involves the removal of a portion of the skull, has been performed to alleviate increased intracranial

pressure and has shown improvement in certain TBI patients. The lack of data regarding the role of decompressive craniotomy in managing severe TBI outcomes stems mainly from the absence of randomized controlled trials (RCTs) evaluating this intervention.

There have been various variations in surgical techniques, timing, and patient populations in most observational studies published in the last two decades. A recent RCT evaluated decompressive craniotomy as a secondary procedure after targeted medical therapy for intracranial pressure (ICP) has failed, and is expected to provide further evidence to support or not support this intervention (Carney et al., 2017).

Prophylaxis

Hypothermia is well known for preserving cells and tissues in the face of metabolic challenges. The available evidence supports the use of hypothermia as the standard treatment for neuroprotection after a heart attack from acute coronary syndrome. There has long been interest in applying hypothermia to reduce tissue damage associated with central nervous system trauma, but the benefits of this approach cannot be assumed. In addition to being suggested for its neuroprotective effects, hypothermia is renowned for its ability to reduce intracranial pressure. However, hypothermia carries risks, including coagulopathy and immunosuppression, and hypothermia itself carries additional risks of cardiac arrhythmias and death.

Hypothermia can be administered both early after injury and before intracranial pressure increases, in this case referred to as "prophylaxis," or as a treatment for refractory intracranial pressure elevation, usually referred to as "therapy." Prophylactic hypothermia has been studied under supervision in studies that have reported conflicting results. The uncertain relevance to adult traumatic brain injury as well as two recent studies in the pediatric population have failed to demonstrate benefits and have confirmed additional risks associated with hypothermia prophylaxis for TBI.

Researchers' interest has shifted towards exploring how specific aspects of induced hypothermia, such as duration and depth, are related to clinical effects. For instance, it is generally suggested that gradual rewarming can reduce the risk of rebound increase in intracranial pressure, and there has been interest in local brain tissue cooling with the hope of achieving desired benefits without systemic side effects (Carney et al., 2017).

Hyperosmolar Therapy

Since 1783, Monro, Kellie, and other researchers have proposed the idea that intracranial volume is constant. The important work of Weed and McKibben refuted this long-held dogma when they showed dramatic changes in brain volume resulting from the administration of hypertonic or hypotonic intravenous solutions. Since then, the administration of intravenous hyperosmolar agents has become routine in the management of intracranial hypertension and herniation syndromes. However, the optimal agent, optimal method of administration (dose and bolus vs continuous infusion), and the exact mechanism of action continue to be investigated.

Manitol and hypertonic saline are routinely used as hyperosmolar agents in North America. Certain conditions may influence the selection of a specific agent. Administration of hypertonic saline solution may be dangerous for hyponatremic patients. Although manitol can be used as a resuscitation fluid, its undesired diuretic effects on hypotensive patients should be taken into consideration, and attention should be given to replacing intravascular volume loss. While manitol was previously considered to reduce intracranial pressure through simple brain dehydration, both manitol and hypertonic saline work, at least partially, by reducing blood viscosity, leading to increased microcirculation blood flow and pial arteriole constriction, resulting in decreased cerebral blood volume and intracranial pressure (Carney et al., 2017).

Cerebrospinal Fluid Drainage

Management of external ventricular drainage (EVD) system in patients with traumatic brain injury remains a controversial topic. Closed EVD allows for monitoring of intracranial pressure (ICP), while open EVD serves for drainage of cerebrospinal fluid (CSF). The practice pattern regarding whether EVD should be maintained in closed or open position varies significantly based on several variables, including patient age, institutional resources, and physician preferences.

Patient age appears to be the key factor in managing Ebola Virus Disease (EVD). In children, continuous cerebrospinal fluid (CSF) drainage is commonly used and has been shown to improve intracranial pressure (ICP) management and serve as a biomarker for brain damage. However, there is more variation in the management of adult patients who have experienced trauma. Some doctors prefer to continuously monitor ICP and only drain intermittently to prevent ICP elevation, while others opt for continuous CSF drainage with intermittent ICP measurements. A third option involves placing an EVD for continuous drainage and using intraparenchymal fiber optic monitors for continuous ICP measurement (Carney et al., 2017).

Ventilation Therapy

Patients with severe traumatic brain injury require definitive airway protection because they are at risk of lung aspiration or respiratory function impairment. They may also need temporary hyperventilation to manage cerebral herniation. Normal ventilation is the goal for severe TBI patients without cerebral herniation and normal arterial carbon dioxide partial pressure (PaCO2) levels ranging from 35-45 mmHg. PaCO2 is a measurement of carbon dioxide pressure in the artery and is highly dependent on the metabolic rate. Exhalation eliminates CO2 as a byproduct of metabolism, and during metabolism, the respiratory rate usually increases, resulting in lower PaCO2 levels. In normal conditions, PaCO2 is the strongest determinant of cerebral blood flow (CBF) with values between 20 mmHg and 80 mmHg. CBF is linearly responsive to PaCO2. Cerebral blood flow is crucial in meeting the brain's metabolic needs. Therefore, low PaCO2 levels result in low CBF and can lead to cerebral ischemia, while high PaCO2 levels can cause cerebral hyperemia and high intracranial pressure (ICP). Therefore, optimal CBF is essential both in normal and abnormal conditions.

A patient with severe traumatic brain injury receives mechanical ventilation that can tightly regulate PaCO2 levels through adjustments in respiratory rate and tidal volume. Research shows that cerebral hyperemia is more commonly found than cerebral ischemia, and hyperventilation is recommended in the treatment of TBI patients. However, newer studies indicate that after severe TBI, brain metabolism levels are not always low and can vary. In fact, cerebral ischemia has been documented in several studies after severe TBI, altering the previous recommendations for ventilation therapy. Since brain metabolism rates are not universally measured after TBI, it is not possible to provide point-of-care CBF therapy to this patient. Therefore, the high prevalence of cerebral ischemia in this patient population suggests safety in providing normal ventilation to prevent further cerebral ischemia and infarction (Carney et al., 2017).

Anesthesia, Analgesia, and Sedation

Anesthesia, analgesia, and sedation are important and commonly used therapies in cases of acute traumatic brain injury for various reasons, including prophylaxis or control of intracranial hypertension and seizure prophylaxis. Barbiturates have a long history of use in controlling intracranial pressure by preventing unnecessary movements, coughing, and suppressing the rate of metabolism and changes in cerebral vascular tone. Suppression of

cerebral metabolism rate and oxygen consumption is said to be neuroprotective in some patients. Anesthetic and sedative drugs, such as barbiturates, can also increase regional blood flow coupling with metabolic needs resulting in higher brain oxygenation with lower cerebral blood flow, as well as reducing ICP by decreasing cerebral blood volume. Other neuroprotective mechanisms include inhibition of lipid peroxidation mediated by oxygen radicals.

Side effects of anesthesia, analgesia, and sedation include hypotension and decreased cardiac output, as well as increased intrapulmonary shunt that can lead to hypoxia (Fajarini et al., 2020). This can result in a paradoxical decrease in cerebral perfusion pressure that may negate the benefits of lowering ICP. Additionally, anesthetic drugs such as propofol have been associated with hyperkalemia, metabolic acidosis, heart failure, rhabdomyolysis, and death. The administration of these medications can impede physical examination in evaluating patient progress; therefore, more advanced therapy modalities such as continuous electroencephalographic (EEG) monitoring may be necessary. Due to the various potential toxic side effects, the duration and dosage of administration also mean that monitoring sedative drug doses needs to be done periodically (Carney et al., 2017).

Prophylaxis of Deep Vein Thrombosis

Patients with traumatic brain injury (TBI) are at significant risk of developing venous thromboembolism (VTE). Knudson et al. found that head injury with an Abbreviated Injury Scale score of 3, among other factors, is an independent predictor of VTE in trauma patients. TBI has been associated with up to 54% incidence of deep vein thrombosis (DVT) without prophylactic treatment and a 25% incidence in patients with isolated TBI treated with sequential compression devices. Ekeh found that DVT occurs in one-third of moderate to severe TBI patients with isolated head injury, with a lower incidence than patients with concurrent extracranial injuries. Age, subarachnoid hemorrhage, Injury Severity Score >15, and extremity injuries are predictors of DVT. Reiff and colleagues demonstrated a three to fourfold increase in the risk of DVT in TBI patients even when using mechanical and chemoprophylaxis. The risk of VTE increases with the severity of TBI.

Severely TBI patients may be at significant risk for VTE due to the hypercoagulability resulting from the primary brain injury, prolonged periods of immobilization, and focal motor deficits. Left untreated, DVT can lead to potentially debilitating or fatal pulmonary embolism. Of particular concern is the initiation of pharmacological VTE prophylaxis, which, in conjunction with mechanical compression stockings, has shown increased effectiveness compared to mechanical prophylaxis alone. The issue lies in the fact that the medication is a low-dose anticoagulant, which has the potential to cause clinically significant intracranial hemorrhage expansion (Carney et al., 2017).

Prophylaxis for seizures

Acute symptomatic seizures can occur as a result of severe traumatic brain injury (TBI). Post-traumatic seizures (PTS) are classified as early when they occur within 7 days of injury or late when they occur after 7 days of injury. Post-traumatic epilepsy (PTE) is defined as recurrent seizures more than 7 days after the injury. In patients with severe TBI, the clinical PTS rate may be as high as 12%, while subclinical seizures detected on electroencephalography may be as high as 20% to 25%. Early PTS risk factors include: Glasgow Coma Scale (GCS) score of 10; immediate seizures; post-traumatic amnesia lasting more than 30 minutes; linear or depressed skull fractures; penetrating head injuries; subdural, epidural hematoma, or intracerebral hemorrhage; cortical contusions; age 65 years; or chronic alcoholism. A 2010 population-based study showed that the rate of PTE is substantially higher than the risk of developing epilepsy in the general population. Those at highest risk for PTE are individuals who have experienced the following: severe TBI and early PTS before

discharge; acute intracerebral hematoma or cortical contusions; post-traumatic amnesia lasting more than 24 hours; age >65 years; or a history of premorbid depression.

Prophylaxis for post-traumatic seizures (PTS) involves the practice of administering anticonvulsants to patients following traumatic brain injury (TBI) to prevent seizures. The rationale for routine prophylaxis is that there is a relatively high incidence of PTS in severe TBI patients, and there are potential benefits to preventing seizures after TBI (e.g., limiting disruption to physiology, preventing the development of chronic epilepsy, and preventing herniation and death). However, it is also desirable to avoid neurobehavioral and other side effects of medications, especially if they are not effective in preventing seizures. Therefore, it is important to evaluate the efficacy and overall benefits, as well as the potential risks, of the anticonvulsants used for PTS prevention.

Levetiracetam, also known by the brand name Keppra, appears to be increasingly used for prophylactic seizure management in various pathologies, including TBI. The available comparative studies are insufficient to support recommendations for or against the use of levetiracetam over other agents. Further studies are needed to better understand the potential benefits or risks of levetiracetam in treating patients with TBI (Carney et al., 2017).

Neuron Specific Enolase

Enolase (2-phospho-D-glycerate hydrolysis; EC 4.2.1.11) is a metalloenzyme that acts as a catalyst in the dehydration of 2-phospho-diglycerate to phosphoenolpyruvate in the glycolytic pathway, and vice versa, the hydration of phosphoenolpyruvate to 2-phospho-diglycerate in gluconeogenesis. It is essential for the anaerobic conversion of glucose into metabolites suitable for oxidation.

The catalytic activity of enolase requires the natural cofactor Mg^{2+}. Two types of metal binding sites contribute to the catalysis. Metal binding at site I, traditionally called the "conformational" site, causes a conformational change in the enzyme and allows for substrate or substrate analog binding. After binding a substrate or substrate analog, the second metal ion, called the "catalytic" ion, can bind at site II and then catalytic reaction occurs. Releasing ligands is more complex. Amidst controversy is the observation that high concentration of metal ions inhibits enolase. Initially, the presence of three inhibitory metal ion binding sites was proposed. In a recent study, data supporting an alternative explanation was obtained.

Two pathways for product release have been proposed. Firstly, in the dominant physiological condition, catalytic metal ion leaves first followed by the product. However, even at very high concentrations of metal ions, enzymatic activity is not completely inhibited and it is suggested, as the second possible pathway, that some product release occurs without dissociation of the metal ion from the complex.

In vertebrate organisms, three different genes express isozymes of enolase. Enolase is found everywhere; enolase is specific to muscle c and enolase is specific to neuron c. All known eukaryotic enolases are dimers. Tissue-specific c isozymes easily form mixed dimers with enolase; the intermediate form is a hybrid molecule containing subunit and; in vivo all possible dimers except have been observed.

The expression of non-neuronal enolase isoenzymes (NNE, -dimer) and NSE (γγ- and -dimer) is stated. NSE is the most acidic enolase in the brain, consisting of two subunits with a relative molecular mass of 39,000. NNE is the most acidic enolase isoenzyme, consisting of two -subunits with a relative molecular mass of 43,500. This form of enolase is designated as non-neuronal enolase, as immunocytochemical studies have established its tight glial localization in neural tissue. The most notable difference between NSE and NNE is the apparent lack of immunological cross-reactivity between the two proteins. NNE is highly sensitive to chloride ions, urea, and temperature.

On the other hand, NSE exhibits much greater stability in terms of being deactivated by chloride, unlike the previous statement. It is quite intriguing that NSE remains relatively

unaffected by chloride ions, despite their accumulation in nerve cells during frequent depolarization cycles. The ability of NSE to resist chloride ions may have evolved as a means of adapting to the intracellular environment in neurons.

A chloride-sensitive enolase in neurons will be deactivated and glycolysis will be disrupted during times of highest energy metabolism demand. Human NSE is the main brain protein, comprising between 0.4% and 2.2% of the total soluble brain protein, depending on the region. In some neurons, NSE contributes 3-4% of the total soluble protein, making it a clinical marker for neuronal and neuroendocrine cells. The amount of this enzyme appears to be much greater than necessary for its catalytic function, suggesting that NSE may have other unknown roles.

The NSE enzyme has been purified, crystallized, and its crystal structure determined. In the enzyme crystal, an asymmetric complex of NSE · Mg^{2} · SO^{4} / NSE · Mg · Cl is formed, with the "/" separating the dimer subunits. The subunit containing sulfate (or phosphate) ions and two magnesium ions is observed in a closed conformation in the enolase complex with substrate or its analog. On the other hand, the other subunit is observed in an open conformation in the enolase subunit without bound substrate or analog. This indicates negative cooperativity for ligand binding between the subunits. The electrostatic charge difference between the isozyme and, -19 at physiological pH, is concentrated in the negatively charged surface region of the molecule, namely the negatively charged surface region in the more negatively charged region, while the neutral or positively charged regions tend to be cost-effective.

Mechanism of Action of Neuron-Specific Enolase

Neuron-Specific Enolase as a Biomarker

NSE is a highly specific marker for neurons, peripheral neuroendocrine tissues, and APUD (Amine Precursor Uptake and Decarboxylase) cells, and therefore can serve as a biochemical marker for tumors originating from these cells. Like chromogranin A (CgA), NSE is generally a neuroendocrine marker that cannot differentiate between various subtypes of neuroendocrine tumors; however, elevated levels of NSE have been associated with poor tumor differentiation.

Using immunostaining technique, NSE is observed in all types of neurons including granule cells, Purkinje cells, projection neurons, and both sensory and autonomic neurons. NSE has also been demonstrated in various normal cells including pinealocytes, pituitary gland cells secreting peptide, parafollicular thyroid cells, medullary chromaffin cells of the adrenal gland, Langerhans islet cells, Merkel cells in the skin, neuroendocrine cells of the lung, and erythrocytes.

Due to NSE discoveries in certain networks under normal conditions, it is hypothesized that increased NSE expression and elevated serum NSE levels may occur with malignant proliferation of this tissue and thus could be valuable in the diagnosis, staging, and treatment of such cancers. The use of NSE determination in medical oncology can be assessed under various headings: determination of NSE content in tissue biopsies; serum NSE measurement as a marker for tumor diagnosis, disease extent, and response to therapy; determination of cerebrospinal fluid (CSF) NSE as an indicator of cranial metastasis and CNS.

Neuron Specific Enolase in Intracranial Disorders

Extensive research has been conducted on the correlation between high levels of neuron-specific enolase (NSE) and intracranial malignancy, specifically brain tumors. The NSE enzyme, predominantly found in neurons, has been recognized as a biomarker for malignant diseases. An increase in NSE levels in blood or cerebrospinal fluid indicates nerve injury associated with brain tumors (Moritz et al., 2010). This encompasses primary neoplasms in the brain as well as secondary cancers originating from other parts of the body

and metastasizing to the brain (Zhu et al., 2017).

Furthermore, an increase in NSE levels has been observed in various types of intracranial tumors, such as neuroendocrine tumors, small cell lung cancer with brain metastasis, and specific types of gliomas. The degree of elevation varies depending on the type and aggressiveness of the tumor (Liu et al., 2017). Higher levels of NSE have been associated with more aggressive malignancy and poorer prognosis in certain situations, indicating its potential prognostic relevance (Mjønes et al., 2017).

An increase in NSE concentration has been documented in relation to stroke, both in cases of ischemic stroke and hemorrhagic stroke. During an ischemic stroke, the affected area experiences a lack of oxygen and nutrients, which can result in damage to neurons and the release of NSE into the bloodstream. This is due to the presence of blood in the brain tissue, which in turn causes damage to neurons. The timing of NSE measurement is crucial, as high levels of NSE may be more prominent in the early hours to days after a stroke, gradually decreasing over time. This provides valuable information about the severity of nerve damage and the recovery process (Brouns et al., 2010). Furthermore, an increase in NSE levels in the context of stroke may have prognostic significance, as higher NSE levels are associated with more severe strokes and indicate a poorer prognosis (Shash et al., 2021). Similarly, an increase in NSE levels in cases of ischemic stroke and hypoxic-ischemic encephalopathy may indicate nerve damage caused by reduced blood supply or oxygen deficiency to the brain (Martens et al., 1998). Research has also investigated the correlation between NSE levels and seizures, suggesting that an increase in NSE levels may be an indication of nerve disturbances or damage during epileptic episodes (Rabinowicz et al., 1996).

Neuron Specific Enolase in Other Disorders

However, it is important to emphasize that although an increase in NSE levels may indicate intracranial abnormalities, there is a possibility that the increase in NSE levels is caused by factors other than intracranial abnormalities. A study presents evidence showing that an increase in NSE levels can serve as a valuable quantitative indicator for diagnosing and assessing the outcomes of patients with metastatic melanoma (Sato et al., 2020).

NSE is also recognized as an important biomarker for lung cancer. NSE, a dimer isoenzyme of enolase that can exist in the form of γ-γ or γ-δ, is mostly found in neurons, neuroendocrine cells, and neuroendocrine tumors (Persson et al., 1987). The relationship between this disease and non-small cell lung cancer (NSCLC) has been thoroughly examined and considered a potentially useful indicator for predicting and assessing the outcome of this disease (Zhou et al., 2017). NSE tests are commonly used for screening, early detection, and prognosis assessment of small cell lung cancer (SCLC) (Zheng et al., 2019). Furthermore, there is a correlation between its presence and the development of lung cancer (Chen et al., 2013). Research has shown that NSE, in addition to other blood tumor indicators such as cytokeratin-19 fragments, is useful in distinguishing between SCLC and non-malignant lung diseases (Mauro et al., 2019). Moreover, the diagnostic efficacy of NSE has been evaluated in many scenarios, such as its relationship with gene mutations in lung cancer and its capacity as a biomarker for diabetic retinopathy (Li et al., 2015; Xu & Zhang, 2021). NSE protein is known as an autoantigen target, indicating that this protein has significance beyond its conventional use as a tumor marker (Ramirez-Celis et al., 2020).

Furthermore, the therapeutic significance of NSE has been examined in cases of multiple myeloma. Its expression level was assessed to evaluate its usefulness as a tumor marker and as an indicator of disease progression and therapy effectiveness (Yang et al., 2014). The diverse range of applications demonstrates NSE's ability to adapt as a biomarker in various disease conditions.

Li et al. (2022) conducted a study that identified NSE as a potential biomarker for various diseases, including renal cell carcinoma (RCC). NSE, in conjunction with other

serum tumor markers, has been recognized as a crucial diagnostic and prognostic signal in patients with recurrent colorectal cancer. Furthermore, NSE has been investigated as a potential biomarker in different malignancies, such as breast cancer and stomach cancer (Soh et al., 2011; Wang et al., 2020).

NSE has been explored as a potential biomarker for nerve injury and prognosis in the context of Guillain-Barré Syndrome (GBS), which is a term referring to a neurological condition. According to Chiang & Ubogu (2013), GBS is an autoimmune condition characterized by rapidly developing weakness and various disturbances in sensory, autonomic, and cranial nerves in the body. The pathogenesis of GBS is marked by immune-mediated damage to neurons and Schwann cell membranes, with antibodies targeting specific gangliosides (Gong et al., 2002).

Clinical Indications for Neuron Specific Enolase Examination

Following the initial description of NSE by Moore & McGregor (1965) and its identification as a neuroendocrine neoplasm marker by Prinz and Marangos, there have been numerous applications of it in clinical practice. NETs may arise from various organs, originating from different embryological cell types but exhibiting similar phenotypic characteristics, including: immunoreactivity to neuroendocrine differentiation markers (referred to as "pan-neuroendocrine"), the ability to secrete specific peptides or hormones, and the expression of multiple receptors. These features are fundamental to the current diagnostic and therapeutic strategies tailored to these tumors.

Primitive tumors, not always identifiable, may originate from cells called diffuse neuroendocrine system (DNES) in various organs. The common sites of origin are the digestive and respiratory tracts. One of the characteristic features of DNES cells is their ability to secrete a wide spectrum of peptides. This forms the basis of the first hypothesis of the APUD system, theorized by Pearse in 1969 and later developed by the same author in the concept of DNES. DNES cells have different embryological origins, but they share the same secretory and/or neuroendocrine markers. In clinical practice, the diagnosis of NET can actually be based on the detection of tissue and/or circulating neuroendocrine markers. The secretion patterns of NET may vary according to the site of origin and degree of differentiation. However, most currently available neuroendocrine markers are relatively specific.

Furthermore, significant variations in the levels of circulation of these markers may not only be generated from the active secretion of cellular processes, but may also reflect cytolysis occurring during tumor growth or as a result of chemotherapy, radiotherapy, or radio-metabolic therapy. The assessment of neuroendocrine markers may therefore play a role in different steps of NET Management: diagnosis, prognostic significance, therapy options, follow-up, and evaluation of treatment response. NSE can be considered as a general marker of differentiation (pan-neuroendocrine tissue marker, important for evaluating neuroendocrine differentiation of tumors) or as a general secretion marker (varied secretory patterns based on embryological origin and disease stage). As a differentiation marker, NSE is reported to be more sensitive than CgA in large cells as well as in poorly differentiated neuroendocrine carcinomas. The role of enolase as a marker of preferential glycolytic metabolism in cancer cell proliferation should be evaluated. The main weakness of these markers is represented by the low specificity currently generally using anti-chain antibodies, which cannot distinguish homo-dimers from other non-specific hetero-dimers for NET.

Although monoclonal antibodies against NSE have been developed, the ones currently in use still exhibit low sensitivity. As a general marker of secretion, NSE shows higher sensitivity and specificity in neuroendocrine carcinoma compared to CgA (77% and 85% vs. 50% and 71%, respectively). In these patients, an inverse correlation between circulating levels and prognosis has been reported. Circulating NSE can therefore be used in follow-up to

evaluate response to therapy and detect early disease recurrence. In all other types of NETs, NSE shows lower sensitivity and specificity compared to CgA. The sensitivity of NSE in diagnosing gastroenteropancreatic (GEP)-NETs is around 40%, but increases to 70% in some studies. Tissue positivity for NSE is independent of tumor secretion activity. In fact, NSE is not considered a secretory protein, as it is only located in the cytoplasm of cells and the amount of NSE in tumor tissue does not seem to correlate with circulating levels. During follow-up, it should be considered that circulating NSE levels may paradoxically increase in response to radio-metabolic or chemotherapy treatment, as a consequence of high cell death rates with neuroendocrine differentiation, which can lead to the release of this cytoplasmic enzyme.

Relationship between Neuron-Specific Enolase and Traumatic Brain Injury

Potential biomarkers from brain tissue damage, such as NSE, glial fibrillary acidic protein, tau protein, myelin basic protein, and S100-β are released into the blood following ischemic stroke from neurons, myelin, and glia. The levels of these markers in the blood can indicate the extent of brain infarction. Additionally, in the early phase of acute stroke, blood marker determination will result in easier and cheaper outcomes than other surrogate endpoints, such as radiological measurements of tissue damage, to evaluate treatment effects. Remarkable blood markers in the volume of brain tissue damage will correlate well with the "true" volume of brain tissue damage due to ischemic stroke. However, this "true" volume is difficult to measure. Different estimates may vary depending on brain imaging modalities, imaging timing, methods used to calculate volume, or whether the method distinguishes lesion swelling from lesion size. The actual "level" of blood markers is also difficult to define; potentially useful statistics for blood marker levels are: a single measurement, peak measurement, or area under the curve (AUC) of blood marker levels over time.

Various studies have shown a positive correlation between NSE levels and infarct volume in patients with acute ischemic stroke, while some studies have failed to demonstrate such a relationship. Studies have also indicated that there is an insignificant relationship between NSE levels and stroke severity upon admission. Conversely, some researchers have not found such a relationship. The ability of NSE levels to predict neurological function outcomes in stroke patients has also been a recent area of interest, with some studies suggesting that NSE is useful in predicting functional outcomes, while others suggest otherwise. Given the contradictory findings from these studies, Zaheer et al conducted a study on 75 patients with acute ischemic stroke to determine: the correlation between NSE levels upon admission and infarct volume, stroke severity, and early neurological functional outcomes. The author discovered: a positive correlation between NSE concentration on day 1 and infarct volume determined by computed tomography scan (the largest infarct volume had the highest average NSE level); a strong negative correlation between Glasgow Coma Scale at presentation and NSE concentration on day 1 (patients with lower Glasgow Coma Scale, and therefore greater stroke severity, had higher average NSE levels); a positive correlation between NSE level on day 1 and early neurological outcome assessed by modified Rankin Scale on day 30 (average NSE concentration in patients with worse outcomes significantly higher than in patients with better outcomes). They concluded that serum NSE levels in the early days of ischemic stroke can be a useful marker for predicting stroke severity and early functional outcomes.

The AUC levels of NSE and S100-β correlate with the radiological volume of infarction obtained in the first week after a stroke. However, it is concluded that plasma biomarker values taken within the first 6 hours of a stroke are unlikely to be good predictors of the extent of infarction in the subacute phase, due to insufficient time for the markers to enter circulation and numerous factors that can influence changes in infarct size during the subacute period.

Furthermore, NSE has been validated to offer quantitative assessment of brain damage and/or to improve diagnosis and evaluation of outcomes in various clinical settings, including intracerebral hemorrhage, seizures, comatose patients post-cardiopulmonary resuscitation for heart attacks, and traumatic brain injury.

Figure 1 depicts the peak levels of biomarkers associated with TBI. The concentration of NSE in the serum does not show a significant increase in response to TBI (only approximately 2 times higher) when compared to other biomarkers like PRDX6, S100β, and BDNF, which can increase by more than 3 times the normal levels. However, in cases of moderate to severe TBI, NSE levels can increase by nearly 12 times compared to all other serum biomarkers for TBI. This suggests that NSE may serve as a more reliable indicator for assessing the extent of nerve damage following a TBI, particularly in moderate to severe cases (Buonora et al., 2015).

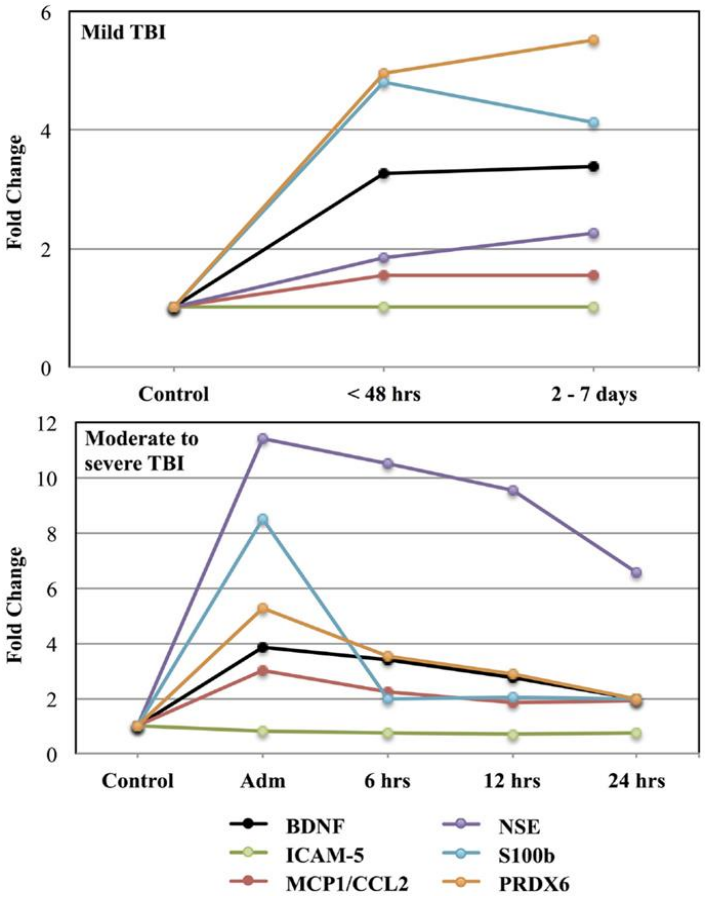

Figure 1. Elevated levels of TBI biomarkers

Relationship between Neuron Specific Enolase and Glasgow Coma Scale

The relationship between serum neuron-specific enolase (NSE) levels and GCS is an intriguing topic in the study of TBI and other neurological disorders. GCS is a clinical tool used to assess the level of consciousness in individuals suffering from brain trauma, while NSE is an enzyme predominantly found in neurons (Berger et al., 2002). Numerous studies have investigated the correlation between serum NSE levels and GCS scores, leading to several comprehensive conclusions.

Increased blood concentrations of NSE are often associated with more severe brain damage and can be used as a prognostic marker, indicating damage to neurons and cell death (Cheng et al., 2014). Lower GCS scores, indicating decreased consciousness, are often linked to higher levels of serum NSE. This suggests that increased NSE levels may indicate the extent of brain injury (Berger et al., 2002). Longitudinal monitoring of serum NSE levels and

GCS scores can reveal temporal variations in their relationship, providing valuable insights into the progression or recovery of brain injury (Moseby-Knappe et al., 2020).

However, although there is a correlation, these characteristics cannot be used interchangeably, and their interpretation may vary depending on specific clinical conditions. Additional variables, such as individual age, pre-existing health issues, and the presence of additional injuries, have the potential to impact the relationship between NSE levels and GCS scores (Yan et al., 2014). Therefore, it is crucial to make management decisions and patient prognosis based on a comprehensive assessment that considers multiple clinical criteria and imaging.

4. Conclusion

Based on the literature review conducted on the comparison of Neuron Specific Enolase (NSE) levels in serum and cerebrospinal fluid in patients with severe traumatic brain injury, a significant difference in NSE levels between the two samples was found. The implication of this finding is the potential use of NSE as a biomarker for the diagnosis and prognosis of severe traumatic brain injury. Therefore, monitoring NSE levels in serum and cerebrospinal fluid can provide valuable information in assessing the patient's condition and making clinical decisions related to the management of severe traumatic brain injury. Further research may be necessary to validate these findings and identify a direct relationship between NSE levels and the long-term prognosis of patients with severe traumatic brain injury.

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Cite this article as: **Praditta Adhi Makayasa, Kohar Hari Santoso, Hamzah, Christrijogo Sumartono Waloejo**

Comparison of Neuron-Specific Enolase (NSE) Levels in Serum and Cerebrospinal Fluid in Patients with Severe Traumatic Brain Injury

African Journal of Biological Sciences. 6(9), *871-887*. *doi: 10.33472/AFJBS.6.9.2024.871-887*