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Overview of Traditional Chinese and Western Medicine Treatment of IgA Nephropathy

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Abstract: IgA nephropathy is a kidney disease in which the deposition of IgA-based immune complexes in the mesangial region of the glomerulus is the main pathological feature. It is the most common primary glomerular disease in the world, and it is the main cause of ESRD patients in my country. Because its etiology and pathogenesis are not yet clear, there is currently no unified treatment plan. The drugs commonly used in western medicine to treat IgA nephropathy include angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, glucocorticoids and other immunosuppressive agents. Traditional Chinese medicine has unique advantages in the treatment of IgA nephropathy. It carries out individualized syndrome differentiation and treatment based on the stage and type of the disease, combined with the personal experience of doctors, and has significant clinical effects. Therefore, we should give full play to the advantages of the integration of Chinese and Western medicine, and intensify the exploration of Chinese and Western medicine treatment options. This article reviews the research progress of IgA nephropathy in traditional Chinese medicine and western medicine.

1. Introduction

IgA nephropathy (IgA nephropathy, IgAN) refers to chronic kidney disease caused by the deposition of immunoglobulin IgA-based immune complexes in the mesangial area of the glomerulus [1]. Although its course usually develops gradually, it causes 25-50% of patients to develop end-stage renal disease (ESRD) within 20 years after diagnosis and shorten life expectancy by 10 years [2]. After many years of research at home and abroad, it has been found that clinically, IgAN has various manifestations, which can be manifested as simple hematuria and/or proteinuria, and can also be manifested as kidney damage such as renal dysfunction. As the disease progresses, more than 30% of patients can develop end stage renal disease (ESRD) 10-20 years after the onset of disease [3]. As

the etiology and pathogenesis of IgAN are still unclear, there is currently no unified treatment plan. Traditional Chinese medicine has certain advantages in the treatment of IgAN, so the integration of Chinese and Western medicine will become a promising development direction for IgAN treatment in the future.

2. The pathogenesis of IgA nephropathy

2.1 Multiple-Hits Theory

The "Multiple-Hits Theory" [4] is the most widely accepted explanation in the academic community for the onset of IgA nephropathy. "Multiple-Hits" are mainly divided into the following four steps: (1) Abnormal IgA1 formation leads to increased levels of IgA1 (Gd-IgA1) for galactose deficiency; (2) Increased Gd-IgA1 causes autoimmune reaction and leads to the production of anti-glycan antibodies. Gd-IgA1 is recognized as a self-antigen by anti-glycan antibody (anti-Gd-IgA1 antibody); (3) Produce Gd-IgA1 immune complex. Increased Gd-IgA1 and anti-glycan antibodies lead to the formation of immune complexes and deposition in the glomerular mesangium; (4) The immune complex deposited in the kidney activates the complement pathway and stimulates the proliferation of mesangial cells. It leads to increased release of cytokines, chemokines and extracellular matrix proteins, leading to inflammation and fibrosis, and proteinuria.

2.2 The theory of Complement activation

Although there is no evidence that IgAN has the activation of the classical pathway of complement, a few studies suggest that some patients with IgAN have C1q deposition in the mesangial area, which is related to renal tubular atrophy/interstitial fibrosis, suggesting that there may be activation of the classical pathway of complement. The alternative pathway of complement [5] is the most common pathway of complement activation in IgAN. 75% to 100% of patients with IgAN have C3 deposition in the kidney tissue, and 30%-90% have the co-deposition of complement H, IgA and C3, and circulating elevated factors B and D are also present in. IgA activates the complement lectin pathway by binding to mannose binding lectin (MBL) [6]. The single nucleotide polymorphism in the promoter region of MBL affects the MBL content of patients with progressive IgAN, while IgAN lacking MBL patients have an increased risk of progression.

3. Western medicine treatment of IgA nephropathy

3.1 Renin-Angiotensin System (RAS) Blockers

RAS blockers mainly include angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor antagonists (ARB). Relevant studies have shown that hypertension is a risk factor affecting IgAN treatment and prognosis. ACEI and ARB can lower blood pressure and selectively dilate renal extrinsic arterioles, reduce intraglomerular hypertension, and reduce glomerular filtration pressure, thereby reducing proteinuria and delaying the progression of renal fibrosis. However, the curative effect of ACEI and ARB is not only for lowering blood pressure, they also have the effect of reducing proteinuria and protecting the kidneys. KDIGO clinical practice guideline recommend that patients with 24h urine protein> 1g/d, need to be treated with ACEI and ARB; The patient's 24-hour urine

protein is 0.5 to 1.0g/d, and ACEI and ARB can also be used for treatment, but if the patient is tolerant to the medication, the dosage should be gradually increased so that the patient's 24-hour urine protein is controlled below 1g/d. ACEI and ARB treatment of IgAN, the patient's urine protein level can be significantly reduced, which can alleviate the patient's condition. Pei et al [7] applied ACEI to 38 children with IgAN and found that the level of oxidative stress in the children was significantly reduced. The new drug Aliskiren is an oral direct renin inhibitor that can completely inhibit RAS. Compared with ACEI and ARB, the treatment of the latter can increase the patient's plasma renin level. The results of Szeto et al [8] suggest that the combination of aliskiren and ACEI or ARB in the treatment of IgAN can effectively reduce the proteinuria content.

3.2 Glucocorticoids

At present, glucocorticoids are widely used in the treatment of IgAN patients, especially for patients with moderate to severe urine protein or severe pathological damage. It is difficult to use RAS blocker alone to make 24h urine protein quantification less than 0.5g/d, so glucocorticoids should be used to improve the patient's condition [9]. In terms of pathological characteristics, the pathogenesis of IgAN is closely related to immune abnormalities. Glucocorticoids can not only adjust the activity of inflammatory cells and improve immune regulation, but also act on vasoactive substances, which can effectively improve glomerular microhemodynamics [10]. The KDIGO guidelines recommend: If the patient’s urine protein remains above 1g/d and his glomerular filtration rate (eGFR)>50 mL/min after applying ACEI or ARB, blood pressure control and other measures for at least 90 days, glucocorticoids can be used for 6 months. In a meta-analysis that included 9 randomized controlled trials (RCT), the experimental conclusions of 536 IgAN patients (24h urine protein quantification> 1g/d, and renal function maintains a normal level) confirmed that short-term and high-dose glucocorticoid therapy can effectively protect kidney function, but long-term and low-dose use But there is no such effect [11]. The study by Rauen et al [12] included 337 patients with IgAN(24-hour urine protein is 0.75~3.5g/d, and the estimated glomerular filtration rate is 30~90mL/min), and the results showed that hormone therapy had no significant effect. A randomized, double-blind controlled trial of budesonide (TRF) (a clinical study for IgAN targeted therapy) of a new oral targeted release drug by Fellström et al [13] showed that TRF combined with RAS blockers can Effectively reduce urine protein in patients with IgAN, but this study did not have long-term follow-up to observe the changes in urine protein levels and renal function in patients, and further large sample tests are needed to confirm.

3.3 Immunosuppressants

3.3.1 Cyclophosphamide (CTX)

CTX can reduce the secretion of antibodies by B cells, reduce or stop the deposition of immune complexes in the glomerulus, and can interfere with cell proliferation, and play a direct or indirect anti-inflammatory effect. However, due to its large side effects, it is generally used as a combination drug, mainly for severe IgAN patients. The KDIGO guidelines recommend that patients with rapidly progressing IgAN can be treated with glucocorticoid combined with CTX [14]. In a retrospective analysis by Peters et al [15], 19 patients with IgAN (renal insufficiency or severe proteinuria) were treated with cytotoxic drugs combined with prednisone, and the results showed that it is beneficial

for patients with advanced IgAN. However, the sample size of this study is small, and further multi-center research with large sample size is needed.

3.3.2 Mycophenolate mofetil (MMF)

MMF is a new type of immunosuppressant. A North American multicenter RCT study by Hogg et al [16] showed that 44 patients with IgAN were randomly combined with MMF or placebo for 6 months and found that MMF had no significant effect on reducing proteinuria. The meta-analysis by Zheng et al [17] included 8 patients with IgAN. The results of the RCT study showed that MMF is more effective than placebo. It may have similar efficacy to other immunosuppressive agents in alleviating the progression of kidney disease, and may not increase the risk of adverse events. The conclusions of clinical research on MMF at home and abroad are inconsistent, so its efficacy is still unclear. And the KDIGO guidelines do not recommend the use of MMF for the treatment of patients with non-Chinese IgA nephropathy [14].

4. Traditional Chinese Medicine(TCM) treatment of IgA nephropathy

4.1 Types of syndrome differentiation and treatment

Chief Chinese physician Fu Yi believes that the most common type of IgAN in the chronic persistent period is the deficiency of both qi and yin, and it can also be routinely identified as deficiency of both qi and yin for those who are more difficult to differentiate. Such patients are usually treated with Shenqi Dihuang Decoction.Zhibai Dihuang Decoction is commonly used for syndrome of yin deficiency of liver and kidney. The syndrome of yang deficiency of spleen and kidney is usually treated with solid spleen drink or Zhenwu decoction. yupingfeng powder is commonly used for spleen and lung qi deficiency. However, the three pathological factors of fluid-dampness, damp heat and blood stasis are more common in the standard evidence [18]. In the early stage of IgAN, qi and yin deficiency are the main aspects, while dampness, blood stasis and wind are trapped at the same time. In the middle and late stages, yang deficiency becomes the main aspect. In the early stage of IgAN, deficiency of both qi and yin are the main aspects, while dampness, blood stasis and wind are trapped at the same time. In the middle and late stages, yang deficiency becomes the main aspect. In clinical practice, according to the syndrome differentiation analysis of the eight outlines, cold, heat, deficiency, and actuality are analyzed, and the proportion of each pathogenic factor is distinguished, so the medication is different. Professor Li Shunmin believes that most patients with IgAN are caused by the leakage of fine substances. The essence and blood are homologous to the spleen, and spleen deficiency will cause biochemical loss, so acquired loss of nourishment can aggravate spleen and kidney deficiency [19]. If things go on like this, it will easily lead to deficiency of both Qi and Yin and Qi deficiency of the spleen and kidneys. In the acute phase, wind-heat in the upper Jiao, dampness in the middle Jiao, and damp-heat in the lower Jiao can be seen, combined with liver depression, water dampness, phlegm dampness, blood stasis and other factors. Deng Yueyi et al [20] included 209 cases of IgAN patients and performed TCM syndrome analysis, and divided IgAN into 4 TCM syndrome types: One is the liver and kidney yin deficiency type, the other is the qi and yin deficiency type, the third is the spleen and kidney yang deficiency and the blood stasis type, and the fourth is the lung and the spleen qi deficiency and the damp-heat type. The results of this study have great reference value for clinical diagnosis and treatment of IgAN and further research.

4.2 Stages of syndrome differentiation and treatment

Professor Shi Wei believes that IgAN should distinguish between the acute attack period and the chronic duration period. The acute attack period is mostly wind-heat and damp-heat, and emphasizes "treatment from the pharynx". Therefore, clinical treatment should pay attention to the treatment principles of dispelling wind, clearing away heat, and relieving throat and detoxification. Taking Qingxuan as the main treatment method for medication, conforming to the characteristic of the wind being opening-letting. Choose Yinqiao powder or Platycodon Decoction for prescription. We should first identify the heavier damp heat, then identify the part where the damp heat stops gathering. For those with severe dampness, the main treatment should be to eliminate dampness. For those with severe heat, clearing away heat is the main focus, and removing dampness is the supplement. According to the part where damp and heat stays to choose the method of division and elimination. Modification of Zhuye Gypsum Decoction, Huanglian Jiedu Decoction, Sanren Decoction, etc. In the chronic persistent period, attention should be paid to the spleen and kidneys, and it is advocated to "treat the kidneys from the spleen", to regulate the acquired spleen and stomach, and to nourish the yin and yang of the innate kidney qi.Modification of Xiangsha Liujunzi Decoction and Liuwei Dihuang Decoction [21]. According to the different clinical symptoms of IgAN, Professor Liu Ming divided it into a positive deficiency and an evil excess. Therefore, the disease is divided into an acute attack period and a chronic prolonged period. The main aspect of acute attack is to eliminate evil. The treatment principle is the combination of dispersing wind, clearing away heat, detoxification and cooling blood to stop bleeding, and the commonly used empirical prescription is Yinlian Dihuang Decoction. In the chronic prolonged period, the main therapies are proposed to invigorate the spleen and kidney and nourish blood to stop bleeding. The commonly used empirical prescription is decoction for strengthening the spleen and kidney [22]. Chief Chinese physician Fu Yi believes that IgAN is often divided into acute phase and chronic phase [18], and the acute phase includes the typical acute phase and acute exacerbation or recurrence due to pathogens after illness. Zhang Duo, an old Chinese doctor, differentiates IgAN from a macro perspective, and divides it into acute phase and chronic prolonged phase. In the acute phase, patients mostly present with the syndrome of excess heat in the kidney meridian, and the main treatment is to purify the kidney and cool the blood. In the chronic prolongation period, the key factor for prolongation is the deficiency of both kidney qi and kidney yin. Therefore, the key to treatment is to replenish kidney qi and kidney yin [23].

4.3 Master's empirical treatment

Professor Qiu Moyan believes that the occurrence of IgAN is related to poor triple-burner, and its pathological products are mostly damp heat and blood stasis. Therefore, in clinical treatment, the treatment method is "Tiao Bu Fen Hua" .Starting from the triple-burner, the main aspect is to eliminate the stagnation of the triple-burner, and then the gasification of the triple-burner is smooth. The movement of qi leads to the movement of blood, and the damp heat and blood stasis can be expelled, so as to achieve a significant effect of removing evil and correcting. The word "Tiao" refers to the Qi machine that adjusts the focal point smoothly. In clinical use drugs for evil-wind, such as charred herba schizonepetae, Radix Saposhnikoviae. A little drugs for evil-wind is used to clarify the lung qi and regulating qi activityThe word "Bu" refers to strengthening the body and replenishing deficiency and replenishing the deficiency of the middle jiao, and a large amount of raw astragalus should be

used clinically. The word "Fen" refers to distinguish the turbidity of secretion and the turbidity of Xiajiao. In clinical treatment, more use of Smilax chinensis, poison yam, ghost arrow feather and rhubarb. The word "Hua" refers to the combination of dissipating dampness, removing blood stasis, clearing heat and detoxication to remove excess pathological products. In clinical practice, drugs for cooling blood and removing blood stasis are often used, such as salvia miltiorrhiza, red peony root, sophora japonicus and bitter-cold rhubarb[24]. Based on years of clinical experience, Professor Mi Xiuhua created a personal characteristic Shipi Gushen Huayu Decoction. This prescription can significantly reduce the fusion and shedding of epithelial cell foot processes, reduce the damage of glomerular basement membrane, and promote the repair of glomerular pathological damage, which has a significant protective effect on podocytes [25]. Professor Mi advocated that in clinical treatment, the spleen should be strengthened while strengthening the kidney. When the spleen qi is full, the fluid-dampness can be cured, and the clear qi can rise naturally, and then it can have the effect of strengthening the innate and promoting the acquired. The clinical prescription drugs are mainly astragalus, codonopsis, yam, atractylodes, poria, white lentils, coix seed, dogwood and other medicines, which have the effect of invigorating the spleen and kidneys and clearing damp. Only in this way can they complement each other, and achieves good results. Professor Ye Chuanhui believes that the pathogenesis of IgAN is the asthenia in origin and asthenia in superficiality. Patients often suffer from repeated attacks due to external evils. It advocates that if IgAN patients feel the invasion of external pathogens, or have both evils and the symptoms are more urgent, the symptoms should be treated first, and the symptomatic treatment in acute condition. After the acute symptom of the mark, the asthenia in origin is treated [26]. Professor Ye often asks patients with IgAN to use medicinal decoction instead of tea as a supplementary treatment. Chinese herbal tea is a method of adjuvant treatment of IgAN. The curative effect of taking traditional Chinese medicine tea and drinking prescription. Professor Ye attaches great importance to treating disease before it occurs, emphasizing preventive treatment of disease.She believes that in the treatment of IgAN, even if there is no exogenous feeling, Yupingfeng powder can be given on the basis of dialectical treatment to prevent exogenous feelings and prevent recurrence. Professor Ye's unique treatment idea has received good clinical results.

5. Outlook

In summary, the clinical manifestations and pathological changes of IgAN are diverse. There is no specific treatment for IgAN in western medicine, and its pathogenesis is not clear, and satisfactory therapeutic effect cannot be achieved. However, in recent years, the understanding of the pathogenesis of IgAN has focused on linking the physical and chemical characteristics of IgA with the genetic background. Regarding the treatment of IgAN with traditional Chinese medicine, doctors will perform syndrome differentiation and treatment according to their staging and classification, and contact their personal experience, and the combined effect will be significant. However, in clinical syndromes, different physicians have relatively large subjectivity and personal characteristics in their understanding of the IgAN condition, which leads to the situation that the prescription and the medicine are different when the syndrome is the same syndrome type. And there is no uniform standard for the judgment of curative effect, and lack of objectivity. Therefore, multi-center, large-sample TCM clinical research and retrospective research of TCM experience are needed to provide

sufficient evidence for establishing the objective of TCM treatment of IgAN. Combining Western medicine pathology type with TCM syndrome differentiation is also of great practical value to the clinic, and it is worthy of further study.

References

[1] Mestecky J, Novak J, Moldoveanu Z, et al.IgA nephropathy enigma[J]. Clin Immunol, 2016, 172: 72-77.

[2] Shang S, Li XK.The Role of Immune Modulation in Pathogenesis of IgA Nephropathy.Front Med, 2020, 7(92): 63-67.

[3] Li Lei-Shi, Liu Zhi-Hong. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. [J]. Kidney international, 2004, 66(3).

[4] Makita Y, Suzuki H, Kano T, Takahata A, Julian BA, Novak J, et al.TLR9 activation induces aberrant IgA glycosylation via APRIL- and IL-6-mediated pathways in IgA nephropathy. Kidney Int. (2020) 97:340–9. doi: 10.1016/j.kint.2019. 08.022

[5] Maillard N, Wyatt RJ, Julian BA, et al. Current understandingof the role of complement in IgA nephropathy. J Am SocNephrol, 2015, 26(7): 1503-1512.

[6] Roos A, Bouwman LH, Van Gijlswijk Janssen DJ, et al.Human IgA activates the complement system via the mannan-binding lectin pathway. J Immunol, 2001, 167(5): 2861-2868.

[7] Pei Y, Xu Y, Ruan J, et al. Plasma oxidative stress level of IgA nephropathy in children and the effect of early intervention with angiotensin-converting enzyme inhibitors [J]. J Renin Angiotensin Aldosterone Syst, 2016, 17(2): 1470320316647240.

[8] Szeto CC, Kwan BC, Chow KM, et al. The safety and shortterm efficacy of aliskiren in the treatment of immunoglobulin a nephropathy -a randomized cross-over study [J].PLoS One, 2013, 8(5): e62736.

[9] Huang JL, Yu SW, Yu DR, et al. The progress of glucocorticoid in the treatment of IgA nephropathy [J]. Chinese Journal of Integrated Traditional and Western Nephrology, 2018, 19(5): 430-432.

[10] Lie CH, Xie YS, Chen XM. Evidence-based study of glucocorticoid in the treatment of IgA nephropathy [J]. Chinese Journal of Integrated Traditional and Western Nephrology, 2008, 9(3): 273-275.

[11] Lv J, Xu D, Perkovic V, et al. Corticosteroid therapy in IgA nephropathy [J]. J Am Soc Nephrol, 2012, 23(6): 1108-1116.

[12] Rauen T, Eitner F, Fitzner C, et al. Intensive SupportiveCare plus Immunosuppression in IgA Nephropathy[J].NEngl J Med, 2015, 373(23): 2225-2236.

[13] Fellström BC, Barratt J, Cook H, et al.Targeted-release budesonide versus placebo in patients with IgA nephropathy(NEFIGAN): a double -blind, randomised, placebo-controlled phase 2b trial [J]. Lancet, 2017, 389(10084): 2117-2127.

[14] KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES.JUNE, 2020 PUBLIC REVIEW DRAFT.

[15] Peters HP, van den Brand JA, Berger SP, et al.Immunosuppressive therapy in patients with IgA nephropathy[J].Neth J Med,2015,73(6):284-289.

[16] Hogg RJ, Bay RC, Jennette JC,et al. Randomized controlled trial of mycophenolate mofetil in children, adolescents, and adults with IgA nephropathy[J].Am J Kidney Dis, 2015, 66(5): 783-791.

[17] Zheng JN, Bi TD, Zhu LB, et al. Efficacy and safety of mycophenolate mofetil for IgA nephropathy: An updated meta-analysis of randomized controlled trials [J]. Exp Ther Med, 2018, 16(3): 1882-1890.

[18] Liu YF, Wang Y. Director Fu Yi's Experience in Treating IgA Nephropathy [J]. Medical Information, 2020, 33(21): 155-156.

[19] Fan YJ, He RM, Yang SD, et al. Professor Li Shunmin's experience in treating IgA nephropathy [J]. Journal of Chengdu University of Traditional Chinese Medicine, 2018, 41(3): 91-94.
[20] Tao R, Deng YY,Chen WJ, et al. Analysis of TCM Syndromes of 209 Cases of IgA Nephropathy and Correlation Study with Clinical Indicators [J]. Chinese Journal of Integrated Traditional and Western Nephrology, 2011, 12(11): 982-987.
[21] Wang XQ, Huang JJ,Xie YX,et al. Professor Wei Shi's experience in treating IgA nephropathy [J]. Chinese Journal of Integrated Traditional and Western Nephrology, 2017, 18(6): 529-530.
[22] Ding N, Liu M. Professor Liu Ming's experience in treating hematuria in IgA nephropathy [J]. Guide of China Medicine, 2018, 16(1): 185-186.
[23] Li GH,Guan J,Zhang L,Zhang D. Professor Zhang Duo's experience in diagnosis and treatment of IgA nephropathy [J]. Nei Mongol Journal of Traditional Chinese Medicine, 2020, 39(12): 66-67.
[24] Wang JD,Zhao CBW,Yu WC,et al. Professor Qiu Moyan's experience in the treatment of IgA nephropathy from "Tiao Bu Fen Hua" [J]. Chinese Journal of Integrated Traditional and Western Nephrology, 2017, 18(6): 475-477.
[25] Wang GQ, Mi XH. Mi Xiuhua's Experience in Treating IgA Nephropathy [J]. JOURNAL OF CHINESE RESEARCH HOSPITALS, 2017, 4(5): 40-43.
[26] Yang Y. Professor Ye Chuanhui's clinical experience in treating IgA nephropathy [J]. Journal of Sichuan Traditional Chinese Medicine, 2018, 36(10): 12-13.