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### **Review Article**

# How does traditional chinese medicine treat attention deficit hyperactivity disorder-A different understanding and treatment strategy

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### Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder, and the incidence in children is increasing year by year. The modern medical field lacks long-acting drugs for the treatment of ADHD and there is an urgent need to investigate new therapeutic drugs or complementary and alternative therapies. Recent studies have found that Traditional Chinese Medicine (TCM) has the advantages of individualization, precise efficacy and minimal side effects in improving attention deficit hyperactivity disorder. This paper reviews the progress of Chinese medicine in the treatment of ADHD in terms of its understanding of the etiology and pathogenesis of ADHD, treatment according to pattern identification and Chinese medicinal preparations.

### Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder in childhood. The core symptoms are attention deficit, hyperactivity and impulsivity. According to the Diagnostic and Statistical Manual of Mental Disorders (5<sup>th</sup> Edition), it can be divided into three subtypes: inattention (inability to maintain attention), hyperactivity (excessive exercise, unsuitable for the environment) and impulsivity (hasty behavior without thinking) [1]. The global prevalence rate of ADHD children is about 7.5%, even up to 8.7%~15.5% in some regions, the prevalence rate of boys is higher than that of girls, and about half of them can be affected into adulthood and with the social development and lifestyle changes, the prevalence rate is on the rise, the development of ADHD has a certain burden for children, parents, families, and society [1,2]. The etiology and pathogenesis of ADHD are still unclear. While ADHD has a strong neurobiological and genetic basis is beyond dispute, there's still a lack of clear biomarkers and other objective indicators [3]. Therefore,

in terms of treatment, there is a lack of long-acting drugs for ADHD in modern medicine and clinical research on new drugs for ADHD has been ongoing [4]. Neuroleptic stimulants such as methylphenidate, atomoxetine and amphetamine are commonly used in clinical practice at present, with obvious adverse reactions. In recent years, nutrients and probiotics have become new targets for children's ADHD treatment research [5]. For Western medicine, built on the overall concept, the diagnosis and treatment of ADHD in Traditional Chinese Medicine (TCM) mainly relies on "look, listen, question and feel the pulse", followed by syndrome differentiation and treatment. According to different syndrome types, appropriate Chinese medicine is used to balance the "qi, blood, yin and yang" of the organs, making the diagnosis and treatment of ADHD more individualized, with stable efficacy and relatively few adverse reactions.

#### **Disease name of ADHD in TCM**

There's no special and unmistakable record of ADHD in the medical books of the past dynasties. The disorder is roughly

013

considered as "hysteria", "amnesia" or "manic and depressive psychosis" and so on, depending on its symptoms and clinical characteristics. These diseases are similar to ADHD in either pathogenesis or symptoms of TCM. However, the environment, fertility and diet now were different from ancient times. Therefore, ADHD should have a new name for TCM to adapt to the changes of the time. Modern Chinese medicine recognizes that ADHD is called child hyperactivity disorder [6].

## Understanding of TCM on etiology and pathogenesis of ADHD

The modern medical pathogenesis of ADHD is still unclear, and it is generally believed that it may be a syndrome caused by a combination of biopsychosocial factors [7]. Recent studies have mostly investigated the pathological mechanisms of ADHD from the perspectives of structural and functional brain abnormalities and genetic variants [8]. According to Chinese medicine, the cause of ADHD is constitutional insufficiency or improper nursing leads to dysfunction of viscera and disharmony of Yin and Yang, and its main pathological changes are heart, liver, spleen and kidney [6]. Different physicians have different emphases on the etiology and pathogenesis of this disease.

Constitutional insufficiency and loss of nourishment of viscera: Traditional Chinese physicians mostly treated ADHD from deficiency before the 20th century. They thought that most of these children have weak constitutions and thin bodies and believed that the basic pathogenesis of ADHD was short of essence and blood and was imbalanced between Yin and Yang [9]. Wang [10] discussed the pathological mechanism of ADHD from the perspective of the heart-kidney-brain. He considered that deficiency of kidney essence, and loss of brain marrow are the key pathogenesis of ADHD. According to the physiological characteristics of the "kidney is often vacuous" in children and the close relations among kidney, marrow, essence and brain, Ma and Zhang [11] put forward the hypothesis of pathomechanism that the sea of marrow growth delay caused ADHD. The insufficiency of kidney essence, growth delay of the sea of marrow and disharmony of Yin and Yang (Yang superabundant and Yin insufficient) are the keys to the pathomechanism of ADHD. LI, et al. [12] also advocated the treatment of ADHD from the "kidney", believing that ADHD is located in the brain, and the core pathogenesis is kidney deficiency, brain marrow deficiency and underdevelopment.

**Improper nursing and viscera imbalance:** Children's internal organs are delicate, and their form and Qi are not full, which is easy to leads to ADHD. According to the physiological characteristics of "Heart is often in superabundance" and "Liver is often in superabundance" in children, Han [13] considered that children's heart fire is easy to be hyperactive, gallbladder fire is easy to be effulgent, which disturbed heart spirit and consumed Yin fluid and finally formed Yang hyperactivity, Yin deficiency, disharmony of Yin and Yang, and loss of mind. Shao, Wang, and Wang [14] also advocated the treatment of ADHD from the heart, believing that ADHD is due to children's exuberant Qi, hyperactivity and restlessness.

Starting from the physiological characteristics of "Three types of Qi is in superabundance and fours are in deficiency" in children and combining with the theory of "combination of phlegm retention and stagnated blood", Feng, Wang and Ren [15] advocated starting with phlegm retention and stagnated blood to summarize the pathogenesis of ADHD as follows: heart desires tranquilization but fire does not extinguish, orifices desire but phlegm retention does not go away, intelligence desires cleverness but blood does not nourish, thought desires wisdom but essence does not work, conduct examination but blood stasis does not disperse. According to the TCM theory of "Yin and Yang balance each other, and spirit will work well" in the Internal Classic of Huangdi's Canon of Medicine, Liu, et al. [16] attributed the cause of disease to Qi and Yin from the perspective of Qi, blood and normal body fluid, thinking that the five internal organs are often deficient: spleen, lung, and kidney are deficient of Qi, heart, and liver are deficient of Yin, so ADHD is treated from Qi and Yin deficiency theory. Chang [17] believed that the etiology and pathogenesis of ADHD are mainly related to heart fire, liver fire, phlegm retention and heat, deficiency of the liver and kidney, and weakness of the heart and spleen, which can be summarized as "wind, fire, phlegm retention, blood stasis, and deficiency". Du, Wei and Wang [18] believed that ADHD is present in the liver and spleen, mainly from spleen deficiency and liver exuberance, wind, and phlegm disturbance so as to treat the root.

## Treatment of ADHD according to pattern identification in TCM

Treatment for the liver and kidney: Zhang, et al. [19] reported that Prof. XUAN Guiqi has treated ADHD considering kidney deficiency and liver exuberance as the principal etiology and pathogenesis. She considered that the treatment of ADHD should start by regulating the liver and kidney Yin and Yang, and focus on benefiting the kidney to open the orifice, which is supplemented by calming the mind and clearing heat and phlegm, and eliminating stasis. So she formulated her own decoction called Xuanshi Guining Tang(formed by Radix Polygoni Multiflori, Fructus Alpinae Oxyphyllae, Carapax et Plastrum Testudinis, Os Draconis, Radix Curcumae, Rhizoma Acori Graminei, Radix Paeoniae Alba and Poria, etc.), which can supplement the Qi of liver and kidney, nourish Yin and Yang, open the orifices and arouse the spirit, being effective in treatment. Zhang, Qin, Ouyang, Zhang and Ouyang [20] studied 29 children with ADHD with a pattern of kidney vacuity and liver depression treated with Ningxin Tang (formed by Rhizoma Anemarrhenae, Radix Rehmanniae Preparata, Corni Fructus, Rhizoma Dioscoreae, Poria, Cortex Moutan, Concha Margaritifera, Radix Ophiopogonis, Concha Haliotidis, and Ramulus Uncariae cum Uncis, etc.) combining auricular pressure pills, have compared with Ritalin for 8 weeks. The results showed that the total effective rate of the treatment group was 62.07% and the control group was 51.72%, which the two groups were comparable, while the improvement of the TCM symptoms in the treatment group was significantly better than that in the control group (p < 0.05). Fan, Zhang, Tian and Zhang [21] reported that Prof. Xilian ZHANG emphasized that ADHD is attributable to root vacuity and tip repletion.

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She treated by boosting the kidney and replenishing essence, calming the liver and subduing the Yang with Kongsheng-Zhenzhong Tang (formed by Carapax et Plastrum Testudinis, Os Draconis, Rhizoma Acori Tatarinowii and Rodix Polygalae) which can supplement the kidney, replenish the essence and calm the mind, having a good effect.

Treatment from the liver and spleen: Li and Chang [22] advocated using Siwu Tang and Si-junzi Tang in the treatment of ADHD because the "liver is in superabundance and spleen is in insufficient" in children. Siwu Tang is able to nourish liver blood to alleviate Yin vacuity stirring wind or liver-Yang hyperactivity caused by liver-Yin deficiency. Sijunzi Tang can strengthen the spleen Qi enough to prevent the liver from damaging the spleen and stomach. And Radix Asparagi, Radix Ophiopogonis, Radix Adenophorae and Radix Glehniae can strengthen the power of nourishing Yin, so as to ease the dysphoria, which is clinically effective. Yang, et al. [23] reported that Prof. ZHOU Zheng based on the theory of the Five Elements and Viscera-State, treating ADHD from the liver and spleen, and formulated Chaishao Zhidong Tang (formed by Radix Bupleuri, Radix Paeoniae Alba, Rructus Aurantii, Radix Pseudostellariae, Poria, Radix Angelicae Sinensis, Semen Ziziphi Spinosae, Rhizoma Atractylodis Macrocephalae and Arillus Longan, etc.) to treat 40 ADHD children with spleen deficiency and liver hyperactivity, comparing with methylphenidate hydrochloride extended-release for 12 weeks. The test group was significantly better than the control group in terms of improvement (p < 0.05).

Treatment from the heart and liver: Gao and Han [24] reported that Prof. Han Xinmin believed that currently most ADHD is due to heart-liver fire, and the treatment should be based on clearing the heart fire, calming the liver, quieting the heart and opening the orifices by transforming phlegm. Prof. Han Xinmin formulated An-Shen-Ding-Zhi-Ling (formed by Bupleurum, Scutellariae Radix, Acorus calamus, Polygala tenuifolia, Fructus Forsythia, Radix Curcumae, Radix Angelicae Sinensis, Semen Cassiae, concretio silicea bambusae and Uncaria, etc.) to treat ADHD of effulgent heart-liver fire being effective. Ding, Ye and Lu [25] reported that Prof. Xiafang WANG based on the theory of "heart and liver are often in superabundance" in children, formulating Xiexin-ningshen Tang(formed by Rhizoma Coptidis, Rhizoma Pinelliae, Scutellariae Radix, Rhizoma Acori Graminei, Cortex et Radix Polygalae, Bulbus Lilii, Radix Rehmanniae, Fructus Tribuli, Folium Bambusae, and Os Draconis, etc.) treated 72 children with ADHD of effulgent heart-liver fire, while the control group was treated with methylphenidate hydrochloride extended-release for 12 weeks. The results showed that the treatment group was better than the control group in terms of improvement of the TCM symptoms (p < 0.05).

**Treatment from the heart and spleen:** Based on the "heart governs the spirit light" and "spleen governs the mind", Zhang [26] thought that a disquieted heart spirit and confused mind are important pathogenesis of ADHD in children. 20 children with ADHD were treated with Shenwei-anshen Tang (formed by Radix Astragali, Radix Codonopsis, Fructus Schisandrae Chinensis, Radix Rehmanniae Preparata, Rhizoma Dioscoreae, Poria, Atractylodis Rhizoma, Radix Angelicae Sinensis, Radix Polygalae and Rhizoma Acori Graminei, etc.) combined with Ritalin tablets, and the control group was treated with Ritalin alone for 4 weeks. The results showed that the total effective rate was 90.0% in the treatment group and 75.0% in the control group, which difference was statistically significant (p < 0.05) and the efficacy of the treatment group was significantly better than that of the control group. Zhang [27] reported the treatment of 40 children with ADHD of heart-spleen deficiency type using Guipi Tang (formed by Rhizoma Atractylodis Macrocephalae, Os Draconis, Poria, Radix Codonopsis, Radix Astragali, Radix Angelicae Sinensis, Arillus longan, Rhizoma Acori Graminei, and Radix Polygalae, etc.) with Tomoxetine Hydrochloride as the control group for 60 days. The results showed that the total effective rate was 92.50% in the treatment group and 72.50% in the control group, and the total effective rate of the treatment group was significantly higher than that of the control group (p < 0.05).

Treatment from wind, phlegm and fire: Jiang reported that Prof. Shen HUANG believed that the manifestation of ADHD can be classified as "mania" and "all mania and madness are fire". The fire has two types: phlegm-heat real fire treated by Wendan Tang and liver-wood stagnant fire treated with Zhengan-Xifeng Tang. If the fire is quenched, the mind will be at ease and ADHD will be relieved. Zou reported 40 ADHD children with treated with Duodongting Tang (formed by Flos Magnoliae, Rhizoma Gastrodiae, parched Radix Paeoniae Alba, Radix Scrophulariae, Carapax Trionycis, Radix Isatidis, Fructus Psoraleae and Alismatis Rhizoma, etc.) formulated by coursing and dissipating external wind and extinguishing internal wind, while with Ritalin as the control group for 2 months. The results showed that the total effective rate was 92.50% in the treatment group and 82.05% in the control group, and the difference between the two groups was statistically significant (p < 0.05), showing that the efficacy of Duodongting Tang was significant.

#### Chinese medicine preparation for ADHD

Compared with traditional Chinese medicine decoction, Chinese medicine preparation is more convenient to carry, with higher compliance and controllable dose and effect. A large number of related studies have proved that traditional Chinese medicine has a definite curative effect on ADHD and has definite advantages in improving core symptoms and reducing adverse reactions. At present, Chinese traditional medicine preparations specially employed to treat ADHD mainly include Jingling Oral Liquid, Xiaoer-zhili Syrup, Xiaoer-huanglong Granule, Longmu-qingxin Mixture and Anshen-dingzhiling Granule [28].

**Jingling oral liquid:** Jingling Oral Liquid is made up of Radix Rehmanniae Preparata, Cortex Moutan, Poria, and Radix Polygalae and other traditional Chinese medicines, all of which are used together, having the effects of nourishing Yin, suppressing Yang, tranquilizing the mind and improving intelligence. Hu, et al. [29] used Jingling Oral Liquid to treat 463 children with ADHD. Clinical observation showed that the effective rate was 91.8% and no toxic or side effects were found.

015

Xu and Teng [30] found that Jingling Oral Liquid combined with central nervous system stimulants has a beneficial effect on children with ADHD, which can improve children's behavior and increase the levels of serum dopamine and 25hydroxyvitamin-D3.

**Xiaoer-zhili syrup:** Xiaoer-zhili Syrup is composed of Carapax et Plastrum Testudinis, Os Draconis, Rhizoma Acori Tatarinowii and Rodix Polygalae, etc. It has the effects of nourishing Yin and Yang, inducing resuscitation, and improving intelligence. Clinical studies by Li, et al. [31] showed that the improvement trend of Xiaoer-zhili Syrup on the core symptoms of ADHD in children aged 4 – 6 years is better than that of Jingling Oral Liquid (p < 0.05). Xiaoer-zhili Syrup originated from the classic traditional Chinese medicine prescription "Kongsheng-Zhen Zhong Dan". Xu, et al. [32] found that Kongsheng-zhenzhong Dan may treat ADHD by affecting the DA nerve signal transmission that regulates the central prefrontal cortex-basal ganglia circuit.

Xiaoer-Huang long granule: Xiaoer-huanglong Granule is composed of Radix Rehmanniae Preparata, Radix Paeoniae Alba, Rhizoma Anemarrhenae, Radix Ophiopogonis, Os Draconis preparata, Concha Ostreae preparata, Fructus Schisandrae Chinensis, Radix Codonopsis, Radix Polygalae, Rhizoma Acori Graminei and Radix Platycodi, having the effects of nourishing Yin, suppressing Yang, quieting the spirit and stabilizing the mind. Liu, et al. [33] adopted a multi-center clinical trial design of randomized, double-blind, double-simulation, positive control drug Jingling Oral Liquid, a parallel control, observing 299 ADHD children with Yin vacuity and Yang hyperactivity, which completely met the inclusion criteria. The study found that the total effective rate of the Xiaoer-huanglong Granule group was 83.48%. Qiao, et al. [34] found that the high and middle doses of Xiaoer-huanglong Granule could obviously inhibit the autonomous activities, stereotyped activities, and climbing behaviors of mice induced by APO (p < 0.05, p < 0.01).

Longmu-qingxin mixture: Longmu-qingxin Mixture is composed of Calcined Longmu, Uncaria Uncaria, Caulis Polygoni Multiflori, Jujube, Floating Wheat, Astragalus membranaceus, Angelica sinensis, Concha Margaritifera, Radix Paeoniae Alba, Fructus Schisandrae Chinensis, Cortex Phellodendri, etc. It can nourish the heart, quiet the spirit, subdue Yang and calm the nerves. Zhang and Jiang [35] used Longmu-qingxin Mixture to treat 30 ADHD children with heart-spleen deficiency and liver hyperactivity, and the control rate was 86.67%. The study concluded that Longmu-qingxin Mixture had a better curative effect on ADHD of heart-spleen deficiency and liver hyperactivity than Xiaoer-zhili Syrup. Sun, et al. [36] have shown through animal experiments that a Longmuqingxin Mixture can increase the contents of norepinephrine and dopamine in the brain of mice, that is, cyclic adenosine monophosphate in plasma, and it can enhance memory and immunity.

Anshen-dingzhiling granule: Anshen-dingzhiling Granule is made up of 12 medicines of Bupleuri Radix, Scutellariae Radix, Fructus Forsythia, Radix Curcumae, Rhizoma Acori Graminei, concretio silicea bambusae, Semen Cassiae, Ramulus Uncariae cum uncis, Radix Angelicae Sinensis, Radix Rehmanniae, Fructus Alpinae Oxyphyllae and Radix Polygalae preparata, having the effects of clearing heart, calming liver, eliminating phlegm and inducing resuscitation. Liu, et al. [37] have found that Anshen-dingzhiling Granule can up-regulate the expression levels of DRD1 and DRD2mRNA and protein in the frontal cortex and striatum of SHR rats, indicating that Anshen Dingzhiling plays an important role in regulating the function of the prefrontal-striatum pathway and DRD1 and DRD2 are involved in this regulation process, finally playing a therapeutic role in ADHD.

### Conclusion

In recent years, the incidence rate of ADHD has been rising, which has a great impact on the healthy growth of children themselves and the harmony of their families. Compared with Western medicine, traditional Chinese medicine is more easily accepted by children and their parents because of its definite efficacy, fewer adverse reactions and difficulty in repeating after drug withdrawal. At present, the treatment of doctors mostly starts from the aspects of clearing the heart fire and calming the liver, strengthening the spleen and kidney, extinguishing the wind and resolving phlegm. In addition to Chinese medicine decoction, the types of Chinese medicine preparation are also increasing, with better taste and more convenient use, enriching the clinical means of treating ADHD. However, there are still some shortcomings in clinical research, such as the lack of large samples, multicenter and randomized controlled clinical trials; Safety evaluation is limited to the observation of adverse reactions, and there is a lack of nonclinical safety evaluations such as acute and chronic toxicity studies. If these issues can be resolved as soon as possible, it is believed that traditional Chinese medicine can better play its role and make more progress.

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016

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017