


Clinical practice guideline for cognitive impairment of cerebral small vessel disease

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Abstract

Cognitive impairment of cerebral small vessel disease (CSVD) is one of the most common cognitive disorders. It has a high incidence and results in heavy social burden; thus, it is essential to provide reasonable diagnosis and treatment in clinical practice. Based on the results of clinical research and related reports, combined with the actual situation in China, we propose a diagnosis and treatment guideline for cognitive impairment of CSVD.

KEYWORDS

cerebral small vessel disease, cognitive impairment, vascular cognitive impairment

1 | INTRODUCTION

Current international guidelines for vascular cognitive impairment (VCI) mainly include: the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria of 1993¹; the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS/CSN) criteria of 2006²; the American Heart Association/American Stroke Association criteria of 2011³; the International Society for Vascular Behavioral and Cognitive Disorders (VASCOG) criteria of 2014⁴; the Guideline for Vascular Cognitive Impairment, published in China in 2011⁵; and the guidelines from the Vascular Impairment of Cognition Classification Consensus Study, formulated by experts from 27 countries around the world and published in 2018.⁶

According to the guidelines above, cerebral small vessel disease (CSVD) is an important cause of VCI. Recently, with the development of the three classic studies—the LADIS,⁷ RUN DMC,⁸ and SPS3⁹ growing evidence has supported cognitive research as the core of clinical research for CSVD. Cognitive impairment of CSVD is

one of the most common cognitive disorders. It has a high incidence and results in heavy social burden; thus, it is essential to provide reasonable diagnosis and treatment in clinical practice. Based on the results of clinical research and related reports, and combined with the actual situation in China, we propose a diagnosis and treatment guideline for cognitive impairment of CSVD.

2 | DEFINITION

CSVD denotes a range of clinical, imaging, and pathological syndromes resulting from various causes affecting the small arteries, arterioles, capillaries, and venules in the brain. Common causes of CSVD include arteriosclerosis, cerebral amyloid angiopathy, genetic small vessel diseases distinct from cerebral amyloid angiopathy, inflammation- and immune-mediated small vessel diseases, venous collagenosis, and others. The typical imaging features of CSVD visible on conventional magnetic resonance imaging (MRI) include lacunes, recent small subcortical infarcts, white matter lesions, enlarged perivascular spaces, cerebral microbleeds, and brain atrophy.¹⁰ The

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above imaging manifestations may also be due to macrovascular disease. Given the clinical operability, we only discuss the cognitive impairment associated with these imaging findings.

Cognitive impairment encompasses impairment of multiple cognitive domains, such as memory, executive function, attention, language, visual spatial function, and so on. *Mild cognitive impairment* refers to the progressive decline in memory or other cognitive functions that has not affected the ability of daily life and does not meet the diagnostic criteria for dementia. Dementia is a syndrome in which cognitive impairment has led to a significant decrease in the ability of daily living, learning, work, and social interaction.

Cognitive impairment of CSVD exhibits similar cognitive decline patterns, mainly involving attention, processing speed, and executive function, while the damage of memory task is relatively mild.⁴

3 | EPIDEMIOLOGY

CSVD is a high-prevalence disease associated with age. In China, lacunar infarction caused by CSVD accounts for 25%-50% of ischemic stroke, which is significantly higher than the rate in Western countries.¹¹ The prevalence rate of white matter hyperintensities is age related, increasing from 50% to 95% in persons aged 45 to 80 years.¹² Similarly, the prevalence rate of cerebral microbleeds is 24%, and gradually increases with age ranging from 17.8% in the population of 60-69 years to 38.3% in those over 80 years.¹³ Cognitive dysfunction caused by CSVD accounts for 36%-67% of all vascular dementia (VaD).¹⁴

4 | DIAGNOSIS

The supportive evidence for cognitive impairment of CSVD derives from comprehensive evaluation, including clinical assessment, neuroimaging examination, and laboratory tests.

4.1 | Clinical features

CSVD is characterized by insidious onset in most patients, and clinical manifestations vary from non-symptom to lacunar infarction and cognitive dysfunction. The location, extent, and number of lesions are the crucial factors of the presence or severity of the patient's symptoms. Cognitive impairment of CSVD may have a characteristic cognitive decline pattern, that is, typically early involvement in the domains of attention, processing speed, and executive function, and relatively complete memory function. It can progress into mild cognitive impairment and subcortical VaD eventually.⁴ Other non-cognitive manifestations may accompany,¹⁵ such as gait disorders, emotional and behavioral disorders, bladder dysfunction, and so forth. The recognition of non-cognitive symptoms should be emphasized in the clinical practice when it comes to differential diagnosis.

Collecting vascular factors related to CSVD, stroke symptoms, and onset time, onset form, specific clinical manifestations,

disease progression, diagnosis, treatment, and outcome is necessary. Furthermore, the dynamics of the ability of daily living and the relationship between CSVD and cognitive impairment should not be ignored. Moreover, it is still requisite to obtain other medical history to rule out other factors that cause cognitive impairment.

Detailed physical examination of the nervous system should be conducted. Apart from cognitive impairment, sphincter dysfunction, gait abnormalities, and pseudobulbar paralysis are concomitant symptoms often observed in CSVD, although the early signs of their related focal lesions are not so obvious to detect. Enough attention should be paid in the early recognition of the symptoms of non-cognitive impairment, for it may assist dramatically in differential diagnosis.

4.2 | Neuropsychological assessment

Neuropsychological assessment can be of great help in the diagnosis and differential diagnosis in cognitive impairment of CSVD, which requires comprehensive cognitive assessment scales. Though executive dysfunction is considered to be the most prominent clinical feature of cognitive impairment of CSVD, there are often damages in memory and other cognitive domains that accompany this condition. Thus, a full-scale cognitive-function evaluation should be carried out.

4.2.1 | General cognitive function screening and evaluation

The Mini-Mental State Examination is a cognitive-function screening scale applied globally. Due to its time saving and easy operation, it is widely used as a primary screening tool in communities and hospitals for the purpose of distinguishing the normal elderly from patients with dementia. The Montreal Cognitive Assessment is widely used in China to screen for mild cognitive impairment. The Vascular Dementia Assessment Scale-Cognitive subscale (VaDAS-Cog) emphasizes the assessment of overall cognitive function with additional tests reflecting attention and executive function. It is a good rating instrument for cognitive impairment of CSVD and is worth further promotion and application.¹⁶ The National Institute of Neurological Disorders and Stroke/Canadian Stroke Network (NINDS/CSN) has proposed three sets of neuropsychological assessment of VCI: a 60-minute protocol, a 30-minute protocol, and a 5-minute protocol.² All three sets of protocols encompass an assessment of executive function and memory, with a selection of short easy-to-use tests that are designed to be short and easy to evaluate.

4.2.2 | Neuropsychological assessment of each cognitive subphase

In clinical practice, memory assessment mainly focuses on episodic memory, with auditory word-learning tests, the Wechsler Memory Scale, and logical memory tests. The contents of auditory

word-learning tests include instantaneous recall, short-term delayed recall, long-term delayed recall, and long-term delayed recognition, which reflect the ability of memory coding, storage, and extraction and help to identify normal physiological aging as well as pathological cognitive impairment. The assessment scales of attention/executive function mainly include line tests, number-symbol tests, word-classification fluency tests, number span tests, and color-word interference tests. As for language dysfunction, the Boston Naming Test, verbal fluency tests, and Chinese aphasia tests are widely used. Currently in China, the Rey-Osterrieth Complex Graph Test, drawing clock experiments, and building block experiments are commonly applied to test visual spatial function. Studies from China have demonstrated that auditory word-learning tests, semantic classification fluency tests, and numerical symbol tests in combination with block tests have good sensitivity and specificity in identifying patients with VCI.⁵

4.2.3 | Ability of daily life

Ability of daily life consists of two aspects: basic activities of daily living and instrumental activities of daily living. The former refers to the basic functions necessary for independent living, such as dressing, eating, going to the toilet, and so forth. The latter represents complex daily or social activities, such as visits, work, housework, and so on. The Activities of Daily Living Scale and the Functional Activities Questionnaire are applied as daily capacity assessment scales.

4.2.4 | Assessment of mental condition and behavior

The NINDS/CSN Vascular Cognitive Impairment Harmonization Standards of 2006 recommends the Neuropsychiatric Inventory-Questionnaire Version to probe most behavioral domains that are affected in VCI as well as other disease conditions.² In order to more thoroughly prove depression symptoms, the Centre for Epidemiologic Studies-Depression Scale developed at the National Institute of Mental Health is recommended. If time permits, take the assessment of apathy into consideration using the Starkstein Apathy Scale.

Recommendation: An assessment of comprehensive cognitive functional domains, including memory, executive function, attention, language, visual spatial function, ability of daily life, mental condition, and behavior, should be performed using neuropsychological tests suitable for Chinese patients with CSVD. Emphasis should be placed on the evaluation of attention and execution function.

4.3 | Imaging examination

Neuroimaging methods can effectively assist in the clinical identification of neurodegenerative pathology and CSVD in elderly patients with cognitive impairment. At present, MRI is the main imaging evaluation basis.

4.3.1 | Magnetic resonance imaging

Cranial MRI is the most important tool to detect cognitive dysfunction of CSVD. MRI sequences should include T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), T2 fluid-attenuated inversion recovery sequence (FLAIR), T2-weighted gradient-recalled echo sequence (GRE), magnetic susceptibility-weighted imaging (SWI), and coronal plane of hippocampus. Computed tomography (CT) is not sensitive to the diagnosis of lacunar infarct and white matter lesions and it cannot show microhemorrhage and microinfarction in the brain.

According to the Standards for Reporting Vascular Changes on Neuroimaging published in 2013¹⁰ and the Chinese Consensus on the Diagnosis and Treatment of CSVD published in 2015,¹⁷ the neuroimaging features of CSVD include recent small subcortical infarct, white matter hyperintensity, lacune of presumed vascular origin, perivascular space, cerebral microbleed, and brain atrophy.

Recent small subcortical infarct

The imaging features of recent small subcortical infarct are small infarct located in the territory of one perforating artery, showing hypointensity on T1WI and hyperintensity on T2WI, DWI, and FLAIR images. The word *small* denotes an infarct that should be less than 20 mm in its maximum diameter in the axial plane. Imaging features or clinical symptoms suggest that the lesion has occurred in the past few weeks.

Some studies have shown that the risk of dementia in patients with recent small subcortical infarct is higher than that in patients with cortical or cerebellar infarct, suggesting that infarct originating from small vascular diseases contributes more to dementia than infarct originating from large vessels.¹⁸

White matter hyperintensity

White matter hyperintensity (WMH) of presumed vascular origin shows abnormal signals of various sizes of lesions in white matter on MRI. The imaging features are hyperintensity in the white matter other than that in the subcortical gray matter or brainstem on T2WI or T2 FLAIR sequences. The most commonly used qualitative or semiquantitative analysis of images in clinics includes the Fazeka Visual Score Scale, the Scheltens Scale, and the Age-Related White Matter Change Scale.

Many prospective studies have provided clear evidence for the correlation between white matter hyperintensity and cognitive impairment, that is, white matter hyperintensity leads to cognitive decline mainly through affecting the speed of information processing and executive function. As most elderly people suffer from WMH, it is very challenging to clarify the impact of different severity of WMH on cognitive impairment. In clinical practice, clinical experience is often used to determine the causal relationship between the existence of WMH and clinical manifestations. The nature and severity of cognitive impairment associated with WMH also depends on the size and location of the lesion, as well as on other factors, such as cognitive reserve. It is generally

considered that extensive and fused white matter lesions are the cause of cognitive impairment. Therefore, it is difficult to determine or obtain a unified standard for the exact threshold of WMH that causes cognitive impairment.

In 2000, Erkinjuntti et al. proposed that the MRI features for diagnosis of subcortical VaD included extensive ischemic white matter damage and lacunar state.¹⁹ Extensive ischemic white matter damage is defined as extensive periventricular injury and deep white matter injury that are present in different shapes, include extensive cap (>10 mm in the diameter measured parallel to the ventricle), irregular halo (>10 mm in the width with irregular margin extending to deep white matter), diffuse fusion of white matter hyperintensity (>25 mm with irregular shape), extensive white matter changes (diffuse white matter hyperintensity without focal injury), and lacunar infarcts in deep gray matter (1 or more). The 2014 VASCOG guidelines indicate that MRI findings of cognitive impairment of CSVD in white matter are extensive or confluent white matter hyperintensity.⁴

Lacune of presumed vascular origin

Lacune of presumed vascular origin is a round or ovoid, subcortical, fluid-filled cavity, whose signal is similar to cerebrospinal fluid (CSF) on MRI. The imaging features are CSF-like hypointensity foci, of between 3 mm and about 15 mm in diameter, possibly surrounded by a rim of hyperintensity on T1WI, T2WI, and FLAIR sequences, consistent with a previous acute small deep brain infarct or hemorrhage in the territory of one perforating arteriole.

Lacunar infarct is demonstrated to have a certain correlation with cognitive dysfunction.²⁰ In 2000, Erkinjuntti et al. proposed that the MRI features for diagnosis of subcortical VaD included extensive ischemic white matter damage and lacunar state.¹⁹ The lacunar state is defined as multiple lacunar infarct in deep gray matter (number of lesions >5) combined with moderate or severe white matter injury. The moderate or severe white matter injury includes extensive cap, irregular halo, diffuse fusion of white matter hyperintensity, and extensive white matter changes.¹⁹ Cognitive impairment caused by lacunar infarct and white matter hyperintensity, that is, subcortical VCI, is more common in patients with more than two lacunar infarcts outside the brainstem and those with one or two lacunar infarcts in critical zones accompanied by extensive white matter hyperintensity at the same time.⁴

Cerebral microinfarction

The diameter of cerebral microinfarction is 0.05–3 mm, which cannot be detected by conventional MRI, and sometimes can be detected in high-field-strength MRI. In the acute phase of microinfarction, focus of hyperintensity is observed on DWI while round or ovoid focus of hypointensity is observed on apparent diffusion coefficient imaging.

There was a significant correlation between the number of microinfarctions and the degree of cognitive impairment.²¹ The total number of microinfarctions in a brain can reach hundreds to thousands. The quantification of cerebral microinfarction is challenging and the best way to detect cerebral microinfarction is ultra-high-field-strength 7T-MRI.²² Patients with more than three cerebral

microinfarctions display significant cognitive decline in language, visual space, and executive function.²³

Cerebral microbleed

The typical features of cerebral microbleed (CMB) on MRI are round or ovoid signal loss, of usually 2–5 mm in diameter, which are visible on T2*GRE or SWI sequence and invisible on CT, FLAIR, T1WI, and T2WI sequences. Cerebral amyloid angiopathy (CAA) is the most common cause of cerebral microhemorrhage.

The number of CMBs is an independent predictor of the severity of cognitive impairment,²⁴ and it has a certain correlation with the location of CMBs. The impact of the type, location, and number of CMBs on cognitive impairment are still under investigation. In a 5.2-year follow-up research involving 2602 subjects, the results showed that three or more CMBs were significantly associated with dementia or VaD regardless of location.²⁵

Perivascular space

The imaging features of the perivascular space are fluid-filled space that surrounds the blood vessels and appears linear when imaged parallel to the blood vessels and round or ovoid when imaged perpendicular to the blood vessels. Similar to CSF, the lesions, of usually less than 3 mm in diameter, are of low signal on T1WI and FLAIR and of high signal on T2WI.

There is a certain correlation between enlarged perivascular space and cognitive dysfunction. A 5-year follow-up study based on 2612 elderly people showed that the short axis of round or ovoid signal loss in the subcortical region was more than 3 mm and the incidence of enlarged perivascular space was 16.2%. Enlarged perivascular space more than quadruples the risk of VaD.²⁶

Brain atrophy

Brain atrophy caused by CSVD refers to the decrease of brain volume, excluding the decrease of local volume caused by cerebral infarct. Brain atrophy in CSVD is mainly due to neurodegenerative changes in the distal brain tissue in addition to local tissue damage caused by CSVD.²⁷

Brain atrophy is a strong predictor of cognitive impairment in patients with CSVD¹⁸ and there is growing evidence that the impact of subcortical ischemic injury on cognitive function is mediated by the following cortical gray matter injury after ischemic injury.²⁸

Other imaging markers

In addition to the traditional MRI plain scan, other new imaging markers can give certain guiding value. Diffusion tensor imaging (DTI) is an MRI-based technique aimed at detecting ultrastructural tissue damage by measuring water molecular diffusion.²⁹ Abnormalities in DTI parameters occur in patients with CSVD and are associated with cognitive impairment and disease progression.²⁹

Arterial spin labeling (ASL) measures cerebral blood flow by directly magnetically labeling blood as an “endogenous” tracer.³⁰ ASL can evaluate cerebral blood flow and can be combined with acetazolamide stimulation test to evaluate vascular reserves in patients

with CSVD. Studies have shown that there is a decrease in cerebral blood flow in patients with CSVD or its related cognitive impairment. However, it deserves further investigation to confirm the diagnostic value of the decreased cerebral blood flow in CSVD and its related cognitive impairment.

The results of fluorodeoxyglucose-positron emission tomography (FDG-PET) showed that there were differences in low metabolic patterns between Alzheimer's disease (AD) and VCI.³¹ In patients with VCI, FDG-PET showed a decrease in metabolism in the local cortex and some scattered subcortical areas, affecting the subcortical region and sensorimotor cortex to a greater extent than AD.³² However, the explanation of these results is limited and needs to be studied further.

Recommendations: At present, there is no clinical examination method to directly demonstrate CSVD. MRI is the most important method to examine CSVD. It is recommended that routine examination sequences include T1WI, T2WI, T2*GRE, T2-FLAIR, SWI, and DWI. This combination can be used to diagnose lacunar cerebral infarct, cerebral microbleed, and white matter lesions caused by CSVD. If the conditions are met, DTI, FDG-PET, ASL, and other multimodal imaging examinations can be performed to assist in the identification of pathological injuries associated with CSVDs.

4.4 | Laboratory examinations

Laboratory examination can also help to find the risk factors of CSVD, and distinguish it from other causes of cognitive impairment, which is helpful to the etiological diagnosis and differential diagnosis of cognitive impairment of CSVD.

4.4.1 | Blood tests

On one hand, to find the risk factors of CSVD, the blood glucose, blood lipid, blood homocysteine, coagulation function, and anticardiolipin antibody should be detected. On the other hand, to exclude other causes of cognitive impairment, the following tests should be performed, including electrolyte testing, liver and kidney function, folic acid, vitamin B12, thyroid function, syphilis, HIV, heavy metals, drug or toxicological testing, tumor markers, paraneoplastic antibodies, immune sets, and so on.

4.4.2 | CSF tests

The levels of A β 40 and A β 42 in the CSF of most patients with cognitive impairment of CSVD are normal, while the levels of A β 40 and A β 42 in the CSF of patients with CAA are decreased. The levels of T-tau and P-tau in the CSF are normal in most patients with cognitive impairment of CSVD.³³

In addition, there are several other biomarkers that can assist in differentiating cognitive impairment of CSVD from AD. In patients with cognitive impairment of CSVD, the increased ratio of the CSF/serum albumin can reflect the breakdown of blood-brain barrier, the changes of matrix metalloproteinases in the CSF can reflect the decomposition of extracellular matrix related to vascular diseases,

neurons in the CSF can reflect axonal injury, and inflammatory cytokines and adhesion molecules in blood can reflect inflammatory injury.³⁴ These markers are not specific but can improve the accuracy of diagnosis for cognitive impairment of CSVD by using these markers alone or in combination.

4.4.3 | Gene tests

Pathogenic or risk gene tests can assist in the etiological diagnosis of cognitive impairment of CSVD. For example, *Notch 3* gene mutation in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), *APP* and *CYSTATIN* gene mutation in hereditary CAA,³⁵ *HBB* and other hemoglobin gene mutation in sickle cell disease,³⁶ *GLA* mutation in Fabry disease,³⁷ and *CBS* and other gene mutations in hypercysteinuria.³⁸

Recommendations: Hematological tests should be performed in all first-time patients to assist in the etiological diagnosis and differential diagnosis of cognitive impairment of CSVD, including blood glucose, blood lipid, blood electrolytes, and liver and kidney function. Some patients need more tests detecting vitamin B, thyroxine, syphilis, HIV, *Borrelia burgdorferi*, and so on.

CSF tests involving content of total tau protein, abnormally phosphorylated tau protein, and A β can be performed when neurodegenerative diseases are suspected or need to be differentiated.

Gene tests can assist in the etiological diagnosis for cognitive impairment of CSVD.

4.5 | Diagnostic criteria

At present, according to the guidelines related to VCI, CSVD is diagnosed by etiology or classification.^{4,5} Therefore, in combination with current international guidelines for the diagnosis of cognitive impairment of CSVD, the following factors must be met: (i) the establishment of the presence of cognitive impairment; and (ii) the determination that CSVD is the dominant pathology that accounts for the cognitive deficits. However, there is currently no uniform diagnostic criteria for cognitive impairment of CSVD. Based on the current international guidelines, we propose the diagnostic criteria for cognitive impairment of CSVD as listed in Table 1.

Recommendations: Detailed medical history collection and neurological examination should be conducted to find evidence of CSVD and its correlation with cognitive impairment, and to exclude other diseases that can cause cognitive impairment.

5 | TREATMENT

5.1 | Preventive strategies

Preventive interventions may have a modest effect at the individual level, but lead to a major reduction in the burden at the population level. The preventive interventions mainly include lifestyle modifications, controlling vascular risk factors, treatment of primary vascular diseases, and so on.

TABLE 1 Diagnostic criteria for cognitive impairment of CSVD

Items	Evidence
Cognitive impairment: subjective cognitive decline; objective evidence of cognitive impairment	Mild cognitive impairment: (i) cognitive decline in one or more cognitive functional domains; (ii) cognitive impairment is not sufficient to affect life independence. Dementia or major cognitive disorder: (i) clear and significant deficits in objective assessment based on a validated objective measure of neurocognitive function in two or more cognitive domains; (ii) the cognitive deficits are sufficient to interfere with independence.
Presence of neuroimaging (MRI) evidence of CSVD (one of the following)	(i) Multiple lacunar infarctions in white matter and deep gray matter; (ii) ischemic white matter lesions; (iii) enlarged perivascular space; (iv) cortical microinfarction and cerebral microbleed.
Identification of CSVD as evidence of cognitive impairment	Clinical evidence: (i) documented history of CSVD, with cognitive decline temporally associated with the event; (ii) evidence for decline is prominent in speed of information processing, complex attention and/or frontal-executive functioning. One of the following features is additionally present: early gait disorder, early urination control disorder (which cannot be explained by urologic disease), personality and mood changes. Imaging evidence of CSVD is sufficient to explain the existence of cognitive impairment: (i) multiple lacunar infarcts (>2) outside the brainstem; one to two lacunes may be sufficient if strategically placed or in combination with extensive white matter lesions; (ii) extensive and confluent white matter lesion—extending periventricular and deep white matter lesions: extending caps (>10 mm as measured parallel to ventricle) or irregular halo (>10 mm broad, irregular margins and extending into deep white matter) and diffusely confluent hyperintensities (>25 mm, irregular shape) or extensive white matter change (diffuse hyperintensity without focal lesions), and lacune(s) in the deep grey matter; (iii) enlarged perivascular space: large sample studies were required to provide corresponding evidence; (iv) cortical microinfarction and cerebral microbleed: large sample studies were required to provide corresponding evidence.
Exclusion criteria	Exclude other imaging changes or diseases sufficient to explain memory or other cognitive impairment, such as no cortical and/or subcortical non-lacunar infarction, cerebral hemorrhage; specific causes of white matter (multiple sclerosis, sarcoidosis, brain radiotherapy); brain lesions (such as Alzheimer's disease, Lewis dementia, frontotemporal dementia, Parkinson's disease, tumor, hydrocephalus, trauma, syphilis, AIDS, Creutzfeldt-Jakob disease, etc.); serious mental illness and epilepsy, alcohol and drug abuse, metabolic abnormalities, and so forth.

CSVD, cerebral small vessel disease.

5.1.1 | Life factors

Lower levels of education are associated with higher risk of dementia for any reason, including vascular, neurodegenerative, or mixed. However, there is no conclusive evidence of the protective effects of education, cognitive training, and other cognitive interventions on vascular or neurodegenerative brain injury. Available evidence suggests that education weakens the impact of brain pathology on clinical manifestations, rather than affecting the emergence or progression of brain pathology³⁹ (level of evidence: IIb).

Physical exercise has beneficial effects on neurogenesis, synaptic formation, and vascular health, so it can reduce the risk of cognitive impairment. Observational studies have shown that physical exercise could reduce the risk of VaD, AD, and dementia⁴⁰ (level of evidence: IIb).

5.1.2 | Vascular risk factors and associated vascular diseases

The effectiveness of lowering blood pressure to prevent cognitive impairment after stroke in the elderly remains controversial. However, in view of the benefits of antihypertensive therapy for vascular outcomes, it is recommended to treat hypertension in people with vascular risk factors³ (level of evidence: IIb).

The level of evidence for treating diabetes and hyperglycemia to reduce the risk of VCI and dementia is quite low.⁴¹ However, the protective effect on multiple target organs is enough to recommend strict glycemic control. Moreover, strict glycemic control can reduce the decrease in cerebral blood volume in diabetic patients⁴² (level of evidence: IIb).

In statins trials, which use cognitive assessment as a secondary endpoint, there is no evidence that statins reduce the risk of cognitive decline or dementia.⁴³ However, these studies were not powered to answer the question because the follow-up period was too short (level of evidence: IIb).

5.1.3 | Cerebral small vessel disease

Few primary or secondary preventive intervention studies have provided cognitive end points. In the SPS3 Trial (Secondary Prevention of Small Subcortical Strokes), 3020 patients with subcortical infarction were enrolled in a multicenter, randomized, controlled, double-blind trial and followed up for 12 months. Compared with the effect of dual antiplatelet therapy versus single aspirin, and intensive blood pressure lowering versus usual targets in patients, dual antiplatelet therapy or intensive antihypertensive therapy had no significant therapeutic effect on cognitive end points⁴⁴ (level of evidence: IIb).

5.1.4 | Comprehensive interventions

In the FINGER Trial, 1260 people at high risk of VCI aged 60–77 years were enrolled in the randomized, double-blind, controlled trial and followed up for 2 years. The participants were randomly assigned to a group of comprehensive interventions (reasonable diet, exercise, cognitive training, and control of vascular risk factors) or a group of general health advice. The results showed that the group with comprehensive interventions could obtain better cognitive results than the control group⁴⁵ (level of evidence: IIb).

Recommendation: Controlling vascular risk factors may be beneficial for the prevention of cognitive impairment in CSVD, but further large-scale clinical trials are needed to confirm this (strength of recommendation: B/level of evidence: IIb).

6 | TREATMENT OF COGNITIVE IMPAIRMENT IN CSVD

Although the incidence of cognitive impairment in CSVD is high and the social burden is heavy, relatively few studies have focused on the treatment of cognitive impairment in CSVD. At present, clinical trials have mainly focused on VaD and only a small number of studies have focused on subcortical VCI and CADASIL.

6.1 | Anti-dementia drugs

6.1.1 | Cholinesterase inhibitors

Cholinesterase inhibitors can increase the content of acetylcholine in synaptic space and significantly decrease the production and deposition of A β protein. The main drugs include donepezil, rivastigmine, and galantamine. Subcortical ischemic lesions have been demonstrated to destroy the acetylcholine pathway, so cholinergic inhibitors can be used to improve the cognitive function of VaD.⁴⁶

A meta-analysis including five randomized, controlled, double-blind clinical trials was conducted to evaluate the efficacy of donepezil in the treatment of VaD. The group treated with donepezil showed significant improvement in Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) as compared to the control group⁴⁷ (level of evidence: IIa). A review of donepezil for VCI based on two large-scale randomized, double-blind, placebo-controlled randomized control trials^{48,49} concluded that this drug had some benefits in improving cognitive function, clinical global impression, and activities of daily living in patients after 6 months of treatment (level of evidence: IIa). A double-blind, randomized, placebo-controlled trial of donepezil in 168 patients (mean age, 54.8 years) with CADASIL and cognitive impairment found no significant improvement in VaDAS-Cog score. However, the executive function benefited significantly⁵⁰ (level of evidence: IIa).

A multicenter, randomized, double-blind, placebo-controlled trial of galantamine in 396 patients with VaD found that galantamine could improve the cognitive function and clinical global impression in patients with VaD after 6 months of treatment⁵¹ (level of evidence: IIa).

Patients diagnosed as having subcortical VaD aged 65–80 years received rivastigmine or cardioaspirin in a study for 22 months. At the 22nd month, patients treated with rivastigmine showed significant improvements in executive function and behavioral symptoms. There were no obvious side-effects or withdrawal reactions.⁵² However, the sample size of this study was small, with only 16 cases (level of evidence: III).

6.1.2 | Memantine

Two multicenter, randomized, double-blind, placebo-controlled clinical trials of memantine focused on mild to moderate VaD patients. The results showed that cognitive function was slightly improved, but the global functioning was not^{53,54} (level of evidence: IIa).

6.2 | DI-3-n-butylphthalidide

DI-3-n-butylphthalidide (NBP), an anti-VCI drug developed in China, has a protective effect on cognitive impairment in rats with ischemic brain injury. NBP is not only for ischemic stroke: it has also been reported to increase the expression of NR2B and synaptophysin in the hippocampus of aged rats after chronic cerebral hypoperfusion and to increase brain acetylcholine level.

In a randomized, double-blind, placebo-controlled trial, Jia et al. enrolled 281 patients aged 50–70 years who had a diagnosis of subcortical VCI without dementia at 15 academic medical centers in China.⁵⁵ Patients were randomly assigned to NBP 200 mg three times daily or matched placebo for 24 weeks. The main outcome measures were the changes of ADAS-Cog and Clinician Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus). The results showed that the ADAS-Cog and CIBIC-Plus scores in the NBP group were significantly better than those in the placebo group. NBP was effective for improving the cognitive function and global functioning of patients with subcortical VCI, and has good safety (level of evidence: IIa).

6.3 | Cytidinediphosphocholine

A meta-analysis including 14 randomized, controlled, double-blind clinical trials was conducted to evaluate the efficacy of cytidinediphosphocholine in the treatment of 1051 patients with memory impairment (VCI or AD). The results showed that citicoline could improve memory, behavior, and overall cognitive function in elderly patients with cognitive impairment (VCI or AD)⁵⁶; level of evidence: IIb).

6.4 | Ginkgo biloba extract

A randomized, double-blind, placebo-controlled trial of ginkgo biloba extract was conducted to determine its efficacy and safety in 90 VCI patients for 6 months. The results showed that ginkgo biloba extract could delay the decline of cognitive function in patients with VCI,⁵⁷ but its efficacy and safety still need to be confirmed by further studies (level of evidence: IIb).

6.5 | Nimodipine

A randomized, double-blind, placebo-controlled clinical trial has shown that nimodipine could improve neuropsychological function.⁵⁸ However, the sample size of this study was small, with only 45 treated cases (level of evidence: III).

Recommendations: Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) have confirmed their therapeutic effects on patients with cognitive impairment of CSVD (strength of recommendation: A/level of evidence: IIa). Memantine can improve the cognitive function of mild to moderate VaD, but its role in cognitive impairment of CSVD still needs to be confirmed in large sample clinical trials (strength of recommendation: B/level of evidence: IIb). Other drugs with evidence-based medical evidence for the treatment of VCI include cytidinediphosphocholine, ginkgo biloba extract, and nimodipine. Further clinical trials are still needed (strength of recommendation: B/level of evidence: IIb).

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CONFLICTS OF INTEREST

Nothing to disclose.

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