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Research Progress in the Treatment of IgG4-related Diseases in Chinese and Western Medicine

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Abstract: ***IgG4-related diseases (IgG4-RD) is a group of diseases characterized by abnormally elevated levels of IgG4 antibodies and infiltration of IgG4+ plasma cells. Currently, Western medicine mainly uses hormones, immunosuppressants, and biologically targeted therapies for treatment. Traditional Chinese medicine mainly uses dialectic therapy to treat the disease. The syndrome types are mostly Yin deficiency of the liver and kidney, phlegm and blood stasis, Yang deficiency of the spleen and kidney, and damp-heat of the liver and gallbladder. This article provides a review of the research progress in epidemiology, clinical manifestations, diagnosis, and treatment of IgG4-related diseases in Chinese and Western medicine.***

Keywords: IgG4-related diseases, Diagnosis, Chinese and western medicine treatment, Research progress**.**

1. Introduction

IgG4-related disease (IgG4-RD) is a relatively rare immune-mediated chronic inflammatory disease with fibrosis. The disease can involve multiple organs or tissues such as the pancreas, lymph nodes, salivary glands, lacrimal glands, retroperitoneum, etc. Its clinical characteristics are elevated serum IgG4 levels with IgG4+ plasma cell infiltration in the affected tissues and organs, resulting in their hyperplasia and enlargement, tissue destruction, and even functional failure [1]. Due to the variability of its clinical presentation, the disease has several former names, such as autoimmune pancreatitis (AIP), Mikulicz's disease (MD), retroperitoneal fibrosis (RPF), etc.In recent years, there have been successive case reports, but due to its low incidence and complexity of clinical manifestations, clinicians do not have enough knowledge, and mass lesions are often misdiagnosed. This article summarizes the research results in recent years and describes the progress of the epidemiology, clinical manifestations, diagnosis, and treatment of this disease in Chinese and Western medicine, with a view to deepening the knowledge of this disease in clinical work and providing ideas for the subsequent research and discussion of IgG4-RD in Chinese and Western medicine.

2. Epidemiology

According to a study in the United States, the incidence and prevalence of IgG4- RD from 2015 to 2019 were reported to be 1.39 per 100,000 person-years and 5.3 per 100,000 persons, respectively [2]. The risk of death in the lgG4- RD population is 2.5 times higher than in the non-IgG4- RD population, and associated risk factors include misdiagnosis and delay in diagnosis of the disease itself, leading to functional impairment of the pancreas, bile ducts, and kidneys, as well as treatment-related infections and cardiovascular events. Of the 8,000 patients with IgG4-RD in Japan in 2009, 5,190 did not show pancreatic involvement, suggesting the current lack of epidemiologic evaluation of the disease for multiple clinical manifestations of the disease.IgG4-RD occurs mostly in middle-aged and elderly people, and no environmental and genetic correlates have been clearly found to be directly associated with IgG4-RD [3]. The current global incidence and prevalence of IgG4-RD remains largely underestimated. The epidemiologic data of lgG4- RD has not been reported in our country for the time being, and is a direction that needs to be studied in the future.

3. Diagnostic Criteria

Currently, the diagnosis of lgG4-RD is mainly based on the 2019 ACR/EULAR categorical diagnostic criteria and the 2020 revised Japanese comprehensive diagnostic (revised comprehensive diagnostic RCD) criteria. It has been shown that the ACR/EULAR criteria remain highly specific for patients with typical clinical presentations without pathologic examination and that the sensitivity of the ACR/EULAR criteria can be further improved by performing pathologic examination. In contrast, RCD criteria are advantageous in diagnosing IgG4-RD patients characterized by rare organ involvement [4]. Flexibly mastering and applying these two diagnostic criteria will help improve the diagnostic efficiency of lgG4 RD.

The RCD classification criteria are the earliest comprehensive classification and diagnostic criteria and one of the most widely used by clinicians to date. The RCD criteria include three main aspects: characteristic clinical manifestations, elevated serum IgG4, and typical pathological features. The development of the RCD criteria has played an important role in the recognition and diagnosis of IgG4-RD by physicians in various countries and specialties around the world in the last decade. The diagnostic criteria for the ACR/EULAR classification primarily incorporate the characteristic clinical manifestations of common organ involvement and emphasize the exclusion of multiple diseases with IgG4-RD.Both of these criteria emphasize the need to exclude tumors, systemic vasculitis, and chronic infections from the diagnosis of the disease [5].

4. Western Medicine

Glucocorticoids are widely recognized as the drug of choice for the treatment of patients in the active phase of lgG4-RD, for both the induction of remission and the maintenance phase. Typically, it works quickly, with improvements occurring

within days to weeks, and the hormones are more than 90% effective [6]. Whether the hormones are effective or not can also be an important basis for determining whether the diagnosis is correct. A moderate starting dose of hormone, equivalent to prednisone 30 ~ 40 mg/d, is generally recommended, but the exact dose should be adjusted on an individual basis. After controlling the disease, it should be gradually reduced to a small maintenance dose [7].

Conventional immunosuppressive agents have been widely used in the treatment of lgG4- RD in recent years, especially in combination with glucocorticoids as co-subtractive agents. Many studies have shown that hormones combined with immunosuppressive therapy are more effective than glucocorticoids alone in controlling the disease and reducing relapses [8-9]. The combination of hormones and immunosuppressants is recommended when the patient has a disease that cannot be adequately controlled by hormone therapy alone, or when the disease cannot be tapered with continued glucocorticoid use, or when the disease recurs during hormone tapering, and when the side effects of glucocorticosteroids are significant. Currently, due to the lack of evidence in high-quality evidence-based medicine, the choice of traditional immunosuppressive agents is mainly based on the experience of other autoimmune diseases, including mycophenolate mofetil, azathioprine, cyclophosphamide, leflunomide, methotrexate, cyclosporine, tacrolimus, thalidomide, and elamectin. Among them, mycophenolate mofetil and azathioprine are the most widely used in the clinic.

Biologically targeted therapies, especially rituximab, have achieved better results in the treatment of IgG4-RD. Rituximab may be considered for patients who have failed conventional therapy, relapsed during hormone tapering, or are hormone resistant or intolerant. However, after using rituximab, it is important to take precautions to prevent infections in order to reduce the probability of recurrence. Rituximab is effective as one of the treatments for IgG4-RD, but its potential risk of infection cannot be ignored. When using rituximab, infection prevention measures must be strictly followed and health education must be done to ensure long-term patient safety and efficacy.

5. Traditional Chinese Medicine Syndrome Differentiation and Treatment

The most common clinical manifestation of IgG4-RD is a mass, but there is no precisely defined description of IgG4-RD in traditional Chinese medicine. The clinical manifestations of this disease are similar to those of "acute suppurative parotitis", "mumps" and "scrofula" , etc.

5.1 Yin Deficiency of The Liver and Kidney

As age increases, the human body gradually depletes its yin, and prolonged illness makes it easier to damage yin, resulting in yin deficiency and yang hyperactivity. Liver belongs to Yin in physique and Yang in function. The liver and kidney are of the same origin. Yin does not control yang, leading to liver and kidney yin deficiency and excessive fire. A retrospective analytical study through Xuan Lei et al. showed that some patients with IgG4-RD were identified as yin deficiency of the liver and kidney in Chinese medicine. The treatment is based on nourishing the liver and kidneys, softening and dispersing hard lumps and choose prescriptions based on the evidence, such as Zhibai Dihuang Pill, Fluid-increasing Decoction, GanLuYing, etc [10]. Gao Ning et al. summarized through analysis of medical records that IgG4-RD patients often have liver and kidney yin deficiency and yin deficiency with excessive fire syndrome. Treatment includes nourishing yin and reducing fire, detoxifying and dispersing nodules, such as modified Zhibai Dihuang Pill. Common medicines include Sedum officinalis, Cornus officinalis, Yam, Paeonia lactiflora, Anemarrhena, Plantago asiatica, Prunella vulgaris, Scutellaria baicalensis, Dandelion, and oysters [11].

5.2 Phlegm and Blood Stasis

IgG4-RD diseases are mostly caused by the imbalance of yin and yang in the body, with no distinction between clear and turbid. The deficiency of positive qi is the basis of the disease, and factors such as blood stasis and phlegm turbidity are the pathogenic factors. Qiu Tiantian et al. conducted a case study on IgG4 related Mikulic disease, which showed that the dialectical classification of the disease includes phlegm and blood stasis, heat and toxin accumulation, and yin deficiency. The treatment includes resolving phlegm, removing blood stasis, clearing heat and detoxifying, and nourishing yin. It can be treated with General Antiphlogistic Decoction. Common medicines include Scutellaria baicalensis, Coptis chinensis, Isatis indigotica, Nepenthes ampullaria, Forsythia suspensa, Mulberry leaves, Panax ginseng, Dendrobium officinale, Curcuma zedoaria, Polygonum multiflorum, Portulaca oleracea, Hedyotis diffusa, etc [12].

5.3 Yang Deficiency of The Spleen and Kidney

The substances such as Qi, blood, fluid, and essence in the human body belong to Yin and rely on the warmth and propulsion of Yang Qi. If Yang Qi is depleted, the Yin essence substances in the body are difficult to distribute throughout the body, and prolonged accumulation of Yin evil can lead to illness. He Qingman et al. explored the traditional Chinese medicine treatment of IgG4 related diseases through the theory of "yang transforming qi, yin forming", and proposed that the syndrome differentiation and type of spleen kidney yang deficiency are more common in this disease. The treatment should combine warming yang and eliminating accumulation, with warming yang and transforming qi as the main treatment principles. Commonly medicines include Codonopsis pilosula, Atractylodes macrocephala, Cinnamomum cassia, Aconitum carmichaelii, Cinnamomum cassia, Epimedium, etc [13].

5.4 Damp-heat of The Liver and Gallbladder

The human body is susceptible to six types of pathogenic factors, with wind being the most prevalent. It is easy to carry various pathogenic factors and invade the body, often causing wind to envelop dampness and dampness, which can accumulate in the middle burner and affect the liver, gallbladder, spleen, and stomach. Ma Guiqin et al. proposed through case studies that some IgG4-RD patients are classified as damp heat in the liver and gallbladder. The treatment method is to clear the dampness and heat in the liver

and gallbladder, such as modifying Longdan Xiegan Tang. Commonly used medicines include Gentiana, Scutellaria baicalensis, Gardenia jasminoides, Atractylodes macrocephala, Alisma, Bupleurum chinense, Angelica sinensis, Phellodendron amurense, gypsum, etc [14].

6. Summarize

Combined Chinese and Western medicine treatment of IgG4-RD is an evolving field, and by complementing the strengths of Chinese and Western medicine, more comprehensive and individualized treatment plans can be provided to patients. Future research requires more high-quality clinical trials and basic studies to further validate and optimize treatment strategies.

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