Corresponding author: Gao Li, Tel: 13611342391, E-mail: xuanwugaoli@126.com
DOI: 10. 7661/j.cjim. 20180908. 258

·Expert consensus ·

Expert Consensus on the Diagnosis and Treatment of Chronic Cerebral Hypoperfusion with TCM-WM

Stroke Specialized Committee of Beijing Association of Integrated Traditional Chinese and Western Medicine

1 Preface

Chronic Cerebral Hypoperfusion (CCH) is a group of clinical syndromes which cause brain dysfunctions due to chronic cerebral hypoperfusion, which was also called "cerebral arteriosclerosis", "chronic cerebral circulatory insufficiency", "chronic cerebral hypoperfusion", "chronic cerebrovascular insufficiency", etc. Compared with acute or subacute cerebral ischemia, CCH has a longer intervention time window for intervention. If early recognition and intervention can be implemented, they can effectively block the progression of the disease and prevent the occurrence of cerebrovascular related events. This is in line with the disease prevention and treatment concept of "prevention of disease before its ocurrence, prevention of the existing disease from exacerbating" in traditional Chinese medicine, which can greatly reduce the economic burden of society, families and patients and produce better social benefits. Currently, no consensus has been reached so far on the diagnostic criteria and treatment plan of CCH. In 2000, the International Classification of Diseases 10th Revision (ICD-10) [1, 2] and the *Classification of Cerebrovascular Diseases in China 2015* issued in 2017 listed it as a kind of ischemic cerebrovascular diseases [3]. There are many basic studies on CCH, most of which use animal models to explore the pathological mechanism and intervention of CCH injuries [4, 5], but few clinical studies have been conducted, and such studies are mainly concentrated in China, Russia and Japan. CCH plays an important role in the occurrence and development of a variety of cerebrovascular-related diseases,, which can lead to demyelination of white matter, cerebral infarction and vascular cognitive dysfunction. Therefore, on the basis of in-depth study of its pathophysiological mechanism, it will be of great clinical significance for the prevention and treatment of ischemic cerebrovascular diseases and vascular cognitive dysfunctions. to explore its clinical diagnosis and intervention.

This consensus is formulated based on relevant literature and clinical research evidence of CCH, and combined with experts' clinical diagnosis and treatment experience. It mainly involves the diagnosis and treatment of CCH, and strives to complement the advantages of both Chinese and Western medicine based on their clinical practice, so as to further improve the standardization of integrated Chinese and Western medicine diagnosis and treatment of CCH, so that the majority of clinicians, especially medical staff engaged in CCH diagnosis and treatment, can fully understand CCH and its clinical diagnosis and treatment strategies, have a clear concept of CCH and improve its clinical diagnosis and treatment.

This consensus includes the concept of CCH and its historical development process, epidemiology, pathophysiology, clinical manifestations and types of TCM (Traditional Chinese Medicine) syndromes, auxiliary examinations, clinical evaluation, diagnosis, TCM syndrome differentiation and treatment, integrated treatment principles of TCM-WM (Traditional Chinese Medicine-Western Medicine) and prognosis.

It should be clear that cerebral blood circulation disorder is the common feature of this disease, and in

principle, the basic treatment should be to promote blood circulation to remove blood stasis and improve blood circulation. The principle of integrated TCM-WM classification is based on the understanding, acceptance and repeatability of the majority of Chinese and Western medicine clinicians. The classification criteria are based on the current reality that various metabolic disorders and psychological disorders are the majority at present, combined with the physical characteristics of the Chinese people, based on the syndrome differentiation of traditional Chinese medicine, and combined with the common pathogenic factors and clinical manifestations of this disease. It should be noted that this consensus is only based on the clinical manifestation characteristics of patients and expert experience, and draws on modern medicine, traditional Chinese medicine concepts and diagnosis and treatment methods in classification and treatment. In order to make it understandable and repeated by the majority of Western medicine colleagues, the complex syndrome differentiation of traditional Chinese medicine has been simplified to form an expert consensus on integrated TCM-WM to enable the medical staff in general hospitals, traditional Chinese medicine hospitals and integrated TCM-WM hospitals to learn from and use them in clinical practice. It is not as a standard or norm of medical behaviors.

2 The Concept of CCH and its Historical Development

2.1 The Concept of CCH According to *Classification of Cerebrovascular Diseases in China 2015* [3], CCH refers to the state of extensive brain or local blood supply reduction in the anterior and posterior circulation blood supply area of the brain. Most of the patients are middle-aged and elderly people with clinical manifestations of are head heaviness, dizziness, fullness of head, headache, decreased memory or concentration and so on. The nervous system examination often shows no focal symptoms or signs, and auxiliary examinations may show cerebral arteriosclerosis, cerebral vascular stenosis, white matter lesion, encephalanalosis, or evidence of chronic cardiac dysfunction and systemic chronic diseases (such as long-term chronic anemia and nutritional deficiency). In view of the lack of a generally accepted definition of CCH, it is recommended that the definition of CCH be summarized as follows: the decrease in cerebral blood supply caused by long-term vascular disease or circulatory disorder, and a series of clinical syndromes caused by decompensation. The symptoms of patients usually appear more than 3 months after decompensation, and may persist or have intermittent attacks. The etiology includes various changes that directly lead to reduced blood supply to the brain, such as various vascular structural changes, heart disease, blood pressure changes, or hemorheological changes caused by various reasons. Chronic cerebral perfusion reduction can be either in the whole brain (such as decreased cardiac output and hypotension) or local (such as one side of intracranial and extracranial artery stenosis). Decompensation refers to the decrease in cerebral blood flow that leads to tissue metabolism and/or mild brain dysfunction.

2.2 Understanding in Modern Medicine Modern medicine’s understanding of this disease originated from the concept of cerebral arteriosclerosis. Clinical observations found that dizziness, headache and other symptoms of the elderly often have evidence of arteriosclerosis (such as fundus artery changes), which was diagnosed as "atherosclerosis" after other diseases had been excluded. ICD-9 and the *Draft of Classification of Cerebrovascular Diseases* revised for the third time by the Second National Conference of Cerebrovascular Diseases of Chinese Medical Association in 1986 [6] also have the name of "cerebral arteriosclerosis". However, due to the long-standing differences between the concept of "cerebral arteriosclerosis" and clinical diagnostic criteria, whether it should be regarded as a disease unit is very controversial. The World Health Organization (1989), the Classification of Cerebrovascular Diseases of the National Institute of Neurological and Communicative Disorders and Stroke (III) (1990), and the Chinese Cerebrovascular Disease Group (1995) successively eliminated the diagnostic type of "cerebral arteriosclerosis" in the classification of cerebrovascular diseases.

In 1990, Japan's Ministry of Health and Welfare commissioned a study on the “Definition and Diagnostic Criteria of Cerebral Arteriosclerosis Diseases”, and put forward the diagnostic name of “chronic cerebral circulation insufficiency (CCCI)”. In 1991, the 16th Stroke Society of Japan proposed that patients with clinical symptoms such as dizziness and head heaviness caused by cerebral circulation disorder, but without focal signs of brain, and without organic cerebrovascular diseases from head CT, should be officially named as "CCCI". In 2000, when Japan revised it again, it excluded patients with cerebral infarction and lacunar infarction, trying to make CCCI an independent disease in cerebrovascular diseases [7, 8]. In diagnosis, it mainly emphasizes the existence of risk factors of cerebrovascular diseases, structural vascular disease of cerebral arteriosclerosis, and hemodynamic disorders. If there are symptoms of chronic brain dysfunction, it is necessary to have clear evidence of vascular stenosis, white matter lesions or decreased cerebral blood flow when the diagnosis is made. In 2000, ICD-10 added CCH again, but there were no diagnostic criteria. In 2001, Japan put forward the diagnostic criteria of CCCI, and regarded it as an independent disease entity in cerebrovascular diseases [7,8].

In 1998, Russian scholars also put forward the concept of "CCH". But different from the concept put forward by Japan, such CCH was divided into three stages: early symptoms and signs of cerebral ischemia in the early stage, transient ischemic attack (TIA) and cerebral infarction appeared in the middle stage, and cerebral infarction sequela and recurrent infarction in the late stage. In 2017, *Classification of Cerebrovascular Diseases in China 2015* listed CCH as one of the ischemic cerebrovascular diseases, but there were still no diagnostic criteria [3]. In order to avoid the ambiguity of concepts caused by complicated pathogenic factors, this consensus follows the opinions of experts from Japan and China, and only focuses on CCH caused by atherosclerosis.

With the rapid development of society and medicine today, in order to adapt to the new situation and reflect the advantages of medicine with Chinese characteristics, CCH is objectively classified into ischemic cerebrovascular diseases, and the diagnostic criteria, syndrome classification, treatment principles and medication of TCM-WM are added, so as to make them easy to understand and have certain guiding significance for clinical diagnosis and medication of cerebrovascular diseases.

2.3 Understanding in Traditional Chinese Medicine There is no disease name corresponding to "CCH" in traditional Chinese medicine, but combined with its clinical symptoms, this disease should be classified as "vertigo", and can also be found in diseases such as "insomnia", "dementia" and "depression" and other diseases. Its etiology and pathogenesis are complex, which are related to factors, such as emotional disorder, improper diet, excessive fatigue, old-age internal injury and deficiency, visceral dysfunction, which ultimately lead to imbalance between yin and yang in the human body, imbalance in functional activities of qi, internal stagnation of phlegm and dampness, upward invasion of turbid qi, blood stasis stagnation, or liver and kidney deficiency and loss of nutrition from brain orifices [9]. Its pathogenesis is divided into two ends of deficiency and excess based on the root causes of deficiency in qi and blood, deficiency in liver and kidney and deficiency in marrow sea. The symptoms are the imbalance in functional activities of qi, upward invasion of turbid qi causing stasis and obstruction in brain orifices. It is a disease of deficiency in origin and excess in symptoms. The disease is located in the brain and is closely related to the heart, liver, spleen, lungs and kidney.

As early as description in the *Huangdi Neijing* (The Inner Canon of Huangdi), similar disease syndromes were discussed. *Ling Shu· Hai Lun* pointed out that "If the marrow sea is insufficient, people will have vertigo and tinnitus, feel tiredness in the tibia, fail to see clearly and feel weak". Zhu Danxi in the Yuan Dynasty put

forward that "phlegm is what causes dizziness," pointing out the "phlegm" is the main pathogenesis of the occurrence and development of this disease. In the Ming Dynasty, Yu Tuan pioneered the theory of "Blood Stasis Causes Dizziness" in the *The True Story of Medicine* [10]. In the Ming Dynasty, Zhang Jingyue advocated vertigo as the theory of deficiency and put forward the theory of “no deficiency, no dizziness". In the Qing Dynasty, Zhang Xichun summarized the symptoms and prognosis of this disease profoundly. In "The Treatment of Cerebral Anemia" in *Integrated Chinese and Western Medicine* [11], he pointed out that the patients with cerebral blood supply deficiency with mild conditions had dizziness, pain and lack of energy, and those with severe conditions had dizziness and hemiplegia in limbs which could lead to stroke. In summary, the understanding of the etiology, pathogenesis and syndromes of similar CCH by traditional Chinese medicine scholars in the past dynasties mostly focused on the three aspects of "phlegm", "stasis" and "deficiency".

3 Epidemiology of CCH

CCH is a common and frequently-occurring disease among middle-aged and elderly people, and it is also an important cause of the occurrence and development of stroke, vascular dementia, Binswanger's disease and other diseases. According to the 2016 epidemiological survey report of China, 2/3 people over 65 years old have a history of CCH, about 50% people aged 50-65 have a history of CCH, and 25% people aged 45-50 also have CCH [12,13]. Age, sex, hypertension, diabetes, dyslipidemia, intestinal flora changes caused by unreasonable diet structure, hyperhomocysteinemia, smoking, alcoholism and metabolic syndrome are the main risk factors leading to CCH [7,14].

4 Pathophysiology of CCH

CCH is a long and progressive process in terms of time. In terms of degree, CCH is different from acute ischemic cerebral infarction, and is a state where cerebral perfusion cannot meet the needs of normal cerebral metabolism but has not yet caused ischemic infarction.

The normal human cerebral blood flow is 50 ~ 60 mL/(100 g·min). When the cerebral blood flow is less than 18 mL/(100 g·min), cell electrical activity and membrane failure will occur, leading to brain cell death, that is, cerebral infarction. When the cerebral blood flow is 20 ~ 40 mL/(100 g· min), glucose utilization and protein synthesis disorders and a series of pathophysiological changes may occur [15]. Long-term hypoperfusion can lead to neurological dysfunction without cerebral infarction [16-18].

Animal model studies found that the brain histopathological changes of CCH include macroscopic cortical atrophy, microscopic cortical and hippocampal neuron degeneration, leukoaraiosis, glial cell proliferation and capillary bed changes, etc. [19-21].

The injury mechanism of CCH includes neurotransmitter changes, oxidative stress, immune inflammatory reaction, abnormal synaptic structure and function, impaired mitochondrial function and neuronal apoptosis [22-24]. With the increase of age, the blood flow of brain tissue decreases slowly in healthy adults [25]. Atherosclerosis, hypertension and other heart diseases can lead to a slight decrease in cardiac output and an increase in the incidence of cerebral artery stenosis [26, 27]. At the same time, the increase of the oxygen uptake fraction in brain tissue, the decrease of venous oxygenation and the decrease of cerebrovascular reactivity become more and more obvious with age [28]. Therefore, the elderly have low cerebral blood flow reserve capacity and high risk of hemodynamic abnormality. In addition, the balance between oxygen supply and oxygen consumption is changed, which reduces their tolerance to ischemia and makes them more prone to

chronic cerebral ischemia injuries.

5 Clinical manifestations and classification of CCH

5.1 Clinical Manifestations of CCH CCH has hidden onset, long duration of symptoms and no specific clinical manifestations.

5.1.1 General Symptoms Patients may have complaints of one or more discomforts, such as headache, vertigo, dizziness, fullness of head, head heaviness, tinnitus cerebri, obvious general fatigue or local discomfort, etc., most of which are not accompanied by focal signs of nervous system, and some patients may have complaints of numbness or weakness of limbs, tinnitus, hearing loss, vision loss, and decreased ability to control urination and defecation.

5.1.2 Sleep Disorder The vast majority of patients may have varying degrees of parahypnosis, often complaining of insomnia, such as difficulty in falling asleep, dreaminess, early awakening, difficulty in falling asleep again, sleepiness during the day and insomnia at night.

5.1.3 Mood Changes They are mostly manifested as low spirits, dysphoria, irritable, indifferent, and not interested in new things. Some patients may have depression, anxiety, etc., and go to psychiatric or psychological specialties.

5.1.4 Cognitive Disorders Patients may suffer from unresponsiveness, attention loss and slow movement, among which near memory disorder may be the early symptom of this disease. Most of these patients complain of amnesia, and the symptoms are mostly nonspecific.

5.1.5 Other Clinical Manifestations Some patients may have dull complexion, dark lips, chest tightness and chest pain, nausea, anorexia, epigastric distention and pain, hypochondriac distention and pain, indigestion, etc.

5.2 Clinical Classification of CCH in Modern Medicine Clinically, it is often classified by etiology, ischemic area and degree, but there is still insufficient basis.

5.2.1 Classification by Etiology (1) Large vessel stenosis type: Atherosclerotic stenosis or occlusion with intracranial and extracranial large vessels. (2) Small vessel perforating artery lesion type: It may have the characteristics similar to cerebral small vessel changes, such as leukoaraiosis and enlargement of perivascular space, including arteriosclerosis and various hereditary cerebral small vessel diseases, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), etc. (3) Circulation disorder type (hypoperfusion type): including cerebral hypoperfusion caused by cardiogenic abnormalities such as hypotension, cardiac insufficiency and aortic valve diseases or other hemodynamic abnormalities. Hypercoagulability caused by changes in blood components, such as polycythemia vera, abnormal proteinosis, etc., may also lead to this disease. This consensus is limited to the first two types.

5.2.2 Classification by Ischemic Site (1) Posterior circulation (vertebrobasilar system) ischemic type. This type is the most common. Once it develops into cerebral infarction in the blood supply area of vertebrobasilar artery, its mortality rate reaches 20% ~ 30% [29]. The classification basis is as follows: ① There are symptoms of persistent vertebrobasilar insufficiency: dizziness, walking instability, inclination, standing instability or top-heavy, generally without nausea. When symptoms are severe, there may be short-term dizziness,

accompanied by mild nausea, blurred vision, limb fatigue and so on. The above symptoms may fluctuate, sometimes mild and sometimes serious. Dizziness increases when the body position changes or when walking for a long time, and decreases or disappears when lying down. ② There are no focal neurological signs in the brain. ③ MRI shows no infarct in the blood supply area of posterior circulation, but there are mild brain atrophy and mild enlargement of the fourth ventricle. MR angiography (MRA) or computer tomography angiography (CTA) can show vertebrobasilar atherosclerosis and irregular stenosis. (2) Anterior circulation (internal carotid artery system) ischemic type. Basis: ①The main manifestation is forebrain dysfunction, which is mainly manifested as mental symptoms: memory loss, especially ecmnesia, name forgetting, etc., unresponsiveness, apathy, inattention, emotional instability (anxiety and irritability), insomnia, decreased working ability, decreased judgment, and even personality changes, paranoia, mild dementia, numbness, soreness and chills of one-sided limbs, etc. ② There are no focal neurological signs in the brain. ③ There is no infarct in the blood supply area of anterior circulation, but there are mild brain atrophy and demyelination of white matter in different degrees. MRA or CTA examination shows that the common carotid artery and internal carotid artery system may have vascular stenosis or atherosclerosis changes, and cerebral arteriosclerosis changes. (3) Global cerebral ischemia type: It has symptoms, signs and imaging manifestations of insufficient blood supply in both anterior and posterior circulations.

5.2.3 Classification by Ischemic Degree Type I: Type a, with risk factors of cerebrovascular diseases (hypertension, diabetes, hyperlipidemia, etc.); with CCH symptoms. Type b, in line with Type a + collateral syndromes of cerebral arteriosclerosis [coronary heart disease, fundus and/or peripheral arteriosclerosis]. Type II: Type a, Type I + demyelination of white matter (accounting for 3/6 or less) and/or abnormal results of color Doppler ultrasound and TCD. Type b, Type I + extensive demyelination of white matter. Type III: Type a, Type II + irregular stenosis of carotid artery and/or vertebrobasilar artery. Type b, Type II + segmental or extensive occlusion of carotid artery and/or vertebrobasilar artery. Type I is mainly manifested as clinical symptoms, Type II is manifested as general imaging changes on the basis of clinical diagnosis, and Type III is manifested as structural changes of blood vessels on the basis of Type II. As a whole, this classification reflects that the higher the classification, the greater the risk of stroke.

6 Auxiliary Examination and Evaluation of CCH A series of examinations and evaluations, including risk factors, etiology, neuropsychology, cerebral vessels and cerebral perfusion, should be carried out for patients with suspected or probable CCH.

6.1 Neuropsychological Assessment

6.1.1 Emotional Assessment Normally the Self-rating Anxiety Scale (SAS), Self-rating Depressive Scale (SDS), Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA) are used for assessment, and the Neuropsychiatric Inventory (NPI) can be used for patients with psychotic symptoms.

6.1.2 Cognitive Function Assessment The Montreal Cognitive Assessment Scale (Mo-CA) and Mini-mental State Examination (MMSE) can be used for screening. Special functional scales, including the Alzheimer's Disease Assessment Scale-cognitivesection (ADAS-cog), digit span test (DST), clock drawing test (CDT), Connection Test, Controlled Oral Word Association Test, and Stroop Color-Word Association Test, may be further used for comprehensive assessment for people with abnormalities.

6.2 Cerebrovascular and Perfusion Assessment

6.2.1 Cerebrovascular Assessment The vascular examination includes TCD, head and neck vascular ultrasound, CTA, MRA or digital subtraction angiography (DSA).

6.2.2 Assessment of Cerebral Perfusion The cerebral blood flow perfusion examination is the key index to determine CCH, including computerized tomography perfusion (CTP), magnetic weight imaging (PWI), arterial spin labeling, (ASL), single-photon emission computed tomography (SPECT), positron emission tomography (PET). PET is the "golden standard" for measuring regional cerebral blood flow and metabolism.

6.3 Brain Function Assessment for CCH EEG, auditory evoked potential, visual evoked potential and event-related potential have certain reference values for extensive and large area ischemia.

7 Diagnostic Criteria of CCH Based on the diagnostic criteria proposed by scholars at home and abroad, as well as the practicability of its clinical application and the current situation in China, this consensus puts forward the following clinical diagnostic criteria: (1) The patient's age is in principle more than 60 years old, with insidious onset. The course of the disease is long, and the medical history is generally more than 3 months. Symptoms can fluctuate. (2) Patients have manifestations of chronic brain dysfunction, such as vertigo, dizziness, head pain, memory loss, unresponsiveness, inattention, emotional instability, decreased working ability, sleep disorder and emotional disorder. (3) Patients have risk factors of cerebrovascular disease, such as medical history of hypertension, diabetes, dyslipidemia and coronary heart disease. (4) Patients have no signs of focal nervous system in the brain. (5) Laboratory examination: there is evidence to support cerebral arteriosclerosis; Peripheral arteriosclerosis such as ophthalmic artery, temporal artery and radial artery, or vascular murmur of cerebral perfusion artery can be heard; Cerebrovascular examination shows evidence of cerebral artery stenosis or obstructive lesions. (6) Head CTA/MRI shows no vascular organic brain changes. (7) Cerebral perfusion imaging confirms that there is cerebral hypoperfusion. It is suggested that CTP and PWI be taken as the basic diagnostic conditions to enrich the accuracy of CCH diagnosis. (8) Eliminate other neurological and mental diseases that can lead to related clinical symptoms; Eliminate chronic brain dysfunction caused by related diseases such as hysteria, anxiety somatization disorder, depression, AD and various degenerative diseases or subjective dizziness.

8 TCM-WM classification of CCH This disease is characterized by a chronic process of occurrence and development, and most of the patients are middle-aged and elderly people. According to traditional Chinese medicine, this disease is mostly caused by aging, dysfunction of viscera, disorder of water and liquid metabolism, accumulation of water into wet, accumulation of wet into phlegm, and mutual accumulation of phlegm and blood stasis, or poor blood circulation due to qi deficiency, or disorder of blood circulation due to depression. Throughout the occurrence and development of this disease, "phlegm turbidity", "qi deficiency" and "qi stagnation" are the most common syndromes, while "blood stasis" is the common manifestation of all the syndromes. Phlegm stagnation and blood stasis type: Most patients are characterized by dizziness, sallow complexion or ecchymosis, sticky mouth, thick sputum which is difficult to spit out, body heaviness, abdominal distension, poor appetite, unsmooth defecation, dribbling urination, white greasy or moist tongue coating, dark fat or dark purple tongue, and weak pulse tracings. Qi deficiency and blood stasis type: most patients have dizziness which is aggravated after fatigue, shortness of breath and weakness, feel "lack of strength" when speaking or moving, sweat easily, are fond of warmth and afraid of cold, have pale complexion, and may have palpitation, dry or unsmooth stool, or soft stool, and have white and moist tongue coating, dim tongue body, and deep and weak pulse tracings. Qi stagnation and blood stasis type: most patients have head fullness, blurred vision, tinnitus or tinnitus cerebri, upset and insomnia, emotional upset or both chest and hypochondriac distension, dry or unsmooth stool, yellowish tongue coating but less fluid, dark red tongue, ecchymosis or petechia on or beside the tongue, and weak or deep pulse tracings.

9 Treatment of CCH

9.1 Principle of Treatment First, evaluate patients as a whole according to the test results of various modern technologies, and use recognized and effective western medicines to actively treat the primary basic diseases and control the risk factors. For patients with obvious clinical symptoms of CCH, relevant Chinese and western medicine injections may be used for intravenous drip, and relevant western medicines may be used for symptomatic treatment or traditional Chinese medicines may be added according to syndrome differentiation. For patients with obvious vascular stenosis, interventional or surgical treatment conditions and no abnormalities in brain tissue imaging, when the effect of conservative treatment is uncertain, priority should be given to interventional or surgical treatment, but before and after interventional treatment, Chinese medicine can be used for systemic conditioning according to syndrome differentiation.

In the process of applying TCM-WM, we should pay attention to the adverse reactions and mutual adverse effects of Chinese and western medicines, and closely observe the changes of symptoms and complaints of discomfort in patients. The liver and kidney function, blood routine, coagulation and other related indicators should be examined for changes on a regular basis.

9.2 Treatment with Modern Medicine

9.2.1 Intervention on Risk Factors Including hypertension, hyperlipidemia, diabetes and smoking.

9.2.2 Etiological Treatment It includes intracranial and extracranial artery stenosis, cerebral small vessel disease and leukoaraiosis. Carotid endarterectomy (CEA), carotid artery stenting (CAS), balloon dilatation and intracranial-extracranial artery anastomosis may be performed for patients with atherosclerotic or inflammatory vascular stenosis with surgical indications.

9.2.3 Treatment to Improve Cerebral Circulation At present, the commonly used drugs are betahistine, flunarizine, nimodipine, Alprostadil Injection, butylphthalide, urinary kininogenase and so on. Specifically, butylphthalide is a national chemical Category I new drug, which was originally extracted from celery seeds. Studies have shown that butylphthalide can improve cerebral blood flow in ischemic areas and protect mitochondria [30-32]. A number of RCT studies have shown that it can improve the neurological deficit and living ability of patients with ischemic stroke with good safety [33]. A double-blind, double-dummy RCT study showed that the functional outcome of the sequential treatment group with Butylphthalide injection and soft capsules was better than that of the control group [33].

9.2.4 Treatment with Cognition Improvement Drugs Such drugs are, for example, cholinesterase inhibitor drugs and drugs for promoting brain cell metabolism, cytidine diphosphate choline, Compound Porcine Cerebroside and Ganglioside Injection, Compound Troxerutin and Poreine Cerebroside Injection, etc. In addition, a clinical study showed that butylphthalide can improve the cognition and overall function of patients with non-dementia vascular cognitive impairment, and has good safety and tolerance [34]. Some drugs for promoting blood circulation and removing blood stasis can also improve cognitive function by improving cerebral blood flow, such as Safflower Extract and Aceglutamide Injection.

9.2.5 Treatment with Other Drugs At present, clinically, patients with CCH symptoms should be given antiplatelet aggregation and anticoagulants as early as possible based on the specific conditions of patients, such as aspirin and clopidogrel.

9.3 TCM-WM Treatment Because CCH patients often have many basic diseases, they need to receive

combined drug therapy, but multiple drugs may increase the incidence of adverse drug reactions, which need to be taken seriously.

At present, the modern pharmacological mechanism of many traditional Chinese medicines is still unclear, and their interaction with western medicines is also unclear. When Chinese and western medicines are used together, we should try our best to choose varieties with evidence of synergistic effect, because improper use (inaccurate syndrome differentiation) may also lead to adverse drug reactions. Therefore, in treating CCH with TCM-WM, the mechanism, links and targets of action of Chinese and western medicines should be fully considered, and the advantages of Chinese and western medicines should be complemented as far as possible to reduce toxicity and increase efficiency.

In TCM-WM treatment, relevant Chinese and western medicine treatment methods and drugs should be selected according to the classification, but the benefits and risks of their combined use should be fully considered.

9.3.1 Phlegm Stagnation and Blood Stasis Type Treatment principle: Eliminating phlegm and blood stasis. Recommended TCM: Tongxinluo Capsule + Daotan Decoction or Erchen Decoction, Lishukang Capsule + Maixuekang Capsule, or Dahuangchong Pill (which must not be taken for a long time) + Xihong Tongluo Oral Liquid are the preferred Chinese medicines. For patients with severe symptoms, Danhong Injection or Danshen Injection may be given intravenously. Recommended prescription: Banxia Baizhu Tianma Decoction, which is composed of Gastrodia elata 10 g, Pinellia tuberifera 9 g, white atractylodes rhizome 10 g, tuckahoe 10 g, dried orange peel 10 g, licorice 6 g, chuanxiong rhizome 15 g and lumbricus 3 g, can be modified based on actual symptoms. Based on patient's needs, Chinese medicine should be used according to syndrome differentiation, and western medicine should be added to patients with no obvious curative effect.

9.3.2 Qi Deficiency and Blood Stasis Type Treatment principle: supplementing qi and activating blood circulation. Recommended TCM: Xiaoshuan Enteric Capsule, Naoxintong Capsule, or Peiyuan Tongnao Capsule + Yangxue Qingnao Granule are preferred [35-37]. Patients with obvious symptoms can be treated with Astragalus Injection and Ginkgo Biloba Injection intravenously. Recommended prescription: Buyang Huanwu Decoction, which consists of raw Astragalus 60 g, angelica tail 6 g, red peony root 5 g, lumbricus 3 g, chuanxiong rhizome 3 g, safflower 3 g, peach kernel 3 g, can be modified based on actual symptoms. Based on patient's needs, Chinese medicine should be used according to syndrome differentiation, and western medicine should be added to patients with no obvious curative effect.

9.3.3 Qi Stagnation and Blood Stasis Type Treatment principle: Promoting flow of qi and blood circulation. Recommended TCM: Shugan Pill (which must not be taken for a long time) + Xuefu Zhuyu Pill or Modified Xiaoyao Pill + Maixuekang Capsule are preferred. Danhong Injection or Compound Danshen Injection can be used for intravenous drip in patients with obvious symptoms. Recommended prescription: Tongqiao Huoxue Decoction, which is composed of peach kernel 15 g, safflower 10 g, Angelica sinensis 12 g, Radix Rehmanniae 12 g, welsh-onion stalk 10 g, red peony root 12 g, chuanxiong rhizome 10 g, liquorice 6 g, can be modified based on actual symptoms. Based on patient's needs, Chinese medicine should be used according to syndrome differentiation, and western medicine should be added to patients with no obvious curative effect.

9.4 Acupuncture Therapy Commonly used clinical acupoints include Fengchi, Baihui, Blood Pressure Point, Yintang, Shenting, Sishencong, Touxia, Taiyang, Xuanzhong, Zusanli and so on. Studies have shown that acupuncture at these points can improve hemodynamics, dilate cerebral vessels, improve blood viscosity

and relieve vertigo symptoms in CCH patients [38, 39]. For patients with Qi deficiency, add Qihai. For patients with blood stasis, add Xiehai and Geyu. For patients with phlegm turbidity, add Neiguan, Zhongwan and Fenglong. Rubbing or tapping the above-mentioned acupoints can also stimulate people's meridian qi, thus achieving the purpose of preventing and treating diseases.

10 Prognosis and Prevention

10.1 Prognosis Because CCH is characterized by a chronic course of disease, whose clinical symptoms often fail to attract patients' attention. Being in CCH for a long time can lead to chronic ischemia of brain tissue, and then develop into demyelination of white matter, cerebral infarction, vascular dementia or hemorrhagic cerebrovascular disease, etc., and the quality of life of patients will gradually decline. It is necessary to give a clear warning on its harm. Once the clinical diagnosis is decided on CCH, patients should adhere to medication, actively control the risk factors first, and at the same time take various measures to relieve symptoms and control their development.

10.2 Prevention In order to control the disease effectively and make it develop reversely, daily health care is equally important in addition to clinical treatment. (1) Control of primary diseases: Pay full attention to hypertension, hyperlipidemia and diabetes. Those who have indications for medication should stick to taking medicine. They should avoid paying no attention to it because they have no symptoms. Examinations of blood-related indicators and cerebrovascular ultrasound should be regularly performed, and drugs should be adjusted according to the examination results. (2) Life: Dress loosely and appropriately, alternate work with rest, and follow the natural law of getting up at dawn and resting at sunset. (3) Emotion: Be optimistic, find joy in life, and have broad interests. (4) Activities: Exercise moderately and stick to the traditional Chinese exercise techniques of Tai Chi, five mimic-animal boxing, and eight trigrams boxing, so as to achieve a natural and healthy state of "integration of body and spirit" and "integration of mind and body". (5) Health care prescription: phlegm-removal prescription: slice 0.5kg of carrots, add proper amount of water, add 10 g of Houttuynia cordata and 10 g of herba eupatorii 10 min before carrots are cooked thoroughly, and take them with soup after thorough cooking on a long-term basis. Prescription for Qi deficiency: Add a proper amount of water into 30 g of Astragalus membranaceus and 15 g of Angelica sinensis, cook them, and drink the soup. Blood stasis prescription: Use 10 g of peach kernel and 50-100 g of japonica rice. Smash the peach kernel and boil it in water, get juice by removing dregs, boil it in a pot with japonica rice to make gruel, and take it daily.

Experts participating in consensus discussions and writing (in order of surname pinyin): Bi Qi (Department of Neurology, Beijing Anzhen Hospital, Capital Medical University); Bi Jianzhong (Department of Neurology, Second Hospital of Shandong University); Gao Li (Department of Neurology, Xuanwu Hospital, Capital Medical University); Gong Tao (Department of Neurology, Beijing Hospital); Guo Rongjuan (Department of Encephalopathy, Oriental Hospital, Beijing University of Chinese Medicine); Guo Fuqiang (Department of Neurology, Sichuan Provincial People's Hospital); Huang Liyuan (Department of Neurology, Xuanwu Hospital, Capital Medical University); Li Wenwei (Institute of Neurology, Institute of Integrated Traditional Chinese and Western Medicine, Fudan University, Shanghai); Meng Yongsheng (Department of Geriatrics, Xuanwu District Hospital of Traditional Chinese Medicine, Beijing); Niu Junying (Department of Neurology, Rocket Force General Hospital); Qu Miao (Department of Neurology, Xuanwu Hospital, Capital Medical University); Song Haiqing (Department of Neurology, Xuanwu Hospital, Capital Medical University); Wang Xinzhi (Cerebrovascular Hospital of First Affiliated Hospital of Henan University of Traditional Chinese Medicine); Wang Zhiyong (Department of Neurology, Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine, Hebei Province); Xu Yinping (Department of Encephalopathy, Pinggu Hospital, Beijing Hospital of

Traditional Chinese Medicine, Capital Medical University); Zhang Yongbo (Department of Neurology, Beijing Friendship Hospital, Capital Medical University)

Penner: Gao Li (Department of Neurology, Xuanwu Hospital, Capital Medical University)

Conflict of interest: There is no conflict of interest in this paper.

Acknowledgement: During the formation of the first draft, this consensus was strongly supported by Professor Ma Xin and Deputy Chief Physician Xue Sufang from Department of Neurology, Xuanwu Hospital, Capital Medical University. During the discussions, dozens of domestic experts in Chinese and Western medicine were consulted and gave their support. These experts are Deputy Chief Physician Chu Changbiao from the Department of Neurology, Xuanwu Hospital, Capital Medical University, Professor Zeng Jinsheng from Department of Neurology, First Affiliated Hospital of Sun Yat-sen University, Professor Peng Bin from Department of Neurology, Peking Union Medical College Hospital, Professor Chu Lan from Department of Neurology, First Affiliated Hospital of Guizhou Medical University, Professor Yang Yi from Department of Neurology, No.1 Hospital of Jilin University, Professor He Zhiyi from Department of Neurology, First Affiliated Hospital of China Medical University, Professor Lu Zhengqi from Department of Neurology, Third Affiliated Hospital of Sun Yat-Sen University, Professor Zhang Lili from Department of Neurology, Daping Hospital of Army Medical University, Professor Fu Jianhui from Department of Neurology, Shanghai Huashan Hospital, Professor Luo Benyan from Department of Neurology, First Affiliated Hospital of Zhejiang University, Professor Xu Yuming from Department of Neurology, First Affiliated Hospital of Zhengzhou University and Chief Physician Nan Hongmei from Encephalopathy Center, Affiliated Hospital of Changchun University of Traditional Chinese Medicine, Chief Physician Liu Hongquan from Department of Encephalopathy, Jiangsu Province Hospital of Integrated Traditional Chinese and Western Medicine, Chief Physician Xu Xiangqing from Department of Encephalopathy, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Chief Physician Wang Yanxi from Department of Encephalopathy, First Affiliated Hospital of Anhui University of Chinese Medicine, Chief Physician Zhang Jingzhi from Department of Traditional Chinese Medicine, Second Affiliated Hospital of Guangzhou Medical University, Chief Physician Lv Guangyao from Department of Encephalopathy, Xinjiang Autonomous Region Hospital of Traditional Chinese Medicine, Chief Physician Cao Kegang from Department of Encephalopathy, Dongzhimen Hospital, Beijing University of Chinese Medicine, Chief Physician Zheng Aijun from Department of Rehabilitation, Yanqing District Hospital of Beijing (Yanqing Hospital of Peking University Third Hospital), Chief Physician Li Fang from Emergency Department, Ershadao Branch of Traditional Chinese Medicine Hospital of Guangdong Province, and Chief Physician Peng Dongqing from Department of Acupuncture and Moxibustion, Changping District Hospital of Traditional Chinese Medicine, Beijing, to whom we hereby express our thanks.

References

[1] World Health Organization. International statistical classification of diseases and related health problems, 10th revision, vol 2: instruction manual [M]. Geneva, Switzerland: World Health Organization, 1993: 12.

[2] World Health Origanization Diseases Classification Cooperation Center of Peking Union Medical College Hospital. International statistical classification of diseases and related health problems, 10th revision (ICD-10) [M]. 2nd edition. Beijing: People's Medical Publishing House, 2008: 28.

[3] Neurology Branch of Chinese Medical Association, Cerebrovascular Disease Group of Neurology Branch of Chinese Medical Association. Classification of Cerebrovascular Diseases in China 2015 [J]. Chinese Journal of Neurology, 2017, 50(3): 168-171.

[4] Duncombe J, Kitamura A, Hase Y, et al. Chronic cerebral hypoperfusion: a key mechanism leading to vascular cognitive impairment and dementia. Closing the translational gap between rodent models and human vascular cognitive impairment and dementia [J]. Clin Sci (Lond), 2017, 131 (19) : 2451-2468.

[5] Zhai Y,Yamashita T, Nakano Y, et al. Chronic cerebral hypoperfusion accelerates Alzheimer's disease pathology with cerebrovascular remodeling in a novel mouse model [J]. J Alzheimers Dis, 2016, 53(3): 893-905.

[6] Wang XD. Draft Classification of Cerebrovascular Diseases (Third Revision of the Second National Conference on Cerebrovascular Diseases of Chinese Medical Association in 1986) [J]. Chinese Journal of Neurology and Psychiatry, 1998, 21(1): 59-60.

[7] Zhang JJ, Zhou S. Chronic cerebral ischemia: an independent disease entity? [J]. Chinese Medical Journal, 2012, 92(41): 2881-2884.

[8] Saura H, Ogasawara K, Beppu T, et al. Hypoxic viable tissue in human chronic cerebral ischemia because of unilateral major cerebral artery steno-occlusive disease [J]. Stroke, 2015, 46 (5): 1250-1256.

[9] Rao R, Wang X, Han YZ. Treatment of chronic cerebral ischemia with traditional Chinese medicine [J]. Clinical Journal of Traditional Chinese Medicine, 2010, 22(4): 365-368.

[10] The Ming Dynasty· Yu Tuan. The True Story of Medicine [M]. Beijing: Chinese Medical Ancient Books Publishing House, 2002: 72-75.

[11] The Qing Dynasty· Zhang Xichun. Integrated Chinese and Western Medicine [M]. Tianjin: Tianjin Xinhua Publishing House, 1909: 74-89.

[12] Zhou D, Meng R, Li SJ, et al. Advances in chronic cerebral circulation insufficiency [J]. CNS Neurosci Ther, 2018, 24(1): 5-17.

[13] Wang DK. Epidemiological analysis and prevention measures of cerebrovascular diseases in China [J]. Journal of Traditional Chinese Medicine Management, 2014, 22(6): 830-831.

[14] Pei QL, Wang AZ. Correlation analysis between hyperhomocysteinemia and chronic cerebral ischemia [J]. Chinese Journal of Practical Nervous Diseases, 2011, 14(11): 65-66.

[15] Sharp FR, Swanson RA, Honkaniemi J, et al. Chapter 4: Neurochemistry and Molecular Biology. Trans. Wu Zhe.//Gao Xuguang. Pathophysiology, Diagnosis and Treatment of Stroke [M]. 3rd Edition. Shenyang: Liaoning Science and Technology Press, 2001: 46.

[16] Okamoto Y, Yamamoto T, Kalaria RN, et al. Cerebral hypoperfusion accelerates cerebral amyloid angiopathy and promotes cortical microinfarcts [J]. Acta Neuropathol, 2012, 123(3): 381-394.

[17] Zhao Y, Gong CX. From chronic cerebral hypoperfusion to Alzheimer-like brain pathology and neurodegeneration [J]. Cell Mol Neurobiol, 2015, 35(1): 101-110.

[18] Lee KM, Bang JH, Bu YK, et al. Fructus mume alleviates chronic cerebral hypoperfusion-induced white matter and hippocampal damage via inhibition of inflammation and downregulation of TLR4 and p38 MAPK signaling [J] . BMC Complement Altern Med, 2015, 15(1): 1-10.

[19] Farkas E, Luiten PG, Bari F. Permanent, bilateral common carotid artery occlusion in the rat: a model for chronic cerebral hypoperfusion-related neurodegenerative diseases [J]. Brain Res Rev, 2007, 54(1): 162-180.

[20] Patel A, Moalem A, Cheng H, et al. Chronic cerebral hypoperfusion induced by bilateral carotid artery stenosis causes selective recognition impairment in adult mice [J]. Neurol Res, 2017, 39 (10): 910-917.

[21] Li N, Gu Z, Li Y, et al. A modified bilateral carotid artery stenosis procedure to develop a chronic cerebral hypoperfusion rat model with an increased survival rate [J]. J Neurosci Methods, 2015, 255:115-121.

[22] Voskresenskaya ON, Zakharova NB, Ivanov MV. Mechanisms of development of chronic cerebral ischemia in arterial hypertension [J]. Zh Nevrol Psikhiatr Im S S Korsakova, 2017, 17(2): 68-71.

[23] Miyanohara J, Kakae M, Nagayasu K, et al. TRPM2 channel aggravates CNS inflammation and

cognitive impairment via activation of microglia in chronic cerebral hypoperfusion [J]. J Neurosci, 2018, 38 (14): 3520-3533.

[24] Xi Y, Wang M, Zhang W, et al. Neuronal damage, central cholinergic dysfunction and oxidative damage correlate with cognitive deficits in rats with chronic cerebral hypoperfusion [J]. Neurobiol Learn Mem, 2014, 109: 7-19.

[25] Claus JJ, Breteler MM, Hasan D, et al. Regional cerebral blood flow and cerebrovascular risk factors in the eldly population [J]. Neurobiol Aging, 1998, 19: 57-64.

[26] Duron E, Hanan O. Vascular risk factors, cognitive decline, and dementia [J]. Vasc Health Risk Manag, 2008, 4(2): 363-381.

[27] Elias MF, Robbins MA, Budge MM, et al. Arterial pulse wave velocity and cognition with advancing age [J]. Hypertension, 2009, 53(4): 668-673.

[28] Lu H, Xu F, Rodrigue KM, et al. Alterations in cerebral metabolic rate and blood supply across the adult lifespan [J]. Cereb Cortex, 2011, 21(6): 1426-1434.

[29] Li JZ. New ideas of chronic cerebral blood supply insufficiency (2) [J]. Chinese Journal of Practical Nervous Diseases, 2007, 10(6): 1-2.

[30] Zhao Y, Lee JH, Chen D, et al. DL-3-n-butylphthalide induced neuroprotection, regenerative repair, functional recovery and psychological benefits following traumatic brain injury in mice [J]. Neurochem Int, 2017, 111: 82-92.

[31] Liu RZ, Fan CX, Zhang ZL, et al. Effects of dl-3-n-butylphthalide on cerebral ischemia infarction in rat model by mass spectrometry imaging [J]. Int J Mol Sci, 2017, 18(11): E2451.

[32] Qin C, Zhou P, Wang L, et al. Dl-3-N-butylphthalide attenuates ischemic reperfusion injury by improving the function of cerebral artery and circulation [J]. J Cereb Blood Flow Metab, 2018, 27(18): 1678.

[33] Cui LY, Zhu YC, Gao S, et al. Ninety-day administration of dl-3-n-butylphthalide for acute ischemic-stroke: a randomized, double-blind trial [J]. Chin Med J(Engl), 2013, 126 (18): 3405-3410.

[34] Jia J, Wei C, Liang J, et al. The effects of DL-3-n-butylphthalide in patients with vascular cognitive impairment without dementia caused by subcortical ischemic small vessel disease: A multicenter, randomized, double-blind, placebo-controlled trial [J]. Alzheimer' s Dement, 2016, 12 (2): 89-99.

[35] Liu T, Zeng PP, Zhang QP, et al. Meta-analysis of therapeutic effect of Yangxue Qingnao Granule on vascular cognitive dysfunction [J]. Pharmaceutical Research, 2016, 35(1): 49-52.

[36] Du H, Dai XH. Meta-analysis of Yangxue Qingnao Granule in treating accompanying symptoms of hypertension [J]. Journal of Anhui Traditional Chinese Medical College, 2014, 33(1): 8-11.

[37] Wu C, Liao L, Yan X, et al. Effects of Yangxue Qingnao Granules on chronic cerebral circulation insufficiency: a randomized， double-blind， double-dummy， controlled multicentre trial [J]. Psychogeriatrics, 2013, 13(1): 29-34.

[38] Zhu FQ, Zhang HY, Tian YY. Clinical study on 66 cases of cerebral blood supply insufficiency treated by TCD at acupoints [J]. Chinese Acupuncture and Moxibustion, 2002, 22 (12): 803-805.

[39] Han DX, Liu Z, Feng PP, et al. Effects of electroacupuncture intervention at different time on focal cerebral blood flow, cognitive function and inflammatory injury in rats with chronic cerebral ischemia [J]. Chinese Journal of Integrated Traditional Chinese and Western Medicine, 2017, 37(6): 721 -725.

(Received on: July 31, 2018　Online: September 30, 2018)

Editor in charge: Tang Jing