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Research paper

Small-vessel disease in the brain

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ABSTRACT

Cerebral small-vessels are generally located in the brain at branch points from major cerebral blood vessels and perfuse subcortical structures such as the white matter tracts, basal ganglia, thalamus, and pons. Cerebral small-vessel disease (CSVD) can lead to several different clinical manifestations including ischemic lacunar stroke, intracerebral hemorrhage, and vascular dementia. Risk factors for CSVD overlap with conventional vascular risk factors including hypertension, diabetes mellitus, and hypercholesterolemia, as well as genetic causes. As in cardiovascular disease, treatment of CSVD involves both primary and secondary prevention. Aspirin has not been established as a primary prevention strategy for CSVD among the general population; however, long-term antiplatelet therapy with aspirin alone continues to be the mainstay of secondary stroke prevention for non-cardioembolic ischemic stroke and high-risk TIA.

1. Anatomy of cerebral small vessels

Small blood vessels include arterioles, capillaries, and venules [1]. They are found ubiquitously throughout the human body, including the brain and heart [2]. These small vessels have been histologically defined by a size of <1 mm in vessel diameter, most often between 50 and 400 μm [3,4]. In the brain, small vessels primarily supply blood to the deep grey matter and subcortical white matter and to a lesser degree the cortical grey matter, juxtacortical white matter, and leptomeninges [3,5].

The cerebral small vessels are classically found in the basal ganglia, thalamus, pons, the subcortical white matter tracts in the location of the lenticulostriate branches from the anterior and middle cerebral arteries, and the paramedian branches of the basilar artery. Cerebral small vessels originate directly from the major cerebral vessels, and microvascular studies have demonstrated that each perfuses a distinct territory, with minimal inherent overlap or anastomosis from neighboring vessels [6]. Because of these features, cerebral small vessels are at high risk from the effects of hypertension given their immediate proximity to large arteries, and occlusion of a small-vessel is likely to result in downstream infarction given the lack of overlapping perfusion.

Compared to the small vessels found in other organs, cerebral small vessels share a unique relationship with adjacent cells in the brain parenchyma, acting as an important component of the neurovascular unit (NVU; Fig. 1). The NVU consists of neurons, endothelial cells found within small blood vessels, vascular smooth muscle cells, pericytes, astrocytes, and other microglial cells [7]. Through a multitude of intracellular and extracellular signaling pathways, these cells work together to regulate cerebral blood flow with regards to neuronal activity, comprise the blood brain barrier, facilitate essential neuronal activities, and remove metabolic by-products that pose a threat to normal cellular functions [3,7].

2. Epidemiology and risk factors

Cerebral small vessel disease (CSVD) is clinically heterogeneous and constitutes the most common cerebrovascular disease. CSVD is responsible for approximately 25 % of ischemic strokes and 45 % of vascular dementia [4,8]. The prevalence of white matter disease increases with age from 5 % at 50 years to near 100 % at 90 years [9]. There are no consistent gender differences reported with CSVD; one study in 1999 found higher incidence of lacunar infarcts in Black Americans, but this has not since been reproduced [10]. It is estimated that for every symptomatic stroke there are about 10 silent (asymptomatic) brain infarcts [11]. The prevalence of silent cerebral ischemia varies from 8 to 31 % and increases with age [12]. Independent of other risk factors, there is a threefold increase in the risk for future symptomatic stroke in patients with silent brain infarcts [4]. Cerebral microbleeds (CMBs) are

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also strongly associated with increasing age with varied prevalence rates, ranging 4.7–24.4 % predominantly due to differences in sensitivity of imaging techniques and CMB definitions [13].

In those who developed intracerebral hemorrhage (ICH) between 1980 and 2008, a systematic review and meta-analysis reported the incidence per 100,000 population was estimated to be 24.6 in White individuals, 22.9 Black, 19.6 Hispanic, and 51.8 Asian [14]. Case fatality was approximately 40 % at 1 month, a finding that did not appreciably change over the twenty-eight year period of review. Age is be a major risk factor, such that every 10-year increase in age doubles the relative risk for spontaneous ICH [15]. Gender is another primary risk factor for ICH, as men are consistently shown to have a higher risk of ICH than women. Modifiable risk factors for ICH overlap significantly with those for ischemic stroke, and with regard to ICH due to CSVD, modification of these risk factors is more influential to reduce ICH risk than with alternative etiologies of ICH, such as with cerebral amyloid angiopathy [16].

Hypertension is the risk factor most classically associated with CSVD (see "Pathophysiology" section below), but other typical vascular risk factors, such as diabetes mellitus, hypercholesterolemia, and tobacco use likely contribute as well. With improvements in vascular risk factor control in recent decades, there has been a concomitant reduction in CSVD among populations [17]. Inheritable or genetic risk factors are estimated to account for approximately 20 % of CSVD cases [18]. When modifiable risk factors remain uncontrolled and the burden of CSVD leads to chronic vascular brain injury, it can produce vascular cognitive impairment and dementia.

Dementia which develops from CSVD (generally referred to as "vascular dementia") increases with age and makes up 15–20 % of all cases of dementia [19]. Vascular dementia is the second-most common cause of dementia after Alzheimer's disease. While a direct ethnic or racial influence has not been revealed to intrinsically affect the incidence of vascular dementia, racial disparities in cardiovascular and cerebrovascular risk factors have been well established [20]. The prevalence of hypertension (56 % versus 27 %) and diabetes mellitus type 2 (18 % versus 7 %) was found to be twice as high among Black individuals compared to White in a cohort study that sought to trace an association between the prevalence of vascular risk factors in mid-life and the incidence of dementia 25-years later [21]. Risk factors identified as being associated with increased incidence of dementia were Black race, older age, less than high school educational attainment, APOE ε4 genotype, midlife smoking, diabetes, prehypertension, and hypertension. The strength of association between risk factor presence and incidence of dementia was similar between racial groups, suggesting that prevalence of modifiable risk factors may be more influential on incident dementia than race.

3. Clinical manifestations of cerebral small vessel disease

While there is an extensive list of conditions that can be considered a result of CSVD, the most common clinical manifestations of this pathology are ischemic lacunar strokes, intracranial hemorrhage, and cognitive impairment/dementia.

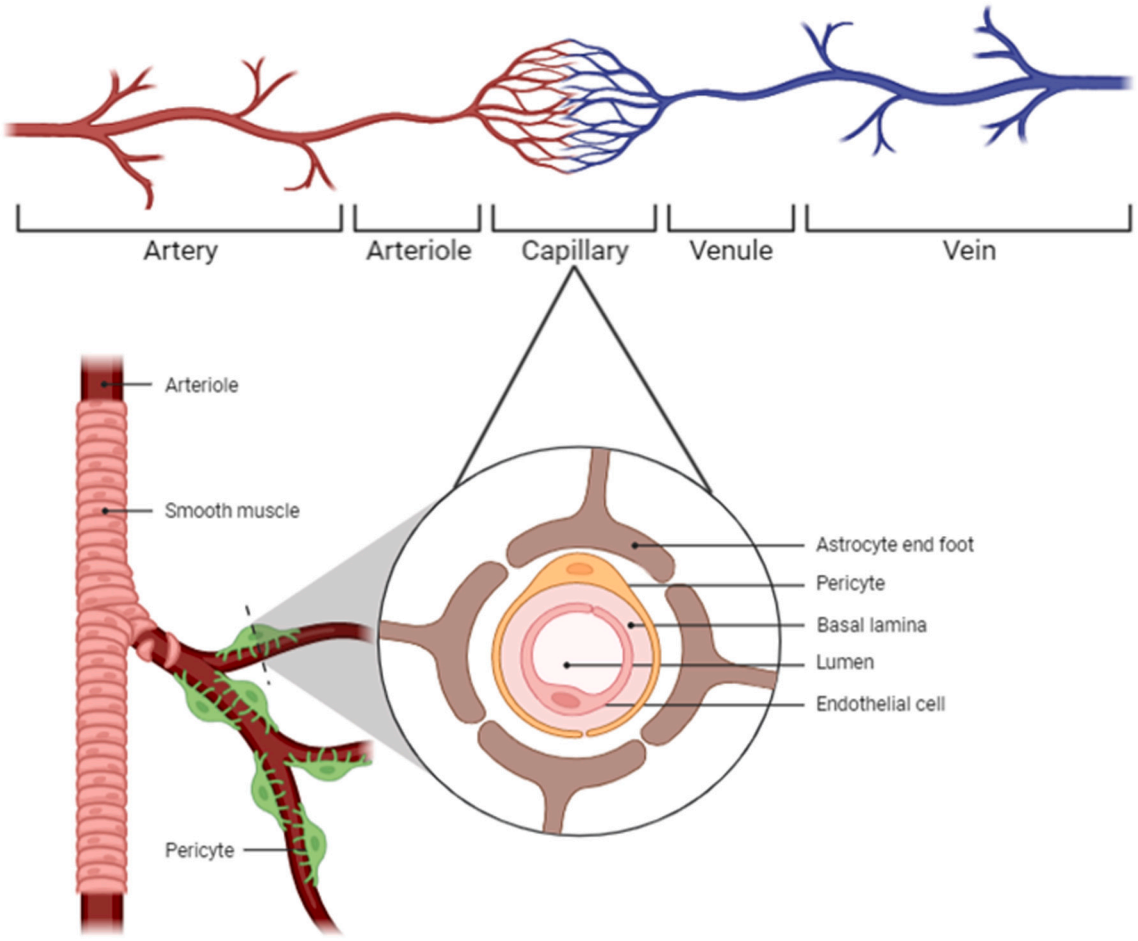

Fig. 1. The neurovascular unit comprises multiple cells within the brain and plays a key role in regulating cerebral blood flow and the blood brain barrier. Adapted from "Brain Vascular System," by BioRender.com. Retrieved from https://app.biorender.com/biorender-templates.

3.1. Ischemic lacunar stroke

Lacunar strokes commonly occur in "deep" grey matter structures and subcortical white matter of the brain due to poor collateralization among the small vessel arteries that supply these areas. Common locations involved include the basal ganglia, thalamus, subcortical white matter (internal capsule and corona radiata), and pontine brainstem. Symptomatic patients may present with one of the"classic" lacunar syndromes, classified as (1) pure motor stroke, (2) pure sensory stroke, (3) sensorimotor stroke, (4) ataxic hemiparesis or (5) dysarthria-clumsy hand syndrome, although multiple other "atypical" lacunar syndromes have been described [22].

Pure motor stroke is characterized by sudden-onset unilateral hemiparesis of the face, arm, and leg in the absence of other localizing symptoms of stroke. It is the most common of the classic lacunar syndromes, accounting for ~50 % of cases overall [23]. Typical locations include the internal capsule, motor fibers in the corona radiata, or pons. Predominantly seen with ischemia to the internal capsule, individuals can develop a capsular warning syndrome, manifested by stuttering or crescendo episodes of neurologic deficits related to hemodynamic ischemia [24].

Pure sensory stroke is characterized by sudden-onset unilateral sensory loss involving the face, arm and leg equally, without accompanying cortical or motor symptoms, and commonly localize to the thalamus, sensory fibers in the corona radiata, or pons. It accounts for approximately 15 % of the classic lacunar symptoms. The sensorimotor syndrome (15 %), as the name implies, includes both hemibody sensory loss and hemiparesis involving the face, arm, and leg, and localizes to overlapping thalamocapsular or pontine regions.

Ataxic hemiparesis presents with unilateral weakness and ataxia which may also include the corona radiata, pons, or thalamus, and accounts for ~10 % of lacunar strokes. Dysarthria-clumsy hand syndrome is the least common (~5 % in case series) and presents with hemifacial weakness, dysarthria, dysphagia, and usually mild ipsilateral hand weakness.

Due to exclusive involvement of subcortical structures, patients with lacunar infarcts do not typically have cortical signs such as aphasia, neglect, or hemianopsia. Given the size and location, these strokes are also less likely to present with common complications of stroke, such as cerebral edema seen with large-volume strokes, or post-stroke epilepsy frequently noted following cortical strokes. It is important to distinguish recent subcortical or lacunar infarctions from silent cerebral ischemia. Silent cerebral ischemia is often detected on neuroimaging, and careful history and examination should be completed to ensure there are no prior transient or current neurologic deficits that localize to this lesion.

Ischemic stroke due to CSVD may have a better short-term prognosis than stroke of other etiologies, with a greater percentage of patients exhibiting few or mild symptoms and a lower mortality at one year [25], although these findings normalize at later time points [26]. Worse outcomes were seen in patients who were men, of Black ethnicity, and/or with a history of diabetes or prior stroke/TIA attributable to CSVD [27].

3.2. Intracerebral hemorrhage

While ischemic manifestations of cerebral small-vessel disease generally portend a relatively good outcome, hemorrhagic complications often represent the most devastating and life-threatening result of CVSD.

Spontaneous, nontraumatic intracerebral hemorrhage that occurs as a result of cerebral small artery rupture leading to bleeding within the brain parenchyma is termed intraparenchymal hemorrhage (IPH). Clinical manifestations of IPH range from minimally-disabling focal neurological deficits to life-threatening, and can present with both subcortical and cortical signs depending on the location. Unlike ischemic lacunar stroke, the severity of IPH can vary greatly due to the potential for life-threatening complications including mass effect, intraventricular extravasation, obstructive hydrocephalus, and increased intracranial pressure. Because of these concerns, initial monitoring and management of patients with acute IPH usually occurs in the intensive care setting [28].

The location of IPH can be predictive of the underlying etiology of cerebral small vessel disease. Pathologically, IPH that occurs in subcortical white matter, as well as the pons, basal ganglia, and thalamus, is classically related to arteriolosclerosis and the effects of chronic hypertension [29]. Lobar and cortical IPH should raise suspicion of underlying cerebral amyloid angiopathy (CAA) or alternative etiology of cerebrovascular disease [30,31]. In the cerebellum, the same pattern of disease applies; deep portions of the cerebellum are at higher risk for IPH due to the effects of hypertension-related CSVD, while cortical cerebellar IPH can be suggestive of CAA [32].

In addition to intraparenchymal hemorrhage, the development of nontraumatic, convexity subarachnoid hemorrhage (SAH) due to cerebral small vessel disease can also be seen when accounting for the manifestations of CAA [33]. Symptoms are usually focal neurological deficits that can wax and wane recurrently due to the presence of juxtacortical subarachnoid blood. The finding of SAH in this pattern can foreshadow the development of future IPH with regard to CAA, and clinicians should be wary of continuing antiplatelet or anticoagulant agents in this context [34,35].

3.3. Cognitive impairment/dementia

While all infarctions may not lead to acute clinical strokes, the progressive development of "silent" cerebral ischemia over time can have an equally devastating toll, and thus it has been proposed that "covert" is a more accurate description of these lesions. As the burden of CSVD accumulates over time, the connections between different areas of the brain are weakened, leading to cognitive impairment and ultimately dementia. CSVD is also thought to worsen all other forms of dementia. By some accounts, vascular disease is thought to contribute to up to 50 % of all dementias.

In a large-scale prospective population study on the incidence of dementia and cognitive impairment following ischemic stroke, the incidence of dementia at 1-year following minor stroke (NIHSS <3) was 8.2 % [36]. Most lacunar strokes will be found to have minor stroke-like symptoms and NIHSS <7, therefore it's likely these findings approximate the expected risk of dementia following lacunar ischemic stroke [37]. In the case of intracerebral hemorrhage, the prevalence of dementia appears to be far greater and with variability depending on whether hypertension-related CSVD or CAA is the causative etiology. Studies have demonstrated that lobar ICH as well as large hematoma size are more highly associated with early incidence of dementia (within 6 months of ICH) and that CAA carries more than twice the risk of dementia than spontaneous ICH due to hypertension-related CSVD [38,39].

Patients with vascular dementia and vascular cognitive impairment classically experience a stepwise cognitive decline, although a more indolent and progressive course is also possible. Executive function may be most prominently impacted, with episodic memory relatively spared (which distinguishes it from the pattern seen in Alzheimer's disease) [40]. Other non-cognitive neurological symptoms include bradykinesia predominantly affecting the lower extremities ("lower body parkinsonism"), urinary incontinence, depression, apathy, and pseudobulbar affect.

4. Diagnosis of cerebral small vessel disease

4.1. Ischemic stroke

It is important to recognize ischemic strokes in a subcortical location may occur for reasons other than CSVD, and even those patients who

present with the "classic" lacunar syndromes should undergo further workup to determine the underlying cause of stroke. The etiology of the stroke will often affect a patient's prognosis, outcome, and choice of long term management. Small-vessel disease is one of five subtypes of acute ischemic stroke recognized in the commonly-utilized "TOAST" classification system [24], which also includes (1) large artery atherosclerosis, (2) cardioembolism, (3) stroke of other determined etiology (rarer causes of stroke such as hypercoagulability, arterial dissection, or paradoxical embolization via shunt), or (4) stroke of undetermined etiology (two or more causes identified, negative evaluation, or incomplete evaluation)

Etiology is determined through diagnostic testing that is guided by a patient's clinical history and risk factors. In order for stroke to be attributed to small-vessel disease, the patient should undergo imaging. CT head is often unremarkable early in a stroke, and it may be particularly challenging to visualize small-vessel disease given the small volume of stroke burden. MRI more readily allows visualization of small strokes, as well as concomitant lesions that would argue towards an alternative stroke mechanism. Even if the stroke burden appears consistent with small-vessel disease, with size <1.5 cm and a subcortical location, the patient should undergo additional workup to further evaluate for alternative mechanisms, including (at minimum) imaging of the cervical and cerebral vasculature to evaluate for large-artery disease, as well as electrocardiography/cardiac telemetry and echocardiography to evaluate for cardiac sources of emboli.

4.2. Intracerebral hemorrhage

As with ischemic lacunar stroke, the etiology of intraparenchymal hemorrhage should be determined through diagnostic testing guided by a patient's history and associated risk factors. An additional consideration with regard to IPH is the location of injury. IPH within a brain region commonly associated with hypertension-related cerebral small vessel disease often can be reassuring that an underlying vascular lesion, mass, or vasculopathy is unlikely. When lobar IPH is identified, a greater suspicion for non-hypertension-related cerebrovascular disease such as CAA, venous sinus thrombosis, brain mass, vasculopathy, or underlying vascular lesion should be considered. Digital subtraction angiography (DSA) is often appropriate for workup in this setting, as is gadolinium-enhanced MRI, both acutely and repeated at outpatient follow-up within 3 months.

With regard to CAA, recently validated updates to the Boston criteria for non-invasive diagnosis are available, now with improved sensitivity and uncompromised specificity. With a sensitivity of 74.5 % and specificity of 95.0 % based on autopsy-proven CAA, a diagnosis of *probable CAA* can be made based on the finding of at least two strictly lobar hemorrhagic lesions (IPHs, CMBs, or cortical superficial siderosis) or at least one lobar hemorrhagic lesion and one white matter characteristic (severe visible perivascular spaces in centrum semiovale or white matter hyperintensities in a multispot pattern) [31]. As previously stated, testing to exclude CAA as a cause of CSVD is often appropriate in individuals with hemorrhagic consequences of CSVD because a diagnosis of CAA is meaningful both clinically and prognostically [34].

4.3. Cognitive impairment/dementia

Diagnosis of vascular dementia is generally made based on a combination of clinical and radiographic features, with evidence of subcortical covert ischemia most suggestive of vascular dementia. A characteristic clinical course with stepwise functional decline can be utilized to distinguish from other more progressive forms of dementia which advance insidiously. Neuropsychiatric testing can help distinguish etiology of dementia, with abnormalities in executive function and praxis most suggestive of vascular dementia. Careful neurological examination can distinguish vascular dementia from other neurological diseases with similar clinical features. For example, other parkinsonian diseases may include more upper extremity involvement and the presence of visible tremors, and the gait abnormalities in normal-pressure hydrocephalus are a wide-based magnetic gait rather than the small shuffling gait seen in vascular dementia. Additional workup should be pursued to exclude pseudodementia, such as screening for depression and thyroid disease.

The Hachinski ischemic score can be used to determine the likelihood of vascular contribution to dementia. It takes into account acuity of onset, fluctuations in symptoms, prior history of stroke, focal neurological signs and symptoms, history of stepwise decline, pseudobulbar affect, hypertension, etc. A score of 7 points or higher indicates likely vascular contribution [41].

5. Neuroimaging of cerebral small vessel disease

With advances in neuroimaging, CSVD is increasingly recognized and efforts have been made to standardize terminology and reporting [42]. Based on the Standards for Reporting Vascular changes on neuroimaging (STRIVE) recommendations, neuroimaging markers of CSVD include (1) recent small subcortical infarct, (2) white matter hyperintensity of presumed vascular origin, (3) lacune of presumed vascular origin, (4) perivascular space, (5) CMB, and (6) brain atrophy (Fig. 2).

Recent small subcortical infarct refers to evidence of recent infarction in the territory of one perforating artery with clinical correlate occurring within a few weeks, which differs from silent cerebral ischemia where an asymptomatic acute infarct is incidentally found on imaging. Recent small subcortical infarcts can range up to 20 mm in size and lesions that involve multiple perforating arteries are classified as striatocapsular infarcts and tend to accompany a lacunar syndrome, as previously described.

A lacune of presumed vascular origin is evidence of chronic or remote small vessel ischemia or hemorrhage in the territory of one perforating artery. Typically, these lesions will be round or ovoid, range between 3 mm to 15 mm in size, and appear as a fluid-filled cavity. If a history or presence of correlating neurological deficit(s) is lacking, then these lesions are often referred to as silent cerebral ischemia or covert brain infarct.

White matter hyperintensities of presumed vascular origin increase with age and vary in severity, with up to 90 % prevalence depending on study design and population [34]. On imaging, these lesions are bilateral and symmetric, seen as white matter hyperintensities on T2-weighted imaging on MRI or white matter hypodensities on CT. These lesions are more common in those with a history of ischemic or hemorrhagic stroke, dementia, migraine, or late-life depression [34]. Distinct patterns of white matter hyperintensity can be suggestive of certain diseases, such as with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), in which there will be hyperintensities in the periventricular white matter, external capsule, corona radiata, and anterior temporal lobes (Fig. 3).

Perivascular spaces are fluid-filled spaces that are extensions of the extracerebral fluid space and follow the typical course of a vessel as it traverses the grey matter. These spaces are round or ovoid and typically <3 mm. Enlarged perivascular spaces can be seen up to 20 mm and are discriminated from small lacunes of presumed vascular origin as these spaces do not have a hyperintense rim on MRI. Clinical relevance of enlarged perivascular spaces remains controversial with higher burden and increased size of enlarged perivascular spaces being reported in dementia, genetic stroke conditions, and intracerebral hemorrhage [43,44].

CMB are small, typically 2–5 mm but up to 10 mm, areas of signal abnormality seen on blood sensitive sequences on MRI imaging. These are not seen on CT and are well defined on specific MRI sequences: T2* weighted gradient-recalled echo (GRE) or susceptibility-weighted imaging (SWI). Subcortical or deep CMB are associated with hypertensive arteriopathy, while superficial or lobar CMB are suggestive of cerebral amyloid angiopathy.

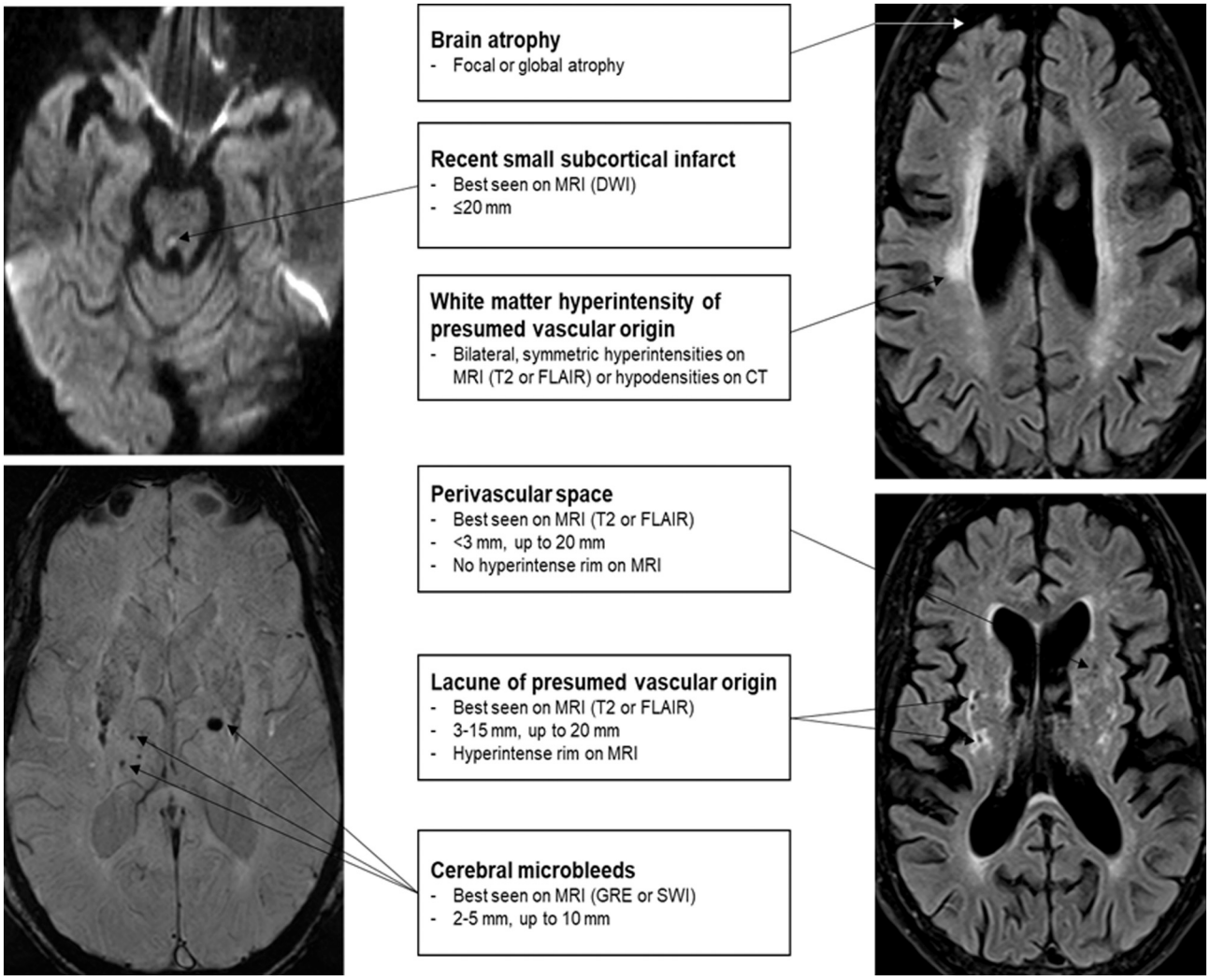

Fig. 2. Neuroimaging features on MRI suggestive of cerebral small vessel disease in a 56 year old man with multiple vascular risk factors who presented with an acute lacunar stroke. DWI: diffusion-weighted imaging; FLAIR: fluid-attenuated inversion recovery; GRE: gradient-recalled echo; SWI: susceptibility weighted imaging.

Brain atrophy in the context of CSVD is characterized by reduced brain volume unrelated to focal injury, such as trauma or infarction. While brain atrophy occurs with normal aging, there is an association between the presence and severity of CSVD and increasing brain atrophy in relation to both global atrophy and focal atrophy, such as cortical thinning related to subcortical infarcts.

6. Pathophysiology of cerebral small vessel disease

While many of the downstream effects of CSVD are well-established (ischemic stroke, dementia, hemorrhage), and it is well-accepted that there is a strong correlation between CSVD and vascular risk factors such as hypertension, diabetes, smoking, and advanced age, the exact physiologic mechanism remains unclear.

The classical model for cerebral small-vessel ischemic disease involves microangiopathy of perforator vessels as a result of uncontrolled hypertension and other vascular risk factors. The resultant arteriolosclerosis develops progressively within the vessel walls, with wall thickening due to lipohyalinosis and fibrinoid necrosis. As this progresses, the internal vessel diameter gradually decreases over time and eventually occludes completely, resulting in downstream infarction of the brain territory dependent upon the vessel. Because this process advances ubiquitously among cerebral small vessels, any significant decrease in blood supply to a susceptible area is at risk for lacunar infarction, especially since these areas typically have a limited collateral blood supply which cannot readily compensate for the decreased blood flow.

A competing model involves branch atheromatous disease from the large-artery parent vessel (anterior cerebral artery, middle cerebral artery, or basilar artery). Visible atherosclerosis of these parent vessels were found more often in patients with strokes in the territory of small vessels than more distal atherosclerosis (for example, in the cervical internal carotid artery), lending suspicion that these proximal lesions are pathologically relevant in the WASID study [45]. Later cohort investigations of this relationship have generated conflicting views as an association between upstream large vessel pathologies and clinical or parenchymal consequences of CSVD is not consistently seen [46]. However, with the increased use of high-powered 7 T MRI, visualization of perforator vessel pathology is becoming more accessible and further definition of the relationship between parent vessel atherosclerosis and CSVD is likely to follow [47,48].

Cerebral small-vessel disease can also be classified into several other types: amyloid angiopathy, genetic, inflammatory/vasculitis, venous collagenosis, and “other”. The most common secondary cause of cerebral small vessel disease is cerebral amyloid angiopathy. CAA is characterized by the progressive and inappropriate accumulation of

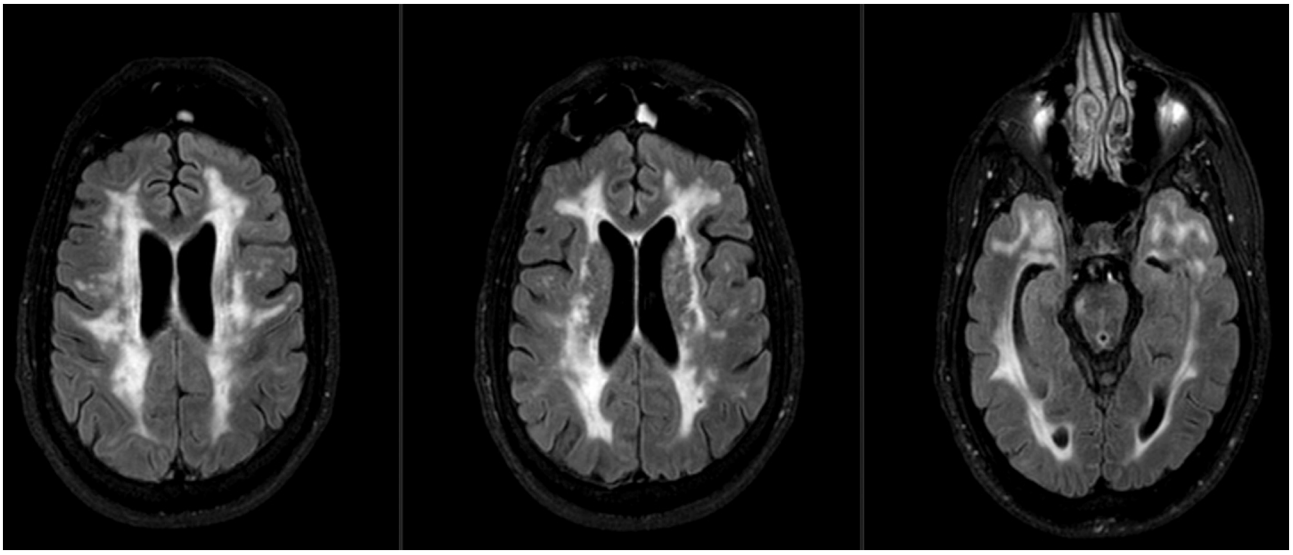

Fig. 3. Example of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Axial FLAIR (fluid-attenuated inversion recovery) sequence images of a 58-year-old patient with CADASIL confirmed by genetic testing. Images demonstrate extensive white matter hyperintensities with notable involvement of the external capsule and anterior temporal lobe bilaterally.

β-amyloid protein in the vessel wall of leptomeningeal and intracortical cerebral small vessels [49,50]. β-amyloid induces fibrinoid necrosis in the vessel wall and impairs the function of endothelial cells, reducing the smooth muscle cell population and ultimately leading to vulnerable and friable vasculature at risk for rupture and bleeding.

Defining the causes of CSVD remains challenging and has become increasingly complex with advancements in knowledge of the disease. CSVD was previously thought of as a manifestation of chronic hypertension; however, the relationship between hypertension and CSVD may likely be primarily associative. As recently as 2010, review articles referred to CSVD as "hypertension-related" small-vessel disease [51]. In the last decade, more research has been done to determine the cause of cerebral small-vessel disease on a cellular level. Using genetic causes of white matter disease as a model for the progression of CSVD, Bugiani et al. showed a strong correlation between decreased maturation of oligodendrocytes and CSVD in patients with CARASIL, a genetic condition defined by strokes and leukoencephalopathy [52]. This study, along with others, has led to an understanding that disruption of the blood brain barrier plays an underestimated role in the development of cerebral small-vessel disease.

Another recent area of research in CSVD has been the association between white matter disease and cerebral blood flow. Prior to the last decade, the traditional wisdom has been that atherosclerosis due to hypertension or other risk factors leads to reduced blood flow through those arteries, and that reduced flow leads to white matter disease [53]. More recently, some (but not all) studies examining the effect between these two factors have shown that white matter disease actually precedes the development of decreased blood flow, suggesting the possibility that pathology of brain parenchyma, rather than stemming from small vessels alone, may serve as a contributing factor to development of CSVD [54,55]. It should be reiterated that not all studies on this subject have led to the same results [56].

7. Treatment

7.1. Primary stroke prevention

For primary stroke prevention, current AHA/ASA guidelines do not recommend the use of aspirin to reduce the risk of ischemic stroke in the general population, which is at low risk [57]. Based on this guideline, lower levels of evidence suggest aspirin could be considered for primary prevention of stroke in women at high risk and in individuals with chronic kidney disease (stages 1–3). Cilostazol may be considered to prevent first stroke in those with peripheral artery disease with a low ankle-brachial index [57]. Subsequent large, randomised trials and one meta-analysis found no significant benefit of aspirin use for primary prevention of nonfatal ischemic stroke [58–60]. Antithrombotic therapy for primary stroke prevention can be used in specific situations, such as atrial fibrillation with high risk or asymptomatic carotid stenosis, but this does not pertain to small vessel disease alone [57]. The effectiveness of aspirin has not been established in silent cerebral ischemia, but it is important to ensure a silent lesion was not previously symptomatic where secondary stroke prevention may then be considered [12].

7.2. Secondary stroke prevention

Aspirin remains the standard of care as the antiplatelet of choice for secondary stroke prevention in non-cardioembolic stroke [61–63]. Current AHA/ASA guidelines recommend early initiation of antiplatelet therapy of acute ischemic stroke if thrombolysis is not administered, and long-term antiplatelet therapy is recommended over anticoagulation to reduce the risk of recurrent ischemic stroke in patients with non-cardioembolic ischemic stroke [64,65]. Aspirin 81 mg is the most commonly used antiplatelet therapy in practice. There is evidence to support use of aspirin 50 to 325 mg daily, clopidogrel 75 mg, or combination of aspirin 25 mg and extended release dipyridamole 200 mg twice daily for secondary stroke prevention [65]. No significant differences with recurrent stroke risk have been found comparing aspirin 325 mg to clopidogrel 75 mg [66]. Cilostazol, dipyridamole, and ticlopidine have been investigated for secondary stroke prevention with or without aspirin or compared to placebo, but results have not been replicated in larger randomised trials to recommend use in general population. Cilostazol in particular has been studied in East Asia with improved safety profiles compared to aspirin or clopidogrel, but further investigation is needed in other populations [67].

In small vessel disease infarcts, long term single antiplatelet therapy (SAPT) compared to placebo is associated with reduction of stroke recurrence, while dual antiplatelet therapy (DAPT) does not have clear benefit over monotherapy [68]. Furthermore, long term DAPT (>90 days) or triple antiplatelet therapy for secondary stroke prevention is recommended against as it has been associated with excess risk of hemorrhage [65]. Short-term courses of DAPT (aspirin plus either

clopidogrel or ticagrelor) initiated early after a stroke are recommended in individuals with minor non-cardioembolic ischemic stroke or high-risk TIA, followed by long term SAPT [65]. Recommended duration for DAPT ranges from 21 to 90 days with reduction in recurrent ischemic stroke in this high-risk period without significantly increased risk of bleeding.

For those who experience recurrent ischemic stroke or TIA while on aspirin monotherapy, it remains unclear whether there is any benefit to increasing the dose of aspirin or changing to alternative therapy [65]. Based on pooled analysis of primary prevention studies, weight based aspirin dosing was more effective in the prevention of vascular events, but this has not been studied in secondary stroke prevention [69]. One meta-analysis suggests it could be beneficial to change therapy in recurrent stroke, but alternatives included both SAPT or DAPT [70]. There has not been a randomised trial addressing optimal method for alteration of long term antiplatelet agents in the setting of recurrent stroke. However, for individuals who experience recurrent stroke while on clopidogrel with medication compliance, alternative antiplatelet agents could be reasonably considered as loss of function variants in the CYP2C19 gene have been increasingly understood to dramatically affect this drug's metabolism [71,72]. Genotyping and platelet function assays are not currently recommended as standard of care if clopidogrel is initiated, so variation remains in clinical practice.

8. Genetic disorders of cerebral small vessel disease

Though CVSD is most commonly sporadic, with an individual's lifestyle playing a key role, there are numerous genes and hereditary conditions that have been associated with its development. Nearly 5 % of all strokes have been attributed to monogenetic disorders [73] and a total of 52 genetic loci were recently described as independent risk factors for developing clinical and radiographic CSVD [74]. These genes may be hereditary or sporadic. The pathophysiology of hereditary CSVD remains largely unknown. Though the more traditional vascular risk factors may play a role, other proposed mechanisms have included accelerated arteriolosclerosis, endothelial cell dysfunction, blood brain barrier breakdown, and malfunction within the extracellular matrix [73,75].

Table 1 describes the most common hereditary causes of CSVD [75–80]. CADASIL is perhaps the most well-known of these conditions (Fig. 3).

Hereditary CSVD should be considered in young patients presenting with ischemic stroke when the following triad is observed: 1) stroke etiology is deemed cryptogenic with absence of identifiable sporadic cause, 2) presence of typical radiographic findings associated with a particular hereditary condition, and 3) positive family history of stroke [76]. A positive family history is not always present and mutations have been reported de novo.

When a hereditary etiology is suspected, genetic testing should be performed to confirm the diagnosis, although negative results do not necessarily rule out the possibility of a genetic origin. Directed mutation analysis can be used if a particular hereditary condition is suspected and unclear cases without a pre-existing familial hereditary diagnosis may pursue next-generation sequencing of known genetic CSVD loci using gene panels or whole-exome sequencing [76].

Of the disorders listed in Table 1, Fabry disease is the only condition with available disease-modifying treatments, including enzyme replacement therapy and pharmacologic chaperones [78]. Otherwise, there are currently no preventative or disease-modifying therapies available for those with genetic cerebral small vessel disease. If these patients experience an ischemic stroke, most providers initiate an anti-platelet agent, though there is minimal supportive evidence specific to this patient population to suggest this treatment is an effective means of secondary stroke prevention [76].

Table 1
Features of most common hereditary cerebral small vessel diseases. CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL: cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; RVCL: retinal vasculopathy with cerebral leukodystrophy and systemic manifestations; FD: Fabry disease; AD: autosomal dominant; AR: autosomal recessive; WM: white matter; SVD: small vessel disease; ICH: intracerebral hemorrhage; TIA: transient ischemic attack.

Disease	Gene (locus)	Protein	Inheritance	Typical onset (years)	Salient clinical features	Salient radiographic features	Histologic features
CADASIL [9–14]	NOTCH3 (19p13)	Transmembrane receptor on vascular smooth muscle cells and pericytes	AD	40–60	Migraine with aura, TIA/stroke, mood disorders, cognitive decline	Typical SVD WM hyperintensities (particularly anterior temporal lobes and external capsule), diffuse microhemorrhages	Granular osmiophilic material in arteriole walls
CARASIL [9–13]	HTRA1 (10q25)	Serine protease involved in regulating cell signaling	AR	20–40	TIA/stroke, cognitive decline, premature alopecia and spondylosis	Similar WM hyperintensities seen in CADASIL	Loss of vascular smooth muscle cells, intimal thickening with luminal narrowing, splitting of internal elastic lamina
RVCL-S [9,12–13]	TREX1 (3p21)	DNA exonuclease	AD	30–50	TIA/stroke, vascular retinopathy, migraine, cognitive decline, seizures, psychiatric disturbance, liver/kidney dysfunction	Enhancing tumefactive brain lesions (pseudotumors), enhancing subcortical WM hyperintensities, focal punctate calcifications	Thickened basement membrane, fibrinoid vascular necrosis, luminal stenosis
FD [9,11–13]	GLA (Xq22)	Lysosomal α-galactosidase A deficiency	X-linked	10–20	Childhood: painful acroparesthesias, angiokeratomas, gastrointestinal distress, corneal opacities Adulthood: TIA/stroke, cardiomyopathy, kidney disease, exercise intolerance, hearing loss	Pulvinar hyperintensities on T1-weighted imaging, subcortical WM hyperintensities, vertebrobasilar dolichoectasia	Deposition of glycosphingolipids in endothelial cells, zebra bodies on electron microscopy
COL4-related disorders [9–13]	COL4A1/ A2 (13q34)	Type IV collagen found in the basement membrane	AD	Highly variable, ranging from prenatal period to adulthood	ICH, stroke, infantile hemiparesis, tortuous retinal arteries, ophthalmic malformations, cystic kidney disease, muscle cramps	Typical SVD WM hyperintensities, microhemorrhages, macrohemorrhages, porencephalic cyst, intracranial aneurysms	Basement membrane defects

9. Comparison of cerebral and cardiac small vessel disease

Coronary microvascular disease is one of the manifestations of cardiac small vessel disease. About 10–30 % of patients with angina have no coronary artery disease present on coronary angiography, and their chest pain can be attributed to coronary microvascular disease (CMD) [81]. Coronary microvascular disease and nonobstructive coronary artery disease account for a significant portion of healthcare costs including procedures such as repeat catheterizations and anti-ischemic therapies [82]. A phenomenon known as microvascular angina has been attributed to the coronary circulation being more sensitive to vasoconstriction, and less capable of vasodilation [83]. Traditional risk factors contributing to endothelial dysfunction such as hypertension, diabetes, and hyperlipidemia play a large role in the development of cardiac microvascular disease, just as they do in CSVD. Diabetes, for example, affects the cardiac microvasculature in a similar fashion to cerebral microvasculature in that chronically hyperglycemic patients have impaired endothelial vasodilator function [84]. By comparison, cerebral microvascular disease related to chronic hyperglycemia leads to destabilization of the endothelial wall which can result in ischemic strokes, hemorrhages, and more broadly vascular dementia and even depression [85].

Another important consideration of cardiac microvascular dysfunction is Takotsubo syndrome, in which the coronary arteries do not appear obstructed on angiography however there is reduced myocardial perfusion [86]. It is thought to be the result of significant psychophysiological stress that causes significant microvascular constriction. Takotsubo cardiomyopathy is often viewed as a consequence of stroke due to significant catecholamine release that can be seen with cerebral ischemia, especially with involvement of the insular cortex. Additionally, due to cardiac hypokinesis often seen in Takotsubo cardiomyopathy, it can predispose to clot formation from which embolic stroke can occur [87].

Patients with vascular dementia often have cardiac comorbidities and it is thought that chronic cardiovascular conditions such as hypertension, obesity, and diabetes mellitus can contribute to endothelial remodeling. Increased peripheral vascular resistance without changes in cardiac output can lead to increased endothelial wall thickness that in turn impairs cerebral autoregulation and reduces cerebral blood flow [88]. The link between cerebral and cardiovascular disease can be further explored by N-terminal pro-B-type natriuretic peptide (NT-proBNP). This peptide is released from the myocardium as a response to wall stress and can be found in conditions such as left ventricular hypertrophy and diastolic dysfunction [89]. Importantly, NT-proBNP as well as its active hormone brain natriuretic peptide (BNP) are easily measured biomarkers in the serum. Studies have shown that increased NT-proBNP levels have been found to be associated with cerebrovascular disease, including subclinical cerebrovascular lesions such as silent cerebral ischemia [90]. A genetic link between cerebral and cardiac small vessel disease has been explored in patients with CADASIL with case reports describing myocardial infarctions in patients diagnosed with CADASIL [91].

The treatment for cardiac microvascular disease aligns closely with that of cerebral small vessel disease, placing a focus on lifestyle modification with smoking cessation, weight loss, and exercise training [92]. Why some patients with cardiac small vessel disease develop cerebrovascular disease such as vascular dementia, and others do not is incompletely understood and an ongoing area of research. Lifestyle modification education is an essential component to caring for patients with cardiac and cerebrovascular disease in the interim.

10. Future directions

Despite the common incidence of CSVD, an exact understanding of the nature and sequence of events involved in its pathogenesis remains poorly understood and is an area of ongoing study [5]. Identification of these pathways would allow for the development of targeted therapeutic interventions. Cilostazol has been identified as a potential secondary stroke preventative agent that is superior to aspirin in East Asian patients with CSVD, but further study on applicability outside of this patient population is warranted [67].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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