



# IgG4-related disease in the eye and ocular adnexa

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## Purpose of review

IgG4-related disease is a multi-organ fibro-inflammatory disease with characteristic histopathology showing lymphoplasmacytic infiltration, increased IgG4+ plasma cells and elevated IgG4/IgG ratios (>40%). The lacrimal gland is the most common ocular site of involvement. Scleritis and intraocular involvement in IgG4-related ophthalmic disease (IgG4-ROD) have recently been reported. The purpose of this review is to describe orbital and intraocular IgG4-ROD with a focus on publications since 2016.

## Recent findings

Case reports of scleritis and uveitis in IgG4-ROD have been described since 2012. Systemic prednisone is recommended as the first-line treatment, but immunosuppressive therapy may be required for steroid-sparing or in steroid-resistant cases. High rates of systemic IgG4-RD involvement exist in patients with bilateral IgG4-ROD or if the lacrimal gland is involved. Rituximab is the most specific immune targeted therapy available with high rates of remission.

## Summary

IgG4-ROD is an emerging cause of scleritis and uveitis and should be considered in any patient with multisystem inflammatory disease. New targeted immune therapies may improve outcomes and lead to clinical remission.

## Keywords

IgG4-positive plasma cells, IgG4-related ophthalmic disease, orbital inflammation, scleritis, uveitis

## INTRODUCTION

IgG4-related disease (IgG4-RD) is a relatively new multisystem organ disease first described in 2001 and characterized by fibro-inflammatory masses or nodules due to infiltration of IgG4-positive plasma cells in various organs simultaneously or consecutively. The first case of IgG4-RD was reported in a Japanese patient with autoimmune pancreatitis and abnormally elevated serum IgG4 levels. Since this initial report of IgG4-related autoimmune pancreatitis, IgG4-RD has been described in many other organ systems, including the hepatobiliary ducts, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, retroperitoneum and aorta. The pancreas and salivary glands are the most frequently involved tissues and the lacrimal gland is the most common ophthalmic site of involvement [1]. The overall frequency of ophthalmic involvement in systemic IgG4-RD is 4–34% [2<sup>••</sup>].

IgG4-related ophthalmic disease (IgG4-ROD) was first linked to a cases of chronic sclerosing dacryoadenitis in 2007 [3], and subsequent reports identified other sites of ophthalmic involvement, including the extraocular muscles, orbital soft tissue, cavernous sinus, sclera, choroid and nasolacrimal duct. IgG4-ROD is considered to be the

underlying cause in patients previously diagnosed with Mikulicz's disease with the identification of elevated serum IgG4 [4] and positive IgG4 plasma cells found in orbital pathological specimens of patients with Mikulicz's disease [2<sup>••</sup>]. More recently, IgG4-ROD has been identified in cases of scleritis, uveitis and choroidal mass lesions.

## CLINICAL FEATURES

Systemic IgG4-RD is a rare disease, which presents in middle to older age, a median age of 58–67 years, (90% patients aged 50–80 years) and a male : female ratio of 4:1–3:1. Salivary and lacrimal gland involvement occurs more frequently in women [5<sup>•</sup>]. IgG4-ROD may present at a younger age, with a mean age of 56.7 years in men and 48.5 years in

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## KEY POINTS

- IgG4-related disease is a fibro-inflammatory disorder affecting multiple organs simultaneously or consecutively characterized by infiltration of IgG4+ plasma cells.
- IgG4-related ophthalmic disease most frequently involves lacrimal gland but can also affect the orbital soft tissue, orbital nerves, sclera, choroid and orbital adnexa.
- Biopsy of the lesions is the gold standard for diagnosis and histopathology shows a dense lymphoplasmacytic infiltrate with more than 10–50 IgG4+ plasma cells per HPF and high IgG4+/IgG plasma cell ratio (>40%).
- Treatment involves systemic steroids initially followed by immunosuppression for steroid resistant and steroid sparing effect.
- Rituximab is the most specific biologic treatment with high rates of remission.

women [2<sup>\*\*\*</sup>]. IgG4-RD is rare in children, with only three cases of orbital disease reported in the paediatric population to date [3]. The majority of reported cases of IgG4-ROD have involved orbital and orbital adnexal structures. Reports of IgG4-ROD involving the scleral and intraocular tissues are less common, and since 2012, only individual case reports of conjunctival, scleral, uveal and choroidal involvement have been published.

The prevalence of IgG4-RD is not known but is more frequently reported in Asia. In Japan, IgG-4 related disease was the second most prevalent cause of orbital lymphoproliferative disease (21.6%) [4]. Prevalence rates in other countries have not been published but are likely underestimated in western countries [6].

The most frequent single ophthalmic site of involvement in IgG4-RD is the lacrimal gland. A French case registry [2<sup>\*\*\*</sup>] of multicentric IgG-RD reported IgG4-ROD in 25 patients, with the following sites of involvement: lacrimal gland (68.4%), orbital soft tissue (57.4%) and extraocular muscles (36.8%), palpebral tissues (21.1%), optic nerve (10.5%) and trigeminal nerve (V1 or V2) (10.5%). Only one patient was found to have sclerokeratitis and no patients were reported to have uveitis. Bilateral involvement occurred in 57.1% cases and was more frequent in patients with dacryoadenitis (90.9%) [2<sup>\*\*\*</sup>].

IgG4+-ROD presents insidiously, with symptoms of painless proptosis, eyelid swelling (in orbital disease) [7] or decreased vision with tearing, pain, redness or photopsias (in cases of scleritis and

uveitis). The disease follows a relapsing-remitting course [8] but can progress to a chronic state [4]. Visual impairment in IgG4-ROD has been reported in 21–40% of cases [2<sup>\*\*\*</sup>].

Extraocular manifestations of IgG4-ROD occur in 75–100% of patients and are strongly associated with bilateral IgG4-ROD (79% extraocular disease in bilateral IgG4-ROD vs. 14% unilateral IgG-ROD cases) [9<sup>\*\*\*</sup>], and are more common when the lacrimal gland is involved [2<sup>\*\*\*</sup>]. The most common sites of extraocular involvement in IgG4-ROD are the pancreas, salivary glands and lymph nodes. Given the high rate of extra-ophthalmic involvement, systemic examination and imaging (head, neck chest, abdomen and pelvis) of new cases of IgG4-ROD is recommended in order to identify other sites of involvement and initiate early systemic treatment [9<sup>\*\*\*</sup>].

IgG4-ROD is now known to be a cause of idiopathic orbital inflammation. Biopsies of 112 patients with nonspecific orbital inflammation identified IgG4-positive biopsies in 19% of cases (81% lacrimal and 71% bilateral) [10]. In a large series of 1014 cases in Japan, IgG4-ROD was the second most frequent cause of orbital lymphoproliferative disease (21.6% IgG4-RD following MALT lymphoma, 39.8%) [4]. Nonspecific orbital inflammation due to IgG4-ROD may be related to systemic sclerosis and must be differentiated from MALT lymphoma. Rare cases of lymphoma developing from IgG4 sclerosing dacryoadenitis have been reported. In-situ conjunctival carcinoma has been reported in a 50-year-old woman with a previous conjunctival IgG4+ lesion [6].

Since 2015, 15 cases of IgG4-ROD causing uveitis or uveal masses (nine cases) [7,8,10–16], scleritis (nine cases) [6,8,10,11,13–15,17–19] or conjunctival infiltration (one case) [6] have been described in the literature (see Table 1). Presenting manifestations were unilateral scleritis, bilateral multifocal choroiditis, choroidal mass and ciliary body mass. Uveitis related to IgG4-ROD is usually associated with scleral or choroidal involvement. Posterior scleritis was associated with vitritis and panuveitis as well as serous retinal detachment. Histologic specimens have shown involvement of sclera, choroid and RPE [14]. One study of panuveitis was associated with cavernous sinus and superior orbital fissure lesions [16]. Most reported cases of intraocular involvement were unilateral.

## DIAGNOSIS OF IGG4-RELATED DISEASE

Diagnosis of IgG4-RD involves physical examination, imaging studies and laboratory studies. Given the high rate of extra-ocular involvement, patients

**Table 1.** Clinical characteristics of intraocular IgG4-related ophthalmic disease or scleritis

Case, age, sex	Ophthalmic site of involvement	Biopsy results	Systemic involvement	Laterality	Treatment	Final VA (if available)
82-year-old woman [11]	Left posterior scleritis, vitritis, choroidal and exudative retinal detachment, and intraconal along with extraconal orbital masses	Biopsy of intraconal mass: IgG4/IgG >40% and >30–40 IgG4+ PC/HPF	none	Bilateral orbital masses; unilateral scleritis and uveitis	Prednisone po	Visual outcome: 6/6 OD and LP
64-year-old man [7]	Multifocal choroidal and orbital lesions	Periteneal biopsy: fibrosis secondary to IgG4-RD	Renal, splenomegaly, mediastinal mass	Bilateral	Rituximab	20/20 OD and OS
20-year-old woman [18]	Nodular scleritis	Biopsy of scleral nodule: IgG4+ >30/HPF; >40% ratio	none	Unilateral	Steroids + methotrexate	
41-year-old man [12]	Choroidal mass lesion	Biopsy of scleral placoid tissue: dense fibrous tissue: Plasma cells CD20+, IgG4+ >55/HPF; IgG4+:IgG >40%, elevated serum IgG4	none	Unilateral	Prednisone	20/20
23-year-old woman [13]	Ciliary body mass, scleritis, panuveitis hypopyon	Enucleated globe: ciliary body mass: IgG4: IgG >30%; increased serum IgG4	none	Unilateral	Subtenons triamcinolone, oral steroids	NLP
79-year-old woman [8]	Necrotizing anterior nodular scleritis, posterior scleritis and panuveitis and serous RD	Enucleated globe: IgG4 >70/HPF and IgG4:IgG >50%	none	Unilateral	Prednisone and cyclophosphamide, indomethacin, MTX, AZA, IFX	NLP
47-year-old man [14]	Choroidal, RPE and scleral mass, uveitis	Enucleation: Choroidal,RPE, sclera mass; IgG4 >20/HPF	none	Unilateral	Steroids, MTX	
49-year-old woman [15]	Scleritis and uveitis, retinal detachment, choroidal lesion	Enucleation: IgG4+ 97–178 HPF IgG4:IgG 51–58.7%	none	Unilateral	Prednisone, Cyclosporine	
17-year-old girl [19]	Scleritis	Scleral biopsy: lymph node bx IgG4+	none	Unilateral	Prednisone, MTX, CSA, MMF → relapse rituximab	
66-year-old man [10]	Anterior scleritis, uveitis, conjunctivitis, IR muscle	Biopsy Conj & IR: IgG4+ PC: 89.7/HPF and IgG4+:IgG ratio 50.3%	none	Unilateral	Depot triamcinolone, prednisone, MTX	
Case 1: 63-year-old woman Case 2: 50-year-old woman [6]	Case 1: Recurrent anterior and posterior scleritis Case 2: conjunctival infiltration	Case 1 Scleral biopsy: IgG:IgG ratio 50%; elevated serum IgG4 Case 2 conjunctival biopsy: IgG4:IgG 85%	None None	Unilateral Unilateral	Prednisone, MTX Prednisone, topical mitomycin	
33-year-old man [16]	Bilateral panuveitis, cavernous sinus, Superior orbital fissure, sphenoid sinus	IgG4+ plasma cells 30/HPF; IgG4:IgG ratio >40%	Sphenoid sinus	Bilateral panuveitis; unilateral cavernous sinus and SOF	Prednisone, MTX, cyclosporine, azathioprine, Infliximab	20/40 OD
Acta ophthalmol, 2017 Letter [17]	Scleritis – 2 definite cases; 3 probably cases	No details	Systemic			

AZA, azathioprine; CSA, cyclosporine A; HPF, high power field; IFX, infliximab; LP, light perception; MMF, mycophenolate mofetil; MTX, methotrexate; NLP, no light perception; OD, oculus dexter (right eye); OS, oculus sinister (left eye); SOF, superior orbital fissure; VA, visual acuity.

should undergo a full systemic workup with particular attention to the salivary glands, lymph nodes and pancreas.

The gold standard for diagnosis of IgG4-ROD requires biopsy of the lesion and histopathologic findings of lymphoplasmacytic infiltrate rich in IgG4+ plasma cells, storiform fibrosis, obliterative phlebitis and frequent germinal centres. Eosinophils and non-obliterative phlebitis are also found [3]. Obliterative phlebitis is less common in biopsies of IgG4-ROD compared with biopsies of systemic IgG4-RD [11].

Immunohistochemical staining of the pathological specimens shows increased IgG4+ plasma cells (>10 to 50 cells/hpf depending on the organ involved) and elevated IgG4/IgG ratios (>40%). Serum IgG4 levels (>135 mg/dl) may be elevated but are normal in 30–40% patients [7]. Immunohistochemical staining of lymphoplasmacytic cells is often positive for CD20 [12].

Guidelines for IgG4-related disease were published as a consensus statement in 2012, based on morphological appearance on biopsy emphasizing clinic-pathological correlation as a basis for diagnosis [1]. The Japanese study group for IgG4-ROD published guidelines for IgG-related ophthalmic disease in 2015, which specifically defined the ocular sites of involvement and suggested less frequent fibrosis, more frequent germinal centres and higher IgG4+ plasma cell/high power field (HPF) (>50 IgG4+ plasma cells in IgG-ROD compared with >10 in IgG4-RD). The Japanese diagnostic criteria are outlined in Table 2. These criteria have not yet been validated by other study groups [4].

## DIFFERENTIAL DIAGNOSIS

IgG4-ROD can mimic many infectious, inflammatory and malignant disorders. More common causes for

**Table 2.** Diagnostic criteria for IgG4-related ophthalmic disease, 2015

- (1) Imaging studies showing enlargement of the lacrimal gland, trigeminal nerve or EOM as well as masses, enlargement of hypertrophic lesions in various ophthalmic tissues
- (2) Histopathologic examination shows marked lymphocyte and plasmacyte infiltration and sometimes fibrosis. A germinal centre is frequently observed. IgG4+ plasmacytes satisfy the following:
  - (a) ratio of IgG4+ cells to IgG+ cells of 40% or above
  - OR
  - (b) more than 50 IgG4 cells per HPF (X400)
- (3) Blood test shows elevated serum IgG4 ( $\geq 135$  mg/dl)

Diagnosis is 'definitive' when (1), (2), (3) are satisfied.  
 Diagnosis is 'probable' when (1) and (2) satisfied.  
 Diagnosis 'possible' when (1 and (3) are satisfied.  
 Reproduced from [4].  
 EOM, extraocular movements; HPF high power field.

lacrimal gland masses, other orbital space-occupying lesions, scleritis and uveitis should be ruled out before suspecting IgG4-ROD. The main differential diagnoses include Sjogren's syndrome, lymphoma, sarcoidosis, granulomatosis with polyangiitis, thyroid related orbitopathy, idiopathic orbital inflammation and infectious dacryoadenitis [4]. In cases of sclerouveitis, the spondyloarthropathies (ankylosing spondylitis, reactive arthritis, psoriatic arthritis, inflammatory bowel disease) and causes of severe scleritis (tuberculosis, syphilis, relapsing polychondritis, rheumatoid arthritis and granulomatosis with polyangiitis) should be ruled out initially. IgG4-ROD is a rare cause of uveitis and should be suspected if concurrent inflammation is identified in the sclera, orbit, orbital adnexae or other organs.

## PATHOGENESIS

The pathogenesis of IgG4-RD is not well understood, but the mechanism most likely involves immune dysregulation, linked to genetic risk factors, bacterial infection (leading to autoantibody formation through molecular mimicry) and autoimmunity [14].

IgG4 is a minor subset of the IgG immunoglobulins (normally constitutes 4% of total IgG) and is normally produced by activated plasma cells [5].

Th2-dominant immune responses are thought to play an important role in IgG4-RD [1]. Studies have reported increased expression of T-helper2 cells and T regulatory cells, with increased cytokine secretion of interleukin (IL)-4, 5, 10, 13 (Th2 cells) and transforming growth factor (TGF)-beta (Treg cells). These studies have therefore proposed a mechanism of Th2 lymphocytes leading to activation of B cells and production of IgG4-expressing B cells and subsequent fibrosis [8,20].

Other studies have found CD4<sup>+</sup> cytotoxic T lymphocytes in biopsy specimens from IgG4-RD lesions and serum, suggesting that they play an important role in disease pathogenesis. ILs secreted by CD4<sup>+</sup> T lymphocytes [IL-1, TGF-beta, interferon (IFN)-gamma] are also important mediators of fibrosis, a histopathologic finding in IgG4-RD [18].

IgG immunoglobulins produced by plasma cells undergo temporal class switching from IgG3 to IgG1 to IgG2 to IgG4 subclasses, therefore IgG4 being the last subclass formed. Tissue IgG2 elevation has recently been reported in orbital IgG4-ROD, thus suggesting that IgG2 serum levels may rise prior to IgG4 serum levels in IgG4-RD; thus, lack of IgG4 detection may indicate an earlier stage of IgG-RD [21].

Patients with IgG4-related disease have been reported to have associated allergic features such

as atopy, asthma, eczema or chronic sinusitis [14], which correlates with Th2 effector responses known to occur in atopic diseases.

## TREATMENT

IgG4-ROD responds well to systemic prednisone [per os, orally or intravenous (IV)] as a first-line treatment at initial doses of 0.6–1.0 mg/kg per day. A limited window of steroid efficiency has been suggested [6]. Initial systemic steroid response rates are high [2<sup>\*\*\*</sup>] with 1-year remission rates of 61% after 1 year of c/s treatment (infliximab paper), but relapses occurring in two-third of patients during steroid tapering or withdrawal, within a mean of 3.5 months [2<sup>\*\*\*</sup>]. Steroids should therefore be tapered slowly over several months in order to prevent relapses. About 72.2% patients may require long-term steroids and/or immunosuppressive agents [2<sup>\*\*\*</sup>]. Immunosuppressive agents such as azathioprine, methotrexate and mycophenolate mofetil have been used in IgG4-ROD for steroid-sparing effect, or in steroid-refractory disease. Successful treatment with infliximab has been reported in two cases [3].

More specific, targeted therapy with rituximab, an anti-CD20 mAb, has been particularly effective as a second or third-line treatment, with possible high rates of remission in both systemic and ophthalmic IgG4-RD. Rituximab leads to depletion of CD20-positive B cells and therefore prevents their differentiation to IgG4-producing plasma cells. Disease response with rituximab with or without corticosteroids is high and reported to be successful in 87.5% cases of IgG4-ROD [2<sup>\*\*\*</sup>] and 97% at 6 months for IgG4-related systemic disease [22]; however, rituximab may only have a temporary effect. A recent retrospective cohort study of 60 patients with IgG4-RD reported a clinical response of 97% but a relapse rate of 37% at median 244 days postinfusion. Relapses were correlated with higher baseline IgG4 serum concentrations [23<sup>\*\*\*</sup>]. The optimal frequency or duration of rituximab infusions for IgG4-ROD is not known [2<sup>\*\*\*</sup>], but studies suggest initial treatment with two doses of rituximab separated by 15 days [23<sup>\*\*\*</sup>]. Other specific targeted immune therapies, directed at abnormal T-cell subsets, may be considered in the future.

Several authors have suggested earlier treatment initiation in order to prevent development of tissue fibrosis and resulting organ damage due to fibrotic changes [3,9<sup>\*\*\*</sup>].

## CONCLUSION

IgG4-ROD is a new diagnostic cause for intraocular, scleral or orbital inflammation, which should be

considered in any patient with multisystem fibro-inflammatory disease with a relapsing-remitting, or chronic course. Ophthalmic manifestations of IgG4-RD include lesions in the lacrimal gland, extraocular muscles, trigeminal nerve, orbital adnexa (nasolacrimal duct, cavernous sinus) and choroid as well as uveitis and scleritis. After ruling out other potential causes of orbital space-occupying lesions, ocular lesions or uveitis, IgG4-RD should be considered, especially if multisystem inflammation is present. The gold standard for diagnosis of IgG4-ROD is biopsy of the involved tissue showing lymphoplasmacytic infiltration, identification of IgG4-positive plasma cells (>50 IgG4 plasma cells/HPF) and an elevated IgG4/IgG ratio (>40%). Serum IgG4 levels may be normal in up to 40% of cases. Treatment involves early institution of systemic steroids (oral or IV), and a slow taper (over several months). If the inflammation recurs, immunosuppressive treatment or biologic treatment should be considered. Rituximab has shown to be particularly effective and can lead to disease remission in a high number of cases. Future direction will lead to improved understanding of IgG4 ophthalmic disease manifestations and more targeted immune therapies.

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## Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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