

# Immunoglobulin G4-related ophthalmic disease – what is it? Part 2: Clinical presentation and treatment

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## Introduction

IgG4-related disease (IgG4-RD) is understood to have a vast clinicopathological spectrum; nearly every organ has had reported involvement. Similarly, IgG4-related ophthalmic disease (IgG4-ROD) is known to affect nearly every part of the eye and adnexae [1].

## Clinical Presentation of IgG4-ROD

The lacrimal gland is by far the most commonly reported structure to be affected by pathologically diagnosed IgG4, followed by the trigeminal nerve, extraocular muscles (EOM) and orbital soft tissue [2]. Most other ocular structures have been affected to a much lesser extent [3-10]. While IgG4-ROD may primarily present as an ocular problem, multidisciplinary input is essential, as this is a disease with systemic implications. Extra-ophthalmic involvement is found in up to 75-100% of cases [11,12].

Several studies suggest between 62% (13/21) to 98.4% (221/225) of IgG4-ROD involved the lacrimal gland and up to 69% (49/71) solely involve the lacrimal gland [2,8,13,14]. This correlates to presenting symptoms usually being painless eyelid swelling, xerophthalmia and proptosis [15]. Bilateral involvement of IgG4-ROD is common though not necessarily symmetrical and has been found in up to 93% of patients [5-8,11,16-18]. The natural history of lacrimal gland IgG4 disease has been observed to be similar to other organs with a slow evolution of lymphoid hyperplasia to significant atrophic fibrosis, though cases of very rapid fibrosis have been reported [10,15]. Bilateral orbital involvement with IgG4 is more highly associated with IgG4-RD elsewhere, compared to unilateral disease; a study demonstrating extra-ophthalmic involvement was present in (69%) 79/114 bilateral cases compared to 29% (20/68) unilateral cases [19]. Extra-ophthalmic organs are commonly local lymph nodes and salivary glands [11,12].

In current literature, up to 39% (25/65) of IgG4-ROD features trigeminal nerve involvement, approximately 64% of these are bilateral [2,8,14]. The common branch affected is the infraorbital nerve (ION), with accompanying enlargement of the infraorbital canal and even expansion into the infraorbital fissure [8]. The frontal nerve, supraorbital nerve and maxillary nerve have also been affected sparingly [8,10,20]. Very few entities cause enlargement of the ION and its canal, adnexal mucosa-associated lymphoid tissue (MALT) is another culprit, and notably this condition is linked to IgG4-ROD [21]. Image 1 is an illustration of ION enlargement demonstrated unilaterally on a computed tomography scan. Almost none other than IgG4-ROD will lead to bilateral ION enlargement [10]. This is a feature highly suggestive of IgG4-ROD. ION enlargement has been defined as larger than the optic nerve by some or two standard deviations above the mean by others [21,22]. Enlargement of the ION is also thought to be a predicting factor of extra-ophthalmic involvement [22,23]. A study of 68 patients found that 20 patients who had infraorbital nerve enlargement of >3.3mm were more likely to have extra-ophthalmic involvement than patients without infraorbital swelling, 29% versus 0% [22]. This change is rarely seen in isolation, usually accompanying other IgG4-ROD signs, enlargement of EOM particularly, lacrimal



Image 1: Illustration of ION enlargement demonstrated unilaterally on a computed tomography scan.

disease and paranasal sinus disease [10,23]. Although rare instances have been reported, involvement of nerves in IgG4-ROD does not often result in sensory loss [24,25]. Unusually, fibrosis is not usually a feature of IgG4 nerve involvement and the disease process appears to involve the epineurium mainly, alleviating fear of long-term implications [10,25].

In our study, 37.5% (3/8) of cases had IgG4 involvement of the EOM, in all involvement was unilateral. Reported frequencies of IgG4-ROD myositis are between 18% (40/225) to 89% (24/27) [2,8,13]. Of these, bilateral involvement is noted in up to 88% [2,8,13]. Single or multiple muscles could be affected [10]. Recent studies have found the lateral rectus most commonly affected and also to the greatest extent [13,26]. The inflammation in IgG4-ROD is tendon-sparing in up to 93-96% [8,13]. Active IgG4-ROD affecting the EOM usually allows better ocular motility, despite enlargement of these muscles, relative to differential inflammatory diseases such as thyroid eye disease and idiopathic orbital myositis [26-29, 30, 31]. Active episodes with increased serum IgG4 levels may produce a large-angle strabismus, but these mostly respond well to steroid treatment [26].

There has been suggestion that EOM / trigeminal nerve involvement in IgG4 ROD may signify a more progressive and recalcitrant disease course. In a large study, patients with EOM / trigeminal nerve enlargements required maintenance low-dose systemic corticosteroid treatment for stability, were more likely to be resistant to corticosteroid treatment and were significantly more likely to relapse after corticosteroid treatment [14]. This same

study found a majority (18/20) of isolated lacrimal gland lesions who opted for watchful waiting, remained dormant or regressed spontaneously [14].

The optic nerve is sparingly affected in IgG4-ROD. The optic nerve sheath infiltration with IgG4 mass forming lesions near the orbital apex has been described, usually bilaterally and in one case associated with an extension to cause pachymeningitis [32-34]. As expected, common presentations include painless vision loss and non-specific visual fields defects. A focal optic nerve IgG4 lesion has been described and thought to represent a form of inflammatory demyelinating IgG4-driven disease, it was interesting to note, however, the absence of pain on presentation, which is a typical feature of inflammatory optic neuritis [35].

IgG4 orbital inflammation is thought to present in two forms: diffuse sclerosing orbital inflammation accounting for up to 23.1% (15/65) of IgG4-ROD, or demarcated orbital mass lesions in 16.9% (11/65); compression of the optic nerve causing visual symptoms and mass effect limiting globe movement are more common than IgG4 disease directly affecting the EOM and optic nerve [8]. In our findings, discrete orbital lesions were noted in 50% (4/8) and 12.5% (1/8) had diffuse orbital soft tissue involvement. However, as discussed, the figures in literature may be under-reported, thus a

proportion of orbital inflammatory diagnoses previously thought to be idiopathic will now come under the IgG4-ROD definition [36]. While difficult to determine in retrospect, a review performed by Winn and Rootman found that a significant proportion (up to 50%) of orbital inflammation case reports had features suggestive of IgG4 disease [36].

IgG4 involvement of the eyelid is uncommon and those affecting the tarso-conjunctival region are rare. Cutaneous eyelid lesions only account for about 12.3% of IgG4-ROD (8/65) and indeed the conjunctiva was previously thought to be a site not affected by IgG4 [5,8,15]. In recent years, only 10 cases involving the tarsal plate and conjunctiva have been confirmed and reported (Table 1) [37-47]. Interestingly, IgG4 disease in this region seems to vary in its presentation while other forms of IgG4-ROD are more uniform; these lesions have been misdiagnosed as chalazions, cicatrising or ligneous conjunctivitis or infection. Also unusually, the cases of IgG4-ROD presenting in this area were rarely associated with systemic IgG4 with the exception of one case who also had cutaneous trunk lesions (38). This has enabled several cases to be treated effectively with either pure local excision or local topical steroids; only three of the 10 cases requiring systemic treatment [37-46].

**Table 1: Summary of published IgG4-ROD cases involving the conjunctiva**

	Author	Age, Gender	Unilateral/ Bilateral	Symptoms	Findings	Length of symptoms	Initial diagnosis	Systemic associations	Treatment	Follow-up	Outcome
1	Philippakis et al. [45].	50 F	Unilateral, right	Not reported	Bulbar conjunctiva; infiltration, chemosis, follicles	2 years	Not specified	Nil	High dose oral prednisolone	2 years	Resolution of symptoms, no recurrence
2	Li et al. [46].	63 F	Unilateral, left	Ocular irritation and conjunctival redness	Bulbar conjunctiva; lesion with evidence of scleral invasion	3 years	Not specified	Nil	Surgical excision and cryotherapy, topical steroids and antibiotics	6 months	Resolution of symptoms, no recurrence
3	Paulus et al. [43].	66 M	Unilateral, right	Ocular irritation and redness	Bulbar conjunctiva; injection, chemosis, iritis, scleritis,	2 weeks	Not specified	Nil	High dose oral prednisolone, periorbital triamcinolone and metretrexate	2 years	Resolution of symptoms, no recurrence
4	Chiang et al. [44].	34 F	Bilateral, upper	Itching, redness and mucinous discharge	Tarsal conjunctiva; woody hyalinised masses	Not specified	Ligneous conjunctivitis	Nil	Surgical excision three times, cryotherapy, triamcinolone injection, application of mitomycin C and amniotic membrane transplantation	Not reported	Not reported
5	Nagai et al. [42].	83 M	Bilateral, lower	Conjunctival redness	Tarsal conjunctiva; hyperaemia, hypertrophic ectropion	Not specified	Not specified	Nil	Topical steroids (ineffective), refused systemic glucocorticoid treatment	6 months	Stable disease
6	Cameron et al. [40].	46 M	Unilateral, right	Ocular discomfort	Tarsal conjunctiva; cicatrising conjunctivitis, trichiasis	6 years	Not specified	Nil	High dose oral prednisolone, methotrexate and rituximab	Not reported	Resolution of symptoms, no recurrence
7	Chong et al. [47].	66 M	Unilateral, right	Ocular discomfort	Tarsal conjunctiva; multiple firm, conjunctival nodules	9 months	Not specified	Nil	Surgical excision, topical steroids	3.6 years	Resolution of symptoms, no recurrence
8	da Fonseca et al. [37].	67 F	Unilateral, left	Not reported	Tarsal conjunctival lesion	5 months	Infection	Nil	Surgical excision	5 months	Reduction in lesion size
9	Leivo et al. [38].	55 F	Unilateral, right	Upper lid mass	Tarsal plate lesion	Not reported	Chalazion	IgG4 cutaneous lesions on the trunk	Surgical excision	9 months	Resolution of symptoms, no recurrence
10	*Kubota et al. [41]	59 F	Bilateral, upper	Upper lid lesions	Tarsal plate lesion, bilateral	Not reported	Not specified	Not reported	Periorbital injection of triamcinolone	Not reported	Not reported

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Other less commonly encountered IgG4-ROD includes ocular inflammatory forms; uveitis and scleritis [43,45,48,49]. IgG4 dacryocystitis is also infrequent; bilateral cases have been observed [8,50-53].

### Treatment

Therapeutic decision-making in IgG4-ROD is often based on clinical experience and expert opinion due to the lack of level one evidence. Furthermore, because the molecular mechanisms sustaining IgG4-RD remain largely unknown, targeted therapies are not available. Active treatment may not always be necessary with careful observation appropriate for some asymptomatic cases, for example isolated lymphadenopathy or mild salivary gland enlargement and a large systematic review found this approach appropriate in 13% of the cohort, with spontaneous resolution [54,55].

Generally, however, IgG4 has a relapsing-remitting nature, and long-term immunosuppression is often needed. Risk factors for relapse include; elevated serum IgG4 at diagnosis, multi-organ involvement, previous relapse, and as discussed above, EOM / trigeminal nerve involvement [56].

Delivering a swift therapeutic response, generally within weeks, regardless of the clinical presentation and organ involvement, glucocorticoids is the central to treatment of IgG4-RD and is the current first-line treatment in patients with active disease [54,57]. With glucocorticoid monotherapy, a 97% therapeutic response was found in a cohort of 1220 patients in a systematic review [55]. Despite an overall good response to glucocorticoid, the recurrence of IgG4-ROD is not uncommon, after glucocorticoids are stopped or tapered off, with a relapse rate of up to 68.4% (17) [58-63]. Periorbital injection of glucocorticoids has been reported as an alternative treatment to systemic glucocorticoids approach for IgG4-ROD, particularly in the anterior orbit to avoid systemic immunosuppression [64]. Topical steroid use in eyelid / conjunctival lesions can be effective, easily applied with ease [39,65]. However repeated treatments may be needed in cases of relapse or incomplete response, which limits its use and increases the risk of local complication.

Immunomodulatory drugs are usually employed in cases of multiple relapses and where long-term maintenance is likely needed. A management consensus has advised that azathioprine, methotrexate or mycophenolate mofetil can be initiated as steroid-sparing agents in IgG4-RD (54) but other agents such as hydroxychloroquine, tacrolimus infliximab, thalidomide, cyclosporine have also been described as effective [54,61]. Within IgG4-ROD, a combination of glucocorticoids and immunomodulatory drugs (including cyclophosphamide, mycophenolate mofetil, methotrexate, leflunomide, azathioprine, iguratimod, and rituximab) has been found to be significantly protective against relapse when compared to glucocorticoid monotherapy alone; 43 months versus 17 months of relapse-free period [9].

The emergence of biological therapies has added to the IgG4-RD therapeutic armamentarium. Rituximab has already demonstrated promising results in refractory disease and has been used especially in IgG4-ROD cases to enable 'medical' orbital decompressions [2,66-69,70,71]. Nevertheless, relapse rates are still high once the therapy is ceased but has been used successfully in maintenance, with a dosage every six months [67]. Rituximab also has the potential to be considered as first-line treatment, an open label trial found that two 100mg doses of rituximab resulted in a IgG4-RD response rate of 97%, largely (26 out of 30 patients) without glucocorticoid use and without re-administration of rituximab [72]. Yamamoto et al. have also reported the successful use of rituximab without glucocorticoids in IgG4-ROD dacryoadenitis [73].

There is also a role for surgery in managing this disease. There have been reports where excisional biopsies confirming IgG4 have inadvertently functioned as effective treatment [73-75]. An example within IgG4-ROD; enucleation where the initial suspicion was a choroidal tumour presenting as a white subretinal mass, IgG4 disease was later diagnosed and serum IgG4 levels reduced after excision without any

other treatment [48]. Subsequently, primary surgical resection of IgG4-related tissues has been described in the thyroid gland, pulmonary tissue, pericardium and pancreas leading to prolonged periods of remission (median 36 months), in some cases without further immunosuppressive therapy [61]. This therefore implies that resection of the lesions and debulking of the target organs involved in the disease may result in a lower recurrence rate than steroid therapy, where the target organs are preserved [61]. There has been some experience to variable success in surgical debulking or excision as primary treatment for IgG4-ROD affecting eyelid lesions, the lacrimal gland, nasolacrimal duct and orbital fat [2,5,76]. Otherwise, IgG4-ROD rarely necessitates surgical treatment, except for sight orbital decompression or enucleation as a last measure for symptom relief [77,78].

### Conclusion

IgG4 can strike almost any ocular region, with varying presentations and with multiple areas affected simultaneously, creating a complicated clinical picture. However, it is an important diagnosis to consider and establish, as lack of treatment may allow the disease to progress unchecked and result in devastating outcomes such as loss of vision, the eye itself and ocular adnexa. Furthermore, there are effective treatments for IgG4-ROD with good response rates, although the long-term management of relapses is still an issue.

### TAKE HOME MESSAGES

- IgG4 disease can affect nearly any ocular and adnexal structure. Multiple areas can be affected simultaneously or synchronously and present variably. Therefore, IgG4-ROD should be considered in presentations of ocular and especially orbital inflammation
- Risk factors for relapses include: EOM / trigeminal nerve involvement, multi-organ involvement, previous relapses plus raised serum IgG4 and male gender (as discussed in Part 1).
- Currently, there are several effective lines of treatment for IgG4-ROD though long-term management of relapses is still an issue.

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