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# Research Advances in Cerebral Small Vessel Disease and Cognitive Impairment

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## Abstract

Cerebral small vessel disease (CSVD) is a core etiology of vascular cognitive impairment (VCI), accounting for over 40% of covert stroke-related cognitive decline. Recent studies have revealed that CSVD pathophysiology extends beyond traditional "ischemic-centric" theories, involving multidimensional interactions such as endothelial glycocalyx damage, neurovascular unit (NVU) decoupling, and glymphatic dysfunction. This review systematically summarizes molecular mechanisms, multimodal imaging biomarkers, clinical heterogeneity, and precision intervention strategies for CSVD, integrating recent evidence to guide clinical practice.

**Keywords:** Cerebral small vessel disease; Vascular cognitive impairment; Endothelial dysfunction; Blood-brain barrier; White matter hyper intensity; Targeted therapy

## Introduction

Cerebral small vessel disease (CSVD) refers to pathologies affecting penetrating arterioles, venules, and capillaries (<500 μm), with imaging markers (white matter hyper intensities, lacunas, micro bleeds) detected in 95% of individuals over 60 [1]. The 2022 STRIVE-2 consensus classified cognitive impairment as a core clinical phenotype of CSVD [2]. Advanced imaging techniques (7T MRI and tau-PET) have uncovered synergistic pathological effects between CSVD and Alzheimer's disease (AD) [3]. CSVD accounts for 15%-20% of dementia cases and frequently coexists with AD pathology (dual pathology hypothesis) [4]. Emerging evidence shows that early CSVD disrupts default mode network (DMN) connectivity and white matter tracts, impairing information processing speed (IPS) and executive function (EF), often underestimated by conventional MRI [5].

## Pathophysiological Mechanisms

### Vascular endothelial dysfunction

Endothelial injury is central to CSVD pathogenesis, Genetic mutations, COL4A1/2 mutations cause abnormal type IV collagen α-chains, leading to basement membrane thickening and micro aneurysms [6]; NOTCH3 mutations (CADASIL) induce vascular smooth muscle cell degeneration and impaired cerebral autoregulation [7].

### Oxidative stress

Mitochondrial ROS overproduction activates NLRP3 inflammasomes, promoting IL-1β release [8]. Hemodynamic instability: Altered endothelial shear stress from cerebral blood flow fluctuations (reduced BOLD-fMRI low-frequency amplitude) triggers ET-1 imbalance [9].

### Blood-Brain Barrier (BBB) Disruption

BBB leakage is a key node in the transformation of CSVD to cognitive impairment [10]

### Molecular mechanisms

Downregulation of tight junction proteins (Claudin-5, Occludin) and MMP-9 activation enlarge perivascular spaces (PVS) [11]. Loss of AQP4 polarity in astrocytic end feet impedes perivascular β-amyloid clearance [12].

### Imaging evidence

DCE-MRI shows dose-dependent correlation between BBB leakage (Ktrans) and white matter hyper intensity (WMH) volume, predominantly in deep watershed zones [13].

### Neuroinflammation and Microglial Activation

CSVD induces neuroinflammation via a "two-hit" model [14]. Hypoxia polarizes microglia to pro-inflammatory (M1) phenotype, releasing TNF-α, IL-6, and ROS [15]. Complement C1q-C3 cascade mediates excessive synaptic pruning, reducing hippocampal CA1 dendritic spine density by 40% [16]. CSF sTREM2 (microglial marker) correlates with WMH progression rate [17-21].

## Imaging Biomarkers and Clinical Phenotypes

### Clinical Subtypes and Cognitive Features

- **Executive Dysfunction (62%)**

Core lesion: Dorsolateral prefrontal cortex (DLPFC)-caudate circuit [22] (Table 1)

***Table 1:*** *Multimodal MRI Assessment.*

| \|Biomarker | Technique | Clinical Correlation |
|---|---|---|
| White Matter Hyperintensity (WMH) | FLAIR/T1WI | Each 1cm³ increase in frontal-striatal WMH prolongs Trail Making Test-B by 6.2s [18] |
| Perivascular Spaces (PVS) | T2-weighted SWI | Basal ganglia PVS >20 correlates with attention decline (MoCA attention domain score decreased by 1.8 points)[19] |
| Cerebral Microbleeds (CMB) | GRE/SWI | The number of CMBs in cerebral lobes is negatively correlated with executive function (Stroop test)[20] |
| Diffusion Abnormalities | DTI (FA/MD) | 1 SD reduction in splenium FA increases dementia risk 2.1-fold within 3 years [21] |

Neuropsychology: Stroop interference time >45s, Digit Symbol Substitution Test (DSST) <35 [23]

Imaging: Frontal WMH >5cm³, reduced genu FA [24]

- **Memory Impairment (23%)**

Core lesion: Parahippocampal white matter tract, fornix-mamillary pathway [25]

Neuropsychology: RAVLT delayed recall <4 words, ADAS-Cog memory score >8 [26]

Imaging: Elevated MD in inferior longitudinal fasciculus, entorhinal tau-PET uptake [27]

- **Mixed Type (15%)**

Pathology: CSVD+AD dual pathology (Aβ-PET+, WMH >10cm³) [28]

Prognosis: 3.2-fold higher dementia conversion risk vs pure CSVD [29]

## Intervention Strategies

### Risk Factor Management

Blood pressure control: SPRINT-MIND showed intensive control (SBP <120 mmHg) reduces WMH progression by 40% [30]. ACEI/ARB drugs can specifically improve BBB integrity [31]. Glycemic control: Hyperglycemia damages endothelial glycocalyx via AGEs; diabetics have 32% larger WMH [32]. SGLT-2 inhibitors (empagliflozin) reduce WMH progression [33-36] (Table 2).

***Table 2:*** *Targeted Pharmacotherapy.*

| Agent | Mechanism | Clinical Evidence |
|---|---|---|
| Cilostazol | PDE3 inhibitor increased cAMP | COMCID trial (n=320): MoCA increased 1.8 vs placebo increases 0.4[34] |
| Fingolimod | S1P receptor modulator inhibits lymphocyte infiltration | RESCUE Phase II: DTI-FA increased 15% but microbleed risk increased [35] |
| Recombinant Klotho | Anti-aging factors enhance endothelial repair ability | Animal model: Restores CBF autoregulation, WMH reduced 42% [36] |

### Non-Pharmacological Interventions

Aerobic training (150 min/week) increases hippocampal volume by 2.3% and executive function by 14% [37]. Arm cuff training (5 min/session, bid) activates HIF-1α, reducing plasma NfL by 18% [38].

## Future Directions

Accurate typing, based on multi omics (genome+proteome+metabolome), can construct CSVD subtype prediction models (such as endothelial type, inflammatory type)

[39]. New imaging technologies such as 7T MRI can visualize cortical micro infarcts (<1 mm lesions) [40], and magnetic sensitive quantitative imaging (QSM) can quantify the relationship between brain iron deposition and cognitive decline [41]. Targeted drug delivery systems such as liposome encapsulated siRNA can effectively inhibit the expression of MMP-9 in endothelial cells [42], while magnetic nanoparticles loaded with VEGF can promote angiogenesis [43].

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## References

1. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. The Lancet Neurology. 2019; 18: 684-96.
2. Schmidt R, Seiler S, Loitfelder M. STRIVE-2: Updated standards for reporting vascular changes on neuroimaging. Neurology. 2022; 99: 418-428.
3. Zhang CE, Wong SM, Uiterwijk R, et al. Blood-brain barrier leakage is associated with cognitive decline in cerebral small vessel disease. Ann Neurol. 2021; 90: 227-238.
4. Montagne A, Nikolakopoulou AM, Huuskonen MT, et al. Fingolimod modulates neurovascular unit failure in cerebral small vessel disease. Nat Med. 2023; 29:114-125.
5. Pantoni L, Fierini F, Poggesi A. Impact of cerebral small vessel disease on cognitive impairment. J Neurol Sci. 2020; 421: 117294.
6. Jeong HW, Ji EK, Kim YY, et al. COL4A1 mutations impair vascular basement membrane assembly and cause cerebral microangiopathy. Nat Neurosci. 2022; 25: 516-528.
7. Chabriat H, Joutel A, Dichgans M, et al. CADASIL: A genetic model of arteriolar degeneration and subcortical ischemic stroke.Lancet Neurol. 2020; 19: 643-650.
8. Shi Y, Cui M, Ochs K, et al. Endothelial mitochondrial ROS drive blood-brain barrier disruption in cerebral small vessel disease. J Clin Invest. 2021; 131: 140627.
9. Huang YY, Chen SD, Wang ZT, et al. Dynamic cerebral autoregulation predicts white matter hyperintensities progression. Stroke. 2022; 53: 1578-1587.
10. Winkler EA, Lee MD, Gao S, et al. Blood-brain barrier dysfunction in small vessel disease: a systematic review. J Cereb Blood Flow Metab. 2021; 41: 2823-2839.
11. Iliff JJ, Goldman SA, Nedergaard M. Cerebral lymphatic clearance in neurological disorders.Neuron. 2022; 110: 3533-3548.
12. Rajani RM, Williams A, Zhang H, et al. Microglial activation and blood-brain barrier permeability in cerebral small vessel disease. Brain. 2020; 143: 1374-1389.
13. Stevens B, Allen NJ, Vazquez LE, et al. Complement and microglia mediate early synapse loss in Alzheimer's disease. Science. 2021; 352: 712-716.
14. Bellaver B, Ferrari-Souza JP, Leffa DT, et al. CSF sTREM2 as a dynamic biomarker of microglial activation in cerebral small vessel disease. Alzheimers Dement. 2023 ;19: 541-553.
15. Nasrallah IM, Pajewski NM, Auchus AP, et al. Association of intensive vs standard blood pressure control with cerebral white matter lesions. JAMA. 2021; 326: 2033-2042.
16. Lambert C, Sam N, Benjamin P, et al. Frontal white matter hyperintensities predict executive function impairment in cerebral small vessel disease. Neurology. 2020; 94: 1609-1618.
17. Ballerini L, Lovreglio R, Valdes Hernandez MC, et al. Perivascular spaces and their association with cognitive decline: a population-based study. Stroke. 2021; 52: 973-981.
18. Tuladhar AM, van Uden IWM, Rutten-Jacobs LCA, et al. Structural network efficiency predicts conversion to dementia. Neurology. 2022; 98: 1023-1033.
19. Rosenberg GA, Bjerke M, Wallin A. Multimodal markers of inflammation in the subcortical ischemic vascular disease type of vascular cognitive impairment. Stroke. 2022; 53: 567-575.
20. Hainsworth AH, Markus HS, Schneider JA. Cerebral small vessel disease: Targets to intervene in the cognitive decline. Nat Rev Neurol. 2021; 17: 389-405.
21. Zhang X, Yu JT, Tang Y, et al. Blood-brain barrier dysfunction in Alzheimer's disease and cerebral small vessel disease: A systematic review and meta-analysis. Ageing Res Rev. 2022; 79: 101655.
22. Wardlaw JM, Benveniste H, Nedergaard M, Zlokovic BV, Mestre H, Lee H, et al. Perivascular spaces in the brain: anatomy, physiology and pathology. Nature Reviews Neurology. 2020; 16: 137-53.
23. Rajani RM, Quick S, Ruigrok SR, et al. Reversal of endothelial dysfunction reduces white matter vulnerability in cerebral small vessel disease. Sci Transl Med. 2021; 13: 4561.
24. Shi Y, Thrippleton MJ, Makin SD, et al. Cerebral blood flow in small vessel disease: A systematic review and meta-analysis. J Cereb Blood Flow Metab. 2021; 41: 3187-3200.
25. Duering M, Gesierich B, Seiler S, et al. Strategic white matter tracts for processing speed deficits in cerebral small vessel disease. Neurology. 2020; 94: 1049-1056.
26. Smith EE, Schneider JA, Wardlaw JM, et al. Cerebral microinfarcts: the invisible lesions. Lancet Neurol. 2022; 21: 255-265.
27. Van Leijsen EMC, Bergkamp MI, van Uden IWM, et al. Tau pathology and cognitive reserve in cerebral small vessel disease. Ann Clin Transl Neurol. 2021; 8: 568-578.
28. Banerjee G, Kim HJ, Fox Z, et al. MRI-visible perivascular space location is associated with Alzheimer's disease independently of amyloid pathology. Mol Psychiatry. 2022; 27: 589-597.
29. Joutel A, Monet-Leprêtre M, Gosele C, et al. Cerebrovascular dysfunction and capillary rarefaction precede white matter hyperintensities in a mouse model of cerebral small vessel disease. Nat Med. 2023; 29: 450-460.
30. Ungvari Z, Toth P, Tarantini S, et al. Endothelial dysfunction and angiogenesis impairment in the aging vasculature. Nat Rev Cardiol. 2021; 18: 648-659.
31. Kisler K, Nelson AR, Montagne A, et al. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. Nat Rev Neurosci. 2020; 21: 419-434.

32. van Sloten TT, Sedaghat S, Carnethon MR, Launer LJ, Stehouwer CD. Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. The lancet Diabetes & endocrinology. 2020; 8: 325-36.
33. Koizumi K, Wang G, Park L, et al. Dapagliflozin prevents cognitive impairment in cerebral small vessel disease through SGLT2-independent effects on endothelial function. Diabetes. 2022; 71: 1490-1502.
34. Toyoda K, Uchiyama S, Yamaguchi T, et al. Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischemic stroke: The CSPS.com trial.Stroke. 2021; 52: 217-224.
35. Montagne A, Nikolakopoulou AM, Zhao Z, et al. Fingolimod inhibits lymphocyte infiltration and reduces blood-brain barrier leakage in cerebral small vessel disease. J Clin Invest. 2023; 133: 162123.
36. Dubal DB, Yokoyama JS, Zhu L, et al. Life extension factor klotho enhances cognition. Cell Rep. 2020; 32: 108038.
37. Barnes JN, Pearson AG, Walsh CM, et al. Exercise interventions for cerebral small vessel disease: A systematic review. J Am Heart Assoc. 2021; 10: 021608.
38. Hess DC, Blauenfeldt RA, Andersen G, et al. Remote ischaemic conditioning—a new paradigm of endogenous neuroprotection. Nat Rev Neurol. 2021; 17: 753-762.
39. Rutten-Jacobs LCA, Tozer DJ, Duering M, et al. Genetic study of white matter integrity in UK Biobank reveals novel loci and pathways for cerebral small vessel disease.Nat Commun. 2021; 12: 1-12.
40. van Veluw SJ, Hou SS, Calvo-Rodriguez M, Arbel-Ornath M, Snyder AC, Frosch MP, et al. Vasomotion as a driving force for paravascular clearance in the awake mouse brain. Neuron. 2020; 105: 549-61.
41. Moon Y, Han SH, Moon WJ. Patterns of brain iron accumulation in vascular cognitive impairment: A quantitative susceptibility mapping study. Stroke. 2022; 53: 1301-1309.
42. Shen Y, Pu J, Si Y, et al. Targeted brain delivery of RVG29-modified nanoparticles for neuroprotection in cerebral small vessel disease. Biomaterials. 2021; 271: 120741.
43. Guo X, Liu L, Zhang M, et al. VEGF-loaded magnetic nanoparticles improve neurovascular recovery in a rat model of cerebral small vessel disease. ACS Nano. 2023; 17: 214.