

Research Progress of Treating Iga Nephropathy from the Perspective of Wind Pathogen and Damp Pathogen

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Abstract: The pathogenesis of IgA nephropathy is complex. Traditional Chinese medicine believes that the cause of this disease is related to the “wind evil” and “dampness evil” in the six exogenous pathogens. Deficiency of viscera is mainly due to deficiency of kidney qi, and the signs are exogenous pathogens, dampness, and blood stasis. IgA nephropathy, IgAN (Immunoglobulin A nephropathy) is a concept of pathological diagnosis, which usually progresses to end-stage renal disease (End stage renal disease, ESRD) and often requires renal replacement therapy [1]. IgAN is a glomerular disease in which immunoglobulins, mainly IgA, are deposited in granules or masses in the glomerular Mesangial area, often with the deposition of complement C3. Under a light microscope, there were various types of lesions, mainly characterized by diffuse glomerular Mesangial hyperplasia and increased Mesangial matrix (See Figure 1 - Figure 3). The clinical manifestations were edema, albuminuria, hematuria and hypertension. Although there is no record of IgAN in ancient books of traditional Chinese medicine, according to its clinical characteristics, it can be classified as “edema”, “urine blood”, “Guange”, “low back pain”, “turbid urine” and other diseases [2]. At present, the pathogenesis of IgAN is not clear, Modern studies have found that its pathogenesis is related to abnormal glycosylation of IgA1 molecules, activation of complement system, gene inheritance, intestinal immune regulation and so on [3]. In treatment, modern medicine can only observe this part of patients with hematuria mainly, no proteinuria or a small amount of proteinuria, and these patients can still develop to the end-stage renal disease stage after many years, and still need renal replacement therapy, although ACEI/ARB can relieve proteinuria and hypertension to some extent, but the effect is still not ideal (See Table 1). However, doctors in ancient China believed that the incidence of IgAN was mainly caused by the invasion of “wind evil” and “damp-heat”, which could aggravate the disease to a certain extent. Therefore, clinicians attach great importance to the treatment of IgAN in rheumatism. This paper summarizes the research progress of traditional Chinese and western medicine “treatment of rheumatism” in the treatment of IgAN (Figure 1 - Figure 3: Pathological picture of IgAN rat model).

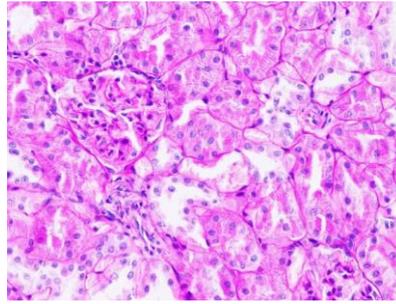


Figure 1: PAS staining

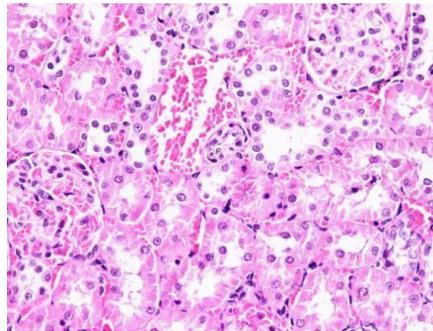


Figure 2: HE staining

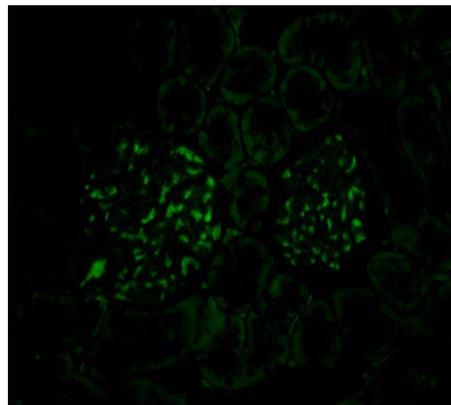


Figure 3: Immunofluorescence staining

Table 1: An overview of western medicine IgAN

Related theory of IgAN	clinical manifestations	Western medical treatment
abnormal glycosylation of IgA1 molecules	edema, albuminuria, hematuria and hypertension	Regular observation of mild disease
activation of complement system		ACEI/ARB
gene inheritance		Hormonal drugs
Intestinal immune regulation		Immunosuppressive agent

1. On the Etiology and Pathogenesis of IgAN from the Angle of Wind Pathogen, Damp Pathogen

1.1. Wind Pathogen Causes Disease

The wind is the length of all diseases, the head of the six masturbations, the wind evil is easy to

combine with him and hurt people, and is the forerunner of the disease caused by external evil. When the evil wind invades the human body, it can enter through the mouth and nose, knot the throat and accumulate in the lungs, or invade the lungs by the skin and fur, combine with the dampness in Taiyin, cement water and blood, become dampness and stasis, and block to qi, which is an important factor in the occurrence and development of IgAN. The wind is Yang evil, with the characteristics of light rising, rising, upward and outward. Suwen says that “about the bright theory of Taiyin and Yangming”; “those who are hurt by the wind are the first to receive it.” The theory of nine needles in the Lingshu Sutra says that the lung covers five internal organs and six internal organs. The lung has the highest position in the internal organs of the body, and the water absorbed by the body from the outside has to be spread all over the body through the rapid descending effect of the lung. It is recorded in the Lingshu Meridian: “the pulse of Shaoyin... It is straight, from the kidney...Into the lungs, along the throat, holding the tongue.” Lingshu originally lost and also said the kidney is connected to the lung. Lung gold is the mother of kidney water, and the kidney is the congenital nourishment of the lung body, indicating that the lung and kidney are closely related to each other. The lung and kidney complement each other to regulate the balance of water and fluid metabolism. The declaration and dereliction of duty of the lung, the loss of subtle matter in the dissemination, congenital loss of the kidney in acquired nourishment, sealing, so it can be seen that the fine matter excreted with urine and albuminuria; lung meridian heat, lung gold spread to the kidney water, heat evil burn the vein of the kidney, forcing blood to misbehave, the blood does not follow the meridian, hematuria can be seen. Suwen Fenglun said the evil in Dongrengui is the kidney wind... The shape of kidney wind, sweating and aversion to wind, swollen face, pain in the spine, unable to stand upright, dull color, unfavorable curvature, and black color when diagnosed on the muscle. Baby Protection Summary Kidney says the lungs belong to the metal, which shoots through the skin, and governs the qi. The kidneys belong to the water and govern the bone marrow and store the essence. The lightness of qi can go up but not go down. When the lung qi gets hot and steams upwards, it cannot go down; it is born in the kidneys and suffers from evil... This kidney disease must first seek the lungs. Professor Ren Jixue, a master of traditional Chinese medicine [4], believes that IgAN belongs to chronic kidney wind, with wind heat attacking externally, leaving the lungs internally, burning the collaterals along the meridians, forcing the blood to descend, and resulting in hematuria. Clinical studies have also confirmed that mucosal immune dysfunction is closely related to the pathogenesis of IgAN. The recurrence and aggravation of the patient's condition are often related to upper respiratory tract infection, and tonsil infection is the most common [5]. The role of the mucosal immune system is basically similar to the defense function of the traditional Chinese medicine “lung guard”. The lungs govern the fur, and if the lungs are not strong, they are vulnerable to external pathogens. Therefore, if the external pathogens do not go away and the lung defenses are not solid, the various symptoms will be difficult to eliminate. The main clinical manifestations are fever, mild aversion to wind and cold, headache, cough, sore throat, red urine or microscopic hematuria. Therefore, for patients with external wind-induced pathogens, consider starting from the lungs to protect the lungs and guard against the pathogens.

1.2. Damp Pathogen Causes Disease

Dampness is the evil of heavy turbidity, belonging to Yin, and its nature is heavy turbid, sticky and downward. Damp pathogens are easy to mix with heat pathogens, and dampness and heat are in harmony, such as oil entering the face, inextricably separated, heat pathogens are controlled by damp pathogens that cannot be dispersed upward, damp pathogens are trapped in heat pathogens and cannot be solved downwards, damp and heat are steamed, and Sanjiao is diffused, blocking qi, resulting in a lingering illness. This is the same as the clinical manifestation of IgAN, although the

primary focus of infection has been controlled, but hematuria and proteinuria are still lingering. Therefore, the evil of dampness and heat is also another important factor affecting the occurrence and development of IgAN. Patients with IgAN may be due to exogenous dampness, or dampness due to spleen deficiency, or diuretic and detumescent drugs caused by edema, excessive yang and dampness in the body, or imbalance of yin and yang caused by long-term use of hormones, or dampness-heat syndrome due to deficiency of spleen and kidney. Clinical TCM syndrome research also confirmed that damp-heat syndrome is the most common in IgAN, and this syndrome has higher activity and glomerular injury than other syndromes [6]. It also provides a new idea for the clinical treatment of IgAN. Damp-heat obstruction, dereliction of duty with the rise and fall of spleen and stomach qi, and transport failure, then fatigue, diarrhea, constipation, discomfort in stool and other symptoms of acute and chronic gastroenteritis. Wet stop coke, then more for the performance of urinary tract inflammation. Kidney and bladder gasification is disadvantageous, then the small abdomen is full, urine dripping is not smooth and so on; seal dereliction of duty, fine material release can occur albuminuria, hematuria. Therefore, the clinical manifestations of IgAN patients are fatigue, edema, diarrhea, turbid urine, thick and greasy tongue coating, and slippery pulse and so on. The examination of the medical prescription said that the disease of Xiajiao is due to dampness and heat. Synopsis of the Golden Chamber says if the heat is in the lower jiao, you will urinate the blood. Xiajiao damp heat accumulation knot, burn blood collaterals, and blood overflow pulse is red urine or microscopic hematuria. From the point of view of the combination of traditional Chinese and western medicine, hematuria is formed by the accumulation of damp-heat toxin in the Xiajiao, so for patients with external damp-heat evil, it should be supplemented by clearing dampness heat, cooling blood and stopping bleeding.

Wind pathogens and dampness pathogens mixed with other pathogens can often induce or even aggravate the condition of IgAN patients. From the point of view of modern medicine, it often represents the occurrence of immune inflammatory reactions and disease activity, which is consistent with the history of recurrent mucosal infection in most clinical IgAN patients. Some studies have shown that the exogenous wind-heat syndrome is mainly capillary endothelial hyperplasia, which can destroy the vascular loop, so it is in the early stage of the disease, so the pathological damage is mild [7]. Some studies have also shown that the renal lesions of damp-heat syndrome are mainly glomerular segment, renal interstitial inflammatory cell infiltration and destruction of capillary loop active lesions, which induce immune response and make cells in an activated state. it leads to the increase of the release of cytokines and inflammatory mediators and the increase of immune complex deposition, which further leads to acute pathological damage of glomeruli and interstitium [8]. This will be specific to the macro of modern medicine, so that we can more intuitively and accurately understand the TCM syndrome type of IgAN, a good grasp of each stage of the disease changes, accurate adjustment of prescriptions and medication, and our clinical doctor experience complement each other, timely control of the active lesions of IgAN, delay the progress of renal damage is of great significance (See Table 2).

Table 2: IgAN overview of traditional Chinese medicine table

The disease name of traditional Chinese medicine corresponding to IgAN	Pathogeny	Rule of treatment
edema, urine blood, Guange, low back pain, turbid urine	Wind pathogen	Protect the lungs and guard against the pathogens.
	Damp pathogen	clearing dampness-heat, cooling blood and stopping bleeding

2. Discussion on the Treatment Principle of Igan from the Angle of Wind Pathogen and Damp Pathogen

As the number of good deeds of wind evil is changing and it is easy to add other evils to the disease, which makes the treatment of IgAN more complicated, we should soothe the evil and calm the pass, and we should evacuate the external wind and put forward the treatment of evacuating the table and dispelling the evil[9]. Professor Zhang Yu [10] based on his many years of clinical experience, put forward a variety of wind treatment methods, such as dispelling wind, resisting wind, searching wind, extinguishing wind and so on, and achieved good results in clinic. Professor Wang Yaoxian [11] through continuous clinical practice and experience summary, put forward through expelling wind and promoting pharynx to clear, search wind to overcome dampness to dredge collaterals to delay the development of IgAN patients. Professor Guo Dengzhou [12] thinks that we should start with the upper, middle and lower triple jiao to treat damp-heat type IgA nephropathy dominated by gross hematuria, soothing wind and clearing heat, clearing dampness and heat, clearing heat and dampness, kidney and bladder, and cooling blood to stop bleeding, dredging Sanjiao, opening depression and removing dampness, so as to achieve the purpose of dredging Sanjiao, controlling infection and protecting patients' renal function.

3. Discussion on the Clinical use of IgAN from the Angle of Wind Pathogen and Damp Pathogen

3.1 Use of Wind-repellent Drugs

Si Shaoe etc. [13] pointed out that no matter whether IgAN is in the acute phase or in the chronic migration phase, several anti-rheumatic drugs should be added on the basis of different prescriptions selected according to different symptoms, Such as Divaricate Saposhnikoviae Root, Herba Schizonepetae, Chuanlong Yam, Angelicae Pubescentis Radix, Largeleaf Gentiana Root, etc, Or add Bupleurum and Astragalus membranaceus to the outside. Professor Mi Xiuhua [14] believes that wind evil runs through the occurrence and development of IgAN nephropathy, and its clinical changes are also consistent with the characteristics of wind evil, especially emphasizing that removing wind evil can better dispel the evil of dampness and blood stasis. It is pointed out that the external wind should be sparse and dispelled, and special attention should be paid to the use of wind medicine in clinic, and good results have been achieved. Professor Zhang Yu [10] believes that the disease occurs in the wind, and the disease of IgAN nephropathy caused by rheumatism must also be treated from the wind. In clinic, it is often used to dispel the wind evil of the skin, such as Divaricate Saposhnikoviae Root, Herba Schizonepetae, and Folium Perillae, in order to dispel the wind evil of the skin, and pointed out that because of the crisscross growth trend of rattan drugs such as Herba Swertiae Mileensis and Tuber Fleeceflower Stem, it can be used to treat IgAN nephropathy by going deep into the blood veins of the extremities and evacuating the wind evil hidden in the kidney collaterals. The above can well confirm that wind pathogen plays an important role in all periods of IgAN, which also reminds us that clinicians have to pay attention to the influence of wind pathogen on the development and changes of the disease in the whole treatment process of IgAN, and timely and accurately apply anti-wind drugs to slow down kidney damage. In addition, it can also be observed that in the active stage of IgAN, the renal pathology is characterized by hyperplasia, inflammation and so on. And in primary IgAN, the deterioration of urine test is often accompanied by acute respiratory or gastrointestinal infection, but when the infection is controlled, the abnormal index of urine test will be improved. An overview of the IgAN Clinical practice guidelines for traditional Chinese Medicine also recommends that in the early stage of IgAN, tonsillectomy can be performed to improve kidney survival if the inflammation is

controlled and the condition is stable [15] (See Table 3).

Table 3: A summary of the experience of various doctors in treating IgAN with wind-repellent drugs

Summary of the experience of doctors	Si Shaoe ect. Emphasized the selection of prescriptions due to syndrome and the use of wind dispelling drugs.
	Professor Mi Xiuhua thinks that the external wind should be sparse and dispelled.
	Professor Zhang Yu believes that the disease occurs in the wind and the disease changes with the wind.

3.2 The Use of Dampness-Removing Drugs

Professor Zhang Daning [16] stressed that IgAN has a long course of disease, often conceals the disease, and is dominated by evil in the early stage of the disease, so efforts should be made to dispel pathogens, for the syndrome of internal accumulation of damp heat caused by exogenous dampness-heat or spleen deficiency dampness, it is appropriate to clear heat and remove dampness and remove blood stasis and stop bleeding, Gegen Qinlian decoction and small thistle decoction can be used to add and subtract on the prescription. The choice of drugs: Scutellaria Radix and Coptis Root clearing heat and dryness, Glabrous Greenbrier and Rhizoma Dioscoreae septemlobae dispel dampness and dissolve turbidity, and emphasize that those with more dampness and heat can add Rhizoma atractylodes and Cortex Phellodendri as appropriate to strengthen the power of clearing heat and dryness. Ren Jixue, a master of traditional Chinese medicine [4], believes that heat-clearing and dampness-relieving drugs still run through the whole process of the treatment of IgAN nephropathy. If dampness and heat are obvious, you can add dampness drugs such as Creeping rostellularia herb, White Chloe, Glabrous Greenbrier, Cortex Phellodendri, Rhizoma atractylodes, Radix angelicae dahuricae, Cablin Potchouli herb, Fortune eupatorium herb, Atractylodes macrocephala and so on. What ' s more, it has drawn up a prescription for clearing and nourishing the kidney, which is mainly treated with dampness and heat. Wu Jinhua, a famous traditional Chinese medicine, found that the patients with IgAN nephropathy dominated by dampness are difficult to recover, which is more consistent with the characteristics of dampness and turbid evil in traditional Chinese medicine. At this time is in the active stage of the disease, renal pathology is mainly proliferative lesions, clinical syndrome differentiation is mostly damp-heat injection of kidney collaterals, when clearing heat, detoxification and dampness, promoting blood circulation and removing blood stasis, Can choose Bazheng Powder, Shuzao Yinzi, Simiao Yongan decoction and other prescriptions to add or subtract. With Radix salviae miltiorrhizae, Radix Paeoniae Rubra, Dandelion, Spreading hedyotis diffusa, rhubarb and other products such as clearing heat, promoting blood circulation and removing blood stasis, while using Hairyvein, Cattail pollen, Rhizoma imperatae and other drugs to cool blood and remove blood stasis to stop bleeding. An IgAN patient with IgAN (WHO) grade IV, diffuse Mesangial hyperplasia with focal globular, segmental sclerosis, segmental membrane proliferation and mild renal interstitial changes was treated. During the second diagnosis, it was judged that the patient belonged to the syndrome type of deficiency of spleen and kidney, dampness-heat and blood stasis. Simiao Yongan decoction combined with self-made Shenshuai mixture was selected as the method of nourishing the kidney, promoting blood circulation and removing blood stasis. The patient's disease was mild after taking medicine, and there was no discomfort after three diagnoses plus dialectical treatment. The condition is stable [17] (See Table 4).

Table 4: An overview of the experience of doctors in the treatment of IgAN with dampness-removing drugs

Summary of the experience of doctors	Professor Zhang Daning has the syndrome of internal accumulation of dampness and heat, which should be treated by clearing heat and removing dampness and removing blood stasis to stop bleeding.
	Ren Jixue, a master of Chinese medicine, believes that heat-clearing and dampness-relieving drugs should run through the whole process of the treatment of IgAN nephropathy.
	Wu Jinhua believes that the lingering and intractable characteristics of IgAN nephropathy are consistent with the characteristics of dampness and turbid evil in traditional Chinese medicine.

4. Discussion and Prospect

The induction and aggravation of IgAN are closely related to wind pathogen and dampness pathogen, which can often be mixed with other pathogens to aggravate the symptoms of patients. Many doctors take each patient as the main body from a different point of view (including a deep study of the characteristics of rheumatism, the pathogenesis of the disease, the pathological changes of the kidney, and the clinical symptoms of the patients). After dialectical treatment and summary, it is pointed out that the two evils of wind and dampness run through the IgAN all the time, but the evil qi is more serious in different stages, mainly wind pathogen in the initial stage of the disease and dampness pathogen in the chronic active stage. Therefore, we need to maintain a certain sensitivity to the patient's condition, and timely adjust the prescription and medication at different stages to reduce the clinical symptoms of patients, in order to protect the renal function of patients, delay the process of IgAN, and improve the quality of life of patients.

The pathogenic mechanism of IgAN is complex, and the pathogenic mechanism is not completely clear. At present, the treatment of this disease is still in the stage of exploration and discovery, Hormone shock and immunosuppression are still the mainstream treatment methods in western medicine, and traditional Chinese medicine has certain advantages in the treatment of IgAN. Therefore, it is particularly important to improve the clinical curative effect by treating IgAN from wind and dampness. Of course, there are also some problems, such as small sample size, short statistical time, difficult return visit and so on. In the future, we should continue to provide evidence-based basis for clinical application, in-depth study of its effective mechanism, in order to faster and better treatment of IgAN nephropathy and improve the quality of life of patients.

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