Review

Progress in Research on the Mechanism and Treatment of Post-stroke Infection

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Keywords

stroke; infection; immune; inflammation; review

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DOI: 10.1515/ii-2017-0134

Abstract

Post-stroke infection hinders the recovery of stroke patients and can even cause death. The main mechanism of post-stroke infection is related with the post-stroke center, the activation of the peripheral immune system, and the release of inflammatory factors caused by the lesion area and pathophysiological changes in the body. Therefore, elucidating the body's abnormal immune inflammatory responses after stroke is crucial for the prevention, treatment, and alleviation of post-stroke infection.

Post-stroke secondary injury is an important factor that affects the prognosis of patients. Post-stroke infection is the most common and deadly complication of stroke. In 2006, Vargas *et al.* [1] proposed the concept of stroke-associated infection (SAI), and that pneumonia, urinary tract infections, and sepsis are the main factors that hinder the rehabilitation of patients and even cause death. The immune inflammatory response induced after stroke is an independent risk factor for the occurrence of SAI in patients. The main presentations of SAI are the activation of dendritic cells, macrophages, other antigen-presenting cells, and T and B lymphocytes, as well as the imbalanced secretion of pro-inflammatory/anti-inflammatory factors. This paper provides a review of the pathophysiological changes associated with post-stroke infections to provide new ideas for the prevention of post-stroke infection.

Relevant Pathways of Post-stroke Infection

Janus Protein Tyrosine Kinase/Signal Transducer and Activator of Transcription Pathway

The Janus protein tyrosine kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway has become widely studied in recent years. Recent studies have shown that the JAK2/STAT pathway is an important signal transduction pathway in immune inflammatory response

after cerebral ischemia. Although this pathway is usually inactive, after brain injury, T-lymphocyte surface cytokine receptor intracellular region JAK are activated to catalyze the phosphorylation of STAT with the SH2 structural domain. Relevant cytokine genes, such as IL-6R and IL-4R, are activated to produce an immune response cascade reaction [3]. The activation of the JAK/STAT pathway could lead to the activation of glial cells and T and B lymphocytes, as well as upregulate the expression of IFN- γ , IL-6, and other immune inflammatory factors [4]. Current studies remain focused on the roles of the JAK/STAT pathway in cardiovascular diseases and tumors. The immune response produced by the pathway after stroke still requires further study.

Fas/FasL pathway

Fas is widely expressed in the surfaces of cell membranes and is also known as apoptotic protein-1 or CD95 molecule. Fas belongs to the tumor necrosis factor/nerve growth factor receptor family. The role of Fas in immune adjustment in the lung, liver, and other organs has been widely studied. Recent studies [5] have found that the Fasligand (FasL), which extensively exists in microglia, astrocytes, lymphocytes, natural killer cells, monocytes, and other immune cells, is highly expressed after brain injury and produces immune inflammatory responses. At the same time, FasL and Fas combine via cross-linking to form a trimer or multimer,

activating the cysteine protease (Caspase) family, which subsequently leads to the apoptosis of T lymphocytes and other immune cells, further intensifying brain injury. Related studies have shown that the activation of the CD95 signaling pathway in the brain after brain injury exerts protective effects by stimulating the regeneration of neural stem cells and promoting the recovery of neurological function [6]. Niu *et al.* [7] found that in cerebral ischemia gld mice with Fas gene mutation, FAS can improve the symptoms of neurological function deficit by inhibiting the infiltration of peripheral and main center inflammatory cells.

Guanine Nucleotide Exchange Factor/Small Molecule G Protein Rho Pathway

The guanine nucleotide exchange factor (GEF)/small molecule G protein Rho (Ras homologous, Rho) pathway also has a regulatory role in the diseases of the central nervous system [8]. In addition, GEF activation has multiple effects on the incidence of infection after cerebral ischemia. Rho belongs to the Ras superfamily, which includes the Rho (RhoA, RhoB, and RhoC), Rac, and Cdc42 subfamilies. Upstream GEFs bind to G protein-coupled receptors (GPCRs) by releasing various growth factors, chemokines, TNF- α , and lipopolysaccharides to activate RhoA and downstream Rho kinases; these interactions cause the dysfunction of brain microvascular endothelial cells (BMECs). Given the close relationship of BMECs and the blood-brain barrier (BBB) with integrity, the dysfunction of BMECs further causes structural and functional damage to the BBB [9] and increases permeability. In turn, the increased permeability of the BBB enables immune response inflammatory factors to permeate the BBB into the cerebral ischemic area after stroke, thus aggravating brain damage.

Mechanisms of Post-stroke Infection

Central immune regulation

Astrocytes, microglia, and neurons in injured brain tissues could activate inflammatory cells after stroke. The secretion of Toll-like receptors (TLR) increases to further activate downstream nuclear factor kappa-B (NF- κ B), mitogen-activated protein kinase (MAPK), and other relevant inflammatory pathways to promote the infiltration of inflammatory factors, such as IL-4, IL-6, IFN- γ , and IL-1 β , in the nidus area of the cerebral ischemia. Meanwhile, the secretion of neutrophils, monocytes, and

macrophages increases, thus up-regulating the expression of major histocompatibility complex I Class I (MHC I) and major histocompatibility complex class II (MHC II) and aggravating brain injury in the ischemic area.

Peripheral immune regulation mechanism

Changes in the peripheral immune system and the functional recovery of the injured brain area after stroke are also closely interrelated. The liver, spleen, lung, and other peripheral immune organs mainly regulate peripheral immune function. After brain damage, the central inflammatory response occurs in the hypothalamic paraventricular nucleus. This response releases glucocorticoid or adrenal cortex hormones through the adrenal cortex axis. The central inflammatory response can also occur through the sympathetic nervous system to directly activate peripheral T lymphocytes, macrophages, other immune cells, and chemokines [10]. These factors ultimately permeate the damaged BBB via blood circulation or osmotic effect to reach the lesion area, thus increasing brain damage.

A study by Stewart *et al.* [11] showed that after cerebral ischemia, the α - and β -adrenergic receptors of the spleen, a major reservoir of peripheral immunity, combine with catecholamines released by the center. This interaction results in the secretion of spleen neutrophils, macrophages, C-reactive proteins, chemokines, and other secreted factors. NK, B, and T cells then undergo apoptosis. Th1 transforms into the Th2 subtype and the secretion of inflammatory factors increases. At the same time, inflammatory markers enter the damaged BBB with blood circulation and reach the cerebral ischemia area to increase brain damage. Wong *et al.* [12] compared the molecular responses of wild-type mice with those of mice with liver iNKT cell deficiency after stroke. They found that liver iNKT cells can inhibit the release of norepinephrine receptor neurotransmitters and decrease inflammatory responses after stroke.

Factors Related to Post-stroke Infection

Pathophysiological factors

Changes in immune organs

The body's immune organs are the bone marrow, thymus, central immune organs, the spleen, liver, lymph nodes, and peripheral immune organs. Drechsler *et al.* [13] pointed out that in mice with Apoe gene knockout, the bone marrow

promotes the release of glial cells, bone marrow cells, and other inflammatory markers, thus increasing the count of the peripheral spleen and blood myeloid cells to induce and aggravate infection. The thymus and spleen indexes are objective indexes for the evaluation of immune function in animal experiments. After stroke, the immune stress response can cause the apoptosis of peripheral immune organ cells, causing the shrinkage of the spleen, thymus, and other immune organs, as well as the decline of immune functions.

Dynamic changes in immune cells/cytokines

In an induced cerebral ischemia animal model, post-stroke infection occurs rapidly given the rapid activation of the body's immune response. The inhibition of immune function can be detected several hours after cerebral ischemia and can last for several weeks^[14]. However, the timing of post-stroke immunosuppression varies in different parts of the body.

Gu *et al.*^[15] showed that 3 days after cerebral ischemia, the numbers of CD4 + T and CD8 + T lymphocytes significantly increased in the ischemic hemispheres of a rat model compared with that in the sham operation group. Leilei *et al.*^[16] observed that the ratio of CD4 + /CD8 + T lymphocytes in the peripheral blood of a cerebral ischemia-reperfusion mouse model 24 h after stroke was higher than that in the sham operation group. The ratio of CD4 + /CD8 + T lymphocytes were not different 6 h and 96 h after stroke. However, at 96 h after stroke, the ratios of CD4 + / CD8 + T lymphocytes decreased and the expression of proinflammatory factors, such as TNF- α and IFN- γ , were inhibited in the spleen. At 6 and 24 h after stroke, the expressions of pro-inflammatory and anti-inflammatory factors in the spleen and serum increased, whereas that of serum IFN- γ did not change 6 h after stroke. Liesz *et al.*^[17] used the cerebral ischemia mouse model to show that lymphocyte counts decreased in the spleen, lymph nodes, and thymus 24 h, 3 days, and 7 days after stroke, whereas TNF- α and IFN- γ secretion increased. By comparing the levels of the inflammatory cytokine CXCL-1 in the brain and peripheral immune organs, Chapman *et al.*^[18] found differences in central and peripheral inflammatory response: at 24 h after stroke, CXCL-1 in the serum, liver, and lung returned to normal but continued to increase in the brain.

Other factors

Approximately 30% of stroke patients with the mass propagation of oral pathogens and malnutrition caused by

swallowing dysfunction^[19] need enteral nutrition supply^[2]. These factors easily induce infection. At the same time, co-occurrence with other diseases (such as diabetes and cardiovascular disease, etc.) or post-stroke limb dysfunction increases the incidence of infection.

Treatment Strategies for Post-stroke Infection

Drug treatment

Antibiotic treatment

The central and peripheral immune systems undergo changes several hours after stroke. Preventive anti-infective treatment is usually needed to prevent stroke. A multi-center and open clinical experiment (Preventive Antibiotics in Stroke Study, PASS) on 2550 stroke patients found that the incidence of post-stroke infection significantly decreased 3 months after using cephalosporins, which are third-generation antibiotics, for 4 d^[20]. However, a study pointed out that^[21] although cephalosporin can prevent post-stroke infection, the therapeutic efficacy of the drug on different infections, drug resistance caused by long-term use, and other problems should be studied further. Studies have shown that^[22] 3–4 d after stroke, treatment with penicillin and sulbactam, a β -receptor retardant, can decrease the incidence of post-stroke infection. The anti-infective effect of the quinolone antibiotic moxifloxacin is superior to that of levofloxacin. However, although some drugs have anti-infective effects, they may also increase brain damage by exerting toxic effects on the central nervous system.

Other therapy drugs

Chen Shuzeng *et al.*^[23] pointed out that preventive treatment with the lipid-lowering drug fluvastatin can down-regulate TNF- α expression and up-regulate IL-10 expression in the brain tissue of rats with cerebral ischemia. These effects decrease post-stroke inflammatory immune responses to protect the brain. However, studies have shown that the early use of statins increases the level of serum interleukin-1 receptor antagonists and increases the risk of infection in stroke patients. Some scholars^[25] have reported that 7 days after levodopa treatment, the up-regulation of peripheral blood CD3 + CD4 + T lymphocyte levels can improve immunosuppression status after stroke. Given the difference in the gender and age of stroke patients, estrogen may exert neuroprotective effects. For example, in a male cerebral

ischemia model, estrogen inhibits immune inflammatory response after stroke. However, estrogen may increase the incidence of stroke in menopausal female models [26]. As an immunomodulator, Graim can reduce the secretion of proinflammatory factors after stroke but does not improve the volume of post-stroke cerebral infarction and neurological deficits [27].

Peripheral immunotherapy

To regulate post-stroke peripheral immune function, Yan *et al.* [28] found that 24 h after stroke, the transplantation of human umbilical cord blood stem cells (HUCBC) can repair BBB damage caused by cerebral ischemia and reduce inflammation factor release, resulting in neuroprotective effects. Zhang *et al.* [29] found that performing splenectomy 2 weeks before permanent cerebral ischemia decreases the number of T cells, neutrophils, and macrophages in the brain tissue of rats and decreases the release of proinflammatory cytokines, such as IL-1 β and other factors, and thus increasing the secretion of anti-inflammatory factor IL-10. Although splenectomy can decrease the incidence of post-stroke infection to a certain extent, its effects on the normal physiological function of the spleen still require further study.

Traditional Chinese medicine

The traditional Chinese medicines Buyang Huanwu decoction [30], an astragalus-based decoction, and Shenlong decoction, a ginseng- and polygonum-multiflorum-based decoction [31], can significantly improve post-stroke immunosuppression to decrease the incidence of post-stroke infection. The results of animal experiments have confirmed that [32] acupuncture at the Baihui and Zusanli acupoints are beneficial for the recovery of brain function in rats with cerebral ischemia. Acupuncture at these acupoints also down-regulates the expression of inflammatory markers, such as IL-1 β and IL-6, thereby alleviating the inflammatory immune response mediated by these markers and attenuating cerebral ischemia-reperfusion injury to exert protective effects on brain tissue.

Other methods

Some natural food and plant ingredients exert effects that decrease inflammatory responses and the likelihood of infection after stroke. Qiao *et al.* [33] reported that luteolin extracted from natural plants could down-regulate the levels

of Toll-like receptor (TLR)-4, TLR5, NF- κ B, and other inflammatory factors in a rat model of cerebral ischemia, thus decreasing inflammatory response and protecting the brain. Wang *et al.* [34] found that after 3 days of continuous lavage with plant-derived shikonin, cerebral ischemia-reperfusion mice exhibited the decreased expression of inflammatory markers, such as TLR4, TNF- α , and phosphorylated p38 mitogen-activated protein kinases. These effects inhibit NF- κ B nuclear translocation, repair the BBB, and exert neuroprotective effects. In addition, the high carnosine content of beef and chicken has a certain immunoregulatory function in cerebral ischemia, thereby reducing the incidence of post-stroke infection to protect the brain [35].

Conclusion

Methods for the prevention of post-stroke infection have mainly focused on the regulation of immune function and the standardization of invasive surgery. Elucidating post-stroke pathophysiological functions is crucial to decrease the incidence of infection in stroke patients. Exploring the dynamic changes in central and peripheral immune regulation after stroke could provide a specific target for combination therapy. The future treatment of stroke patients with infection should be based on molecular markers, immune cells, and immunoinflammatory pathways. To improve the recovery of the patient from post-stroke infection, clinicians should provide customized and comprehensive treatment via medication, diet, and physical therapy.

Declarations

Acknowledgements

No.

Competing interests

The author declares that he has no competing interest.

Authors' contributions

HT Zhang made the literature analysis and wrote, discussed and revised the manuscript of this review.

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