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Cerebral small vessel disease and cognitive impairment

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ABSTRACT
Cerebral small vessel disease (CSVD) is a pathophysiological process involving small arteries such as cerebellar arteries, arterioles, capillaries, and veinlets. Imaging features vary; they are mainly composed of recent subcortical infarcts, lacunes of presumed vascular origin, white matter hyperintensities (WMHs) of presumed vascular origin, cerebral microbleeds, enlarged perivascular spaces, and global and regional brain atrophy. CSVD is a common cause of vascular cognitive dysfunction, and in its end stage, dementia often develops. CSVD has been a major research hotspot; however, its causes are poorly understood. Neuroimaging markers of CSVD can be used as the basis for etiological analysis. This review highlights the relevance of neuroimaging markers and cognitive impairment, providing a new direction for the early recognition, treatment, and prevention of cognitive dysfunction in small cerebral angiopathy.

1 Introduction
Cerebral small vessel disease (CSVD) refers to the brain’s small vessels having lesions; these lesions are noted on pathological examination or brain imaging using magnetic resonance imaging (MRI) or computed tomography (CT) [1]. Cognitive impairment and even dementia in clinical end stage may develop, but the pathogenesis is poorly understood. The current total number of patients with dementia worldwide is approximately 36 million, which is estimated to reach 66 million by 2030 and increase to approximately 110 million by 2050 [2]. In recent years, several studies found that neuroimaging results are associated with cognitive dysfunction, and can be used to predict the progression of cognitive impairment. Jokinen et al. [3] found that lacunes can cause impaired executive function and reduce psychomotor speed. A prospective cohort study [4] on 503 non-dementia patients aged 50–85 years with CSVD showed that cerebral microbleed (CMB) was associated with the early manifestation of cognitive dysfunction, particularly in non-dementia
CSVD patients with satisfactory objective cognitive performance. This review will help in understanding the relationship between various imaging markers and cognitive dysfunction, and provide new potential therapies and interventions for the treatment of cognitive impairment.

2 Cerebral small vessel disease

2.1 Overview

Cerebrovascular disease is a serious threat to human physical and mental health. It is characterized by high morbidity, high mortality, high recurrence rate, and high disability rate. It is a common cause of cerebral apoplexy, vascular cognitive dysfunction, and dementia. CSVD is a common clinical, imaging, and pathological syndrome involving the brain’s small perforating arteries, arterioles, capillaries, and venules [5] and is a significant marker of cerebrovascular disease. CSVD accounts for approximately 25% of ischemic cerebrovascular diseases [6]. The etiology, pathology, and risk factors of CSVD have become a hot topic worldwide, and the pathogenesis of CSVD remains controversial.

Different from common large vascular diseases, CSVD often involves small blood vessels in the brain. Anatomically, small blood vessels originate in cerebral arteries, including the terminal small artery, arteriole, arteriovenous anastomosis, capillaries, micro vein, and terminal venules. Small blood vessels nourish the basal ganglia and deep white matter and mark the end of brain blood circulation, also known as the terminal artery [7]. This vascular wall lacks outer membrane cells; it has vascular endothelial cells and a small number of smooth muscle cells, which are vulnerable to several factors, such as inflammation, toxin, leading to vascular damage and injury to the brain parenchyma, resulting in corresponding neurological symptoms and signs. Although vascular endothelial cells, smooth muscle cells, peripheral cells, glial cells, and neurons constitute the neurogliovascular unit and play a key role in the pathogenesis of cerebral microvascular disease, their mechanism is unclear.

Currently, CSVD diagnosis mainly depends on imaging examination. The presentation of other potential methods [8] increases the detection rate of CSVD in the elderly year after year, gradually attracting extensive attention from medical researchers. Although the medical community paid more attention on CSVD and has made great achievements in the corresponding clinical research, more studies to understand deeper details are needed.

Whether the onset of CSVD is with individual or collective is unclear, and the progress is slow. Several studies in humans identified various clinical manifestations of CSVD including ischemic or hemorrhagic stroke, cognitive impairment, dementia, abnormal gait, and mental disorder. Studies have shown that CSVD progression is associated with vascular risk factors and the increase of CSVD load, whereas cognitive dysfunction further aggravated. Therefore, targeting vascular risk factors could prevent CSVD-related brain injury and reduce cognitive impairment [9].

2.2 Clinical pathological changes and types

Based on pathological changes, CSVDs can be categorized into arteriosclerotic small vascular diseases, sporadic and hereditary cerebral amyloid angiopathy (CAA), inherited or genetic small vessel diseases distinct from cerebral amyloid angiopathy, inflammatory and immunologically mediated small vessel diseases, radioactive microangiopathy, venous collagenous disease, and other small vessel diseases [10, 11], with arteriolosclerosis and cerebral amyloid angiopathy as common types.
Arteriolosclerosis pathological changes include fibrinoid necrosis, microatheroma, microaneurysms, and segmental arterial disorganization. The pathological feature of CAA is the accumulation in small blood vessels of the cerebral cortex and pia mater [12], with the vessel wall thickened and the lumen narrowed, occluded, or dilated. They also occur in these diseases: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), hereditary multi-infarct dementia of the Swedish type, MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), Fabry’s disease, hereditary endotheliopathy with retinopathy, nephropathy, stroke, small vessel diseases caused by COL4A1 mutations constitute inherited or genetic small vessel diseases, inflammatory and immunologically mediated small vessel diseases including Wegener’s granulomatosis, Churg–Strauss syndrome, microscopic polyangiitis, Henoch–Schönlein purpura, and cryoglobulinemic vasculitis.

2.3 Pathogenesis

The pathogenesis of CSVD is unclear, and how it leads to the occurrence and development of CSVD remains inadequately understood. Endothelial dysfunction can cause increased permeability of the blood–cerebrospinal fluid (CSF) barrier which aggravates parenchymal injury [13]. Poggesi et al. [14] detected blood–CSF barrier defects in CSVD animal models with chronic cerebral perfusion insufficiency, suggesting that the blood–brain barrier (BBB) function may be impaired due to endothelial dysfunction and secondary inflammatory changes. Recent studies [15] suggested that vascular endothelial dysfunction caused by inflammatory mechanism and oxidative stress may be noted in cases with white matter lesions. Inflammatory reactions that are a cascade amplification process of and around the ischemic foci after cerebral ischemia were determined. Keith et al. [16] found that collagen deposition caused interstitial fluid reflux obstruction and increased vascular resistance, leading to cerebral perfusion insufficiency, which plays a role in the occurrence and development of CSVD. The pathogenesis of CSVD which may be related to factors such as BBB disruption, genetic factors, chronic ischemia, and inflammatory response has not been completely described.

2.3.1 Blood–brain barrier disruption

The BBB is located between the plasma and brain cells (formed by the capillary wall of the brain and glial cells), and between the plasma and CSF (formed by the choroid plexus), potentially preventing some substances (mostly harmful) from entering the brain tissue through the blood. The barrier mainly has three layers, from the inside to the outside: the endothelial cells of cerebral capillaries, the basal membrane, and the end foot of glial cells. Besides oxygen, carbon dioxide, and blood glucose, nothing can pass through the BBB. Most molecular drugs and proteins are too big to pass through the barrier.

The exact pathogenesis of CSVD is unclear, but some studies [17] have shown that blood–CSF barrier dysfunction is one of its causes. Poggesi et al. suggested that impaired cerebral small vessels may be due to endothelial dysfunction and secondary inflammatory changes [18]. The endothelial cells and basal membrane are continuous and closely connected to each other, making it difficult for certain substances in the blood to pass through. The end feet of glial cells are located around capillaries, blocking the passage of certain substances from blood vessel walls to the brain tissue. Petersen et al. reported [19] that certain blood components can pass through the impaired BBB, activating microglia, recruiting surrounding macrophages, and promoting
inflammation. A study [20] showed that BBB can be destroyed, and blood components then leak into the brain, impairing the normal neuronal function. A study conducted by Topakian et al. [21] showed that endothelial dysfunction can impair blood vessel function and blood flow regulation, leading to tissue damage.

2.3.2 Genetic factors

Genetic factors, especially genotype, are also the focus of current research. Studies suggested [22] that mutations may affect hereditary and nonhereditary CSVDs. CSVD is associated with cerebral hypoperfusion, chronic ischemia, endothelial dysfunction, genetic factors, and inflammatory response [23]. Although vascular endothelial cells, smooth muscle cells, peripheral cells, glial cells, and neurons constitute the neurogliovascular unit and play a key role in cerebral microvascular disease pathogenesis, the mechanism is unclear. A genome-wide association study [24] of 2230 white people demonstrated that the gene responsible for the effect of loose white matter size was located on chromosome 4.

2.3.3 Hypoperfusion and ischemia

Chronic ischemia/hypoperfusion plays a key role in CSVD pathogenesis. Cerebral arterioles are mostly terminal arteries prone to hypoperfusion and ischemia in an injured area [25]. Hypertension is the key factor of the condition, mainly because it poses a small vascular lumen in the brain, wherein chronic hypoperfusion of the white matter is likely, resulting in neuronal apoptosis, selective oligodendrocyte death, and myelin fiber degeneration that lead to CSVD [26]. Several scholars [27] also found that limb remote ischemic preconditioning can induce cerebral ischemia tolerance, which has a potential protective effect on CSVD patients and is indirectly related to chronic cerebral ischemia. Researchers found that in cerebral ischemia or hypoperfusion, the supply of glucose, oxygen, and other nutrients to the nervous system may be reduced, resulting in damage or death of neurons due to lack of energy, resulting in impaired neuronal function and triggering CSVD [10].

2.4 Imaging of cerebral small vessel disease

With the rapid development of modern medical imaging technology, imaging features vary, mainly include recent subcortical infarcts, lacunes of presumed vascular origin, white matter hypointensities (WMHs) of presumed vascular origin, CMB, enlarged perivascular spaces, and full and regional brain atrophy. Imaging changes are often found in patients with small cerebral vessels, and MRI is often used to detect small blood vessel damage in the brain.

In recent years, MRI has been widely used in CSVD diagnosis and has provided ideal results. Neuroimaging markers are a potential independent risk factor for CSVD. A study showed that MRI manifestations are related to the cognitive dysfunction in patients with CSVD [28]. There has been a considerable increase in the application of brain imaging in the studies of CSVD [29].

3 Cognitive impairment

Cognitive impairment refers to severe problems in pathological process of learning and memory accompanied by aphasia, agnosia, and disuse, caused by abnormal brain senior intelligence processing related to learning, memory, thinking, and judgment. Vascular cognitive impairment (VCI) has three clinical subtypes, namely, mild cognitive impairment (MCI), vascular dementia (VaD), and mixed dementia [30].

In 1995, Bowler et al. proposed that VCI is the only cognitive impairment type that can be prevented and controlled during the mild stage [31]. Overton et al. [32] thought that MCI is a diverse condition as the prevalence and incidence
estimates differed substantially according to age, MCI subtype, and cognitive impairment severity that the prevalence estimates ranged from 5.13% to 29.9% depending on age and severity of impairment. Moreover, executive function is a recognized feature. In addition, there may be attentional impairment, however the retention relatively remains [32, 33].

Dementia is caused by several factors. Cerebrovascular disease is the second common cause of senile cognitive impairment and dementia, and CSVD accounts for a large proportion in cerebrovascular disease. O’Brien et al. also noted that the incidence of dementia in the general population of over age 65 is approximately 7% and the condition is twice as common. The morbidity of MCI is high; thus, it should be detected early, and effective prevention and treatment should be done to minimize the incidence of dementia.

4 Cerebral small vessel disease and cognitive impairment

4.1 Recent subcortical infarcts and cognitive impairment

The centrum semiovale, basal ganglia, corona radiata, and brain stem are the recent areas of infarctions in the brain. Its maximum axial diameter is generally less than 20 mm, but the diameter on the coronal plane may be above 20 mm. Long T1 and long T2 signals were noted, fluid-attenuated inversion recovery (FLAIR) sequences showed hyperintensity, and diffusion-weighted imaging revealed hyperintensity on brain MRI [34].

Lesions in the posterior horn of the inner capsule were associated with impaired executive function, whereas lesions in the frontal lobe were associated with impaired memory and executive function, coding, and information management. Temporal lobe lesions are related to memory, language, hearing, and affective disorders. Moreover, anterior thalamus lesions are associated with amnesia [35]. Studies have shown that the number and volume of infarcts is an independent predictor of processing speed and executive function impairment [36].

4.2 Lacunes and cognitive impairment

Lacune is a round or oval fluid-filled cavity in the small perforating artery infarction and hemorrhage. The lacune usually has a diameter of 3–15 mm [37]. T2-FLAIR is characterized by a low signal of the central CSF and the periphery surrounded by the high-signal ring. The maximum diameter of lacunar lesions was estimated to be less than 15 mm, different from the 20 mm defined diameter for recent subcortical infarcts [1].

The frontal, temporal, parietal, and occipital lobes are the cortical centers of memory, language, execution, and motor and visual space, respectively. Most studies [38] showed that post-lacune cognitive impairment involved multiple cognitive domains, including information-processing speed, attention, executive function, memory, language, and visuospatial function. The Leukoaraiosis and Disability Study (LADIS study) [39] demonstrated on MRI that lacunes correspond a steeper rate of decline in executive functions and psychomotor speed. The basal ganglia has extensive and complex fiber connections with each cortex. Thong et al. [40] found that damage to connecting fiber bundles between the white matter of the brain and corresponding brain regions could lead to cognitive impairment. Moreover, disrupted extensive fibrous connections were found between the anterior medial thalamus and the orbitofrontal, and prefrontal cortex decrease the processing speed [41]. A meta-analysis [42] showed that even small amounts of lacune can cause cognitive impairment. An explanation [43] to this is that infarction increases the risk of dementia.

Furthermore, lacunes, with location and quantity...
closely related to the severity and type of cognitive impairment, may lead to the disruption of specific cognitive function circuits in the brain, leading to the dysfunction of attention and information-processing speed barriers.

### 4.3 White matter hyperintensities and cognitive impairment

WMHs are deep brain or patchy or dotted high-signal areas around a ventricle in T2-weighted imaging or FLAIR. It is a clinical syndrome characterized by diffuse patchy or patchy changes of white matter in the lateral ventricle and the center of the semi-oval on CT, whereas it is a T1-weighted low signal in white matter around the lateral ventricle on MRI, basically symmetrical on both sides [44]. WMH usually occurs in the lateral ventricle and the center of hemispheres. The CSF with a low central signal and a high peripheral signal was observed in the FLAIR phase.

Based on different imaging sites, white matter hypersignals can be categorized into periventricular white matter hypersignals (PVH) and subcortical deep white matter hyperintensity (SDWMH) [45]. The following are the SDWMH grades [46]:

- **Level 0**, normal MRI;
- **Level 1**, abnormal high point signal;
- **Level 2**, abnormally high patchy signal (fusion tendency between lesions) or single lesion diameter greater than 3 mm;
- **Level 3**, lamellar and abnormally high signal (interfusion of lesions).

PVH grades [46] are as follows:

- **Level 0**, normal MRI;
- **Level 1**, abnormal high signal of lateral ventricle frontal angle and / or occipital angle cap;
- **Level 2**, abnormally high signal of lunar halo around the lateral ventricle;
- **Level 3**, the anomalous signal extends to the deep white matter.

Mortamais et al. [47] reported that white matter lesions are associated with decreased cognitive function. Studies [39, 48, 49] have shown that white matter impairment is closely related to stroke, cognitive and affective disorders, dementia, gait and urination difficulties, and especially cognitive impairment and dementia. WMHs were associated with an increased dementia in the general middle-aged and elderly population [50, 51]. Therefore, WMH may be a predictor of vascular cognitive dysfunction.

### 4.4 Cerebral microbleeds

CMBs are parenchymal subclinical lesions characterized by tiny hemorrhages and appear primarily in small cerebral vessels [52]. Consensus manifests the definition of CMBs is as follows [8]:

1. a small round or ovoid shape, distinct border, homogeneity, and signal missing stove;
2. diameter < 10 mm (generally 2–5 mm);
3. surrounded by brain parenchyma;
4. T2GRE sequence showed blooming effect;
5. T1 and T2 sequences of corresponding parts have no high signal;
6. identification of bone vessel empty with iron and calcium deposition;
7. diffuse axonal injury caused by trauma was excluded.

Poels et al. [53] reported that CMBs can gradually cause psychosocial symptoms, cognitive dysfunction, and dementia. Gormley et al. [54] have shown that the incidence of CMBs is 16%–45%, among which the cognitive impairment is the most important trait. In the autopsy results of 1143 elderly patients, Arvanitakis et al. [55] found that the incidence of arterial atherosclerosis was up to 54% and its severity was positively correlated with cognitive dysfunction severity. CMBs may be associated with hypertensive vascular damage. Li et al. [56] conducted a meta-analysis on 25 studies involving 9343 patients, and the results revealed that the higher the number of microhemorrhage is, the lower the
clinical score of mini-mental state examination is, the slower the information-processing speed and behavior of the patient are. Akoudad et al. [57] indicated that cerebral lobe CMBs were associated with decreased executive function information processing and memory, whereas deep CMBs affected motor function.

In summary, the cognitive impairment caused by CMBs depends on various factors, including the size, number, distribution, and location of CMB lesions and the presence or absence of other associated diseases.

4.5 Enlarged perivascular spaces

Perivascular spaces, also known as Virchow–Robin spaces (VRS), are normal anatomical structures that have certain physiological and immune functions. It is the space between the blood vessels in the brain and the soft meninges filled with CSF. The basal ganglia area or the center of the semi-oval is circular or elliptic and dotted or linear, similar to the signal of the CSF. T1-weighted imaging (T1WI) and FLAIR sequences have low signals, whereas T2-weighted imaging (T2WI) has a high signal. Enlarged perivascular spaces (EPVS) have three characteristic sites [58]:

Type 1, the anterior transposition of the zona pellucida into the basal ganglia;

Type 2, the subcortical white matter that the convex surface and deep of the brain, the medulary artery, enters;

Type 3, the brainstem.

Many studies determined a strong correlation between increased perivascular clearance and cognitive impairment. Based on clinical study results, Ding et al. [59] reported that 3-mm EPVS was associated with cognitive decline and vascular dementia. Maclullich et al. [60] showed that EPVS may lead to nerve fiber destruction in the basal ganglia associated with cognitive functions, resulting in the reduction of nonverbal reasoning and visuospatial ability. The study [61] found that increased perivascular space in the center of the semi-oval and basal ganglia can indicate subcortical vascular cognitive dysfunction. Thus, EPVS is also associated with cognitive dysfunction.

4.6 Atrophy

Cerebral atrophy is the reduction of brain volume not correlated with specific focal brain injury such as cerebral infarction and hemorrhage surgery. Numerous studies have shown that brain atrophy can affect cognition.

Frontotemporal gray matter volume, hippocampal atrophy, and whole-brain atrophy were associated with memory loss [62]. A cohort study [63] found that progressive brain atrophy is related to decreased cognitive function. Tong et al. [64] found that the slowing down of brain circulation and nutritional disorders in brain atrophy patients led to decreased excitatory neurotransmitters, degeneration of neurons, and demyelination, which will lead to cognitive decline. In a study by Cao et al. [65], 30.2% (13/43) of CSVD patients showed a moderate to severe atrophy of the medial temporal lobe. In some CSVD patients, MRI revealed gyrus narrowing, sulcus deepening, and ventricle enlargement, and cortical atrophy was related to the severity of CSVD [66]. A study [67] that included 35 CSVD patients showed that brain volume was closely related to executive function.

To summarize, brain atrophy was closely related to cognitive dysfunction, which can be considered as a risk factor for CSVD.

5 Conclusion

It is clearly that CSVD is a common contributor to stroke, functional decline, VCI, dementia, and is also a significant risk factor for VCI and dementia. This report summarized recent advances in the pathogenesis of CSVD, and CSVD and
cognitive impairment using neuroimaging markers. Although their pathogeneses vary, they have similar neuroimaging markers that can be used as the basis for etiological analysis [68]. In recent years, the linkages between CSVD and MCI have attracted much interest. These neuroimaging markers provide new opportunities for the evaluation of the relationship between CSVD and cognitive impairment.

Therefore, CSVD was found to be associated with an increased risk of dementia in the general population. Considering the imaging results of CSVD, it is important to evaluate the role of stroke prevention in the prevention of cognitive decline. Combined with the imaging manifestations of CSVD lesions, strategies to prevent cognitive decline are needed. This review highlights that the correlation between MCI and imaging markers of CSVD should be paid more attention to provide new ideas for potential treatments and interventions for cognitive impairment, and to explore the relationship between CSVD and cognitive dysfunction, to provide theoretical reference for early clinical prevention and treatment, which in turn, can predict the damage degree of CSVD.

**Conflict of interests**

All contributing authors have no conflicts of interest related to this paper.

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