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Research progress on biomarkers of cerebral small vessel disease

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Abstract: Relevant data show that with the accelerating aging population in China, cerebral small vessel disease the diagnosis rate of Cerebral small vessel disease (CSVD) is also increasing year by year. Patients may have cognitive decline, gait disorder, mental and emotional changes, swallowing disorder, and abnormal urine and stool, which seriously affect the quality of life. At present, the pathogenesis of CSVD is still unclear. The author believes that the research on biomarkers of CSVD may have broad prospects. Therefore, this paper analyzes the inflammation-related markers of CSVD, Immune-related markers, and genetic-related markers to provide a new reference direction for early diagnosis, disease monitoring, and clinical treatment of CSVD.

1. Introduction

CSVD is a syndrome caused by various causes affecting small cerebral arteries and their distal branches, arterioles, capillary, venules, and venules. International Neuroimaging Criteria for Vascular Changes (2013) states for the diagnosis of CSVD: recent small subcortical infarct (RSSI), lacunar infarcts (Li), white matter hyperintensity (WMH), cerebral microbleeds (CMBS), perivascular space (PVS), and brain atrophy (BA)[1]. The early clinical manifestations of patients with CSVD are not prominent and have no specificity. The diagnosis of CSVD is still limited to the imaging findings of the late stage of the disease[2.3].

According to the etiology, CSVD has six types: (1) age-related small vessel disease, (2) cerebral amyloid angiopathy , (3) hereditary small vessel disease, such as CADASIL, (4) inflammatory or immune-mediated small vessel disease, (3) cerebral amyloid angiopathy, (5) venous collagenization, (6) other diseases, in which age-related CSVD was the most common. With the global population aging, the prevalence of CSVD has increased significantly and has become a significant cause of stroke, cognitive impairment, and disability-related death in the elderly [4.5]. This paper briefly analyzes the pathogenesis of CSVD. It summarizes the latest research progress of CSVD-related biomarkers from the aspects of inflammatory markers, immune-related markers, and gene-related markers, as follows:

2. Pathophysiological mechanism

Because of the particular anatomic structure and the limitation of detection technology, the small cerebral vessels are difficult to be detected directly. The exploration of the pathogenesis of CSVD is limited, and the lack of understanding of pathophysiology hinders the progress of related therapies. Therefore, early postmortem examination plays an essential role in studying microvascular pathology. Believe there may be a synergistic effect of multiple factors and pathways in the occurrence and development of CSVD. Found Blood-brain barrier (BBB) injury, chronic inflammatory reaction, and leukocyte infiltration in clinical imaging and autopsy studies of CSVD. Therefore, endothelial and blood-brain barrier dysfunction and chronic cerebral ischemia and hypoxia may be its basic mechanism[6]. The pathological process includes arteriosclerosis, hyaline degeneration and so on[7].

Other mechanisms, such as senescence and immune-inflammatory responses[8], have also been widely implicated in CSVD, including cellular senescence, mitochondrial dysfunction, defects in autophagy, and Dysbiosis[9] of the gut microbiota. Jalal[10] explored this by establishing a mouse model of CSVD and found that hypoxia can induce matrix metalloproteinase-9(MMP-9)-mediated leukocyte infiltration, which is secondary to BBB destruction. At the same time, tetracycline showing various neuroprotective effects in vascular injury models. These results suggest that immunomodulators play a role in preventing or delaying the progression of CSVD.

CSVD is different from large artery atherosclerotic cerebrovascular disease. genetic factors play an essential role. Several authoritative studies have elucidated the association between gene mutations such as NOTCH3[11], HTRA1[12], COL4A1/COL4A2[13], TREX1, and some rare familial CSVD. While several reports of sporadic CSVD have been REPORTED[12.14] suggested that polymorphisms such as COLGALT1[15] play a vital role in the development of CSVD, suggesting a possible common mechanism of action between the two.

3. Inflammatory markers

A growing body of research has identified inflammation as a significant risk factor for cognitive impairment, stroke, and small-vessel Disease[16]. However, the mechanism of inflammation in CSVD remains unclear. Shoamanesh, By a cross-sectional studying [17] of 1762 subjects, found that up to 15 inflammatory markers can act on CSVD through different inflammatory pathways. Vascular inflammation is an independent risk factor for CSVD; systemic inflammation appears to be involved in the vascular damage associated with amyloidosis. Nevertheless, there is insufficient data to establish a causal relationship between the two: is inflammation the cause of CSVD, or is it secondary to CSVD.

3.1 Soluble intercellular adhesion molecule-1

Soluble intercellular adhesion molecule-1(Sicam-1)as a biomarker of endothelial cell injury, Sicam-1 mediates the adhesion of leukocytes, platelets, and vascular endothelium plays a vital role in BBB destruction and brain tissue damage induced by chronic cerebral ISCHAEMIA[18]. Study [19] has found that higher levels of Sicam-1 are an independent risk factor for WMH, consistent with Saadimahdiye[20] et al.However, most studies on Sicam-1 are limited to small-sample experiments, and more large-scale evidence-based medical research is needed.

3.2 Homocysteine

Homocysteine (Hcy) can lead to chronic ischemia and hypoxia in brain tissue through many

pathological pathways. By interfering with Nitric Oxide anabolism, cause abnormal vasodilation. Changes in Epigenetics, such as protein n-homocysteine and hypomethylation, can also trigger CSVD[21]. In a cross-sectional study that included 256 patients with CSVD versus 1377 controls[22] concluded that Hcy was independently associated with white matter damage in stroke patients by comparing HCY levels in vivo between the two groups. Even mild hyperhomocysteinemia could significantly increase the severity of CSVD, a positive correlation between them. HCY could function as an independent predictor of cognitive impairment in CSVD.

3.3 Von Willebrand factor

von Willebrand factor (vWF) is considered a significant Von Willebrand disease of vascular endothelial damage factors. Zhang[23]first reported Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The deposition of vWF in the vascular wall suggested that vWF might be involved in developing CSVD. Postmortem studies have suggested that the loss of capillary in the progression of CSVD leads to pathological processes such as cerebral hypoperfusion and hypoxia [24]. The latest research found that A disintegrin and metalloproteinase with a thrombospondin motif repeat 13 (ADAMTS13) can regulate the activity of vWF and play its anti-inflammatory and antithrombotic roles. Meanwhile, by multiple regression analysis, Sun[25] found that lower ADAMTS13 activity and higher vWF levels were closely related to WMH.

3.4 Hypersensitive C-reactive protein and interleukin 6

Hypersensitive C-reactive protein [26](HS-CRP), hs-CRP is a critical acute inflammatory marker produced and released by the liver; current testing techniques can accurately detect sample size within minutes of onset.Interleukin-6 [27] (IL-6) is considered the main stimulator of CRP synthesis. Liu et al [28]found that the increase of hs-CRP can induce vascular smooth muscle cells to produce interleukin 6 through rat vascular smooth muscle cell experimental model and promote atherosclerosis through TLR4/IRF3/NF-κB signaling pathway, resulting in white matter lesions.

The Atherosclerosis Risk in Communities Study (Aric) [29] similarly concluded that people with higher levels of c-reactive protein have more pronounced structural abnormalities in the brain's white matter.

3.5 Fibrinogen

Fibrinogen(FIB) is a plasma coagulation protein synthesized by liver cells, which plays an essential role in the coagulation system, plasma protein organisms such as plasmin and fibrinogen are usually not detectable in the brain parenchyma protected by BBB, FIB is a sign of blood-brain barrier disruption and an essential driver of neuropathology and inflammation. After passing Through BBB, FIB can activate microglia and recruit peripheral macrophages, promoting neuroinflammation, scar formation, and demyelination [30]. In [24] autopsied specimens, the level of FIB in the gray and white matter of hypoperfused brain tissue was significantly increased. However, other studies [31] have suggested that fibrinogen is an independent risk factor for WMH in patients with CADASIL but not in patients with the sporadic small-vessel disease.

4. Immune-related markers

Impairment of the blood-brain barrier integrity and extravasation of plasma components may simultaneously activate the immune response, resulting in oligodendrocyte and neuronal cell

damage. On the one hand, systemic inflammatory markers such as IL-6, c-reactive protein, and neopterin are related to CSVD and can activate monocytes and macrophages; on the other hand, In the pathogenesis of arteriosclerosis, monocyte-derived macrophages play a decisive role. Suggested that immunomodulation may be a new therapeutic strategy to improve the prognosis of patients with CSVD

4.1 Monocytes

hs-CRP has been found to promote monocyte adhesion to endothelial cells ; the enhanced adhesion of monocytes to endothelial cells is a precursor to arteriosclerosis [32].Noz [33.34]found that the immune characteristics of monocytes are related to the severity of CSVD and the progression of the disease. Suggests that the immune system is crucial in arteriosclerosis cardiovascular disease.

4.2 T cells and NK Cells

T cells and NK Cells [35] have prima facie evidence that CSVD can participate in brain injury through humoral immune responses and that the immune system contributes to the initiation and progression of the disease. However, due to the lack of appropriate research models, Further exploration is limited. Use Spontaneous hypertensive rats [36] (SHR) as models of early-onset CSVD. The magnetic resonance imaging showed brain atrophy and reduced white matter volume. Flow cytometry and histological analysis found that the number of T cells and NK cells increased significantly in the small cerebral vascular system of SHR. Suggesting that T cells and NK cells are not only directly involved in endothelial dysfunction but also play an essential role in the pathogenesis of SHR.

4.3 Vascular-related microglia

Vascular-related microglia(VAM)is involved in the pathophysiological processes of synaptic pruning, maturation, Some scholars [37] believe that the rapid recruitment of VAM at the site of vascular injury can close the blood-brain barrier leakage. Takashi Koizum [38] suggested that the rapid mobilization of microglia after ischemic injury suggests that VAM may be the first cell to initiate BBB repair early in injury, and activation precedes BBB dysfunction. An experimental model of transient middle cerebral artery occlusion reached A similar conclusion[39].

4.4 Triggering receptor expressed on myeloid cells 2

Triggering receptor expressed on myeloid cells 2 （TREM2） can regulate its activation, inflammation and other functions. It regulates anti-inflammatory microglia activation and pro-inflammatory response in Alzheimer's disease [40]. Evidence[41] supports that the presence of soluble TREM2 in cerebrospinal fluid may act as a surrogate biomarker of microglia activation in many Neurodegeneration. Activation of TREM2 may be a significant cause of blood-brain barrier dysfunction, and Tsai H study [42] showed that plasma-soluble TREM2 was significantly correlated with WMH, suggesting that plasma-soluble TREM2 could be a powerful predictive marker of WMH, proposing a new idea of targeted therapy for the innate immune response.

5. Genetic related factors

Some scholars[43] studied the genetic research of CSVD in recent years and found that sporadic CSVD showed a high degree of genetic characteristics, especially in young stroke patients, and

proposed that there might be a common mechanism between the genes of sporadic and hereditary CSVD[14].

5.1 NOTCH3 protein

As the most common single gene CSVD, NOTCH3 protein CADASIL is often manifested as a recurrent subcortical ischemic attack. The progression of the disease can also lead to dementia, migraine aura, and other symptoms. NOTCH3 mutation can lead to the accumulation of granular osmotic substances[44.45], the thickening of the vascular wall, the narrowing of the arteriole lumen, and the dysfunction of cerebral autoregulation. Joutel[46]confirmed the correlation between NOTCH3 and CSVD.So far, NOTCH3 DNA sequencing has become the gold standard for diagnosing CADASIL and has 100% specificity in detecting the number of mutations of cysteine residues.

5.2 High character requirement protein A1(HTRA1)

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is rarer than CADASIL, which can be caused by HTRA1 gene mutation and is more common in young people. Some clinical manifestations of the two are similar. However, CARASIL encephalopathy starts earlier, often presenting with progressive impairment of brain function, and may appear as dry skin disease, alopecia, hunchback, deformation of cervical spondylosis, and other symptoms outside the nervous system.

5.3 COL4A1/COL4A2

COL4A1 and COL4A2 genes. The collagen chains a1 and a2[47] encoded by them are the main components of the vascular basement membrane. Dominant missense mutation of COL4A1/COL4A2 leads to rare familial CSVD, and imaging manifestations include WMH and CMBs. A meta-analysis13 proposed for the first time that there was a significant association between an intron in COL4A2 and deep cerebral hemorrhage. Ilaria Di Donato15 also found that the variation of double allele COLGA1T1 may be related to CSVD caused by COL4A1/COL4A2.

5.4 TREX1 protein

TREX1 protein with abnormal activity can cause retinal vasculopathy with cerebral leukoencephalopathy (RVCL). A cross-sectional study[48] in the Netherlands concluded that retinal vasculopathy was significantly correlated with WMH, suggesting that fundus examination could provide predictive information for WMH

6. Discussion

With the attention paid to CSVD, there are more and more studies on biomarkers of CSVD. However, no mature research has found specific biomarkers of CSVD in study. On the one hand, the disease early lacks specific performance, On the other hand, due to the existence of the blood-brain barrier, it is challenging to detect peripheral blood by conventional means accurately. The large vessel occlusion/stenosis model is still the most widely accepted and applied experimental model. At the same time, in addition to structural anatomy MRI, new imaging methods such as diffusion tensor imaging (DTI) and voxel-based voxel-based morphology (VBM) can quantitatively analyze the small changes in brain structure, find hidden brain structure damage,

and make it possible to objectively evaluate the early changes in living brain structure. To explore more specific biological markers and development of CSVD by associating imaging features, pathological mechanisms, serum markers, and Epigenetics to provide new ideas for the early diagnosis, course monitoring, and medication evaluation of CSVD.

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