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Cerebral microvascular disease and its associated cognitive dysfunction research progress

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Abstract: *Cerebral small vessel disease is a kind of aging cerebral microvascular disease, accounting for 83.8% of all cerebrovascular diseases, and gradually become an important disease affecting human health. When cerebral small vascular disease is in the early stage, the damage to cognitive function is not obvious, and the onset is often hidden.With the further development of the disease, cognitive and behavioral dysfunction gradually appears, which can eventually cause dementia and seriously decline the quality of life of patients. Early diagnosis and intervention are of great value in controlling the cognitive impairment caused by CSVD and even preventing the occurrence of dementia. The potential benefits of TCM in the treatment of cognitive dysfunction in CSVD, which provides novel insights for the treatment of small cerebral vascular disease-related cognitive impairment. Integrated Traditional Chinese and Western medicine (TCM-WM) treatment is the trend in the development of the complementary benefits of TCM-WM treatment in the future.This article has reviewed the cognitive impairments associated with CSVD in order to provide a reference for clinical diagnosis and prevention of CSVD.*

Keywords: *cerebral small vessel disease; cognitive dysfunction; traditional Chinese and western medicine; research progress*

1. Introduction

Cerebrobral microvascular disease is a kind of cerebral microvascular disease closely related to age, and the probability of developing cerebral microvascular disease will be greatly increased with age. A study in Rotterdam showed that CSVD accounted for 83.8% of all cerebrovascular diseases, and epidemiological surveys found that about half of dementia and a quarter of ischemic stroke worldwide were [1-2] caused by cerebral small vessel disease. In recent years, the incidence of CSVD is increasing, and the incidence forms are increasingly diversified, and CSVD has gradually become an important threat to human health. The decline of cognitive function is a large group of neurological syndromes associated with memory, language, recognition, logical thinking, orientation or other mild cognitive impairment. The manifestations of cognitive impairment can be single region or multi-region, and the onset of various forms. Cognitive dysfunction is one of the important clinical symptoms of CSVD, cerebral small vascular disease early hidden, easily overlooked, with the further development of the disease, gradually appear cognitive and behavioral dysfunction, and eventually can cause dementia, seriously affect the quality of life of patients after disease, also makes CSVC become one of the common causes of disability in the elderly. Early definition of the relationship between cerebral small vessel disease and cognitive dysfunction is of great value for controlling the cognitive impairment caused by CSVD and even preventing the occurrence of dementia. Summary of cerebral small vessel disease existing research progress of traditional Chinese and western medicine for further study of cerebral small vessel disease related cognitive disorders is significant, this paper reviewed in recent years CSVD induced cognitive dysfunction related to traditional Chinese and western medicine literature, review the main research results, in order to clinical guidance CSVD high-risk groups for more accurate individualized diagnosis and prevention to provide reference. The proportion of CSVD in all cerebrovascular diseases is shown in Figure 1.

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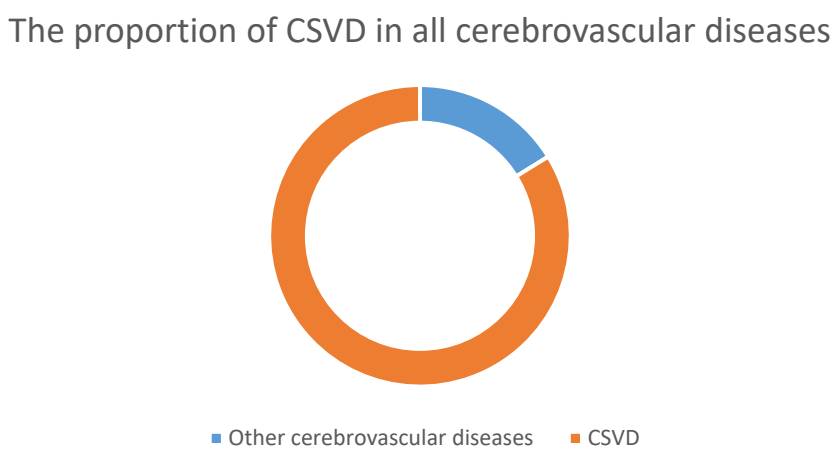

Figure 1: The proportion of CSVD in all cerebrovascular diseases

2. Definition and classification of CSVD

From an anatomical perspective, cerebral small vessels include tiny arteries, small arteries and venules with diameters of 40-200 μm. These slender pipes travel between brain tissue, forming the most complex and large blood supply network in the body. On this basis, CSVD generally refers to a series of characteristic clinical symptoms and nervous system diseases, caused by microscopic and imaging diseases in the brain. CSVD can be divided into six types according to pathology and etiology: type I: small artery sclerosis or small vessel disease related to age and vascular risk factors; type II: sporadic and hereditary cerebral amyloid vascular disease; type III: different from cerebral amyloid vascular disease, it is a genetic small vessel disease, such as autosomal dominant hereditary cerebral artery disease with subcortical infarction, leukoencephalopathy; type IV: inflammatory and immune-mediated small vessel disease; type IV: intravenous collagen disease; type VI: other types of small vessel disease [3-4]. At present, in view of the high complexity of brain tissue and the observed limitations of external detection methods, the diagnosis and differential diagnosis of CSVD is mainly based on imaging data. Recent small subcortical infarction (RSSI), vascular space, white matter lesions (WMH), cerebral microhemorrhage (CMBs), the enlarged peripheral vascular space (EPVS) and brain atrophy [5]. Patients with different types of CSVD may have two or more imaging findings, and the degree of cognitive dysfunction in patients also varies with [6]. The clinical features of cognitive impairment in the CSVD type is shown in Table 1 and the CSVD imaging classification is shown in Figure 2.

Table 1: Clinical features of cognitive impairment in the CSVD type

Clinical features of cognitive impairment in the CSVD type	(1) With no history of stroke, or transient stroke manifestations but rapid recovery. Cognitive impairment gradually starts and progressed slowly.
	(2) The clinical manifestations are slow response, slow speech, thinking, slow initiation, planning, organization, and abstract thinking, and decreased attention.
	(3) Imaging showed diffuse white matter changes in the periventricular and deep white matter and / or multiple lacunar cerebral infarction, multiple cortical / subcortical microhemorrhages, and hemosiderin deposits on the cortical surface.
	(4) Early gait changes, such as gait instability, dragging gait or broken steps, bradykinesia, mild increased muscle tone, or early onset of frequent urination, urgency, and other urinary symptoms that cannot be explained by urinary system or other neurological diseases.
	(5) Can be accompanied by depression, emotional indifference, lack of initiative, social activity withdrawal, personality characteristics changes, emotional instability and other emotional behavior symptoms

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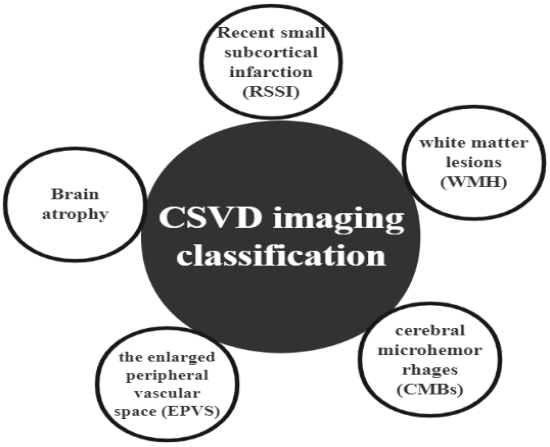

Figure 2: CSVD imaging classification

3. The pathogenesis of cognitive dysfunction triggered by CSVD

The pathogenesis of CSVD is inconclusive, and the principle of the occurrence of cognitive dysfunction remains to be studied. Up to now, a large number of studies have believed that the pathogenesis of CSVD and its relationship with the occurrence of cognitive dysfunction may be related to the following processes. The assessment of cognitive domains and recommend evaluation tools is shown in Table 2.

Table 2: Assessment of cognitive domains and recommend evaluation tools

Assessment of cognitive domains	Recommend evaluation tools
Cognitive function screening	MOCA
Assessment of living ability	IADL
Working memory	digit span test
Information processing speed	TMT-A
Note / perform the function test	Stroop Test,TMT-A
Memory	HVLT
Language	The aphasia test, The Boston naming test
Visual space function test	Copy the cube Test, CDT

3.1. Focal brain ischemia and disruption of blood-brain barrier (BBB)

The damage and structural changes in the cortical function of the cortex of small blood vessels in the brain can directly form a hypoperfusion of cerebral blood flow. In the long run, ischemic changes in brain tissue appear [7]. The endothelial smooth muscle cells of the blood vessel wall gradually fail under the influence of this lesion, which further reduces the blood flow and then aggravates the injury. Such long-term chronic ischemic changes and acute occlusion of small blood vessels in the brain will cause different degrees of ischemia of the brain tissue in the blood supply area, causing damage to the neuronal function, thus causing CSVD through a variety of mechanisms. The destruction of BBB is closely related to the occurrence of CSVD [8]. The physiological mechanism of BBB forms a barrier to protect the brain tissue. When this barrier is damaged, the BBB permeability will increase, and the structure and function of endothelial cells will be damaged to varying degrees, leading to the vascular wall and surrounding brain parenchyma, and even induce secondary perivascular edema and nerve cell damage. Munoz et al. [9] found that in the overall pathology of cognitive impairment, impaired BBB increased the total WMH burden, and this pathological impairment is involved in the pathogenesis of CSVD.hypothesis that [10], the risk factors such as age, high blood pressure will weaken the cerebral blood flow self-regulation ability, cerebral arterioles have to higher blood flow speed and greater flow beat to deal with, the change of the shear force will make BBB permeability change, further cause BBB endothelial damage, this damage is also one of the main pathogenesis of CSVD [11].

3.2. Inflammatory changes

Inflammatory changes are considered to be one of the secondary damage caused by cerebral

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ischemia. The ischemic focus of ischemic brain tissue and its surrounding areas will be infiltrated by inflammatory cells. When tissue reperfusion, inflammatory factors will be triggered to produce inflammatory metabolites, thus inducing vascular endothelial damage, occluding blood vessels, leading to blocked blood flow [12]. Such responses will increase the extent of vascular cognitive impairment to some extent. However, further research is needed to confirm the relationship between inflammatory factors and cognitive impairment caused by such reflection.

3.3. Others

In numerous mechanisms, the current mainly brain tissue focal ischemia and BBB destruction of the change, inflammation for the core of CSVD induced cognitive dysfunction, in addition, brain tissue ischemic change late apoptosis [13], excessive release of nitric oxide neurotoxicity [14], excitatory amino acid irreversible damage to neurons, brain tissue ischemia large oxygen radical attack biological membrane damage brain tissue neuronal autolysis, neurotransmitter acetylcholine pathway damage may also be involved in the process of CSVD induced cognitive dysfunction. The diagnosis process for CSVD is shown in Figure 3.

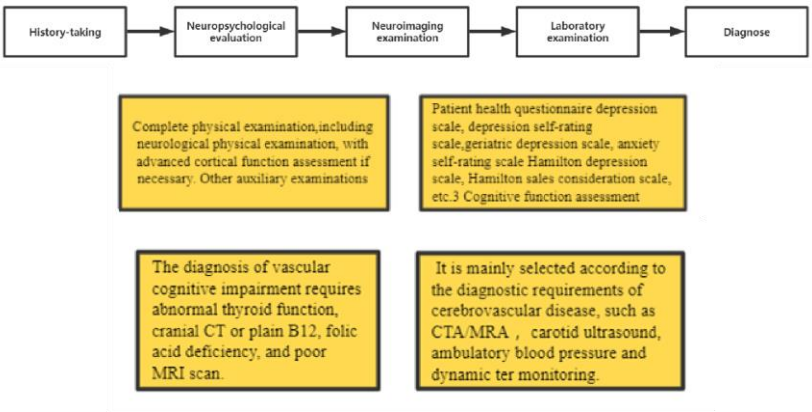

Figure 3: Diagnosis process for CSVD

4. CSVD imaging classification and cognitive dysfunction

4.1. Lacunar infarction and cognitive dysfunction

Lacunar infarction is an important part of CSVD, is considered to be one of the earliest signals of cognitive dysfunction after stroke, and when this kind of lesions accumulated to a certain extent, there will be lacunar infarction this specific CSVD focal performance, further progress, will cause damage to cognitive function. After long-term clinical treatment experience and observation, it is found that lacunar infarction is impaired executive function, which is the decrease of movement and processing speed, while the memory ability is relatively preserved, and some patients can also show abnormal symptoms such as apathy [15]. Cognitive impairment is closely related to the number, area and location of infarct areas, and the degree of cognitive impairment in a specific area can lead to different degrees [16-17]. The clinical manifestations of cognitive impairment caused by different infarct sites also vary: the fornix is closely related to memory, and the involvement of this area can seriously affect the anterograde memory ability [18]. Involvement of the corpus callosum causes different degrees of reading loss [19]. Lacunar infarction in the internal capsule can show signs of frontal lobe function impairment, such as indifference, distraction, and slow psychomotor symptoms [20]. Lacunar infarction itself causes damage to the frontal subcortical fiber junction, which is involved in the regulation of multiple cognitive domains and increases the risk of dementia by more than one-fold [21].

4.2. White matter hyperintense signal (WMH) and cognitive dysfunction

WMH is mostly distributed in the basal ganglia and centrum semiovale regions, and such lesions disrupt the fiber bundles of cholinergic neurons and damage the white matter fiber bundles of the brain, leading to a reduction in the connections between nerve fibers related to concentration and a disruption of the cognitive network integrity of the brain. This process is closely related to learning, memory, and other cognitive functions in physiology [22], which seriously affects the systemic cognitive and effective

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processing of information in the brain. This process severely affects the systemic cognitive and effective information processing functions of the brain, resulting in varying degrees of impairment in patients' executive ability, attention and speed of information processing, and ultimately cognitive impairment [23-24]. WMH onset location, lesion size and cognitive impairment occurrence are correlated. Hairu et al. [25] suggested that the size of WHM foci was related with decreased executive ability, and the larger the volume of WMH, the more pronounced the cognitive representation deficit in this region [26]. WMH can be classified into periventricular WMH in the adjacent location and WMH in the deep subcortical white matter near the lateral ventricles. Because periventricular nerve fibers link the cortex to subcortex and other more distant brain regions, and are more susceptible to fluid mechanics changes in distal arteries, cognitive functional impairment induced by periventricular WMH is more pronounced than impairment in non-periventricular areas [27-28]. Biesbroek et al. [19] identified prethalamic radiation and WMH in the corpus callosum area as one of the main symptoms of imaging pathological changes resulting in reduced execution, memory and visual motor speed. Moreover, poor clinical performance of executive function and processing speed can also be associated with hyperintensity in subfrontal cortex or interhemispheric white matter, and WMH located in the temporal lobe, parieto-occipital white matter and corpus callosum is associated with memory impairment, while deep WMH is associated with depressive symptoms [28]. In addition, in addition to different degrees of cognitive impairment accompanied by different degrees of affective disorders, it is also closely related to the onset of Alzheimer's disease (AD), the disease will eventually induce AD, especially parietal WMH, which is considered to be an independent predictor of AD onset [16]. As one of the early warning signs of cognitive impairment, WMH can be used as one of the early prevention and treatment bases of vascular dementia caused by CSVD [29].

4.3. Brain perivascular space enlargement (EPVS) and cognitive dysfunction

With the growth of age, the cerebral blood vessels gradually thickened and distort, forming an enlarged perivascular space, this phenomenon is also known as the "empty phenomenon". As an important imaging marker of cerebral small blood vessel disease, EPVS indicates that specific lesions of cerebral small blood vessels damage the ability of tissues to remove waste protein, resulting in toxin accumulation, neuronal hypoxia and tissue damage [30]. EPVS is closely related to stroke, cognitive and affective disorders. High-load EPVS can damage the cortical cholinergic pathway, cause degenerative lesions of brain neurons, and lead to impaired cognitive function [31]. Huang Shan et al found that imaging changes in EPVS were relatively common in patients with cognitive dysfunction related with cerebral small vessel disease, and were considered to be an independent risk factor for cognitive dysfunction related with cerebral small vessel disease [32]. The extent of cognitive impairment caused by EPVS may be closely related to the site and amount of EPVS occurrence. Some scholars have found that EPVS at the basal segment is more likely to cause the damage of cognitive functions such as the decline of information processing speed [33], and there is a certain degree of correlation between signs such as non-literal reasoning ability and decreased visuospatial ability [34]. A study on the association of cognitive impairment induced by acute ischemic stroke and EPVS showed that EPVS in the basal ganglia could be used as an early indicator in the evaluation of cognitive impairment in patients with acute ischemic stroke [35]. Jimenez-Balado et al. [36] found that the decrease in verbal reasoning function was positively correlated with the number of EPVS on the hippocampus. On this basis, EPVS will have an impact on the cognitive level and promote the emergence of in AD [34]. Clinically, the three factors of EPVS, WMH and CMBs often appear interactively, however, the relevant data about EPVS, cognitive impairment and dementia are very limited, so the relevant research between EPVS and cognitive impairment still needs to be verified.

4.4. Cerebral microhemorrhage (CMBs) and cognitive dysfunction

Cerebral microhemorrhage is caused by the pathological changes of tiny blood vessels in the brain. The subclinical damage of the brain parenchyma is mainly characterized by minor hemorrhage. The bleeding amount of this damage is generally small, and the early clinical symptoms of small brain damage of CMBs are hidden, so it is often ignored when cognitive function is impaired. With the increasing development of medical imaging technology, the relationship between the focal damage of the nervous system and the impaired cognitive function in specific cognitive domains is becoming increasingly clear [37-38]. CMBs can cause focal damage to small brain vessels and surrounding brain tissue, and this damage may disrupt the connection between cortical and subcortical tracts and eventually become an important in inducing impaired cognitive function and the destruction of neural network integrity [39]. Yang et al. [40] found through a large number of clinical studies that patients with

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CMBs type of cerebral microvascular disease showed different degrees of cognitive impairment in logical thinking ability, memory and visual spatial cognitive ability. The manifestation of cognitive impairment in specific cognitive domains varies by the spatial location of CMBs. According to the different locations of CMBs, they can be divided into cerebral lobe microhemorrhage (SL-CMBs), deep microhemorrhage (DI-CMBs) and mixed CMBs. The Rotterdam study reported that cerebral microhemorrhage can be divided into large lobe microhemorrhage and deep lower microhemorrhage. Lobe microhemorrhage is often located in the temporal lobe of the brain, which is mostly induced by amyloid angiopathy. In the simple CMBs of the brain lobe, the decline of cognitive ability in different cognitive domains, among which, the executive ability and directional function are significantly impaired. Deep and lower bleeding, suggests that have hypertensive arteriopathy, the regional lesions can involve the deep brain hemisphere, and then affect the motor function, in addition, have deep or lower bleeding, the number of micro lesions generally more than other bleeding, and mixed bleeding frequency and probability will also increase [41]. The impaired cognitive function caused by deep or mixed CMBs is mainly manifested in memory, executive ability and information processing speed, and the decreased memory function is particularly obvious in patients with mixed CMBs [40]. To further explore the intrinsic link between deep CMBs and cognitive impairment, deep CMBs were refined into basal ganglia CMBs, thalamic CMBs, substentorial CMBs and deep CMBs [42]. Patients with CMBs in the basal ganglia have severe impairments in executive and concentration skills; patients with thalamic CMBs can experience poorer performance in attention, orientation and language functions; the correlation between impaired cognitive function and the occurrence of CMBs in patients with subscreen CMBs still needs to be confirmed by further studies. Unlike the underlying vascular lesions, CMBs may imply broader microvascular damage in addition to the cognitive domain of the specific focal sites, and the damage caused by such damage may affect broader cognitive domain function and even impair cognitive ability in the whole brain [43].

4.5. Brain atrophy and cognitive dysfunction

Cerebral atrophy caused by small blood vessel disease caused by brain atrophy and brain atrophy caused by brain trauma and infarction, this form of brain atrophy needs to be related to brain small blood vessel disease, and for the specific focal damage caused by the brain volume, MRI for groove, brain narrowing, ventricle widening, the lesions distribution, can be widespread, can also partially exist, and even organized selective. Brain atrophy caused by cerebral small vessel disease is closely related to cognitive impairment [44], and the incidence of brain atrophy is not the same clinical symptoms. The main lesions of medial temporal lobe atrophy spread to the temporal lobe, and the damage is the hippocampus. If this area is damaged, the memory, attention, execution, learning ability and other aspects are damaged to varying degrees, and these symptoms are particularly obvious in the middle-aged and elderly groups. Parietal atrophy causes decreases in attention and execution, and impaired verbal memory and learning. Basal ganglia and thalamus are the most important areas of limb movement control. This area, especially thalamic atrophy, will cause serious obstacles of movement initiation, control and learning ability [45]. Previous studies [46-47] confirmed that different imaging findings suggest dynamic interaction between CSVD lesions, such as RSSI, WMH lesions can also cause secondary brain atrophy in different degrees, means that the same cognitive domain damage may be caused by one or more imaging changes, multiple imaging changes caused by the characteristics of cognitive damage and related relationship still need to be further explored.

5. Summary and outlook

In today's post-epidemic era, the progress of the field of neuromedicine has never stopped. With the increasing development of medical technology and the research on CSVD-related cognitive dysfunction in recent years, people have further knowledge and understanding of CSVD. More and more evidence about CSVD inducing cognitive dysfunction from multiple mechanisms has emerged, and CSVD undoubtedly plays an important role in the pathogenesis of cognitive dysfunction. But there are still more controversies about the relationship between CSVD and cognitive dysfunction, and more evidence is needed to support it, and the pathogenesis of CSVD impairing cognitive function still needs to be investigated. In the future, with more studies on CSVD and cognitive dysfunction and its pathogenesis, it is hoped that the correlation between CSVD and cognitive dysfunction and the pathogenesis of CSVD damaging cognitive function can be clarified as soon as possible, so as to provide reference for more accurate and individualized diagnosis and effective prevention plan of CSVD.

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