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Acute cerebral small vessel disease: Classification, mechanism, and therapeutic implications

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Cerebral small vessel disease (CSVD) is a significant cause of stroke and dementia. CSVD causes up to 30% of ischemic strokes and 80% of spontaneous intraparenchymal hemorrhages.[1] Compared with data from developed countries, Asian populations exhibit a heavier burden of strokes caused by CSVD.[2] The clinical manifestations of CSVD can vary. We propose the concept of acute CSVD (aCSVD) describing the phenotypes with sudden-onset stroke symptoms. This aims to draw equal attention to both ischemic and hemorrhagic aCSVD and to promote a better understanding of the discrepancies and connections between aCSVD and nonacute or covert CSVD. We focus on the heterogeneous mechanisms and discuss the therapeutic challenges and potential strategies.

Definition, Classification, and Pathogenesis

We define the term aCSVD as stroke events occurring in the past few weeks, with imaging changes in the territory of small arteries and arterioles compatible with clinical symptoms. Pathologically, aCSVD can be classified as ischemic or hemorrhagic [Supplementary Figure 1, http://links.lww.com/CM9/C152]. Supplementary Table 1, http://links.lww.com/CM9/C152 provides details on the epidemiology and risk factors of aCSVD.

Ischemic aCSVD is considered a synonym of lacunar stroke. Supplementary Table 2, http://links.lww.com/CM9/C152 provides definitions and differentiations of several synonymous terms used in studies. The pathological processes mainly include arteriolosclerosis, lipohyalinosis or fibrinoid necrosis, and arteriosclerosis. Branch atheromatous disease (BAD) is another important mechanism of ischemic aCSVD which involves large artery atherosclerosis. A smaller percentage of cases might be due to cardioembolism, microdissection, inflammatory arteritis, or other causes.[3]

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Hemorrhagic aCSVD consists of two forms of intracerebral hemorrhage (ICH): hypertensive ICH and cerebral amyloid angiopathy (CAA)-related ICH. More than 50% of primary ICHs are associated with hypertension, and CAA accounts for approximately 30%. Hypertensive ICH is caused by arteriolosclerosis and the rupture of deep perforators, whereas amyloid-beta (Aβ) accumulation in small- to medium-sized leptomeningeal and cortical arteries leads to vessel wall fragmentation in CAA-related ICH.[4] These two pathogeneses may share some pathological processes and mechanisms.

Non-aCSVD is defined as clinical symptoms without a clear-cut onset caused by small vessel disorders, such as cognitive decline, gait imbalance, and neurobehavioral problems. Some magnetic resonance imaging (MRI) markers of CSVD (white matter hyperintensities [WMHs], lacunes, cerebral microbleeds [CMBs], etc.) are commonly reported. Supplementary Figure 2, http://links.lww.com/CM9/C152 summarizes the classification.

Notably, here we focus on prevalent sporadic CSVD and do not discuss rare hereditary or venous-involved disorders, although the latter need to be considered in clinical situations.

Clinical and Imaging Manifestations

Lacunar syndromes are typical symptoms of ischemic aCSVD. Approximately one-third of ischemic aCSVD patients experience early neurological deterioration (END), leading to worse outcomes.[5] The underlying mechanisms of END include local thrombosis formation, thrombus propagation, plaque vulnerability, blood–brain

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barrier (BBB) disruption, inflammation, and excitotoxicity. In addition to some conventional risk factors (e.g., baseline National Institute of Health Stroke Scale score), certain imaging features, such as parental artery atherosclerosis, lesion size, and location, can predict END occurrence.[5,6] The typical symptoms (headache, vomiting, seizure, decreased consciousness, etc.) and differential risk profiles[7] can help distinguish hemorrhagic aCSVD from ischemic stroke.

We recommend the presence of a recent small subcortical infarct (RSSI) without obvious stenosis of ipsilateral parental arteries evaluated by conventional angiography as a practical imaging criterion to diagnose ischemic aCSVD. We should realize that the upper limit of lesion size is not an absolute standard for etiology differentiation in ischemic aCSVD, although larger lesions increase the likelihood of large artery atherosclerosis or embolism. Any possible embolic sources should be carefully excluded.

Hematomas can be easily detected using noncontrast computed tomography and susceptibility-weighted imaging. Cerebral angiography is necessary to exclude other causes. The location and shape of hemorrhagic lesions, the apolipoprotein E genotype, and white matter lesions (high-burden perivascular spaces in the centrum semiovale or multispot WMHs) help to improve CAA diagnosis and distinguish between the two hemorrhagic aCSVD subtypes.[4] Instead of selecting a single-cause phenotype for ICH patients who might have multiple causes or concomitant presence of imaging features, the concept of "mixed CSVD (arteriolosclerosis and CAA)" has been used to efficiently assess potential etiology and prognosis.

Advanced imaging techniques can provide further information. The morphology of the small perforators and atherosclerotic plaques within the parental vessel wall can be directly visualized using ultra-high-field or high-resolution MRI [Supplementary Figure 3, http://links.lww.com/CM9/C152]. Vessel wall imaging studies have revealed a surprisingly high frequency (41.7–77.5%) of parental artery atherosclerosis in patients with single subcortical infarction and normal angiography, indicating that BAD is one of the critical mechanisms in ischemic aCSVD. Indicators of culprit plaques include plaque enhancement, positive remodeling, T1 hyperintensity, surface irregularity, and superior distribution within the vessel wall.[8,9] Perfusion imaging can be used to measure BBB integrity and microvasculature function, potentially providing early clues for clinical outcomes. Moreover, advanced diffusion and functional imaging can assess brain microstructure and function from a network and global perspective.[10] Although these sequences are not yet widely applied in clinical practice, they hold promise for enhancing our understanding of the mechanisms of aCSVD.

A comprehensive evaluation of small vessels in other organs like the retina may also provide evidence of disease due to shared risk factors. Studies have shown that retinal microvascular changes (e.g., arteriolar narrowing and arteriovenous nicking) are associated with stroke subtypes and prognosis.[11] Retinal and choroidal structures assessed by optical coherence tomography/optical coherence tomography angiography have the potential to serve as surrogate markers of CSVD burden, brain volume, and optic tract shrinkage. These findings suggest that fundus imaging could be a practical and time-saving measure for detecting brain microvasculature and structural changes.[12,13]

aCSVD Imaging Features and Other CSVD Markers

RSSI has different morphological fates [Supplementary Figure 4, http://links.lww.com/CM9/C152].[10] Some lesions might temporarily disappear and recur silently before reaching the end-stage appearance. Cavitation and lesion shrinkage were the most common changes, occurring in 60.5–93.9% of patients. A small number of RSSIs remain indistinguishable from nonspecific WMHs or vanish after several weeks or months. Hemorrhagic focus may be observed at the RSSI lesion on follow-up images.

Although WMHs can shrink and grow, WMH progression and brain atrophy are the two most frequently observed secondary changes occurring in normal-appearing tissue after aCSVD.[1] Incident lacunes and CMBs can be detected during follow-up period as the manifestations of CSVD progression. These secondary brain injuries are considered to correlate with cognitive decline and determine prognosis.[1]

Previous studies have indicated that imaging features of non-aCSVD may have predictive value for clinical outcomes.[10] However, whether pre-existing CMBs, cortical superficial siderosis, or WMHs influence ICH volume, hematoma expansion, or perihematomal edema remains controversial.

Therapeutic Strategies and Challenges

There are limited consensuses for aCSVD management.[14,15] Notably, most of the previous studies were not specifically designed to treat aCSVD, and the pathogenesis has rarely been distinguished.

Standard-dose intravenous thrombolysis (0.9 mg/kg alteplase) tends to be beneficial for patients with suspected ischemic aCSVD. The concurrence of other CSVD markers should not be considered as an absolute exclusion criterion even though it might increase the risk of ICH.[14] For hemorrhagic aCSVD, achieving a systolic blood pressure (SBP) below 140 mmHg within a few hours after stroke onset is safe and can improve functional outcomes, which is one of the critical management in hyperacute and acute stages.[16]

Risk factor management is the main approach for secondary prevention. Maintaining SBP below 130 mmHg might be a rational long-term goal for aCSVD patients.[14,15] Despite a weaker antiplatelet effect, cilostazol has potential benefits in terms of endothelial stabilization, BBB protection, and myelin repair. Cilostazol and isosorbide mononitrate have been confirmed to be well-tolerated and might improve clinical outcomes in the ischemic aCSVD population.[17]

Treatment approaches tailored to heterogeneous mechanisms in ischemic aCSVD are encouraging in clinical trials. Antithrombotic medication may be less effective

for lacunar stroke of lipohyalinotic origin.[18] In this subgroup, repurposing existing drugs or developing novel agents to improve endothelial function could be promising.[14] Conversely, high-risk patients with atherosclerosis (i.e., BAD-related stroke patients with a progressive worsening of neurological deficit) may benefit from aggressive antithrombotic therapy using dual antiplatelet agents or combined with short-term argatroban or tirofiban. These approaches may help terminate clinical fluctuations, reduce END risk, prevent stroke recurrence, and improve functional outcomes.[19] Some randomized controlled trials are currently underway to evaluate these strategies.[20,21]

In conclusion, aCSVD describes a spectrum of small vessel disorders with sudden-onset stroke symptoms and corresponding imaging changes. This disease can be classified as ischemic (lacunar stroke) and hemorrhagic aCSVD (hypertensive and CAA-related ICH) and is caused mainly by arteriolosclerosis and CAA. BAD is another significant pathological mechanism of ischemic aCSVD. Although advanced imaging is a promising approach to provide valuable information for precise diagnosis, further effort is needed to find efficient and cost-effective measures for precise pathological phenotyping. Aggressive antithrombotic therapy may be effective in reducing END risk and improving outcomes in BAD-related stroke. More longitudinal research and randomized trials designed for aCSVD should be conducted to optimize evidence-based and individualized strategies for therapy.

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Conflicts of interest

None.

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