Title:
IgG4: What is it good for?

Learning Objectives:
1. The attendee will learn the current diagnostic criteria for IgG4-related disease
2. The attendee will understand the potential pathophysiologic mechanisms of tissue injury for IgG4-RD
3. The attendee will know when to consider screening for IgG4-RD in a clinical setting

CME Questions:
1. What are the most common neuro-ophthalmic manifestations of IgG4-related disease?
2. What is the sensitivity of serum IgG4 in IgG4-related disease?
3. T or F: IgG4 activates the classic complement pathway

Keywords (Max 5):
1. IgG4
2. Orbital inflammatory syndrome
3. Pachymeningitis

Introduction/Abstract (Please see instructions for formatting details):
IgG4 related disease is an increasingly recognized condition which can mimic other, immune-mediated inflammatory diseases. The diagnostic criteria are still evolving and a number of previously unclassified or eponymic diseases are now falling under the category of IgG4-related disease. This condition has several distinct neuro-ophthalmic manifestations, including orbital inflammatory syndrome and pachymeningitis, and others may follow. Neuro-ophthalmologists should have increased awareness of this condition and be familiar with diagnostic testing for, and treatment of, IgG4 related disease.

Body (Please see instructions for formatting details):
Introduction:

IgG4-related disease (IgG4-RD) is an increasingly recognized condition characterized by sclerosing inflammation, a lymphoplasmacytic infiltration full of IgG4-positive plasma cells, and frequently associated with elevated serum IgG4 concentrations. It was first described as a systemic condition in 2003 when extrapancreatic manifestations were identified in patients with autoimmune pancreatitis, a condition known to be associated with elevated levels of IgG4. Since that discovery, the presence of IgG4-related inflammation has been detected in virtually all organs, particularly the pancreas, liver, kidney, lung, and thyroid.

Over the past several years, more and more previously unclassified or eponymous conditions have been re-classified as IgG4 related disease, several of which are particularly relevant to neuro-ophthalmologists. The increased awareness of this condition has led many clinicians to search for IgG4 RD in patients, either by screening with serum IgG4 levels, or re-reviewing previous pathology specimens. However, the diagnostic criteria for IgG4-RD are still evolving, and to some degree remain a moving target. Indeed, the nomenclature for IgG4-RD varies considerably in the literature - it is variably referred to as IgG4-RD, IgG4-associated disease, IgG4 sclerosing disease, and others. Serum IgG4 levels may be elevated in other, unrelated autoimmune and infectious diseases, and some (but not all) of the pathologic findings are non-specific.

Historical background:

The first reported manifestation of IgG4-RD was autoimmune pancreatitis, initially described as a possible immune mediated condition by Sarles et al in 1961. Harano et al found increased IgG4 levels in patients with a subtype of autoimmune pancreatitis - lymphoplasmacytic sclerosing pancreatitis. This condition typically affects elderly men, with a prevalence of ~2-11% among patients with chronic pancreatitis. Characteristic pathologic features, which serve as the basis for the diagnostic criteria for IgG4-RD, include interstitial infiltration by plasma cells, small lymphocytes, and some eosinophils. The infiltrate is organized in a storiform (matted and whorled) pattern, and obliterative phlebitis is a frequent feature, although this may vary depending upon the target tissue. Response to steroids is usually good and there are multiple reports of favorable response to a variety of immunomodulatory agents. As more patients with IgG4 related sclerosing pancreatitis were identified, it became clear that extra-pancreatic involvement was common, in some series in up to 80% of cases. More and more organ systems were implicated, as pathologic specimens in extra-pancreatic sites showed similar histologic features. Indeed, blind biopsies of clinically normal organs can show increased IgG4 plasma cells.

The epidemiology of IgG4-RD is almost exclusively drawn from the Japanese literature, focusing primarily on IgG4-related autoimmune pancreatitis. The epidemiology of non-pancreatic IgG4-RD, and particularly IgG4 related eye disease, is poorly studied. However, a recent review of 1,014 cases of orbital lymphoproliferative disease in Japan found that nearly 25% of cases had histopathologic features consistent with IgG4 related disease.

The diagnostic criteria for IgG4-RD are evolving. An international symposium was held in Boston, MA in 2011 to generate a consensus statement on the nomenclature, pathologic features, and diagnostic criteria for IgG4-RD. The diagnosis of IgG4-RD cannot be established with certainty without increased numbers of IgG4 plasma cells (or elevated IgG4/IgG ratio) in tissue and an appropriate histological appearance. This represents the current “gold standard” for confirmation of the diagnosis of IgG4-RD. They propose a three-tiered approach to diagnosis, acknowledging the while the general histologic features of IgG4-RD are broadly similar across organ systems, some sites vary. Therefore, careful examination of the biopsy specimen by an experienced pathologist who is expert in that organ system is crucial. IgG4 serum levels are not included in this histopathology based diagnostic criteria.

To complicate matters further, elevated IgG4 and IgG4-mediated immune dysfunction can be seen in variety of conditions that are clearly distinct from IgG4-RD, including pemphigus vulgaris, idiopathic membranous glomerulonephritis, and possibly thrombocytopenic thrombotic purpura. Therefore, it is possible that IgG4-RD may be overdiagnosed or misdiagnosed by relying solely upon clinical findings and serum IgG4 levels. Serum IgG4 levels are still useful as a rapid, easily performed screening test, but should not be used in isolation to make the diagnosis.

Systemic manifestations of IgG4-RD:

Table 1 summarizes the major organ systems that have been implicated in IgG4-RD (excluding neuro-ophthalmic conditions). Allergic condition such as bronchial asthma and chronic sinusitis may occur in up to 40% of patients with IgG4 RD, perhaps providing a clue to diagnosis. Indeed, many patients with IgG4 RD have allergic manifestations such
as atopy, eczema, and asthma\textsuperscript{1,13}. The clinical manifestations of extra-pancreatic IgG4-RD are quite variable: some patients have disease restricted to a single organ for many years, while others have subclinical involvement of other organs. One study\textsuperscript{14} found that 30% of patients with autoimmune pancreatitis also have interstitial nephritis, suggesting more widespread disease. The development of multi-system involvement can occur simultaneously, or evolve over many years\textsuperscript{1,13}. This highlights the need for thorough systemic evaluation once IgG4-RD has been found in a single target organ.

A number of previous eponymous diseases have now been reclassified as IgG4-RD (Table 2). In one review, 92-100% of cases of chronic sclerosing sialoadenitis (Kuttner tumor) were IgG4 related\textsuperscript{15}. Mikulicz disease is characterized clinically by bilateral, painless, symmetric swelling of the lacrimal, parotid, and submandibular glands. Recent reports suggest that IgG4-RD is a major cause of Mikulicz disease\textsuperscript{5,16}. Ormond syndrome is a condition characterized by the proliferation of fibrous tissue in the retroperitoneum\textsuperscript{5}. This condition has several associations, including Riedel thyroiditis, sarcoid, and malignancy. Comings et al\textsuperscript{17} reported retroperitoneal fibrosis, Riedel thyroiditis, orbital pseudotumor, and sclerosing cholangitis in two family members, perhaps one of the earliest reported cases of multi-system IgG4 related disease with neuro-ophthalmic features. Further reports described the co-occurrence of 2 or more of these entities in a single patient\textsuperscript{18}. These lesions share histologic features of lymphoplasmacytic infiltrate, sclerosis, and phlebitis. Many of these cases have been shown to harbor large numbers of IgG4 plasma cells, and may represent another manifestation of IgG4-RD. It should be noted that many of these reports do not fulfill the consensus statement defining the histopathologic criteria for IgG4-RD, and in some cases may best be termed “Probable IgG4-RD”. It is expected that with increasing awareness of IgG4-RD, more and more previously uncategorized or poorly categorized conditions and syndromes may be reclassified as IgG-RD. However, as noted, neither the presence of IgG4 plasma cells in the biopsy specimen nor increased IgG4 serum levels alone is specific enough to warrant classification as IgG4-RD. A careful review of pathology and exclusion of alternate diagnoses (such as sarcoidosis, lymphoma, Wegener’s, and others) remains paramount.

**Neuro-Ophthalmic manifestations of IgG4-RD:**

Of particular importance to neuro-ophtalmologists are the conditions which present with visual dysfunction that have now been shown to be associated with IgG4-RD. We will review the conditions that have now been reported to occur in association with IgG4-RD, and also discuss currently poorly categorized disorders which might potentially be candidates for IgG4-RD.

**Orbital inflammatory syndrome:**

Orbital inflammatory syndrome is a heterogeneous disorder characterized by inflammation in the orbit and ocular adnexal tissues. It is best thought of not as a specific syndrome but as a localized response secondary to a number of different causes\textsuperscript{19}. Up to 8% of patients have no identifiable underlying disease, even with biopsy, and are classified as Idiopathic Orbital Inflammatory Syndrome (IOIS). This has traditionally been considered a diagnosis of exclusion. In 1993, an association between IOIS and systemic fibrosclerosis (a condition now known to be one of the IgG4 related conditions) was reported\textsuperscript{19}. Over the past decade, more reports have emerged, largely from Japan, linking IOIS with IgG4-RD. Sato et al\textsuperscript{20}, in 2008, reviewed 112 cases of ocular adnexal lymphoproliferative disease; 78 were orbital and 34 had conjunctival involvement. 21/112 (19%) had >10 IgG4 positive plasma cells/tissues section. All of these patients had orbital lesions but no conjunctival involvement. Of this group, 17 had lacrimal gland involvement, 12/17 bilateral. The majority had elevated serum IgG4 levels, but these were obtained from stored samples, and several of these patients had undergone treatment, which could potentially alter serum IgG4 levels. It should be noted that the criteria used for the diagnosis of IgG4-RD in this paper (>10 IgG4 = cells/hpf) is less strict than current proposed criteria, which require >30/hpf. Matsuo et al\textsuperscript{21}, in 2010, reported a series of 9 cases of lymphoproliferative disease of the orbit and ocular adnexa. Bilateral lacrimal gland lesions were present in 7/9 cases, with orbital extension in 4 of these. Four cases showed >10 IgG4= plasma cells/hpf, with pathology showing lymphoplasmacytic infiltration, fibrosis and atrophy of tissue. A group of investigators reviewed the pathology of orbital specimens collected between 1993 and 2006\textsuperscript{22}. Of this group, 11/21 (53%) had increased IgG4 + cells (using the criterion of >10/hpf). A review of these patients’ medical records revealed that they had associated diagnoses of asthma (5/11), idiopathic pancreatitis (1/11), inflammatory pseudotumor of the liver (1/11) and cholangitis (1/11). These disorders either preceded or followed the orbital biopsy. Of this group, 3/11 had stored serum samples available for analysis, and 2/3 showed elevated serum IgG4. Clinical findings on the IgG4 + patients included eyelid edema, bilateral orbital involvement, and a more prolonged course than the IgG4 – group. Histology in the IgG4+ group compared with the IgG4– group showed a higher degree of follicular hyperplasia, background fibrotic changes, plasma cells, and eosinophilia.

These reports and others\textsuperscript{23,24} suggest that IgG4-RD can present in a manner indistinguishable from IOIS. Multisystem involvement is not rare in the reported cases, suggesting that other organ involvement should raise suspicion of IgG4 RD in patients with presumed IOIS; or conversely, patients with IgG4 related OIS should undergo screening for other systemic involvement. This may include standard bloodwork including metabolic panel, body scanning with CT or PET-CT, or involving the patient’s primary care physician to coordinate the systemic evaluation.

**Idiopathic pachymeningitis**
Pathogenesis of IgG4-RD:

Although the pathogenesis of IgG4-RD remains incompletely understood, more precise mechanisms of tissue injury are being clarified over time. Some of the clues likely lie in the distinct histopathologic features of this condition, as well as the unique molecular feature of IgG4. Eosinophilia and elevated IgE levels (both features of allergic disorders) are present in approximately 40% of patients with IgG4-RD. These responses are mediated primarily by cytokines produced by Th-2 cells. These cells (Th2) produce cytokines (IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13) which promote recruitment of eosinophils, and inhibit some of the antimicrobial activity of Th1 cells. In contrast to many autoimmune conditions, activation of T regulatory cells is common with IgG4-RD. These cells can produce transforming growth factor beta (TGF-B), which may play a central role in the development of fibrosis in IgG4-RD. Stone et al provided a comprehensive overview of the current theories of pathogenesis in a recent review article.

IgG4 molecule:

Immunoglobulins are protein complexes comprised of 4 peptide chains (Figure 4), two heavy chains and two light chains. They are secreted by plasma cells. There are 5 major immunoglobulin isotypes, or classes: IgA, IgD, IgE, IgM, and IgG. Immunoglobulin G (IgG) is the most abundant antibody class in humans, accounting for ~75% of immunoglobulins found in the circulation. IgG molecules are major players in the humoral immune response and help control infection of body tissues. This occurs via several immune mechanisms: IgG-mediated binding of pathogens causes their immobilization and binding together via agglutination; IgG coating of pathogen surfaces (known as opsonization) allows their recognition and ingestion by phagocytic immune cells; IgG activates the classical pathway of the complement system, a cascade of immune protein production that results in pathogen elimination. The IgG4 molecule is distinct from other immunoglobulins in structure and function. It accounts for <5% of total IgG and is by far the least abundant IgG subclass. The serum IgG4 concentrations vary by a factor of more than 100 in normal adults, a feature not shared by other IgG subclasses. The IgG4 subclass also has unique immunologic features, related in part to its molecular structure. First, amino acid differences within the second constant domain result in poor binding to C1q and Fc-gamma receptors. This suggests that IgG4 does not activate the classic complement pathway, and historically, IgG4 has been thought to play a limited role in immune activation. Second, as opposed to other IgG subclasses, the disulfide bonds between the heavy chains of
IgG4 are unstable. It is estimated that ~50% of IgG4 molecules have heavy chains linked weakly by non-covalent forces. This means that the chains may separate and recombine randomly, resulting in an inability to form immune complexes. The production of IgG4 is controlled primarily by type 2 T helper cells (TH2), with TH2 cytokines shifting the balance of between IgE and IgG4, favoring IgG4. The precise role of IgG4 in normal immune function is still unclear. It may play a significant role in allergic reactions. It may also act as a protective blocking antibody in IgE-mediated responses to parasitic infection.

The specific role of IgG4 antibodies in IgG4-RD is still open to debate. They may simply act as tissue-destructive immunoglobulins. However, the tendency for IgG4 antibodies to promote anti-inflammatory responses and the fact that disease-specific IgG4 autoantibodies have not yet been identified in IgG4-RD could suggest that the overabundance of IgG4 molecules in this condition is a response to an as yet unknown primary inflammatory stimulus. Autoimmunity (whether due primarily to IgG4 molecules or another stimulus) remains the most widely accepted explanation for the Th2 response associated with IgG4-RD. Serum IgG4 obtained from patients with IgG4-RD binds to the normal epithelia of the pancreatic ducts, bile ducts, and salivary gland ducts. Ultrastructural studies have identified electron-dense granular deposits at the basement membrane of renal tubules and pancreatic ducts in patients with IgG4-RD. However, it is unclear whether these deposits are involved in immune-complex mediated tissue injury or are a bystander phenomenon. Further, the degree to which the interaction between IgG4 and IgG is involved in the formation of these immune deposits is not clear.

As with many immune-mediated diseases, there may be genetic factors contributing to IgG4-RD. The HLA haplotypes DRB*0405 and DQB*0401 appear to confer increased risk of IgG4-RD in the Japanese population. Other non-HLA genes which have been implicated are single nucleotide polymorphisms which encode proteins such as T-lymphocyte associated antigen 4, tumor necrosis factor alpha, and Fc receptor-like.

Serologic studies in IgG4-RD:

The incidence of elevated serum IgG4 levels in IgG4-RD varies widely. Most studies suggest that ~70% of patients have increased serum IgG4 levels. However, most of this data is drawn from patients with Autoimmune Pancreatitis. There is a great deal of heterogeneity, depending upon organ involvement, and less than strict adherence to the consensus guidelines for pathologic diagnosis of IgG4-RD. Although screening for IgG4-RD with serum IgG4 levels is a reasonable first line strategy, the sensitivity and specificity of this test, particularly for extra-pancreatic disease, is yet to be determined. The validity, as well as the sensitivity and specificity, of CSF IgG4 levels also remains unknown.

It is also unclear whether, in patients who have confirmed IgG4-RD, serum IgG4 levels can be used to monitor treatment or disease activity. The literature shows conflicting data. A large, multi-center Japanese study showed that IgG4 levels failed to normalize in 115/182 patients (63%) treated with corticosteroids. Some patients in that study remained in remission, despite persistent elevation in serum IgG4 levels. Monitoring of serum IgG4 may predict early relapse in some patients, but relapse occurs in up to 10% of patients with normal IgG4 levels, and most studies assessing the predictive value of serum IgG4 concentrations suffer from limited follow up.

Neuroimaging in IgG4-RD:

The neuroimaging of IgG4-RD is dependent upon the clinical presentation and primary organ/soft tissue involvement. Orbital involvement typically involves the lacrimal glands. Concurrent salivary gland involvement is common. The abnormalities are usually bilateral and relatively non-specific. The affected tissues show soft tissue attenuation on CT and hypointensity on T1 weighted images on MRI. One feature perhaps more distinct to IgG4-RD is low signal intensity on T2 weighted images relative to the normal nasal and paranasal mucosa.

Involvement of the pituitary stalk can occur, with an appearance similar to lymphocytic hypophysitis, as noted previously. Typical MRI imaging findings include thickening or mass formation within the pituitary stalk, less commonly in the pituitary gland itself. Post contrast T1 weighted images usually demonstrate homogeneous enhancement. These findings are non-specific, and can be seen in a wide variety of other inflammatory disorders, including sarcoidosis, Langerhans cell histiocytosis, and tuberculosis. Pachymeningitis may occasionally co-exist with hypophysitis.
**Treatment of IgG4-RD:**

There are no high quality evidence based guidelines for the management of IgG4-RD. Treatment should be individualized, and based upon existing medical literature. For example, not all systemic manifestations of IgG4-RD need to be treated. IgG4-related lymphadenopathy is usually asymptomatic, and may persist for years with no consequences. Some patients may have widespread disease which remains indolent, and not require treatment, whereas a patient with single organ involvement may have devastating consequences and require aggressive therapy. Patients with vision-threatening manifestations such as pachymeningitis and orbital inflammatory syndrome (particularly with optic nerve involvement) often need more aggressive treatment once the diagnosis has been established.

Corticosteroids are the first line of treatment in most cases. Although steroids are effective initially in IgG4-RD, relapses during taper are common, and many patients require long term steroid sparing therapy. A consensus statement from 17 referral centers in Japan (primarily related to IgG4-related autoimmune pancreatitis) recommended starting prednisone at a dose of 0.6 mg/kg daily for 2-4 weeks, with a taper over the next 3-6 months to 5 mg daily, and continued treatment with prednisone for up to 3 years.

The choice of a steroid sparing agent is also highly individualized, as no evidence based treatment guidelines exist, and there is no clear evidence favoring one treatment over another. Azathioprine, mycophenolate mofetil, and methotrexate have all been used successfully for IgG4-RD.

Since IgG4-RD is (presumably) mediated by plasma cells, B cell depletion with rituximab has been advocated. Rapid and dramatic clinical responses have been reported, with marked decline in serum IgG4 levels, and clinical improvement.

Treatment response may be influenced by organ involvement, severity of disease and perhaps most importantly, the degree of fibrosis within the affected tissue. In patients with well established fibrosis, treatment response is usually minimal, although there are reports of clinical improvement after treatment in patients with widespread fibrotic disease.

**Screening for IgG4-RD in Neuro-Ophthalmology:**

Given the increasing attention that IgG4-RD has received, it is tempting to consider this condition in any patient with an unexplained inflammatory process involving the visual pathways. However, it should be noted that the diagnostic criteria for IgG4-RD remain a moving target, and there is a risk of over-diagnosis, particularly if the diagnosis rests solely upon serum IgG4 levels.

At this time, the consensus statement establishing diagnostic criteria for IgG4-RD should be considered the "gold standard", until new data emerges. This means that careful histopathologic examination is critical before arriving at a definitive diagnosis of IgG4-RD. Good communication with the neuropathologist reviewing the specimen is also of vital importance.

Screening for IgG4-RD with serum IgG4 levels should be strongly considered in patients with the two most frequently reported neuro-ophthalmic manifestations: orbital inflammatory syndrome and pachymeningitis. Lymphocytic hypophysitis likely falls within this category as well, perhaps scleritis also, although only two cases to date have been reported. Screening for IgG4-RD in some of the other conditions mentioned above (optic perineuritis, Tolosa-Hunt syndrome, etc) should be considered on a case-by-case basis.

Since there is no high quality evidence guiding treatment of IgG4-RD, it could be argued that management of IgG4 related OIS or pachymeningitis would not differ from management of the idiopathic forms of OIS or hypertrophic pachymeningitis- that is, exclusion of infectious and neoplastic etiologies, initial treatment with corticosteroids, and steroid sparing therapy in refractory patients. However, there are rational arguments for pursuing a diagnosis of IgG4-RD:

1. Other organ involvement. Since multi-organ involvement is frequent, once IgG4-RD disease is identified in one organ, screening for other organ involvement may identify potentially serious disease and prevent future complications.

2. Limiting further testing. Any disease which includes the term “Idiopathic” carries a degree of uncertainty regarding the accuracy of the diagnosis. This often results in periodic re-testing and re-evaluation, with further expense and lost time for the patient. Achieving a specific, biopsy-supported diagnosis may preclude “re-inventing the wheel” during monitoring and treatment, particularly with treatment failure.

3. More confidence instituting potentially toxic treatments.

4. Less uncertainty for the patient, as it is often helpful for the patient to have a “named” disease.

**Screening for other systemic involvement:**

All patients with confirmed IgG4-RD in one target organ should be suspected of harboring disease in other organs as well, particularly the pancreas. A thorough physical examination, and selective laboratory and imaging evaluation for other organ involvement should be considered once the initial diagnosis is secured. It is clear that this condition evolves over time, so if the initial surveillance screening for other organ involvement is negative, periodic re-evaluation may be considered. This may require the involvement of the patient’s primary care physician or specific consultation with
specialists or sub-specialists, depending upon specific organ-involvement.

CME Answers:

1. Orbital inflammatory syndrome and pachy meningitis
2. The true sensitivity is still unclear, but approximately 70% of patients with IgG4-related autoimmune pancreatitis have elevated serum IgG4 levels
3. F

References: Author(s) Last Name separated by a Comma, Title/Article, Source (i.e. Journal Name), Volume #, Page #, Year


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Histologically highly suggestive of IgG4-related disease:
1. Dense lymphoplasmacytic infiltrate
2. Fibrosis, usually storiform
3. Obliterative phlebitis
4. IgG4+/IgG+ >40% (>50% for aortitis)

Probable histologic features of IgG4-RD:
1. Cases with only a single histopathologic feature (e.g., dense lymphoplasmacytic infiltrate and IgG4+ cells
2. Needle biopsies (full histological picture often not represented with needle biopsy)
3. Meningeal and cutaneous disease (limited data)
4. Additional clinical, serological, or radiological confirmatory evidence (serum IgG4> 135 or other organ involvement)

Insufficient histopathological evidence of IgG4-RD:
1. Cases that fall outside of first two categories
2. May still be IgG4-RD- consider sampling artifact, effect of previous therapy, progression to fibrotic stage
Figure 4
Figure Legends:

Figure 1a-b:

Pathology specimen from a dural biopsy in a patient with pachymeningitis. Figure 1a is a high-power view (100X) demonstrating mature appearing plasma cells, singly dispersed and clustered. Figure 1b shows a section with IgG4 staining. The stain is positive in the majority of the plasma cells, with over 20+ cells/HPF. The IgG4 to IgG ratio is markedly increased.

Figure 3a-b:

These images show T1, post-gadolinium sagittal (3a) and axial (3b) MRI cuts of a patient presenting with headache, weight loss, and profound visual loss. They demonstrate diffuse leptomeningeal enhancement and thickening, suggesting pachymeningitis. The arrow highlights subtle perineural enhancement of the optic nerve. Subsequent dural biopsy confirmed IgG4-related disease.

Figure 4: Schematic diagram of the basic unit of immunoglobulin (antibody)

1. Fab
2. Fc
3. heavy chain (consist of VH, CH1, hinge, CH2 and CH3 regions: from N-term)
4. light chain (consist of VL and CL regions: from N-term)
5. antigen binding site
6. hinge regions

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<tr>
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