

# *Progress of Chinese and Western medicine research on cognitive dysfunction due to cerebral small vessel disease*

Yun Yedong<sup>1</sup>, Yin Jun<sup>1</sup>, Hu Zhouyuan<sup>1</sup>, Yan Yongmei<sup>2,\*</sup>

<sup>1</sup>Shaanxi University of Traditional Chinese Medicine, Xianyang, Shaanxi, 712046, China

<sup>2</sup>Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine, Xianyang, Shaanxi, China

\*Corresponding author

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**Abstract:** Cerebral small vascular disease is a common clinical neurological degenerative disease, is an important risk factors of stroke, cognitive impairment and death. CSVD can be acute onset, manifested as cerebral hemorrhage or ischemic stroke, but most of its onset hidden, and slow progress, some of patients with cognitive dysfunction can be manifested as dementia, memory loss, cognitive decline, etc, serious harm to the health of the elderly and the quality of life. There is a lack of early diagnosis methods and intervention measures for this disease, so to clarify the current situation and future development direction of TCM and western medicine research with cognitive impairment can provide new ideas for basic and clinical research. This paper reviews the current situation and new progress of the diagnosis and treatment of CSVD cognitive impairment.

## 1. Introduction

With the gradual aggravation of the aging degree of China's society, the incidence of cardiovascular and cerebrovascular diseases is increasing year by year, among which the incidence of cerebral small vascular diseases is on a straight upward trend. Cerebral small vessel disease is a group of clinical syndromes, mainly manifested as imaging, pathological and cognitive changes<sup>[1,2]</sup>. Previous studies have shown that CSVD is a high risk factor for the development of stroke, vascular dementia and mixed dementia<sup>[3]</sup>. Further studies have shown that about 20% of stroke patients are caused by CSVD<sup>[4]</sup>. CSVD as a common chronic progressive cerebrovascular disease, it refers to the brain arterioles, microarteries, capillaries, microveins and venules affected by various etiologies, neurological dysfunction leading to a range of vascular diseases. CSVD can be acute, prespresented as cerebral hemorrhage or ischemic stroke, but most of its onset is insidious, and the progress is slow, without obvious and specific clinical symptoms, so much so that patients and even doctors cannot unaware. Some patients with cognitive dysfunction can show dementia, memory loss, cognitive decline and various neurodegenerative changes; often leads to a deterioration over time. This paper summarizes the epidemiology of cognitive disorders, the pathogenesis, characteristics and the treatment status of the disease, in order to provide new ideas for the clinical diagnosis and treatment of integrated Chinese and western medicine.

## 2. Definition and classification of the CSVD

Cerebral small vascular disease, refers to a series of clinical, imaging and pathological syndromes caused by various causes affecting arterial arteries, microarteries, capillaries, microveins and small veins in the brain. CSVD is an important risk factor for stroke, dementia and death, seriously endangering the life health and quality of life of the elderly. The onset of CSVD is insidious, and there is a lack of early diagnostic methods and intervention measures. Therefore, clarifying the current research status and future development direction of CSVD can provide new ideas for basic and clinical research. Cerebral small blood vessel disease refers to a group of clinical, imaging and pathological syndromes caused by lesions of small perforator arteries, small arteries, capillaries and small veins with a diameter of 40 ~ 200  $\mu$  m, mainly manifested by brain white matter injury, recent small subcortical infarct, lacunar focus, cerebral microhemorrhage, the enlarged perivascular space and brain atrophy. Depending on the different pathological mechanisms, currently, CSVD has the following categories: type I, the arteriolar sclerosis or aging type, accounting for 80% of all CSVD, in relation with hypertension and age, its pathological features are celluloid necrosis, lipid hyalinosis, small artery atherosclerosis, microaneurysm, small artery segmental structural disorder or disintegration; type II, Inherited brain amyloid CSVD; type III, the genetic CSVD, including CADASIL, CARASIL, MELAS, Fabry, hereditary brain retinal microvessel disease; type IV, inflammatory and immune-mediated CSVD; type V, venous collagen disease; type VI, other types of CSVD. Modern western medicine rarely studies cerebral small vascular disease associated with cognitive impairment as an independent disease, and the disease is often treated as "vascular dementia (VD)" in clinical practice<sup>[5]</sup>. CSVD has insidious clinical onset slow progression, and lack of specific symptoms and signs, and patients can develop symptoms<sup>[6,7]</sup>, such as cognitive dysfunction, gait abnormalities, mood disorders, urinary incontinence and decreased living ability. CSVD is prone to lacunar infarction and cerebral parenchymal hemorrhage, accounting for 20%<sup>[8,9]</sup> of all symptomatic stroke types; chronic phase lesions show hypoperfusion, causing persistent and progressive damage to the corresponding brain tissue, including cognitive impairment and dementia, abnormal gait, motor disorders, urinary retention, abnormal mood, and personality disorder<sup>[10]</sup>.

## 3. Progress of modern medicine on cognitive impairment in CSVD

### 3.1 Pathological mechanisms of CSVD-induced cognitive impairment

Study found that CSVD causes 45% of cognitive impairment<sup>[5]</sup>, have underpinned a serious social burden. It is currently considered that, the incidence of CSVD with cognitive impairment was positively associated with age, previous studies found that more factors of cognitive impairment due to CSVD. Among them, the most common cause of CSVD with cognitive impairment is perforator small artery stiffness, stenosis, or occlusion supplying the white matter and deep gray matter nuclemass, its manifestations are various pathological changes. Such as celluloid necrosis, lipid hyalinosis, small artery atherosclerosis, and microaneurysm, which lead to vascular endothelial damage, it further leads to blood-brain screen (blood-brainbarrier, BBB) destruction. Increased vascular permeability after endothelial injury leads to the extravasation of the intravascular material, cause damage to the vascular and peripheral vascular tissues, pathological changes such as vascular inflammation, blood vessel wall thickening, vascular lumen stenosis, and demyelination of nerve cells occur, thus affecting the perfusion of multiple blood vessels, further leading to chronic, progressive ischemic hypoperfusion in the arterial marginal zone, even occurs with vascular occlusion, in turn, it damaged the deep white matter and lateral ventricles, to disrupt the frontal-subcortical loop, which then leads to cognitive impairment. Secondly, arterial hypertension

is the most important and reversible vascular risk factor for CSVD with cognitive impairment<sup>[11]</sup>, but due to the widespread use of statins, it is difficult to evaluate the influence of hyperlipidemia on the risk of CSVD in modern population<sup>[11,13]</sup>. Other common risk factors include diabetes, smoking, sleep apnea, chronic kidney disease, branch atherosclerosis and other<sup>[12]</sup>. Hyperlipidemia is a major risk factor for macrovascular disease; individual gene mutations rarely cause CSVD, mutations in NOTCH3, HTRA 1, MT-TL 1, GLA, COL4A1 / COL4A2, and TREX1 genes are thought to be associated with the occurrence and development of cognitive impairment due to CSVD, but clinically extremely rare. Immune or infectious diseases of the central nervous system can cause CSVD, Thus inducing cognitive impairment<sup>[11]</sup>.

CSVD is closely linked to the occurrence of cognitive impairment. Imaging studies have found that CSVD manifestations including WMHS, lacunar cerebral infarction, CMBs, cerebral atrophy and disturbance infarction are closely related to the occurrence and development of cognitive impairment. Diagnosis and evaluation of CSVD relies on magnetic resonance scanning of the head, whose imaging markers include recent small subcortical infarcts, WMH, lacunae, CMBs, enlarged perivascular space, and brain atrophy. Typical luminal lesions are 20 mm fluid spaces of subcortical white matter or deep gray matter on T2 weighted imaging or fluid attenuation inversion recovery sequence, with abnormally high signals surrounding gliosis, usually secondary to small subcortical infarcts. WML, also known as white matter loose or white matter hyperintense, is an abnormal high signal of subcortical punctate, patchy or fused on T2WI or FLAIR, and is the most common imaging manifestation of CSVD. CMBs are small areas of focal hemosiderin deposits indicating prior extravasation of blood from damaged small vessels, exhibiting round or elliptic hypointensity of 3 to 10 mm in diameter on magnetically sensitive weighted imaging or gradient echo sequences. EPVS is an abnormal gap filled with cerebrospinal fluid around a perforating small artery or vein with a diameter > 2 mm and magnetic resonance as an oval, round, linear, or tubular lesion of 2 to 5 mm in diameter, usually symmetrical bilaterally, consistent with the behavior of the perforating artery. Brain atrophy is a kind of neurons and link loss between disease, can lead to reduce brain volume<sup>[14,15]</sup>, the decrease of brain volume can usually be identified by CT and MRI, can show the brain tissue changes closely related to brain atrophy, CT and MRI can show cortical atrophy, but MRI is more sensitive to some types of atrophy, such as focal atrophic changes within the nucleus<sup>[16,17]</sup>.

### 3.2 Western medicine treatment of cognitive impairment in CSVD

Prevention and treatment of CSVD due to the unclear pathogenesis of CSVD, effective prevention and treatment methods are lacking clinically. Currently, the prevention and treatment of CSVD is mainly based on the profile of risk factors, the type of biomarkers and the severity of CSVD. Blood pressure is the ultimate modifiable risk factor for CSVD, and a meta-analysis of the efficacy of antihypertensive drugs on CSVD showed that the progression of WML in patients with intensive antihypertensive therapy significantly reduced<sup>[18]</sup>, but these studies did not evaluate the efficacy of intensive antihypertensive therapy on CMBs, expanded PVS or acute small subcortical infarction; therefore, further studies are needed to explore the effect of intensive antihypertensive therapy on CSVD in the future. Antiplatelet therapy is an effective prevention and treatment of recent small subcortical infarcts, and a pooled analysis of randomized trials showed that aspirin therapy alone after acute subcortical infarction can reduce the risk of stroke recurrence by 30%<sup>[18]</sup>. For acute non-disabling stroke, dual antiplatelet therapy within 24 h of stroke onset but aspirin treatment could effectively reduce the recurrence rate of 90 d stroke<sup>[19]</sup>. Another multicenter clinical trial study found that dual antiplatelet therapy effectively reduced the recurrence rate of transient ischemic or mild 90 d stroke within 12 h of onset, but increased the incidence of

hemorrhagic adverse events. Intravenous thrombolytic therapy is the standard treatment for acute subcortical cerebral infarction within 4.5 h of disease onset, a study in patients with small acute subcortical infarcts showed that, Patients receiving intravenous thrombolysis had a better neurologic outcome than patients receiving placebo <sup>[20]</sup>, yet, a Meta-analysis showed that, the presence of pretreatment CMBs and WML increased the risk of symptomatic ICH by > 50%, severe WML increased the risk of symptomatic ICH by 2.5-fold <sup>[21]</sup>, therefore, for patients with CMBs and WMH on MR, thrombolytic therapy should be used with caution, individualized treatment was performed according to the specific condition of the patient. Statin lipid-lowering therapy is an effective prevention and treatment of cerebrovascular diseases. Studies have shown that taking statins in WML patients can reduce the risk of stroke and delay the progression of WMH and cognitive decline <sup>[22]</sup>. Moreover, the SPARCL study reported that 80 mg daily atorvastatin was equally effective in <sup>[23]</sup> in preventing ischemic stroke in patients with CSVD and patients with macrovascular disease, however, the study showed a corresponding increased risk of intracranial hemorrhage in patients with CSVD receiving high-dose statin therapy. Other studies have shown that the use of statins, while effective in preventing the recurrence of stroke, increases the risk of intracranial hemorrhage, especially for <sup>[24]</sup> in patients with a history of intracranial hemorrhage and CAA. Therefore, statins should be used carefully in CSVD patients with CAA or a history of intracranial hemorrhage.

#### **4. Progress in TCM research on CSVD with cognitive impairment**

##### **4.1 Knowledge of the etiology of cognitive impairment in CSVD.**

According to traditional Chinese medicine, cognitive impairment caused by cerebral vascular disease belongs to the category of "dementia" and "stroke", more often in the elderly group, the disease is in the brain, "Medical Introduction" : "the sea of the brain", "Su Wen · Five zang generation" also mentioned: " all the patients, all belong to the brain."Ancient doctors very early thought that the brain is the house of the yuan god, dominate the whole body, the marrow breeds the yuan god, the commander of the human soul, god, meaning, soul, ambition, if the brain lost temperature, the pulp sea loss of hair for the disease. Dementia etiology pathogenesis can be divided into two aspects, mostly because of the old age, kidney deficiency, qi and blood, the essence of the brain, brain reduction, the brain empty, phlegm stagnation, phlegm stagnation, blood disorder, blood stasis, bi obstruction, blind, or because of the fire, fire evil consumption Yin jin, fire, eventually appear cognitive disorders, affect the daily life of patients.

##### **4.2 Traditional Chinese medicine treatment for cognitive impairment in CSVD**

With the development of modern medical technology and the continuous optimization of clinical research, the treatment of TCM in cognitive impairment has shown vigorous vitality, and its efficacy has also been confirmed clinically. Some studies <sup>[25]</sup> found that insect TCM is effective in the treatment of cognitive impairment after stroke. Some scholars analyzed the drugs for treating dementia, and found that the drugs with high frequency were: Yuanzhi, ginkgo, calamus, ginseng, epimedium; the commonly used compounds are: happy powder formula, Angelica peony powder, Qingxin open body prescription, Shenghui soup, spleen soup and other <sup>[26]</sup>. Liu Junyi et al. <sup>[27]</sup> used the decoction to treat mild cognitive impairment after cerebral infarction, and the results showed that the effect of the decoction was better than that of piracetam in treating mild cognitive impairment after ischemic stroke. Stanche total glycoside capsule <sup>[28]</sup> for treating patients with dementia, not only improves cognitive function, but also has good effect in non-cognitive symptoms, but also improves the neuropsychiatric symptoms of patients. Kidney-tonifying and

educational granules is effective in the treatment of MCI after ischemic stroke, and it is better than nimodipine [29] in improving clinical symptoms and intelligence. Fuhong et al. [30] treated MCI patients with flavored Wuyan particles, and the results showed that they could improve the memory function of MCI patients and prevent hippocampal volume atrophy. Li Zhijie et al [31] used Tiandi Jing pill to treat mild cognitive impairment. The total response rate of the treatment group reached 86.96%, and no toxic side effects were seen, and the safety rate was high.

Study: kidney deficiency, blood stasis and phlegm turbidity are the main pathogenesis of dementia. Since the disease is mostly related to stroke and vascular lesions, blood stasis runs through the whole process of the disease, blood stasis is more critical than phlegm and turbidity, so we believe that kidney deficiency and blood stasis is the main pathogenesis of cognitive dysfunction. The treatment should be to promote blood circulation, remove blood stasis and smooth collaterals, tonifying the kidney and invigorate the brain. Puzzle brain pills for our hospital preparation, in the liver and kidney, blood, improve the blood circulation, improve the brain blood supply, ripe, dogwood kidney Yin, kidney pulp, kidney pulp, filling the kidney, gastrodia elata, gastrodia elata dispel wind to make the empty Yang, qi and blood circulation; leeches, leeches through the meridian. Modern pharmacological studies show that hmannia can significantly increase the biological activity of serum glutathione peroxidase, reduce the peroxy lipid in serum, has the effect of anti-aging. Gastrodia elata has a protective and regulatory effect on the cerebral nervous system, and can also improve the decline of cognitive function caused by chronic cerebral blood supply. Salvia miltiorrhiza can dilate blood vessels, increase organ blood flow, and improve microcirculation. Leech can inhibit platelet aggregation, have antithrombotic effect, and the association with Salvia miltiorrhiza can improve the formation of atherosclerosis. Dogwood meat, bidirectional regulates blood sugar, and has antioxidant effect, can improve vascular lesions caused by hyperglycemia. It can improve the fatigue state, and with the antihypertensive effect, can improve the vascular lesions caused by hypertension. It has an anti-aging and anti-atherosclerosis effect, and can improve the cognitive decline caused by chronic cerebral blood supply insufficiency.

## 5. Conclusions

In recent years, with the increasing aging of society, CSVD cognitive impairment has attracted the general attention of scholars. At present, the effective means to delay the cognitive decline of patients is effective in the early stage, but it can have serious adverse reactions, easy to cause complications, and little long-term treatment potential. With its unique advantages, TCM uses the principle of the overall concept to emphasize individualized syndrome differentiation and treatment, adds and decreases the drug to improve the cognitive function, achieves relatively satisfactory results, and has the advantages of reducing the dosage of western medicine and reducing adverse reactions. In clinical practice, the effect of both is better, but there are also many deficiencies in TCM treatment. For example, most doctors order drugs according to clinical experience, lack of standardized and unified understanding, cannot form standardized treatment, the efficacy effect is large, and the number of clinical study samples is small. Therefore, in the future, in-depth research on the mechanism and clinical syndrome of CSVD cognitive impairment should be conducted to expand the sample size, promote the collaborative treatment of integrated Chinese and western medicine, and provide more accurate treatment principles, so as to improve patients' symptoms at multiple levels and obtain better efficacy.

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