

Research Progress of Inflammatory Biomarkers in Patients with Post-stroke Cognitive Impairment

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Abstract: *Post-stroke cognitive impairment (PSCI) is a common complication of stroke, which seriously affects the quality of life of stroke survivors. Inflammatory response is considered to be an important link in the pathogenesis of PSCI. The neuroinflammatory response is activated, releasing more inflammatory factors, leading to a large number of neuronal apoptosis, and then inducing related cognitive dysfunction. Serum marker as an important index reflecting the state of inflammation, become one of the key breakthrough research PSCI pathomechanism. Therefore, this article mainly discusses the role of these markers in PSCI and its research progress, to promote the individualized treatment strategies to develop and improve patients' quality of life.*

Keywords: Poststroke cognitive impairment, Inflammatory biomarkers, Ischemic stroke.

1. Introduction

The increasing incidence of stroke and the ageing of the population are placing a huge social and economic burden on the world [1]. Post-stroke cognitive impairment (PSCI) refers to a series of syndromes caused by stroke from mild cognitive impairment to dementia, which is a major complication of stroke [2]. It not only seriously affects the quality of life of patients, but also significantly reduces the survival time of stroke patients, which brings a heavy burden to the family and society. Up to 60% of stroke survivors develop PSCI within 1 year after stroke [3]. Previous research and interventions have focused on physical disability, whereas an important aspect of stroke survivors with cognitive impairment has been rather neglected [4]. Cognitive function encompasses a range of neuropsychological domains, including: orientation, attention/concentration, judgment/problem solving, memory, verbal and visual/spatial function [5]. Impaired cognitive function may affect daily life activities.

Conventional PSCI diagnosis relies on neuropsychological assessment, but this assessment scale is subjective, and it is not enough to diagnose and prognosis the disease for some patients who are unable to speak or have severe physical disabilities [6]. At present, there are studies at home and abroad that its pathogenesis may be related to inflammation [7]. Based on this, more and more researchers have paid attention to the relationship between PSCI and inflammatory response to find meaningful inflammatory biomarkers [8,9]. Therefore, this article summarizes and discusses the relationship between inflammatory biomarkers and PSCI.

2. PSCI

PSCI encompasses cognitive impairments manifesting in the 3 to 6 months after incident stroke [10]. PSCI is a form of Vascular cognitive impairment (VCI), especially 6 months after the stroke event of cognitive impairment, etiology can be vascular, degenerative or a hybrid of both. The cognitive dysfunction caused by stroke, but also include neurological degenerative diseases such as alzheimer's disease (AD) in progress within 6 months after stroke caused by cognitive dysfunction, Covers everything from non dementia cognitive

dysfunction after stroke (PSCIND) to post-stroke dementia (PSD) or vascular dementia (VD) of various degrees of cognitive dysfunction. Although post-stroke delirium is a common clinical phenomenon, its relationship to future PSCI remains unclear. Post-stroke delirium can take several months to resolve, and most neuropsychologists delay assessment until at least 3 months after delirium in hospitalized patients, making temporal association difficult [11]. Different from post-stroke delirium and transient cognitive impairment, which can be recovered early, PSCI is closely related to the characteristics of stroke lesions, AD pathology and brain plasticity, and is a kind of persistent cognitive impairment. There is a certain overlap between the pathogenesis of PSCI and dementia, and there is an interactive relationship between stroke and cognitive impairment. Patients with stroke are more likely to develop cognitive impairment, and patients with dementia are more likely to develop stroke [12]. The diagnosis of PSCI should have three elements: (1) clear diagnosis of stroke: clinical or imaging evidence for diagnosis of stroke, including transient ischemic attack. (2) presence of cognitive impairment: patients complained/informants reported/experienced clinicians judged cognitive impairment after the stroke event, and neuropsychological evidence confirmed the presence of functional impairment in more than one cognitive domain or evidence of cognitive decline compared with the past. (3) the temporal relations of stroke and cognitive impairment: after stroke events occur, and for 3 ~ 6 months.

The major clinical manifestations of PSCI for computing power, attention, executive force comprehensive expression of cognitive dysfunction [13]. According to the severity of cognitive impaired PSCI can be divided into PSCIND and dementia PSD. PSCIND patients may only show the related cognitive function is impaired, ability is not significantly affect the daily life. In some cases of early after stroke, cognitive impairment is reversible, but as many as one-third of the stroke patients within five years for the development of dementia, caused serious negative impact on the lives of patients [3]. Ischemic stroke (IS) accounts for about 85% of all stroke types [14]. Therefore, there is an urgent need to deeply explore the cognitive impairment caused by IS, and in order to identify as early as possible PSCI and develop

intervention strategies.

3. Pathogenesis of PSCI

At present, the specific pathogenesis of PSCI is still unclear. Experimental research shows that cerebral ischemia or hemorrhage caused by cerebrovascular diseases for the main reason, which leads to the damage of cerebral nerve anatomical structure, such as the left frontal and temporal lobe, left thalamus and right parietal lobe infarction angular gyrus, frontal lobe, deep, and the left cerebral hemisphere infarction, these parts of the infarction and the severity of AD are closely related [15]. In addition, the hippocampus is one of the important components of the memory network in the brain. Posterior cerebral artery ischemia can cause damage to the hippocampus, leading to cognitive decline and permanent memory impairment. Acute cerebral ischemia (AIS) can lead to neuronal death directly, chronic cerebral ischemia can cause nerve fibers in white matter axonal degeneration and myelin depigmentation, thus hurting memory neural network, make information can not be passed, eventually leading to cognitive dysfunction [16].

AD as a kind of typical neural degenerative diseases disease, the patients with brain tissue pathology change of medial cortex, hippocampus and temporal lobe or atrophy with minor volume, can be found on histopathology is characterized by amyloid plaque deposits of senile plaques and tangles nerve fibers and neurons depigmentation. In terms of the mechanism of brain neurodegeneration, the pathological changes in the brain of PSCI patients are similar to those in the onset of dementia, and a variety of phenomena such as senile plaques characterized by amyloid deposition, neurofibrillary tangles and neuronal loss may occur simultaneously in the brain tissue [17]. Examination of the CSF may reveal an increased level of tau protein in the CSF, which can lead to degeneration of nerve fibers [18]. The pathological mechanism of relevant components in the changes of brain tissue and cerebrospinal fluid change and predict PSCI molecular markers have some overlap.

In addition to the above and cerebrovascular lesions, and neurological degenerative diseases can cause PSCI, studies have proved that the onset of PSCI and inflammation factors also have a connection [19]. Inflammatory response can occur in the brain under ischemic injury, which is manifested as the activation of stromal cells (microglia, astrocytes and endothelial cells). At the same time, inflammatory mediators will increase the recruitment of immune cells. In addition, the blood-brain barrier is damaged, which may lead to brain edema and neuronal death under the action of reactive oxygen species, cytokines and chemokines. The studies have shown that cerebral ischemia and inflammation are closely inter-related: ischemia is a robust stimulus for the potential damaging inflammation, while infection as well as its associated inflammation is an important risk factor for ischemic stroke [20].

The occurrence of PSCI is the result of the interaction between cerebrovascular mechanism and brain neurodegeneration mechanism, in which inflammation, oxidative stress and cytotoxicity of excitatory amino acids play an important role in neuronal injury and neurovascular

unit dysfunction. Exploring the pathogenesis of PSCI is helpful for the early intervention of PSCI.

4. Challenges of PSCI

At present, mainly depends on clinical manifestation, diagnosis of PSCI neuropsychological assessment and neural imaging examination, the most commonly used being the Montreal Cognitive Assessment (MoCA) [6]. However, PSCI often coexist with other neural psychological problems, Such as language disorders (Frenchay Aphasia Screening Test), mood disorders (Hospital Anxiety Depression Scale), fatigue Severity Scale (fatigue Severity Scale), delirium (Confusion Assessment Method) and apathy (apathy assessment scale), which should be assessed using validated tools [12]. In addition, there are various diagnostic methods found in the current research, the most commonly used method is still the scale. The scale evaluation method has strong subjectivity, and there are different differences among individuals, so the measurement results have large errors. In addition, the method for elderly people with aphasia and the low level of culture has significant limitations, therefore, should give full consideration to the above limitations in the study of the following factors, optimize the evaluation way reform, as far as possible with accurate experimental data is given priority to, with sufficient objectivity, is not subject to the limitations of the external environment [21]. In these rule out into the group of patients, lost to follow-up, or cognitive tests can not be completed, the incidence of dementia was likely to be higher.

Accumulating data suggest that important markers of PSCI may be present in peripheral blood. In addition to imaging techniques, precise indicators of PSCI may require the inclusion of fluid biomarkers, which can provide a rapid, easily accessible, and potentially valuable tool that may serve as both risk and prognostic biomarkers [22]. Different post-stroke injury cascades may influence the development of PSCI, such as inflammatory response, oxidative stress, and apoptosis. In the peripheral blood could be important markers of PSCI window into the process. As a result, many liquid biomarkers can be the risk and prognosis of PSCI reliable tool, used to enhance the clinical and imaging evaluation. Of course, The idea needs to be studied through the experiment of continuously and try to be realized.

5. Inflammatory Reaction and PSCI

Inflammatory response is an important defense response of the body, which aims to eliminate the causes of cell damage. At present, the pathogenesis of PSCI has been proposed, including inflammatory response, oxidative stress and apoptosis. Among them, neuroinflammation is a significant feature of the pathogenesis of cognitive dysfunction after stroke [23]. Inflammatory response to participate in neurological damage after stroke, show the host cell activation and peripheral immune cells to raise quickly. The brain's inflammatory response to IS has significant consequences for secondary neuronal death, effective resolution of the ischemic injury, and stroke outcomes [24]. The mechanism of secondary injury after cerebral ischemia may be due to the production of inflammation in the brain after ischemic stroke, which accelerates the formation of ischemic injury and affects neuronal death and nerve tissue

regeneration. These inflammatory sequelae begin early on and continue well past the period of acute injury. This postischemic inflammation may explain the delayed clinical consequences of acute stroke including poststroke cognitive impairment and dementia [19]. Under the condition of ischemia hypoxia, most clinical and experimental data suggest that neuroinflammation has a dual effect [10]. On the one hand, neuroinflammation can maintain the stability of the microenvironment; On the other hand, due to the excessive activation of inflammation and damage brain cells and neurons. Circulating markers of inflammation can cross the blood-brain barrier (BBB) and may modulate neuroinflammation processes that may cause neurodegeneration and cognitive impairment [23]. Currently, studies have shown that increased levels of inflammatory markers are associated with increased incidence of cognitive dysfunction after stroke, and their levels can be used as an additional criterion for long-term cognitive impairment [25,26]. Not only the inflammatory response of the central nervous system (CNS) can affect ischemic stroke, but also the inflammatory response of the peripheral system can also play a role in ischemic brain injury to a certain extent.

Background Population-based studies have demonstrated the association of inflammation and cognitive impairment [9]. In recent years, research on inflammation and PSCI mainly concentrated in interleukin-6 (IL-6), C-reactive protein (CRP), neutrophil to lymphocyte ratio (NLR) and tumor necrosis factor (TNF) [27]. Therefore, next, we aimed to summarize the relationship between these inflammatory markers and PSCI.

6. Inflammatory Biomarkers and PSCI

In the study of biomarker of PSCI, should concentrate on finding and PSCI pathophysiological mechanism is closely related to the marker.

Interleukin is a class of multifunctional cytokines including IL-1 β , IL6, IL-7, IL-8, IL-10 and IL-16. The interleukin-6 (IL-6) is a pleiotropic cytokine that plays a key role in interaction between immune and nervous system. IL-6 has both neuroprotective and neurotoxic effects in the process of brain injury. At normal physiological concentration or low content, IL-6 can protect or promote neuronal repair, but when IL-6 is highly expressed, it can cause neuronal damage and aggravate brain tissue damage [28]. A meta-analysis of inflammatory markers and the risk of dementia reported that IL-6 was significantly associated with increased risk [29]. In recent years, more and more scholars have found that IL-6 can be used as a reliable biological indicator to judge the severity of cognitive impairment, and the degree of cognitive impairment in PSCI patients is directly proportional to the plasma IL-6 level [30]. In ischemic PSCI, patients with larger infarct size had higher plasma IL-6 levels and more severe cognitive impairment [30]. Kulesh et al. found that serum IL-6 levels and levels of IL-1 β and IL-10 in the CSF of patients with executive dysfunction were significantly higher than those in patients without cognitive impairment [31]. Therefore, we can predict the cognitive function of patients in advance by their level.

A number of studies suggest that CRP might be associated

with cognitive impairment [27]. CRP is an inflammatory biomarker of inflammation and may reflect progression of vascular disease, that plays a crucial role in the human immune system [32]. In the acute phase of stroke, the synthesis of a large number of CRP in the body and induce the expression of endothelial cell adhesion molecules, causing vascular inflammation, so as to make the brain injury is more serious [33]. In patients with IS, elevated plasma CRP levels have been shown to be associated with decreased cognitive function [33]. Increased CRP may cause cognitive impairment through two different mechanisms. The first is the impairment of endothelial function. Macrophages take up low-density lipoprotein and promote the formation of foam cells, which mediate the abnormal migration and proliferation of vascular smooth muscle cells and cause brain lesions. Brain injury disrupts the integrity of prefrontal-subcortical circuits, leading to cognitive impairment. Secondly, the complement system may be activated, which in turn leads to brain tissue damage and cognitive decline [34].

When AIS occurs, circulating neutrophils are the first to recruit to the ischemic area and induce a destructive cascade, while stress conditions lead to a decline in lymphocyte numbers. Therefore, as a combination of the two different inflammatory markers mentioned above, The NLR in peripheral blood can comprehensively represent the systemic and central nervous system inflammation in AIS [35]. Therefore, individuals with higher NLR levels in the acute stage of IS may be more susceptible to inflammation and ischemic injury, leading to ischemia and shrinkage of memory-related hippocampus and other regions, and then PSCI. A Korean prospective study on ischemic stroke [36] first demonstrated that elevated NLR in the acute phase was independently associated with PSCI at 3 months after stroke. In addition, a community of cross-sectional study [37] also found higher NLR is associated with an increased risk of cognitive impairment. In conclusion, systemic inflammation is a driver of cognitive decline, and NLR is a viable tool for assessing cognitive dysfunction [38].

The TNF is a cytokine that signals via tumor necrosis factor receptor TNFR1 and TNFR2, plays a key role in brain health. The progression and outcome of stroke is affected by the intricate relationship between the BBB and tumor necrosis factor α (TNF α) [39]. TNF α crosses the intact BBB by a receptor-mediated transport system that is upregulated by CNS trauma and inflammation. TNF α can activate cytoprotective pathways by pretreatment or persistent exposure to low doses. This explains the paradoxical observation that transport of this proinflammatory cytokine improves the survival and function of hypoxic cells and of mice with stroke. The dual effects of TNF α may be related to differential regulation of TNF α trafficking downstream to TNFR1 and TNFR2 receptors. Recent studies have shown that the genetic variation in TNF α and IL-6 might increase the risk for development of vascular dementia and lacunar infarction [40].

To sum up, the levels of inflammatory markers in peripheral blood closely associated with cognitive dysfunction after stroke patients, objective measure of clinical evaluation cognitive dysfunction, is guidance for clinical scientific treatment.

7. Conclusion and Prospect

Up to now, although some progress has been made in the research of PSCI, many experimental studies still end in failure, resulting in there is still no accurate and efficient early warning mechanism and intervention measures for PSCI, so that PSCI patients often miss the best time point for treatment and rehabilitation. In addition, at present, the diagnosis of PSCI is mainly based on scale as the main diagnostic method, and there are many subjective factors, and the scale content is also different from different studies. As a result, its diagnostic criteria are not completely unified, and the criteria for distinguishing PSCI from normal aging and dementia are not clear, and the research on the mechanism of the occurrence and transformation of PSCI to dementia is limited.

In conclusion, the early screening and identification of PSCI is of great significance for the early intervention of patients. Many studies have shown that nerve can accentuate inflammation in patients with cognitive dysfunction after stroke, and more and more people through cognitive function in patients with serum biomarkers to predict. Therefore, the future still need a lot of clinical research to explore the inflammatory reaction and the relationship between the cognitive dysfunction after stroke, and to find feasible inflammatory biomarkers as prediction and evaluation tools. Whether lowering inflammation can also prevent post-stroke cognitive decline needs to be addressed in further clinical trials. Although there are few studies on the inflammatory response in the peripheral system of cerebral ischemia, there are reasons to believe that with the in-depth research in this area in the future, the new mechanism of IS will be revealed, and then more targeted new therapeutic targets will be found.

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