Novel Advances in the Study of IgG4-Related Disease in the Eye and Ocular Adnexa

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Abstract

Immunoglobulin G4 (IgG4)-related disease in the eye and ocular adnexa (IgG4-ROD) is a newly discovered autoimmune disease that histologically exhibits extensive lymphocyte and plasma cell infiltration, occlusive phlebitis, and mat or whorled fibrosis. The disease can affect multiple ocular tissues and organs, such as the lacrimal gland, extraocular muscles, orbital fat, and trigeminal nerve. The main clinical manifestations are chronic, painless swelling of the orbit or unilateral orbit and proptosis, which may be accompanied by peripheral lymphadenopathy. Usually, visual impairment is not apparent, but in severe cases, it can cause a loss of function of the tissues and organs involved and affect the daily lives of patients. The pathogenesis of IgG4-ROD is not clear. Based on existing literature, it is speculated that it may be related to factors such as autoantibody production, microbial infection, and genetic inheritance. For the treatment of IgG4-ROD, glucocorticoids, immunosuppressive agents, biological agents, and surgery are mainly used in clinical practice. Although these treatment methods can achieve a particular effect, they have limitations, such as high recurrence rates, serious side effects, and postoperative complications. With the increase in IgG4-ROD-related reports, some progress has been made in the current understanding and research of the disease.

Introduction

Immunoglobulin G4 (IgG4)-related disease in the eye and ocular adnexa (IgG4-ROD) is a type of autoimmune disease with extensive lymphocyte and plasma cell infiltration, occlusive phlebitis, and mat or whorled fibrosis [1]; it belongs to one of the IgG4-related diseases (IgG4-RD). The concept of autoimmune pancreatitis was first introduced and officially proposed by Yoshida et al. [2] in

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1995, and to date, IgG4-RD has been recognized only by the medical community. Subsequently, Hamano et al. [3] also found significantly elevated IgG4 expression in the peripheral blood of patients with autoimmune pancreatitis. In 2004, Yamamoto et al. [4] found that the enlarged lacrimal gland and salivary gland of a patient with Mikulicz disease contained a large number of IgG4+ plasma cell infiltrates, thus identifying the link between IgG4+ plasma cells and orbital lacrimal gland lesions for the first time. Subsequently, many cases of orbital lacrimal gland masses with a large number of IgG4+ plasma cell infiltrates have been reported [5–7].

The orbital lacrimal gland is the most commonly involved site in IgG4-RD following the pancreas, and IgG4-ROD also has many different clinical and pathological characteristics compared with tissues such as the pancreas [7, 8]. Therefore, this article reviews the research published in recent years on orbital IgG4-ROD.

**Epidemiology**

The incidence of IgG4-RD in the population is relatively low, and studies have reported the incidence of IgG4-RD in the Japanese population to be (0.28–1.08)/100,000, with the IgG4-ROD incidence accounting for 4%–34% of total IgG4-RD cases [9, 10]. The prevalence of IgG4-RD has been reported more frequently in Asia. In Japan, IgG4-related diseases are the second major cause of orbital lymphoproliferative diseases (21.6%) [11]. The prevalence rate in other countries has not yet been revealed, but it is likely to be underestimated in Western countries [12]. In Sato’s research, 21 cases of IgG4-ROD were screened from 112 patients diagnosed with ocular adnexal lymphoid tissue disease from 1990 to 2006 via retained tissue samples [5]. Australian researchers reviewed 55 cases of orbital lymphoid tissue benign hyperplasia or idiopathic orbital inflammatory pseudotumour. The proportion of IgG4 diagnosed by immunohistochemical staining was as high as 50%.

The presentation of IgG4-ROD occurs in middle to older age, i.e., a median age of 58–67 years (90% of patients are aged 50–80 years) and a male:female ratio of 4:1–3:1 [13]. In the affected sites involved in IgG4-ROD, there is a difference in prevalence between males and females; in the lung, pleura, breast, liver, gallbladder, pancreas, and retroperitoneal tissues, the incidence in males accounts for 75–86%. However, there is no significant difference between males and females in terms of prevalence [14]. It has also been shown that IgG4-ROD can develop in children and is more common in girls. Although studies on IgG4-RD have revealed gender differences in prevalence, a survey conducted in Japan, South Korea, the USA, and Taiwan found that IgG4-ROD has an equal proportion of males and females, with a mean onset age of 56.3 years [15]. Due to the low incidence of IgG4-ROD, large-sample epidemiological data are still lacking.

**Clinical Features and Manifestations**

The onset of IgG4-ROD can occur at any age, with a male to female ratio of approximately 1:1. Most patients have a history of allergic diseases, such as allergic asthma and rhinitis [16]. Most reported IgG4-ROD cases involve orbital and appendage structures, and reports of IgG4-ROD involving sclera and intraocular tissues are rare. Since 2021, only individual cases involving the conjunctiva, sclera, uveitis, and choroid have been reported. The most common single-eye involvement site of IgG4-RD was reported to be the lacrimal gland.

Orbital IgG4-ROD is most commonly caused by chronic sclerosing dacrocyoadenitis and is manifested as chronic, painless swelling or proptosis of the orbit or unilateral orbit (Fig. 1) [17]. Twenty-five patients with IgG4-ROD were reported in the French Multicenter IgG-RD Register. The involved sites included the lacrimal gland (68.4%), orbital soft tissue (57.4%), extraocular muscle (36.8%), eyelid tissue (21.1%), the optic nerve (10.5%) and the trigeminal nerve (V1 or V2) (10.5%). Only 1 patient was found to have sclerosing keratitis and no patient was reported with uveitis. Bilateral involvement accounted for 57.1%, mainly in patients with dacryocystitis (90.9%) [18].

Patients may exhibit restricted eye movements, diplopia, or strabismus when extraocular muscles are involved. When the involved lesion is located around and compresses the optic nerve, the patient’s vision will decrease dramatically because of damage to the optic nerve [19].

**Clinical Examination and Diagnosis**

Computed tomography (CT) examination of the orbit can reveal lesions involving the lacrimal gland, with symmetrical diffuse enlargement of the lacrimal gland. The results of CT examination showed homogeneous density and significant enhancement in the lesion area, and nodular or mass shadows were observed in the lacrimal gland, inside and outside the muscle cone and around the optic nerve (Fig. 2). The disease may involve the extraocular muscles, eyelids, orbital fat bodies, supraorbital and infraorbital nerves, inferior orbital fissure, and pterygopalatine fossa. The supraorbital and infraorbital nerves are commonly involved, making the supraorbital and infraorbital nerves dilated and thickened. Lesions can also af-
Fig. 1. Clinical features and manifestations of IgG4-ROD patients.
Fig. 2. Coronal CT of the orbit and mass shadow in the orbital lacrimal gland area in IgG4-ROD patients.
fect extraocular glands, such as the biliary system, parotid gland, pancreas, submandibular gland, and lymph nodes, resulting in glandular enlargement [5, 6, 20–23]. In magnetic resonance imaging in patients with orbital inflammation, the infraorbital nerve is thicker than the optic nerve, which is considered a characteristic change in IgG4-ROD [24]. In addition, Takano et al. [25] further confirmed a significant correlation between infraorbital nerve thickness and orbital inflammation.

Fig. 3. Characteristics of tissue caseology in IgG4-ROD patients.
nerve thickening and serum IgG4 levels. Sogabe et al. [26] analysed the imaging data of a total of 65 cases of IgG4-ROD in seven institutions in Japan and found that the preferential site of IgG4-ROD was highest in the lacrimal gland (87.7%), followed by the trigeminal branches (38.5%), extraocular muscles (24.6%), orbital fat (23.1%), and eyelids (12.3%).

In 2012, a preliminary international consensus was formed on the clinical and pathological diagnosis of IgG4-ROD as follows: dense infiltration of lymphocytes and plasma cells, lamellar fibrosis, occlusive phlebitis (as well as non-occlusive phlebitis) and eosinophilia under pathology (IgG4+/IgG+ cells >40 and >10 IgG4+ plasma cells at high magnification; serum IgG4 concentration >135 mg/dL) [27]. After the introduction of the 2012 consensus on the diagnosis of IgG4-ROD [28], the diagnostic criteria for orbital IgG4-ROD were made available in 2014 [29], as follows: (1) imaging studies show enlargement of the lacrimal gland, extraocular muscles, or trigeminal nerve, with masses or enlargement of various ocular tissues; (2) histopathological examination shows lymphocyte and plasma cell infiltration with fibrosis, and IgG4+ plasma cells are present and meet the following criteria: IgG4+ plasma cells/IgG+ plasma cells >40%, or IgG4+ plasma cells >50 cells/high-power field (HPF) (Fig. 3); and (3) blood tests reveal elevated serum IgG4 at concentrations exceeding 135 mg/dL. When criteria (1), (2), and (3) are met, IgG4-ROD can be diagnosed; when (1) and (2) are met, IgG4-ROD is likely. When (1) and (3) are met, IgG4-ROD is suspected.

Lymphocytes are predominantly T cells and a few B cells and do not require all diagnostic conditions to be met [30]. In 2015, Japan proposed specific diagnostic criteria for IgG4-ROD, which describe the lesions of ocular tissues in more detail, emphasizing the increase in germinal centres and increasing the number of IgG4+ plasma cells to 50 and above per high power [11]. The positive rates of T-cell markers CD2, CD3, CD4, CD5, CD7, and CD8 along with other cell surface markers, such as CD10, CD23, CD38, and CD138, are generally high in IgG4-ROD, while there is low expression of CD25 and CD19 [31, 32]. In addition, their B-cell marker (CD79) is also positive [33].

**Differential Diagnosis**

In terms of diagnosis, IgG4-ROD should be differentiated from diseases such as thyroid-associated ophthalmopathy, orbital inflammatory pseudotumour, Sjögren’s syndrome, and orbital lymphoma. (1) Thyroid-associated ophthalmopathy: the clinical manifestations of thyroid-associated ophthalmopathy are mainly diplopia, limited eyeball rotation, upper and lower eyelid retraction, and proptosis, often with thyroid dysfunction; the imaging examination of the disease is mainly characterized by proptosis, the symmetrical involvement of extraocular muscles, and thickened muscle belly. There is no trigeminal nerve involvement [34]. (2) Orbital inflammatory pseudotumour: the clinical manifestations of orbital inflammatory pseudotumour are mainly protrusion and displacement due to compression of the eyeball, ocular motility disorders, pain, swelling, decreased visual acuity, diplopia, and orbital mass or papilloedema; the imaging examination of the disease is mainly manifested as a mass in contact with the eyeball with a blurred boundary and an irregular shape, often with extraocular muscle and lacrimal gland enlargement [35]. (3) Sjögren’s syndrome: this is a systemic immune disease in which the exocrine gland function is damaged and absent. It occurs mainly in females. In IgG4-ROD, the lacrimal gland and parotid gland are significantly enlarged, while the symptoms of dry mouth and dry eyes are mild. Often, there are extraocular lesions, and the response to glucocorticoid therapy is better. In addition, the serum IgG4 concentration in IgG4-ROD is increased, and IgG4+ pascal cell infiltration is obvious, while Sjögren’s syndrome does not involve these manifestations [36]. (4) Orbital lymphoma: orbital lymphoma may be a primarily localized lymphoma in orbit, or it may be secondary to systemic lymphoma, unilateral or unilateral disease. In the early stage of the disease, there may be only local mass or mild limitation of eye movement, and in most cases, there may be no symptoms of discomfort. As the disease progresses, proptosis, diplopia, ptosis, limited eye movement, and other symptoms may occur. The imaging examination of the disease reveals a mass with an irregular local shape, which can cover the growth of the eyeball, especially in the medial and lateral orbit, causing changes in the intrapyramidal and extrapyramidal systems and around the optic nerve. There is no moderate to severe enhancement on contrast-enhanced CT or magnetic resonance imaging scans, and there is a clear boundary between the lesion and the surrounding tissues [37].

In clinical practice, it is challenging to distinguish IgG4-ROD from the above-related orbital diseases, and there is a certain rate of misdiagnosis. For instance, Zhao [38] reported a case of IgG4-ROD misdiagnosed as orbital inflammatory pseudotumour in clinical practice; the misdiagnosis was related to factors between IgG4-ROD and orbital inflammatory pseudotumours, e.g., similar clinical and imaging findings and the particular efficacy of using hormones and immunosuppressive agents.
Therefore, it is still difficult to differentiate the two without pathological examination. It should be noted that the increase in serum IgG4 is not a specific manifestation, and the rise in serum IgG4 may occur in some MALT lymphomas, orbital inflammatory pseudotumour, and Castleman’s disease [39].

**Treatment and Prognosis**

There is no consistent standard for treating IgG4-ROD, and the existing therapies are mainly glucocorticoids, rituximab, surgery, or radiation therapy.

**Glucocorticoid Therapy**

Surgical treatment is generally not preferred for the disease, especially when the involved organs are still functional. Glucocorticoids are currently the drugs of choice for the treatment of IgG4-ROD, and the treatment regimen of 0.6 mg·Kg⁻¹·d⁻¹ for 2–4 weeks is usually implemented, followed by a reduction of 5 mg every 2–4 weeks [40]. One study has reported that after 3–6 months of prednisone treatment in 19 patients, the orbital mass of the vast majority of patients was reduced, and the symptoms improved; 13 patients relapsed after glucocorticoid treatment, and the patients who relapsed were treated with glucocorticoids again [18]. After retreatment for these patients with degeneration, during a mean follow-up of 40.2 months, about 72.2% of these patients maintained the disease stably after the long-term use of immunosuppressive agents (azathioprine, methotrexate, and mycophenolate mofetil) or low-dose glucocorticoids.

In addition to oral glucocorticoid therapy, local application, such as the intraorbital injection of glucocorticoids, can also be used in clinical practice. One study included 10 patients with IgG4-ROD who underwent a local application of glucocorticoids, and it was found that 50% of patients were relieved or stable after the orbital injection of hormones [41]. Although this treatment involves local administration, it can prevent some of the complications of the systemic application of glucocorticoids. However, it requires repeated injections and is not convenient for oral administration, thereby limiting its clinical use.

**Rituximab Therapy**

In recent years, clinical treatment of the disease with the biological agent CD20 monoclonal antibody has reduced CD20⁺ B cells, thereby preventing their further differentiation into plasma cells that can secrete IgG4. Wu et al. [42] administered rituximab to 5 patients with glucocorticoid-dependent or -resistant IgG4-ROD, and none showed any recurrence within 33 months of follow-up, with an excellent therapeutic effect. However, the number of cases included in this study was small. There is still a lack of high-level evidence-based medical evidence to support the analysis of the effect of rituximab in the treatment of IgG4-ROD. Although the impact of rituximab treatment in patients with IgG4-ROD is evident, rituximab is expensive, and there is no consistent standard for the frequency of administration, initial dose, and drug duration of rituximab, which limits its clinical application. Therefore, rituximab is used as a second-line drug for the treatment of IgG4-ROD. Rituximab is generally used in patients with glucocorticoid dependence or refractory. For the initial therapeutic dose and frequency of administration, Wallace et al. [43] suggested a rituximab dose of 1 g each time, 15 days apart. A total of 57 out of the 60 patients who participated in the trial had remission or maintained stability in the disease after the application of rituximab. Twenty-one patients had a recurrence during the follow-up period, which revealed that rituximab treatment of IgG4-ROD also had a certain recurrence rate.

**Surgical Treatment**

In clinical practice, patients with lacrimal gland involvement have significant dry eye symptoms after surgical resection of the diseased lacrimal gland. Therefore, surgery is generally not preferred as a treatment modality when the lacrimal gland is still functional. The long-term observation of the surgical resection of the diseased lacrimal gland has not been reported.

**Radiotherapy**

Radiotherapy can be applied to various orbital diseases, such as lymphoma, inflammatory pseudotumour, and thyroid-associated ophthalmopathy. Based on this principle, Lin et al. [44] used low-dose radiotherapy for IgG4-ROD; they reported that all 3 patients achieved good outcomes after radiotherapy, and none recurred within 19 months of late follow-up. However, orbital radiotherapy for IgG4-ROD is currently only an adjunct to systemic medical therapy in patients with IgG4-ROD. The efficacy of this treatment modality still lacks the support of high-level evidence-based medical data.

**Pathological Changes**

The main site of involvement of IgG4-ROD is the lacrimal gland, which is wholly characterized by a fibrous film wrapping the nodular diseased lacrimal gland; the average size of the mass is about 3 cm × 2.5 cm × 1 cm,
and the mass is greyish-white in colour. In histological findings, there was decreased atrophy of primary acini and glandular duct tissues in lacrimal gland tissues and replacement by plasma cells, lymphocytes, lymphoid follicles, and fibroproliferative tissues [11]. Plasma cells were distributed mainly between the remaining acini and ducts of the lacrimal gland, between lymphoid follicles and between some already fibrotic tissues. Immunohistochemical staining showed that the absolute values of the IgG4+ plasma cells were >50 cells/HPF, and the IgG4+/IgG+ plasma cell ratio was >40%. Immunohistochemical staining and serological examination of IgG4-ROD can reveal elevated IgG4+ plasma cells and IgG4+/IgG+ plasma cell ratios and elevated serum IgG4 [45]. It should be noted that ocular IgG4-related lesions appear to be less likely to develop occlusive phlebitis than other parts of the body [46].

The exact aetiology and pathogenesis of IgG4-ROD are still not well understood. Most scholars believe that the occurrence and development of this disease are related to various factors, including genetic susceptibility, environmental factors, autoimmune factors, and allergenic factors, along with the unique role of IgG4 molecules [47, 48]. A series of possible pathogenic autoantibodies have been detected in patients with IgG4-ROD, including anti-trypsin inhibitor antibody, anti-heat shock protein 10 antibodies, anti-carbonic anhydrase II antibody, lactoferrin antibody, anti-carbonic anhydrase IV antibody, anti-amylase a antibody and anti-thrombin-binding protein antibody [49–51], which has also led most researchers to recognize IgG4-RD as an autoimmune disease. Studies in microbial infections have found that carbonic anhydrase II and ubiquitin-protein ligase in the pancreatic acinar epithelial cells of the human body are homologous to α-carbonic anhydrase plasmin-binding proteins of Helicobacter pylori, respectively [52, 53]. The genetic population is likely to induce abnormal autoimmune responses in the human body after infection with H. pylori, resulting in inflammatory reactions and tissue damage. In terms of genetics, during the study of autoimmune pancreatitis, it was found that human leukocyte differentiation antigen made patients more likely to have IgG4-ROD, and the expression of non-aspartate DQBI57 was closely related to the recurrence of autoimmune pancreatitis [54, 55].

In addition, some scholars speculate that innate immunity, adaptive immunity, and allergic reactions are involved in the pathogenesis of IgG4-ROD, but no specific allergen has been found [56]. Studies have been conducted on innate immunity and IgG4-ROD, as follows: (1) Akiyama et al. [57] suggested that microbe-associated patterns produced by intestinal microbial bacteria may also play a role in the pathogenesis. (2) Arai et al. [58] found toll-like receptors 7 and 9 to be present on the surface of the plasmacytoid dendritic cells of IgG4-ROD. These receptors can specifically recognize microbial nucleotides, resulting in the increased secretion of IFN-α, thereby promoting Th1 and Th17 cells to differentiate and release B-cell activating factor; subsequently, B cells are activated and proliferated. Activated B cells secrete TGF-β and platelet-derived growth factor, promote angiogenesis, exert immune regulation, and promote wound repair and the formation of tissue fibrosis. (3) Clinical studies [45] found that 30% of patients with IgG4-ROD had increased eosinophils, and after drug treatment, the number of eosinophils in the peripheral blood of these patients was reduced compared with before treatment. Therefore, it can be speculated that eosinophils have some correlation with the pathogenesis of IgG4-ROD.

Additionally, adaptive immunity and IgG4-ROD studies found the following: (1) Activated IgG4+ B cells and plasmablasts can indirectly activate CD4+ T cells, resulting in IgG4-ROD development [59]. (2) The secretion of IL-21 by Th2-type cells promotes germinal centre formation and IgG4 production. Studies have found that about half of IgG4-ROD patients have elevated immunoglobulin E (IgE), and Th2 cells can mediate hypersensitivity and produce IgE, suggesting that Th2 cells play an essential role in the pathogenesis of IgG4-ROD [60]. (3) Akiyama et al. [61] found that the higher the number of Th2 cells, the higher the serum levels of IL-4 and IgG4 and the higher the organ involvement, suggesting that Th2 cells have some correlation with the pathogenesis of IgG4-ROD. (4) Another study [62] found that in an investigation of newly treated patients with IgG4-related autoimmune pancreatitis, the serum IgG4 levels in those patients with IgG4-ROD had more CD4+ CD25 high regulatory T cells. The finding also suggested that regulatory T-cell abnormalities may have some relationship with the pathogenesis of IgG4-ROD.

Summary

The pathogenesis of orbital IgG4-ROD is not clear. The treatment mainly involves glucocorticoids, rituximab, surgery, and radiotherapy. For IgG4-related diseases involving the lacrimal gland, irreversible damage occurs due to lacrimal gland fibrosis as the disease progresses. Often, medical treatment does not achieve the
expected effect, and patients will experience dry eye symptoms after surgical resection. Under the premise that the pathogenesis of the disease cannot be clarified at present, it will be meaningful for the treatment of patients if early detection and effective measures can be applied to avoid lacrimal gland fibrosis. It has been reported in the existing literature [63] that the Fibulin-5 matrix protein is involved in the fibrosis and sclerosis processes of lacrimal gland tissue. Therefore, if a treatment that can inhibit lacrimal gland fibrosis can be found, it may provide a new direction and basis for preventing orbital IgG4-ROD in clinical practice.

**Statement of Ethics**

All patients gave written informed consent for their images to be published.

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