Cerebral small vessel disease

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Cerebral small vessel disease (SVD) is a group of conditions that affect the small arteries, arterioles, capillaries, and small veins in the brain. It is a major cause of stroke and dementia

Classification

The classification of cerebral SVD can be broadly categorized into two main types: sporadic (or non-genetic) SVD and hereditary (genetic) SVD. Here’s an overview of the classification:

1. Sporadic (Non-Genetic) Cerebral Small Vessel Disease

This type of SVD occurs due to factors not related to inherited genetic mutations. Common causes include aging, hypertension, diabetes, and other cardiovascular risk factors.

Lacunar Infarcts: Small, deep infarcts usually caused by occlusion of small penetrating arteries. White Matter Hyperintensities (WMH): Areas of increased signal on T2-weighted MRI, indicative of ischemia or demyelination in the white matter. Microbleeds: Small, chronic hemorrhages visible on MRI, usually associated with hypertensive arteriopathy or cerebral amyloid angiopathy. Perivascular Spaces: Enlarged fluid-filled spaces around small blood vessels, often seen in aging and associated with hypertension. Cerebral Amyloid Angiopathy (CAA): A condition characterized by the deposition of amyloid proteins in the walls of the small arteries and capillaries of the brain, often associated with lobar hemorrhages.

2. Hereditary (Genetic) Cerebral Small Vessel Disease

see Hereditary Cerebral Small Vessel Disease.

The term cerebral small vessel disease refers to a group of pathological processes with various aetiologies that affect the small arteries, arterioles, venules, and capillaries of the brain. Age-related and hypertension-related small vessel diseases and cerebral amyloid angiopathy are the most common forms. The consequences of small vessel disease on the brain parenchyma are mainly lesions located in the subcortical structures such as lacunar infarcts, white matter lesions, large hemorrhages, and microbleeds. Because lacunar infarcts and white matter lesions are easily detected by neuroimaging, whereas small vessels are not, the term small vessel disease is frequently used to describe the parenchyma lesions rather than the underlying small vessel alterations. This classification, however, restricts the definition of small vessel disease to ischaemic lesions and might be misleading. Small vessel disease has an important role in cerebrovascular disease and is a leading cause of cognitive decline and functional loss in the elderly. Small vessel disease should be a main target for preventive and treatment strategies, but all types of presentation and complications should be taken into account [1)].

Age and high blood pressure appear to play key roles in the progression of cerebral small vessel burden after mid-life [2)].

NOTCH3 variants are the leading cause of hereditary cerebral small vessel disease (SVD). While monoallelic cysteine-involving missense variants in NOTCH3 are well-studied in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), patients with biallelic variants in NOTCH3 are sporadic and not well characterized.

Iruzubieta et al. present clinical and genetic data from 25 patients with biallelic NOTCH3 variants and conduct a literature review of another 25 cases (50 patients in total). Brain magnetic resonance imaging (MRI) was analyzed by expert neuroradiologists to better understand the phenotype associated with biallelic NOTCH3 variants.

The systematic analyses verified distinct genotype-phenotype correlations for the two types of biallelic variants in NOTCH3. Biallelic loss-of-function variants (26 patients) lead to a neurodevelopmental disorder characterized by spasticity, childhood-onset stroke, and periatrial white matter volume loss resembling periventricular leukomalacia. Conversely, patients with biallelic cysteine-involving missense variants (24 patients) fall within the CADASIL spectrum phenotype with early adulthood onset stroke, dementia, and deep white matter lesions without significant volume loss. White matter lesion volume is comparable between patients with biallelic cysteine-involving missense variants and individuals with CADASIL. Notably, monoallelic carriers of loss-of-function variants are predominantly asymptomatic, with only a few cases reporting nonspecific headaches.

They propose a NOTCH3-SVD classification depending on dosage and variant type. This study not only expands our knowledge of biallelic NOTCH3 variants but also provides valuable insight into the underlying mechanisms of the disease, contributing to a more comprehensive understanding of NOTCH3-related SVD [3)].

Risk Factors

Arterial Stiffness as the Prevailing Risk Factor for Cerebral Small Vessel Disease in Stroke-Free Individuals [4)]

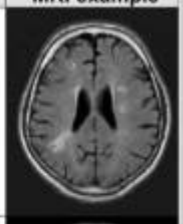
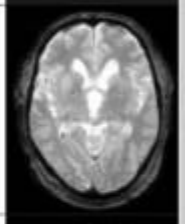
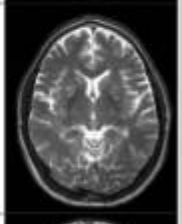
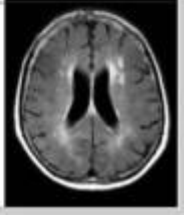
Higher circulating PCSK9 levels were independently associated with an intracranial artery stenosis (ICAS) prevalence but not with a cerebral small vessel disease (CSVD) prevalence. The quantification of circulating PCSK9 levels may help to identify individuals at high risk for cerebrovascular disease in the general population [5)].

Clinical features

The main clinical manifestations of CSVD include stroke, cognitive decline, dementia, psychiatric disorders, abnormal gait, and urinary incontinence.

Diagnosis

Neuroimaging features of CSVD include recent small subcortical infarcts, lacunes, white matter hyperintensity, perivascular spaces, microbleeds, and brain atrophy.

MRI feature	Visual assessment	Definition	Score	MRI example
Lacunes	International consensus definition[14]	≥1 Lacune	1 point	
Microbleeds	International consensus definition[14]	≥1 Microbleed	1 point	
Perivascular spaces	Semiquantitative scale[7]	Moderate to severe perivascular spaces in basal ganglia	1 point	
White matter hyperintensities (WMH)	Fazekas scale[19]	Periventricular WMH Fazekas 3 (extending into the deep white matter) and/or deep WMH Fazekas 2-3 (confluent or early confluent)	1 point	

Differential diagnosis

arteriolosclerosis (age-related and vascular risk factor-related small vessel disease): see Binswanger disease

cerebral amyloid angiopathy (sporadic or hereditary)

inherited/genetic small vessel diseases other than cerebral amyloid angiopathy, such as

CADASIL

CARASIL

MELAS

Fabry disease

retinal vasculopathy with cerebral leukoencephalopathy

COL4A1 brain small-vessel disease

inflammatory and immunologically mediated small vessel diseases (CNS vasculitis)

venous collagenosis

other small vessel diseases, such as

post-radiation angiopathy

non-amyloid microvessel degeneration in Alzheimer disease

Complications

Hypertension, obesity, smoking, and cerebral small vessel disease were important factors associated with non-lesional spontaneous intracerebral hemorrhage in young patients. Radiologic changes corresponding to cerebral small vessel disease appeared in young patients (in their 30s) and they were associated with hypertension [6].

Treatment

Currently, there are no specific preventive or therapeutic measures to improve this condition.

Test

What does the term “cerebral small vessel disease” primarily refer to?

a) Lesions in the large arteries of the brain

b) Lesions in the brain parenchyma's subcortical structures

c) Lesions in the cerebral cortex

d) Lesions in the brainstem

Which of the following is NOT mentioned as a common form of cerebral small vessel disease?

a) Age-related small vessel disease

b) Hypertension-related small vessel disease

c) Cerebral amyloid angiopathy

d) Alzheimer's disease

What are the primary consequences of small vessel disease on the brain parenchyma?

a) Lesions in the cerebral cortex

b) Lesions in the brainstem

c) Lesions in the subcortical structures such as lacunar infarcts and white matter lesions

d) Lesions in the ventricles

Why is the term “small vessel disease” often used to describe parenchyma lesions rather than the underlying small vessel alterations?

a) Because small vessels are easily detected by neuroimaging

b) Because it simplifies the diagnosis

c) Because small vessels are not easily detectable by neuroimaging

d) Because it doesn't affect the diagnosis

What role does small vessel disease play in cerebrovascular disease?

a) It has no significant role in cerebrovascular disease.

b) It is the primary cause of cerebrovascular disease.

c) It is a leading cause of cognitive decline and functional loss in the elderly.

d) It only affects young individuals.

Which two factors are mentioned to play key roles in the progression of cerebral small vessel burden after mid-life?

a) Genetics and diet

b) Hypertension and age

c) Smoking and obesity

d) Alcohol consumption and exercise

What is PCSK9, and how is it associated with cerebrovascular disease?

a) A protein found in the brain

b) A genetic mutation

c) Higher circulating PCSK9 levels are independently associated with cerebral small vessel disease

d) It has no association with cerebrovascular disease

What are the main clinical manifestations of cerebral small vessel disease?

a) Joint pain and skin rashes

b) Stroke, cognitive decline, dementia, psychiatric disorders, abnormal gait, and urinary incontinence

c) Vision problems

d) Hearing loss and vertigo

What are some of the neuroimaging features of cerebral small vessel disease?

a) Enlarged ventricles and brain atrophy

b) Recent large cortical infarcts

c) White matter hyperintensity, perivascular spaces, and microbleeds

d) Clear brain scans with no abnormalities

Currently, what is the status of preventive or therapeutic measures for cerebral small vessel disease?

a) Several effective preventive measures are available.

b) There is a specific treatment to cure the disease.

c) Currently, there are no specific preventive or therapeutic measures.

d) It can be managed with over-the-counter medications.

Answers:

b) Lesions in the brain parenchyma's subcortical structures d) Alzheimer's disease c) Lesions in the subcortical structures such as lacunar infarcts and white matter lesions c) Because small vessels are not easily detectable by neuroimaging c) It is a leading cause of cognitive decline and functional loss in the elderly. b) Hypertension and age c) Higher circulating PCSK9 levels are independently associated with cerebral small vessel disease b) Stroke, cognitive decline, dementia, psychiatric disorders, abnormal gait, and urinary incontinence c) White matter hyperintensity, perivascular spaces, and microbleeds c) Currently, there are no specific preventive or therapeutic measures.

Cohort studies

A cohort study used pooled individual patient data from the Microbleeds International Collaborative Network, including patients from 38 prospective cohort studies in 18 countries between 2000 and 2018, with clinical follow-up of at least 3 months (up to 5 years). Participants included patients with acute ischemic stroke or transient ischemic attack with available brain MRI. Data were analyzed from April to December 2023.

Main outcomes and measures: Outcomes of interest were presence of CMB, lacunes, and severe white matter hyperintensities determined on MRI. Additionally, mortality, recurrent ischemic stroke, and intracranial hemorrhage during follow-up were assessed. Multivariable random-effects logistic regression models, Cox regression, and competing risk regression models were used to investigate sex differences in individual SVD markers, risk of recurrent cerebrovascular events, and death.

A total of 20 314 patients (mean [SD] age, 70.1 [12.7] years; 11 721 [57.7%] male) were included, of whom 5649 (27.8%) had CMB. CMB were more frequent in male patients, and this was consistent throughout different age groups, locations, and in multivariable models (female vs male adjusted odds ratio [aOR], 0.86; 95% CI, 0.80-0.92; P < .001). Female patients had fewer lacunes (aOR, 0.82; 95% CI, 0.74-0.90; P < .001) but a higher prevalence of severe white matter hyperintensities (aOR, 1.10; 95% CI, 1.01-1.20; P = .04) compared with male patients. A total of 2419 patients (11.9%) died during a median (IQR) follow-up of 1.4 (0.7-2.5) years. CMB presence was associated with a higher risk of mortality in female patients (hazard ratio, 1.15; 95% CI, 1.02-1.31), but not male patients (hazard ratio, 0.95; 95% CI, 0.84-1.07) (P for interaction = .01). A total of 1113 patients (5.5%) had recurrent ischemic stroke, and 189 patients (0.9%) had recurrent intracranial hemorrhage, with no sex differences.

Conclusions and relevance: This cohort study using pooled individual patient data found varying frequencies of individual SVD markers between female and male patients, indicating potential pathophysiological differences in manifestation and severity of SVD. Further research addressing differences in pathomechanisms and outcomes of SVD between female and male patients is required [7)]

Case series

Ide et al. conducted a longitudinal study with a neurologically healthy cohort composed mostly of middle-aged adults (n = 665, mean age, 57.7 years). Subjects, who had both baseline data of brain health examinations including MRI and follow-up MRI at least 1 year after the baseline MRI, were included in this study. The presence of features of SVD, including lacunes, cerebral microbleeds, white matter hyperintensity, and basal ganglia perivascular spaces was summed to obtain a “total SVD score” (range, 0-4). Progression of SVD was evaluated among subjects with a total SVD score of ≤ 3 and was defined as a ≥ 1 point increase in that score at follow-up relative to baseline. As the primary analysis, multivariate logistic regression analyses were performed to determine the associations of progression of SVD at baseline. The median follow-up period was 7.3 years and progression of SVD was observed in 154 subjects (23.2%). Even after adjustment with confounders multivariate logistic regression analyses showed that progression of SVD was associated with age (per 10-year increase, odds ratio [OR]: 2.08, 95% confidence interval [CI] 1.62-2.67), hypertension (OR 1.55, 95%CI 1.05-2.29), systolic blood pressure (BP) (per standard deviation [SD] increase, OR 1.27, 95%CI 1.04-1.54), diastolic BP (per SD increase, OR 1.23, 95%CI 1.01-1.50), and mean arterial pressure (per SD increase, OR 1.27, 95%CI 1.04-1.55). Age and high blood pressure appear to play key roles in the

progression of cerebral small vessel burden after mid-life [8].

Wang et al. enrolled 398 small-vessel occlusion (SVO) and 175 large artery atherosclerosis (LAA) acute ischemic stroke (AIS) patients. Functional outcomes were assessed using the modified Rankin Scale (mRS) at 90 days. MRI was performed to assess white matter hyperintensity (WMH), perivascular space (PVS), lacune, and cerebral microbleed (CMB). Logistic regression (LR) and machine learning (ML) were used to develop predictive models to assess the influences of SVD on the prognosis.

In the feature evaluation of SVO-AIS for different outcomes, the modified total SVD score (Gain: 0.38, 0.28) has the maximum weight, and periventricular WMH (Gain: 0.07, 0.09) was more important than deep WMH (Gain: 0.01, 0.01) in prognosis. In SVO-AIS, SVD performed better than regular clinical data, which is the opposite of LAA-AIS. Among all models, eXtreme gradient boosting (XGBoost) method with optimal index (OI) has the best performance to predict excellent outcome in SVO-AIS. [0.91 (0.84-0.97)].

The results revealed that different SVD markers had distinct prognostic weights in AIS patients, and SVD burden alone may accurately predict the SVO-AIS patients' prognosis [9].

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418 consecutive patients admitted with primary lobar hemorrhage or deep ICH to a single tertiary care medical center between January 1, 2000, and October 1, 2012. Data were analyzed on March 4, 2016. Participants were consecutive patients with computed tomographic images allowing ICH volume calculation and MRI allowing imaging markers of small vessel disease (SVD).

The ICH volumes at baseline and within 48 hours after symptom onset were measured in 418 patients with spontaneous ICH without anticoagulant therapy, and hematoma expansion was calculated. Cerebral microbleeds, cortical superficial siderosis, and white matter hyperintensity volume were assessed on MRI. The associations between these SVD markers and ICH volume, as well as hematoma expansion, were investigated using multivariable models.

This study analyzed 254 patients with lobar ICH (mean [SD] age, 75 [11] years and 140 [55.1%] female) and 164 patients with deep ICH (mean [SD] age 67 [14] years and 71 [43.3%] female). The presence of cortical superficial siderosis was an independent variable associated with larger ICH volume in the lobar ICH group (odds ratio per quintile increase in final ICH volume, 1.49; 95% CI, 1.14-1.94; P = .004). In multivariable models, the absence of cerebral microbleeds was associated with larger ICH volume for both the lobar and deep ICH groups (odds ratios per quintile increase in final ICH volume, 1.41; 95% CI, 1.11-1.81; P = .006 and 1.43; 95% CI, 1.04-1.99; P = .03; respectively) and with hematoma expansion in the lobar ICH group (odds ratio, 1.70; 95% CI, 1.07-2.92; P = .04). The white matter hyperintensity volumes were not associated with either hematoma volume or expansion.

In patients admitted with primary lobar or deep ICH to a single tertiary care medical center, the presence of cortical superficial siderosis was an independent variable associated with larger lobar ICH volume, and the absence of cerebral microbleeds was associated with larger lobar and deep ICHs. The absence of cerebral microbleeds was independently associated with more frequent hematoma expansion in patients with lobar ICH. We provide an analytical framework for future studies aimed at limiting hematoma expansion [10].

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