

Research Progress of Traditional Chinese Medicine Treatment of Henoch-schonlein Purpura Nephritis

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Abstract: Henoch-Schonlein purpura nephritis (HSPN) is a common vascular allergic disease, the pathogenesis of this disease is still unclear, If it is not treated in time, it will easily develop into chronic renal failure. At present, there is a wide variety of western medicine treatment drugs, but there is no unified plan. Recent studies have shown that traditional Chinese medicine has a good effect on the treatment of Henoch-Schonlein purpura nephritis. Therefore, the article will review the treatment of Henoch-Schonlein purpura nephritis with Chinese medicine in terms of etiology and pathogenesis, dialectical staging, and prescription and medicine.

1. Background

HSP is the most common systemic small-vessel vasculitis in children. Because numerous systemic small vessels are involved, the multiple manifestations of the disease include nonthrombocytopenic purpuric rash. Henoch-Schönlein purpura (IGAV/HSP) or IgA vasculitis (IgAV) is the most frequent form of vasculitis in childhood, with an annual incidence of 13–20/100000 children under 17 years of age (Fig 1). The European League Against Rheumatism (EULAR), Paediatric Rheumatology International Trials Organization (PRINTO) and Paediatric Rheumatology European Society (PRES) (EULAR/PRI NTO/PRES) defined the criteria for Classification of IgAV/ IGAV/HSP[1] (Tab.1). According to this classification, HSPN is graded as follows: grade I: minimal glomerular abnormalities; grade II: mesangial proliferation without crescents or sclerosing lesions; grade III: focal segmental (IIIa) or diffuse (IIIb) mesangial proliferation with <50% crescents or sclerosing lesions; grade IV: mesangial proliferation with 50%-75% crescents or sclerosing lesions; grade V: mesangial proliferation with >75% crescents or sclerosing lesions; and grade VI: membranoproliferative-like lesions(Fig.2).



Figure 1. Skin lesions in children with Henoch-Schönlein purpura. Petechiae and palpable purpurae are the most common skin lesions (A), but erythematous, macular, urticarial or even bullous rashes (B) are observed occasionally (Department of Nephrology, Children's Hospital, Zhejiang University School of Medicine)

Table 1. The International Study of Kidney Disease in Children (ISKDC) classification of Henoch-Schönlein purpura nephritis (modification according to ref

ISKDC grade	Description
Grade I	Minimal alterations
Grade II	Mesangial proliferation
Grade III	Proliferation or sclerosis with <50% crescents((a)focal or(b)diffuse)
Grade IV	Mesangial proliferation or sclerosis with 50% -75%,crescents((a)focal or(b)diffuse)
Grade V	Mesangial proliferation or sclerosis with >75%,crescents((a)focal or(b)diffuse)
Grade VI	Membranoproliferative like glomerulonephritis

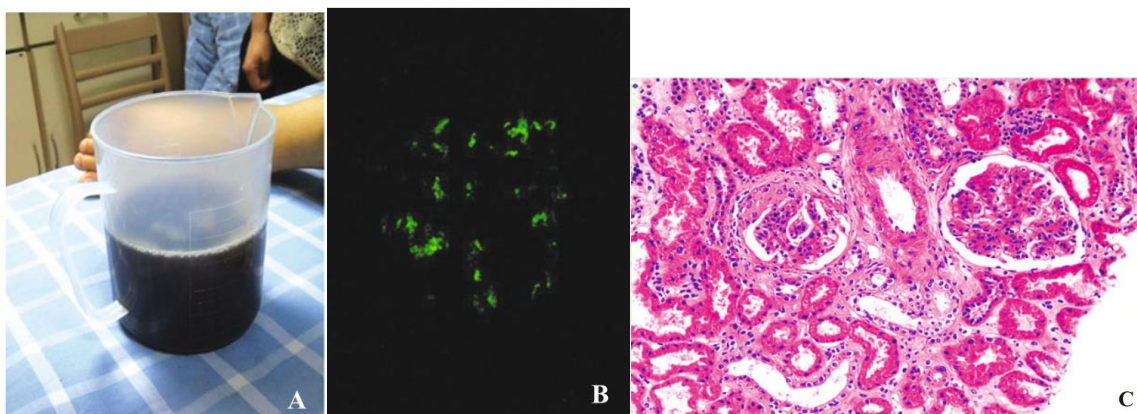


Figure 2. Renal involvement in children with Henoch-Schönlein purpura

A: Gross hematuria; B:Immunohistochemical staining demonstrates the granular deposition of immunoglobulin A in the mesangium of the affected glomerulus (original magnification $\times 200$); C: Mesangial cell proliferation is observed in both glomeruli, and crescent formation is observed in the glomerulus on the left (original magnification $\times 200$) (Department of Nephrology, Children's Hospital, Zhejiang University School of Medicine).

Henoch-Schonlein purpura nephritis (HSPN) is a common clinical renal disease secondary to allergic purpura, the main pathological change is systemic necrotizing small vasculitis, which can involve the skin, gastrointestinal tract, joints and kidneys and other system and organs[2]. A series

of renal involvement manifestations such as urinary protein and urinary occult blood can be seen in clinic. Renal puncture biopsies are dominated by proliferative glomerular tract lesions, often with segmental glomerular capillary collaterals, necrosis, crescent formation, and other vasculitis manifestations[3]. Kidney biopsy is usually performed in patients with uncertain diagnosis and in those with more severe kidney involvement (rapidly progressive nephritis, nephrotic syndrome). In general, there is a correlation between the severity of renal manifestations and findings on kidney biopsy. Light microscopy findings can range from mild mesangial proliferation to severe crescentic glomerulonephritis. Diffuse mesangial IgA deposits seen on immunofluorescence are the hallmark of HSP nephritis and co-deposition of C3 complement (75%) might also be present[1]. Due to the fact that glomerulonephritis is the major cause of mortality and morbidity among children suffering from IGAV/HSP, the prognosis of the disease largely relies on the renal involvement of IGAV/HSP. A kidney biopsy is mandatory for the diagnosis of HSPN. However, its value as a predictor of the outcome depends on many variables, principally on the classification used. Today we use different histological classifications for HSPN, utilized in clinical practice and research studies which are described below (Tab2, Tab3.) The disease is most commonly seen in children and adolescents, but is not uncommon in adults. At present, the pathogenesis is not clear, and its specific mechanism may be related to humoral and cellular immune disorders, inflammatory response, coagulation and fibrinolysis mechanism disorders, and genetic susceptibility [4]. Western medicine often uses anti-infective, anti-allergic, hormone, immunosuppressant and cytotoxic drugs, anticoagulation, application of immunoglobulins and other programs, but the long-term treatment effect is not good, easy to relapse, significant side effects, and bring heavy economic burden to the patient's family. Although the term "allergic purpura nephritis" has not been systematically described in ancient Chinese medicine, the clinical manifestations of this disease (skin petechiae, edema, blood in urine, vomiting blood, etc.) can be classified as "purpura", "hematuria", "chyluria" and "edema" in Chinese medicine, according to the syndrome differentiation of etiology and pathogenesis, a series of treatment methods such as clearing heat, cooling blood and activating blood circulation are put forward, which have unique cognitive and therapeutic advantages for the disease. This paper reviews the literature reports on the treatment of the disease with traditional Chinese medicine in recent years.

Table 2. The Oxford classification of IgA nephropathy

Histological variable	Description
Mesangial hypercellularity	M0 < 50% of glomeruli showing mesangial hypercellularity M1 > 50% of glomeruli showing mesangial hypercellularity
Endocapillary hypercellularity	E0 absent E1 present
Segmental glomerulosclerosis/adhesion	S0 absent S1 present presence or absence of podocyte hypercellularity/tip lesion in biopsies with S
Tubular atrophy/interstitial fibrosis	T0 25% of the cortical area affected by tubular atrophy or interstitial fibrosis T1 26-50% of the cortical area affected by tubular atrophy or interstitial fibrosis T2 50% of the cortical area affected by tubular atrophy or interstitial fibrosis
Cellular/fibrocellular crescents	C0 absent C1 present in at least one glomerulus C2 present in 25% of glomeruli

Table 3. Histologic classification of IgA nephropathy of Haas

Haas classification	Description
Class I-Minimal histologic lesion	Glomeruli are normocellular without segmental sclerosis, necrosis, or crescents
Class II-Focal-segmental glomerulosclerosis (FSGS)-like	Glomeruli show focal and segmental sclerosis without mesangial or endocapillary hypercellularity, crescents, or necrosis
Class III-Focal proliferative glomerulonephritis	50% or fewer of the glomeruli not including globally sclerotic glomeruli) are hypercellular. This hypercellularity may be limited to mesangial areas, or include endocapillary hypercellularity. crescents, or necrosis
Class IV-Diffuse proliferative glomerulonephritis	More than 50% of the glomeruli not including globally sclerotic glomeruli are hypercellular. This hypercellularity may be limited to mesangial areas, or include endocapillary hypercellularity. crescents, or necrosis
Class V-Advanced chronic glomerulonephritis	40% or more of the glomeruli are globally sclerotic and or there is >40% estimated tubular atrophy or loss in the cortex. If these criteria are met, the biopsy specimen is graded as class V regardless of other histologic features.

2. Etiology and Pathogenesis

Doctors of all ages have many unique views on the etiology and pathogenesis of the disease, one of which is to feel the evil spirit of the four seasons, Chen Shigong, in "The Authenticity of Surgery", said: "Grapevine disease, which affects mostly children, feels the incorrect qi of the four seasons and is not dispersed in the skin, forming small and large blue and purple spots, colored like grapes, on the head and face of the whole body". Children's internal organs are delicate, and their infantile energy is not yet full, so their ability to resist evil is weak. The second is that heat is forced by abnormal blood operation, overflowing skin, skin purpura and hematuria can be seen down to the bladder, Li Yongchui in "Zheng Zhi Hui Bu": "extreme heat boiling into spots, heat will hurt the blood, blood heat does not disperse, solid surface deficiency, out of the skin and as spots"; "The Taiping Shenghui Fang - Recipe for Blood in Urine" indicates that "blood in urine is caused by heat in the bladder and blood seeping into the bladder, blood gets heat and delusional, so because of heat flow dispersion, seeping in the bladder and urinating blood also"; the third is the body of children with Yin and Yang, lung spleen and kidney deficiency, Qi deficiency is not taken, and the disease occurs. The "Spiritual Pivot - The Beginning of All Diseases" says that "wind, rain, cold and heat must not be deficient, evil cannot hurt people alone". In children, it is said that "the liver is always surplus, the spleen is always deficient, the heart is always surplus, the lungs are always deficient, and the kidneys are always deficient". Therefore, the symptoms of edema in children and recurrent attacks and delayed healing are related to the dysfunction of the lungs, spleen, and kidneys.

Modern medical practitioners have new insights and understanding of the etiology of HSPN, which is mainly divided into two aspects: internal and external causes. Most of the internal causes are Qi deficiency that cannot control the blood or Yin deficiency and blood heat, damp-heat injection that forces the blood to move. Most of the external causes are wind, damp, heat, poisonous, evil, or excessive consumption of fatty and sweet food, or consumption of fish, shrimp, crab, and other products that move the wind (especially wind evil [5]), or improper medication, or because of insect bites, resulting in wind and heat knot, heat poison into the empty space, burn blood collaterals, blood heat jump, extravasation skin, forced gastrointestinal, fluid joints, even damage kidney collaterals and hair for the disease. Xu Yun [6] believed that HSPN was mainly caused by

wind, dampness and heat evil in the initial stage, and in the middle stage, dampness and heat evil moved, the blood, burned the blood collagals, forced the blood to move, and caused blood extravasation to form blood stasis, and the skin was red spots. According to Professor Ma Hongjie[7], the pathogenesis of the disease lies in internal and external factors, internal because of congenital deficiency of endowment or acquired loss of nourishment, resulting in deficiency of internal organs, deficiency of qi and blood, and deficiency of positive qi;external because of external evil, dietary disorders and other pathological products such as wind, dampness, heat, toxicity, stasis, the disease is a deficiency of the internal organs of Qi, blood, yin and Yang deficiency, especially in the lungs, spleen, kidneys, the symptoms are in the wind and dampness, heat, toxicity, blood stasis. Professor Lei Genping [8] believed that the etiology of purpura's wind was mainly wind dampness, heat (poison), deficiency and blood stasis, etc. In the early stage, wind, dampness, heat (poison), and blood stasis were all found, but heat (poison) and blood stasis were the main ones. In the middle and later stage, there is usually a combination of blood stasis and heat and insufficient qi and Yin.The disease is caused by various pathogenic factors, such as damaged veins, imbalance of Yin and Yang, or imbalance of qi and blood. Chen Meixue [9] believed that the key pathogenesis of HSPN was bruising, heat, and collateral injury. Blood stasis, heat injury, and blood collaterals, thus appearing skin purple spots, blood stasis, heat injury, kidney collaterals, blood stasis, heat obstruction of kidney gasification, sealing loss, blood urine, foam urine. Chen Jianping [10] et al. concluded that HSPN mostly has blood heat and blood stasis, therefore, blood should be cooled and stasis should be removed in the treatment. According to Liu Chunying [10], blood stasis exists in purpura, nephritis, hematuria from the beginning of the disease, blood stasis in the veins, forced blood delusion, blood stasis does not go, blood does not return to the meridian. According to Liu Chunying [11], blood stasis exists in purpura nephritis, hematuria from the beginning of the disease, blood stasis in the veins, forced blood delusion, blood stasis does not go, blood does not return to the meridian.According to Liu Chunying [11], blood stasis exists in purpura nephritis, hematuria from the beginning of the disease, blood stasis in the veins, forced blood delusion, blood stasis does not go, blood does not return to the meridian.

3. Progress in TCM Treatment

3.1. Syndrome Differentiation and Staging

Dong Zhigang [12] divided purpura nephritis into an acute active phase and a chronic recovery phase. In the acute active stage, the syndrome of wind heat attacking the surface and the syndrome of dampness-heat stasis are mainly used, and the treatment is mainly on exorcise evil, supplemented by tonifying the lung and kidney; in the chronic recovery stage, it is mainly positive deficiency, and the clinical symptoms are yin deficiency, fire exuberance syndrome and qi deficiency without ingestion syndrome, and the treatment should be based on strengthening the body, supplemented by expelling evil. In the acute active stage, the syndrome of wind heat attacking the surface and the syndrome of dampness-heat stasis are mainly used, and the treatment is mainly on exorcise evil, supplemented by tonifying the lung and kidney; in the chronic recovery stage, it is mainly positive deficiency, and the clinical symptoms are yin deficiency, fire exuberance syndrome and qi deficiency without ingestion syndrome, and the treatment should be based on strengthening the body, supplemented by expelling evil. In the acute active stage, the syndrome of wind heat attacking the surface and the syndrome of dampness-heat stasis are mainly used, and the treatment is mainly on exorcise evil, supplemented by tonifying the lung and kidney; in the chronic recovery stage, it is mainly positive deficiency, and the clinical symptoms are yin deficiency, fire exuberance syndrome and qi deficiency without ingestion syndrome, and the treatment should be based on

strengthening the body, supplemented by expelling evil. Zhao Qian et al. [13] summarized Professor Yan Huimin's experience in treating HSPN with the theory of collagoratology, and believed that the main pathogenesis of HSPN was stagnation, and that it was necessary to remove humidity and detoxification, promote blood circulation and remove blood stasis in the acute stage. The course of the disease is mainly to nourish Yin and qi, remove blood stasis and remove dampness. Zhao Qian et al. [14] summarized Professor Yan Huimin's experience in treating HSPN with the theory of collagoratology, and believed that the main pathogenesis of HSPN was stagnation, and that it was necessary to remove humidity and detoxification, promote blood circulation and remove blood stasis in the acute stage. The course of the disease is mainly to nourish Yin and qi, remove blood stasis and remove dampness. Chen Yanlin [15] summed up Professor Zou Yanqin's experience in treating HSPN with blood stasis, he believed that the disease was mainly based on the treatment of blood, promoting blood circulation and removing blood stasis throughout, and that the acute stage was mainly gross hematuria, skin purple spots, treatment should be mainly to clear heat and cool blood; purple spots in remission period, mostly with varying degrees of hematuria and proteinuria, treatment should be to tonify the kidney and cool blood, replenish qi and nourish yin. Good clinical results can be seen through staging and dialectical treatment. Zhang Libo [16] et al. summarized the academic thoughts of Professor Sun Yuzhi on the treatment of HSPN in Chinese medicine, and Sun Yuzhi taught that the pathogenesis of the disease is mainly based on toxicity (feeling wind heat and poisonous evil), stasis (blockage of blood and blood stasis in the ligaments), and deficiency (deficiency of the vegetative body or the decay of the body after a long illness). In the gradual exploration of clinical treatment, he proposed the "eight evidence and eleven methods of dialectical treatment of purpura nephritis", and at the same time, according to the stage of HSPN, the patient's physical factors and the evolution of the disease, combined with the eight evidence and eleven treatment methods of dialectical treatment, and clinical results have been repeatedly seen. Xu Yanan [17] dialectically treated HSPN according to the theory of Wei, Qi, Ying, and Blood, and according to the clinical onset stage (generation stage, transmission stage, and development stage) of the disease, combined with the theory of Wei Qi and Blood, put forward that the disease should be divided into Weifen syndrome, which is mainly treated by soothing wind and clearing heat, Ying Fen syndrome is mainly treated by Qingying and detoxification, and Xue Fen syndrome is treated mainly by cooling blood, stopping blood, tonifying qi and invigorating spleen, blood intake, promoting blood circulation and removing blood stasis. Through the dialectical combination of Weiqi Yingxue theory and traditional Chinese medicine in the treatment of HSPN, it gives full play to the effect of dialectical treatment of traditional Chinese medicine, and provides a basis for the development of traditional Chinese medicine in the treatment of the disease. Wu Erli [8] summarized the experience of Professor Lei Genping in treating HSPN with dampness, who divided the disease into deficiency and actual evidence, specifically damp-heat evidence, cold-damp evidence, and deficiency with dampness, and proposed the method of anti-allergy and dampness removal, the method of clearing damp-heat in the Sanjiao, the method of warming the meridians and dispersing cold, and the method of tonifying the spleen and benefiting the kidneys to treat the disease, paying attention to prevention and regulation, and taking into account various aspects to achieve significant clinical results. Ren Xiumin [7] et al. summarized Professor Ma Hongjie's diagnosis and treatment experience according to the TCM differentiation and hormone staging, which was considered staged as wind-heat, heat-poison stasis, yin-deficiency internal heat, spleen-kidney deficiency, and qi-yin deficiency according to the pathogenesis. HSPN is dialectically typed according to clinical, hormonal, and immunosuppressive interventions such as hormone sufficiency phase, hormone maintenance phase, and hormone withdrawal phase. In terms of treatment, during the period of hormone dosage (wind-heat, blood-heat, heat-poison stasis, and yin-deficiency internal heat), drugs to clear heat and cool blood are mostly used with drugs to dispel

wind; during the period of hormone maintenance (spleen-kidney deficiency), drugs to clear heat and detoxify blood are mostly used with drugs to activate blood circulation and remove blood stasis; during the period of hormone withdrawal (qi-yin deficiency), drugs to strengthen the spleen and kidney are mostly used with drugs to benefit qi and nourish yin. Through the synergy of Chinese medicine and hormone staging, we can improve the symptoms of the disease and slow down the progression of the disease. The disease is a process, with the development of the disease, the evidence type is also changing, through the dialectical treatment, giving full play to the advantages of the appropriate time, reflecting the "developmental perspective" to see the problem.

3.2. Treatment of Prescription and Medicine

Professor Zheng Pingdong [18] subdivided the disease into six types of evidence and prescribed according to the evidence, which among them, the prescription of wind heat and blood stasis is modified by Yinqiao Powder, the prescription of heat toxin by Xijiao Dihuang decoction, the prescription of deficiency of liver and kidney yin by Qiju Dihuang Pill, the prescription of deficiency of spleen and kidney qi by Shiquan Dabu decoction, the prescription of deficiency of Qi and Yin by Shenqi Dihuang decoction, and the prescription of turbid phlegm with Wenpi decoction, and the clinical treatment of the disease is guided according to the principle of "tracing the source of examination and syndrome differentiation". According to Professor Wang Shirong [19], this disease is mostly associated with wind-heat disturbance, and the treatment is mainly based on dispelling wind-heat and invigorating blood circulation, with the prescription of allergy decoction combined with Yin Qiao San plus reduction, specifically: Jin Yin Hua, Lian Qiao, Dandelion, Yin Chai Hu, Thornbush, Burdock, Peppermint, Wu Mei and Wu Wei Zi. Ma Li [20] used Qingre Liangxue Huayu decoction to treat HSPN in children. 85 patients were randomly divided into a control group (n = 42) and experimental group (n = 43). The control group was treated with western medicine, and the treatment group was treated with Qingre Liangxue Huayu decoction. After 12 weeks of treatment, the effective rate of the experimental group was better than that of the control group, and the recurrence rate was lower than that of the control group. Wang Haijun [21] used self-designed Xiaofeng Qudu Decoction to treat children with Henoch-Schonlein purpura nephritis. 82 children with Henoch-Schonlein purpura nephritis were randomly divided into control group and experimental group. The control group was given tripterygium wilfordii polyglucoside tablets, while the study group was given self-designed Xiaofeng Qudu Decoction for continuous treatment for 14 days. Results: The effective rate of Xiaofeng Qudu decoction in the treatment of child Henoch-Schonlein purpura nephritis was better than that of the control group. Cheng Jiang [22] used Huoxue Huayu recipe to treat HSPN in children. 72 patients were randomly divided into treatment group and control group. The control group was treated with routine western medicine. The treatment group was treated with Huoxue Huayu decoction (Wulingzhi, lotus root charcoal, Puhuang charcoal, moutan, small thistle, Angelica sinensis, Jing mustard charcoal, alisma, Polyporus umbellata, Poria cocos, Panax notoginseng) for 8 weeks. The treatment group was superior to the control group in improving the curative effect, the level of related coagulation index factors, delaying the damage of renal function, and reducing adverse reactions. Traditional Chinese medicine can give full play to the advantages of traditional Chinese medicine in the treatment of HSPN, but in the treatment, we should adhere to the syndrome differentiation of traditional Chinese medicine in order to achieve a better effect.

3.3. External Treatment of Traditional Chinese Medicine

Yang, Hongjuan [23], and others used moxibustion combined with Tuomin Xiaoban decoction to treat HSPN. 60 patients were randomly divided into moxibustion group and piercing group. Moxibustion group was treated with moxibustion combined with d-Tuomin Xiaoban decoction. The treatment course was one month. The results showed that the clinical cure rate of the moxibustion group was significantly higher than that of the pricking collateral group, and the recurrence rate decreased significantly. External treatment of traditional Chinese medicine can well assist traditional Chinese medicine in the treatment of HSPN. According to experiments, external treatment of traditional Chinese medicine plays an important role in promoting the regression of purpura and controlling the symptoms of HSPN. Ren Dewei [24] studied the clinical efficacy of collateral puncture therapy combined with western medicine in the treatment of HSPN. 80 patients were randomly divided into the control group and the experimental group. The control group was treated with western medicine, and the treatment group was treated with collateral puncture therapy on the basis of the control group. The experiment shows that acupuncture combined with western medicine is effective in the treatment of HSPN. Erdun Duleng [25] used Mongolian medicine combined with moxibustion to treat HSPN. 61 patients were randomly divided into the control group and the observation group. The control group followed the HSPN Mongolian medicine diagnosis and treatment scheme, and the observation group was treated with Mongolian medicine combined with moxibustion for 7 days. The experimental results showed that the combined moxibustion group was effective in relieving skin purpura, reducing urinary occult blood, and improving proteinuria.

4. Summary

To sum up, the pathogenesis of HSPN is mainly four periods of evil qi, heat forcing, blood flow, lung, spleen, and kidney deficiency. In the early stage, the main evidence is to feel external evil, blood heat, jumping, etc. The treatment is mainly to clear heat and cool blood, and in the late stage, the deficiency syndrome of lung, spleen, and kidney deficiency, qi does not take blood, etc. The treatment should be mainly to replenish the kidney and lungs, strengthen spleen and qi. Whether the use of glucocorticoids and immunosuppressants in western medicine can treat HSPN or improve its development to end-stage renal disease remains controversial. At present, many doctors have integrated traditional Chinese and Western medicine to treat the disease. Traditional Chinese medicine can not only improve the symptoms of patients, reduce the recurrence rate, but also have certain treatment ability for the side effects of western medicine treatment. In clinical observation, traditional Chinese medicine has certain advantages in the treatment and prevention of HSPN, but the standard of dialectical classification and medication has not formed a unified opinion, and the clinical report of traditional Chinese medicine is also in the stage of personal experience introduction, lack of large sample study, long-term follow-up and other work is not in place. In the later stage, it will be the way for us to further explore the treatment of this disease with traditional Chinese medicine and give full play to the advantages of the integration of traditional Chinese and western medicine.

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Data Availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Conflict of Interest

The author states that this article has no conflict of interest.

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