



The Relationship between Cerebral Small Vessel Disease and Inflammation-Immune Response: A Review

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Abstract

Cerebral Small Vessel Disease (CSVD) is not only a single disease, but a kind of clinical and pathological syndrome caused by various factors, such as intracranial arterioles, perforating arteries and venules, which can result in structural and functional changes. CSVD accounts for about 25% of ischemic stroke. It is related to cognitive dysfunction, emotional disorder and even defecation disorder in the elderly, which seriously affects the quality of life. The clinical manifestations and prognosis that different patients suffer from are different. The reasons why some patients' clinical symptoms are different from others' are that besides stroke location, stroke area and other factors we talked about usually, in addition, inflammatory immune response also plays a significant role in CSVD. Inflammatory response is a defense mechanism for us, so that we can respond to a variety of stimulating factors quickly, by causing a series of effects such as activating inflammatory cells to release inflammatory factors and other bioactive substances. Similarly, the immune system of our body is composed of a variety of immune organs and immune cells, which has the functions of immune defense and immune regulation. Inflammatory immune response occurs in all systems of the body, which is regulated by immune cells, inflammatory factors and other mediators, and plays an important role in the occurrence and development of diseases.

Keywords: Cerebral small vessel disease; Inflammatory response; Inflammatory factors; Atherosclerosis; Immune cells

Introduction

Cerebral Small Vessel Disease (CSVD) is a disease involving a series of dynamic, whole brain and whole vascular diseases caused by a number of pathological and imaging changes of intracranial small vessels caused by many different causes [1,2]. CSVD is short of typical clinical symptoms in the early stage. However, with the passage of time and the progression of the disease, recurrent stroke and progressive cognitive decline which will put patients under great pressure will be the main clinical manifestations [3-5]. It will mainly cause damage to the subcortical structure of the brain, characterized by high signal intensity of White Matter Hyperintensities (WMH), Lacune Infarction (LI), Cerebral Micro bleed (CMB), brain atrophy and other imaging manifestations [3]. Stroke that is characterized by high disability rate and other characteristics is divided into

haemorrhagic and ischemic [6]. Studies have shown that when stroke occurs, our brain tissue quickly responds to ischemia, hypoxia and other stimuli to activate the inflammatory response, which will further aggravates the brain injury to some extent, and the brain damage caused by these inflammatory changes even exceeds the ischemia itself. Besides, the inflammatory reaction is not limited to the ischemic site, but develops and spreads to the whole brain tissue and exists for a long time, causing and aggravating the brain tissue injury, which is closely related to the improvement and recovery of the injured brain tissue [7-9]. CSVD can be divided into the following types: 1) Atherosclerotic (also known as age-related) CSVD; 2) II, hereditary/sporadic CAA (Cerebral Amyloid Angiopathy, CAA); 3) Except for CAA, other hereditary CSVD; 4) CSVD related to inflammation and immunity; 5) CSVD related to inflammation and immunity CSVD; 6) Other CSVD. Among all the types we list above, I and

Received date: 22 May 2022; Accepted date: 26 May 2022; Published date: 31 May 2022

Citation: Jiaxin Z, Libo L, Zhenyun Y, Caili H, Jie Y, Sha H (2022). The Relationship between Cerebral Small Vessel Disease and Inflammation-Immune Response: A Review. SunText Rev Med Clin Res 3(2): 160.

DOI: <https://doi.org/10.51737/2766-4813.2022.060>

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II are the most common in the clinical. At present, the pathogenesis of cerebral microvascular disease is not completely clear. In addition to the core mechanism of blood-brain barrier damage and vascular endothelial dysfunction which are more familiar to us, inflammatory reaction, immune factors, radioactive factors, heredity, A β protein deposition, oxidative stress and other factors that play a role in changing the structure and function of blood vessel wall and vascular reactivity can indirectly cause vascular endothelial injury and increase the permeability of blood-brain barrier, which will promote the occurrence and development of cerebrovascular disease eventually [10-16]. The influence of inflammatory immune response on the occurrence and development of cerebral microvascular disease has been further recognized. By releasing inflammatory factors, the inflammatory-immune response in the brain will inevitably lead to changes in vascular endothelial structure, and damage the blood-brain barrier, increase the permeability of blood vessels to harmful substances, and accelerate intracranial arteriosclerosis. At the same time, inflammatory factors can directly lead to vascular wall damage, vascular reactivity changes, and damage its self-regulation function, thus promoting the occurrence and development of cerebrovascular disease [17]. In this paper, the relationship between inflammatory immune reaction and cerebrovascular disease (mainly type I and type II) is summarized as follows, in order to better understand the role of inflammatory immunity in its pathogenesis and lay a foundation for early prevention and treatment of cerebral small vessel disease [18-20].

Inflammatory reaction and Atherosclerotic Cerebral Small Disease (aCSVD)

Inflammatory factors and aCSVD

Atherosclerotic Cerebral Small Vessel Disease (aCSVD) is a common type compared with others, while its pathogenesis is not completely clear. Clinically, it is not difficult to find that some patients suffered with CSVD who do not have vascular risk factors such as senility, blood pressure variability, hyperlipidaemia, hyperhomocysteinemia and so on, which shows routine risk factors are not enough to fully explain the overall burden of atherosclerosis. Studies have shown that atherosclerosis is closely related to the drive of inflammatory response. The release of inflammatory factors and bioactive mediators also plays an important role in many stages of the pathological process of atherosclerosis, such as foam cell formation, plaque formation, thrombosis and so on. It is interesting for to find that infection is not limited to vascular damage caused by intracranial inflammation, but peripheral inflammation can also migrate and release inflammatory factors, directly or indirectly aggravating atherosclerosis [22,23]. As early as the 1980s, Professor ROSS

first defined the concept that atherosclerosis is a kind of chronic inflammation, which has been widely concerned and recognized by experts and scholars, and has made important and fruitful achievements in related research fields. Atherosclerosis is closely related to vascular endothelial cell dysfunction, which is not only a pathological change of vascular wall in response to various stimulating factors, but also an important pathophysiological basis of ischemic cardio-cerebrovascular diseases and an independent risk factor. Studies have shown atherosclerosis has the remarkable characteristics of inflammatory reaction such as metamorphosis, exudation and hyperplasia, which exists in all stages of the process of atherosclerosis and is related to the occurrence, development and prognosis of the diseases caused by atherosclerosis. In the process of inflammation, it will be accompanied by the activation of many inflammatory cells, so a large number of serum biological inflammatory markers, growth factors and adhesion molecules will be released. For example, tumor necrosis factor α , interleukin, lipoprotein a, fibrinogen, C-reactive protein, all of which can result in vascular endothelial cell injury and blood-brain barrier damage. Endothelial function and blood-brain barrier dysfunction can increase the permeability of small vessels, further aggravate the infiltration of inflammatory cells, and even lead to cerebral microhemorrhage caused by vascular rupture, which will increase the risk of CSVD [22,23]. In addition, it can also reduce cerebral blood flow and impaired brain self-regulation function, which increase the opportunity of cerebral stroke caused by the lackness of ischemia and anoxia. A cross-sectional study of imaging findings and risk factors of cerebral microvascular disease shows that long-term insufficient cerebral blood flow and low cerebral perfusion can lead to chronic and diffuse subcortical ischemia, which is called white matter damage that is the most prominent imaging feature of cerebral microvascular disease; Besides it can cause acute severe local ischemia, named lacunar cerebral infarction, which adversely affects the quality of life of patients. The research progress on the relationship between several common inflammatory factors and atherosclerosis (Atherosclerosis, As) is stated as follows [24,25].

Homocysteine (Hcy)

Homocysteine is a kind of amino acid, which is related to the metabolism of vitamin B12, folic acid and vitamin B6. At the same time, Hcy is an index that can reflect the systemic inflammatory response, and it is a vascular endothelial inflammatory factor. The increase of homocysteine in vivo will lead to vascular endothelial damage, promote the occurrence and progress of atherosclerosis, and is a potential pathogenic factor for the occurrence of cardio-cerebrovascular diseases [26]. Studies have shown that high levels of Hcy aggravate oxidative stress and are closely related to the occurrence, progression and overall burden of high signal intensity in white matter. Another

study shows that homocysteine can induce both of the release of representative inflammatory factor C-reactive protein and inflammation in the brain, which will cause blood-brain barrier dysfunction, and lead to vascular lesions of the nervous system eventually [28,29]. Long-term atherosclerosis is an independent risk factor for the occurrence of cerebrovascular disease and is closely related to its prognosis. So, to some extent, inhibiting inflammation by reducing the level of homocysteine may slow down the progression of cerebrovascular disease.

Interleukin

Interleukin (IL) is a kind of cytokines secreted by a variety of immune or non-immune cells, which plays an important role in the process of inflammatory response, immune cell activation, functional regulation, lymphocyte activation and so on. IL-6 mediates platelet aggregation, C-reactive protein expression and the release of other inflammatory mediators, which leads to the inflammatory development and poor reactivity of vascular endothelium [30]. In addition, other studies have shown that IL-6 may accelerate the decline of mitochondrial function, resulting in brain tissue hypo perfusion, blood-brain barrier function damage and brain balance damage. The experimental studies of have shown that IL-1 β has an anti-atherosclerotic effect by reducing the expression of inflammatory factors, achieving the goal that reducing the occurrence of cerebrovascular disease [31,32]. In recent years, the relationship between new interleukin subtypes such as IL-18,IL-37,IL-38 and plaque formation and stability has gradually become clear, and valuable results have been obtained, which has been widely recognized by people[33,34].IL-18 may be closely related to white matter lesions, but the relationship between IL and atherosclerosis and imaging features of cerebral microvascular disease still needs further study, so that it may provide new theories and ideas for the prevention and treatment of cerebral microvascular disease.

Tumor Necrosis Factor (TNF)

Tumor necrosis factor (TNF) is a key cytokine with multiple functions secreted by peripheral immune cells such as mononuclear macrophages and neutrophils. A study on the relationship between cerebral infarction and serum TNF levels shows that TNF promotes T cell subsets and immune function disorder by directly or indirectly acting on CD4,CD8 and other immune cells; In addition, Tumor Necrosis Factor Associated Factors (TRAFs)can also promote the progression of inflammation by regulating the expression of receptors in the process of inflammation, and they jointly participate in the inflammatory response, which can accelerate the progression of cerebral atherosclerosis [9,35,36]. Both of long-term atherosclerosis and even thrombosis can lead to insufficient

cerebral blood flow, and low perfusion of brain tissue which will promote the progression of cerebrovascular disease. In addition, other studies suggest that there is a correlation between TNF and CSVD imaging findings proposed for the first time that patients with CMB have higher levels of serum TNF, while according to the relationship between TNF and lacunar infarction and high signal intensity of white matter, it is not completely clear, so much more researches are needed to explore the relevance between them [37,38].

Matrix metalloproteinases (MMP)

Matrix metalloproteinase (MMP) is a biomarker of endothelial injury mediated by extracellular matrix metalloproteinase inducer (EMMPRIN) on the surface of many kinds of cell membranes [39,40]. MMP is a large family, among which MMP-2, MMP-3, MMP-9 is the most widely distributed in the brain. The biological factors secreted by MMP-2, MMP-3, MMP-9 may mediate inflammation and damage the function of blood-brain barrier [41]. Therefore, inhibiting the release of various inflammatory factors from MMP would be an effective and ideal target for new drug development. In addition, other studies have shown that MMP hydrolyzes the proteins of the basement membrane, which is the key structure of the blood-brain barrier, and degrades the extracellular matrix to make it dysfunctional, resulting in the increase of the permeability of the blood-brain barrier and the entry of lipids and proteins into the brain parenchyma, resulting in brain damage [42]. MMP causes small vascular endothelial dysfunction through a variety of ways, such a through resulting in increased permeability, promoting blood-brain barrier damage and brain tissue damage, resulting in the occurrence of cerebrovascular disease finally. A study reported on the relationship between MMP-9 and mild cognitive impairment in patients with OSA showed that MMP was associated with WMH load, an imaging marker of cerebrovascular disease [43]. Some studies have shown that MMP-9 may be associated with hypertensive intracerebral hemorrhage and spontaneous cerebral microhemorrhage by increasing oxidative stress, but it is not completely clear so far [44]. An study based on animal model has found that inhibition of EMMPRIN can reduce brain injury and inflammatory response after stroke, which may promote the recovery of neurological function, which is hoped to become a new target for the treatment of cerebral microvascular disease [45,46]. According to the conclusion of Paritzz, basing on the concentration and expression characteristics of EMMPRIN in serum, we may can use EMMPRIN as a new biomarker to predict the prognosis of stroke patients. Through the intervention of MMP and its inducible regulatory factors, it may become a new strategy for the prevention and treatment of cerebrovascular diseases. At present, the research on the relationship between serum inflammatory factors and cerebrovascular disease is still

absolutely unclear. In the future, it is hoped that more studies will start from many aspects and dimensions, such as the related pathological process of serum inflammatory factors and cerebrovascular disease, iconic imaging changes, cognitive dysfunction after stroke caused by cerebral microvascular disease, post-stroke emotional disorder and so on to explore the pathogenesis of cerebrovascular disease. Standing on great findings, we may provide strong help for patients who are suffered with cerebral small vessel disease to lighten the burden of economy, life and society.

Immune response and aCSVD

The immune system of the body is a huge and complex system. When the body is stimulated by external stimuli or abnormal changes in itself, expect for the occurrence of inflammatory reaction, the activation of the immune system also plays an important role, and the two complement each other to aggravate brain injury and promote the occurrence and development of cerebrovascular disease[47,48].With the rapid development of modern science and technology, the influence of immune response in cerebral microvascular disease has gradually been widely concerned by scholars and achieved fruitful results. Immune responses include congenital and adaptive. Physical barrier and mononuclear macrophages, neutrophils, natural killer cells, chromophilic granulocytes, dendritic cells and other cells constitute the innate immune system, while the adaptive immune system is divided into T-lymphocyte-mediated cellular immunity and B-lymphocyte-mediated humoral immunity [49,50]. What is discussed below is a brief introduction about the study of neutrophils, lymphocytes and atherosclerotic cerebrovascular disease.

Neutrophils and aCSVD

Neutrophils relying on their strong chemotaxis and phagocytosis become an important factor in acute inflammation and innate immunity, and play an important role in various processes of atherosclerosis [51]. The basis of vascular pathological changes is endothelial damage, which can quickly activate inflammatory cells to release a variety of inflammatory mediators with different functions to produce inflammatory response. Neutrophils are closely related to the occurrence, progression and outcome of inflammatory response [52]. Studies have shown that neutrophils and myeloperoxidase and other biomarkers stored in them cause vascular endothelial injury, adverse interaction between inflammatory cells and endothelial cells, and enzymatic hydrolysis of extracellular matrix through a series of pathological processes, which may accelerate the formation of unstable plaques, thrombosis, and promote the occurrence and progress of atherosclerosis and cerebrovascular diseases [52]. Since an index

called Neutrophil extracellular traps (NET) was put forward in 2004, it has been paid more and more attention. It may be involved in many pathological processes, such as inflammatory reaction, oxidative stress, thrombosis and so on, which may become a new target for treatment [53,54].

Lymphocytes and aCSVD

Lymphocytes (B lymphocytes, T lymphocytes) make the body produce immune response through the process of transformation, production of antibodies and secretion of factors, which is the key factor of adaptive immune response. T lymphocytes are mainly composed of two cell subtypes: helper (Th) and cytotoxic (CTL).Different subtypes of lymphocytes are involved in the occurrence of atherosclerosis by secreting a variety of functional cytokines [51,55]. They have a two-sided effect in the process of atherosclerosis. For example,Th1,Th2, Th17 and other different cells can secrete many kinds of cytokines, such as interferon- γ ,IL-2,IL-17 and so on, which promote vascular inflammation, and cause vascular endothelial dysfunction, blood-brain barrier destruction, decrease vascular reactivity, all of which will lead to brain tissue hypo perfusion, and promote the occurrence of cerebral small vascular disease. Regulatory T cells, as immunosuppressive cells, can inhibit inflammatory response by remodelling plaques and enhancing their stability, which play a significant role in slowing down the development of atherosclerosis, and protecting blood vessels and reducing the occurrence of cerebrovascular disease. Similarly, B lymphocytes have a dual effect on atherosclerosis [56-58]. Studies have shown that B1 lymphocytes can produce anti-As IgM antibody, act on oxidized low density lipoprotein (ox-LDL), which is closely related to As formation, prevent the release of related inflammatory factors, endothelial cell injury, plaque formation, and achieve the effect of anti-atherosclerosis [59,60]. On the contrary, B2 lymphocytes promote the formation of unstable plaques by secreting IgM antibodies on vascular smooth muscle cells and increasing the risk of atherosclerosis [51]. In a word, innate immune cells such as neutrophils and adaptive immune cells dominated by lymphocytes play an important role in the occurrence and development of as through different pathological mechanisms. Therefore, two more objective and comprehensive serum detection indexes called NLR (neutrophil/lymphocyte) and PLR (platelet/lymphocyte), have attracted more and more attention. These two indicators take more into account the effect of the balance of immune cell subsets on as, and the study shows that NLR and PLR have predictive value in intracranial atherosclerotic stenosis and are related to the degree of intracranial atherosclerotic stenosis [61-63]. It is familiar to us that long-term arterial stenosis will lead to a series of brain lesions, such as insufficient intracranial cerebral blood flow, cerebral ischemia and hypoxia, endothelial dysfunction, blood-

brain barrier damage and so on, all of which will promote the occurrence of cerebral microvascular diseases finally.

Autoimmune antibodies and aCSVD

With the deepening of the study on the vital role of atherosclerosis in the pathogenesis of cerebrovascular disease, the incidence of cerebrovascular disease in some autoimmune antibody positive patients is higher [64]. Autoantibodies are involved in all pathological stages of atherosclerosis. It has been found that anticardiolipin antibody (ACA) can be used as an independent risk factor for the occurrence and development of atherosclerosis, although its mechanism needs further study [65]. Absolutely, the relationship between autoimmune antibodies commonly used in clinic, such as ANCA, ENA, antinuclear antibody, and cerebrovascular disease and atherosclerosis needs a large number of studies to find out in the future. Through the inhibition of autoimmune reaction and inflammatory reaction, it may provide a new direction for the prevention and treatment of cerebrovascular disease. In summary, atherosclerosis is a pathological process characterized by long-term chronic inflammatory reaction. At the same time, the study of the relationship between autoantibodies and it is gradually clear. Inflammation and autoantibodies are involved in all stages of its development and affect its prognosis. As the most common cerebrovascular disease, it is particularly important for the prevention and treatment of aCSVD. Inflammation and immune response play an important role in the formation and progression of atherosclerosis. Therefore, by detecting the level of related antibodies and inhibiting the release of related inflammatory factors, we can achieve early prevention and treatment of atherosclerosis and slow down the progress of As, so as to provide a new direction for the treatment of cerebrovascular diseases such as atherosclerosis, cerebrovascular disease and stroke, and make it beneficial for more and more patients.

Inflammatory Reaction and Cerebral Amyloidosis

Cerebral amyloidosis (CAA) is another common type of cerebral microvascular disease. The main pathological manifestation is the deposition of A β protein in the vascular wall of the brain, which is a common intracranial vascular disease in the elderly. The balance of A β protein in the brain is maintained by enzymatic hydrolysis or internal and external transport of the blood-brain barrier. When the excessive deposition of A β protein exceeds the clearance capacity of the enzyme, and the transport capacity of the blood-brain barrier is decreased due to various reasons, the abnormal accumulation of A β protein produces CAA [66]. CAA is an important cause of spontaneous and recurrent cerebral lobe micro haemorrhage, especially occipital lobe haemorrhage in the elderly. In addition, strictly speaking, cerebral micro haemorrhage

is associated with cognitive impairment. Therefore, as an important cause of lobar micro haemorrhage, CAA may be an important cause of cognitive impairment in the elderly [2,67]. As another common type of cerebrovascular disease, the study on the relationship between inflammatory factor secretion, immune system activation and CAA is also of great value. It is absolutely necessary to further explore the role of inflammatory immune response in the process of CAA, so as to improve the life and health of the people who are suffered with it. Presently, the research on the relationship between immune response and CAA is not supported by a large number of data, so further research is needed to provide a new method for the effective prevention and treatment of cerebral microvascular diseases. To sum up, with the rapid development of economy, the progress of medicine and the change of population structure in China, post-stroke cognitive impairment and post-stroke depression caused by cerebral microvascular disease have brought great burden to individuals and society. More and more evidence supports that the detection indexes of serum inflammatory factors, inflammatory reaction and autoimmune related antibodies are closely related to the occurrence, progression and prognosis of cerebrovascular disease and atherosclerosis (lipid stripes, plaque formation, thrombosis and other pathological processes), but its pathogenic mechanism is not completely clear. At present, the treatment of cerebral microvascular diseases is mainly anti-platelet aggregation, lipid-lowering plaque and other conventional stroke treatment, and its prevention focuses on bad lifestyle changes. Therefore, there is more and more consensus on the early detection of a new direction for the prevention and treatment of cerebrovascular diseases. The serum indexes such as inflammatory factors and autoimmune antibodies are easy to obtain and economical in clinic, and it is particularly important to study the correlation between them and cerebrovascular diseases. Through the detection of these serum indexes, we can better and more quickly screen out the high-risk population of cerebral small vascular disease and make early intervention, so that we may provide a new strategy for the early diagnosis and treatment of cerebral small vascular disease.

Funding

This work was supported by Hebei Provincial Science and Technology Program (Hebei Key Research and Development Project-Minsheng Science and Technology Project 19277707D) and Medical Science Research Program of Hebei Health Commission (20221417).

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