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Progress in the Pathogenesis of Cerebral Small Vessel Disease

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Abstract: *Cerebral small vessel disease (CSVD) is a common cause of small vessel damage in the brain caused by various etiologies, and is a common cause of stroke and cognitive impairment in the elderly. Although its pathogenesis is not yet clear, this article aims to provide a solid reference for clinical diagnosis and treatment by delving into the possible causes and pathogenesis of CSVD. We hope to provide more accurate diagnosis and treatment plans for CSVD patients through continuous research.*

Keywords: *cerebral small vessel disease; pathogeny; pathogenesis mechanism*

1. Background

Cerebral small vessel disease (CSVD) is a complex neurological disorder that involves a series of clinical, imaging, and pathological syndromes affecting small arteries, microarterioles, capillaries, microvessels, and small veins in the brain[1]. In recent years, with the new understanding brought by some studies, cerebral small vessels include not only the above small vessels, but also the vascular structures in the brain parenchyma and subarachnoid space of 2-5 mm around these small vessels[2]. It makes our understanding of this disease more complete. It is noteworthy that the prevalence of CSVD increases with age, especially in the elderly population, where it even exceeds the prevalence of stroke. This means that CSVD has gradually become the main culprit affecting the cognitive function and living ability of the elderly with the aging of the population[3]. However, the current status of CSVD diagnosis and treatment is not encouraging. Due to the insidious onset of the disease and the lack of early symptoms, the best time for treatment is often missed. At the same time, because the etiology and pathogenesis of CSVD are not fully understood, the results of existing treatments are often unsatisfactory. This condition not only brings great physical and mental pain to the patients, but also creates a heavy economic burden on the family and society. Therefore, it is necessary to conduct in-depth research on CSVD with a view to finding more effective treatments and preventive strategies. This is not only to alleviate the sufferings of patients, but also to cope with the worsening problem of an ageing population and to alleviate the burden on families and society.

CSVD is strongly associated with a wide range of neuropsychological symptoms, including emotional apathy, mood instability and depression. These symptoms may occur in the absence of an obvious cerebral infarction, so early recognition of CSVD is critical[4]. It is worth noting that older adults often co-exist with CSVD when they present with gait disorders. Studies have shown a strong causal relationship between gait disturbance and cerebral white matter damage in CSVD. Damage to the brain's white matter not only leads to a decrease in the efficiency of transmission of whole-brain networks[5], which in turn correlates with gait decline, And it reflects the disruption of white matter pathways in complex brain networks[6]. Therefore, we should have a high suspicion of the possibility of CSVD for neuropsychological symptoms and gait disorders in the elderly, and provide timely diagnosis and treatment.

Various magnetic resonance imaging (MRI) markers play a crucial role in the diagnosis and study of cerebral small vessel disease (CSVD). Among them, new-onset subcortical infarction (SI), lacunar infarction (LI), enlarged perivascular spaces (EPVS), white matter hyperintensities (WMHs), cerebral microbleeds (CMBs), and cerebral atrophy are closely associated with impaired gait[7]. Specifically, SI was defined as a recent cerebral infarction less than 2 cm in diameter on diffusion-weighted imaging magnetic resonance sequences (DWI) [8]. LI, refers to lacunar infarcts that are located in the basal ganglia or white matter region and are 3 to 15 mm in size. EPVS, are small penetrating interstitial fluid-filled cavities around blood vessels, which play an important role in removing fluid and waste products

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from the body[8]. The WMH, was demonstrated as a fused region in the white matter of the cerebral hemispheres on MRI and showed high signal features on T2-weighted and FLAIR imaging[9]. As for CMBs, which are areas of focal ferritin deposition, susceptibility weighted imaging (SWI) is currently the method of choice for the assessment of CMBs, and its detection sensitivity is also affected by the MRI field strength, with 7T MRI having a higher detection rate compared to 3T MRI[10]. These MRI markers not only provide us with important clues for the diagnosis of CSVD, but are also key to our understanding of the relationship between CSVD and impaired gait. Through the in-depth study of these markers, we will be able to better understand the pathogenesis of CSVD, and thus provide more precise therapeutic strategies for the clinic. At the same time, with the continuous development and innovation of MRI technology, our understanding of CSVD will surely deepen along with it, so as to protect the health of the elderly.

2. CSVD Etiology

In 2010, Italian academic Pantoni presented an exhaustive report that meticulously classified CSVD into six categories based on etiology[9]. Each of these categories, small atherosclerotic CSVD, disseminated and hereditary cerebral amyloid angiopathy, other hereditary small-vessel disease, inflammatory/immune-mediated small-vessel disease, CSVD secondary to venous collagenous disorders, and CSVDs of other aetiologies such as radiculoencephalopathy, has its own distinctive characteristics and pathomechanisms. CSVD pathological changes are predominantly small atherosclerotic arteries and cerebral amyloid angiopathy (CAA) [11]. Small atherosclerotic CSVD, also known as age-associated CSVD, is largely influenced by a variety of vascular risk factors, such as aging and hypertension. Common pathological changes in this pathological process include fibrinoid necrosis, vitreous degeneration, and microatherosclerosis, which together contribute to the ageing and hardening of blood vessels. In the case of disseminated and hereditary cerebral amyloid angiopathy, the cause of the disease is the gradual deposition of β-amyloid proteins in the middle and outer layers of the walls of the soft meninges and small cortical vessels. This deposition not only triggers structural changes in the blood vessels, but also leads to the development of recurrent multiple lobar haemorrhages, cognitive deficits, and psycho-behavioural abnormalities. As for other hereditary small-vessel diseases, it includes a series of cerebral small-vessel diseases with hereditary characteristics, such as CADASIL(cerebral autosomal dominant arteriopathy with sub-cortical infarct and leukoencephalopathy), CARASIL (cerebral autosomalrecessive arteriopathy with subcortical infarcts and leucoencephalopathy), Fabry's disease, and so on. These diseases all stem from specific genetic mutations that lead to pathological changes in small blood vessels. In addition, inflammatory/immune-mediated small-vessel disease, a group of small-vessel disorders mediated by inflammation and immune response, includes diseases such as Sneddon syndrome and Wegger's granulomatosis. The main pathophysiological change in CSVD secondary to venous collagenous disease is collagenous hyperplasia around the paraventricular veins, which can lead to an increase in hydrostatic pressure around the vessels, which in turn affects blood return, resulting in perivascular circulatory obstruction of the small blood vessels and reduced cerebral perfusion. Finally, other causes of CSVD, which includes diseases such as radiation encephalopathy. Radiation encephalopathy is mainly due to the effects of radiotherapy on the small blood vessels in the white matter of the brain, leading to the development of diffuse white matter encephalopathy and myelin degeneration. Although we can clearly understand the etiological typing of CSVD through pathological examination, brain tissue biopsy is limited in clinical application, which undoubtedly poses a great challenge to clinical diagnosis and treatment as well as related research.

3. CSVD Pathogenesis

The pathogenesis of CSVD is still unclear[12]. Previous studies have revealed a strong association between CSVD and cognitive impairment. In non-amyloid CSVD, using DTI and fibre bundle imaging, the scientists found that the complex white matter network was disrupted. In addition, tomographic studies have further demonstrated the involvement of this network damage in the cognitive effects of WMH, lacunar and diffuse white matter damage[13]. In recent years, academics have preferred to view CSVD as a whole-brain dynamic disease rather than a single pathological process[4].Current research focuses on a variety of factors including chronic ischaemia/hypoperfusion, blood-brain barrier disruption, vascular endothelial dysfunction, impaired interstitial fluid return, inflammatory responses, and genetic factors. These factors may combine to contribute to the onset and progression of CSVD. Although our understanding of CSVD is not yet in-depth, with the advancement of science and

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technology and the depth of research, we believe that in the future we will be able to understand this complex disease more comprehensively and provide more effective treatments for patients.

3.1 Chronic Ischaemia/Low Perfusion

The brain, a vital organ in human life, accounts for one-fifth of the oxygen consumed in the resting state. Hypoxia is a key factor in the development of neurological disorders. Especially in the complex condition of CSVD, the role played by hypoxia cannot be ignored. Numerous studies have pointed out the pivotal role of cerebral blood flow hypoperfusion and chronic cerebral ischaemia in the pathogenesis of CSVD. From atherosclerosis, cerebral amyloid angiopathy (CAA) to venous collagen disease, these pathological changes in CSVD may not only cause stenosis of the lumen, but furthermore lead to abnormalities in the autoregulation of cerebral blood flow, which can severely affect the blood supply to the brain. Of particular note is the fact that capillary endothelial cells are particularly vulnerable in this environment, where they are susceptible to the double whammy of high shear and low perfusion, a whammy that in turn exacerbates cerebral ischaemia. A prolonged state of hypoperfusion can even induce marked changes in morphological small vessels, such as thickening of the capillary wall and increased fibrosis, which are distinctive features of human CSVD[9]. The damage that hypoxia does to the brain is not just limited to its effect on the blood supply. It also accelerates the aging process in the brain by increasing oxidative stress, inflammation, and mitochondrial dysfunction, which can lead to a host of neurodegenerative problems[14]. More importantly, persistent cerebral hypoperfusion is thought to be a key factor in white matter attenuation, which is both strongly associated with Alzheimer's disease (AD) and a common feature of CSVD-associated dementia[15]. Recent studies have gone a step further by examining rodent models of white matter ischaemia, revealing a new pathway linking inadequate perfusion and hypoxia to blood-brain barrier (BBB) disruption and inflammation[16]. This undoubtedly provides new ideas for us to gain a deeper understanding of the pathogenesis of CSVD, as well as to find effective therapeutic strategies.

3.2 Blood Brain Barrier (BBB) Disruption

Disruption of the blood-brain barrier (BBB) is a key component of neurological disorders and is closely linked to the onset and progression of brain diseases. The blood-brain barrier (BBB), a neurovascular unit (NVU) [17]made up of brain endothelial cells, pericytes, glial cells, basement membranes and neurons, it's an indispensable protective layer for the central nervous system. Its presence ensures the stability of the microenvironment of the central nervous system and provides a suitable place for neurons to survive and function. When the extracellular matrix and matrix bodies are damaged, BBB permeability increases and vascular responses are impaired[18]. Some evidence suggests that the function of the blood-brain barrier declines exponentially, rather than linearly, with age[19], blood-brain barrier permeability is almost twice as high in patients aged 70-80 years compared with those under 70 years, and the increase in blood-brain barrier permeability per decade up to the age of 60 years may not be as pronounced as in those over 60 years of age[2]. Not only does this change increase the risk of brain damage, it is also strongly associated with a decline in cognitive function. BBB dysfunction manifests itself in a variety of ways, including altered paracellular and transcellular transport, reduced tight junction proteins, basement membrane abnormalities, and pericyte dysfunction. These changes lead to increased plasma protein leakage and leukocyte infiltration of the brain parenchyma, which in turn triggers glial cell activation, demyelination and neurodegeneration[20]. Amyloid also increases BBB permeability[21], this provides a possible explanation for our understanding of the altered BBB permeability detected in patients with Alzheimer's disease[19]. In CSVD, the observed structural anomalies further reduce the integrity of the BBB. Indeed, the destruction of the BBB in the region predicts the evolution of the WMH. Neuroimaging studies also showed that BBB leakage was greater in WMH areas than in normal white matter areas and showed a positive correlation with severity of WMH, age and hypertension[22]. This means that the integrity and proper functioning of the BBB is essential to maintain its permeability. In summary, the destruction and increased permeability of the BBB not only plays a key role in the aging process in normal humans, but is also an important factor in the pathogenesis of CSVD. They are strongly associated with brain damage in patients with CSVD and may be a key factor leading to high signal changes in brain white matter on imaging and concurrent cognitive dysfunction[23], the higher the permeability of the blood-brain barrier, the higher the degree of cerebral white matter high-signal loading, the more pronounced the decline in cognitive function and the worse the prognosis for the patient.

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3.3 Vascular Endothelial Dysfunction

Damage to the cerebrovascular endothelium increases with age and becomes a key factor in the increased permeability of the blood-brain barrier. This endothelial failure or exogenous injury may have more serious consequences[24]. In addition to normal ageing, many non-specific factors whose mechanisms have not been elucidated affect the cerebrovascular endothelium[25]. For example, in experimental models, non-specific peripheral pain (e.g., footpad pain in rats) increases blood-brain barrier permeability[26].

Vascular endothelial dysfunction is a possible mechanism contributing to the development of chronic cerebrovascular disease. Studies have shown that cerebrovascular endothelial cell dysfunction has a variety of manifestations, including blood-brain barrier dysfunction, impaired vasodilatation, and vascular sclerosis[27-28]. In brain tissue, endothelial cells are key components in the construction of the blood-brain barrier and the neurovascular unit (NVU), and play an important role in maintaining homeostasis of the brain's internal environment. Brain microvascular endothelial cells are rich in unique protein components with multiple functions such as ion channels, receptors and enzyme barriers[29], these cells are commonly used to explore the pathogenesis of stroke, to delay cerebral atherosclerosis, and to construct BBB models. Cerebral white matter lesions and intracranial microhaemorrhagic foci in CSVD are thought to be associated with endothelial dysfunction, which correlates with the severity of cerebrovascular disease and vascular risk factors in chronic cerebrovascular disease patients[30]. Endothelial dysfunction has been found to be one of the major causes of CSVD brain white matter vulnerability and may be a key link in the development of CSVD. Experiments have shown that functionally impaired vascular endothelial cells secrete heat shock protein 90α, leading to damage to myelin, and that this lesion can be reversed by pharmacological treatment that stabilises vascular endothelial cells, providing a new strategy for disease treatment. These findings are also potentially applicable to the treatment of human CSVD. Therefore, by thoroughly investigating the role of vascular endothelial dysfunction in the pathogenesis of CSVD, new ideas and methods can be provided for the prevention and treatment of CSVD. Looking forward, we can further explore the specific mechanism of vascular endothelial cells' role in CSVD and develop more effective therapeutic strategies to bring better clinical outcomes and quality of life for CSVD patients[31].

3.4 Inflammation Response

Inflammatory or immune-mediated small vessel disease is often caused by systemic systemic diseases such as vasculitis and systemic lupus erythematosus. Unlike acute inflammation, the inflammatory response in chronic cerebral small vessel disease is due to low levels of inflammatory mediators produced by immune cells stimulated by risk factors, including interleukins, tumour necrosis factor (TNF-α), and C-reactive protein (CRP). The rise in these pro-inflammatory mediators activates immune and inflammatory cells, leading to the production of more inflammatory mediators, which in turn creates a systemic pro-inflammatory environment. Vascular inflammation can lead to oxidative stress, vascular endothelial dysfunction, disruption of the blood-brain barrier, atherosclerotic plaque formation, and lumen narrowing, ultimately contributing to CSVD. Vascular inflammation has been found to be associated with CSVD in deep penetrating artery-fed brain regions such as the basal ganglia. Elevated macrophage-derived pro-inflammatory enzyme lipoprotein phospholipase A2 has been shown to be a risk factor for white matter high signal foci (WMH), cardiovascular disease and stroke[32]. In addition, elevated levels of systemic inflammatory markers, such as C-reactive protein and interleukin-6, are likely to predict the severity and progression of CSVD. The inflammatory response plays a crucial role in the development of CSVD. Studies have shown that altered cytokine levels may lead to vascular endothelial cell damage, contributing to nerve fibre demyelinating lesions and exacerbating the progression of CSVD[27.33.34]. Several studies have shown that minocycline has anti-inflammatory properties in the brain, promising to reduce activation of cerebellar glial cells and effectively stabilise the blood-brain barrier. In summary, the development of CSVD is directly influenced by vascular inflammation, with the production and release of inflammatory mediators contributing to disease progression. Therefore, focusing on the inflammatory response and its regulatory mechanisms is important for the prevention and treatment of CSVD. By gaining a better understanding of the inflammatory process, CSVD can be intervened and managed more effectively, reducing its adverse effects on patients and improving treatment outcomes.

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3.5 Hereditary Factor

Although hereditary SVD types such as CADASIL, CARASIL, and Fabry disease have been identified, there is little insight into the genetic underpinnings of most CSVDs. One common single-gene cerebral small-vessel disease is CADASIL, whose gene is localised to the NOTCH3 gene region at 19p13.2-13.1. Although a large number of studies have been conducted in the past on monogenic inheritance of CSVD, a genetic predisposition has only been found in about 5% of patients with CSVD[35]. Through proteomic and biochemical studies, it has been found that impaired function of the extracellular matrix plays an important role in patients with CSVD. Recent studies have shown that type IV collagen, an important component of the extracellular matrix that maintains the aggregation of NOTCH3 genes and alters signalling between molecules, plays an important role in patients with hereditary and sporadic CSVD[36]. A meta-analysis revealed that mutations in the type IV collagen gene αl may cause familial vasculopathy, which manifests itself on imaging as cerebral leukoaraiosis (LA) and CMB, and is strongly associated with CSVD progression[37]. This finding provides important clues and guidance for further research and diagnosis of CSVD patients. In summary, in-depth research on the genetic mechanism of cerebral small vessel disease such as CSVD is of great significance, which helps to better understand the process of disease occurrence and development, and provides a theoretical basis for early diagnosis, intervention and treatment of patients. In future studies, the genetic basis of CSVD should be further explored and combined with clinical practice to provide more effective strategies and methods for the prevention and treatment of this type of hereditary cerebral small vessel disease.

3.6 Poor Drainage of Interstitial or Cerebrospinal Fluid

Pathological changes in the perivascular space play an important role in the pathogenesis of cerebral infarction. Abnormal dilatation of the perivascular space may represent an obstruction to fluid flow around the cerebral vasculature, ultimately leading to impaired clearance of interstitial fluid[38]. In addition, disruption of glial lymphatic pathways can also negatively affect the elimination of waste products from the brain, leading to the accumulation of harmful proteins or cellular debris in the brain and exacerbating the cognitive deficits associated with cerebrovascular diseases[39]. In the presence of impaired drainage pathways around the arterial wall, the white matter PVS may expand and contribute to CAA formation. Recent studies have found that diffusion tensor imaging analysis indices along the perivascular gap reflect clearance by the cerebral lymphatic system, with values that negatively correlate with imaging features of cerebrovascular disease[40]. In addition, AQP4 in astrocytes plays a key role in maintaining brain water homeostasis and the lymphatic clearance system. Abnormal localisation or reduction of AQP4 in white matter tissue of CSVD patients may adversely affect the development of cerebrovascular disease[41]. The in-depth study of these pathophysiological processes may provide new ideas and methods for the treatment and prevention of cerebrovascular diseases.

4. Summary

CSVD has received much attention in recent years, and an in-depth understanding of its various aspects is vital for clinicians. Research on etiology, pathogenesis, etc. is the basis for improving the diagnosis and treatment of CSVD and laying a theoretical foundation for early intervention. Therefore, a comprehensive understanding of the pathophysiology, clinical manifestations, diagnosis and treatment of CSVD is essential for front-line clinicians. It is only through in-depth research that we can better improve our understanding of the disease, thereby achieving better results in clinical practice and early effective intervention and treatment of CSVD.

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