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High Serum S100B Protein Levels as a Risk Factor for Impaired Cognitive Function in Acute Non-Hemorrhagic Stroke: A Literature Review

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ABSTRACT

The incidence of acute non-hemorrhagic stroke disease has a high disability rate and mortality rate and is a serious threat to people's health and life and can burden families and society. The development of stroke after the onset of acute stroke, especially acute non-hemorrhagic stroke is not uncommon and has become a popular research topic in recent years. Various mechanism can occur, one of which is neuroinflammation. Stroke often leads to lifelong disability, including motor impairment, cognitive impairment, language impairment, and psychological impairment. Serum S100B is a calcium-binding protein that can determine disease severity and predict clinical outcomes to monitor disease progression and response to treatment. It was reported that serum S100B protein levels were detected to be higher in patients with cognitive impairment compared to normal ones.

Keywords: Serum S100B protein, cognitive impairment, non-hemorrhagic stroke

INTRODUCTION

The incidence of acute non-hemorrhagic stroke disease is increasing globally. Acute non-hemorrhagic stroke disease has a high disability rate and mortality rate and is a serious threat to people's health and life and can burden families and society. The development of stroke after the onset of acute stroke, especially acute non-hemorrhagic stroke is not uncommon and has become a popular research topic in recent years. Various mechanisms can occur, one of which is neuroinflammation. Stroke often leads to lifelong disability, including motor impairment, cognitive impairment, language impairment and psychological impairment.

The incidence of stroke is a health problem in developed and developing countries. This is due to an unhealthy lifestyle, resulting in an increase in the incidence of stroke. The incidence of stroke ranks in the top five in the world, stroke is the biggest cause of death in society where the death rate in 2021 is 7.44 million worldwide, where non-hemorrhagic stroke accounts for 3.38 million people, namely 25% of the total[1]. Meanwhile, in Indonesia itself, the incidence of stroke in 2020 according to the results of basic health research shows an increasing trend in stroke disease with a total of 1.7 million cases[2]. Stroke data at Prof. Dr. I.G.N.G Ngoerah Hospital found that the proportion of non-hemorrhagic stroke was 56.7% while bleeding stroke (hemorrhagic stroke) was 43.3%[3].

Cognitive impairment is a complication of stroke that affects up to 30% of patients worldwide with decreased memory function, language use, executive function, attention disorders that can cause limitations in daily activities and dependence on others[4]. Some studies report that 64% of patients who have had a stroke have cognitive impairment (either mild vascular cognitive impairment or dementia) and one third have dementia[5].

Serum S100B is a calcium-binding protein that can determine disease severity and predict clinical outcomes to monitor disease progression and response to treatment. In non-hemorrhagic stroke, serum S100B has been reported to have a significant relationship with infarct volume, prediction of outcome and complications[6]. In another study it was reported that serum S100B protein levels were detected to be higher in patients with cognitive impairment compared to normal ones. In addition, the MoCA score was also reported to be lower in the same group. This suggests that early detection of serum S100B levels in patients can prevent further cognitive impairment in non-hemorrhagic stroke[7].

LITERATURE REVIEW

Non-Hemorrhagic Stroke

Stroke according to the World Health Organization (WHO) is defined as clinical signs that occur rapidly or suddenly in the form of focal (or global) deficits in brain function, with symptoms that last for 24 hours or more or cause death, without clear causes other than vascular causes. The National Guidelines for Medical Services (PNPK) for Stroke Management 2019 defines stroke as an acute clinical manifestation due to neurological dysfunction in the brain, spinal cord, and retina either partially or completely that persists for ≥ 24 hours or causes death due to vascular disorders[8]. Non-hemorrhagic stroke is an episode of neurological dysfunction due to decreased blood perfusion to the brain. The diagnosis of non-hemorrhagic stroke is made according to anamnesis and neurological clinical examination and confirmed by CT-scan examination of the head for ischemia and/or infarction according to the distribution of cerebral vascularization. The acute phase of non-hemorrhagic stroke starts from the onset of the first day to the seventh day[9].

Etiology and Pathophysiology of Non-Hemorrhagic Stroke

The causes (etiology), pathogenesis, and molecular, biochemical, and structural changes underlying the changes that occur in each disease condition constitute its pathophysiology. Non-hemorrhagic stroke occurs almost suddenly within minutes of interruption of blood supply to brain tissue due to blockage of the arteries supplying the brain by a blood clot formed by atrial fibrillation or a thrombus formed over fatty deposits called atherosclerotic plaques. Like various other neurodegenerative conditions, non-hemorrhagic stroke is characterized by numerous changes within the affected ischemic core and surrounding penumbra. These macro and microscopic changes are generally categorized under five overarching terms: neuroinflammation, excitotoxicity, oxidative stress, apoptosis and autophagy. Cell death in non-hemorrhagic stroke occurs due to complex interactions between independent but mutually reinforcing sets of pathological events[10].

Acute non-hemorrhagic stroke disrupts calcium homeostasis, releasing calcium in the brain and activating pathways that generate ROS and oxidative damage. This imbalance of oxidants and antioxidants generates excessive ROS and hydroxyl radicals, causing extensive damage to the brain. Cellular ROS formation is further increased during ischemic stroke due to glucose and oxygen deprivation, exacerbating oxidative stress and brain damage. Superoxide anion production during ischemia is due mainly to xanthine oxidase (XO) and NADPH oxidase (NOX). ATP depletion during ischemia causes accumulation of hypoxanthine and xanthine,

substrates for XO leading to ROS formation. Increased expression of XO in the infarcted area after ischemic stroke has been observed. NOX, another significant source of ROS, is upregulated post-stroke, with NOX2 identified as a major source of superoxide production activated by NMDAR receptors[10].

Post-Stroke Cognitive Impairment

Stroke can cause disability in sensory, motor and even cognitive functions if left untreated. This can affect the patient's quality of life and will indirectly affect the patient's prognosis. Cognitive function is an intellectual ability that includes understanding and use of language, perception and use of numeracy, attention (information processing), memory, and executive functions such as planning, problem solving, and self-monitoring. Impairments in cognitive function when left unchecked will interfere with daily activities. An example is memory impairment that often occurs in post-stroke patients[11,12].

Stroke increases the risk of cognitive impairment by 1.8 times compared to the elderly without stroke. Cognition declines linearly with age due to changes in brain neurotransmitters, oxidative accumulation, and changes in body biochemistry[13].

Following a stroke the core injured tissue is irreversibly damaged due to metabolic failure leading to massive cell death and inflammatory response. The surrounding tissue, named the peri-infarct area, becomes metabolically compromised due to reduced blood flow and susceptible to the inflammatory response triggered by the injury. This triggers a multicellular response that may ultimately favor cells in the peri-infarct tissue to survive or follow cell death[14].

The development of brain injury after non-hemorrhagic stroke can be divided into 3 main stages: acute phase (0-2 days post injury in rodents, < 2 months in humans), subacute phase (2-30 days post injury in rodents, 2-3 months in humans) and chronic phase (> 30 days post injury in rodents, > 3 months in humans). The acute phase is characterized by massive cell death, initiation of an inflammatory response, and astrocyte reactivation. The subacute phase is characterized by spontaneous functional recovery underlined by endogenous mechanisms that can stimulate synaptic plasticity, dendritic spine remodeling, axonal sprouting and brain map reorganization. The chronic phase is where endogenous plasticity is greatly reduced, and functional impairment occurs[14].

Neuroinflammation is a cascade of innate immune-mediated responses from central nervous system glial cells, especially microglia and astrocytes, that can be triggered by damaging processes such as ischemia and hypoxia. Excessive inflammatory response can cause neuronal damage, death and destroy neurological function[15].

Brain injury in non-hemorrhagic stroke causes various pathological changes resulting in neuronal damage affecting neurons and glia cells in brain tissue followed by the release of specific neuronal and glia cell biomarkers such as S100B protein, glial fibriallary acidic protein (GFAP), myelin basic protein (MBP), and neuron specific enolase (NSE)[16,17].

Protein S100B

Intracellular S100B protein is a normal part of calcium homeostasis that transfers signals from second messengers. S100B protein is also involved in cell differentiation and cell cycle progression. This protein has been shown to inhibit apoptosis when applied under experimental conditions. The physiology that occurs in extracellular during traumatic conditions with the administration of S100B protein can increase neurogenesis and neuronal plasticity, disrupt the action of neuromodulation and improve processes involved in memory and learning[18,19].

The physiological effects and functions of S100B protein have been shown to be concentration dependent. Lower

concentrations (nanomolar levels) are beneficial, and higher concentrations (micromolar levels) correlate with harmful effects. Persistent activation of RAGE by micromolar concentrations of S100B protein results in increased amounts of oxygen radicals and this can lead to mitochondrial dysfunction and induction of apoptosis. Nanomolar concentrations of S100B protein produce low amounts of oxygen radical signaling leading to activation of the anti-apoptotic factor Bcl-2, Increased extracellular levels of S100B protein have been shown to result in neuronal dysfunction or cell death due to an inflammatory response that stimulates astrocytes and microglia to recruit and produce pro-inflammatory cytokines with a further increase of extracellular calcium levels and activation of nitric oxide which leads to neuronal dysfunction or cell death due to an inflammatory response that stimulates astrocytes and microglia to recruit and produce proinflammatory cytokines with further increase of extracellular calcium levels and activation of nitric oxide which has harmful effects[20].

Increased levels of S100B have also been demonstrated in different biological fluids (cerebrospinal fluid, peripheral and cord blood, amniotic fluid, saliva, urine and feces) during various pathological conditions involving the sraph system neurodegenerative diseases (Alzheimer's dementia, Parkinson's, Amyotrophic Lateral Sclerosis, Multiple Sclerosis), traumatic and vascular acute brain injury (stroke), epilepsy and also inflammatory bowel disease, perinatal neurological disorders, gliomas, psychiatric disorders. But also, outside the nervous system such as obesity, diabetes and melanoma[20]. In cases of traumatic brain injury, the S100B protein can be secreted into the systemic circulation along with the BBB. In the early phase S100B protein is secreted as a compensator of traumatic brain injury with the effect of a neurotrophic agent that has a neuromodulating action and supports memory and thinking processes. In the late phase, which is characterized by a very high inflammatory process and the BBB has been disrupted, S100B protein acts as a neuron destructor. This is due to the stimulation of proinflammatory cytokines and free radical activity that is often found in the pathophysiology of neurodegenerative disorders[21].

Serum S100B, non-hemorrhagic stroke and cognitive impairment

In non-hemorrhagic stroke, S100B is released into the blood and cerebrospinal fluid. Increased levels of S100B in the extracellular space promote neuroinflammation thereby exacerbating brain tissue damage. Since S100B has a short biological half-life, its presence in the blood indicated an active process that damages brain tissue. Significantly, S100B release does not appear to occur in the infarct core (where there is a lack of perfusion allowing its release into the blood), but in the penumbra and areas of local brain edema in response to the presence of adenosine and glutamate. It is hypothetically possible to control the course of non hemorrhagic stroke and formulate a prognosis for recovery[22].

Damage to the BBB can lead to the inflow of larger molecules such as leukocytes which will increase the osmotic pressure in the brain. This condition will lead to increased intracranial pressure which is directly related to ischemic and cell death. BBB damage will have an impact, namely a decrease in cognitive function. The hippocampus is an important cognitive area of the brain. At micromolar concentrations S100B protein can cause an increase in glutamate in the extracellular that binds to NMDA receptors so that calcium enters the intracellular which cause mitochondrial dysfunction and causes apoptosis in hippocampal astrocytes. There are changes in synapse plasticity that interfere with learning and memory processes[23].

CONCLUSION

High serum S100B protein levels may be one of the risk factors and biomarkers for

impaired cognitive function in acute non-hemorrhagic stroke patients where there is underlying mechanism.

Declaration by Authors

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