

To Explore the Research Progress of Traditional Chinese Medicine on the Pathogenesis of Alzheimer's Disease

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Abstract: *Alzheimer's disease, as the most common type of dementia, has become an important public health problem due to the lack of effective diagnosis and treatment measures. Traditional Chinese medicine has outstanding advantages in the prevention and treatment of AD. This article will summarize the pathogenesis and treatment methods of AD in traditional Chinese medicine, in order to provide help for further clinical prevention and treatment of AD.*

Keywords: Alzheimer's disease, Pathogenesis of traditional Chinese medicine, Treatment methods.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease of the central nervous system (CNS) characterized by gradual decline of cognitive function [1]. Currently, there are approximately 50 million AD patients worldwide, and this number is expected to double every 5 years, reaching 152 million by 2050 [2]. Its incidence increases with age, with about 5%-8% of people over the age of 65 affected, and this number increases to 25%-50% with age [3]. According to the World Health Statistics Report 2021 released by WHO, Alzheimer's disease and other forms of dementia rank eighth among the top 10 causes of death worldwide [4]. Moreover, it is accompanied by progressive memory loss, behavioral changes and other characteristics. In addition to severe cognitive dysfunction, moderate to severe AD patients are often accompanied by mental symptoms, such as apathy, irritability, hallucinations, delusions and other symptoms [5], which will seriously affect the quality of life of patients, lead to increased medical costs, and create a heavy burden on the family economy of patients. Traditional Chinese medicine believes that the pathogenesis of AD is mainly spleen and kidney deficiency, blood stasis and phlegm obstruction. Combined with the pathogenesis of traditional Chinese medicine, TCM compounds have the advantages of multi-component, multi-target and multi-channel comprehensive regulation in the prevention and treatment of AD. Through the combination of syndrome differentiation and disease differentiation, it has remarkable effect in the prevention and treatment of AD. This review will discuss the research progress on the pathogenesis of Alzheimer's disease from the perspective of TCM.

2. Pathogenesis of AD in Traditional Chinese Medicine

2.1 Go Back to the Source

There is no specific name of "Alzheimer's disease" in traditional Chinese medicine, but according to its symptoms, it can be summarized in the categories of "dementia", "dumb disease", "forgetfulness" and "amnesia". The name "dementia" first appeared in the Tang Dynasty Sun Simiao's

"The Secret Legend of Hua Tuo's Divine Doctor, Hua Tuo's Divine Prescription for Treating Dementia". The Ming Dynasty Zhang Jingyue's "Jingyue Complete Book" recorded "gradually causing dementia." It is pointed out that the onset symptoms of dementia are gradual [6]. In the Qing Dynasty, Zhu Shijin's "One can see Medicine" said: "People who do not know personnel and act out of order are called crazy; Those who do not speak, but sit and meditate, are called dumber." Contemporary Wang Qingyuan "Medical prescription brief" said: "dementia, no knowledge also." The corresponding symptoms were discussed [7]. The doctors of the past dynasties have formed a complete system of syndrome differentiation and treatment through the investigation of the etiology, pathogenesis and corresponding treatment of dementia. On this basis, through the observation and study of the corresponding clinical symptoms and signs, modern doctors believe that AD is mostly due to unclean diet, excessive fatigue, emotional and internal injury, etc., coupled with aging, spleen and kidney deficiency, Qi and blood body fluid and other fine substances, Qi deficiency and blood stagnation, and blood stasis caused by time, resulting in the failure of Qi and blood fine to rise to the top of the brain, the loss of marrow sea, and the loss of spiritual machinery. The disease is located in the brain, the basic pathogenesis is mainly spleen and kidney deficiency, blood stasis and phlegm obstruction.

2.2 Spleen Loss of Health Transport, Lack of Qi and Blood Source

The spleen and stomach is the foundation of the acquired nature, which is the basic place for the formation and transportation of human body substances such as water and grain, Qi, blood and body fluid. Chen Wuzhe, "Three causes of the pole and one disease Syndrome Prescription: Forgetfulness Syndrome Treatment", said: "When the spleen suffers from disease today, the mind is not clear, the mind is restless, so that people are forgetful and do their best to think about it." [8] The function of the viscera in the elderly is weakened, the spleen and stomach transport is unbalanced, and it is easy to cause stupidity, mainly for the following reasons: First, the spleen is the source of Qi and blood biochemistry. "Ling Shu · Pingren Yu Gu" cloud: "God, the

essence of water and valley is also", "the body fluid of five grains, and harmony as the paste, infiltrated into the bone empty, tonifying the brain, and flowing down the Yin stock" [9]. Spleen transport is lost, then the water valley can not honor in the brain, brain orifice loss. Second, the spleen is the main transport of body fluid metabolism. "The spleen is a solitary viscera, and the central soil is filled four along." The spleen is not healthy, then the water and liquid metabolism is lost, the water and wet stop, breeding phlegm turbidity, and the upper Mengqing orifice. "*Jing Yue Shu · Sputum Drink*" put forward: "the five viscera disease, although all can produce sputum, but all by the spleen and kidney", the five viscera can produce sputum, but "the spleen is the source of sputum." Third, mood failure, improper diet, damage to the spleen and stomach and cause dementia. For example, "*Yan's prescription for health, palpitation, palpitation forgetful door*" said: "The husband forgetful, often like to forget. Cover spleen idea and thought, excessive thinking, meaning is not clear, Jingong is not working, making people forgetful" [10]. Joy, anger, worry, thinking, sadness, fear, panic too much can lead to zang-fu qi Yin and Yang imbalance, rise and fall disorder, Qi machinery reverse disorder, disturb the gods, and cause dementia. "*Syndrome Dialectical Record · Volume 4*" believes that numbness "about its beginning, from the depression of liver qi", Ye Tianshi also pointed out that "God's numbness, obtained from the depression of anger" [11], "*Yellow Emperor's Internal Meridian Question*" pointed out that "blood qi, easy to forget" all pointed out that the patient's normal seven emotions are too much, which can lead to the reversal of Qi and blood, liver-yang hyperactivity, disrupt the spirit machine, easy to cause dementia [12]. "*Plain Question · Six Sections of Tibetan Image*" cloud: "Five taste entrance, hidden in the stomach, taste is hidden, to nourish the five Qi, Qi and life, body fluid, God is self-security", "*Plain Question · Five viscera Other*": "The stomach is the sea of water valley, the great source of the six fu-organs, five taste entrance hidden in the stomach, to nourish the five viscera Qi" [13]. The food enters the stomach and intestines, and is transported upward to the spleen, through the transfer of the temper, the heart and lung, the qi and blood, the whole body and the limbs are dispersed, and the limbs are irrigated to achieve the dynamic balance of "Yin Pingyang secret, spirit and even".

2.3 Kidney Essence Deficiency, Marrow Sea Loss

The kidney is the congenital base, the main stinging, storing essence, main will, its physiological function runs through the whole process of body growth, development, aging. The Yin and Yang of the main body are the root of the five viscera. "Lingshu · Benzang": "Kidney essence is insufficient, then the ambition is weak, can not pass on the heart, so confused good forget also. "Kidney qi is damaged, kidney does not store essence, and the imbalance of Yin and Yang in the body will affect the body function and lead to dementia [14]. There are mainly three aspects: First, if kidney essence deficiency, it is easy to cause dementia." Medical Xinwu" cloud: "kidney rules wisdom, kidney deficiency is lack of wisdom, so I like to forget its preface" [15]. Ming Dynasty Wanquan "Wanshi female branch": "the mother injury is easy to fall, her son injury is dirty qi discord, disease more than Yi. "Blindness, deafness, dumb, dementia, epilepsy, are all due to the wrong causes." It shows that the kidney contains the innate

essence, the first nature receives the wrong qi, and the kidney essence is insufficient, which is prone to dementia [16]. "Lingshu · Tiannian": "At the age of 60, the heart qi begins to fail, suffering sorrow...Eighty years old, lung qi failure, soul away, so the words are good and wrong...One hundred years old, the five viscera are deficient, and the air is gone", stating that dementia in the elderly is mostly caused by old age and weakness, the five viscera deficiency, and the kidney essence deficiency, and the marrow sea loss [17]. Second, kidney main bone, marrow, brain." Class Classics" cloud: "Where the bone has marrow, but the brain is the largest, the marrow belongs to the brain, the kidney stores essence, and the refined marrow passes in. Brain, brain is the sea of marrow, kidney essence deficiency, brain marrow is not full, and stay for a long time", kidney main bone marrow, kidney essence deficiency, brain marrow emptiness, can not nourish the brain and dementia [18]. Wang Qingren discussed in the "Medical forest correction": "The memory in the brain...Into the pulp, from the backbone up into the brain, the name of the day brain pulp; It is called the sea of marrow...Therefore, children without memory, the brain is not full; High years without memory, brain gradually empty. "It shows that the function of viscera in the elderly is weakened, pulp production is insufficient, the pulp sea is empty, and gradually dementia [19]. Three, kidney main Zhi."Lingshu Ben Zang" said: "The mind, so the spirit, to receive the soul, cold and warm, and moody people also...When the will and intention are in harmony, the spirit is straight, the soul is not scattered, the regrets and anger are not allowed, and the five Zang are not subject to evil."Zhiyi regulates the human body's spirit and controls psychological activities. When Zhiyi and the body are in harmony, the liver Qi is sparse, the body is in balance with Yin and Yang, and the resistance to evil qi is strong [20]. "Ling Shu · This God": "The kidney is angry and not only hurt the will, the will is happy to forget its preface. "It is clearly pointed out that zhi injury can lead to the symptoms of "happy amnesia" [21].

2.4 Qi Deficiency and Blood Stagnation, Blood Stasis Blocking Brain Collaterals

"Lingshu · Pingren Jigu" cloud: "The five viscera are stable, blood and interest, and the spirit is in" shows that the five viscera function is coordinated, the human body is full of Qi and blood, and the viscera tissues can be nourished [22], then the God is calm, energetic, and agile. In Article 237 of Treatises on Febrility, "This has a long history of blood stasis, so it is pleasant to forget. "Blockage of blood stasis can easily cause stupor. Aging body, zangfu function decline, Yingwei disharmony, unfavorable blood, coupled with old diseases for a long time, qi deficiency and blood stagnation, blood stasis blocking the brain and collaterals, prone to AD [14]. "Saint Chi General Record" said, "the disease of forgetfulness, this is due to the deficiency of the heart, less blood and qi, the spirit of dizziness, so the will of turmoil and more forget also. "The aging body becomes weak, the production of qi and blood decreases, and AD is caused by blood stasis due to deficiency [23]. "Qi deficiency is not enough to push blood, then blood must be stasis" "Qi movement is blood, Qi deficiency is blood stagnation", "Blood Syndrome Theory" said: "Qi knot is blood coagulation. "The elderly have been suffering from chronic illness with blood stasis, coupled with the weakness of the body, the gradual decline of the kidney qi, the loss of

harmony of the ying and wei, and eventually the internal stagnation of blood stasis, damage to the brain network, and obstruction of the brain network, resulting in AD[24].

2.5 Phlegm Drink Stops Inside, Blinds Clear Orifice

Phlegm and fluid is a corresponding disease caused by the obstruction of water transport and accumulation in a certain part of the body. It has the characteristics of "with the rise and fall of Qi, both inside and outside the body", the treatment is extensive and varied, so there is the saying that "all diseases are caused by phlegm", easy to block the operation of Qi and blood, blind the orifice and cause dementia. "Shi Shi Secret Record" cloud: "The most abundant sputum potential, the deepest dull qi", "sputum saliva, will be the disease of vitality." AD is caused by Qi deficiency, body fluid metabolism disorder, phlegm turbidities, blocked qi and blood movement, and brain network obstruction [25]. "Danxi heart Law · Forgetfulness" cloud: "Forgetfulness, the spirit is short, there are many phlegm also." Phlegm is easy to cause mental shortness, forgetfulness and gradually lead to AD [26]. Ming Wang Lun "Ming Medicine Miscella" put forward: "The root of phlegm, water also, originated from the kidney; The movement and dampness of phlegm are mainly in the spleen "[13]. "Spleen as the source of phlegm", "lung as the storage of phlegm", "kidney as the source of phlegm" the formation of phlegm and lung, spleen and kidney The three Zang are closely related, if the invasion of external evil, excessive worry and fatigue, diet unclean, etc., lead to the damage of the lung, spleen and kidney three Zang, there will be spleen dysfunction, water and wet internal stop, and the accumulation of phlegm; Lung Xuanfa Su down disorder, body fluid condensed into sputum;" Kidney is the water viscera, the main body fluid" the warm transpiration of Yang qi in the kidney dominates the whole body fluid metabolism. If the kidney Yang deficiency, transpiration and gasification is out of order, opening and closing is unfavorable, water and liquid transport is abnormal, water and wet stop, and wet sputum becomes sputum over time. Or life gate fire failure, fire does not produce earth, water back by the spleen, gathered into phlegm.

3. Treatment of AD

3.1 Treatment from Spleen

The dementia caused by the loss of health of the spleen and the lack of qi and blood source can be the method of strengthening the spleen and stomach and supplementing qi and blood. Such as seven Fu drink, Tianwang Buxin Dan, plus or minus dioscorea pills, plus Yi Qi smart soup, spleen soup and so on. Qifu Drink has the effect of invigorating the spleen, calming the mind and invigorating qi and blood. Liu Jiping et al. [27] detected the levels of AGEs, RAGE, NF- κ B and IL-1 β in rat hippocampus by western blot, and found that Qifuyin may play an anti-AD role by inhibiting the activation of AGEs/RAGE/ NF- κ B pathway and reducing inflammation in the brain. Tianwang Buxin Dan has the effect of invigorating qi, invigorating spleen, nourishing blood and calming nerves. Xie Guangjing et al. [28] found that it has antioxidant effects and can play an anti-oxidative stress effect by regulating the expression of Trx system related proteins in SCN, thus playing an effective therapeutic role in the prevention and

treatment of AD.

3.2 Treatment from Kidney

AD caused by kidney essence deficiency and marrow sea loss should be treated by invigorating kidney qi and filling lean marrow. Such as Rehmannia decoction, Liuwei Rehmannia pill, Shenghui decoction, etc. Rehmannia decoction has the effect of nourishing kidney Yin and tonifying kidney Yang. Through Y maze test and transmission electron microscopy, Li Quan et al. [29] observed that Rehmannia decoction can improve the working memory ability of APP/PS1 mice that declines with age, inhibit the apoptosis of nerve cells, and improve the morphological structure of mitochondria. Liuwei Dihuang pill has the effect of filling essence, nourishing Yin and tonifying kidney. Through experimental studies, Yuan Yong et al. [30] found that Liuwei Dihuang Pill can regulate the expression levels of FoxO3a and p-FoxO3a in cells, affect the expression of downstream genes, and then regulate the antioxidant and anti-apoptotic factors in cells, promote cell proliferation, and protect the nerve cell damage caused by A β , so as to realize the prevention and treatment of AD.

3.3 Treatment from Silt

In view of AD caused by Qi deficiency and blood stagnation and blood stasis, it is easy to use the method of activating blood stasis and activating brain. Such as Tongqiao blood activating decoction, buyang also five decoction, Naoxintong capsule and so on. Buyang Huowu Decoction has the effect of invigorating qi, activating blood and clearing collaterals. Xue Hui et al. [31] found through network pharmacological studies that Buyang Huanwu Decoction regulates biological processes such as proteolysis, protein phosphorylation, estrogen response and hypoxia response by acting on corresponding targets, inhibits the generation of A β , reduces neuronal inflammatory response and nerve cell apoptosis, and reduces cholinesterase activity, so as to achieve the purpose of treating AD patients. Zhang Wenhua et al. [32] found through clinical comparative observation experiments that Tongqihuoxuet combined with Western medicine had significant curative effect on mental and behavioral symptoms of Alzheimer's disease and had clinical promotion value.

3.4 Treatment from Phlegm

In view of the dementia caused by the internal stopping of phlegm and the blinding of clear orifice, the basic treatment methods can be dispelling dampness and eliminating phlegm and awakening the brain. "To treat stupidity without any method, to treat phlegm is to treat stupidity also" such as cleaning phlegm soup, happy powder, Banxia Baizhu Tianma soup, turn stupidity soup, warm gall soup, etc. Distan decoction has the effect of removing dampness and clearing phlegm to wake up the brain. Tang Ying [33] divided 98 clinical patients into control group (nepezil) and observation group (Donepezil + Distan Decoction) for 6 months to observe the clinical efficacy, and the results showed that there was no significant difference in MMSE and BI scores between the two groups before treatment ($P>0.05$). After treatment, the scores of the observation group were significantly higher than those of the control group, while TESS scores at different stages were lower than those of the

control group ($P < 0.05$). The results indicated that Donepezil combined with Ditan Decoction could effectively improve the mental state of patients with AD, with high safety, and could promote the improvement of patients' quality of life. Xingxin Powder has the function of diuresis and turbid, invigorating qi and calming. Zhang Jie et al. [34] summarized relevant literature and concluded that Xingxin Powder has functions of protecting neurons, anti-oxidative stress, inhibiting pro-inflammatory factors, regulating cholinergic system, etc. Therefore, clinical application of Xingxin Powder plays an important role in the prevention and treatment of AD.

4. Deficiencies and Prospects

This paper mainly discusses the basic pathogenesis of AD from the three aspects of asthenia, phlegm and stasis. The pathogenesis of AD also includes congenital deficiency, emotional internal injury and other aspects, which should be considered as a whole in clinical application. At present, the main research on the treatment of AD in traditional Chinese medicine is mainly aimed at the mechanism of action of traditional Chinese medicine and the clinical observation of the combination of traditional Chinese medicine and Western medicine. Clinical diseases are complex and changeable, so can we take into account the secondary pathogenesis on the basis of the main pathogenesis? For example, for the dementia caused by the loss of health of the spleen and the lack of qi and blood source, can we take into account the tonifying of the kidney in the treatment of strengthening the spleen and stomach, supplementing the qi and nourishing the blood, or can we take into account the prevention of removing blood stasis and resolving phlegm? In view of the dementia caused by Qi deficiency and blood stagnation and brain stasis, can we give consideration to tonifying spleen and kidney and eliminating phlegm at the same time when promoting blood circulation and removing blood stasis and awakening brain? In view of the dementia caused by the internal stop of phlegm and the blinding of clear orifice, can the therapist give consideration to tonifying the spleen, tonifying the kidney and removing blood stasis? These problems need to be confirmed by further research in order to provide help for the treatment of AD.

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