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Small Vessel Disease and Memory Loss: What the Clinician Needs to Know to Preserve Patients' Brain Health

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Abstract Small vessel disease (SVD) in the brain manifests in the periventricular and deep white matter and radiographically is described as "leukoaraiosis". It is increasingly recognized as a cause of morbidity from middle age onward and this clinical relevance has paralleled advances in the field of neuroradiology. Overall, SVD is a heterogenous group of vascular disorders that may be asymptomatic, or a harbinger of many conditions that jeopardize brain health. Management and prevention focuses on blood pressure control, lifestyle modification, and symptomatic treatment.

Keywords Cerebral small vessel disease · CSVD · Lacunar infarct · SVD · Silent brain infarct · SBI · CMB · White matter hyperintensities · WMH · Leukoaraiosis · Dementia · Cognition · Neuropsychology · Behavioral neurology · Memory loss · Brain health

Introduction

Small vessel disease (SVD) is a heterogeneous group of vascular disorders resulting from a diverse set of physiological processes and blood vessel pathologies [1]. In this review article, we focus on SVD of the brain and its role in producing disability from cognitive decline and stroke. Awareness of SVD has exploded in recent years due to advances in neuroimaging, especially MRI scans, where small vessel disease is manifested mainly as periventricular and deep white matter hyperintensities (WMH); MRI is also exquisitely sensitive to cerebrovascular pathologies associated with SVD such as lacunar infarcts and microhemorrhages.

Part of the difficulty in communicating the concepts of SVD results from various and overlapping terminology used over the past 150 years. Historical entities include pathological findings of "Binswangers disease", "etat criblé", and "etat lacuniere". "Leukoariaosis" emerged in the 1980s and refers to white matter changes on CT and MRI scans of the brain and has since been replaced with the phrase "white matter hyperintensities".

Adding to the confusion in terminology is the role of SVD in the pathogenesis of cerebral infarction and cerebral hemorrhage. Lacunar infarcts are an ischemic stroke subtype that result from occlusion of small penetrating arteries (<20 mm diameter) and therefore occur in predictable regions: the thalamus, basal ganglia, posterior limb of the internal capsule, corona radiata, and brainstem. Due to their predictable location, they are recognized clinically by their clinical presentations. Lacunar infarct syndromes have been described for centuries and include pure motor hemiparesis, ataxic hemiparesis, sensorimotor stroke and dysarthria-clumsy hand syndrome [2]. Bilateral or multifocal lacunar infarcts may also cause pseudobulbar palsy, contribute significantly to the development of vascular dementia (VaD), or complicate primary degenerative dementias such as Alzheimer's disease (AD). While lacunar infarcts and white matter hyperintensities (WMHs) are often due to arteriosclerosis, there are other causes of SVD, which share different risk factor profiles [3].

Another form of SVD identified by advances in MRI sequences such as gradient echo or susceptibility weighted imaging is cerebral microbleeds (CMB). These may occur at low frequency in normal individuals, but are also increased in patients with vascular risk factors and are also associated with sporadic or familial cerebral amyloid angiopathy (CAA)

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[4, 5]. The relationship of cerebral microbleeds, which are typically asymptomatic, to the risk of symptomatic or fatal cerebral hemorrhage is unclear and a subject of current research [6]. Table 1 summarizes the various forms of SVD and their imaging characteristics.

Imaging and White Matter Hyperintensities

WMHs are best appreciated on MRI FLAIR and T2-Weighted sequences [7, 8••]. Several grading schemes have been proposed for clinical research but they are not used in routine clinical practice [9, 10]. Volumetric quantification of SVD is complex and limited to research studies of white matter volumes calculated with either MRI-voxel morphometry or diffusion tensor imaging (DTI) [11].

WMHs are cataloged by their location [12, 13], size, and confluency. WMHs related to ischemia are more likely to be "punctate", "early confluent", and "confluent" while non-ischemic changes are often "caps", "lining", and "bands" or a "halo" of high T2 signal [13]. Pathological heterogeneity lessens with increasing lesion severity [14••]. Assessing the clinical significance of SVD on MRI requires close clinical correlation and lesions are assessed by their patterns, anatomy and presumed or actual etiology [15–17, 18••, 19]. WMH or CMB may be incidental findings on imaging performed for other indications (e.g., headache, dizziness, falls in older patients, or migraine) [20, 21••, 22–25].

Epidemiology

SVD is quintessentially considered to be related to hypertension and aging, and is common after the age of 50 [26, 27]. Lacunar infarcts due to SVD accounts for 20 to 25 % of all ischemic strokes, with an annual incidence of approximately 15 per 100,000 individuals. WMHs are found randomly in about 40-50 % in adults of similar age groups [1]. Racial differences regarding lesion distribution exist, with higher rates of distal lesions (small vessel disease) observed in non-white races [28].

Physiology and Pathology of Small Vessel Disease

Given the heterogeneous nature of SVD, it is not surprising that they are associated with a variety of physiologic and pathologic changes including stasis [29], ischemia, microhemorrhage, failing vasodilation [30], changes in vasoreactivity [31••], and

Table 1 Terminology and imaging characteristics of cerebral small vessel disease

Equivalent terms	MRI sequences	Associated conditions		Location
Microangiopathic disease *Leukoaraiosis* (confluent lesions) ARWMC WMH ILA	• FLAIR • T2	Aging Hypertension Migraine Toxic insults (e.g., Chemotherapy, radiotherapy, toluene, alcohol, smoking) Chronic kidney disease Diabetes Vasculopathies* Lupus CADASIL Fabry's disease	Subcortical ischemic vascular dementia	Hemispheric and brain stem white matter Rarely in cerebellum
Lacunar Infarcts *Silent brain infarcts* when clinical correlate is unidentified ILI	• FLAIR • T1 • T2 • DWI	Stroke risk factors	Lacunar syndromes	5-20 mm Infarcts most commonly in: Basal ganglia Thalamus Internal and external capsule Brainstem Cerebellum
CMB Microhemorrhages	• GRE • SWI	• Aging • Alzheimer's disease • ICH • CAA		Hemispheric white matter Brainstem white matter Lobar when associated with CAA

CAA Cerebral amyloid angiopathy; *CADASIL* Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; *MRI* Magnetic resonance imaging; *FLAIR* Fluid attenuated inversion recovery; *DWI* Diffusion weighted imaging; *GRE* Gradient echo; *SWI* Susceptibility weighted imaging; *CMB* Cerebral microbleeds; *WMH* White matter hyperintensities; *ARWMC* Age-related white matter changes; *ILA* Ischemic leukoaraiosis; *ILI* Isolated lacunar infarcts; *ICH* Intracerebral hemorrhage

* Inflammatory or infectious vasculopathies

arterial stiffness [32•, 33, 34]. WMHs are characterized by reduced cerebral blood flow (CBF) [29, 35•], cerebral vascular resistance (CVR), endothelial [18••, 36•, 37•] and blood brain barrier dysfunction [38, 39], and thrombin leakage [40] among others (plasma proteins, albumin, inflammatory cells) [37•, 40, 41]. Consistent with these changes are findings of local thrombosis, whereas it is estimated that only about 10-15 % of SVD are embolic in nature [42].

The effects of SVD are more pronounced in white matter areas of the brain, where axons and their myelin coating compose about 40-50 % of the brain's volume. SVD and WMH are associated with myelin pallor, enlargement of perivascular spaces, gliosis, axonal loss [43••], disruption of the ependymal lining, and subependymal astrogliosis [44, 45••, 46]. Normal aging may have similar white matter pathology, but scattered WMHs are much more diverse [47].

SVD induces cortical atrophy when demyelination of axons leads to cortical-subcortical deafferentation and sequelae related to neuronal loss. SVD related vascular dementia preferentially damages frontal-basal ganglia networks and thalamocortical circuits [48–50]. Attention and memory depend on widely distributed neural networks and are not as highly modular and localizable as other aspects of perceptual and cognitive performance. Dorsolateral prefrontal and cingulate cortex circuit hubs are strategic brain networks [50, 51] as processing speed deficits in VCI are influenced by frontal-subcortical neuronal circuit lesions. The functional disruption of brain networks from SVD probably depends on the degree of brain plasticity in combination with other factors (genetics, demographic, lesion extent) and the ability to compensate for a given lesion [52, 53•].

Cerebral microbleeds (CMB) are small, less than 5 mm in diameter, regions of remote hemorrhage typically located in the basal ganglia, thalamus, posterior fossa, or posterior subcortical white matter and often occur in relationship to hypertension [54•, 55]. On MRI, CMB's are hypointense foci with sensitivity highest for susceptibility weighted imaging (SWI) vs gradient echo T2 (40 % vs 23 % [56]), however the clinical correlation of lesion number is limited and depends more on location and size.

CMBs are associated with cognitive dysfunction in non-demented older individuals, independent of ischemic SVD changes [57]. They can also be found in asymptomatic individuals for unclear reasons [58••, 59, 60••, 61–63]. Although there is a trend for higher ICH risk with CMBs, they have not been definitely associated with greater risk of symptomatic ICH following thrombolysis [64•, 65].

Cerebral amyloid angiopathy (CAA) is an alternative cause for CMBs and can be associated with AD, in autosomal dominant forms as well with or without dementia. Sporadic CAA is seen almost exclusively in the elderly and is a major cause of large cortical (lobar) ICH in the absence of hypertension [66].

Genetic Conditions and Small Vessel Disease

The genetics of SVD is a developing story [26, 67–69]. Apolipoprotein E type ε4 allele carriers have decreased integrity of white matter in corpus callosum, cingulate gyrus, and parahippocampal formation [70]. Small vessel pathology may be influenced by metabolic variants suggested by the association between common genetic variants in oxidative phosphorylation genes and SVD, stroke and ICH [71]. When comparing 19 candidate genes with neuroimaging from the Alzheimer's dementia neuroimaging initiative, no other genetic associations were found [72, 73•, 74]. Genetic tendencies for increased inflammation are associated with increased volume of WMHs [75].

A number of hereditary forms of cerebral amyloid angiopathy (CAA) have been described including mutations in presenilin (PS) 1 and PS2 genes, some due to mutations in the amyloid precursor protein on chromosome 21, and other forms cause SVD in a cortico-medullary territory distribution [84]. In these familial forms of CAA, the cause of the amyloid build up is likely due to increased production rather than poor clearance [85].

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant hereditary form of SVD. CADASIL usually presents with a history of migraine with aura, a mid-adult onset of cerebrovascular disease, mood disturbance, apathy, dementia, and diffuse white matter lesions and subcortical infarcts [76–78]. It carries a 5-10 % misdiagnosis in multiple sclerosis [79, 80], CADASIL is due to the effect of NOTCH-3 mutations on endovascular tissue.

Fabry's disease is due to an X-linked deficiency in alpha-galactosidase. It should be considered when stroke and proteinuria occurs in young males. Strokes are either small or large vessel in nature and diffuse white matter changes are commonly found. A relatively specific finding is a high signal intensity signal on MRI in the pulvinar, occurring in 20-30 % of Fabry's disease patients [81–83].

Small Vessel Disease in NeuroPsychiatric Disorders

It is increasingly recognized that severe WMH on neuroimaging is not benign and is linked to several forms of dementia [8••, 14••, 86] and hippocampal atrophy [87–89]. Longitudinal studies have linked WMH progression to mild cognitive impairment (MCI) and acceleration of brain atrophy over the rate experienced in normal aging of approximately 0.5 % per year [89]. Cerebral atrophy predicts the occurrence of MCI, and MCI conversion to dementia [90–92], most commonly AD, at a rate often estimated to be 15 % per year [93].

SVD effects are predicted by their location: frontal lobe lesions are associated with progressive cognitive decline

(38 %), gait apraxia (27.8 %), stroke related symptoms, seizures (24.2 %), transient ischemic attack (TIA) (22 %), and vertigo (17 %). Parietooccipital lesions may present as TIA and seizures. Basal ganglia lesions correlate with gait apraxia and vertigo [94]. Urinary incontinence is less frequent as a symptom of SVD [95].

Post-Stroke Dementia

Post-stroke dementia resulting from medium-to-large vessel brain infarcts is a common form of VaD [96] and is also closely related to SVD severity and brain atrophy [97, 98]. In symptomatic large artery atherostenoses, the presence and progression of periventricular WMH and lacunar infarcts are associated with greater progression of brain atrophy independent of vascular risk factors [19, 98].

Vascular Dementia

Vascular dementia and vascular cognitive impairment (VaD/VCI) accounts for about 20 % of all cases of dementia. The diagnosis of "probable VaD" requires evidence of cerebrovascular disease (CVD), usually confirmed by neuroimaging. SVD often has an insidious onset, challenging the temporal link of cognitive changes and stroke by the NINDS-AIREN criteria [99, 100]. In addition, VaD often co-exists with Alzheimer's disease pathology [12, 101]. The vascular component includes infarct(s), ischemia, hemorrhage or blood vessel pathology, while AD components are related to beta-amyloid (Aβ-42) deposition in brain, and hyperphosphorylated tau protein [87, 102, 103].

Common clinical features of VaD include slowed thinking, forgetfulness and disorientation [104]. Deficits in executive function, also known as "frontal lobe function" may result with relatively preserved language and recognition memory. Perseveration, depression or disinhibition may also occur [105]. Standard screening tests like the mini-mental state examination are insensitive to the cluster of features in primarily subcortical VaD [106, 107]. Testing executive function is more challenging than testing memory or visuospatial function, and detailed neuropsychological testing is often needed. Finger tapping tasks differentially engage attentional control systems and appear useful in the differentiation of AD, VaD and healthy subjects [108].

Differential Diagnosis of Vascular Dementia

In some patients, VaD is associated with progressive motor dysfunction termed vascular parkinsonism [109, 110], and presents as psychomotor slowing, gait disturbance [111] and falls [112, 113], urinary incontinence, emotional lability and pseudobulbar palsy [114] and is distinguished from Parkinson's disease in its lack of response to levodopa therapy. Other conditions include *normal pressure hydrocephalus* [115], and other synucleinopathies such as *dementia with Lewy bodies* [116], Parkinson's disease, and multiple system atrophy.

Depression

SVD has been implicated in the neurobiology of late life depression [105, 117]. The vascular depression hypothesis posits that SVD disrupts fiber tracts within frontostriatal circuits that regulate mood [118], and has been described as a type of "disconnection syndrome", leading to a clinical and neuropsychological profile of depression [119]. Vascular mediated depression may be recurrent and respond poorly to SSRI's [120]. Severe deep WMH remains an independent predictor of post-stroke depression [121] and periventricular WMH may be a strong predictor of suicide attempts in bipolar and unipolar depression [122].

Other Conditions Associated with Small Vessel Disease

Rarer conditions associated with SVD include Susac's and Sneddon's syndromes. The former presents with combinations of encephalopathy, hearing loss and branch retinal artery occlusions [123]. Sneddon's syndrome is characterized by stroke and TIAs, livedo racemosa of the skin, headache (62 %), vertigo (54 %), seizures, mental deterioration, and dementia [124].

Systemic Risk Factors for Small Vessel Disease

The risk of SVD and WMH increases steadily with age and are associated with a variety of systemic disorders, metabolic derangements and lifestyle variables including hypertension, chronic kidney disease, diabetes, alcohol use and homocysteine levels [125] (see Table 2).

Hypertension and Chronic Kidney Disease

Midlife hypertension is a risk factor in the development of later cognitive impairment [79, 126–129]. Progression is faster in women and depends on the volume of lesions at baseline [105, 130], older age, cigarette smoking, and elevation of blood

Table 2 Main risk factors for small vessel disease

Hypertension
Diabetes
Coronary artery disease
Obesity (body mass index of 30 or higher)
High homocysteine levels
Inactive lifestyle
Age: Older than 45 in men and older than 55 in women

pressure [131–133]. Chronic hypertension leads to changes in cerebral blood flow autoregulation. A shifted "set point" adapted to higher perfusion pressures, also leads to increased risk of symptomatic hypotension. Cautious use of antihypertensives is recommended as even small periodic hypotensive episodes contribute to WMHs [134–136]. Ambulatory blood pressure monitoring has identified nocturnal patterns of blood pressure shifts, with extreme falls in blood pressure being associated with SVD [137•, 138, 139]. Obstructive sleep apnea often complicates hypertension [140, 141••] produces widespread structural and functional changes in the brain [142], and is a recognized factor for TIA and small vessel stroke. Chronic kidney disease is highly correlated with SVD [58••, 143, 144] and chronic kidney disease increases the risk of lacunar infarcts, possibly through a shared pathophysiology of small vessel injury [58••, 145, 146].

Diabetes

Diabetes is a risk of vascular dementia (VaD), AD, MCI, and all-cause dementia, and cross-sectional studies have shown that diabetics have reduced performance in numerous cognitive domains [144]. SVD seen on MRI in diabetics is also a good marker for predicting future cognitive decline [145]. There is an inverse correlation between hemoglobin A1c levels, motor speed, and psychomotor response [147–149]. In patients with type-1 diabetes, specific and global deficits involving speed of psychomotor efficiency, information processing, mental flexibility, attention, and visual perception [150] are seen. Type-2 diabetes patients show an increase in memory deficits [151], reduced psychomotor speed, and reduced executive functions. It also causes an autonomic dysfunction that is implied in the pathophysiology of SVD [152, 153].

From a clinical perspective it is important to consider the patient's age at the onset of disease, the glycemic control status, and the presence of complications when estimating the interactive effect of diabetes and SVD on the brain [154•]. The role of glycemic control is still uncertain but may have a U-shaped association with cognitive impairment [155].

Other Vascular Risk Factors

Other possible SVD risk factors include alcohol, cigarette smoking, diet and elevated serum homocysteine [156•, 157, 158]. After a period of abstinence, alcoholics show partially reversible pathology of widespread micro and macrostructural and metabolite changes [159] of the white matter by MRI diffusion tensor imaging (DTI), that contrast with the vulnerability of tracts in the frontal lobe, thalamus and middle cerebellar peduncle to acute alcohol consumption on DTI. Mild to moderate alcohol consumption is not associated with a higher risk of cognitive decline and may have a protective effect against dementia [160•].

In some population-based studies chronic smoking increase the risk of WMH on MRI [161, 162]. Longer-term tobacco use is associated with increased risk of cognitive impairment and dementia including AD [162]. In elderly individuals, smoking was associated with decrease in cerebral perfusion and reduced cerebral gray matter volume, possibly mediated by SVD.

The location of WMHs in association with smoking seems to differ among age groups when comparing WMH burden on smokers under and over the age of 65. Multivariate regression analysis showed that cigarette smoking was an independent risk factor for periventricular-WMHs in the younger age group and for deep-WMHs in the older age group [163]. The effects of diet on SVD are only beginning to be assessed. In a large cross sectional study, the Mediterranean diet was associated with lower burden of WMHs [164].

Interventions

The cornerstone of SVD and small vessel stroke prevention has been identification and modification of risk factors such as diabetes and hypertension [165, 166]. Aspirin may exert a partial effect due to mechanisms that decrease superoxide radicals, which abolishes amyloid mediated vasoactivity and damage [167], and also reduce endothelial disruption through inhibition of cyclooxygenase and matrix metalloproteinase production by microglia/macrophages [168]. Overall, data specific to isolated WMH or SVD- stroke subtype prevention or disease modification is scarce [169].

Blood Pressure (BP) Lowering Therapy

The relationship between BP and risk of cognitive impairment is a complex one. Midlife hypertension (40–60 years of age) increases VaD and AD risk. Previously, it was thought that control of blood pressure in the range of 135 to 150 mmHg might be useful to maintain cognitive function in people with hypertension and VCI, or the use of aspirin might improve cerebral perfusion. The ACCORD study in hypertensive diabetics failed to show significant decreases in dementia risk, but a BP goal of 120/80 mmHg significantly reduced stroke risk [170••]. Beyond the questionable utility of anti-hypertension strategies to decrease the incidence of dementia, there is much to be learned about anti-hypertensives modifying dementia progression. In the oldest old (>90), hypertension may be protective for dementia risk [171–173]. Trials targeting aspirin and aggressive blood pressure management will provide further insight into prevention and treatment strategies (ASPREE, SPRINT-MIND) [174]. The effects of nocturnal blood pressure

"dipping" and BP variability as a risk factor for SVD is only beginning to be recognized [137•, 175•].

Lifestyle Modification

Multiple biological pathways link cognitive lifestyle to protection from dementia [8••, 73•, 176–178]. Prevention includes modifying cardiovascular risk factors through physical, cognitive and social activity, balanced nutrition, smoking cessation, limiting alcohol use, and promoting sleep-quality. Because of its long prodromal phase, the timing of the interventions remains a therapeutic challenge [179, 180].

Physical and Mental Activity

Physical activity may reduce risk of dementia by increasing oxygen saturation and neurogenesis, decreasing vascular risk factors [181], inflammation, and depressive symptoms [182]. Cardiovascular exercise is one of the few interventions that increases neuronal plasticity and replication, and plays a role in neuroprotection, and has neuroimmunological effects in depression, and other chronic conditions [183, 184]. Body fat distribution is associated with both SVD and atherosclerotic and ischemic cerebral lesions [185]. There is also a positive relation of lesion load with age, arterial hypertension, and obesity [31••]. Weight loss has been linked with improvements in executive-function and attention [186]. Regular mental exercise, popularly known as "brain games", is considered a positive lifestyle intervention, but unproven in its efficacy, and its effects in terms of improving *all* cognitive domains ambiguous [187–190].

Symptomatic Treatment

Memantine and nimodipine both have statistically significantly better outcomes in cognition in the setting of some key endpoints in large trials of VaD. A clinical trial of donepezil for 24 weeks in VaD improved ADAS-Cog scores, but had no significant effects on global function [191].

The recommendations for drug treatments of VaD from the AHA-ASA are: 1) donepezil may be useful for improving cognition (Class IIa, LOE A); 2) galantamine may be useful for patients with mixed AD/VaD (Class IIa, LOE A); 3) the benefits of rivastigmine and memantine are not established. Overall the data is insufficient to recommend the widespread use of these medications in VaD [178, 192•].

Conclusion

Medical advances have shown that SVD is frequently seen and linked with many common disorders and finding an optimal prevention and treatment of SVD and vascular dementia remains a challenge, especially given the uncertainties of causation and complex pathophysiology [94]. Treatments to reverse or halt SVD progression are not yet available or have not been validated and there is clinical and pathological overlap between VaD and AD. Further research addressing the complexity of SVD by integrating data from brain MRI and innovative in-vivo imaging, screens of cognitive function, and DNA analysis [193] may help define biological subtypes for designing intervention studies [9, 128].

Enhancing Brain Health and quality of life across the lifespan should be a priority when intervening in brain disorders. Clinicians need to integrate many sources of information including genetic and environmental factors along with patient preferences and risk benefit calculations in formulating an individualized diagnostic approach and treatment plan. SVD is frequently not a benign sign of "aging", but must be interpreted and treated in context of the above issues.

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Compliance with Ethics Guidelines

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- • Of importance
- •• Of major importance

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