REVIEW

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2021.3484
Cyprus J Med Sci 2022;7(2):156-162

Immunoglobin G4-Related Diseases

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ABSTRACT

IgG4-related disease (IgG4-RD) is characterised by its pathological, serological, and clinical features, and its recognition is gradually increasing in the literature. This disease is generally observed in middle-aged males and older groups. IgG4 positive plasma cells and T lymphocytes infiltrate various organs, characterised by the etiology of an unknown disease. Almost all organs of the body are affected, but those most frequently affected are the pancreas, bile duct, gallbladder, salivary glands, retroperitoneal region, kidneys, lungs, and the prostate. The histopathological features of this disease are storiform fibrosis and obliterative phlebitis. Corticosteroids are useful in the treatment of this disease.

This study aims to increase the awareness of IgG4-related disease through a review of the recent literature.

Keywords: IgG4-related disease, clinical manifestations, diagnosis, treatment, recent literature

INTRODUCTION

IgG4-related disease (IgG4-RD) is an immune-mediated, systemic, fibroinflammatory disease.[1,2] However, it is not a new disease: "Mikulicz disease", "Ormond disease", "Riedel thyroiditis", "Küttner tumour" and a variety of other diseases are seen in the IgG4-RD spectrum.[3] Its most important features include tumour-like masses, IgG4-positive plasma cells, lymphoplasmacytic deposits, and typical storiform fibrosis. Serum IgG4 levels are increased in 60 to 70 percent of IgG4-RD patients.

Most patients with early-stage disease respond to glucocorticoids, but exacerbation of the disease may occur in patients after the steroids are reduced or discontinued.

Different names are used for IgG4-related diseases.[4,5] These include:

- IgG4-related disease,
- IgG4-related systemic disease,
- IgG4-syndrome,
- IgG4-associated disease,
- IgG4-related sclerosing disease,
- IgG4-related systemic sclerosing disease,
- IgG4-related autoimmune disease,
- IgG4-positive multi-organ lymphoproliferative syndrome,
- Hyper-IgG4 disease,
- Systemic IgG4-related plasmacytic syndrome,
- Systemic IgG4-related sclerosing syndrome,
- Multifocal fibrosclerosis,
- Multifocal idiopathic fibrosclerosis.

In 2001, serum IgG4 levels were detected to be high in patients with sclerosing pancreatitis (Autoimmune pancreatitis-Type 1). In 2003, these autoimmune cases were shown to be due to the involvement of other organs and blood, and autoimmune pancreatitis was considered a systemic disease. In 2012, an international study group suggested the concept of IgG4-RD.[6] IgG4-RD can affect all of the organs in the body.

To cite this article: Tınazlı M, Tınazlı R. Immunoglobin G4-Related Diseases. Cyprus J Med Sci 2022;7(2):156-162

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Received: 22.12.2020
Accepted: 20.02.2021

IgG4 related disease, its diagnosis, prognosis, treatment approaches, and current discussions are examined in this review.

Epidemiology

IgG4-related disease (IgG4-RD) is mostly seen in middle-aged males and older groups. However, IgG4-related sialadenitis and dacryoadenitis are slightly more predominant in women.[7] Retroperitoneal fibrosis, IgG4-related tubule interstitial nephritis (TIN), autoimmune pancreatitis (AIP), and other organ manifestations are slightly more predominant in elderly males. The gender distribution varies, according to patients with head and neck involvement.[8] In men, the disease is more common but the degree and severity of the disease in both women and men seem to be similar.[9]

Pathogenesis

The pathogenesis of IgG4-RD remains unknown.[10] Genetic predisposition, abnormal immune response (an autoimmune disorder), and allergic disorder are thought to be the underlying factors in the development of this disease.[6,11-13] No autoantigenic gene specific for this disease has been detected, and the pathogenicity of IgG4 antibodies is not fully known.[14] It was shown that the HLA-DRB1*0405 and HLA DQB1*0401 haplotypes in the Japanese population, and the HLA-DRB1*0701, and DQB1*0202 haplotypes in Koreans were related to a predisposition to type 1 AIP.[15] It was thought that the factor triggering the abnormal immune response might be microorganisms, and *Helicobacter pylori* were particularly emphasized.[16] However, later studies have shown that antibodies against PBP are associated with type 2 AIP rather than type 1 AIP. Also, it is thought that natural immunity is effective in disease development. It is mainly thought that foreign pathogen-associated with molecular patterns (PAMPs), potential self-factors, and damage-related molecular patterns (DAMPs) could be the possible triggering factors.[17]

It is still not fully understood whether IgG4-RD is an autoimmune disorder or an allergic disorder. IgG4 allergens have also been suggested to be involved in tolerance and response to specific infectious agents. Nevertheless, its physiological role is unknown.[17] High serum and tissue IgG4 levels are not specific in IgG4-related diseases. These may increase in many other diseases such as allergic disorders, Churg-Strauss syndrome, Castleman's disease, and sarcoidosis.[18] Evidence relating to allergic response includes eosinophilia seen in 40% of patients, high Th2 cytokine levels and serum IgE in the tissues affected by the disease, and a raised association with allergic rhinitis and bronchial asthma.[17] Antinuclear antibodies and rheumatoid factors may also be detected in some of those patients mentioned above.[19] There are a large number of T regulatory cells (Tregs) in peripheral circulation and the levels of interleukin (IL)-10 and transforming growth factor (TGF) produced by Tregs in the affected tissues are increased.[20,21] These cytokines help the output of IgG4.[22]

Previously, the IgG4 molecule was thought to be a direct cause of tissue injury. However, it is now known that IgG4 is not a primary element in this pathophysiology. It seems that T follicular helper cells drive the passage of the class into IgG, perhaps through the secretion of IL-4.[23]

B cells, plasmablasts in particular, play an essential role in IgG4-RD. IGG4$^+$ plasmablast may present the antigen to T cells.[24]

According to recent evidence, T-cells play a primary role in IgG4-RD pathogenesis. In IgG4-RD-affected tissues, CD4$^+$ T-cells accumulate throughout the lesions.[25]

Clinical Manifestations

One or more organs may be affected in IgG4-RD. Patients usually show the development of a mass in the affected organ (e.g., an orbital pseudotumor, nodular lesions in the lung, a renal mass resembling renal cell carcinoma) or diffuse enlargement of an organ (e.g., the pancreas).[1,8,26]

Painless swelling is observed in the organs. There may be multiple organ involvement in more than 60 percent of IgG4-RD cases.[27,28] Standard features in the affected tissues are histopathological, storiform fibrosis, obliterative phlebitis, and high serum IgG4 concentrations. Lymphadenopathy is quite common, and allergy and asthma symptoms occur in about 40% of patients.[17,29] Symptoms of systemic disease such as fever and weakness are usually not seen. IgG4-RD is often incidentally diagnosed during radiological imaging or histopathology.[17]

The most common clinical manifestations are as follows:

Type 1 (IgG4-related) autoimmune pancreatitis (AIP)

IgG4-related sclerosing cholangitis

IgG4-related dacryoadenitis and sialadenitis (Mikulicz disease)

Sclerosing sialadenitis (Küttner's tumour, IgG4-related submandibular gland disease)

IgG4-related orbital inflammation or orbital inflammatory pseudotumor

IgG4-related thyroid disease

IgG4-related respiratory disease

IgG4-related aortitis or periaortitis (chronic sclerosing aortitis and periaortitis)

Ormond's disease (IgG4-related retroperitoneal fibrosis),

IgG4-related kidney disease

Hypophysitis

Pachymeningitis

IgG4-RD is relatively rare, but recently, the awareness of this disease has increased, rheumatologists consult it more frequently, and earlier diagnosis is made.[1,2,11,17,30] Nevertheless, IgG4-RD it is usually detected incidentally by a radiologist or pathologist. Sometimes IgG4-RD remains localized to a single organ for months or even years, e.g., the salivary or lacrimal glands. It may also sometimes show signs of multiple organ involvement at the time of diagnosis.[31] According to different studies, the organ frequencies of the disease are different.[32]

Lymphadenopathy: In IgG4-related diseases, asymptomatic lymph node enlargement is the most common finding in 80 percent of patients with AIP.[32] The diagnosis of IgG4-RD by lymph node biopsy alone is quite difficult because lymph node biopsy rarely shows the degree of storiform fibrosis observed in other organs.[31]

Salivary and lacrimal gland involvement: Painless swelling in the upper eyelid, changes in facial appearance, and swelling of the submandibular gland, and parotid gland areas provide clues to the diagnosis.[17]

For example; Mikulicz disease is lacrimal, parotid and submandibular gland enlargement, and was previously called sclerosing sialadenitis (Küttner tumour).[33] Sikka symptoms are so mild that differential diagnosis with Sjögren syndrome is required. Dry mouth, dry eyes, and arthralgia are less common findings, compared to those patients with Sjögren syndrome. Allergic rhinitis, asthma, AIP, and interstitial nephritis are common. RF, ANA, Anti-SSA, and anti-SSB positivity is lower.[17,34]

Orbital disease: 25%–50% of orbital pseudotumors appear to be caused by IgG4-RD which was previously known as benign lymphoid hyperplasia. With the use of IgG4-RD diagnostic criteria, it was found that 5%–25% of cases called non-granulomatous idiopathic orbital inflammation are IgG4-RD.[35]

Autoimmune pancreatitis (AIP): AIP constitutes 2% of chronic pancreatitis cases. Its main clinical features are upper abdominal disturbance and jaundice. Due to endocrine and exocrine dysfunction of the pancreas, patients may sometimes complain of impaired glucose tolerance and also develop diarrhoea. Type 1 (IgG4-related) AIP should be differentiated from pancreatic cancer. Radiological methods such as ultrasonography (USG), computed tomography (CT), and endoscopic retrograde cholangiopancreatography (ERCP) can be used for differential diagnosis.[17]

Thyroid gland (Riedel thyroiditis): The two forms of involvement of IgG4-RD in the thyroid gland are IgG4-related thyroid disease and Hashimoto's disease.[36,37] There is usually massive growth in the thyroid gland due to lymphocytic infiltration; therefore, surgery is often required for treatment.[17]

IgG4-related sclerosing cholangitis: For a long time, such patients were defined as having "primary sclerosing cholangitis", which was responsive to glucocorticoids. Nowadays, according to histopathological findings obtained from biopsies of such patients (for example renal biopsies), they are considered to have IgG4-RD.[31]

Lungs (IgG4-related interstitial pneumonitis, IgG4-related lung disease): Many respiratory diseases have been reported that include bronchial and alveolar conditions. Most patients are asymptomatic but some patients can have cough, dyspnoea, chest pain haemoptysis and pleurisy. Furthermore, interstitial pneumonia and pseudotumor can be seen.[38,39]

Bronchi and bronchial wall thickening may also be detected via a CT scan. The affected tissues demonstrate characteristic lymphoplasmacytic infiltrates enriched in IgG4-positive plasma cells; some patients show abundant storiform fibrosis. Patients with bronchial lesions have asthma-like symptoms. Sometimes, interstitial and organized pneumonia is detected on CT.[17] Pulmonary involvement of IgG4-RD may be confused with sarcoidosis.[40] The use of the specific criteria for IgG4-RD is recommended for differential diagnosis.[17]

Retroperitoneal fibrosis and related disorders: Retroperitoneal fibrosis is a rare disorder characterized by the presence of inflammatory and fibrous retroperitoneal tissue, often involving the ureter or abdominal organs.[41] This condition is prevalent in IgG4-RD. Most of the cases with retroperitoneal fibrosis were considered "idiopathic" in the past.[42] Some drugs and malignancies are involved in the etiology of retroperitoneal fibrosis. However, an etiologic factor cannot be detected in most patients. Generally, the affected areas are around the thoracic and lumbar vertebrae, abdominal aorta, major branches of the aorta, and the ureter. CRP levels are usually found to be elevated.[17]

The association of retroperitoneal fibrosis and chronic periaortitis was previously known as Ormond's disease, which is currently classed as an IgG4-related disease.[43] Other IgG4-related diseases include sclerosing mesenteritis, sclerosing mediastinitis, and multifocal fibrosclerosis.[44-46]

Renal disease: Renal involvement in IgG4-RD is mainly seen in two significant presentations: One is a mass lesion similar to renal cell carcinoma, and the other is tubulointerstitial nephritis. The mass lesions may be bilateral and multiple, and tubulointerstitial nephritis characteristic features are observed in biopsy in IgG4-related kidney disease. Laboratory findings are subnephrotic proteinuria and moderate hypocomplementemia with levels of serum C3 and C4 components in this situation. In some patients, azotemia may occur later, and end-stage renal failure has also been observed and reported on.[31]

Other system involvements:

CNS involvement, IgG4-related hypophysitis, and pachymeningitis

Skin disease

Prostate gland

Pericardium (constrictive pericarditis)

Bone-destructive lesions in the middle ear[31]

The IgG4-related disease of the ovary[46]

Sclerosing mastitis and inflammatory pseudotumor of the breast[47,48]

Hepatic inflammatory pseudotumor, and similar to autoimmune hepatitis

Diagnosis

In Japan, diagnostic criteria have been used routinely since 2011. These criteria include:

Diffuse/focal swelling or mass in a single or multiple organs (clinic, physical examination, imaging)

IgG4 levels (≥135 mg/dL)

In histopathological examination; Lymphocyte and plasmocyte infiltration and fibrosis, Ig-G4 (+) plasma cell infiltration (IgG4 (+) / IgG (+) plasma cell ratio> 40% and> 10 IgG4 (+) plasma cells at each high magnification field)

Definitive Diagnosis: 1+2+3

Probable Diagnosis: 1+3

Possible Diagnosis: 1+2

(Other diseases should be excluded, criteria for specific diseases should be used) (Figure 1).

All criteria must be met for a definitive diagnosis. The 'Probable IgG4-RD' diagnosis is made when the physical and histopathological

criteria are met but the serological criteria are not met. In cases where serological and physical criteria are met but histopathological criteria are not met, a "possible IgG4-RD" diagnosis is made. Moreover, another important consideration is the exclusion of malignancy in the diagnosis of IgG4-RD.[17]

Diagnostic Studies

Serum IgG4 concentration: Serum IgG4 levels of most IgG4-RD diagnosed patients are high. However, serum IgG4 concentration is found to be normal in approximately 30% of patients despite the classic pathological findings of IgG4-RD. Monitoring IgG4 concentrations during treatment is not appropriate for the disease activity. As IgG4 concentrations are high at the baseline, in most patients, corticosteroid may decrease IgG4 concentration during treatment and it may even reach normal levels. Each patient should be evaluated individually for their follow-up and treatment.[31]

Other laboratory findings: Only a small number of patients may show mild high C-reactive protein (CRP) and erythrocyte sedimentation rates (ESR). In most cases, acute phase reactants are normal. Mild to moderate peripheral eosinophilia is frequent in IgG4-RD patients, being at a rate of approximately 20%. Also, mild hypocomplementemia can be detected in IgG4-RD, which is mainly the third and fourth components of the complement. IgG4-RD with tubulointerstitial nephritis may also have subnephrotic proteinuria.[31]

Imaging studies: A computed tomography (CT) scan of the chest, abdomen, and pelvis is generally preferred for the diagnosis of IgG4-RD, due to the numerous subclinical diseases and the lack of specific laboratory findings. CT scans are useful in the major conditions of pulmonary, pancreatic, and renal disease of IgG4-RD.[31]

Additional imaging studies may be required in some patients, particularly if orbital involvement is suspected. Typical imaging features on magnetic resonance imaging (MRI), CT or PET scans involve organs wrapped by inflammatory and fibrous tissue, and diffuse or focal organ infiltration.[46]

The algorithm for IgG4-RD diagnosis is shown in Figure 1.

Differential Diagnosis

Many diseases are included in the differential diagnosis of IgG4-RD. The diagnosis depends on the patient's clinic and the place of the affected organ or tissue. Firstly, it should be distinguished from other rheumatologic, oncologic, or infectious diseases.[17,30] In Table 1, the differential diagnosis of IgG4-RD is shown (Table 1).[30]

Treatment

The optimal treatment for IgG4-RD is unknown. The general approach is to manage the follow-up and treatment of the disease based on the

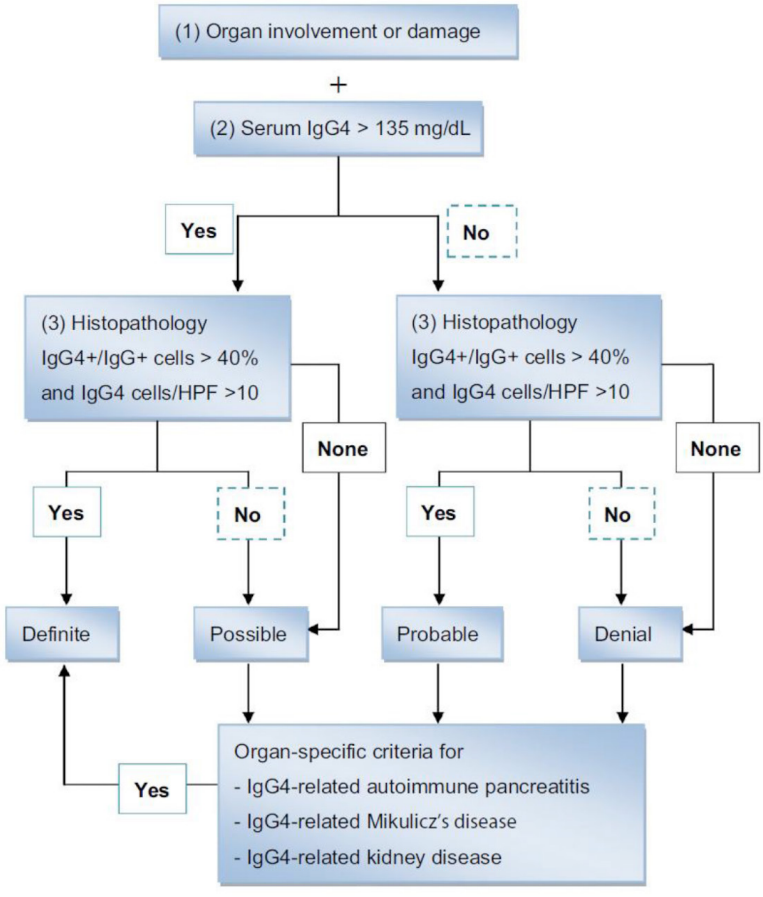

Figure 1. Diagnostic approach algorithm.
HPF: high-power field

dysfunction status of the involved organ and the case studies in the literature.

Treatment is usually started with 0.6 mg/kg/day prednisolone. This dose is continued for 2–4 weeks, followed by a 10% reduction in the dose every two weeks.[17,29] While it is not known whether maintenance therapy is required after remission, it is recommended to continue the prednisolone treatment at a dose of 5–10 mg/day due to high recurrence rates.[17] Some patient with IgG4-RD, whose disease cannot be controlled with steroid monotherapy, require glucocorticoids and other immunosuppressive agents (e.g. methotrexate, azathioprine, mycophenolate mofetil). B cell depletion with rituximab appears to be successful due to the long-term toxic effects of steroid therapy or in cases of resistance to conventional therapies or in patients with relapse. There are no randomized studies regarding the effects of rituximab. However, since rituximab provides a rapid decrease in blood plasmablast concentrations, it appears to be a useful approach for those patients with recurrent or refractory disease.[24,29]

Prognosis

Until recently, the natural course of IgG4-RD was not precisely defined. Organ dysfunction often improves with treatment. Primary unresponsiveness to glucocorticoid therapy is extremely rare in IgG4-RD patients. Therefore, the prognosis is particularly good with treatment, but relapse rates are quite high.[13,17] Problems causing morbidity and even mortality can be observed in many untreated patients that have retroperitoneal fibrosis, aortic aneurysms, portal hypertension and cirrhosis, diabetes mellitus, and kidney diseases.[46] For this reason, systemic and long-term follow-up is particularly needed in patients with IgG4-RD.

Complications: IgG4-RD can cause severe organ failure and tissue damage if early diagnosis and appropriate evaluation are not performed. However, most patients show a subacute course. Some patients may become fulminant from the onset of the disease for several weeks. Destructive bone lesions similar to Wegener's granulomatosis may occur in the sinuses, middle ear spaces, and head in some patients with IgG4-RD. Untreated cholangitis may progress to fulminant hepatic failure within months. Aortitis and periaortitis due to IgG4-RD can cause aorta aneurysms and dissections. When IgG4-RD tubulointerstitial nephritis occurs, renal functions are impaired, and even end-stage renal failure may develop.[29,30] Consequently, early diagnosis, appropriate evaluation, and optimal treatment modalities should be implemented. Patients should be monitored closely, and awareness about their relapse management should be kept in mind.

Table 1. The differential diagnosis of IgG4-related disease

Systemic autoimmune conditions and vasculitis
Sjögren syndrome
Granulomatosis with polyangiitis (Wegener granulomatosis)
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)
Giant cell arteritis
Takayasu arteritis
Granulomatous disorders
Sarcoidosis
Fungal infections (histoplasmosis, blastomycosis, coccidioidomycosis)
Malignancies
Lymphoma, particularly MALT lymphoma
Multicentric Castleman disease
Adenocarcinoma of the pancreas
Renal cell carcinoma
Bronchoalveolar carcinoma of the lung

MALT: mucosa associated lymphoid tissue.

Risk of malignancy: There are some studies showing that the risk of malignancy increases within a few years after patients are diagnosed with IgG4-RD, but other studies have found it to be unrelated.[47] In a study conducted on 158 patients in Japan between 1992 and 2012, it was found that the risk of malignancy was slightly increased in 109 patients with type 1 autoimmune pancreatitis. The most common malignancies were as follows: the lung, colon, prostate, stomach, and pancreas (the total number of malignancies was 34).[48]

Several cancer cases have also been reported in case reports including salivary duct carcinoma, pancreatic cancer, small cell and adenocarcinoma of the lung and gastrointestinal clear cell sarcoma.[11]

CONCLUSION

In the future, studies are needed to better explain the risk of malignancy in patients with IgG4-RD.

MAIN POINTS

- IgG4-RD is a chronic inflammatory disorder that shows various organ involvement.
- Serum IgG4 levels may be high in the disease and show specific histopathological features.
- There is an increase in T helper-2 and Treg-associated cytokines in IgG4-RD.
- It is essential to assess systemic organ deficiencies at diagnosis and during the follow-up of the disease and to screen for underlying malignant diseases.
- Glucocorticoids are highly effective in treatment; nevertheless, it is quite common to discontinue treatment due to relapses after reduction or side effects.[17]

ETHICS

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.T., R.T., Design: M.T., R.T., Data Collection and/or Processing: M.T., R.T., Literature Search: M.T., R.T., Writing: M.T., R.T.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study had received no financial support.

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