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CARDIOVASCULAR DISEASE AND STROKE (S. PRABHAKARAN, SECTION EDITOR)

Subclinical Cerebrovascular Disease: Epidemiology and Treatment

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Abstract

Purpose of Review Subclinical cerebrovascular disease (sCVD) is highly prevalent in older adults. The main neuroimaging findings of sCVD include white matter hyperintensities and silent brain infarcts on T2-weighted MRI and cerebral microbleeds on gradient echo or susceptibility-weighted MRI. In this paper, we will review the epidemiology of sCVD, the current evidence for best medical management, and future directions for sCVD research.

Recent Findings Numerous epidemiologic studies show that sCVD, in particular WMH, is an important risk factor for the development of dementia, stroke, worse outcomes after stroke, gait instability, late-life depression, and death. Effective treatment of sCVD could have major consequences for the brain health of a substantial portion of older Americans. Despite the link between sCVD and many vascular risk factors, such as hypertension or hyperlipidemia, the optimal medical treatment of sCVD remains uncertain.

Summary Given the clinical equipoise about the risk versus benefit of aggressive medical management for sCVD, clinical trials to examine pragmatic, evidence-based approaches to management of sCVD are needed. Such a trial could provide much needed guidance on how to manage a common clinical scenario facing internists and neurologists in practice.

Keywords Subclinical cerebrovascular disease · White matter hyperintensity · Silent cerebral infarct · Cerebral microbleed

Introduction

Subclinical cerebrovascular disease (sCVD) is highly prevalent and is estimated to be present in greater than 70% of community-based adults aged 60 years and above [1–3]. The main neuroimaging findings of sCVD include white matter hyperintensities (WMHs) and silent brain infarcts (SBIs) on T2-weighted MRI and cerebral microbleeds (CMBs) on gradient echo and susceptibility weighted imaging MRI (Fig. 1) [4]. The risk factors that have the strongest association with sCVD are advanced age, hypertension, hyperlipidemia, smoking, and intra- and extracranial large artery atherosclerotic disease [5–8]. The symptomatic cognitive manifestations of sCVD were first described by the Swiss neurologist Otto Binswanger in the late nineteenth century, shortly thereafter expanded upon by Alois Alzheimer's histopathological description in 1902 of diffuse loss of cerebral white matter myelin and axons accompanied by gliosis and atrophy [9, 10]. Subsequent research after the advent of MRI has shown that sCVD, in particular WMH, is an important risk factor for the development of diverse symptomatic manifestations including dementia, stroke, worse outcomes after stroke, gait instability, late-life depression, and death [6, 11–18].

The number of publications on sCVD has increased dramatically in the last decade as the focus has transitioned from longitudinal studies of its epidemiology to clinical trials testing intervention to treat the condition. Longitudinal studies have shown that hypertension and smoking are associated with the progression of WMH burden [19–21], and effective hypertension control can prevent WMH progression [22–24]. Effective treatment of sCVD could have major consequences for the brain health of a substantial proportion of older Americans. Despite the link between many vascular risk factors and sCVD, the optimal medical treatment of sCVD remains uncertain, and no guidelines exist concerning sCVD medical

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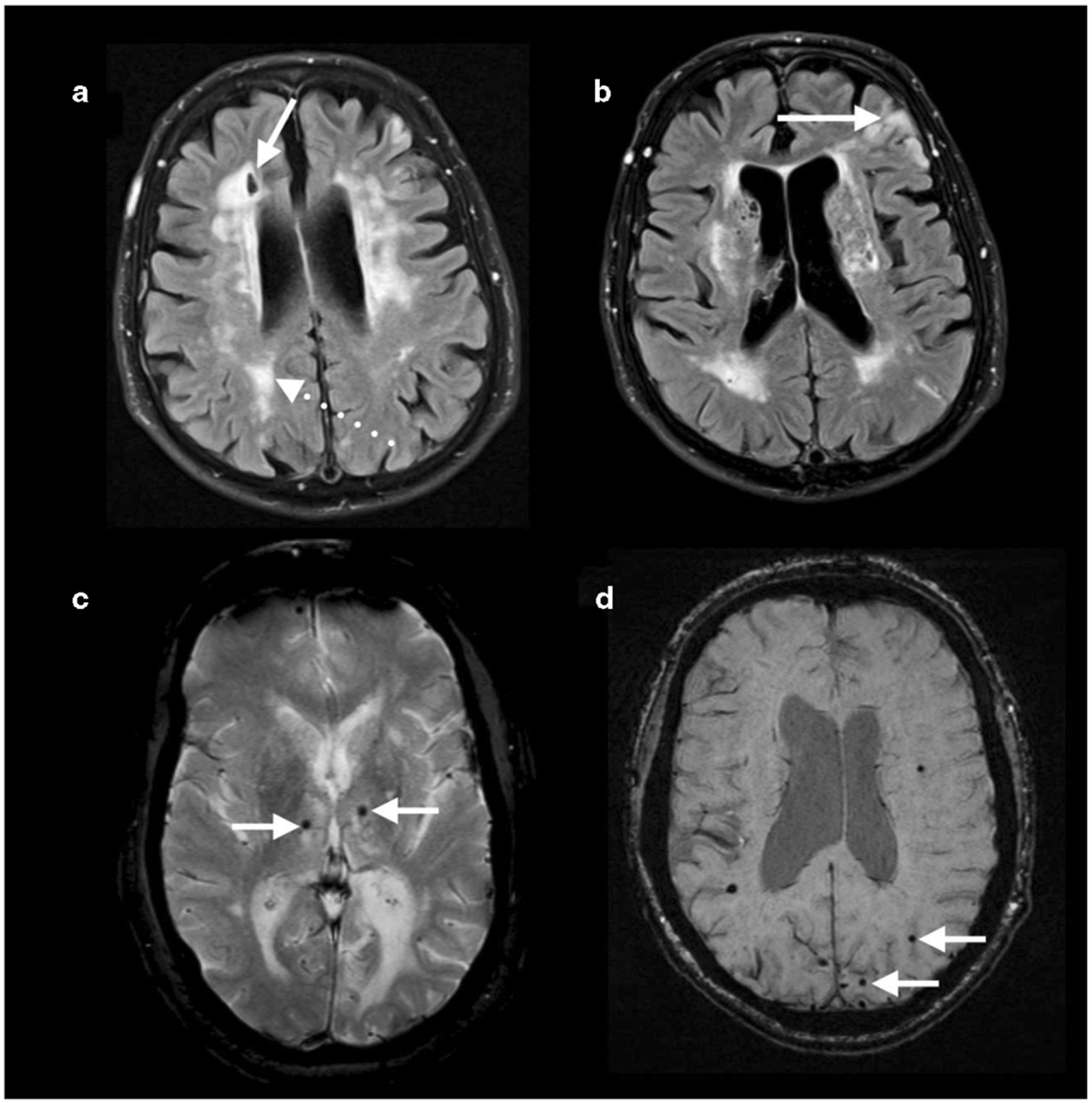

Fig. 1 MRI examples of subclinical cerebrovascular disease. **a** Axial FLAIR showing WMH (dotted arrow) and a lacunar SBI (solid arrow) with a central area of necrotic hypointensity surrounded by a hyperintense area of gliosis. **b** Axial FLAIR showing a cortical SBI (solid arrow) with hyperintense signal reflecting gliosis of the cortical and subcortical parenchyma. **c** Axial gradient-recalled echo showing two CMBs in the basal ganglia (solid arrows), consistent with a hypertensive etiology. **d** Axial susceptibility weighted imaging showing two CMBs in the left occipital lobe (solid arrows), consistent with cerebral amyloid angiopathy

management in otherwise asymptomatic patients. Although aggressive medical management is effective at preventing stroke, we do not know if it is effective and safe in the primary prevention of stroke and cognitive decline in patients with sCVD [25]. The Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT MIND) study recently provided evidence that aggressive blood pressure (BP) control may reduce the development of mild cognitive impairment, but the parent SPRINT trial utilized a unimodal intervention and was terminated early for overall cardiovascular benefits without a clear stroke preventive effect [26, 27]. Given these findings, there is renewed interest in sCVD. In this paper, we will review the epidemiology of sCVD, the current evidence for best medical management, and future research directions.

Epidemiology

Although autopsy studies have long shown that asymptomatic stroke is a common finding [28], the high prevalence of sCVD was not fully appreciated until the advent of modern CT and, more importantly, MRI [29]. WMH, SBI, and CMB can all be relatively asymptomatic and likely share overlapping pathophysiology. Patients frequently have concomitant features of

sCVD, such as both WMH and CMB [30–34]. There is conflicting data on the prevalence of sCVD by gender, but it does appear to be more prevalent in Blacks and Caucasians than Hispanics, but this difference may be largely explained by risk factors [5, 35].

Although the burden of perivascular spaces has been proposed as part of the sCVD spectrum, there are too few high-quality studies to include them in the definition of sCVD for this article. However, as additional data becomes available, a large burden of dilated perivascular spaces may emerge as part of sCVD in its own right [4]. sCVD can accompany additional imaging findings that may not be clinically apparent, namely brain volume loss [36, 37]. While the prevalence of sCVD and brain volume loss both independently increase with age, there is some evidence of an independent association between sCVD and brain atrophy that is independent of age [38].

WMHs are more common than SBI or CMB and are thought to be secondary to degenerative changes of small vessels with a range of possible pathological mechanisms including lipohyalinosis and loss of myelinated axons [39]. WMHs are most commonly seen in the deep and periventricular white matter, pons, and cerebellum [40]. Measurement of WMH can be done qualitatively using ordinal scales, most commonly the Fazekas scale, which ranges from 0 to 3 and has been validated in numerous publication. [40–42]. WMH volume can also be measured in cubic centimeters (cm^3) using validated algorithmic approaches that rely on computer segmentation of the abnormal hyperintense T2 signal from normal T2 signal in brain parenchyma [43, 44]. WMHs increase significantly with age and medical comorbidities, but they can be seen even in healthy young populations. The WMH prevalence also varies significantly depending on the study design and patient population. For example, in a cohort with a mean age of 34, there was a 6% prevalence of WMH, whereas the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA) study found a prevalence of 42% in non-migraine control individuals aged 30 to 40 years old. [45, 46] In the Rotterdam Scan Study of 1077 participants ages 60–90 years old who underwent brain MRI, investigators found that 92% had periventricular or subcortical WMH [47].

Several studies have established a cross-sectional relationship between hypertension and WMH [48–50]. Longitudinal studies have also established the relationship between hypertension and progression of WMH over time [51]. Perhaps the most important study is Atherosclerosis Risk in Communities (ARIC), which looked at BP measurements and WMH progression over nearly 20 years. In this cohort, a 20-mmHg higher estimated mean daily systolic BP was associated with an adjusted odds ratio of 2.0 for being in the top quintile of WMH progression [52]. WMH has also been linked to intracranial atherosclerosis, for both symptomatic and asymptomatic intracranial steno-occlusive disease [53, 54]. The burden of WMH is correlated with risk of stroke, worse outcome after stroke, gait impairment, and cognitive impairment [6, 11–18]. The cognitive impairment primarily involves executive function, visuospatial memory and organization, visual scanning and motor speed, and new learning, but seems to spare verbal memory [42, 55]. WMHs are also associated with depression in elderly patients, leading to a vascular depression hypothesis [56–58]. These lesions are often found in the dorsolateral prefrontal cortex [59].

Lacunar SBI is associated with older age and other cardiovascular risk factors, such as hypertension, diabetes mellitus, and smoking, while subcortical SBI is associated with subclinical atrial fibrillation or large artery atherosclerosis [35]. Lacunar infarcts, in particular, are often asymptomatic and found incidentally on MRI imaging [60]. In the Rotterdam Scan Study, SBIs were five times more common than symptomatic infarctions [61]. In their study population, aged 60 to 90 years old, there was an overall 20% incidence of SBI. Some studies report an incidence as high as 49%, but most agree with ~ 20% incidence in asymptomatic populations [62, 63]. Age has the strongest association with SBIs, which are prevalent in only 8% of patients aged 60 to 64 years old, but up to 35% of patients > 80 years old [61].

The main risk factor for lacunar SBI is undiagnosed hypertension, which affects over 12 million Americans [64]. There is some evidence that asymptomatic and symptomatic lacunar infarcts may result from two distinct entities. For example, asymptomatic lacunar infarcts are more closely associated with hypertension and WMH than symptomatic lacunar infarcts [65]. Lacunar SBIs were associated with a higher stroke recurrence rate, mortality, and disability compared to symptomatic lacunar infarcts in a prospective cross-sectional study [66]. Lacunar SBIs are also found more frequently in patients with vasculopathies such as sickle cell anemia and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Fig. 2) [67, 68]. Cortical SBIs are associated with atrial fibrillation, both as a known or new diagnosis [69, 70]. Large artery atherosclerosis also frequently coexists in patients with cortical SBI, which manifests as both intracranial and extracranial stenosis [71]. In patients with unilateral carotid stenosis and SBI, cortical SBIs are more often ipsilateral to their carotid disease [72, 73].

CMBs are often seen incidentally seen on MRI with no clear associated symptoms. The prevalence of CMB is 6% in individuals aged 45–50 years old but increases to 36% after the age of 80 years [3]. CMBs related to hypertension are most often in the same locations as WMH and lacunar SBI, specifically the basal ganglia, pons, and cerebellum (Fig. 2) [34, 74]. Hypertension is also shown to increase the risk for longitudinal progression of the CMB burden [75]. Multiple lobar CMBs are more closely related to cerebral amyloid angiopathy (CAA) than with hypertension. The prevalence of moderate to severe CAA is 2.3% between 65 and 74 years

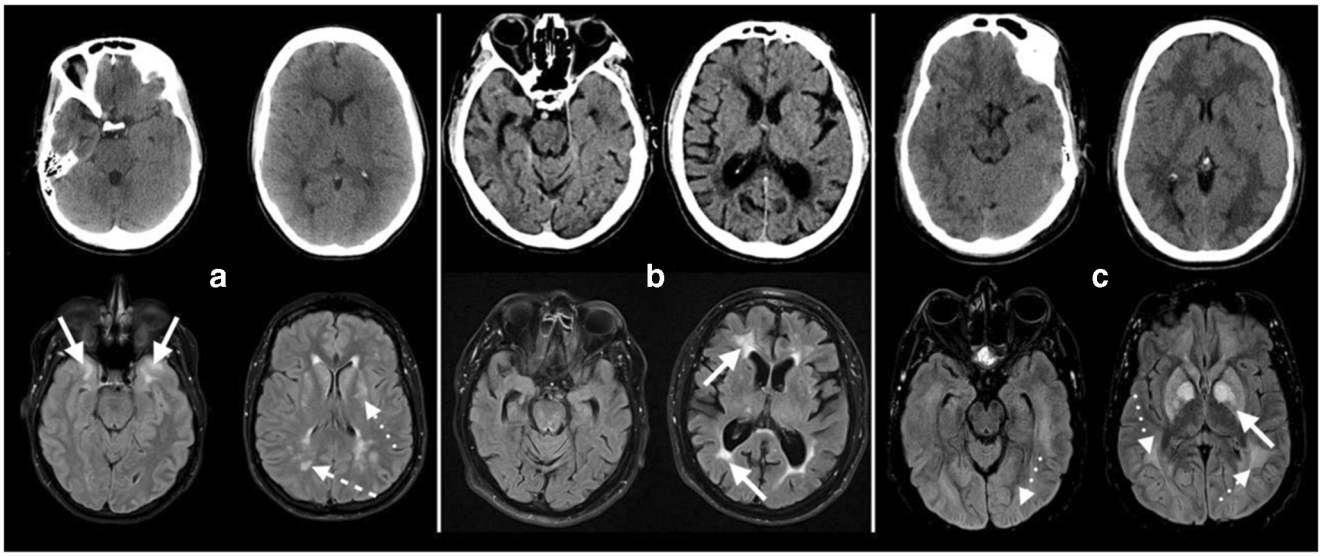

Fig. 2 CT and MRI examples of various presentations of white matter disease. **a** Thirty-five-year-old woman with migraine with aura, typically peripartum since age 24, presented with acute encephalopathy that resolved after about a week. Low attenuation areas on CT (top) were better depicted on MRI (bottom), where there were multiple FLAIR hyperintensities localizing to the anterior temporal subcortical white matter (solid arrows), lenticulostriate distributions (dotted arrow), and periventricular/subcortical white matter (dashed arrow). The distribution and age were highly suggestive of CADASIL, which was confirmed with genetic testing. **b** Sixty-year-old male with history of hypertension and hyperlipidemia underwent workup for a transient ischemic attack. CT (top) showed volume loss and periventricular hypoattenuation. MRI (bottom) demonstrated periventricular FLAIR hyperintensities (solid arrows) and relative sparing of the anterior temporal subcortical white matter in a pattern compatible with sCVD. **c** Thirty-two-year-old man with hypoxic respiratory failure related to polysubstance abuse. Toxicology screen was positive for opiates, methamphetamine, and amphetamine. CT (top) showed global cerebral edema with periventricular and basal ganglia low attenuation. This was better depicted on MRI (bottom), with FLAIR hyperintense basal ganglia (solid arrows) and diffuse periventricular FLAIR signal (dotted arrows). This pattern was compatible with opiate-induced toxic leukoencephalopathy and superimposed hypoxic/ischemic injury

of age but rises up to 12.1% in those over 85 years old [76]. Lobar CMBs are also associated with elevated high-density lipoprotein cholesterol and decreased triglycerides, and the APOE e4 allele [77]. Although a definitive CAA diagnosis is confirmed on postmortem evaluation showing amyloid deposition in the arterial walls, the Boston criteria allow for probable and possible diagnosis in the living [78].

There are conflicting data regarding whether the presence of CMB is a risk factor for the development of symptomatic intracranial hemorrhage after thrombolysis with intravenous Alteplase for acute ischemic stroke. [79–81]. However, the number of CMB mediates this risk. Compared to patients with only a handful of CMB, those with > 10 CMBs have considerably more risk of sICH and poor clinical outcome at 3 months [82]. Finally, CMBs are also associated with autonomic dysfunction such as postprandial hypotension [83].

Medical Management of Subclinical CVD

sCVD is a common and meaningful finding in the general population, particularly the elderly. The optimal medical treatment of sCVD remains a major knowledge gap that has important implications for brain health. Despite the heterogenous imaging findings in sCVD, ranging from microvascular ischemia to large cortical infarcts to microhemorrhages, the risk factor profiles have considerable overlap. As such, the medical treatments that are effective for one component of sCVD may well be effective for other components. There are, of course, exceptions. For example, cortical SBI should trigger an evaluation for atrial fibrillation and large artery atherosclerosis, while lobar CMB could suggest cerebral amyloid angiopathy.

Nevertheless, hypertension is, by far, the single most important modifiable risk factor for sCVD and the one for which we have the most data, especially in relation to WMH. In a secondary analysis of ACCORD-MIND, we recently showed that the progression of WMH was lower in the intensive (< 120 mmHg) versus standard BP control (< 140 mmHg) randomization arm (ΔWMH = 0.67 ± 0.95 cm^3 versus 1.16 ± 1.13 cm^3, $p < 0.001$) [24]. Similar findings were shown in SPRINT MIND, although the results have only been presented at conference at the time of this article [84]. SPRINT MIND also reported a lower incidence of MCI with intensive BP control [26]. The ROCAS study reported that statins could slow the progression of WMH [85]. The FINGER trial also showed that a multidomain intervention, including diet, exercise, and vascular risk monitoring, could reduce cognitive decline [86]. These results support the possibility that altering longitudinal exposure to hypertension, hyperlipidemia, and poor cardiovascular health could slow sCVD progression and decrease sCVD-related morbidity.

However, data are scarce and conflicting on whether aggressive medical management is safe in sCVD. Statin therapy may increase the risk of hemorrhagic forms of stroke, a particular concern in patients with advanced WMH or CMB at baseline [87, 88]. In ACCORD-MIND, BP lowering to < 120/80 mmHg was associated with greater loss of total brain volume [89]. The cardiovascular and cognitive benefits of lowering SBP to < 120 mmHg seen in SPRINT and SPRINT MIND came with an increase in other adverse events such as syncope and kidney injury [27]. The Aspirin in Reducing Events in the Elderly (ASPREE) trial recently showed higher mortality in healthy elderly patients taking aspirin, mainly due to cancer-related death [90]. As such, the benefit of aspirin in sCVD is not clear unless there is a compelling alternate indication such as symptomatic coronary artery disease.

Conclusions

sCVD is an important disease state that is an effect of aging but also of common cardiovascular risk factors such as hypertension and hyperlipidemia. The current evidence base does not have adequate detail to determine if aggressive treatment of cardiovascular risk factors translates into risk reduction for stroke, heart disease, or dementia for this patient population. Primary prevention trials typically require large sample sizes and extended follow-up to detect small decreases in absolute risk. sCVD is unique in that the clinical manifestations are numerous, such as cognitive impairment, stroke, or depression, possibly allowing for larger effect sizes in absolute risk reduction for composite outcomes that include several symptomatic manifestations of sCVD. In addition, the neuroimaging components of sCVD, such as WMH, are robust enough biomarkers to be a viable primary outcome in a phase III trial. The number of eligible patients for such a trial would be substantial given the high prevalence of sCVD and the frequent use of CT and MRI in healthy adults in the USA [91–94]. Given the clinical equipoise about the risk versus benefit of aggressive medical management for sCVD, a clinical trial to examine pragmatic, evidence-driven approaches to management of sCVD is warranted. Such a trial could provide much needed guidance on how to manage this common clinical scenario with a high impact on the brain health of the overall population.

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Compliance with Ethical Standards

Conflict of Interest Adam de Havenon, Chelsea Meyer, J. Scott McNally, Matthew Alexander, and Lee Chung declare no conflict of interest.

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