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Research Progress of Traditional Chinese Medicine in Treating Mild Cognitive Impairment

Miao Zhang[1], Shiyang Lu[1], Yiyun Li[1], Jie Chen[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Shaanxi Provincial Hospital of Chinese Medicine, Xi'an 710003, Shaanxi, China
Correspondence Author

Abstract: ***Mild cognitive impairment is a transitional period between normal aging and dementia. Nowadays, due to the aging of the population, the incidence of mild cognitive impairment is increasing. At present, due to the medication limitations and adverse effects of western drugs, Chinese medicine has certain advantages in the treatment of mild cognitive impairment. This paper summarises the research progress of Chinese medicine in the treatment of mild cognitive impairment in recent years, and aims to provide theoretical reference and practical guidance for the treatment of mild cognitive impairment with Chinese medicine by elaborating on the pathogenesis of mild cognitive impairment and the treatment of mild cognitive impairment with Chinese medicine.***

Keywords: Mild cognitive impairment, Traditional Chinese medicine, External Chinese medicine**.**

1. Introduction

Mild cognitive impairment (MCI) refers to a slight decline in cognitive function, usually characterized by memory loss, but without sufficient functional impairment to meet the criteria for dementia. It is considered a transitional stage between normal aging and dementia. With the rapid development of population aging, the prevalence of MCI is increasing. Among elderly people over 60 in China, the prevalence of MCI is 15.5%, with an estimated 38.77 million people affected [1]. Currently, the pathogenesis of MCI is not fully understood, and Western medical treatments primarily include pharmacological and non-pharmacological approaches (such as diet, exercise, and cognitive rehabilitation training), with limited clinical efficacy. Currently, traditional Chinese medicine (TCM) treatments for MCI include oral herbal medicine and external therapies such as traditional exercises and acupuncture, which have shown significant efficacy. The following is a review of commonly used TCM methods for treating MCI in recent years.

2. Traditional Chinese Medicine's Understanding of MCI

MCI does not have a corresponding disease name in traditional medicine. The earliest record of this condition is found in the "Huang Nei Jing," which states, "Blood accumulates below, Qi accumulates above, resulting in disturbance and forgetfulness." Based on the description of the disease, it is generally classified under "forgetfulness," and is also referred to as "habitual forgetfulness," "good-forgetfulness," "amnesia," and "dementia." The Sui Dynasty work "Zhubing Yuanhou Lun" proposed the concept of "frequent forgetfulness." In the Tang Dynasty, Sun Simiao's "Beiji Qianjin Yaofang" described MCI as "good-forgetfulness." The term "amnesia" first appeared in the Song Dynasty book "Taiping Shenghui Fang." Traditional Chinese medicine considers MCI to be a syndrome of deficiency in the root with a surplus in the manifestation. The causes of the disease are mainly related to phlegm, blood stasis, and deficiency. Deficiency often involves damage to the heart, spleen, and kidney, leading to insufficient brain essence, while excess is often caused by obstruction from phlegm and blood stasis. The "Suwen" mentions, "The disease of forgetfulness originates from heart deficiency." The "Yixue Xinwu" states, "Kidney deficiency leads to insufficient wisdom, hence frequent forgetfulness of words." The "Yifang Jijie" notes, "When kidney essence is insufficient, it cannot communicate with the heart, leading to confusion and habitual forgetfulness." Modern research shows [2] that the main syndromes of MCI are Qi and blood deficiency, spleen and kidney insufficiency, blood stasis blocking the meridians, and phlegm turbidity obstructing the clear orifices. Based on deficiency in the brain, heart, spleen, and kidney, the combination of phlegm turbidity and blood stasis contributes to the disease, making the pathogenesis complex.

3. Current Status of Western Medicine Research

At present, the pathogenesis of MCI is still unclear, but it is generally believed to be similar to the pathogenesis of dementia. The main pathological mechanisms of MCI are related to amyloid pathology, neurofibrillary tangle pathology, neuronal deficits, and impaired synaptic plasticity in the hippocampus [3]. Among them, β-amyloid (Aβ) and intracellular tau defibrillation tangles (Nets) are hallmark anthropological substrates of MCI. In addition, inflammatory responses and oxidative stress are important factors leading to cognitive decline. Currently, treatments for MCI [4] include pharmacological treatments, symptomatic treatments such as stress reduction and treatment of demonstrativeness and systemic diseases, as well as non-pharmacological therapies, such as exercise, dietary habits, cognitive rehabilitation, psychotherapy, aromatherapy, and light therapy. However, evidence on the effectiveness and safety of these therapies is limited. Moreover, there is currently no clearly approved medication for treating MCI; in clinical practice, drugs such as donepezil, neolithic, and vitamin E are commonly used to slow cognitive decline.

4. Traditional Chinese Medicine Internal Treatments

Traditional Chinese medicine and Chinese herbal formulas have been shown to have certain efficacy in the treatment of MCI. Their mechanisms for improving cognitive function may be related to regulating neurotransmitters, combating oxidative stress, reducing inflammation, modulating brain metabolism, and inhibiting neuronal apoptosis.

4.1 Single Chinese Herbal Medicines

The efficacy and clinical applications of Chinese medicine have been confirmed, but it is also important to clarify the active ingredients and specific mechanisms of action of these medicines. Astrological IV can improve Aβ-induced PC12 cell injury by activating the PI3K/Akt signaling pathway, thereby inhibiting cell apoptosis and protecting neurons [5]. Zhu Jumei et al. [6] found that Acorus tatarinowii and α-asarone can improve learning and memory in fatigued exercising rats, increase superoxide dismutase (SOD) and nitric oxide synthase (NOS) activity in the hippocampal tissue, as well as neuronal nitric oxide synthase (nNOS) protein expression, and reduce malondialdehyde (MDA) levels. Wu Xiaorong et al. [7] found that total glycosides of Cistanche can mediate specific androgen receptors to enhance synaptic plasticity in prematurely aging mice, thereby improving cognitive dysfunction. Gastrodin can improve learning and memory abilities by reducing hippocampal tumor necrosis factor (TNF-α), interleukin-1β (IL-1β), and levels of P-Tau, Tau, and Aβ proteins in rats [8]. Wang Haoyu et al. [9] found that a medium dose of Ginkgo leaf extract can significantly improve learning and memory in AD mice and reduce the expression levels of Aβ1-42 and phosphorylated tau protein (pT181-tau). Sun Zexuan et al. [10] found that Astragalus-Zhimu can reduce IL-1β, TNF-α, MDA levels, as well as p-JAK2 and p-STAT3 protein expression levels, significantly improving cognitive function in rats with diabetic cognitive dysfunction.

4.2 Traditional Prescriptions

Traditional prescriptions have been proven to be effective in the treatment of MCI. Yiqi Smart Decoction works by reducing inflammation, improving antioxidant capacity, protecting nerve function and improving cerebral blood supply, reducing the level of serum hypersensitive C-reactive protein (hs-CRP) and homocysteine (Hcy) to alleviate the inflammatory response, regulating serum superoxide dismutase (SOD) to improve antioxidant capacity, and regulating the level of neuron-specific enolase (NSE) to protect nerve function and improve cerebral blood supply [11]. The addition and subtraction of Gui Bi Tang and He Xue Fu Zhu Yu Tang significantly improved the scores of the Montreal Cognitive Assessment Scale (MoCA), Rivermead Behavioral Memory Test (RBMT), Activity of Daily Living (ADL), and Connected Test-B (TMT-B) in patients with MCI after cerebral infarction, as well as the scores of 8-hydroxydeoxyguanosine (8-OHDG), MDA, oxidized low-density lipoprotein (ox-LDL), superoxide dismutase (SOD), homocysteine (Hcy), levels of interleukin-8 (IL-8), C-reactive protein (CRP), etc. [12]. After the addition and subtraction of Huanglian Wendan Decoction combined with donepezil in the treatment of MCI patients, the Mini-Intelligence State Examination Scale (MMSE) and MoCA scale scores were significantly improved compared with donepezil alone [13]. For MCI with qi deficiency and blood stasis, Buyang Huanwu Decoction can improve MMSE and MoCA scale scores [14]. Zuo Gui Pill can increase the MMSE and MoCA scale scores of patients with Parkinson's disease MCI, and improve cognitive function by regulating the expression level of the P38 MAPK pathway and p-JNK protein to inhibit the apoptosis of inflammatory factors and nerve cells [15]. Confucius Pillow Zhongdan reduced the levels of IL-1β, interleukin-6 (IL-6), IL-8, and TNF-α in MCI mice, and improved cognition by regulating the NLRP3/Caspase-1 signaling pathway and inhibiting the protein deposition of Aβ [16].

4.3 Modern Empirical Prescriptions

Empirical prescriptions refer to formulas that physicians have developed based on long-term clinical practice combined with the experiences of predecessors, showing good therapeutic effects. The Kidney-Tonifying, Qi-Boosting, and Blood-Activating formula reduces levels of HCY, CRP, IL-6, and NLR in patients with MCI of Qi-deficiency and blood-stasis pattern, and improves MMSE and MoCA scores, thereby enhancing cognitive function by modulating inflammatory responses in MCI patients [17]. For MCI due to kidney-deficiency and blood-stasis pattern, the Kidney- Tonifying and Blood-Activating Decoction improves MMSE and MoCA scores and significantly enhances patients' mental state and cognitive abilities [18]. Sanjiao Yanghua Capsules (Lung-Tonifying, Yang-Warming, and Phlegm-Resolving formula) can protect nerve cells, reduce plasma Aβ1-42, p-Tau, urinary AD7c-NTP levels, and APOE-4 expression, while improving MMSE, MoCA, HDS, MMAS, and WMS scores [19].The Kidney-Tonifying, Spleen-Strengthening, and Blood-Activating formula for patients with type 2 diabetes combined with MCI significantly lowers HbA1c and CRP and increases MoCA scores [20].

4.4 Chinese Patent Medicine

Chinese patent medicines are convenient to take, have clearly defined active ingredients, and offer certain advantages compared to conventional Western medicine treatments. Fufang Congrong Yizhi Capsules can treat MCI by protecting nerves, inhibiting neuroinflammation, and preventing cell apoptosis. They protect neurons by activating the PI3K/AKT signaling pathway, enhance the viability of Aβ25-35-induced damaged PC-12 cells, reduce the secretion of IL-1β, IL-6, and TNF-α in PC-12 cells, and upregulate the Bcl2/Bax ratio to inhibit neuroinflammation and neuronal apoptosis [21]. Shenwu Yizhi Capsules can lower inflammatory factor levels, increase cerebral blood perfusion, and inhibit patients' IL-6, TNF-α, hs-CRP, and Hcy levels, significantly improving MMSE, MoCA, and ADL scale scores [22]. Dengzhan Shengmai Capsules have the effects of benefiting qi and nourishing yin, invigorating blood, and enhancing brain health, and can significantly improve MoCA scores in MCI patients and increase the reversal rate [23].

5. Traditional Chinese Medicine External Treatments

5.1 Traditional Exercise Therapy

Studies have shown that exercise can improve cognition, especially executive function and memory in mild cognitive impairment, independent functioning in mild cognitive impairment and dementia, and mental health in dementia [24]. The mechanism by which exercise improves cognitive function may be related to the fact that exercise stimulates the metabolism of neurotransmitters, neuronutrients, and endocrine hormones, promotes the regeneration of cerebral blood vessels, and increases the volume of gray matter in the brain [25]. Baduanjin is a traditional Chinese health exercise. Studies have shown that Baduanjin can improve overall cognitive function, memory, and executive ability in older adults with mild cognitive impairment. Tao et al. [26] also found that 24 weeks of continuous Baduanjin exercise significantly improved cognitive function, regulating regional fluctuations and gray matter volume in the hippocampus and anterior cingulate cortex. Tai Chi is another traditional Chinese health exercise. Studies have shown that older adults experience increased volume in cerebral cortical gray matter, improved neural activity and uniformity, and increased neural connections in different brain regions, including the frontal, temporal and occipital, cerebellum, and thalamus [27]. In addition to Baduanjin and Tai Chi, other traditional Chinese sports such as Yi Jin Jing and Wuqin Xi have also improved cognitive function to a certain extent. Li Shaohua [28] found that after 40 sessions of the Five Birds Opera exercise, the Montreal cognitive score of the elderly was significantly increased. All of the above suggest that traditional Chinese exercise may have positive benefits for improving overall cognitive function and memory in older adults with mild cognitive impairment.

5.2 Moxibustion Treatment

Moxibustion treatment is a therapy that uses the heat generated by burning dried wormwood to stimulate one or more related acupuncture points. In recent years, several studies have shown that moxibustion can improve cognitive impairment. Moxibustion improves cognitive impairment. Its mechanisms [29] may include inhibition of oxidative stress and apoptosis, regulation of inflammation and Aβ production, enhancement of vascular endothelial growth factor activity, and metabolites that modulate tricarboxylic acid cycling and fatty acid metabolism. Mai et al. [30]used H-MRS to detect the effects of moxibustion and donepezil on the metabolism of the hippocampus and bilateral posterior cingulate gyrus in patients with MCI and normal controls, and found that the ratio of bilateral hippocampal and bilateral posterior cingulate gyrus in the acupoint group and drug group increased after 2 months of treatment, and observed that moxibustion regulated the abnormal levels of N-acetylaspartate/total creatinine in the bilateral posterior cingulate gyrus and was comparable to that of donepezil. Wang Xuewei [31] found that the cognitive function and complex daily living skills of MCI patients were significantly improved compared with before treatment, and speculated that the mechanism of MCI cognitive improvement may be related to the reduction of plasma Hcy and the reduction of oxidative stress damage to protect brain neurons. Patients were randomly divided into moxibustion treatment group and placebo moxibustion group, and memory function was assessed separately by RBMT and working memory by N-back task. After treatment, the RBMT score of the treatment group changed significantly compared with the placebo group. After moxibustion intervention, the posterior cingulate gyrus, posterior central gyrus, upper temporal gyrus, lingual gyrus, thalamus, etc. were significantly activated, and the changes in N-back score were related to the posterior cingulate gyrus and lingual gyrus, and the RBMT score was correlated with changes in the upper temporal gyrus, posterior central gyrus, and thalamus. Moxibustion may be associated with activating relevant brain regions to improve memory function [32].

5.3 Acupuncture Treatment

Acupuncture is a therapeutic method that regulates physiological functions by stimulating specific acupoints. The mechanism by which acupuncture improves cognitive impairment [33] may be related to the downregulation of Aβ accumulation and tau protein phosphorylation, reduction of neuroinflammation and neuronal apoptosis, improvement of mitochondrial activity, and enhancement of synaptic plasticity. Yin et al. [34], through a ReHo-based meta-analysis, found that after acupuncture treatment for MCI patients, brain regions involved in cognition, emotion, and decision-making showed increased activity, including the right insula, left cingulate gyrus/paracentral lobule, right thalamus, right middle frontal gyrus, right medial cingulate gyrus/parietal gyrus, and right middle temporal gyrus. This partly confirms the regulatory effect of acupuncture on the brain regions of MCI patients. Shi Zongyan [35] found that the Tiaoshen Yizhi acupuncture method can improve MMSE scores and the levels of serum γ-aminobutyric acid (GABA) and serum Tau, thereby improving cognitive function, and speculated that its mechanism may be related to increased serum GABA levels and decreased Tau levels. Li Yu [36] found that electroacupuncture at Baihui and Zusanli can effectively enhance learning and memory abilities in SAMP8 mice, reduce IL-1β, IL-6, IL-18, and TNF-α levels in the serum of MCI mice, and suggested that its mechanism for improving cognitive impairment may involve inhibiting the NLRP3/ Caspase-1 pathway-mediated inflammatory responses, thereby preventing apoptosis of hippocampal neurons. Luo Jianchang et al. [37] found that Xiangba acupuncture can accelerate vertebrobasilar artery blood flow, improve cerebral blood supply, and thus enhance cognitive function. Yao Qingping et al. [38] used acupuncture at the Sishencong points combined with donepezil hydrochloride to treat subcortical arteriosclerotic encephalopathy MCI. The control group received oral donepezil hydrochloride, and after 60 days, The treatment group showed significantly better MMSE and ADL scores than the control group.

5.4 Other Therapies

Auricular therapy is a traditional Chinese medicine method that uses the ear to diagnose and treat diseases. Studies have found that techniques such as ear seed pressing and auricular acupuncture can improve cognitive impairment to some extent. Ear seed pressing is a TCM therapy that involves pressing seeds, such as Vaccaria seeds, on specific points of the ear. Zhao Lingfei [39] used ear seed pressing combined with rehabilitation training to treat elderly patients with mild cognitive impairment. After four weeks, patients showed varying degrees of improvement in MMSE, RAVLT, and TMT scores. Acupoint massage is a treatment method that

uses specific techniques to stimulate corresponding acupoints. Liu Xuezhen et al. [40] conducted a 6-month intervention involving head acupoint massage combined with ear exercises in 40 elderly patients with mild cognitive impairment and found that patients had significant improvements in MMSE, MoCA, activities of daily living (Barthel Index), and the Quality of Life in Alzheimer's Disease scale (QOL-AD), effectively enhancing their cognitive abilities, daily living skills, and quality of life.

6. Conclusion

With the increasing attention to mild cognitive impairment (MCI), traditional Chinese medicine (TCM) has certain advantages in the treatment of MCI due to its holistic regulation, syndrome differentiation and treatment, and multi-target effects. The adjustment of herbal decoctions can more effectively address specific symptoms, and patent Chinese medicines are convenient for oral administration. TCM external therapies, such as acupuncture, moxibustion, and traditional exercises, are easy to perform, economical, safe, and have minimal side effects. Moreover, combining multiple TCM treatments in clinical practice can enhance efficacy.

Although TCM has shown significant effects in treating MCI, there are some shortcomings: (1) Many clinical studies on TCM treatments for MCI have a small sample size, lacking multi-center, large-sample clinical trials to verify their exact efficacy; (2) Although there has been some research on the mechanisms of TCM, how it works at the cellular and molecular levels, and its relationship with neurotransmitters and brain metabolism, remains unclear; (3) Different practitioners have certain variations in syndrome differentiation, formula selection, acupuncture points, and prescriptions for MCI, making it difficult to form a unified standard.

Therefore, future research should focus on: (1) Conducting high-quality, multi-center, large-sample, randomized controlled trials to fully verify the exact efficacy of TCM treatments; (2) Combining modern medical imaging, molecular biology, genetic testing, and other technologies to more accurately evaluate the efficacy of TCM, further clarify its mechanisms, and promote more scientific treatment approaches; (3) Organizing authoritative experts in the field to establish uniform syndrome types and treatment methods based on patients' constitutions and symptoms, improving targeted treatment and providing better guidance for clinical practice.

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