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Cerebral small vessel disease (CSVD)-related dementia:more questions than answers

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Abstract

Cerebral small vessel disease (CSVD) has emerged as a common factor driving age-dependent diseases, including stroke and dementia. CSVD-related dementia will affect a growing fraction of the aging population, requiring improved recognition, understanding, and treatments. This review describes evolving criteria and imaging biomarkers for the diagnosis of CSVD-related dementia. We describe diagnostic challenges, particularly in the context of mixed pathologies and the absence of highly effective biomarkers for CSVD-related dementia. We review evidence regarding CSVD as a risk factor for developing neurodegenerative disease and potential mechanisms by which CSVD leads to progressive brain injury. Finally, we summarize recent studies on the effects of major classes of cardiovascular medicines relevant to CSVD-related cognitive impairment. While many key questions remain, the increased attention to CSVD has resulted in a sharper vision for what will be needed to meet the upcoming challenges imposed by this disease.

Introduction

The broad term cerebral small vessel disease (CSVD) describes heterogeneous conditions affecting blood vessels of 50 to 500 micrometers in diameter. Multiple distinct pathologies can cause CSVD, most commonly hypertensive vasculopathy and cerebral amyloid angiopathy (CAA). The clinical challenge is that rarely are there indications for obtaining tissue for a definitive diagnosis. Neuroimaging, however, is readily available, and standards exist for using imaging to diagnose CVSD [1] (Fig 1). The STRIVE group proposed standardized terminology and suggested minimum standards for imaging suspected CSVD,

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though imaging technology continues to evolve. Current and future standards for CSVD diagnosis will certainly depend on feasible, reliable, and quantitative neuroimaging.

CSVD can manifest as symptomatic cerebral hemorrhages, small ischemic strokes, and cognitive impairment. Symptomatic hemorrhages are easily recognized and diagnosed. Small ischemic strokes are also easy to recognize, but small strokes from CSVD must be distinguished from strokes due to small emboli. Thus, even when pre-test probability is high, neuroimaging is essential for diagnosing CSVD.

Diverse CSVD markers seen on MRI (Fig 1) correlate in aggregate with cognitive and functional decline [2]. Findings such as white matter hyperintensity raise suspicion for CSVD. Additional imaging findings with greater specificity but unknown sensitivity for CSVD include enlarged perivascular spaces [3], abnormal diffusion measures [4], and blood-brain barrier (BBB) leakage seen with dynamic contrast enhanced MRI (DCE-MRI) [5]. Other lesions, such as recent small subcortical infarcts, lacunae of vascular origin, and microbleeds are the most specific, clinically available CSVD biomarkers.

CSVD-related dementia is a major subgroup within vascular cognitive impairment and dementia (VCID). VCID is a challenging disorder to ascertain, prompting numerous groups to evaluate diagnostic criteria to make the diagnosis more reliable and enable cross-study comparisons. A comparison of 5 major diagnostic criteria for vascular dementia applied to consecutive ischemic stroke patients followed for 3 months with MRI and cognitive testing found wide variability in the prevalence of vascular dementia depending on criteria used from 32.7% (ADDTC criteria) to 91.6% (ICD-10 criteria)[6]. The same study found that only 37.4% of patients had focal neurological deficits at 3 months, highlighting the importance of imaging to detect cerebrovascular disease.

The limited clinicopathological studies of VCID highlight the challenges of making a premortem diagnosis that correlates well with pathology. An autopsy study of 89 patients with dementia found no statistically significant relationship between a neuropathological diagnosis of vascular dementia and any of three clinical criteria (ICD-10, ADDTC, and NINDS-AIREN) [7]. Another challenge is that there is no agreed upon histopathological diagnosis for VCID [8], though commonly cited features of CSVD include wall thickening, vascular cell loss, and laminar protein accumulation (Fig 2). Ongoing studies correlating imaging with pathology should help in making reliable premortem diagnosis of clinically significant CSVD[9].

CSVD-related dementia is thus in a state of evolution: though well-recognized as an important entity, many improvements in understanding await. Since many excellent discussions have already been presented, this review focuses on five common questions.

My patient has CSVD. Will it cause dementia?

CSVD does not always lead to dementia or even cognitive impairment. In routine practice, MRI obtained for a variety of concerns in cognitively normal middle aged or older individuals will frequently demonstrate findings associated with CSVD. Although the presence of CSVD does not ensure dementia, there appears to be a strong correlation between CSVD and development of dementia in diverse populations. The best evidence of this is provided by longitudinal studies. At least 20 studies[10–21] have investigated white matter hyperintensities and incident dementia that, in large part, include European and North American populations; two studies of these investigations were performed in East Asia.

A meta-analysis of studies over the last two decades by Debette et al [22] places the hazard ratio imposed by CSVD as 1.84 (p<0.001; over 9,338 study subjects); the total incidence of dementia among these subjects was 12%, though the length of observation for each of the studies varied significantly. Two separate overlapping meta-analyses by Rensma [23] and Bos [24] concluded that white matter hyperintensities presented a significant risk of incident dementia. As such, the pragmatic counseling for patients found to have CSVD is that this condition does not always cause dementia, but that it substantially increases the risk.

Although in practice these principles are applied broadly, current studies do not adequately cover all ethnicities and races. It is also not known whether there are other clinical characteristics, combinations of risk factors, or genetic determinants that render CSVD deterministic in some individuals.

Since CSVD is associated with several abnormalities on MRI, there could be subtypes of sporadic age-related CSVD [25]. One question that has emerged is whether specific MRI markers of CSVD could be useful in prognostication of dementia. Debette et al [22] analyzed several CSVD features for as predictors of dementia. Although white matter hyperintensities were clearly associated with increased risk of incident dementia, subcortical brain infarcts or cerebral microbleeds did not reach significance, despite the size of the aggregate study population (8,736 individuals). Rensma [23] and Bos [24] found that dementia was increased or borderline significant in studies of patients with lacunar infarcts but not microbleeds. The ability to compare these MRI findings is limited because most studies lacked direct comparison of MRI features. Studies on perivascular space[3] , have reported increased incident dementia risk in a small number of studies [26 27] .

My patient has dementia. Is this CSVD-related dementia?

In dementia, especially late-life sporadic disease, definite diagnoses are based on neuropathological examination only available at autopsy [28,29]. Marching back from that, select *in vivo* biomarkers, such as Alzheimer's disease Amyloid/Tau/Neurodegeneration (A/T/N) biomarkers, aid in pre-mortem diagnoses with high confidence. In contrast, outside of monogenic causes of VCID, cognitive impairment due to CSVD faces diagnostic obstacles. The first problem is lack of clear neuropathological consensus criteria. The second is the scarcity of sensitive and specific *in vivo* biomarkers for CSVD-related VCID. The third is lack of distinct clinical syndromes for VCID. The fourth is the variable lag between diagnosis of vascular risk factors or vascular disease and onset of cognitive and neurobehavioral symptoms, diminishing the power of predictive models with limited longitudinal follow-up.

In post-mortem analyses of individuals with dementia, vascular disease, especially CSVD lesions and tissue abnormalities, such as microinfarcts, microbleeds, and arteriolosclerosis, have been noted as common pathologies and co-pathologies, increasing the odds of dementia in the aging brain[30]. The challenge, however, has been in attributing the cause of pre-mortem dementia to CSVD, especially in the setting of quantifiable non-vascular neurodegenerative diseases [31].

The likelihood of causal assignment of cognitive impairment to vascular disease is further decreased in the setting of co-existing non-vascular neurodegenerative disease syndromes that have syndromic presentations and/or biomarkers (e.g., AD)[29]. This in part is due to lack of clear clinical syndromes associated with CSVD and, critically, a lack of highly accurate CSVD *in vivo* biomarkers. For example, in AD, post-mortem analyses have demonstrated that 80–100% of individuals with parenchymal amyloid plaques have CAA. When CAA is significant, especially in *APOE4* carriers, cortical microbleeds can be seen on brain imaging. These microbleeds can be seen prior to significant cognitive and functional impairment, and in some instances are the first imaging abnormality noted for a patient who may also demonstrate white matter hyperintensities, arteriolosclerosis, and lipohyalinosis [32]. Even so, attribution of brain dysfunction to AD in patients with mixed AD and CSVD has traditionally underestimated vascular contributions.

AD has several clinical syndromes such as the typical amnestic-predominant or limbic AD, behavioral-executive AD (bvAD), posterior cortical atrophy (PCA), and logopenic variant primary progressive aphasia (lvPPA). The syndromic presentations of these variants are assumed to be non-vascular, but the prevalence of CAA is thought to be similar across AD syndromes; thus, in such syndromes, the vascular contribution to dementia deserves more investigation. Outside of AD, additional clinical syndromes, such as frontotemporal dementias and Lewy body disorders are considered non-vascular neurodegenerative diseases. The prevalence of CSVD in these syndromes remains understudied. Yet, CSVD affects white matter and brain connectivity, causing cognitive speed and executive function decline which are common to non-vascular disorders and CVSD. Symmetric parkinsonism is another clinical symptom that could be due to subcortical CSVD. These motor manifestations are also not sufficiently specific enough to point the diagnostic compass toward VCID.

Teasing apart diverse CSVD contributions to clinical symptoms would require *in vivo* molecular biomarkers that are not currently available. MRI-apparent CSVD lesions, detailed above, are unlikely to be the earliest manifestations of disease. Moreover, none have been demonstrated to be both sensitive (as an early abnormality) and specific (capturing disease of vasculature rather than neuro-glial degeneration). Importantly, dysfunction of the BBB (discussed below), measured by DCE-MRI as well as with CSF/serum albumin quotient, is an uncommonly assessed parameter in practice and research, though recent studies suggesting a potentially early causal association with brain dysfunction and degeneration.

Notwithstanding, according to the 2020 Lancet Commission's Report on Dementia Prevention, Intervention, and Care, up to 40% of dementias worldwide are preventable [33]. Many of these modifiable risk factors either directly or indirectly fall under the rubric of vascular disease. Therefore, CSVD is an important contributor to brain dysfunction and an ideal therapeutic target for cognitive impairment and dementia. Brain blood vessels have numerous roles, such as gating communication between peripheral organs, blood, and brain, interacting with immune cells and controlling entry and exit of molecules, and cells to and from the brain. In addition, a molecular cross-talk between blood vessel cells and neurons control steady state perfusion as well as rapid on-demand increases in cerebral blood flow to active neuronal networks[34]. Therefore, CSVD is a reasonable contributor to disorders of cognition.

In summary, in routine clinical practice, whether CSVD causes dementia in a particular patient is not easily answerable. Brain dysfunction frequently occurs in the setting of multiple pathologies. Current barriers to assignment of roles of CSVD in neuropsychiatric symptoms, motor dysfunction, and cognitive impairment include the need for better *in vivo* molecular and imaging biomarkers, methods to disentangle mixed vascular and non-vascular pathologies, and better clinical recognition of mechanisms connecting CSVD to brain dysfunction.

My patient has CSVD-related dementia. What is the differential diagnosis of CSVD dementia?

Vascular risk factors and qualitative evaluations of small and large vessel diseases are considered treatable, potentially modifiable risk factors for neurodegenerative disorders. But the extent to which CSVD and other vasculopathies contribute to brain degeneration in each patient generally remains a matter of opinion and escapes a specific diagnosis. Monogenic vasculopathies are the exception to the diagnostic ambiguity regarding VCID. Clinical syndrome, family history, and imaging biomarkers raise suspicion for a genetic cause of SVD-related dementia (Table 1), which genetic testing can confirm. Several are described below.

CADASIL, caused by *NOTCH3* mutations, is a uniquely pure form of CSVD that features insidious onset, gradually progressive neurobehavioral decline, chronic white matter disease (with involvement of anterior temporal lobes), lacunes, microbleeds, and migraines [35]. Less frequently, parkinsonism or seizures have also been reported [36]. Separate from CADASIL, *NOTCH3* mutation disease can present with either syndromic findings or lead to other neurological presentations[37]; NOTCH3 mutations are also associated with AD [38] and Parkinson’s disease syndromes [39]. Recent studies indicate that up to 1:300 individuals carry mutations in *NOTCH3* [40,41].

CARASIL, an autosomal recessive disease related to mutations in *HTRA1*, presents with CSVD and non-neurological symptoms of alopecia, spondyloarthropathies and changes in vision. Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic manifestations (RVCL-S), affects mainly brain and retina and is caused by mutations in *TREX1.* A unique feature of RVCL is that lesions may appear and behave like tumors.

Gould syndrome caused by mutations in *COL4A1* and *COL4A2* leads to defects in extracellular matrix, notably vascular basement membranes with multi-organ involvement including a characteristic CSVD, cerebral cortical developmental abnormalities, myopathy, renal and lung dysfunction, and marked ophthalmic abnormalities with developmental defects (ocular dysgenesis). Mutations in the 3’ untranslated region of COL4A1 mRNA can cause PADMAL (Pontine Autosomal Dominant MicroAngiopathy with Leukoencephalopathy), characterized by early adult-onset pontine strokes.

Although these genetic CSVD syndromes can be confirmed easily using genetic testing, they are uncommon. Sporadic, age dependent CSVD is by far the most common cause of this condition in the general population. But discoveries in rare genetic VCID syndromes could inform the mechanisms and therapy of sporadic disease.

What is the biological basis of CSVD dementia?

Advanced morphological and molecular techniques have enabled a more nuanced understanding of the structural changes that result from CSVD. Further, advanced imaging has enabled investigations in cross-sectional and longitudinal cohorts. Physiological studies of animal models of CSVD, modeling human genetic disorders, permit investigation of how CSVD leads to functional alterations of the brain that are presumed to cause dementia. What has emerged from these multidisciplinary studies are three core potential mechanisms by which CSVD leads to imaging changes – an imperfect proxy for dementia.

Decreased cerebral blood flow.—Lowering of overall blood flow in CSVD has been suggested as a mechanism driving dementia. It is reasoned that CSVD results in chronic hypoperfusion, particularly to watershed regions such as the deep white matter, which demonstrates the most severe MRI abnormalities. If true, one would expect lower cerebral blood flow (CBF) in patients with CSVD; moreover, lower blood flow should predict development of MRI changes and dementia.

The drop in global cerebral blood flow in patients with CSVD has been observed in numerous populations in cross-sectional analyses [42–48], though not universally [49–51] . Meta-analysis describes an association between low cerebral blood flow and CSVD inferred by MRI [49] . In many studies in which blood flow dropped, the fall in flow was associated with atrophy, suggesting to some that flow changes were a result of tissue injury and not the cause of brain parenchymal damage. In longitudinal studies, there have been mixed results: some studies show CBF deficiency predicting MRI hyperintensities while others find falling CBF after development of lesions [52] [53] [54] [55] . Further complicating the issue, regulation of flow may change at different stages of disease [56]; in early CSVD, resting CBF may increase, raising the possibility of shunting that may injure tissue.

Protein markers of hypoxia within white matter lesions have been presented [57] in a histopathological study of postmortem brain. But whether these markers presage the development of structural changes is not clear.

Alteration of the blood brain barrier.—Other investigations have been presented that support CSVD causes brain parenchymal damage via changes in two vascular functions: 1) blood brain barrier integrity and 2) vasoreactivity determined by activity.

Structural abnormalities observed in CSVD can decrease BBB integrity. Pathological studies performed on autopsy-derived samples from patients with sporadic CSVD have shown extravasation of blood proteins [58–63]. The ultrastructural components of the BBB are affected in mice expressing NOTCH3 mutant protein [64] . In CSVD patients [65–70], BBB breakdown has been described in multiple cohorts. Longitudinal studies suggest that areas of BBB breakdown predict evolution of WMH [71,72] . The relative importance of specific substances that leak through the BBB to damage brain parenchyma remains an unknown, but serum proteins have been suspected to be harmful. For example, fibrinogen can cross a leaky BBB [58,60] and has multiple cellular targets, including activation of microglia [73,74] and blockade of oligodendrocyte replacement [75].

Not all investigations support a role for BBB breakdown in CSVD. There was little evidence of BBB breakdown in neuropathological investigations of general CSVD [76] or in CADASIL pathological samples [77] and pre-clinical models [78] . Nonetheless, a causal role of BBB impairment deserves further investigation.

Attenuation of regional cerebral vasoreactivity.—The brain vasculature features an autoregulatory system that couples flow to demand at a microscopic level. Impaired activity-related changes in flow may selectively stress regions of metabolic demand, resulting in chronic and intermittent hypoperfusion that may not be appreciated in bulk CBF investigations.

Sam et al [79] reported decreased cerebrovascular reactivity in regional patterns that correlated with abnormal diffusion and perfusion patterns. Importantly, in longitudinal analysis, areas of loss of cerebrovascular reactivity developed white matter hyperintensities at one year follow-up [80,81] . Further, Blair and colleagues [82] described decreased vascular reactivity in CSVD as assessed by MRI BOLD during a hypercapnic challenge that was related to the burden of white matter hyperintensities.

In CADASIL, Chabriat et al [55] did not observe decreases in vasoreactivity in normal appearing white matter, although blood flow and reactivity were decreased in areas of white matter hyperintensity. But Liem et al described a cohort of CADASIL subjects with decrease reactivity to acetazolamide [83] that correlated with worsening of white matter hyperintensities 7 years later. Although total cerebral blood flow was decreased in this CADASIL cohort, unlike reactivity, it did not correspond with radiological worsening. Separately, ASL demonstrated impaired vascular reactivity in CADASIL in response to visual and motor stimulation [84] , with unimpaired evoked potentials.

In CADASIL animal models of CSVD, arteriolar vasoreactivity to chemical stimulation of downstream endothelial cells or to whisker stimulation is impaired via attenuation of an endothelial inward rectifying potassium channel Kir2.1. Features upstream of Kir2.1 impairment, including TIMP3-mediated suppression of EGFR signaling, implicates a potential comprehensive pathological pathway to CSVD[85].

Other pathways to dementia.—A role for pathology of oligodendrocytes has also been investigated, though these sites of injury are likely downstream from the initiating vascular problem [86,87]. In line with this, oligodendrocyte precursor cell progression, which is thought to aid in repair of white matter injury, has been shown to be inhibited by endothelial damage in cathepsin A-related arteriopathy[88].

What are the core recommendations for the management of CSVD dementia?

Antihypertensives.—Treating hypertension prevents first and recurrent stroke, and, as the SPRINT trial demonstrated, intensive blood pressure targets reduced fatal and non-fatal cardiovascular events and all-cause mortality 8[89]. Meta-analyses of randomized trials of antihypertensive treatments found that antihypertensive treatment reduces white matter hyperintensities, and more intensive therapy is more effective [90,91].

However, evidence for intensive blood pressure control having a beneficial effect on cognitive outcomes (cognitive decline, MCI, or dementia) is not certain. SPRINT found that intensive blood pressure control reduced the incidence of MCI but did not significantly reduce risk of dementia [92]. A SPRINT substudy did not show benefit from intensive therapy on memory or speed of mental processing [93]. This lack of clear benefit on dementia, memory, or speed of mental processing is particularly disappointing because SPRINT found favorable effects of intensive blood pressure lowering on white matter disease, whole brain volume, and cerebral blood flow (Table 2). A meta-analysis involving over seventeen thousand patients found no association of lower versus standard blood pressure targets with incidence of cognitive decline, MCI, and dementia [98]. It is possible that the neutral results from intensive blood pressure trials are the product of intervening later in life and not following patients long enough to detect treatment group curve separation.

While blood pressure lowering has been shown to improve radiographic and physiological parameters, on balance one cannot currently conclude that intensive pharmacological blood pressure lowering definitively protects patients from dementia. However, there does not appear to be cognitive harm from lowering blood pressure. Elderly patients are at greatest risk of incident cognitive impairment and dementia, and older patients show the same relative risk reduction of cardiovascular events as younger patients from pharmacological lowering of blood pressure [99].

Antiplatelet therapy.—Antiplatelet therapy has been studied extensively in patients with ischemic strokes due to CSVD. A meta-analysis of seventeen trials found that single antiplatelet therapy (SAPT) effectively reduces risk of recurrent stroke in patients with recent small subcortical infarct [100]. However, the SPS3 trial found that dual antiplatelet therapy (DAPT) with aspirin and clopidogrel doubled risk of bleeding without lowering the risk of recurrent stroke [101]. Much less is known about the effects of antiplatelets on dementia associated with CSVD.

Table 3 proposes how to manage antiplatelet therapies in patients with cognitive impairment based on clinical and imaging characteristics. In patients without recent small subcortical infarct who are found to have signs of CSVD either incidentally (e.g., for evaluation of headache) or during evaluation of MCI or dementia probably ought not be prescribed aspirin unless they have manifest atherosclerotic disease. A series of recent randomized trials do not support aspirin for primary prevention in several adult populations without manifest atherosclerosis [102]. Also, when the timing of occurrence of a radiographically detected lacune is unknown (asymptomatic and not DWI+), aspirin may well be of no benefit in reducing recurrence. A meta-analysis of secondary prevention trials showed that benefits in reducing recurrent stroke seen before 12 weeks of stroke onset were no longer evident beyond 12 weeks [103]. To add further concern about broad use of antiplatelets for CSVD, microbleeds are a marker of risk of hemorrhagic stroke in patients taking aspirin, and meta-analysis of 37 observational studies showed that antiplatelet therapy increases the risk of lobar CMBs and intracranial hemorrhage [104].

Statins.—A meta-analysis of studies through 2017, found that use of statins reduces the risk of all-type dementia, mild cognitive impairment, and AD [105]. Interestingly, statin use did not significantly lower the risk of vascular dementia [105]. Ott et al analyzed the literature up to 2015 and suggested that fears that statins impair cognition appear unfounded [106].

Though trial data are limited, statins appear to reduce new silent infarcts and reduce white matter hyperintensities [107]. Statins have no appreciable effect on microbleeds overall but may increase risk of lobar bleeds [108]. Interestingly, a 2×2 factorial trial of telmisartan and low dose rosuvastatin in elderly hypertensive individuals, found that rosuvastatin lowered the incidence of Fazekas ≥2 white matter changes and that there was a favorable interaction with telmisartan [109]. At this point, it is appropriate to use statins in accordance with primary and secondary guidelines for prevention of cardiovascular and cerebrovascular disease [110].

Diabetes control.—Randomized trials have shown that intensive glycemic control in patients with diabetes reduces risk of microvascular complications (neuropathy, nephropathy, and retinopathy), but has not been shown to reduce risk of impaired memory or cognitive function[111]. There is limited evidence for intensive glycemic control preserving small vessel function. However, diabetes is not a contraindication to tight blood pressure control. Secondary analysis of the ACCORD MIND trial showed that in patients with type 2 diabetes mellitus tight blood pressure control reduced progression in white matter hyperintensities [112].

Cholinesterase inhibitors.—Many patients with vascular cognitive impairment will have CSVD. Cholinesterase inhibitors have demonstrated modest significant benefit in cognition in patients with vascular dementia [113]. However, this modest benefit comes at a cost of side-effects that may include dizziness, nausea, vomiting, and diarrhea. If the patient is willing to accept the risks, a therapeutic trial is reasonable, but if clinically significant benefits are not observed by 3 months, the medication should be discontinued.

Conclusions and future directions

CSVD has attracted significant attention due to its high prevalence, impact on neurological health, and clear role in dementia. Several features of CSVD-related dementia have been highlighted: 1) CSVD-related dementia is a group of heterogenous pathologies that currently depend on MRI imaging for diagnosis; 2) CSVD is not deterministic of cognitive impairment but is an important risk factor for dementia; 3) CSVD-related dementia very often co-exists with other neurodegenerative conditions that are obscure its recognition; 4) CSVD may cause brain injury via physiological mechanisms which extend beyond simple blood flow reduction; 5) monogenic forms of CSVD dementia have been described and promise to provide important footholds to understand mechanisms of disease; and 6) emerging evidence indicates that wisely selected cardiovascular medications could modify disease. Many of these features have been supported by recent work, but none are definitive; what is more certain is that rigorous investigations are still needed, particularly with respect to establishing robust, standardized disease markers that enable refinement of natural history, mechanistic, and therapeutic studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms

ACCORD MIND	Action to Control Cardiovasular Risk in Diabetes - Memory in Diabetes
AD	Alzheimer’s Disease
ADDTC	Alzheimer’s Disease Diagnostic and Treatment Centers
ARIEN	Association Internationale pour la Recherche et l’Enseignement en Neurosciences
BBB	blood brain barrier
CAA	cerebral amyloid angiopathy
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CBF	cerebral blood flow
CMB	cerebral microbleeds
CSF	cerebral spinal fluid
CVSD	cerebral small vessel disease
DAPT	dual antiplatelet therapy

DCE-MRI	dynamic contrast enhanced magnetic resonance imaging
DWI	diffusion weighted imaging
ICD-10	International Statistical Classification of Diseases and Related Health Problems Version 10
MRI	magnetic resonance imaging
NINDS	National Institute of Neurological Disorders and Stroke
SAPT	single antiplatelet therapy
SPRINT	Systolic Blood Pressure Intervention Trial
STRIVE	STandards for Reporting Vascular changes on Euroimaging
VCID	vascular cognitive impairment and dementia
WMH	white matter hyperintensity

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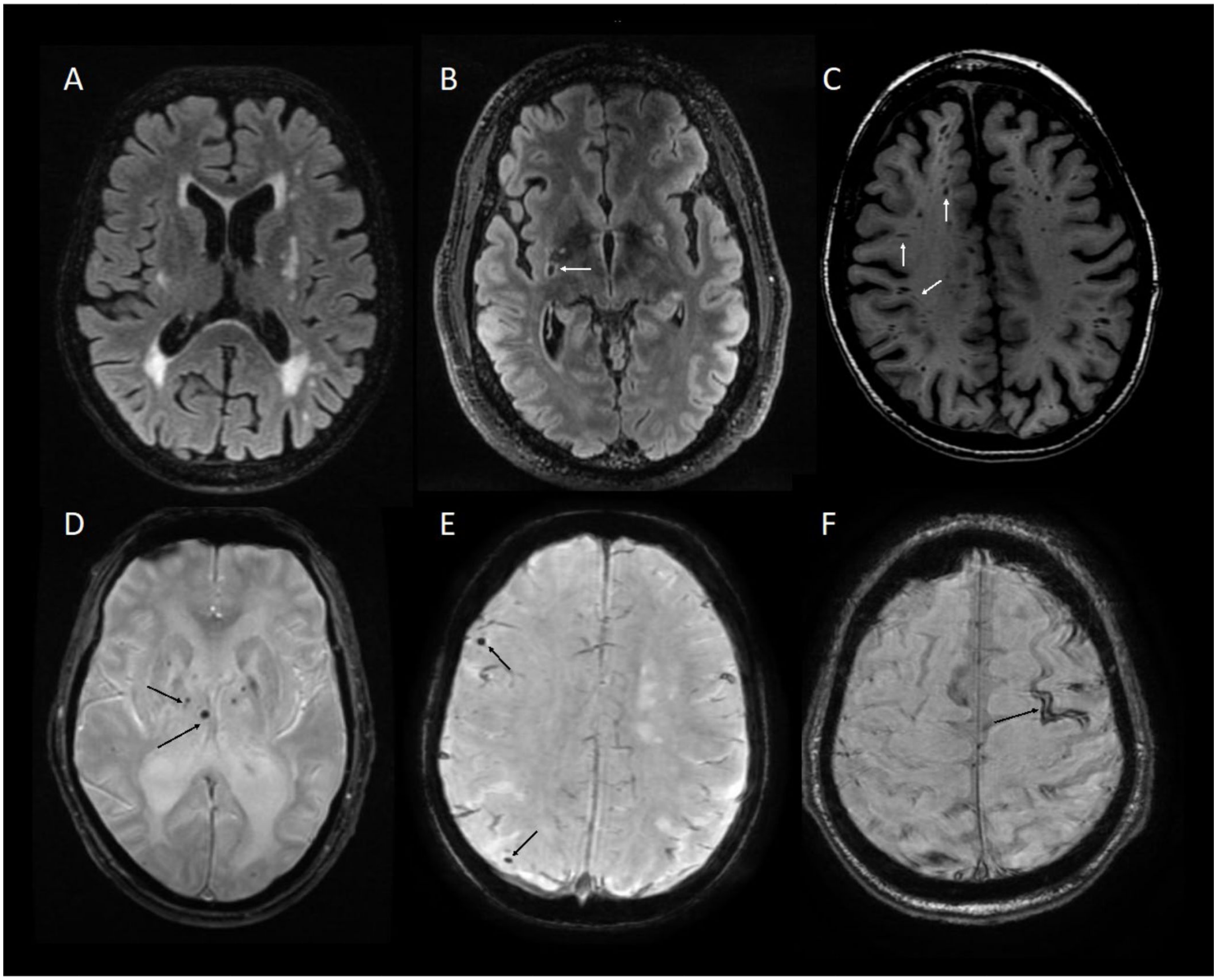

Figure 1.
Neuroimaging in CSVD-VCID. (A) subcortical and periventricular white matter hyperintensities (WMH) on T2/FLAIR (fluid-attenuated inversion recovery) sequences. (B) Lacunar stroke a cavity with a rim of hyperintensity on FLAIR. (C) Enlarged perivascular spaces (ePVS) on T1 sequence, can appear both as streak-like spaces as well as punctate. (D) Subcortical microhemorrhages on T2* SWI (susceptibility weighted imaging) sequence. (E) Cortical microhemorrhages on T2* SWI sequence. (F) Superficial siderosis on T2* SWI sequence.

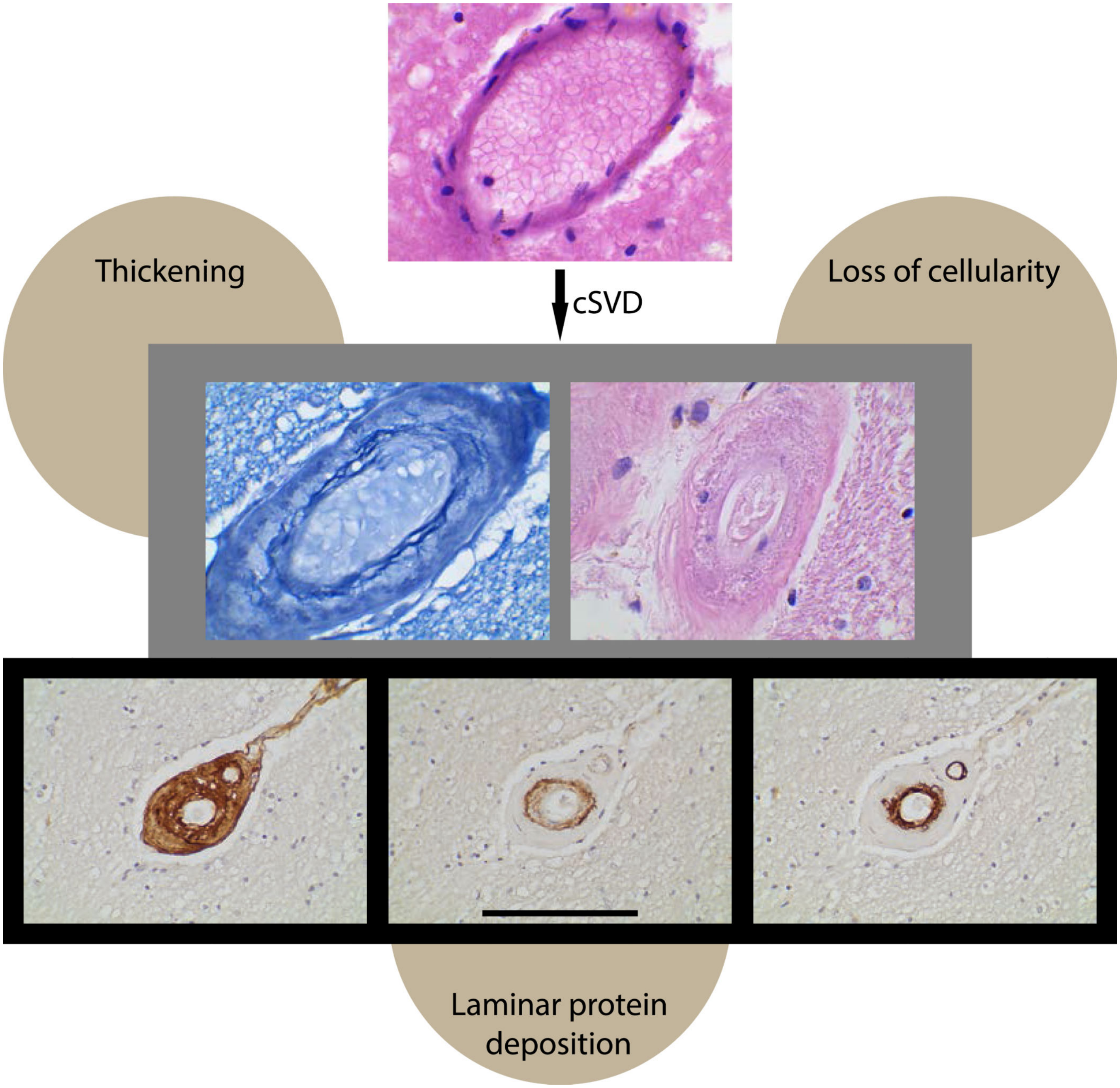

Figure 2.
Histopathological features of CSVD. Common histopathological features include arterial wall thickening, vascular cell loss, and protein accumulation in a laminar pattern. The top photo shows a normal appearing white matter artery stained with hematoxylin and eosin (H&E). The middle row shows markedly thickened small arteries in a patient with CADASIL, an inherited CSVD. On the left is a vessel after Miller's staining, which shows massive vessel thickening and fraying elastin fibers of the intimal/medial function. Cell loss is demonstrated in the H&E stained CADASIL artery on the right. The lower panel illustrates layered protein accumulation in a patient with CADASIL. The left photo shows

staining for all collagens using a collagen binding peptide probe (B-CHP) that stains all three layers of the vessel (adventitia, media, and intima). The middle photo shows staining with a NOTCH3 neo-epitope antibody that principally highlights the media; in CAA, the media accumulates Aβ. The right photo shows staining for COL4A that localizes predominantly to the intima. Scale bar span 40 microns for rows 1–2 and 100 microns for row 3.

Table 1.

Monogenic CSVD disorders

Syndrome	Gene	Mutation Prevalence	Disease Incidence	Clinical Syndrome	Imaging	Pathological Findings
Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)	*NOTCH3* Autosomal dominant	>230 mutations in 34 EGFR regions, >95% missense, mainly cysteine altering; cysteine-sparing mutations are less common Mutations lead to aggregation of *NOTCH3* Extra-cellular domain (ECD)	Classical syndrome: 2–5 in 100,000 Mutations discovered 2.2 in 1,000	Transient ischemic attacks and strokes, neuropsychiatric symptoms, cognitive impairment, apathy, mood disturbance including depression, rarely psychosis; migraine with or without aura; seizures (5–10%)	Confluent WMH by fifth decade of life in anterior temporal lobes, external capsule, periventricular areas, centrum semiovale, superior frontal gyrus Lacunar infarcts, enlarged perivascular spaces, cerebral microhemorrhages Brain atrophy (late life)	• Deposition of granular osmiophilic material (GOM) adjacent to VSMCs caused by mutated *NOTCH3* ECD, containing other proteins • Arteriopathy, most severe in small penetrating cerebral and leptomeningeal arteries • Widespread cortical neuronal apoptosis • Arterial wall thickening and fibrosis, stenosis • Degeneration of VSMCs and pericytes • Myelin degeneration • Blood-brain barrier dysfunction
Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL)	*HTRA1* Autosomal recessive (mainly)	Missense and nonsense mutations, and a few compound heterozygous individuals affecting protease activity of this serine protease	~5100 cases reported	Brain: ischemic strokes, cognitive decline and dementia by 30–40yo, gait disturbance, Spine: lumbago (low back pain), Hair: alopecia (hair loss) Heterozygous HTRA1 CSVD has milder presentation without extra-CNS symptoms, and some HTRA1 mutation carriers can be asymptomatic	Symmetrical WMH in periventricular and deep WM, occasionally in anterior temporal lobes and external capsules Notable hyperintense arc from pons to middle cerebellar peduncle in late disease stages. Lacunar infarcts in basal ganglia and thalamus, Cerebral microhemorrhages Herniated lumbar and cervical disks with degeneration Brain atrophy	• Loss of VSMCs • Hyalinosis, fibrosis and thickening of blood vessel walls • Thinning of cerebral arterioles ECM leading to enlargement, loss of vascular elasticity and collapse
Gould syndrome	*COL4A1/2* (Collagen IV A1 and A2) Autosomal dominant	Missense mutations mainly in highly conserved glycine residues in the triple helical domain of the COL4A1 gene. Other mutations impairing translation; insertions also		Highly variable multi-system disease BBB dysfunction and recurrent subcortical hemorrhages. Disease affects brain, spinal cord, eye,	White matter disease, lacunar infarcts, intracranial aneurysms of carotid siphon even in asymptomatic PADMAL: lacunar infarcts of	• Intra and extracellular accumulation of defective collagen in vessel walls, small vessel fragility and barrier dysfunction • Basement

Syndrome	Gene	Mutation Prevalence	Disease Incidence	Clinical Syndrome	Imaging	Pathological Findings
		reported. Mutations in the 3' untranslated region of COL4A1 cause Pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL).		muscles, and kidneys. Brain: cerebral SVD, cerebral aneurysms, stroke (hemorrhagic and ischemic). Eye: retinal arterial tortuosity, cataract, developmental microphthalmia, and Axenfeld–Rieger syndrome Other affected organs: kidney, anemia, muscular cramps, cardiac arrhythmias, and Raynaud's PADMAL: dysarthria, ataxia, paresis, mood disturbance, gait abnormality, stroke and dementia.	BG, brain stem, pons, and periventricularly, pyramidal tract degeneration	membrane instability • PADMAL: proliferation of intima, increased elastic fibers, atrophy of tunica media of arterioles
Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic manifestations (RVCL-S)	*TREX1* (Three prime Repair EXonuclease 1) Autosomal dominant	C-terminal frameshift mutations, mis-localization, immune dysfunction	Exceedingly rare (<100 families known)	Brain capillary rarefaction, strokes, tumor-like lesions, proteinuria, hematuria, macular edema with perifoveal microangiopathic telangiectasias, migraines, psychiatric disturbances, possibly early death	Focal T2 hyperintense lesions (tumor like in appearance) in periventricular and deep WM Contrast-enhanced pseudotumors focal calcifications visible before symptoms Frontal lobes heavily affected; corpus callosum and infratentorial tissue spared	• Thicker and multilayered vascular basement membrane • Vessels with fibrinoid vascular necrosis or thickened hyalinized walls
Fabry's disease	GLA (α galactosidase A) X-linked recessive	Insufficient activity of αGAL (early and late onset depend on x-inactivation and other factors)	1 in 3,100–117,000	Neuropathy, angiokeratomas, hypohidrosis, corneal opacity, and hearing loss. Internal organs, such as the kidney, heart or brain, may also be affected, leading to progressive kidney damage, heart attacks, and strokes (type 1 or early onset); diffuse white matter lesion with severe intracerebral hemorrhage and epilepsy can occur. Type 2 or	Deep WM lesions, T1 hyperintensities in pulvinar (thalamus) are pathognomic infarcts in posterior circulation and vertebrobasilar dolichoectasia microbleeds, lacunar infarcts	• Accumulation of glycosphingolipids in ECs/VSMCs

Syndrome	Gene	Mutation Prevalence	Disease Incidence	Clinical Syndrome	Imaging	Pathological Findings
				late onset spears kidney and other organs		
Hereditary Cerebral Hemorrhage with Amyloidosis (HCHWA)	Dutch, Italian, Flemish, Iowa and Piedmont types: Aβ precursor protein (APP) Icelandic type: cystatin C (CST3)	CAA associated disease	Rare			Misfolded Aβ 42 amyloid deposition in arteries, arterioles, capillaries, and veins, and parenchyma, degeneration of VSMCs Icelandic: amyloid fibril deposition in cerebral arteries, lymphoid organs, skin, salivary glands, testes

Table 2.

Lessons from SPRINT trial and SPRINT MIND substudy. Target for intensive systolic BP control was <120 mm Hg and for standard systolic BP control <140 mm Hg.

Clinical outcomes	
Wright et al [89]	Intensive BP therapy did not reduce risk of stroke but did reduce all-cause mortality by 27%.
Williamson et al[92]	Intensive BP group had a significantly reduced risk of MCI and composite endpoint of MCI and dementia compared to standard group.
Rapp et al[94]	No clinically significant difference was observed between intensive and standard treatment groups for memory or processing speed.
Radiographic and physiological outcomes	
Nasrallah et al[95]	Intensive BP group had 0.54cm^3 less increase in white matter lesion volume than the standard group over a median follow-up of 3.40 years.
Goldstein et al[96]	SPRINT-MIND post hoc analysis showed that use of ACE inhibitors was most consistently associated with decreased white matter progression.
Nasrallah et al[95]	Intensive BP group had 3.7 cm^3 less total brain volume loss than standard BP group.
Dolui et al[97]	Intensive BP group had 2.30 ml/100g/min higher whole brain perfusion change than standard BP group.

BP denotes blood pressure; MCI, mild cognitive impairment.

Table 3.

Use of antiplatelet therapy in patients with MCI or dementia and CSVD.

	Recent small subcortical infarct	Lacune of presumed vascular origin with symptomatic atherosclerosis	Lacune of presumed vascular origin without symptomatic atherosclerosis	Lacune of presumed vascular origin with >5–10 CMBs and no symptomatic atherosclerosis	CSVD without lacunes, with symptomatic atherosclerosis	CSVD without lacunes, without symptomatic atherosclerosis
Indicated	SAPT & DAPT	SAPT			SAPT	
Possibly indicated			SAPT			SAPT
Contraindicated		DAPT	DAPT	SAPT & DAPT	DAPT	DAPT

CMB denotes cerebral microbleeds; DAPT, dual antiplatelet therapy; and SAPT, single antiplatelet therapy.

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