

Research Progress of Traditional Chinese Medicine on Idiopathic Membranous Nephropathy

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Abstract: As a major type of membranous nephropathy, the incidence of idiopathic membranous nephropathy is increasing year by year, but its pathogenesis has not yet formed a unified consensus. Traditional Chinese medicine summarizes the basic etiology and pathogenesis of idiopathic membranous nephropathy with spleen and kidney deficiency as the basis and phlegm, dampness, heat and blood stasis as the standard. Combined with their own clinical practice and experience, modern doctors have innovatively put forward many new theories, empirical prescriptions and flexible application of classic prescriptions, In order to provide the corresponding theoretical basis and reference value for the treatment of idiopathic membranous nephropathy with the combination of traditional Chinese and Western medicine.

Keywords: Idiopathic membranous nephropathy, Spleen and kidney deficiency, New theory, Experience prescription.

1. Introduction

Membranous nephropathy (MN) is a glomerular disease characterized by the deposition of immune complexes under the glomerular basement membrane epithelial cells under the microscope, accompanied by diffuse thickening of the glomerular basement membrane [1]. Clinically, MN can be divided into two categories: secondary membranous nephropathy (SMN) and idiopathic membranous nephropathy (IMN).

Secondary membranous nephropathy (SMN) has a clear etiology and pathogenesis, but the etiology and pathogenesis of IMN have not yet formed a unified consensus. At present, relevant studies have shown that IMN is closely related to the patient's own immune and/or inflammatory response, family inheritance, and even environmental pollution [2-3]. Related epidemiological studies have shown that the incidence of IMN accounts for about 70 % of the total incidence of MN [1], and its incidence is increasing year by year [4]. The main clinical manifestations of IMN are similar to nephrotic syndrome: high edema, high proteinuria, hyperlipidemia and hypoproteinemia.

At present, the treatment of IMN in western medicine is mostly based on glucocorticoid combined with immunosuppressive agents, and with the progress of science and technology, biological agents are becoming another new choice for the treatment of IMN, However, the simple western medicine treatment has the disadvantages of large toxic and side effects, many complications, intolerance or high recurrence rate, high treatment cost and long cycle, which has caused great trouble to the daily life and physical and mental health of patients. China's excellent traditional Chinese medicine has the advantages of small side effects, low patient cost and low recurrence rate in the treatment of IMN, and has become one of the dominant diseases in the clinical treatment of traditional Chinese medicine.

There is no name of IMN in ancient books of traditional Chinese medicine. According to its clinical symptoms, modern doctors attribute it to traditional Chinese medicine

diseases such as 'edema', 'ointment shower', 'water vapor' and 'consumptive disease'. With the extensive clinical practice of IMN disease in traditional Chinese medicine and the experience summary of excellent Chinese medicine practitioners, Chinese medicine has made further development in the treatment of IMN. Therefore, the relevant research progress is integrated and discussed in order to provide the corresponding theoretical basis and reference value for the clinical treatment of IMN with integrated traditional Chinese and Western medicine.

2. Cause of Disease, Pathogenesis

2.1 By consulting a large number of relevant literatures and combining with their own clinical practice, the general understanding of the occurrence and development of IMN disease by excellent Chinese medicine practitioners is mainly the following two points:

2.1.1 Spleen and kidney deficiency is the foundation

IMN patients with edema as the external symptoms, and 'Huangdi Neijing-Suwen' proposed 'kidney water dirty, main body fluid', 'pathogenesis 19' proposed 'all wet swelling, all belong to the spleen', therefore, spleen and kidney deficiency is clinically regarded as the internal basis of IMN. The dysfunction of the acquired 'spleen', which is the main transportation and the main ascending and clearing, will lead to the internal stop of water and grain essence, body fluid and water fluid, which can not be distributed to the five internal organs and the whole body. The metabolic disorder of body fluid and water fluid overflows the skin and shows edema. The dysfunction of spleen qi in the main ascending function will cause the water and grain essence to sink in the bladder and show proteinuria. The kidney is the congenital foundation. The gasification of the main viscera tissue of the main water, the formation and excretion of the main urine, and the imbalance of the metabolic body fluid function will cause edema symptoms, and the main storage of the kidney and the main intake function are abnormal, which will cause the kidney to be unable to prevent the loss of water and grain essence, and proteinuria will occur clinically. As the

congenital and acquired foundation of the human body, the dysfunction of the spleen and kidney interacts with each other, resulting in the clinical symptoms of edema and massive proteinuria in IMN patients.

2.1.2 Phlegm, dampness, heat, blood stasis as the standard.

The internal stop of body fluid and water fluid will become the evil of phlegm and water dampness in the human body. Both of them are the pathological products of IMN patients and the secondary causes of aggravation. Dampness is yin evil, which is easy to damage the yang qi of the spleen and kidney, and the wet heavy turbidity and viscosity hinder the operation of the whole body qi. Phlegm not only affects the metabolism of water and fluid in the whole body, but also aggravates the symptoms of edema, and it can hinder the operation of qi and blood, and block the ascending and descending of qi movement in the whole body. In turn, the two diseases will not only aggravate the symptoms of spleen and kidney deficiency, but also cause the delay of IMN patients. At the same time, because most IMN patients receive hormone and other treatment regimens, and hormone drugs are easy to consume qi and damage fluid, and dampness is easy to turn into heat, the patients are prone to damp-heat accumulation. The clinical manifestations are: edema and a large amount of proteinuria. At the same time, the patient's tongue coating is yellow and greasy, and the pulse condition is slippery, or even the tongue coating is yellow and dry, and the patient wants to drink.

The evil of water dampness and phlegm retention hinders the whole body's qi movement, and 'qi is the commander of blood'. Therefore, the disorder of qi movement will cause people to have the evil of blood stasis. This evil has a certain correlation with the critical illness of western medicine in which the patient's blood is in a hypercoagulable state, with hyperlipidemia or thrombosis and embolism [5], Blood stasis is easy to become a mass for a long time, and then the pathogenic person is lingering and difficult to heal, increasing the risk of death and medical burden of IMN patients.

2.2 On the basis of 'spleen and kidney deficiency as the foundation, phlegm, dampness, heat and blood stasis as the standard', modern doctors have a new understanding and opinion on the etiology and pathogenesis of IMN based on their own years of clinical practice and experience summary, as follows :

2.2.1 Xuanfu theory

'Xuanfu' was first recorded in 'Suwen': 'The so-called Xuanfu is empty. Later generations of doctors such as Zhang Jingyue, Liu Wansu and so on have continued to expand its connotation, making it an indispensable part of Chinese medicine culture.

Han Shisheng et al. [6] believed that the slit diaphragm composed of Xuanfu and glomerular visceral epithelial cells, namely podocytes, was highly similar in morphology, characteristics, functions, pathological manifestations and clinical manifestations. It was proposed that the slit diaphragm of glomerular visceral epithelial cells in Western medicine cytology was one of the fine structures of Xuanfu in

the kidney of traditional Chinese medicine.

Based on the theory of Xuanfu, Jolin et al. [7] proposed that the diagnosis and treatment of IMN in traditional Chinese medicine can be divided into three stages: the initial stage of wind invading the lung and kidney, resulting in the loss of Xuanfu opening and closing; in the middle stage, phlegm, dampness, heat and blood stasis obstruct the spleen and kidney, resulting in spleen and kidney deficiency and Xuanfu stagnation. In the later stage, the chronic diseases such as wind and phlegm caused the loss of function of Xuanfu, the imbalance of yin and yang, and the failure of lung, spleen and kidney, resulting in renal failure such as anuria.

2.2.2 Phlegm dampness and blood stasis

Zeng Qin et al. [8] believed that phlegm, dampness and blood stasis are not only the pathological products of IMN, but also the important pathogenic factors throughout the disease. The premise of phlegm-dampness and blood stasis in IMN patients is that the gasification function of lung, spleen, kidney and other organs is impaired, resulting in poor qi movement of the whole body. The whole body dampness and blood stasis, local phlegm and blood stasis, in turn, cause lung, spleen and kidney and other viscera damage. Phlegm dampness and blood stasis three diseases and evil transformation so that IMN repeated, difficult to heal.

2.2.3 Kidney collateral theory

Zhao Pengbo et al. [9] proposed that IMN is located in the collaterals of the kidney based on the 'Yellow Emperor's Inner Canon' that 'the meridians are the interior, the branches and the transverse are the collaterals'. The functions of the kidney, such as water, gas and essence, are closely related to the operation of qi, blood and essence in human collaterals. And the kidney and the collaterals are mutually causal, and the poor operation of the collateral channel will cause damage to the physiological function of the kidney, and the damage to the physiological function of the kidney will also aggravate the collateral disease. Loss of renal collateral function, resulting in blood stasis, abdominal mass accumulation, which is similar to the glomerular basement membrane deposition of immune complexes; and easy to cause wind invasion.

Professor Zhao Yuyong combined with his own clinical practice and experience in the treatment of IMN proposed [10]: 'Kidney collaterals stasis' theory, that IMN is a virtual standard real, based on spleen and kidney deficiency, standard real for phlegm dampness, blood stasis, qi stagnation and other diseases, and evil in the kidney collaterals in the formation of Zhengjia, resulting in kidney collaterals stasis, renal dysfunction, and ultimately lead to IMN.

2.2.4 Yang gas, Yin forming

Based on the theory of 'yang transforming qi and yin forming' in the 'Yellow Emperor's Internal Classic' Wu Tong and Li Jing proposed [11]: the imbalance of yin and yang, the transformation of tangible substances such as essence, blood and body fluid into the 'yang transforming qi' of the human body is not enough, resulting in the operation disorder of

water and fluid the patient has edema, and the kidney qi mainly stores essence, seals and absorbs insufficiently, resulting in the slight leakage of water and grain in the human body, and proteinuria. The excessive 'yin formation' of the tangible substances such as body fluid, essence and blood transformed from the qi of the human body can cause qi stagnation and blood stasis, phlegm and dampness, and even dampness and heat toxicity, which aggravates the damage to its renal function. Wu Tong and Wu Tong also believe that IMN disease is mainly based on the deficiency of 'Yang transforming Qi', and the excess of 'Yin forming' is its standard. At the same time, phlegm, blood stasis, toxin and deficiency of human body are the key to the evolution of IMN. The four are interrelated and promote each other, which together lead to the aggravation of the disease.

2.2.5 Wet theory

He Peihua et al. [12] believed that the 'wet' pathogen in the six evils is not only the pathological product of IMN, but also its main cause. Dampness is yin evil, which is easy to damage spleen yang, so that the spleen mainly transports water and drinks, and the main function of ascending clear, and then there are symptoms such as edema and proteinuria. And because of the wet viscosity, hindering the operation of the whole body, it in turn aggravates the internal stagnation of dampness, and the patient's condition aggravates and relapses. At the same time, He Peihua et al. [12] also proposed that dampness syndrome is not only consistent with the external clinical symptoms of IMN patients, such as thick and greasy tongue coating, heavy body trapped, fatigue, but also consistent with the internal characteristics of edema and proteinuria. Moreover, the detection value of proteinuria in IMN patients was positively correlated with the degree of dampness, that is, the more severe the dampness, the higher the urine protein value.

Liu Fuli and Ba Yuanming [13] further put forward the theory of 'viscera rheumatism' on the basis of the theory of dampness, that is, the onset of disease is due to the fact that the human body is feeling the wind, cold and dampness of the six evils between heaven and earth. After the three evils, these three evils are gradually introduced into the body from the body surface, tendons, veins, flesh, skin and bone; or through the eyes, tongue, mouth, nose, ears and two yin straight in the five zang-organs and six fu-organs, the three evils are hidden in the zang-organs and cannot be prolonged, and then become a stubborn disease; and when the three evils of wind, cold and dampness are re-infected, the disease will recur or worsen. According to the theory of 'viscera rheumatism' the pathogenesis of IMN can be summarized as follows: the lack of healthy qi in the human body, the deficiency of the spleen and kidney, and the invasion of the three evils of wind, cold and dampness, so that the three evils of wind, cold and dampness are not dispelled in the kidney. In addition, the three evils of wind, cold and dampness block the blood vessels and meridians, so that the kidney collaterals are blocked and the blood circulation is not smooth, so that the disease can not be recovered.

2.2.6 Water depression theory

Yang Fan, Jin Jinsong [14] according to the clinical symptoms

of IMN patients, such as edema and proteinuria, the theory of 'water stagnation' is put forward, that is, the evil of water and dampness in the human body can not be blocked and the disease occurs, and it is the central link of the disease. Based on the theory of 'water depression', the incidence of IMN can be divided into four types. The first is the wind evil, the first of the six evils. The wind and water attack the muscle surface, resulting in the stagnation of lung qi, the disorder of dispersing and descending, and the kidney of the wind and water. As a result, the grain essence is slightly leaked into proteinuria, the kidney collaterals are burned into hematuria, and the internal and external attacks cause water to be suppressed and stopped. Second, the acquired spleen is weak, resulting in abnormal operation of water and water in the whole body, and the spleen can not control the evil of water and dampness, so that the water is stagnant. The third is the congenital kidney, the main body of the yang is weak, the kidney yang qi of the transpiration gasification, the warmth of the power is weak and the water cold endogenous, stagnation. Fourth, 'blood is unfavorable for water', blood stasis for a long time, the water wet more, water gas is very depressed.

2.2.7 Distinguishing pathogenesis theory

Wang Yao, the first Qihuang scholar in China, dedicated his famous traditional Chinese medicine [15]. On the basis of decades of clinical practice of learning kidney disease from the master of traditional Chinese medicine Lyu Renhe, and combined with his own clinical experience, he summed up the characteristics of TCM pathogenesis of IMN disease from multiple perspectives, that is, the initial pathogenesis of wind-dampness disturbing kidney. Derivative pathogenesis of damp heat, blood stasis, spleen and kidney deficiency; micro-pathogenesis of damp heat block and blood stasis blocking collaterals; spleen and kidney qi deficiency, dampness stagnation of the syndrome pathogenesis; combined with the patient's specific symptoms of symptomatic pathogenesis environmental pathogenesis related to the environment; and the common pathogenesis of kidney collaterals micro mass. Wang Yaoxian, a famous Chinese medicine doctor, put forward a relatively complete theoretical system of TCM pathogenesis, treatment methods and prescriptions for different stages of development and symptoms of IMN disease, which is helpful for the clinical treatment of IMN with the combination of traditional Chinese and Western medicine.

2.2.8 Intestinal flora theory

Wang Xiangpeng et al. [16] combined with the academic thought of national famous old Chinese medicine Yu Renhuan for IMN: intestinal flora is closely related to IMN in inflammatory response, immune imbalance and lipid metabolism ;based on the theory of intestinal flora, the treatment of IMN by spleen has achieved good results in animal experiments and clinical practice, which also confirms the importance of regulating intestinal flora for the treatment of IMN.

Xu Yupei, Li Jing et al. [17] found that the metabolites and microbial molecules of the intestinal flora can not only regulate the level of inflammation and oxidative stress of the human body itself, but also regulate its immune balance,

thereby reducing its kidney damage; it can also aggravate the damage to podocytes and the process of renal fibrosis by affecting the homeostasis of intestinal barrier. At the same time, the intestinal flora is closely related to the function of the spleen. The function of the intestinal flora in helping the human body to digest and absorb nutrients is the same as the spleen's main function of transporting water and grain essence to disperse, nourishing the whole body and ascending the clear; moreover, the acquired spleen transports water and grain essence to enhance the body's vital force and the physiological function of internal and external anti-evil defense is similar to the regulation of intestinal flora on the human immune system. Therefore, it is of far-reaching clinical significance for regulating spleen Chinese medicine to intervene in the development of IMN and enhance the stability of intestinal barrier by targeting intestinal flora.

3. Treatment, Prescription

3.1 Qidi Gushen Recipe

Professor Lei Genping, a famous Chinese medicine doctor in Shaanxi Province, combined with his own years of clinical practice and experience, put forward the etiology and pathogenesis of spleen and kidney deficiency and damp-heat stasis of IMN, and based on this, he added and subtracted on the basis of Shenqi Dihuang Decoction to obtain Qidi Gushen Decoction. The efficacy of Qidi Gushen Decoction is: tonifying spleen and kidney, clearing damp heat, promoting blood circulation and removing blood stasis; there are six herbs, respectively: Astragalus, Rehmannia, Euryale, Hedyotis diffusa, Schizonepeta, Salvia. Relevant clinical and animal experiments [18] show that: Qidi Gushen Decoction can not only reduce the deposition of immune complexes in renal tissue and reduce the thickening level of glomerular basement membrane, but also improve the body's immunity, protect podocytes and reduce the damage of glomerular filtration barrier. At the same time, the clinical effective rate of Qidi Gushen Decoction combined with Western medicine was significantly higher than that of Western medicine alone.

3.2 Zhenwu Decoction and Shenzhuo Decoction Addition and Subtraction

Yan Junhui et al. [19] found through the clinical observation of 106 patients with IMN complicated with acute kidney injury of spleen and kidney yang deficiency syndrome: Zhenwu decoction combined with Shangshenzhuo decoction plus western medicine combined with western medicine treatment compared with simple western medicine treatment, the combination of traditional Chinese and western medicine treatment can not only better reduce the patient's urea nitrogen, serum creatinine value, 24h proteinuria, reduce total cholesterol, triglyceride value to reduce hyperlipidemia, improve creatinine clearance rate, serum albumin; it can also reduce the levels of blood homocysteine and serum anti-phospholipase A2 receptor antibody, which are positively correlated with renal injury, and reduce the levels of urine N-acetyl- β -D-glucosaminidase, urine β 2-microglobulin and renal injury molecular values that can dynamically reflect the progression of renal injury in the early stage to assist clinicians in evaluating the patient's condition changes. At the

same time, the combined treatment of traditional Chinese and Western medicine can also significantly reduce the levels of tumor necrosis factor- α , interleukin-1 β , interleukin-17 pro-inflammatory factors, and increase the anti-inflammatory factor interleukin-135 to reduce its inflammatory injury; it can regulate the immune function of the body by increasing the CD4+, CD4+/CD8+ in T cell subsets and reducing the CD8+ level of T cell subsets.

3.3 Yishen Qingli Prescription

Through network pharmacology and in vitro cell experiments, Bao et al.[20] found that the Yishen Qingli prescription of Kong Wei, a famous traditional Chinese medicine in Jiangsu Province, composed of eight herbs, such as Radix Astragali seu Hedysari, Cornus officinalis, Fried Atractylodes macrocephala, Eucommia ulmoides, Panax notoginseng, Alisma orientalis, Pyrrosia, and Hedyotis diffusa, can reverse the apoptosis of podocytes in the development of IMN through multiple signaling pathways such as TNF, MAPK, and PI3K/AKT, so as to alleviate the clinical symptoms and progressive development of IMN.

3.4 Shengyang Yiwei Decoction and Buyang Huanwu Decoction

An Hengtong et al. [21] found through animal experiments that the pure Chinese medicine treatment of Shengyang Yiwei Decoction and Buyang Huanwu Decoction and the western medicine benazepril can significantly reduce the 24-hour urinary protein in urine, the total cholesterol level in the abdominal aorta, and increase the albumin value in the blood to reduce the clinical symptoms of proteinuria. At the same time, the pure Chinese medicine treatment of Shengyang Yiwei Decoction and Buyang Huanwu Decoction can also reduce glomerular volume and deposition by increasing the protein levels of Nephryn and CD2 AP in renal tissue, so as to protect the kidney of IMN.

3.5 Jianpi Qushi Heluo Prescription

Lang Rui, Wang Xiangpeng et al. [16, 22] showed that the national famous old doctor of traditional Chinese medicine Yu Renhuan teacher with their own years of clinical practice and experience, based on the theory of intestinal flora created by astragalus, Fangji, atractylodes, coix seed, poria cocos, perilla leaf, angelica, coptis, Chuanshanlong, ginseng and other drugs composed of spleen and dampness and collaterals, with spleen and qi, dampness, blood stasis, and collaterals. This prescription can not only improve the patient's plasma albumin level, reduce the patient's proteinuria to reduce the patient's clinical symptoms; it has significant advantages in safety and long-term effectiveness. At the same time, this prescription can also adjust the immune level by improving the structure of intestinal flora-increasing the abundance of beneficial bacteria such as bifidobacteria and reducing the abundance of harmful bacteria to make it dynamically balanced, reduce the inflammatory response of the whole body and play a role in protecting the kidney and slowing down the damage. The treatment of IMN through the effect of intestinal flora is similar to the current clinical use of biological agents to treat IMN.

4. Conclusion

At present, the etiology and pathogenesis of idiopathic membranous nephropathy (IMN) are unknown, and the number of patients is increasing. However, there are many complications and other deficiencies in simple western medicine treatment. Therefore, how to relieve the clinical symptoms of IMN patients more safely and effectively and improve their quality of life has become a major problem in the clinical treatment of IMN. On the basis of the theory of traditional Chinese medicine, which is based on the deficiency of spleen and kidney, phlegm, dampness, heat and blood stasis, combined with their own years of clinical practice and experience, the excellent famous doctors of traditional Chinese medicine put forward many new theories such as Xuanfu, kidney collaterals, pathogenesis, intestinal flora theory, and many effective empirical prescriptions for IMN, such as Qidi Gushen Prescription, Jianpi Qushi Heluo Prescription, and the flexible use of the famous prescriptions of ancient excellent doctors, which provides more and more solid theoretical and practical basis for the excellent traditional Chinese medicine and the combination of traditional Chinese and Western medicine in the treatment of IMN. However, at present, there are still few basic experiments such as animal and clinical experiments on the effective treatment of IMN by relevant new Chinese medicine theories, empirical prescriptions and ancient classic prescriptions. Further research and demonstration are still needed in order to play an excellent Chinese medicine culture for the effective and lasting treatment of IMN.

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