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REVIEW

Cerebral small vessel disease: neuroimaging markers and clinical implication

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Abstract

Cerebral small vessel disease (CSVD) is a broad category of cerebrovascular diseases which primarily affect the perforating arterioles, capillaries and venules with multiple distinct etiologies. In spite of distinctive pathogenesis, CSVD shares similar neuroimaging markers, including recent small subcortical infarct, lacune of presumed vascular origin, white matter hyperintensity of presumed vascular origin, perivascular space and cerebral microbleeds. The radiological features of neuroimaging markers are indicative for etiological analysis. Furthermore, in sporadic arteriosclerotic pathogenesis associated CSVD, the total CSVD burden is a significant predictor for stroke events, global cognitive impairment, psychiatric disorders and later life quality. This review aims to summarize the radiological characteristics as well as the clinical implication of CSVD markers and neuroimaging interpretation for CSVD symptomatology.

Keywords Cerebral small vessel disease · Arteriolosclerosis · Neuroimaging markers · Cognition

Introduction

Cerebral small vessel disease (CSVD) is a wide spectrum of cerebrovascular diseases which are characterized with similar clinical manifestation and neuroimaging markers. CSVD frequently coexist with neurodegenerative diseases, in particular to Alzheimer's disease and Parkinson disease, in elderly population. The symptoms of CSVD can range from asymptomatic radiological markers occurrence to various neuropsychological symptoms, mainly including cognitive deficits, gait imbalance, sleeping disorder and urinary incontinence. Patients suffering from a recent small subcortical infarct may present with focal neurological deficits, also known as lacunar syndromes. Clinically, for one thing, there is considerable overlap of clinical manifestation between CSVD and other neurogenerative diseases, such as cognitive decline, gait disturbance, psychiatric symptoms. For another, it is difficult to evaluate small vasculopathy since small vessels are not commonly visualized neither on computed tomography angiography (CTA) nor magnetic resonance angiography (MRA). Therefore, inadequate attention is attached to the early recognition for CSVD in clinical practices. Actually, there is an increasingly substantial burden of CSVD for global public health in the aging population.

The therapeutic strategies for cerebral small vessel diseases, both the medication and nonmedication therapeutics, should be individualized according to the etiopathogenesis. Usually, the etiologic diagnosis of CSVD are mainly based on the medical history, clinical manifestation, neuroimaging features and genetic detection, pathological biopsy if necessary. The term "cerebral small vessel disease" with different aetiopathogenesis emphasizes the pathological significance for the diagnosis of CSVD since small vessels cannot be visualized in routine noninvasive angiography. However, brain pathological biopsy can only be conducted in a minority of patients with confusing diagnosis. Besides, clinical manifestation is nonspecific, subjective and heterogeneous in individuals. For reasons given above, it is challenging for diagnosing CSVD and the clinical diagnosis are highly dependent on the neuroimaging technique. Though CSVD of

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distinct etiologies share similar neuroimaging markers, the neuroimaging features including the predominant topographical distribution and radiological morphology may indicate the etiopathogenesis of CSVD. In this review, we focus on the most prevalent sporadic CSVD which results from aging and vascular risk factors associated atherosclerosis. We primarily discuss the radiological profiles of CSVD markers as well as corresponding clinical implication and symptomatology interpretation from neuroimaging perspective.

Definitions and etiological classifications of CSVD

The cerebral small vessels broadly refer to the small arteries, arterioles, capillaries tree and the small veins, venules in the subarachnoid space and brain parenchyma. But most often, the narrow definition of cerebral small vessels refers to the artery system and little attention has been paid to the venous vessels, such as venous collagenosis. Cerebral small vessels stem either from the superficial leptomeningeal vessels in subarachnoid space or perforating vessels in deep parenchymal structure. Rigorously speaking, small vessel diseases are systematic vascular diseases which may affect multiple organs vessels, such as kidney and retina. According to the etiologies, CSVD can be classified as six categories [1] and share similar characteristic clinical manifestation, neuroimaging markers (Table 1). The arteriolosclerosis type which is mainly related to aging or vascular risk factors is the most prevalent etiological type in common sporadic CSVD. The characteristic pathological features of arteriosclerotic CSVD present on the loss of smooth muscle cells in the tunica media and the deposition of fibro-hyaline material, leading to the thickening of the vessel wall and narrowing of the lumen [1]. Microaneurysms formation caused by disrupted and dilated vessel wall, is another vascular remodeling features in arteriolosclerosis, particularly in patients with hypertension.

Neuroimaging markers of CSVD

The cerebral small vessels cannot be visualized but the corresponding parenchymal lesions can be captured on MRI [1]. The Standards for Reporting Vascular changes on nEuroimaging (STRIVE Recommendation) [2] is an international neuroimaging consensus standard of CSVD, including the classification, terminology and definitions CSVD markers. According to the STRIVE recommendation, the neuroimaging markers of CSVD include recent small subcortical infarct, lacune of presumed vascular origin, white matter hyperintensity of presumed vascular origin, perivascular space, cerebral microbleed (Fig. 1). We omit discussion of brain atrophy in this review due to no specificity of atrophy in neurodegenerative disease. All above-mentioned neuroimaging markers commonly cooccur with different degree of severity. Total CSVD score is calculated by counting the presence of lacune of presumed vascular origin, WMH of presumed vascular origin, PVS and CMB [3]. An ordinal scale from 0 to 4 represent the total MRI burden, which implicates the severity of CSVD. Accumulating attention has been attached to the clinical significance of total CSVD burden and each separate marker burden. And evidence from observational studies reveal that the global CSVD burden is associated with blood–brain barrier (BBB) integrity destruction [4] and subsequent cognitive impairment, post-stroke depression [5, 6], lower health-related quality of life after stroke [7].

Above figure shows the schematic features of CSVD neuroimaging markers on different MR imaging sequences and a brief description of the characteristics of each marker respectively. Arrows indicate the lesions of each CSVD marker on different MR sequences. 3D-TOF MR angiography give a representation for confirming the confluent white matter hyperintensity is not attribute to hypoperfusion caused by large arteries stenosis. Abbreviations: CSVD, cerebral small vessel disease; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; SWI, susceptibility-weighted imaging.

Recent small subcortical infarct

Recent small subcortical infarct (RSSI), also called "lacunar infarct", "lacunar stroke", approximately accounts for 25% in acute ischemic stroke [8]. RSSIs are hyperintense regions with maximum lesion diameter less than 20 mm in the axial plane on the FLAIR sequences [2]. They can be distinguished from old infarct lesions on diffusion-weighted imaging (DWI) with hyperintense signal. The pathogenesis of RSSIs has been mainly presumed to result from the occlusion of penetrating artery in the brain. Histopathology of subcortical infarcts is characterized with irregular cavities with surrounding gliosis, haemosiderin-rich macrophages and arteriosclerosis, fibrinoid necrosis of vessels [9]. Epidemiological evidences show that age, hypertension, diabetes mellitus, hyperlipidemia, alcohol consumption, obesity, smoking and headache at stroke onset are independently associated with lacunar infarcts [10, 11]. Metabolic syndrome and diabetes mellitus correlate to recurrent lacunar infarcts in SPS3 study [12]. Of the above risk factors, hypertension, as an independent vascular risk factor for CSVD burden, contributes to arteriolosclerosis and small vessels occlusion [13]. In accordance, blood pressure control in recent subcortical stroke provides beneficial effect in CSVD management and stroke secondary prevention [14]. It is

Table 1 Brief summary of cerebral small vessel diseases

Cerebral Small Vessel Diseases	
Affected Vessels	Perforating Arterioles, Capillaries and Venules
Etiologic Spectrum [1]	**Arteriolosclerosis (vascular risk factors-related)** **Sporadic and Hereditary Cerebral Amyloid Angiopathy (CAA)** **Inherited Small vessel Diseases distinct from CAA** CADASIL, CARASIL, MELAS, Fabry's disease, hereditary multi-infarct dementia of Swedish type, retinal vasculopathy with leukodystrophy with TREX1 mutation (CRV, HERNS, HVR), small vessel disease with COL4A1 mutation **Inflammatory and Immune Diseases Mediated Small Vessel Diseases** Systematic Vasculitis: Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, cryoglobulinemic vasculitis, cutaneous leukocytoclastic angiitis, Henoch-SchÖnlein purpura Primary Central Nervous System Vasculitis Vasculitis Secondary to CNS Infections (tuberculosis, syphilis, HIV, leptospirosis) Vasculitis Secondary to Connective Tissue Disorders (SLE, scleroderma, rheumatoid vasculitis, dermatomyositis, SjÖgren's syndrome) **Venous Collagenosis** **Others** radiation related angiopathy, non-amyloid microvessel degeneration in AD
Neurological Symptoms	Lacunar Syndrome Cognitive Impairment: vascular origin/accompanied with Alzheimer's disease Gait/Balance Disturbance Parkinsonism Emotion/Psychiatric Stress: depression, apathy Sphincteric Function: urinary urgency to urinary/fecal incontinence Others: sleep disorder
Neurological Signs	Patchy to Global Cognitive Domains Impairment Movement System: slightly slowing/shuffling/ataxic gait; postural imbalance Focal Neurological Signs: pyramidal tract sign (+) pseudo-bulbar sign (+)
Neuroimaging Markers (Identified Sequence)	Recent Small Subcortical Infarct (DWI) Lacune of Presumed Vascular Origin (FLAIR) White Matter Hyperintensity of Presumed Vascular Origin (FLAIR) Perivascular Space (T1, T2) Cerebral Microbleed (T2*-weighted GRE/ SWI)

CADASIL, cerebral autosomal dominant arteriopathy with subcortical ischemic stroke and leukoencephalopathy; CARASIL, cerebral autosomal recessive arteriopathy with subcortical ischemic and leukoencephalopathy; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; CRV, cerebroretinal vasculopathy; HERNS, hereditary endotheliopathy with retinopathy, nephropathy and stoke; HVR, hereditary vascular retinopathy; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus; AD, Alzheimer's disease; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; SWI, susceptibility-weighted imaging

noteworthy that hypertension and diabetes, both of which are the contributors of atherosclerosis, show a strong correlation with lacunar stroke recurrence [15]. It is acknowledged that hypertension, as well as diabetes, initiate and accelerate the development of atherosclerosis, including lipohyalinosis, fibrinoid necrosis and microatheroma in perforating arteries. As mentioned in the aetiopathogenic classification of CSVD, lipohyalinosis, fibrinoid necrosis and microatheroma finally

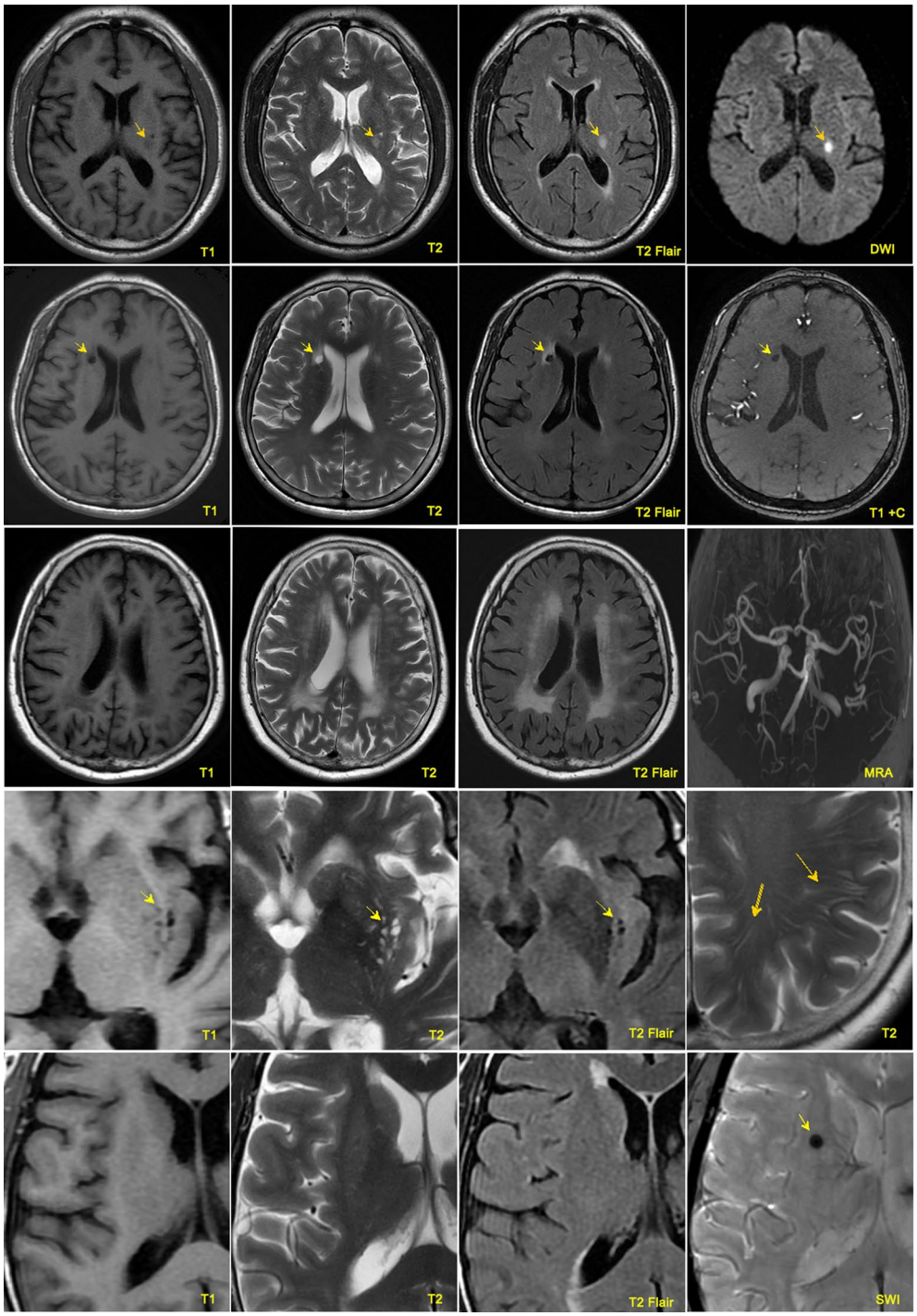

Fig. 1 Neuroimaging characteristics of cerebral small vessel diseases in MRI

contribute to the narrowing of lumen and thrombotic occlusion of perforating arteries. Therefore, management of hypertension and diabetes is as important to lacunar stroke secondary prevention as antithrombotic therapy. Besides the above conventional risk factors, genome-wide analysis has confirmed the genetic susceptibility of lacunar stroke [16]. Loci at chromosome 6p25 near FoxF2, a transcription factor involved in cerebral vessel development, has been found to be associated with increased risk of ischemic stroke and WMH burden of cerebral small vessel disease [17]. A community population study also finds a correlation between WMH-associated single nucleotide polymorphism and risks of lacunar infarcts, implying that lacunar infarct and WMH may share some genetic susceptibility factors [18]. Anyway,

the pathogenetic relationship between lacunar infarcts and white matter hyperintensity needs further studies.

Clinically, RSSI can be symptomatic with lacunar symptoms, including pure motor hemiparesis, pure sensory stroke, sensory-motor stroke, ataxic-hemiparesis, and dysarthria-clumsy hand, or occasionally detected as silent infarct on MRI. The incidence of asymptomatic RSSI with DWI positive signal is rarely reported in literature and less attention is paid to asymptomatic RRSI which may not be easily recognized by patients and physicians due to the absence of neuronal deficits. With regard to symptomatic lacunar stroke, clinicopathological study of 20 patients from C. Miller Fisher shows that the most frequent lacunar syndrome is pure motor hemiparesis, followed by pontine syndromes, pure sensory stroke and sensory-motor stroke [19]. Apart from the above typical lacunar syndromes, atypical lacunar syndromes, mostly manifesting as dysarthria facial paresis and isolated dysarthria, account for 6.8% of lacunar stroke. And compared with typical lacunar syndromes, atypical lacunar syndromes seem to have better outcome and approximately one-fourth of cases are absence of neurological disability at discharge [20]. Another symptom of lacunar stroke is neuropsychological disturbance which is paid less attention to usually. Actually, mild cognitive impairment of subcortical vascular origin characterized with executive impairment is common in patients with lacunar stroke, especially in atypical lacunar syndrome and pure motor hemiparesis [21]. Furthermore, multiple silent lacunar infarcts instead of leukoaraiosis are found to be significantly associated with post-stroke cognitive decline, particularly for the executive function and short delayed verbal memory in patients with first-ever lacunar stroke [22]. In another word, patients with first-ever lacunar stroke and radiology confirmed multiple silent lacunar infarcts deserve long-term cognition follow-up since they are more vulnerable to vascular dementia. Besides the neurological syndromes described above, sleep-related breathing disorders (SRBD) which can be assessed by apnea/hypopnea index (AHI), has gained attention in patients with ischemic stroke and TIA. It is found that 69.1% of acute lacunar stroke patients show AHI $\geq$ 10, 44.1% $\geq$ 20, 25% AHI $\geq$ 30 and smoking, the topography of lacunes in the internal capsule or pons are significantly associated with AHI $\geq$ 30 [23]. It is presumed that leukoaraiosis and lacunar infarct affecting pyramidal tract, contributing to pharyngeal disfunction, participate in the development of SRBD after stroke.

Though different radiological subtypes of lacunar stroke share similar vascular risk factors, different vascular risk factor profiles are found to be associated with different neuroimaging subtypes of lacunar stroke, indicating distinctive underlying pathogenesis in different lacunar stroke subtypes [11]. For instance, multiple RSSIs adjacent to cortex may indicate an embolic occlusion. Mostly, lacunar stroke is attributed to lacunar infarct resulting from arteriolosclerosis and occlusion of penetrating arteries. However, uncommon stroke subtypes or etiologies including embolic cardiopathy, cholesterol/carotid plaque embolism, hematological diseases, infectious or inflammatory arteritis, account for less than 5% of all lacunar stroke [24]. Hence, echocardiography, Holter monitoring electrocardiogram, autoimmune biomarkers detection, etc. should be under consideration as a complementary examination for screening unusual etiologies, especially for younger-onset stroke or cryptogenic stroke. Accordingly, the secondary prevention strategy should be individualized and targeted on the etiology of lacunar stroke [25]. Radiologically, RSSIs occur frequently in the perfusion territory of perforating arteries or arterioles in subcortical hemisphere, such as posterior limb of the internal capsule, centrum semiovale, lentiform nucleus, lateral/anterior thalamus and infratentorial regions (brainstem/cerebellum) [26–28]. Consistently, clinicopathological investigation confirms that lacunar stroke is mostly attributed to the occlusion of penetrating arteries in middle cerebral artery territory, followed by the territory of basilar artery, posterior cerebral artery and anterior choroidal artery [19]. Of note, the lacunar infarcts which locate in the territory of proximal parent artery are more likely to experience early neurological deterioration and may predict poor prognosis [29, 30]. In addition, lacunar stroke secondary to penetrating branch atheromatous disease has higher rate of exacerbation and recurrence and double antiplatelet therapy combined with high-dose of statins in acute phrase may be beneficial for secondary prevention [25].

There is no significant interhemispheric difference of RSSI burden and no association between the spatial distribution of RSSI and the burden, location of other CSVD markers including WMH, lacune, PVS and microbleed in CSVD patients [27]. However, distribution discrepancy remains between the topography of isolated lacunar infarct and multiple lacunar infarct. For acute lacunar infarcts, a study based on younger-onset stroke patients finds that isolated lacunar infarcts frequently occur in deep grey nuclei/internal capsule, whereas multiple lacunar infarcts often occur in centrum semiovale and coexist with confluent white matter hyperintensities [11]. Similarly, for chronic silent lacunar infarcts, isolated lacunar infarcts predominantly locate in internal capsule, thalamus and multiple lacunar infarcts preferentially locate in corona radiata, thalamus [22]. Compared with asymptomatic RSSI, symptomatic RSSI are more likely to locate in the internal capsule where the corticospinal tracts and spinothalamic tracts pass through tightly [28]. Anatomically, the lacunar syndromes subtypes may clinically indicate the infarct territory. Concretely, pure sensory stroke mostly accounts for infarction in thalamus, the topography of

posterior cerebral artery [31], while pure motor stroke principally locates in internal capsule, the topography of middle cerebral artery [32].

Lacune of presumed vascular origin

Lacune of presumed vascular origin is defined as a CSF-filled cavity of 3–15 mm in diameter, with CSF-signal and surrounding rim of FLAIR hyperintensity on MRI. The boundary size of diameter less than 3 mm strongly indicates perivascular space instead of lacune, but the maximal diameter of lacune may exceed 15 mm in sagittal or coronal plane rather than axial plane. Actually, lacunes preferentially develop proximal to white matter hyperintensities associated perforating arteries, indicating lacunes are susceptible to white matter hyperintensity penumbra [33]. And the continuum shape of lacune is mainly determined by the orientation of surrounding perforating arteries [34]. It is noteworthy that lacune shares some neuroimaging characteristics with perivascular space, including CSF-like signal on all sequences of MRI and the frequent locations. Similar to perivascular spaces, lacunes are predominantly distributed in centrum semiovale and basal ganglia [34]. Perivascular spaces in centrum semiovale frequently link to lobar cerebral microbleeds and amyloid deposition, indicative of cerebral amyloid angiopathy. Similarly, lobar lacunes burden is independently associated with lobar microbleed and amyloid deposition in patients with intracranial hemorrhage [35], though the underlying pathogenetic relationship between lobar lacunes and lobar microbleeds as well as cerebral amyloid angiopathy is not fully understood. Actually, PVS is a perivasculature around penetrating arteries for exchanging ISF and CSF, while lacunes are the pathological and radiological sequelae of a vasculopathy. Discriminating from the lacunar infarct or silent lacunar infarct, the term "lacune of presumed vascular origin" indicates that the lesion may develop from either an ischemic or hemorrhagic origin in the absence of onset images or definite stroke history [2]. Clinically, most lacunes are asymptomatic and detected incidentally by CT or MR examination. However, lacunes which often co-occur with other neuroimaging markers of CSVD, also correlates to subcortical vascular cognitive decline and dementia [36]. Furthermore, lacunes of presumed silent lacunar infarcts origins have been found to be associated with brain atrophy, white matter integrity destruction and subsequent cognitive decline, indicating a potential role of small subcortical infarcts in the neurodegeneration diseases [37–40]. Additionally, baseline silent lacunar infarcts are related to post-stroke depression [6] and post -stroke cognitive impairment [41] in patients with lacunar stroke.

White matter hyperintensity of presumed vascular origin

White matter hyperintensity (WMH) is hyperintense on T2-weighted and FLAIR sequences on MRI. In addition to traditional MRI, the microstructure integrity impairment of white matter, which predicts the progression of WMH [42], can be visible on diffusion tensor imaging (DTI). According to the STRIVE recommendation, T2-weighted hyperintense in subcortical grey matter and brainstem is not included into the category of white matter hyperintensity and is termed as subcortical hyperintensity alternatively [2]. White matter hyperintensity is a radiological description for white matter demyelination which may results from a variety of etiologies. Whereas WMH of presumed vascular origin refers in particular to white matter lesions caused by vascular diseases, excluding WMH mimics of neuroimmune, neuroinfectious, metabolic or toxic origins, such as multiple sclerosis, acute disseminated encephalomyelitis, leukodystrophy or Wernicke's encephalopathy. Clinically, WMHs of vascular origin are commonly categorized into periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) according to Fazekas Rating Scale [43], which is widely applied to visual evaluation of white matter hyperintensity severity. In healthy elderly, age-related WMHs are often PVH, which symmetrically distribute adjacent to lateral ventricles [33, 44]. Periventricular hyperintensities seem to be more prevalent in elderly with atherosclerosis [45] and hypertension. Diffuse and symmetric WMHs predominantly located in the periventricular white matter, external capsule, corona radiata, temporopolar white matter are the most prominent spatial imaging characteristics of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a genetic small vessel disease with mutations of NOTCH3 gene [33]. The pathogenesis of WMH of presumed vascular origin may involve multiple contributable factors, including blood–brain barrier leakage [46], chronic hypoperfusion, disturbance of amyloid clearance and subsequent β-amyloid deposition [47, 48], axonal injury [47] iron deposition [49]. Conventional vascular risk factors, including hypertension, age, diabetes mellitus, smoking, elevated glomerular filtration rate (eGFR) have been confirmed to be associated with WMH of presumed vascular origin [50]. Confluent WMH is associated with increased age, hypertension and decreased estimated glomerular filtration (eGFR) [11]. Apart from demographical risk factors, carotid artery diastolic diameter [51], carotid intima-media thickness [52] and intracranial atherosclerosis [50], intracranial atherosclerotic stenosis (ICAS) [53],

sleep-disordered breathing [54] has been found to be positively associated with WMH burden. Hemoglobin A1C (HgbA1C) [55, 56] and homocysteine (HCY) [55], which imply endothelia disfunction and oxidative stress in atherogenesis, are indicative biomarkers for WMH in elderly.

Abundant of studies have been drawn attention to the correlation between WMH and aging, dementia. Additionally, WMH is the predictor of post-stoke depression [5, 6], post-stroke cognition decline [57], tension-typed headache [58] and lower extremity function [59]. There is a high correlation between regional WMH burden and aging-related brain atrophy [60] as well as decreased cortical thickness in specific brain regions related to cognitive performance [61]. Accumulating evidences have confirmed that WMHs of presumed vascular origin are associated with memory, attention, executive function and social cognition [62]. Moreover, compared with other neuroimaging markers of CSVD, WMH has a stronger correlation with the specific cognitive domains impairment including attention, executive functions, processing speed [63]. Notably, there is relationship between the topographical distribution of WMHs and corresponding cognitive and behavior domains decline either in healthy elderly cohort or dementia population [44, 63]. Concretely, periventricular WMHs or frontal WMHs adjacent to anterior ventricles have stronger relation with executive function than subcortical WMHs, while parietotemporal WMHs correlate with memory decline.

Perivascular space

Perivascular spaces (PVS), also known as Virchow–Robin spaces, surround penetrating vessels in the brain parenchyma. They are defined as round or tubular fluid-filled spaces which have signal intensity similar to cerebrospinal fluid (CSF) on all MRI sequences, Generally, the diameter of perivascular spaces is smaller than 2 mm while enlarged perivascular spaces (EPVS) may extend to a diameter ranging from 2 to 4 mm. PVS is a potential space between the endothelia cells and astrocyte end-feet. Because the water channel aquaporin-4 (AQP4) on astroglial cells play a critical role for the absorption of interstitial fluid (ISF), this perivasculature is designated as "glial lymphatic system" or "glymphatic system" [64, 65]. Given that CSF is reabsorbed into the blood circulation mainly via arachnoid villi in subarachnoid space and the cranial nerve sheaths entering into the lymphatic vessels on the nasal mucosa [66], there is a long-held common view in neuroscience that the central nervous system is lack of lymphatic vasculature and is immune-privileged. Recently, it has been proved that small sinus-associated meningeal lymphatic vessels communicate directly with cervical lymphatic nodes, providing a novel pathway for immune cells migrating into CNS and metabolite clearance from the interstitial fluid (ISF) [67, 68]. In summary, both the meningeal lymphatic network in the dura matter draining into the extracranial cervical lymphatic nodes and glymphatic system in perivasculature draining into the subarachnoid space, ultimately into the venous system, maintain the metabolic homeostasis in CNS and keep balanced cerebral venous pressure.

The mechanism underlying EPVS has not been fully understood and may be multifactorial. As mentioned above, PVS, a perivasculature of glymphatic system, is widely distributed in the central nervous system for exchanging of ISF in brain parenchyma and CSF. Hence, disturbance of CSF circulation or astroglial aquaporin-4 water channel dysregulation may contribute to the development of EPVS. The most common topographies of PVS are centrum semiovale and basal ganglia, whose distinctions as well as clinical indications are summarized in Table 2. Age and hypertension [69–71] are the most common vascular risk factors shared by PVS in centrum semiovale (CSO-PVS) and PVS in basal ganglia (BG-PVS). And there is a higher risk of BG-EPVS in male than that in female [71]. Other common systemic risk factor associated with increasing EPVS burden include elevated glomerular filtration rate (eGFR), proteinuria [72] and hyperuricemia [73]. Though there is an overlap of risk factors for CSO-PVS and BG-PVS, location-specific risk factor profiles and genetic heritability pattern [74] between CSO-PVS and BG-PVS may indicate distinct aetiopathogensis of PVS in different regions. CSO-PVS has higher correlation with lobar cerebral microbleeds [70] which is suggestive of cerebral amyloid angiopathy, while BG-PVS has more significant correlation with deep cerebral microbleeds [70, 75], lacunes [69, 70], arterial stiffness [76] and intracranial atherosclerosis [77], all of which are suggestive of hypertensive angiopathy. Consistently, CSO-PVS burden is positively related to global amyloid-β deposition as well as pathology-confirmed cerebral amyloid angiopathy severity [78], which is strongly indicative of Alzheimer's disease [79], whereas BG-PVS burden has stronger relationship with vascular dementia [80]. In contrast with CSO-PVS and BG-PVS, hippocampus EPVS have weaker correlation with dementia [81] but may be associated with decline in verbal reasoning [82].

The clinical implication of PVS has remained controversial historically since PVS can be detected in the ostensibly healthy elderly population [83]. Nonsignificant correlation of perivascular spaces visible on 7.0 T MRI with age or common vascular risk factors may also support the existence of non-pathological PVS in general population [84]. However, accumulative epidemiological evidences have revealed that the global EPVS burden is associated with both dementia of vascular origin and Alzheimer's disease origin [80], post-stroke depression [85], post-stroke cognitive impairment [86]. Moreover, perivascular space, in particular to EPVS,

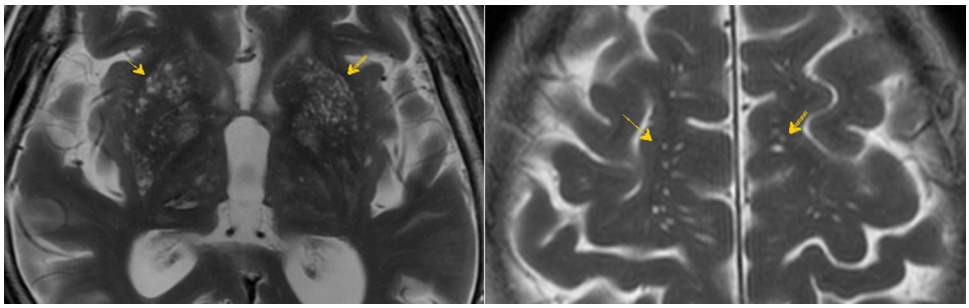

Fig. 2 Left: perivascular spaces distribute densely on bilateral basal ganglia in a hypertensive patient with patchy cognitive function decline in executive function, verbal language and delayed memory. Right: scattered perivascular spaces on bilateral centrum semiovale is detected in a mild cognitive impairment patient with primary complaint of memory decline

Table 2 The distinctions between CSO-PVS and BG-PVS

	CSO-PVS	BG-PVS
Shape in Axial MRI	Linear or Tubular	Round or Ovoid
Common Risk Factors	Age, Hypertension, Elevated eGFR	Age, Hypertension, Elevated eGFR, Male, Arterial Stiffness, Intracranial Atherosclerosis
Risk Association with Other CSVD Markers	Lobar CMB	Deep CMB
	Lacune	Lacune (higher risk association)
	Deep WMH	Deep WMH and Periventricular WMH
Genetic Correlation with WMH	Lower	Higher
Indicative Etiopathology	Cerebral Amyloid Angiopathy	Hypertensive Angiopathy
Suggestive Origins of Cognitive Impairment	Alzheimer's Disease	Vascular Origin of Cognitive Impairment

CSO-PVS, centrum semiovale perivascular space; BG-PVS, basal ganglia perivascular space; eGFR, evaluated glomerular filtration rate; CMB, cerebral microbleed; WMH, white matter hyperintensity

may account for the progression of CSVD and dementia. A recent cohort study with 5-years follow-up showed that EPVSs (diameters > 3 mm) are associated with the progression of subcortical infarcts, microbleeds, white matter hyperintensity and selective cognition decline [87]. Of note, the topographical distribution of PVS may be indicative of dementia aetiophathogenesis. CSO-PVS which begins to develop at middle age and increase with aging [88], has higher prevalence in general elderly and are regarded as the imaging marker of inadequate clearance of ISF. Generally, CSO-PVS appear to be more prevalent in CAA [75, 89] and associated with Alzheimer's disease, whereas the burden of BG-PVS appears to be correlated with subcortical vascular cognitive impairment [90]. Hence, the location and burden of PVS may provide ancillary neuroimaging information for the differentiation between Alzheimer's disease and vascular dementia.

Of particular note, global PVS, especially BG-PVS, are associated with increasing WMH burden [69, 74, 75, 91]. Increased deep WMH burden is associated with more severe EPVS both in basal ganglia and white matter, whereas periventricular WMH is associated with BG-EPVS [71]. Furthermore, there is a nominally significant association between EPVS burden in basal ganglia and genetic risk tendency from integrating susceptible variants in WMH development [74]. As described above, EPVS are considered as the indicator of inadequate drainage in glymphatic system, increased cerebral venous pressure and subsequent

neuroinflammation of blood–brain barrier, all of which lead to white matter disruption. The positive relation between WMH volume and elevated right atrial pressure which may reduce the drainage of glymphatic fluid as well as the return of cerebral venous in patients with chronic valvular heart diseases [92], indirectly support the close tie between WMH and PVS burden. Whether there is an overlap on etiopathogenesis between EPVS and WMH needs further evidence (Fig. 2).

Cerebral microbleed

Cerebral microbleed (CMB) is defined as a small, round or oval hypointense which is visible on T2*-weighted gradient-recalled echo (GRE) and susceptibility-weighted imaging (SWI) but generally can not be seen on computed tomography (CT) or FLAIR, T1-weighted, T2-weighted sequences [2]. In general, the boundary size of cerebral microbleed is 2–5 mm in diameter, while the maximal diameter can be up to 10 mm. In contrast, cerebral hemorrhage is larger and irregular shape of cavity which is visible on CT, T1-weighted and T2-weighted sequences of MRI. Pathologically, CMBs are the perivascular hemosiderin deposition, leaking form small vessels and usually phagocytized by macrophages, indicating that blood–brain barrier disruption and endothelia disfunction is an important pathogenesis of CMBs. This presumption is supported by the evidence of increased CSF/serum albumin ratios in patients with CMBs [93]. Common vascular risk factors, including age [94–97], gender of men [96], hypertension [94], smoking [94], hyperlipidemia, obesity and higher carotid intima-media thickness [98], large artery atherosclerosis [99, 100], carotid arterial stiffness [101], lower eGFR [95, 102–104] have found to be associated with the presence of CMBs. Apart from conventional vascular risk factor, serum cystatin C (CysC) [104], an indicator of early kidney function, and lipid-lowering/antithrombotic medication [94] also increase the prevalence of CMBs. Generally, cerebral microbleed can mainly be classified into lobar CMBs and deep/infratentorial CMBs according to the distribution of CMBs. Epidemiological investigation reveals different risk factor profiles between strictly lobar CMBs and deep/infratentorial CMBs, suggesting distinct underlying etiologies of CSVDs with CMBs [98, 102, 105]. Internal carotid artery atherosclerosis/stenosis [100], carotid arterial stiffness [101], internal carotid artery calcification [106], lower eGFR [95, 104] have stronger relationship with deep/infratentorial CMBs, while lower cholesterol level, APOEε4 [96], Aβ amyloid deposition [107] and chronic hypoperfusion [108] correlate with strictly lobar CMBs. Yet, hypertension is the independent risk factor for both deep/infratentorial CMBs and strictly lobar CMBs [96]. Usually, strictly lobar CMBs and deep/infratentorial CMBs mainly attribute to cerebral amyloid angiopathy (CAA) and hypertensive angiopathy respectively [109]. Lower CSF $A\beta_{42}$ level in CAA-related CMBs and higher WMH burden in CAA-unrelated CMBs also indicate distinct pathogenesis of CMBs in different types of CSVD [93]. Similar to other imaging markers of CSVD, the topographical distribution of CMBs seem to be correlated with distinct cognitive domains impairment. Strictly lobar CMBs have higher significance with global cognitive decline, executive functions, information processing and memory impairment [110, 111], whereas deep/infratentorial CMBs correlate with motor speed [110].

Clinically, cerebral microbleeds, which are regarded as asymptomatic precursor of intracranial hemorrhage, have strong relationship with intracranial hemorrhage (ICH). High burden (> 10 CMBs) of CMBs on baseline is a radiological predictor for indicating higher risk of hematoma expansion in intracranial hemorrhage [112] and symptomatic intracranial hemorrhage (sICH) in acute ischemic stroke treated with intravenous thrombolysis [113]. Actually, deep intracranial hemorrhage has been considered as one of the radiological phenotypes of CSVD and show strong correlation with other CSVD neuroimaging markers as well as the mortality and morbidity of CSVD [9]. Nevertheless, the contribution of CMBs burden in ICH recurrence differs between CAA-related ICH and CAA-unrelated ICH, and only CAA-unrelated ICH recurrence is associated with high CMBs burden (> 10 CMBs) [114]. Besides, healthy elderly with lobar CMB which may indicate a CAA involved pathogenesis, are prone to ICH, while others with deep CMBs are prone to both ischemic stroke and ICH, suggesting that the location of CMBs may have a predictive implication for stroke types as well as the underlying etiologies [94]. Therefore, cerebral microbleeds have been given increasing attention as an indicator for the evaluation of ICH recurrence and antithrombotic therapy in clinical practice. For one thing, increasing CMBs burden is associated with increasing risk of both recurrent ischemic stroke and intracerebral hemorrhage after ischemic stroke or transient ischemic attack [115, 116], though there is also contradictory evidence showing that neither CMBs burden nor location is associated with ischemic stroke recurrence [117]. For another, there is a yearly progressive increase of ICH risk, which may outweigh the risk of ischemic stroke and coronary events in patients with more than 5 CMBs [115]. Moreover, ischemic stroke or TIA patients with atrial fibrillation and CMBs have higher intracranial hemorrhage risk when given anticoagulation therapy [118, 119]. Therefore, it challenges physicians to balance the benefits of stroke prevention with the risk of ICH. Given that increasing evidences have validated the predictive effect of CMBs in ICH, it is proposed that CMBs should be included into the ICH risk assessment in patients with antithrombotic therapy. Meanwhile, it is noteworthy that application of statin increases the risk of CMBs

independent of cholesterol level and antithrombotic therapy [96], supporting by the evidence that progression of carotid IMT in hypertensive individuals is associated with lower risk of CMBs [100]. Yet, the potential mechanism of statin medication increasing CMBs risk remains elusive and controversial. Inhibition of statin on platelet activation and aggregation may be a postulated mechanism for explaining higher CMBs risk in patients treated with statin drugs. In conclusion, CMBs burden should be taken into consideration when defining prognosis, recurrence of stroke events and secondary prevention strategies for stroke.

Cerebral microbleeds are common in neurodegenerative diseases, cerebrovascular diseases. Secondary analysis from Framingham Herat Study reveals that CMBs are associated with increased all-cause mortality [120], incidence of dementia [121]. Beside, CMBs are associated with the presence of neuropsychiatric symptoms in elderly population [122]. Actually, cerebral microbleeds may present with no or slight clinical manifestation and are usually detected incidentally by MR scanning. However, even incidental lobar CMBs increase the prevalence of subjective cognitive decline [123], mild cognitive impairment [110] and stroke events [94] in nondemented elderly. Interestingly, there seems to be a higher prevalence of incidental lobar CMBs than that of incidental deep/infratentorial CMBs in general population [110]. More concretely, frontal, parietal and temporal lobes are the most frequent locations of incidental CMBs, followed by occipital lobe, infratentorial regions and deep brain parenchyma [110]. Nevertheless, both lobar CMBs and deep/infratentorial CMBs are associated with increased Alzheimer's dementia [110]. But lobar CMBs have higher indicative risk of developing Alzheimer's dementia in elderly population [110]. As mentioned above, lobar CMBs are mainly attributed to cerebral amyloid angiopathy, which is the pathological hallmark of Alzheimer's disease. In view of the close relationship between CAA and Alzheimer's disease, high burden of lobar CMBs may be regarded as one of the neuroimaging precursors of Alzheimer's disease in addition to hippocampus atrophy.

Interpretation of CSVD symptomatology from neuroimaging perspective

Atherosclerotic cerebral small vessel diseases usually progress slowly with an insidious onset in aging population. Gradual cognitive decline is the most common clinical manifestation in symptomatic CSVD but usually gain inadequate attention. Historically, atherosclerotic CSVD once was recognized as a subcortical disease since it mostly affected the perforating arterioles in the deep brain parenchyma and diffuse white matter hyperintensity is a characteristic neuroimaging feature of CSVD, typically in subcortical atherosclerotic encephalopathy. Actually, total CSVD burden is correlated with widespread cognitive decline and cortical atrophy [124], indicating that CSVD should be considered from a global neural network perspective. Nevertheless, the pathogenetic interpretation of white matter disruption, as well as other neuroimaging markers in CSVD symptomatology, has remained elusive. It is acknowledged that the white matter is crucial for information communication in the neural circuit among different brain regions. Long-term persistent hypoperfusion and energy metabolic failure resulting from the microvasculature atherosclerosis, stenosis contributes to the demyelination of white matter tracts (namely, the above mentioned WMH). The disruption of white matter leads to the dysconnectivity of subcortical–cortical regions linking to diverse cognitive domains including executive function, attention, information processing and memory. Consequently, the subcortical–cortical and interhemispheric dysconnectivity result in global cognitive deterioration. Accordingly, the white matter hyperintensity was conventionally presumed to be the most contributing factors for subcortical vascular cognitive impairment. For example, the white matter tracts destruction between prefrontal–subcortical circuit which are crucial for executive function, self-control and psychiatric regulation [125] may be partially responsible for some cognitive impairment including difficult execution, disinhibition and pseudo affective disorder in CSVD. Notably, periventricular WMH instead of subcortical deep WMH may be more strongly related to cognitive impairment though the underlying mechanism has not fully understood [126]. For one thing, periventricular white matter is more susceptible to ischemia since such territorial blood supply is originated from the terminal branches of subependymal arteries, striato-lenticular arteries and lack of collateral circulation. For another thing, according to the anatomical topography of white matter tracts, periventricular regions distribute a high density of long associating fibers connecting the various distant cortical territories and subcortical nuclei, while deep subcortical regions distribute more densely short-looped U-fiber connecting adjacent cortical regions [127]. Actually, periventricular WMH is prevalent in normal aging population, but their definite implication for cognitive decline needs further investigation. Finally, lacunes in strategic brain regions such as thalamus and temporal lobe may directly damage the pivotal connection for information processing.

As discussed above, the global network integrity disfunction is responsible for the cognitive impairment in CSVD. Apart from traditional MRI, diffusion tensor imaging (DTI) tractography technique and functional MR (fMR) delineates the brain structural and functional connectivity respectively. Accordingly, graph theory, an emerging hypothesis for illustrating the structural and functional connectivity from a global perspective, conceptualizes the brain as a network

reconstructed by a variety of nodes (brain regions). Highly centralized nodes form multiple hubs, such as precuneus, superior frontal and parietal cortex, hippocampus, putamen and thalamus [128]. And the hubs which are highly connected and interconnected with each other are defined as "rich clubs" [128]. The structural and functional connectivity among rich clubs is crucial for brain network organization and efficient information integration. It is found that CSVD burden has inverse correlation with structural network connectivity [124] and reduced rich clubs organization is associated with poor processing speed and executive functions [129]. The global network efficiency represented by shortest path for information integration partly mediate the association of CSVD neuroimaging markers with cognitive decline and progression in a longitudinal cohort [130]. And new surrounding white matter hyperintensity locates adjacent to previous lacunar infarct supports the hypothesis of CSVD penumbra [131] and global network perspective.

Movement disorders, another common symptom of CSVD, present as gait/balance disturbance and parkinsonism of presumed vascular origin, also known as vascular parkinsonism (VP). Epidemiological investigations show that CSVD burden has a significant correlation with gait/balance disturbance and parkinsonism in elderly with vascular risk factors [132] and baseline CSVD burden, in particular white matter volume and lacunes, increases the incidence of parkinsonism [133]. The white matter integrity disruption of bilateral frontal-subcortical basal ganglia circuit may contribute to gait disturbance [125, 134]. Longitudinal study shows that decreased stride length is associated with lower fractional anisotropy (FA) and higher mean diffusivity (MD) of white matter tracts along with the progression of CSVD [135]. Besides, cortical atrophy is another neuroimaging markers of gait disturbance and such correlation also may be mediated by the FA of white matter in frontal, parietal and bilateral corpus callosum [136]. With respect to parkinsonism, VP usually has an acute or insidious onset after stroke events and is characterized with bradykinesia, muscle rigidity and shuffling gait but less common for rest tremor compared with Parkinson disease [137]. Autopsy in patients with VP confirms the characteristic pathological features of CSVD including arteriolar lipohyalinosis, thickening vessels walls, enlarged perivascular space and lacunes, with the absence of Lewy bodies and tau inclusions [137]. Tract-based spatial statistics from DTI demonstrates decreased FA in bifrontal white matter tracts involved in movement control in vascular parkinsonism [133]. It is hypothesized that the destruction of white matter integrity in basal ganglia-thalamocortical circuit contributes to the inhibition of motor cortex and subsequent parkinsonism, similar to the pathogenesis of Parkinson disease.

With respect to emotional stress, systemic review demonstrates that both individual CSVD neuroimaging marker and combined CSVD burden is consistently related to the incidence of depression [138]. The pathology of CSVD including demyelination, infarction, microbleed may disrupt the structural and functional connectivity of neural fiber tracts linking among regions important for emotional regulation. Clinically, though physical disability is closely related to depression development in non-CSVD ischemic stroke patients, the association between CSVD and depression is mainly mediated by the white matter ultrastructure destruction but not by the disability caused by lacunar stroke in CSVD patients [139]. Besides, baseline WMH burden may predict the development of post-stoke depression though the potential mechanism has not been fully illustrated [5]. The interruption of cortical-subcortical network is postulated to account for the depressive symptoms and psychiatric disorders [140]. Apathy, a suggestive symptom of depression, is associated with reduced white matter integrity in limbic–cortical–thalamic–striatal network which includes anterior cingulum, corpus callosum, fornix, uncinate fasciculus, anterior thalamic radiation, anterior limbs of the external capsule [141]. It is noteworthy that limbic–cortical–thalamic–striatal network manipulates various cognitive activities, such as episodic memory, behavior initiation, linguistic processing. Hence, it seems there is a structural and functional neuronal network overlap between emotion and cognition. Accordingly, we suppose that multifactorial effects including physical disability due to vascular events, cognitive impairment and quality of life are all contributive to depression in CSVD.

Conclusion

In summary, neuroimaging markers of cerebral small vessel diseases are prevalent in general aging population. Though the underlying mechanism for the above imaging markers remains to be fully illustrated, abundant of clinical evidences mainly from retrospective studies reveal the complicated link between CSVD markers and neurodegenerative diseases. The radiological characteristics of CSVD markers are of guiding significance for differential diagnosis, prognosis evaluation and even personalized antithrombotic therapy, especially in absence of pathological proof. Along with more advanced structural and functional radiological technique, further efforts should strengthen more accurate interpretation of CSVD markers for the pathogenesis of diseases. Finally, more evidences from prospective studies are needed to verify the clinical implication of CSVD markers.

Compliance with ethical standards

Conflicts of interest We declare that we have no conflicts of interest to this work.

Ethical standards The manuscript does not contain any clinical studies or animal experiments.

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