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Review Article

IgG4-related disease: a review with an Indian perspective

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ABSTRACT

IgG4-related disease (IgG4-RD) is a recently discovered (2003) complex disease, manifesting in various organs with symptoms mimicking other diseases. Progression of the disease leads to organ failure and hence early diagnosis is an urgent requirement in these patients. There is scarcity in reporting of IgG4-RD globally and in India. The aim of the study was to generate awareness on the epidemiology, diagnosis, and practice trends for IgG4-RD in India and globally, and to aid Indian physicians in early diagnosis of IgG4-RD in patients. Additionally, the evidence currently available in the Indian subpopulation has been evaluated. A preliminary literature search was performed using the PubMed database with the keywords including 'IgG4-related disease' in the title and abstract to obtain the relevant data. In total, PubMed identified 2071 publications comprising world-wide studies published in the English language before 30 April 2021. Studies were filtered region-wise by adding 'India' to the search strategy and total 60 publications were identified. The relative newness of IgG4-RD and the ensuing paucity in literature limits diagnosis by clinicians. Awareness of the disease among Indian clinicians would improve understanding of the disease and development of a country-specific consensus-based management guideline might lead to better prognosis in Indian patients with IgG4-RD.

Keywords: Epidemiology, IgG, IgG4-related diseases, India, Treatment practices

INTRODUCTION

IgG4-related disease is a newly discovered group of multi-organ fibroinflammatory diseases. Early seminal work in this field was published in medical literature as recently as 2003, wherein distinct histopathological evidence of IgG4 disease such as massive infiltration of IgG4 positive plasma cells and interstitial fibrosis as well as obliterative phlebitis were observed in Japanese patients with autoimmune pancreatitis.[1]

Later numerous studies reported similar histopathological evidence in conjunction with diseases such as Mikulicz's disease, Kuttner tumor, Ormond disease, sclerosing cholangitis, mediastinal fibrosis, Riedel's thyroiditis, autoimmune hepatitis, etc.[2,3] Diseases related to IgG4 have now been reported to be affecting different organs of the body across various ethnic populations world-wide.[1,2,4] Multiple terminologies have been used to describe this variety of seemingly unrelated diseases manifested as tumefactive lesions in different organs of the body, connected by the underlying tissue infiltration of IgG4 positive plasma cells accompanied mostly by high IgG4 concentrations.

The requirement of a unified nomenclature to organize this umbrella of diseases led to the coining of the term 'IgG4-related disease' (IgG4-RD). This term was arrived at based on a consensus between two Japanese research teams and found continuum in other nomenclature guidelines as well, thus making it a globally accepted term for this disease.[3,5] Recommendations by Stone et al further suggest that for each of the individual organ conditions, the disease could be simply pre-fixed with the term 'IgG4-related' such as

IgG4-related autoimmune pancreatitis, IgG4-related orbital inflammation, IgG4-related sialadenitis, IgG4-related thyroid disease, IgG4-related lymphadenopathy, IgG4-related skin disease, etc.[5]

Patients with IgG4-RD usually present with swelling or enlargement of the involved organ. Not all patients may be symptomatic at presentation and the inflammation may accidentally be identified at imaging. IgG4-RD may manifest in a single organ or multiple organs either in a span of 6 months or beyond. The similarities in symptoms between IgG4-RD and malignancies such as multifocal-tumor-like masses or other inflammatory diseases adds to the diagnostic dilemma. The identification of this disease thereby requires exclusion of a variety of 'IgG4-RD mimics' and rigorous clinicopathologic correlations for definitive diagnosis.[6] Since the discovery of these diseases is relatively new, there is a paucity of literature to understand the pathology, epidemiology and the criteria for disease identification leading to ambiguity in diagnosis of disease. Progression of IgG4-RD results in irreversible fibrosis and eventually organ failure. At an early stage, the disease is treatable with good prognosis for the patients.[1] Hence, early and accurate detection along with subsequent therapy is critical.

A preliminary search from the PubMed database using the key word 'IgG4-related disease' in the title and abstract identified 2071 publications world-wide published in the English language before 30 April 2021. Filtering the results region-wise by adding 'India' to the search strategy led to 60 publications overall. The publication trends (Figure 1) demonstrate a scarcity in reporting of IgG4-RD in India that may possibly be attributed to a lack of knowledge about the disease or the ambiguity in diagnosis. This gap in the information widens further when the disease has been discovered recently and the pathological features governing the disease, which assist in segregating this disease from a myriad of infectious, inflammatory and neoplastic conditions, are not clearly elucidated. This may cause under-diagnosis due to low awareness or may also lead to an over-diagnosis of IgG4-RD as it may be mistaken for other diseases that mimic IgG4-RD. An increase in the awareness of IgG4-RD among Indian clinicians would aid in early identification and treatment of the disease to achieve better clinical outcomes for Indian patients with IgG4-RD. In the current report, we present the recent developments with regards to IgG4-RD globally and discuss the evidence currently available in the Indian subpopulation.

IMMUNOPATHOLOGY AND CLINICAL FEATURES

IgG4 is produced post long-term exposure to an antigen as a response to IL-4, IL-10 and is the least abundant IgG subtype (1-4%) in the body in healthy individuals. This is an antibody with a weak hinge region, hence the heavy and light chains can dissociate from each other to undergo 'Fab arm exchange' and associate with other such IgG4 molecules generating bispecific antibodies that have the capacity to bind different antibodies.[7] The cytokine milieu created via the antigenic activation of a naïve T-cell and antigen presentation to B-cells leads to increase in the eosinophils, fibroblasts and activated macrophages. This environment causes fibrosis, which is a hallmark of IgG4-RD.[7] However, the exact antigen causing the downstream immune signalling leading to fibrosis has not yet been clearly elucidated.

IgG4-RD presents sub-acutely in the majority with a lack of explicit clinical symptoms. Mass lesions occurring in various organs most commonly include orbital region, lung, kidney, lymph nodes and salivary glands. With IgG4-RD, the meninges, skin or aorta may also be affected with more diffuse infiltrative lesions.[7] High levels of inflammatory cytokines such as IL-4, IL-5 along with an increase in TGF-β and IL-10 have been observed, resulting in IgE elevation and eosinophil migration to tissues. This leads to allergic disease-like clinical picture, and thus patients with IgG4-RD often present with asthma, atopy, eczema or peripheral eosinophilia (Figure 2).[7]

Patients may present with disease restricted to one organ or may also have multiorgan involvement. Symptoms for IgG4-autoimmune pancreatitis include mild abdominal symptoms, obstructive jaundice, increased IgG4 concentrations, enlargement of pancreas, irregular narrowing of pancreatic duct, etc., however, some patients may additionally have tubulointerstitial nephritis, non-glomerular haematuria and mild proteinuria.[8] Although, multiorgan disease may be detected at initial diagnosis of disease, it may also evolve over a period of months or years (Figure 3). Some of the most common IgG4-RD are discussed below.

IgG4-related autoimmune pancreatitis (type 1)

Type 1 autoimmune pancreatitis or lymphoplasmacytic sclerosing pancreatitis is an IgG4-RD that can be difficult to diagnose due to similarities in clinical presentation with autoimmune pancreatitis or adenocarcinoma of the pancreas. Painless jaundice, increase in IgG4 plasma cells and IgG4 serum concentration are commonly observed in all 3 diseases. One of the differentiating factors of type 1 autoimmune pancreatitis that is distinguishable radiologically (abdominal computerized tomographic scanning) is the diffuse pancreatic enlargement (sausage-shaped pancreas) and edema. Diabetes mellitus and malabsorption are commonly co-existing conditions with pancreatitis.[7] Other commonly associated secondary conditions include gall bladder and bile duct disease such as sclerosing cholangitis.

According to the International consensus diagnostic criteria, type 1 autoimmune pancreatitis seems to be the IgG4-related pancreatitis, characterized by mild abdominal symptoms, usually without acute attacks of pancreatitis; occasional occurrence of obstructive jaundice; increased serum gammaglobulin, IgG; presence

of autoantibodies; diffuse, segmental, or focal enlargement of the pancreas with a capsule-like low-density rim on dynamic computed tomography/magnetic resonance imaging images; irregular narrowing of the main pancreatic duct on endoscopic retrograde cholangiopancreatography images; histopathologically, lymphoplasmacytic sclerosing pancreatitis: abundant infiltration of lymphocytes and IgG4-positive plasmacytes and fibrosis, and obliterative phlebitis; and occasional association with other organ involvement.[9]

IgG4-related sclerosing cholangitis

This disease can be differentiated from primary sclerosing cholangitis based on deep tissue biopsies that reveal interstitial fibrosis, high levels of IgG4+ plasma cells, and high IgG4 concentrations.

Since prognoses for the two diseases are different, it is essential to differentiate the disease. IgG4-related sclerosing cholangitis is usually responsive to glucocorticoids.

IgG4-related sclerosing cholangitis is a biliary tract symptom of IgG4-RD, characterized by systemic, inflammatory, sclerosing lesions with massive infiltrations of IgG4-positive lymphocytes involving many organs including the eye, salivary, and lacrimal glands; lungs, pancreas, retroperitoneum, kidneys, and vascular systems. The presentation of IgG4- related sclerosing cholangitis and primary sclerosing cholangitis are similar but the comorbidities, treatment response, and outcomes differ significantly, and therefore, it is strongly recommended to be familiar with these two diseases to make a correct diagnosis. Prednisolone is a very effective treatment for IgG4-related sclerosing cholangitis as in other IgG4-RD.[10]

IgG4-related sialadenitis, dacryoadenitis and orbital pseudotumours

Salivary (sialadenitis), lacrimal (dacryoadenitis) gland and orbital involvement have also been observed with IgG4-related pancreatitis. Submandibular tissue samples reveal fibrosis, obliterative phlebitis and lymphoplasmacytic infiltration of IgG4+ plasma cells. These clinical features along with increased IgG4 and IgE levels distinguish IgG4-related sialadenitis and dacryoadenitis from Sjögren's syndrome.[11]

The existence of IgG4 sclerosing sialadenitis and dacryoadenitis with rhinosinusitis occurs very rarely. However, recently a rare presentation of IgG4 sclerosing sialadenitis and dacryoadenitis causing a rapidly progressive swelling of the head and neck in an African American patient was reported.[12]

IgG4-related retroperitoneal fibrosis

Involvement of the infrarenal aorta and iliac arteries along with chronic inflammation and fibrosis is commonly observed in IgG4-related retroperitoneal fibrosis. Many cases of this disease were commonly diagnosed as idiopathic, however later IgG4 was discovered to be the cause.[13,14] Many cases of IgG4-RD involving organs such as liver, ovary, heart (pericardium), prostate and the central nervous system have also been reported.

Recently IgG4-related retroperitoneal fibrosis is included in the IgG4-related spectrum of sclerosing disease. Researchers have proposed that clinical and laboratory characteristics of IgG4-related retroperitoneal fibrosis are similar to those of idiopathic retroperitoneal fibrosis, except for male predominance, older age, and higher incidence of postrenal acute kidney injury in IgG4-related retroperitoneal fibrosis.[15]

EPIDEMIOLOGY

Studies have reported that the incidence of IgG4-RD is 0.28-1.08/100,000 in the adult population in Japan with 336-1300 newly diagnosed patients per year with the estimated prevalence of 62 per million subjects. IgG4-RD mostly affects patients of middle to upper age, with an onset at 50-70 years.[3,16]

There is a lack of studies reporting disease epidemiology in the Caucasian population and this may be suggestive of lesser prevalence as compared with the Asian counterparts.[17] An Asian study on consecutive patients (n=235, largest study) demonstrated that the median age of the patients was 67 years with a greater proportion of men having the disease than women (men: women, 4:1).[2] A Chinese cohort (N=28) also corroborated the findings of this study with men having a higher predilection for the disease (1.8:1).[18]

In a caucasian study of 125 patients with disease confirmation based on biopsy, the mean age (56.1 years) was slightly lower. Although men were more susceptible to disease, the ratio of men to women (1.6:1.0) was not as pronounced as in the Asian cohort.[4] The results of a small cohort of IgG4-RD patients (N=25) registered in the French national study were similar to the Asian study.[19] In India, isolated case reports and case series have been published with IgG4-RD.[20-25]

A small cohort (N=13) analysis from a tertiary care center in South India, reveals a male predominance in the patients (2.4:1) for IgG4-RD. The mean age of the patients was 44.1 years, which is younger as compared to other reports from the Asian subcontinent.[26] Another study conducted in 70 patients from a tertiary care center in North India also corroborates the findings of this study and reports a lower age at presentation of IgG4-RD (mean age= 41.4 years). The female-to-male ratio was 0.94:1, which increased with multiorgan involvement. Involvement of orbital and peri-orbital tissues was the highest (52.9%).[27]

Further studies are warranted to understand disease epidemiology especially the age at disease presentation

across different parts of India. This would lead to timely diagnosis of the disease even if present at an early age.

Efforts have also been undertaken to identify if the pediatric population is at risk of IgG4-RD. A systematic literature review demonstrated that very few cases have been reported, however, the analysis suggests that the median age of children with IgG4-RD was 13 years and girls (64%) were more susceptible to disease. Studies identifying disease epidemiology in the pediatric population are required so as to avert organ dysfunction at a later stage.[28] IgG4-RD with sinonasal involvement was confirmed in two 15 years old patients in a case series from South India, confirming that IgG4-RD should not be excluded from diagnosis in the pediatric population.[29]

DIAGNOSIS AND RELATED ADVANCES IN THE FIELD

The presence of enlargement or lesion in the body is analyzed by imaging techniques such as ultrasound, CT scan or 18F-fluoro-2-deoxyglucose positron emission tomography/computed tomography. However, in order to confirm if these enlargements are due to IgG4-RD, histology and immunostaining are required. The imaging techniques are also required further on in tracking therapy outcomes and recurrence of disease. Definitive diagnosis of IgG4-RD involves physical examination, histopathological and radiology findings, and immunohistochemical staining reports along with associations with the clinical history of the patient to distinguish neoplastic, inflammatory, and infectious mimickers.[30-32]

Histopathology

The fundamental histopathological signs for characterization of IgG4-RD lesions are lymphoplasmacytic infiltrates, storiform fibrosis and obliterative phlebitis (Figure 3). Other signs associated with the disease include increased eosinophils and phlebitis without lumen obliteration, however, these two features alone are not specific enough to confirm IgG4-RD diagnosis in the absence of the fundamental signs.[30]

The dense lymphoplasmacytic infiltrate mostly comprises plasma cells, T cells, B cells and in some cases eosinophils and macrophages as well. Fibroblasts (spindle-shaped cells) may have a storiform appearance but sample extraction via needle biopsy may impede detection of such fibrosis.[30]

Phlebitis accompanied by partial or complete obliteration of the veins is also indicative of IgG4-RD. Arteritis may also occur in certain cases with infiltrates with or without obliteration in certain IgG4-RD cases.[30] Necrosis, dense neutrophilic infiltration and presence of epithelial cell granulomas are incongruent to the histopathological features associated with IgG4-RD.[2]

Immunostaining

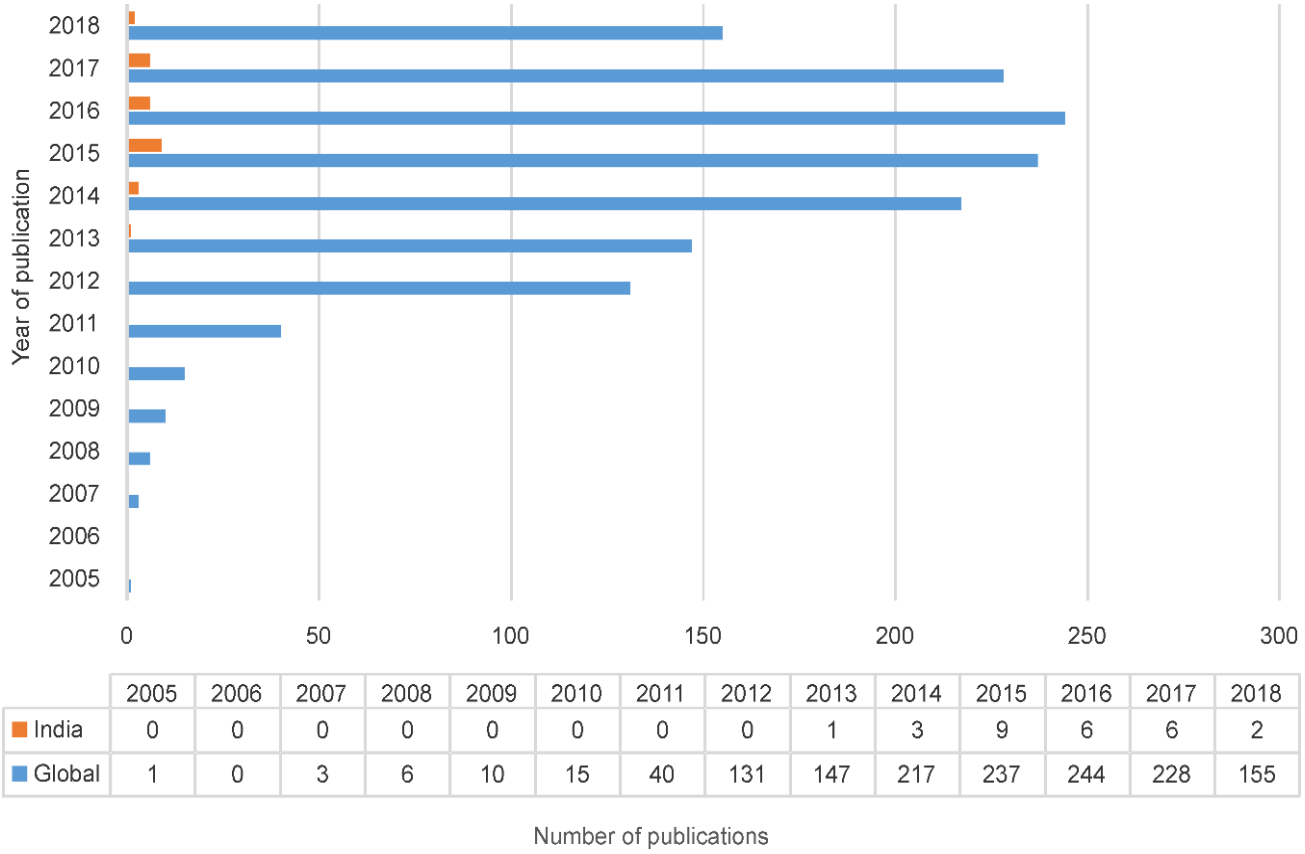
Elevated levels of IgG4 concentrations are observed in patients with IgG4-RD (normal level <135 mg/dl), however since these levels are also found in other diseases, these concentrations cannot be relied on as the sole test for diagnosis.[33] IgG4 staining in tissue is highly recommended even if high levels of IgG4 are not estimated in serum as it provides crucial evidence for IgG4-RD diagnosis. The proportion of IgG4 cells in histology sections from patients with IgG4-RD differ with respect to each organ.

For the meninges, bile duct biopsy and kidney biopsy, a cut-off of 10 IgG4+ plasma cells/high power field (HPF) whereas for lacrimal gland, salivary glands, lymph node >100 IgG4+ plasma cells/HPF and for the skin >200 IgG4+ plasma cells/HPF are considered to be highly indicative of IgG4-RD. Hence an organ-wise stratification of the cell numbers has been discussed by Deshpande et al. in their consensus on the pathology of IgG4 disease.[30] The ratio of IgG4 to IgG4+ plasma cells is considered to be a more dominant factor in the diagnosis of IgG4-RD as compared with the IgG4+ plasma cell counts alone. The cut-off value for this ratio has been set to >40% based on various studies as well as the Japanese consensus statement.[34] However, a recent consensus on the disease pathology discusses that this value should not be considered in isolation especially if the cell numbers are low.[30] The diagnosis of IgG4-RD is almost confirmed if IgG4+ plasma cells are observed in immunohistochemistry, the IgG4:IgG4+ plasma cells ratio is >40%, and is in conjunction with histopathology and clinical manifestations of the disease. If the above mentioned criteria are fulfilled then the organ specific criteria recommended for IgG4-related Mikulicz's disease, autoimmune pancreatitis, and kidney disease should also be considered for confirmation of disease diagnosis.[34]

At the first international meeting for IgG4-RD held in Boston, USA in 2011, a consensus was formed on the IgG4-RD disease pathology with a panel comprising experts from radiology, pathology, clinicians, and scientists with subspecialty in rheumatology, oncology, ophthalmology, surgery etc. from different parts of the world.

The diagnostic terminology formulated via consensus for IgG4-RD for all organs (exceptions may be some sites such as lymph nodes, pulmonary IgG4 and oral mucosa biopsies) is based on a 3-tier approach (Figure 4).[30] The second international consensus guidance statement was issued in 2015 that focused on the management and treatment of IgG4-RD.

The panel included experts from different countries in North America, Europe and Asia who had contributed to the advancement of IgG4-RD awareness in literature. The consensus was formed via questionnaires (web-based), discussions (held face-to-face) and supported by a thorough literature review.[31]



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
India	0	0	0	0	0	0	0	0	1	3	9	6	6	2
Global	1	0	3	6	10	15	40	131	147	217	237	244	228	155

Figure 1: Publication trends in IgG4-related disease: Global and Indian studies.

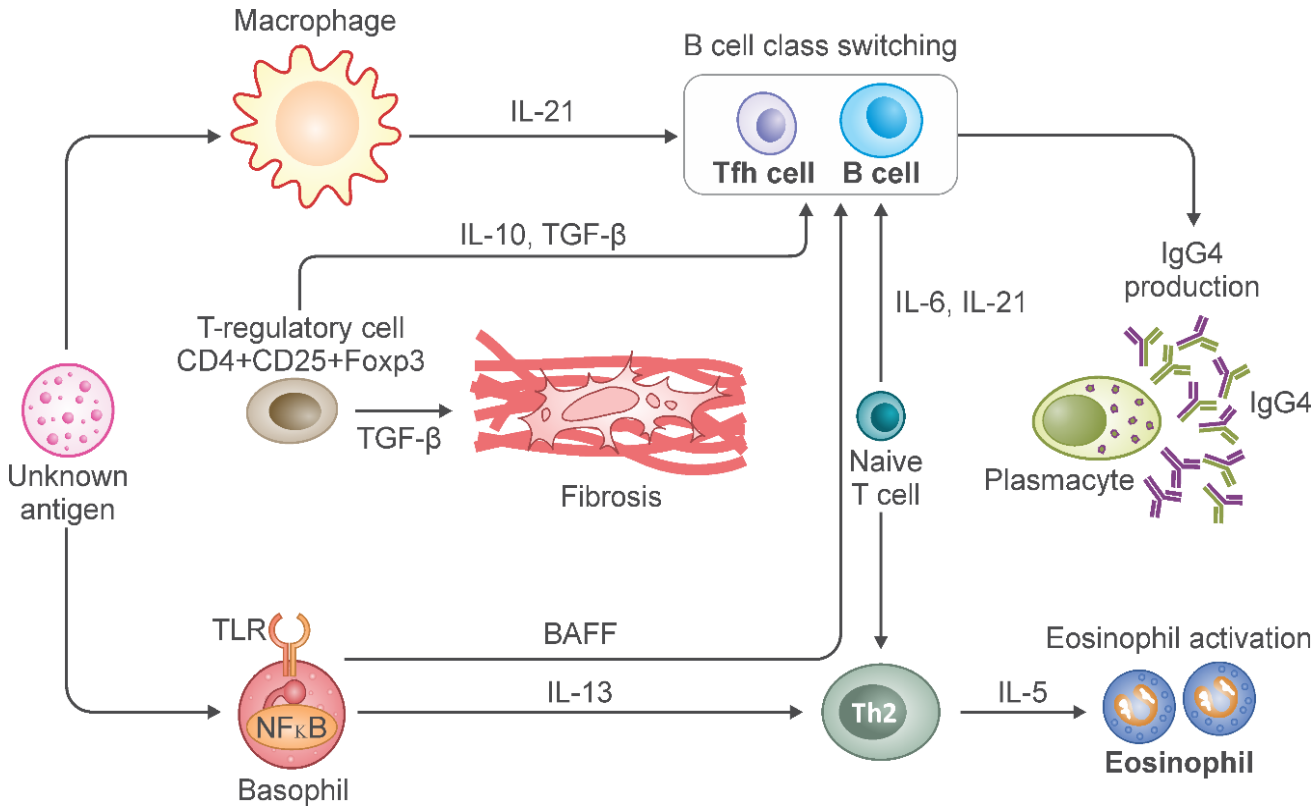


Figure 2: Schematic pathogenesis model of IgG4-related disease.

Note: BAFF: B-cell-activating factor of the tumor necrosis factor family; CD: cluster of differentiation; Ig: Immunoglobulin; IL: interleukin; NF: nuclear factor; Tfh: follicular T-helper cell; TGF: tumor-growth factor; TLR: toll-like receptor ligands.

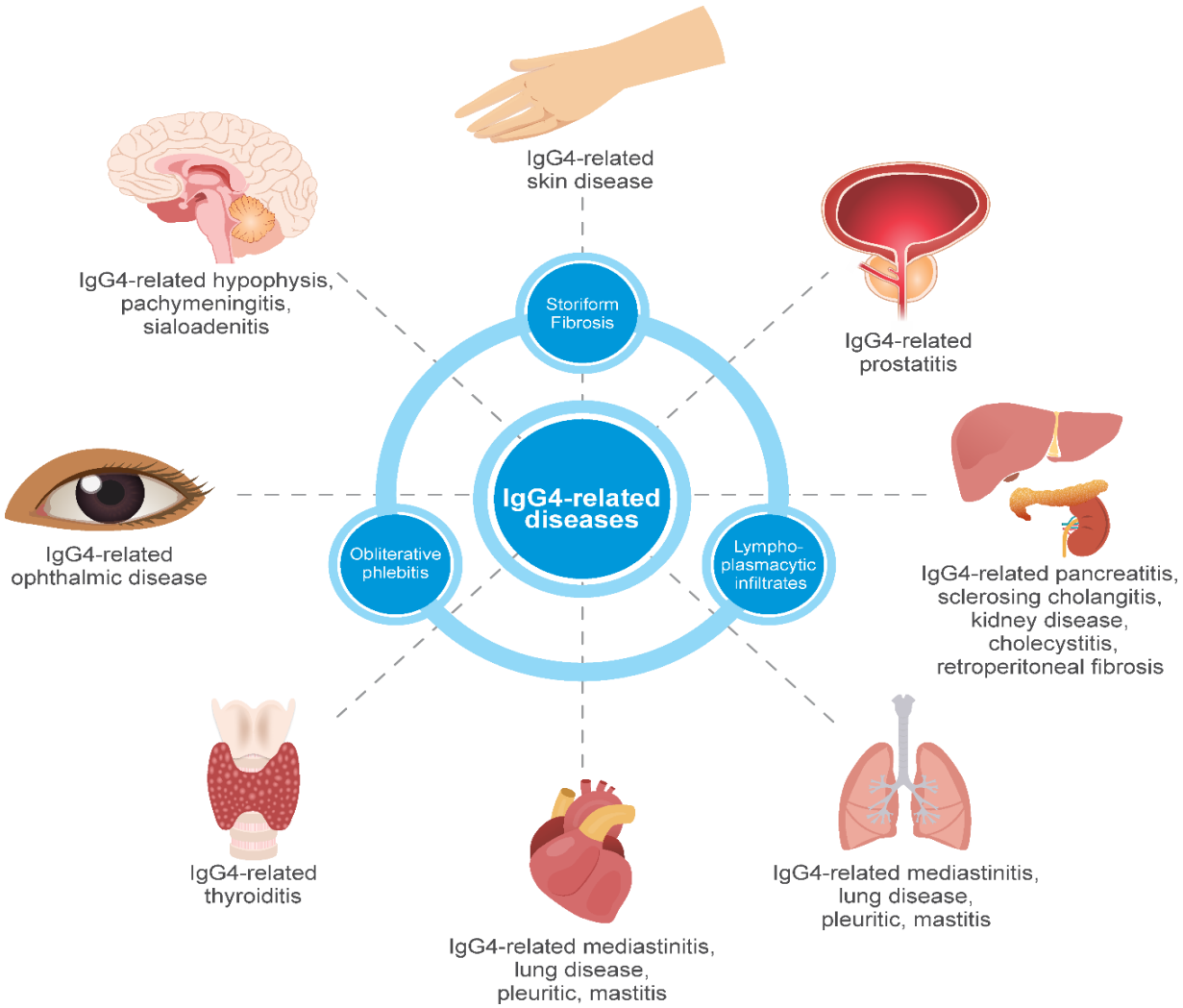


Figure 3: IgG4-RD fundamental histopathological signs and organ involvement in disease.

Note: IgG4-RD: IgG4-related disease.

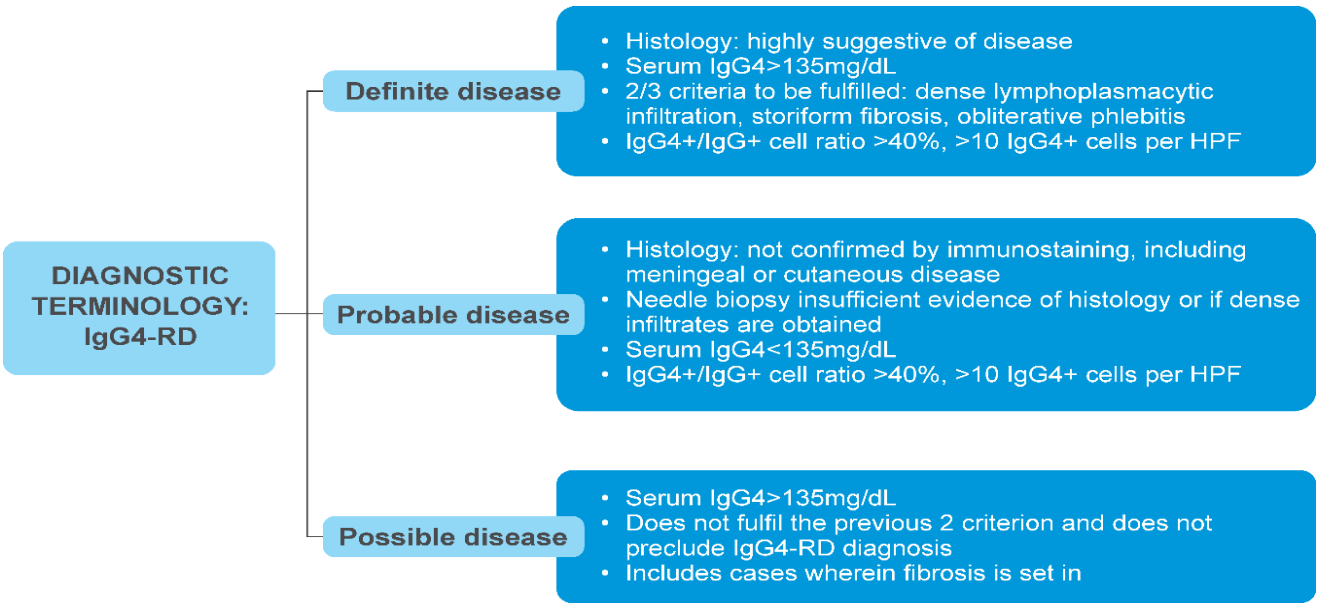


Figure 4: Diagnostic terminology for IgG4-related disease classification.

Note: IgG4-RD: IgG4-related disease.

Other markers of disease

Histology and immunostaining are the gold standard for diagnosis of IgG4-RD. However, variations in histology may be observed in some cases.[35] Additionally, serum IgG4 concentrations alone do not have high predictive value for disease and the concentrations are not always lowered on remission. In such cases an alternate confirmatory marker, such as plasmablasts, an intermediate state between the B-cells and the formation of plasma cells may be followed. Plasmablasts is absent in the circulation of healthy people, albeit, is elevated in autoimmunity. Studies revealed that higher concentrations of plasmablasts at IgG4-RD presentation and elevation of plasmablast in IgG-RD with multiple organ manifestations was observed.[36] The pursuit of plasmablasts for diagnosis, tracking and managing IgG4-RD as an alternative disease marker seems to be an effective strategy, however, its use requires further validation.

IgG4 responder index

For the systematic clinical assessment of disease, an instrument that estimates the intensity of disease and incorporates the clinician's judgment on current status of disease is crucial. For this purpose, the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS-WG) scale was modified to adapt it for disease assessment in IgG4-RD.[37] The scoring pattern is segregated into organ/site, symptomatic/not, urgent treatment required/not and whether damage is present/not. For organ/site, the score is divided from 0-4 wherein 0= absence of disease (also in condition when the prior present disease symptoms have now cleared), 1= improvement observed however some evidence of disease persists, 2= disease status unchanged from last visit, 3= new/recurrent disease present, and 4= disease worsened in spite of treatment. For the symptomatic category, the clinician has to go through a list of symptoms of IgG4-RD in the particular organ and record if it is present or not. An important aspect of IgG4-RD management is identifying the urgency of immunosuppressive treatment required to prevent permanent organ damage. The presence of such urgency would double the organ score present in the organ/site column. The damage assessed by the clinician would indicate whether the damage to the organ is permanent or not.

The serum IgG4 concentration is also allotted a score (normal, improved, persistent, new, recurrent, or worsened despite treatment), with higher concentrations corresponding to higher scores. The total responder index score is the summation of the individual organ/site scores and the serum IgG4 concentration. The glucocorticoid usage is also noted down carefully along with the scores. This scoring pattern would be helpful for assessing patients.[37]

This has recently been validated to measure disease activity and record damage associated with the disease and would perhaps be an important tool in clinical trials.[38] Recently, the 2019 ACR/EULAR classification criteria for IgG4-RD have been released, providing a useful framework based on the integrated approach involving all four domains i.e., clinical, serological, radiological and pathological, as none of these approaches alone provides definitive evidence for the accurate classification of patients. A case meets the classification criteria for IgG4-RD if the following 3-step criteria are met: the entry criteria (step 1), no exclusion criteria are present (step 2), and the total inclusion criteria points are ≥20 (step 3).[32]

Step 1

Ensures presence of characteristic clinical or radiological involvement of at least one of 11 possible organs (e.g., pancreas, salivary glands, bile ducts, orbits, kidney, lung, aorta, retroperitoneum, pachymeninges or thyroid gland) or pathological evidence of an inflammatory process accompanied by a lymphoplasmacytic infiltrate of uncertain aetiology in one of these same organs except in the bile ducts, where narrowing tends to occur, the aorta, where wall thickening or aneurysmal dilatation is typical and the lungs, where thickening of the bronchovascular bundles is common.

Step 2

Involves assessment for the presence or absence of exclusion criteria in all the four domains: (a) clinical- fever and no objective response to glucocorticoids; (b) serological- leucopenia and thrombocytopenia with no explanation, peripheral eosinophilia, positive antineutrophil cytoplasmic antibody (specifically against proteinase 3 or myeloperoxidase), positive SSA/Ro or SSB/La antibody, positive double-stranded DNA, RNP or Sm antibody, other disease-specific autoantibody, cryoglobulinemia; (c) radiological- known radiological findings suspicious for malignancy or infection that have not been sufficiently investigated, rapid radiological progression, long bone abnormalities consistent with Erdheim-Chester disease, splenomegaly; and (d) pathological-cellular infiltrates suggesting malignancy that have not been sufficiently evaluated, markers consistent with inflammatory myofibroblastic tumour, prominent neutrophilic inflammation, known diagnosis of multicentric Castleman's disease, Crohn's disease or ulcerative colitis.

Step 3

Involves eight weighted inclusion criteria domains, addressing clinical findings, serological results, radiological assessments and pathological interpretations; only the highest weighted item in each domain is scored.

TREATMENT PRACTICES WORLDWIDE

The salient features on the management of disease include disease assessment, categorization of patients based on

whether disease was symptomatic or not, and strategies during remission, maintenance and relapse of IgG4-RD. Also, to rule out malignancies and IgG4-RD mimics, testing of biopsies from affected tissue are a pre-requisite. Asymptomatic patients may also need treatment since symptoms may appear only during fibrosis of tissue at which stage irreversible damage would occur to tissue for e.g. in the pancreas and salivary glands. However, patients with lymphadenopathy or mild submandibular enlargement which is asymptomatic may not be in urgent need for therapy.

Therapy should be started in symptomatic patients. Although cases of temporary remission may be observed in the absence of therapy, disease may relapse with symptoms at sites different from the site of origin. Thus, it would be preferable to start treatment to prevent long-term IgG4-RD complications. In some cases, the treatment may also be started for cosmetic reasons.

Glucocorticoids are the preferred first line of therapy in the absence of contraindications for all IgG4-RD diagnosed patients. Prednisone (30-40 mg/day) is usually prescribed as initial therapy for the first 2-4 weeks post which tapering of dose should be done. Different tapering regimens are practiced: lowering dose by 10 mg every 2 weeks to achieve 20 mg dose, maintained for 2 weeks and then tapering at 5 mg/week for 2 weeks followed by treatment discontinuation to complete 3-6 months of treatment is mostly followed; whereas in Japanese patients, maintenance therapy is continued for 3 years.

If active disease lingers for a longer period or the same glucocorticoid is to be used for a longer time as maintenance therapy, then the use of steroid sparing agents (azathioprine, cyclophosphamide, mycofenolate mofetil, methotrexate, tacrolimus, etc.) is recommended. B-cell depletion therapy, such as rituximab is recommended in patients who have failed other steroid-sparing agents or in patients resistant to or dependent on steroids. If remission induction was appropriately managed by glucocorticoids then retreatment on relapse can be continued in the same manner as done at start of disease to prevent further disease flares. However, for maintenance post-relapse, steroid-sparing agents are strongly recommended.

There are many drugs currently under investigation for IgG4-RD, including obexelimab, inebilizumab, belimumab etc. Clinical trials are ongoing for B-cell-targeted agents such as zanubrutinib and rilzabrutinib, which are oral, molecular-targeted Bruton's tyrosine kinase inhibitors.[39]

PRACTICE TRENDS IN INDIA

Multiple cases of IgG4-related interstitial nephritis, IgG4-related retroperitoneal fibrosis, IgG4-related sclerosing mastitis, IgG4-related prostatitis, IgG4-related cholangiopathy, etc. have been reported from India.[4, 11,13,14,18,19,34,35,37] A brief analysis of these case reports and case series published in India, revealed that the average age at presentation of IgG4-RD is approximately 45 years.[20-26,29,40-50] which is a decade younger as compared to other studies world-wide.[2,4,18,19]

Detailed epidemiology studies are required to further understand the age of the at-risk population. However, keeping in mind that the initial reports suggests that the 40-50 years age group is prone to disease, IgG4-RD must be ruled out in patients presenting with tumefactive lesions before initiation of therapy. A recently published study from a tertiary care center in North India revealed that of total 70 patients diagnosed with IgG4-RD (possible 38.6%, probable 32.9%, and definite 28.6%).[27] All patients with multi-organ involvement (orbital and peri-orbital tissues, lymph nodes, paranasal sinuses, retroperitoneal tissue, pancreas, gastrointestinal tract, aorta and its branches, and heart) had elevated IgG4 levels, whereas only 74.3% of patients with single-organ involvement had such high IgG4 levels. This finding corroborates the observations made in the Japanese and US cohort of IgG4-RD patients.[2,4] As observed previously, difference in average age at IgG4-RD presentation exists among these cohorts with 91% patients being >50 years of age in the Japanese cohort, with mean age being 56.1 years in the US cohort, 51.5 years in the Chinese cohort, and 58 years in the French cohort but most of the patients in this North Indian cohort were <50 years of age.[2,4,18,19,27]

In accordance with the guidelines suggesting the 3-tier diagnostic approach, it has been observed that most of the reported studies follow the guidelines and classify disease based on the histopathology and immunostaining as highly suggestive (definite), possible or probable cases. Most of the case reports demonstrate that patients present with disease symptoms that seem to be similar to inflammatory diseases. For example, patients with symptoms of pedal edema and proteinuria that are classical for renal failure were diagnosed as IgG4-RD upon histopathology and immunostaining.[40] Thus, such IgG4-RD mimics must be excluded prior to prescribing IgG4-RD therapy.

The common treatment strategy for patients with confirmed diagnosis of IgG4-RD, as mentioned in the Indian studies was corticosteroids especially prednisolone as recommended in the 2015 consensus guidelines. This is usually followed by steroid sparing agents like mycophenolate mofetil, azathioprine, and/or methotrexate. Rituximab was also prescribed to patients non-responsive to prednisolone.[22,29] Also, per the recently published Indian study the majority of patients (94.3%) were on immunosuppressive medications along with prednisolone (0.6 mg/kg for 2-4 weeks). Azathioprine was the most commonly used (72.8%) immunosuppressive medication. Rituximab was prescribed to 17.1% of the patients who had a disease recurrence despite initial therapy and were responding well at the time of this report.[40] Corticosteroids were prescribed to the Japanese, US, French, and Chinese cohort however sustained remission could not be achieved in all patients.[2,4,18,19]

CONCLUSION

IgG4-RD is a complex disease, manifesting in various organs with symptoms mimicking other diseases. The family of IgG4-RD is a recent discovery and as compared to other well-investigated diseases, there are very few publications globally. Reports published from India on this topic are also few. This impedes its diagnosis and management in the Indian subpopulation. Awareness of the disease among Indian clinicians would lead to a better understanding and country-specific consensus-based management guidelines would pave the way for a better prognosis in Indian patients with IgG4-RD.

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Ethical approval: Not required

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