RELATIONSHIP BETWEEN SERUM S100B PROTEIN AND GLUTAMATE LEVELS WITH THE SEVERITY OF TRAUMATIC BRAIN INJURY

Arum Kristiana1, Prihatma Kriswidyatomo2, Bambang Pujo Semedi3, Prananda Surya Airlangga3, Hamzah3
1 Clinical Medicine Study Program, Master's Degree, Faculty of Medicine, Airlangga University,
Dr. Soetomo Hospital, Surabaya, Indonesia. Corresponding Author)
2 Airlangga Teaching Hospital, Airlangga University, Surabaya, Indonesia.
3 Anesthesiology and Reanimation Department, Faculty of Medicine, Airlangga University,
Dr. Soetomo Hospital, Surabaya, Indonesia.

Objectives: Traumatic brain injury (TBI) is brain damage resulting from external forces, often caused by accidents and falls. The pathophysiology of TBI involves disruptions in blood flow, metabolism, oxygenation, and inflammatory processes. TBI therapy aims to prevent secondary brain damage and address brain inflammation and edema through various interventions. Understanding the pathophysiology of TBI is crucial for the development of effective therapies.

Results: The Glasgow Coma Scale (GCS) is used to assess the level of consciousness in head trauma patients. Additionally, GCS is employed in various medical contexts, including prognosis evaluation, brain injury categorization, and as a predictor of mortality. GCS exhibits good predictive value, although in cases of stroke hemorrhage, the volume of bleeding becomes more critical. GCS remains essential in the assessment and management of patients with consciousness disorders. Protein S100β, found in the brain and central nervous system, has been associated with various medical conditions, including traumatic brain injury. Measuring S100β levels as a biomarker for brain damage has become a research focus, though further studies are needed to validate these findings and determine the optimal sampling time. Glutamate plays a crucial role in brain neurotransmission mechanisms.

Conclusion: In TBI, there is an increased release of glutamate, which can lead to cognitive and emotional disturbances. Elevated glutamate levels can damage cytoskeletal structures and disrupt intracellular ion balance, contributing to brain damage after TBI. Recommendations for future research include conducting more in-depth studies on the mechanisms underlying increased glutamate release after TBI. This may involve in vitro experiments or animal models to better understand the relationship between elevated glutamate and cognitive and emotional disturbances in TBI.

Keywords: Serum S100β Protein Levels, Glutamate, Severity Level, Traumatic Brain Injury

Citation: Kristiana, A., Kriswidyatomo, P., Semedi, B. P., Airlangga, P. S., & Hamzah. Relationship Between Serum S100B Protein and Glutamate Levels with the Severity of Traumatic Brain Injury. Pak Heart J. 2023; 56(4).

INTRODUCTION

Traumatic brain injury (TBI) is a change in brain function or pathology due to external forces, often caused by traffic accidents and falls from heights, particularly in males and young adults (Prabhakar, 2017). The pathophysiology of TBI continues to be a growing research focus, with recent studies highlighting disruptions in brain blood flow, metabolism, oxygenation, and inflammatory processes as major factors (Powers, 2010; Prins et al., 2013). TBI therapy aims to prevent secondary brain damage, such as brain hypoperfusion and oxidative stress, which can lead to irreversible tissue damage (Sahni & Weinberger, 2007; Xi et al., 2002). Inflammation and brain edema formation are also consequences of TBI, which can be managed through intracranial pressure management, supportive therapy, surgical interventions, and pharmacological therapies like progesterone and antiepileptic drugs (Algattas & Huang, 2013; Patro & Mohanty, 2009). Understanding the pathophysiological mechanisms of TBI is a key step in developing effective therapies to address brain damage.

The Glasgow Coma Scale (GCS) was first introduced in 1974 by Teasdale and Jannet as a standard tool to assess the level of consciousness in head trauma patients. The GCS is widely used in medical and trauma settings to evaluate neurologic dysfunction, monitor progress, predict prognosis, and facilitate communication among healthcare professionals (Sedain & Bhusal, 2019). Originally designed to simplify the assessment of the level of consciousness, the GCS is now also used for prognosis evaluation and categorizing brain damage and neurological status. However, its utility has expanded and is used in various medical contexts. The GCS consists of three components: eye opening response, verbal response, and the best motor response achievable by the patient. GCS assessment should be performed periodically, with the initial score ideally assessed 6 hours after the head trauma occurs. GCS can be used as a tool to assess the severity of diseases with decreased consciousness, provide

information during patient transfers, and as a triage tool. Additionally, GCS is used as a mortality predictor in ICU patients with head injuries or non-traumatic conditions. Studies show that GCS has good predictive value for mortality. Nevertheless, in cases of hemorrhagic stroke, the volume of bleeding becomes a determinant for surgery rather than GCS. Therefore, GCS remains an essential tool in the assessment and management of patients with consciousness disorders (Matis & Birbilis, 2008).

Protein S100β, primarily found in the brain and central nervous system, plays a crucial role in regulating various biological processes. Elevated levels of this protein have been associated with several medical conditions, including neurological disorders, neoplasms, Alzheimer's, diabetes, melanoma, Down syndrome, and epilepsy. Research also indicates that this protein is produced by astrocytes in the central nervous system and is involved in various physiological processes. Increased levels of S100β protein in serum or cerebrospinal fluid are linked to central nervous system damage, particularly in traumatic brain injuries. The measurement of S100β protein as a biomarker for brain damage has been a focal point of research, as differences in its levels can predict the outcomes of patients with traumatic brain injuries. However, further research is needed to validate these findings and determine the optimal timing for blood sample collection.

Research by Guerriero et al. (2015) revealed that glutamate plays a critical role in brain neurotransmission mechanisms (Guerriero et al., 2015). Glutamate is synthesized, stored in presynaptic vesicles, and released into the synaptic cleft during presynaptic cell depolarization. This triggers AMPA and NMDA receptors, affecting intracellular ions. Glutamate is reuptaken by GLT-1/EAAT transporters into astrocytes, converted into glutamine, and then into GABA. Acute traumatic brain injury (TBI) results in increased glutamate release, NMDA downregulation, and increased IEG activation. In the chronic phase, glutamate interacts with different receptors, leading to hyperpolarization, hyperexcitability, and GABA interneuron cell death. Elevated glutamate levels after TBI can disrupt intracellular ion balance, increase gene transcription, and damage the cytoskeleton. Mouse studies by Dorsett et al. (2017) show disturbed behavior following TBI associated with increased extracellular glutamate, contributing to cognitive and emotional disturbances in TBI patients (McNamara et al., 2010; Thomas et al., 2012).

RESULTS

Traumatic Brain Injury

Traumatic Brain Injury (TBI) is defined as a change in brain function or pathology caused by external forces, characterized by a period of loss or decreased level of consciousness, loss of both anterograde and retrograde memory, neurological deficits, and changes in mental status (Prabhakar, 2017).

The exact global incidence of TBI in the population is not known, but it has become a significant social issue. In the United States, at least 1.4 million TBIs occur annually, resulting in 5.3 million individuals experiencing disabilities due to their TBI. In a study in Europe, the overall incidence of TBI ranged from 47.3 to 694 per 100,000 population per year, with an overall mortality rate ranging from 9 to 28 per 100,000 population per year. The most common causes of TBI are traffic accidents and falls from heights. TBI predominantly occurs in young adults under the age of 30 and is more frequent in males (Prabhakar, 2017).

The pathophysiology of traumatic brain injury is not yet fully understood, and ongoing research and clinical analysis are being conducted to expand our knowledge of TBI pathophysiology. Some recent theories on the pathophysiology of TBI suggest a decrease in Cerebral Blood Flow (CBF), disturbances in brain metabolism and autoregulation, inadequate brain oxygenation, damage to cells due to excitotoxicity, the formation of edema, and inflammatory processes leading to apoptosis and necrosis. Understanding the pathophysiology following traumatic head injury is crucial for providing adequate patient-oriented therapy. Primary effects in brain injury result from direct mechanical damage to the brain, which cannot be intervened upon. The goal of TBI therapy is to limit secondary damage (Powers, 2010; Prins et al., 2013).

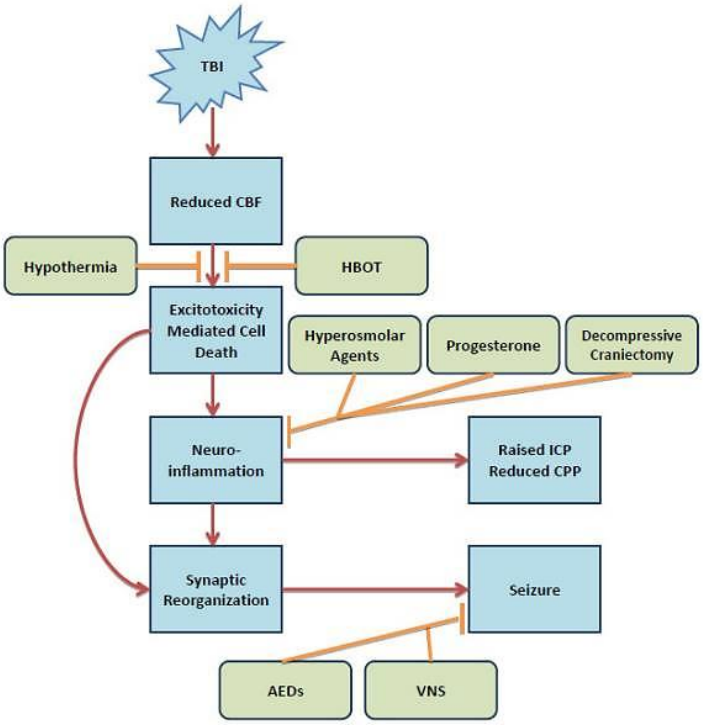

Figure (1) Traumatic Brain Injury (TBI) Pathology process and therapeutic targets

Source: (Algattas & Huang, 2013)

Based on several studies, focal or global brain ischemia often occurs even though the total ischemic volume of the brain averages less than 10%. The mechanisms of ischemia following trauma include morphological damage, blood vessel distortion, autoregulation failure, and vasospasms due to a lack of nitric oxide or cholinergic neurotransmitters and the potential for prostaglandin-induced vasoconstriction.

The reduction in Cerebral Blood Flow (CBF) that occurs in the early phase is the primary target in therapy. Adverse consequences resulting from extracranial disturbances in the early phase of injury (hypotension, hypoxemia) worsen secondary damage. Injured brains are at high risk because they cannot mount an appropriate vasodilatory response during additional disturbances. Brain ischemic events are associated with poor neurological outcomes (death or vegetative state (Powers, 2010; Prins et al., 2013).

The frequent relationship between brain hypoperfusion and poor outcomes suggests that head injury and ischemic stroke share fundamental mechanisms (although this assumption is correct, there are major differences between the two diseases). In TBI patients, the critical CBF threshold for causing irreversible tissue damage is 15 ml/100 grams/minute, whereas in ischemic stroke patients, it's 5-8.5 ml/100 grams/minute. Brain ischemia predominantly leads to metabolic stress and ion disturbances, while in TBI, it also exposes brain tissue to frictional forces, causing successive morphological damage to neuronal cell bodies, astrocytes, microglia, damage to microvascular and endothelial cells. Post-trauma ischemic mechanisms result from morphological damage (blood vessel distortion) due to mechanical energy, hypotension due to autoregulatory failure, a lack of nitric oxide or cholinergic neurotransmitters, and prostaglandin-induced vasoconstriction (Xi et al., 2006).

Patients with brain injuries may experience brain hypoperfusion (CBF > 55 ml/100 grams/minute) in the early phase. Similarly, hyperemia can also occur immediately after post-traumatic ischemia. These pathological conditions appear to be equally detrimental as ischemia in terms of the final outcome because an increase in CBF exceeding metabolic demands is associated with vasoparalysis, which increases cerebral blood volume and ultimately leads to an elevated Intra-Cranial Pressure (ICP). It is important to note that diagnosing valid hypoperfusion or hyperperfusion can

only be done after measuring CBF, which is related to cerebral oxygen consumption. Brain ischemia and hyperemia result in an imbalance between CBF and brain metabolism (Prins et al., 2013; Werner & Engelhard, 2007).

Primary and secondary brain injuries are associated with the release of Excitatory Amino Acid neurotransmitters (EAAs), particularly glutamate. Excitotoxicity is a process in which glutamate and other EAAs cause neural damage. The presence of extracellular glutamate leads to overstimulation of ionotropic and metabolic glutamate receptors, causing a continuous flow of Ca^{2+}, Na^{+}, and K^{+}. Although this process results in catabolic processes, including BBB breakdown, cells attempt to compensate for ion gradient changes by increasing Na^{2+}/K^{+} ATPase activity, leading to increased metabolic demands. This results in poor coupling between flow and metabolism.

Exposure to glutamate causes neural damage in two phases. Within minutes of exposure, there is sodium-dependent neural swelling, followed by calcium-dependent degeneration through various receptor activities that cause calcium influx. Increased intracellular calcium concentration is a trigger for several processes leading to cell damage or death. Despite some studies using anti-excitotoxic therapies, they have not been able to improve the final outcomes of brain injuries (Sahni & Weinberger, 2007; Xi et al., 2002).

Oxidative stress is associated with the generation of Reactive Oxygen Species (ROS), which come in various forms, including superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite, as a response to brain injury. Excessive ROS production, due to excitotoxicity and a deficiency in endogenous antioxidant systems (such as superoxide dismutase, glutathione peroxidase, and catalase), leads to peroxidation of cellular and vascular structures, protein oxidation, DNA fragmentation, and inhibition of mitochondrial electron transport chains. While these mechanisms are sufficient to induce immediate cell death, they also lead to inflammation and apoptosis due to oxidative stress (Prevention, 2015; Werner & Engelhard, 2007).

Brain injury triggers a complex array of tissue immune/inflammatory responses similar to ischemic-reperfusion injury. Both primary and secondary disorders activate the release of cell mediators, including proinflammatory cytokines, prostaglandins, free radicals, and complement. This process induces chemotaxis and adhesion of molecules, which, in turn, mobilize immune and glial cells in parallel and synergistically. For example, activated polymorphonuclear leukocytes adhere to damaged endothelial cell layers but also to intact ones through adhesion molecules. These cells infect injured tissue along with macrophages and T-cells. Leukocyte tissue infiltration is facilitated by increased regulation of cell adhesion molecules such as P-selectin, Intercellular Adhesion Molecule-1 (ICAM-1), and Vascular Cell Adhesion Molecule-1 (VCAM-1). In response to this inflammatory process, the injured and adjacent tissue (based on 'spreading depression') will be cleared, and within hours, days, and weeks, astrocytes produce microfilters and eventually neurotrophins to synthesize scar tissue. Proinflammatory enzymes such as tumor necrosis factor, interleukin-1ß, and interleukin-6 are regulated within hours of injury. Tissue damage development is associated with the direct release of neurotoxic mediators or indirectly with the release of nitrate oxides and cytokines. Additional vasoconstrictor release (prostaglandins and leukotrienes), microvascular destruction through leukocyte and platelet adhesion, blood-brain barrier lesions, and edema formation further reduce tissue perfusion and consequently worsen secondary brain damage (Prevention, 2015).

Edema formation often occurs after a brain injury. There are four putative mechanisms for brain edema formation due to traumatic brain injury. Firstly, vasogenic edema can form in the extracellular space as a result of blood-brain barrier (BBB) disruption, typically caused by mechanical or autodigestive disturbances or functional damage to the brain vessel endothelium (an important blood-brain barrier structure). The disintegration of cerebral vascular endothelial walls allows the uncontrolled transfer of ions and proteins from the intravascular to the extracellular (interstitial) brain compartments, leading to water accumulation. Anatomically, this pathology increases the volume of the extracellular space. On the other hand, cytotoxic edema involves the swelling of brain cells, including neurons, astrocytes, and microglia, due to ion pump failure caused by ischemia or trauma, resulting in sodium and water accumulation. Cytotoxic brain edema is characterized by intracellular water accumulation in neurons, astrocytes, and microglia, regardless of vascular endothelial integrity. This pathology is caused by increased membrane permeability to ions, ion pump failure due to energy depletion, and cellular reabsorption of osmotically active solutes. Although cytotoxic edema is more common than vasogenic edema in patients after brain injury, both events are associated with increased intracranial pressure (ICP) and secondary ischemic events. The current classification of brain edema is related to structural damage or water and osmotic imbalances caused by primary or secondary injuries (Klemenc-Ketis et al., 2011; Prevention, 2015).

Cerebral edema in traumatic brain injury results from secondary damage triggered by the cascade of events following head trauma. Traumatic brain injury-related cerebral edema can be divided into two types: vasogenic and cytotoxic. Vasogenic edema is caused by BBB disturbances, leading to the leakage of intravascular fluid

through the compromised endothelium or leaky tight junctions. Cytotoxic edema results from the accumulation of fluid within neuronal cells, microglia, and astrocytes. Both types of edema lead to an increase in intracranial pressure (ICP) and contribute to ischemic events (Patro & Mohanty, 2009).

The initial management of traumatic brain injury (TBI) primarily focuses on prevention and supportive therapy, such as monitoring blood pressure and oxygenation, prophylaxis for infections and deep vein thrombosis, analgesia, and establishing limits for vital signs like Intracranial Pressure (ICP) and Cerebral Perfusion Pressure (CPP). Dysregulation of metabolism, blood flow, and brain perfusion are early changes that occur following traumatic brain injury. Hypothermia and Hyperbaric Oxygen Therapy (HBOT) are therapeutic options to address these regulatory disturbances.

The subsequent phase in TBI involves neuro-inflammation, where the main pathological impact is increased Intracranial Pressure (ICP). Treatment options to prevent this condition include pharmacological therapy, such as progesterone administration and hyperosmolar fluids, as well as surgical interventions like decompressive craniotomy. Understanding the inflammatory cascade in TBI and its variability becomes crucial in selecting effective therapies to address the occurring damage.

Long-term complications of TBI include the occurrence of seizures that may become persistent and progress into epilepsy. However, guidelines from the Brain Trauma Foundation (BTF) state that prophylactic anticonvulsants are not necessary for seizure prevention. Antiepileptic drugs like phenytoin and valproic acid are only administered if seizures occur and are not used for long-term use. Another option for managing post-TBI seizures is the surgical placement of a Vagal Nerve Stimulator (VNS) (Algattas & Huang, 2013).

Glasgow Coma Scale (GCS)

Teasdale and Jannet introduced the Glasgow Coma Scale (GCS) in 1974 as a standardized instrument for evaluating the consciousness level of individuals with head trauma. In recent years, the GCS has also been used for prognostic evaluation, categorizing patients based on the severity of brain abnormalities, and assessing neurological status. However, due to its expanded use beyond its original purpose, some limitations have been identified. Initially, the GCS was designed to standardize the assessment of consciousness levels in TBI patients by physicians, nurses, and other healthcare providers, as its assessment method is simple and easy to understand. However, it is now used to evaluate the level of consciousness, prognosis, and prediction in patients with decreased consciousness (Matis & Birbilis, 2008).

The GCS should be assessed periodically to gauge the extent of brain damage resulting from TBI. It is advisable to assess the initial GCS score 6 hours after the trauma to avoid overestimation, taking into consideration other factors that may influence it, such as hypoxia, hypotension, and alcohol intoxication. The GCS is a neurological scale consisting of three components: eye opening response, verbal response, and the best motor response a patient can perform. These three components can be seen in Table 1 (Sahni & Weinberger, 2007).

Table (1) Criteria for assessing GCS

	ening response	**response**	**response**
	-	-	Able to follow commands
	-	Orientation to person, place, and time	Localizes pain
	Open eyes spontaneously	Can be spoken to but is disoriented	Withdraws from pain
	Open eyes in response to sound stimulation	Inappropriate words	Flexion (decorticate) response to pain
	Open eyes in response to painful stimulation	Unintelligible words	Extension (decerebrate) response to pain
	No response	onse	onse

Source:(Sahni & Weinberger, 2007)

The Glasgow Coma Scale (GCS) can be used as a tool to assess the severity of a disease with a decreased level of consciousness, provide information during patient transfer, and serve as a triage tool for patients with brain injuries. In cases of brain damage, the GCS can be used to monitor therapy in the early stages after injury, allowing for the detection of complications at an earlier stage. Patients with GCS scores of 13 to 14, along with signs of head trauma, have a lower risk of complications.

The GCS can also be used as an indicator for specific therapies, such as intubation for patients with a total GCS score of 8 or a motor score of less than 4, and the placement of ICP monitoring in patients with a GCS score of 13 to 15 and evidence of traumatic brain injury. Additionally, the GCS can be used as a predictor of

mortality in ICU patients with traumatic brain injuries, as well as those without trauma.

Based on existing research, the GCS has been shown to be a better predictor of mortality than the Mainz Emergency Evaluation System (MEES) and APACHE II in non-trauma patients. In trauma patients, the GCS has been proven to be superior to the Acute Physiology Score (APS), Simplified Acute Physiology Score (SAPS), and Therapeutic Intervention Scoring System (TRISS). The GCS has a predictive value for mortality of 95% (for the minimum GCS score) and 93% (for the initial GCS score).

In cases of hemorrhagic stroke, it has been found that the volume of bleeding is a more decisive factor for surgery than the GCS. Conservative therapy is recommended for patients with putaminal and thalamic hemorrhages with a GCS score of 13 or a bleeding volume of less than 30 ml, while surgery is recommended for GCS scores of less than 12 or a minimum bleeding volume of 30 ml.

There are some limitations where the GCS cannot be evaluated, and these conditions are listed in Table 2 (Matis & Birbilis, 2008).

Table (2) conditions that make GCS assessment difficult

ion			
uma			
nerve damage			
ation (alcohol or drugs)			
tion (anesthesia or sedatives)			
ia			
tric disorders			
omental disorders			
ge differences between the patient and examiner			
ated, tracheostomized, or post-laryngectomy patients			
g of the tongue			
rauma			
patients			
impairment			
and nerve damage			

Source : (Matis & Birbilis, 2008)

Protein S100β

Protein S100β is a member of the S100 protein family, the largest subgroup of EF-hand (helix E-loop-helix F) calcium-binding proteins. Protein S100β has a homodimeric structure, and each beta monomer has a weight of approximately 10.5 kDa with a biological half-life of 30 minutes to 2 hours. Protein S100β induces a large conformation that exposes hydrophobic residues and allows interaction with other proteins to exert biological activity. This protein triggers the expression of proinflammatory cytokines and induces apoptosis in nerve cells (Yardan et al., 2011).

Protein S100β is primarily located in the cytoplasm and nucleus of astrocytes, where it functions to regulate cytoskeletal structure and cell proliferation. However, this protein is also found in other cell types such as Schwann cells, adipocytes, chondrocytes, lymphocytes, bone marrow cells, and melanocytes (Golden et al., 2018). Therefore, elevated levels of protein S100β can be detected in patients with neurological disorders, neoplastic conditions, and other diseases such as Alzheimer's, diabetes mellitus, melanoma, Down syndrome, and epilepsy (National Library of Medicine, 2022).

Protein S100β accounts for 96% of the total S100 protein content in the human brain and only 0.5% of all brain proteins. It is primarily produced by astrocytes and exerts paracrine and autocrine effects within the central nervous system. This protein is involved in regulating various intra- and extracellular physiological processes that can have either protective or toxic effects on nerves (Arrais et al., 2022). Protein S100β is produced by astrocytes within the CNS and indicates astrocyte activation. An increase in the concentration of S100β in serum or cerebrospinal fluid (CSF) is associated with markers of CNS injury (Yardan et al., 2011).

Under physiological conditions, protein S100β is most strongly expressed in the hippocampus, periventricular regions, cerebral cortex, and cerebellum. Protein S100β is involved in the regulation of intra- and extracellular activities. Intracellularly, it acts as a stimulator of cell proliferation, migration, and differentiation, as well as an inhibitor of apoptosis, indicating its influence on brain development and repair. Extracellularly, protein S100β promotes the survival of neurons, astrocyte differentiation, proliferation, and neuronal degradation

through apoptosis and the regulation of cellular inflammatory activity (Yardan et al., 2011).

When a TBI occurs, in the early phase, protein S100β is secreted as a compensatory response with neurotropic agents that have neuromodulatory effects and support memory and thought processes. When there is disruption of the blood-brain barrier (BBB) and high levels of inflammation, S100β acts as a neuronal destroyer due to the stimulation of proinflammatory cytokines and free radical activity often found in the pathophysiology of neurodegenerative disorders (Golden et al., 2018). This protein is released into the peripheral circulation immediately after TBI, and its levels increase rapidly within the first few minutes to 5-20 µg/L. Protein S100β levels in moderate and severe TBI increase shortly after the trauma and then gradually decrease but do not return to normal values. The effects of protein S100β depend on its concentration. At nanomolar concentrations, it stimulates neurite outgrowth into neurons in the brain cortex and enhances the survival capability of neurons. However, at micromolar concentrations, protein S100β causes damage by stimulating the release of proinflammatory cytokines and triggering apoptosis. High concentrations of this protein also lead to the release of nitric oxide from astrocytes, which also triggers neuronal cell death. This indicates that an increase in protein S100β over the long term suggests continuous release from damaged tissue (Dharmajaya et al., 2017).

The measurement of brain damage biomarkers to assess or predict outcomes in cases of TBI has been developed in recent decades, and one such biomarker is protein S100β (Stefanović et al., 2017). In vitro research shows that astrocytes release protein S100β rapidly into the extravascular space 15 seconds after a lesion forms due to trauma or metabolic stress. The measured concentration of protein S100β in the blood can originate from both synthesized and newly synthesized proteins, but the majority of S100β levels come from dead or dying brain tissue. Most of the serum protein S100β levels come from cerebrospinal fluid (CSF) that enters circulation through arachnoid villi, where the levels can be up to 100 times higher than in the serum. Elevated levels of protein S100β in the serum of TBI patients are suspected due to disrupted BBB, causing protein leakage. High levels of protein S100β trigger the production of oxygen radicals, leading to mitochondrial dysfunction and the induction of apoptotic pathways. The ratio of protein S100β levels in serum and CSF can be considered as a marker of BBB permeability, although there is limited research supporting this theory. Another emerging theory is the existence of the glymphatic system, a route between para-arterial inflow, interstitial fluid in brain tissue, CSF, and venous blood flow. The glymphatic system has only been found in experimental animals so far, but it is challenging to monitor in humans, and there are no specific biomarkers for this system (Michetti et al., 2019; Thelin et al., 2017).

A meta-analysis found differences in protein S100β levels in TBI patients between those who survived and those who died. The average protein S100β level in the first 24 hours predicting short-term mortality was 0.328 ± 0.198 µg/L, while in the period longer than 1 month, it was 0.399 ± 0.19 µg/L (Golden et al., 2018). Another study indicated that a decrease in S100β levels to less than 2 µg/L after 120 hours post-trauma was associated with favorable outcomes (assessed with GOS). However, a decrease in protein S100β levels at 4-6 hours post-TBI had a better prognosis (Dharmajaya et al., 2017).

Other research suggests differences in protein S100β levels in TBI patients with good and poor outcomes. In this study, an increase in S100β levels > 0.695 µg/L within the first 6 hours was associated with a poor prognosis. The study noted different cutoff values based on the timing of blood sample collection. According to the best Area Under the Curve (AUC), examination of protein S100β levels at 24 hours post-trauma yielded an AUC of 0.788 (95% CI 0.704-0.873) with a cutoff value of 0.258 µg/L (Stefanović et al., 2017). This aligns with the schematic representation of S100β protein release (Figure 2). According to the figure, at the onset of trauma, there is a contribution from extracranial factors, resulting in higher S100β levels. Early in the trauma, S100β is released from extracranial tissues into the serum and is rapidly cleared within the first few hours after trauma (dashed gray line in Figure 2). S100β released by the brain remains elevated for a longer period, as indicated by the black line in Figure 2. The graph illustrates the possibility of patients experiencing subsequent disturbances and potential secondary peaks around 48 hours to 3 weeks after trauma. Another study mentioned that the mean protein S100β levels over 5 days (Thelin et al., 2017) were related to the outcome measured with GOS. The average GOS score for patients with GOS 1-3 was 3.01 ± 0.725 (Dharmajaya et al., 2017).

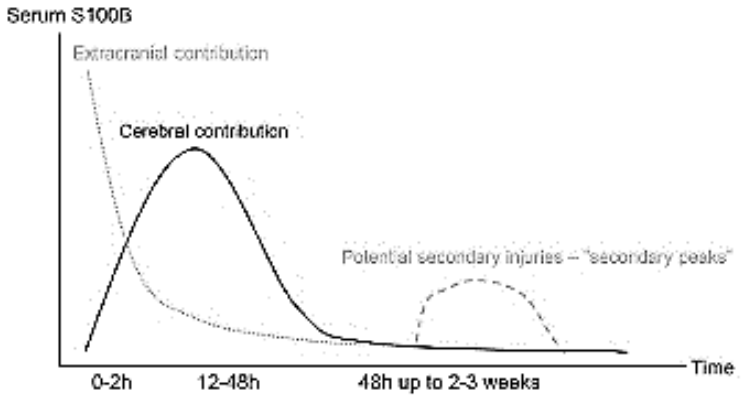

Figure (2) Schematic overview of S100β protein release to serum

Source: (Thelin et al., 2017)

Glutamate

Glutamate is synthesized from glutamine in presynaptic glutamatergic neurons and is subsequently stored in presynaptic vesicles. Depolarization triggers calcium influx into presynaptic cells, which then releases vesicles containing glutamate into the synaptic cleft. The release of these vesicles is mediated by voltage-gated channels. When glutamate is released and acts on alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors, Na^+ enters the cell, leading to depolarization, followed by Ca^{2+} influx through NMDA receptors and immediate early gene (IEG) activation. After being released, glutamate is taken back up by GLT-1/EAAT (Glutamate Transporter-1/Excitatory Amino Acid Transporter) transporters into astrocytes. Glutamine synthase converts glutamate into glutamine, which is then transported to presynaptic cells and interneurons to be converted into gamma-aminobutyric acid (GABA) by glutaminase and glutamate decarboxylase. GABA is released from interneurons and acts on GABA-A and GABA-B receptors, which are subsequently taken back up by GAT-1. Cl^- and K^+ enter presynaptic cells and return the cell membrane to its resting state (Guerriero et al., 2015).

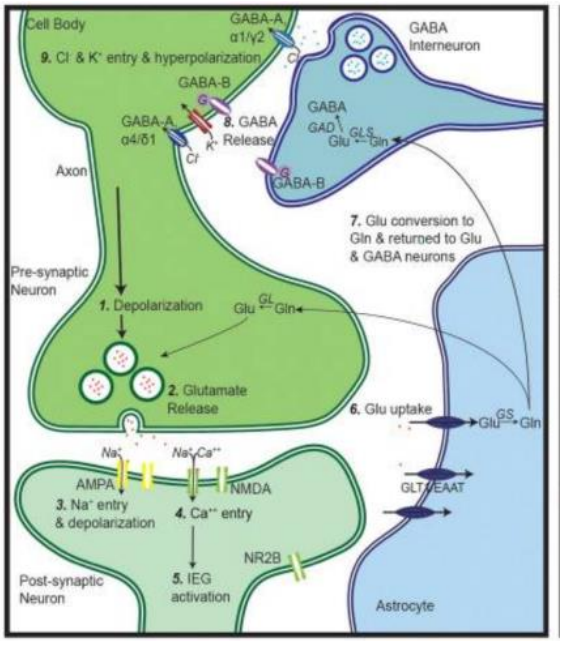

Figure (3) Glutamate and GABA Homeostasis

Source: (Guerriero et al., 2015)

Traumatic Brain Injury in the Acute Phase results in rapid depolarization of presynaptic cells and an increased influx of Ca^{2+} into the cells, leading to an elevated release of glutamate into the presynaptic cleft. Glutamate acts on AMPA and NMDA receptors, but changes occur due to compensation for increased glutamate levels, including NMDA downregulation and increased IEG activation. Glutamate taken from the synapse decreases because GLT-1/EAAT transporter levels in astrocytes are reduced. However, the absorbed glutamate is rapidly converted to glutamine. GABA is released from interneurons, but there is a change in the expression of GABA-A subunits, resulting in the inhibition of presynaptic pyramidal cells and a deficit in cell membrane repolarization (Guerriero et al., 2015).

In the Chronic Phase, the depolarization of presynaptic cells and the release of glutamate into the synaptic cleft still occur, but glutamate acts on different receptors, such as NR2A becoming NR2B receptors. Na^{+} enters the cells, triggering depolarization, followed by Ca^{2+} via NMDA, IEG activation, and the transport of glutamate by GLT-1/EAAT into astrocytes, where it is converted into glutamine. There is cell death among GABA interneurons and dysfunction of GABA-A receptors, resulting in hyperpolarization and hyperexcitation of presynaptic cells (Guerriero et al., 2015).

The increase in glutamate levels that occurs in Traumatic Brain Injury (TBI) is a process that can continue for days or even months after the TBI. This will result in elevated intracellular sodium levels, triggering cellular swelling due to osmotic pressure. The high glutamate levels will also disrupt intracellular calcium, causing a decrease in ATP production by mitochondria and activating proteases and kinases, including nitric oxide synthase. These active enzymes will induce the formation of reactive oxygen species, damage the cytoskeleton, and increase gene transcription through the apoptosis pathway (Dorsett et al., 2017).

A study examined the behavior of mice 1-8 weeks post-TBI, and the results indicated that when stimulated, the mice exhibited aggravated behavioral responses starting one week after TBI, most prominently at four weeks post-TBI, with persistent behavior observed up to eight weeks. Further studies suggest that this behavior in mice is likely due to hypersensitive glutamate and increased extracellular glutamate levels. Persistent glutamate hemostasis disruption may be a mechanism for cognitive and emotional disturbances in patients after experiencing TBI (McNamara et al., 2010; Thomas et al., 2012).

CONCLUSION

Protein S100β and glutamate are two biomarkers that can be used to assess and predict the degree of brain damage in patients with traumatic brain injury (TBI). Both biomarkers play crucial roles in the pathophysiology of TBI. Protein S100β is a calcium-binding protein primarily produced by astrocytes in the central nervous system. During TBI, the levels of S100β protein in serum and cerebrospinal fluid (CSF) can significantly increase. The elevation in S100β protein levels often occurs within minutes after trauma and can persist for some time. High levels of S100β protein can serve as an indicator of brain damage and disrupted Blood-Brain Barrier (BBB) permeability. Furthermore, the increase in S100β protein levels is also associated with the release of oxygen radicals and proinflammatory cytokine activity, which can lead to nerve cell damage. Serum S100β protein levels can be used to predict the outcomes of TBI patients, with higher levels indicating a poorer prognosis. However, it should be noted that the cut-off value for prognosis determination may vary depending on the timing of blood sample collection after trauma.

On the other hand, glutamate is a neurotransmitter that plays a role in the transmission of signals between nerve cells in the brain. Glutamate is produced, stored, and released by presynaptic glutamatergic neurons. During depolarization, glutamate is released into the synaptic cleft and interacts with glutamate receptors on postsynaptic cells. Increased levels of glutamate can occur in the context of TBI, especially due to excitotoxicity, a process in which glutamate causes damage to nerve cells due to excessive receptor stimulation. Elevated glutamate levels can trigger the entry of ions such as calcium into nerve cells, resulting in cellular damage and even nerve cell death. This can contribute to the brain damage that occurs in TBI. In related studies, both S100β protein and glutamate have been used as biomarkers to identify the level of brain damage and predict the prognosis of TBI patients. Increased levels of S100β protein and glutamate in blood or cerebrospinal fluid can provide clues to the presence of serious brain injuries. Monitoring the levels of these biomarkers at various times after trauma can provide additional information about the progression of brain injury and the prognosis of patients.

AUTHORS' CONTRIBUTION

AK & PK : Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. BPS, PSA & H: Data acquisition, interpretation, drafting, final approval and agree to be accountable forall aspects of the work.

Conflict of interest: Authors declared no conflict of interest.

REFERENCES

1. Algattas, H., & Huang, J. H. (2013). Traumatic brain injury pathophysiology and treatments: early, intermediate, and late phases post-injury. International Journal of Molecular Sciences, 15(1), 309–341.
2. Arrais, A. C., Melo, L. H. M. F., Norrara, B., Almeida, M.

A. B., Freire, K. F., Melo, A. M. M. F., Oliveira, L. C. de, Lima, F. O. V., Engelberth, R. C. G. J., & Cavalcante, J. de S. (2022). S100B protein: general characteristics and pathophysiological implications in the Central Nervous System. International Journal of Neuroscience, 132(3), 313–321.

3. Dharmajaya, R., Sari, D. K., & Ganie, R. A. (2017). Elevated Serum S100B Protein Level as a Parameter for Bad Outcome in Severe Traumatic Brain Injury Patients. INDONESIAN JOURNAL OF CLINICAL PATHOLOGY AND MEDICAL LABORATORY, 24(1), 70–75.
4. Dorsett, C. R., McGuire, J. L., DePasquale, E. A. K., Gardner, A. E., Floyd, C. L., & McCullumsmith, R. E. (2017). Glutamate neurotransmission in rodent models of traumatic brain injury. Journal of Neurotrauma, 34(2), 263–272.
5. Golden, N., Mahadewa, T. G. B., Aryanti, C., & Widyadharma, I. P. E. (2018). S100B serum level as a mortality predictor for traumatic brain injury: a meta-analysis. Open Access Macedonian Journal of Medical Sciences, 6(11), 2239.
6. Guerriero, R. M., Giza, C. C., & Rotenberg, A. (2015). Glutamate and GABA imbalance following traumatic brain injury. Current Neurology and Neuroscience Reports, 15, 1–11.
7. Klemenc-Ketis, Z., Bacovnik-Jansa, U., Ogorevc, M., & Kersnik, J. (2011). Outcome predictors of Glasgow Outcome Scale score in patients with severe traumatic brain injury. Turkish Journal of Trauma and Emergency Surgery, 17(6), 509–515.
8. Matis, G., & Birbilis, T. (2008). The Glasgow Coma Scale–a brief review Past, present, future. Acta Neurol Belg, 108(3), 75–89.
9. McNamara, K. C. S., Lisembee, A. M., & Lifshitz, J. (2010). The whisker nuisance task identifies a late-onset, persistent sensory sensitivity in diffuse brain-injured rats. Journal of Neurotrauma, 27(4), 695–706.
10. Michetti, F., D'Ambrosi, N., Toesca, A., Puglisi, M. A., Serrano, A., Marchese, E., Corvino, V., & Geloso, M. C. (2019). The S100B story: from biomarker to active factor in neural injury. Journal of Neurochemistry, 148(2), 168–187.
11. National Library of Medicine. (2022). S100B: S100 calcium binding protein B [Homo sapiens (human)]. National Center for Biotechnology Information.
12. Patro, A., & Mohanty, S. (2009). Pathophysiology and treatment of traumatic brain edema. The Indian Journal of Neurotrauma, 6(1), 11–15.
13. Powers, W. J. (2010). Intracerebral hemorrhage and head trauma: common effects and common mechanisms of injury. Stroke, 41(10_suppl_1), S107–S110.
14. Prabhakar, H. (2017). Essentials of neuroanesthesia. Academic Press.
15. Prevention, C. for D. C. and. (2015). Report to congress on traumatic brain injury in the United States: epidemiology and rehabilitation. National Center for Injury Prevention and Control, 2, 1–72.
16. Prins, M., Greco, T., Alexander, D., & Giza, C. C. (2013). The pathophysiology of traumatic brain injury at a glance. Disease Models & Mechanisms, 6(6), 1307–1315.
17. Sahni, R., & Weinberger, J. (2007). Management of intracerebral hemorrhage. Vascular Health and Risk Management, 3(5), 701–709.
18. Sedain, P., & Bhusal, M. K. (2019). Knowledge Regarding Glasgow Coma Scale among Nurses Working at Selected Hospitals of Chitwan, Nepal. Journal of College of Medical Sciences-Nepal, 15(4). https://doi.org/10.3126/jcmsn.v15i4.24529
19. Stefanović, B., Đurić, O., Stanković, S., Mijatović, S., Doklestić, K., Stefanović, B., Jovanović, B., Marjanović, N., & Kalezić, N. (2017). Elevated serum protein S100B and neuron specific enolase values as predictors of early neurological outcome after traumatic brain injury. Journal of Medical Biochemistry, 36(4), 314.
20. Thelin, E. P., Nelson, D. W., & Bellander, B.-M. (2017). A review of the clinical utility of serum S100B protein levels in the assessment of traumatic brain injury. Acta Neurochirurgica, 159, 209–225.
21. Thomas, T. C., Hinzman, J. M., Gerhardt, G. A., & Lifshitz, J. (2012). Hypersensitive glutamate signaling correlates with the development of late-onset behavioral morbidity in diffuse brain-injured circuitry. Journal of Neurotrauma, 29(2), 187–200.
22. Werner, C., & Engelhard, K. (2007). Pathophysiology of traumatic brain injury. British Journal of Anaesthesia, 99(1), 4–9.
23. Xi, Z.-X., Gilbert, J. G., Peng, X.-Q., Pak, A. C., Li, X., & Gardner, E. L. (2006). Cannabinoid CB1 receptor antagonist AM251 inhibits cocaine-primed relapse in rats: role of glutamate in the nucleus accumbens. Journal of Neuroscience, 26(33), 8531–8536.
24. Xi, Z.-X., Ramamoorthy, S., Baker, D. A., Shen, H., Samuvel, D. J., & Kalivas, P. W. (2002). Modulation of group II metabotropic glutamate receptor signaling by chronic cocaine. Journal of Pharmacology and Experimental Therapeutics, 303(2), 608–615.
25. Yardan, T., Erenler, A. K., Baydin, A., Aydin, K., & Cokluk, C. (2011). Usefulness of S100B protein in neurological disorders. JPMA-Journal of the Pakistan Medical Association, 61(3), 276.

Address for Correspondence:
Arum Kristiana, Clinical Medicine Study Program, Master's Degree, Faculty od Medicine, Airlangga University, Dr. Soetomo Hospital, Surabaya, Indonesia.
Email: arum.kristiana89@gmail.com