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Orbital IgG4-associated diseases

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Abstract

IgG4-related disease (IgG4-RD) is a distinct entity that frequently occurs in an ophthalmic location. IgG4-RD is not limited to the orbit, but may also involve other anatomical structures in and around the eye. Careful clinicoradiologic examination and the use of immunohistological examination are key diagnostic methods. Serum IgG4 levels are neither sensitive nor specific enough for the diagnosis of IgG4-RD and should not be relied upon solely. Careful evaluation of histologic and immunophenotypic features and clinical correlation are required to distinguish orbital IgG4-RD from other inflammatory lesions in the orbit. Glucocorticoids are the primary therapeutic choice for treatment of IgG4-RD. Azathioprine or Mofetil can be used as a second possibility. Rituximab can be effective in the patients with relapse IgG4-RD.

Keywords: IgG4, eye, inflammation, ophthalmology

Introduction

In 1892, Johan von Mikulicz-Radecki first described clinical manifestations in a case report of a 42-year-old farmer with symmetric bilateral lacrimal, parotid and submandibular gland enlargement associated with lymphocytic infiltration [1-3]. Since then, there have been additional cases of patients with the same clinical manifestation, labeled Mikulicz disease. The clinical symptoms of Sjögren disease are similar to Mikulicz and, in 1953, these similarities and the possibilityof uniting these diseases were reviewed [4]. Yamamoto and colleagues detailed the pathological and clinical differences between Sjögren syndrome and Mikulicz disease [5].

In 2001, several studies revealed a connection between Mikulicz disease and high levels of IgG4, which significantly lowered after glucocorticoid therapy [1,2,6-9]. Based on these observations, Mikulicz disease is now classified as IgG4-related disease (IgG4-RD) [10]. Additional IgG4-RDs have been identified, based on systemic fibroinflammatory disease characterized by the presence of lesions with lymphoplasmacytic infiltrate with high levels of IgG4-positive plasma cells. In addition,a correlation between higher levels of IgG4 and good response to therapy with corticoids has been observed [2,6-9,11-18]. Hamano et al., [19,20] observed not only elevated levels of IgG4 in autoimmune pancreatitis, but also found characteristic histopathological manifestations accompanying retroperitoneal fibrosis. These observations formed the basis for recognition of multiorgan defect, which was later defined as IgG4-RD [6]. Unified classification and defined, precise diagnostic criteria of IgG4-RD appeared much later [21,22]. It is important to note that IgG4-RD is an idiopathic, multiorgan inflammatory state, possibly manifestin gas chronic, relapsing inflammation in virtually any organ [23]. For current concepts on ophthalmic IgG4-RD, see review by Mulay and Wick [24]. For background and pathology of IgG4-related ophthalmic disease, see review by McNab and McKelvie [25].

Review

Diagnosis

The diagnosis of IgG4-RD uses a wide spectrum of diagnostic criteria and, in combination with organ-specific criteria, is based on evaluation of impaired organ (such as size increase, nodular lesions, and dysfunction). Additional criteria involve IgG4 levels above 1.35 mg/ml, histological findings of lymphoplasmacytic infiltrate, fibrosis, obliterating phlebitis, or eosinophil infiltrate. Vascular pathology is highly specific for IgG4-RD and helps to distinguished between IgG4-RD and similar diseases [2,7,8,21,22,26]; it is necessary to remember the limits of fine needle biopsy though,and to obtain an adequate

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tissue sample. An analysis of 64 cases of IgG4-RD showed significant pathological and clinical differences, and even suggested a new clinical entity [27].

Detection of low levels of IgG4 plays an important role in the differential diagnosis of orbital lymphoproliferative diseases [28]. Histologic features are not present in some clinical manifestations of IgG4-RD. However, in patients fulfilling organ-specific criteria for IgG4-RD, the diagnosis is definitive [22]. Specificity and sensitivity of diagnosis is improved with IgG4/IgG ratio levels higher than 0.08 [29,30]. Our own laboratory uses ratio levels higher than 0.1–0.12. In case of clinical manifestations with no possible histological verification, it is necessary to use the level of IgG4 (our group uses limit of 2.0 mg/ml). It is important to remember, however, that even this limit is not always unequivocal, as elevated levels of IgG4 can be found in several additional diseases such as autoimmune diseases, cancer, cystic fibrosis, interstitial pneumonitis, vasculitis, allergic problems, sarcoidosis, etc. [3,6,14,31]. An interesting study described topiramate-induced maculopathy in IgG4-RD [32], and interruption of treatment prevented risk of nonreversible loss of vision. Polyclonal increase of IgG4 levels as a result of common food and animal-derived allergens supports the idea of potential damage of regulatory mechanisms of immune system [33]. It is important to note that IgG4-RD can be diagnosed even without elevated levels of IgG4 [18,34]. Despite clear progress, dependable diagnostic criteria remain to be found [21,22]. Therefore, the search is still on for additional testing necessary to improve specificity and sensitivity. One of the most promising tests evaluates the level of plasmablasts in peripheral blood. Studies have shown this test to be independent of IgG4 levels [35], but with varying results in patients being treated [36]. Plasmablast counts ($CD19^+$, $CD20^-$, $CD38^+$, $CD27^+$ cells) can be an important diagnostic biomarker in IgG4-RD diagnosis. Another test under evaluation measures free light chains. However, their elevated levels can be found not only in IgG4-RD, but also in otherdiseases,including most autoimmune diseases [37], making the use of this test rather questionable. Another possible clinical addition is an IgG4-RD index, which offers the possibility to further evaluate the conditions without the risk of overlooking possible diagnosis of multiorgan problems. In addition, this evaluation allows us to monitor the effects of treatment on clinical manifestation [30].

Clinical observations

The discovery of systemic disease characterized by high levels of IgG4 and by significant changes of cellular substrate has resulted in changes of diagnostic and therapeutic managements in several clinical domains. IgG4-RD can influence any cellular system in different organs. Eye problems are one of the main manifestations of this disease [12,17,38]. **Table 1** summarizes the guidelines for diagnosis of IgG-RD, **Table 2** shows our current knowledge of clinical manifestations, occurring in different frequencies and often in connection with impairment of other organs such as lungs, kidney, salivary glands, or thyroid gland [6,14-16,18]. Clinical manifestation in patients with suspected IgG4-RD can be accompanied by additional symptoms including ataxia, loss of weight,

Table 1. Guidelines for diagnosis of IgG4-RD (1,7,8,9,12,13,14,15, 16,18,22,34,38,40).

• Clinical features highly suggestive of IgG4-RD
- Symmetrical swelling of lacrymal, parotid, submandibular glands
- Autoimmunne pancreatitis
- Inflammatory pseudotumor
- Suspicion of Castleman´s disease
- Interstitial nephritis
• Laboratory data highly suggestive of IgG4-RD
- Serum IgG4 >1,7 g/L
- IgG4+ cells /IgG+ cells >40% in biopsy
- Serum IgG4/IgG > 10%
- Bloood plasmablasts
• Clinical features suggestive of IgG4-RD
- Unilateral swelling of at least one lacrymal, parotid or submandibular gland
- Orbital pseudotumor
- Sclerosing cholangitis
- Prostatitis
- Interstitial pneumonitis
- Thyroiditis / hypofunction of thyroid
• Laboratory data suggestive of IgG4-RD
- Hypergammaglobulinemia
- Immune complex
- Hypocomplementemia

Table 2. IgG4-ROD (Related Orbital Disease)–clinical involvement of other organs (1,7,8,11,12,15,18,28,34,38,40).

Occullar manifestation	Other clinical manifestation	Prevalence
Dacryoadenitis	Autoimmune pancreatitis	40%
Dacryoadenitis	Mikulicz´s disease	--
Dacryoadenitis	Unilateral sclerosing sialadenitis	--
Dacryoadenitis	Sjögren´s syndrome	--
Dacryocystitis	Tubulointerstitial nephritis	83%
Sialadenitis	Autoimmune pancreatitis	17%
Sialadenitis	Arthralgia	16%
Sialadenitis	Sick eye syndrome	33%
Sialadenitis	Tubulointerstitial nephritis	--
Idiopathic orbital inflammation	Lymphadenitis	--
Idiopathic orbital inflammation	Dacryoadenitis	--
Graves orbitopathy	Thyroiditis	--
Graves orbitopathy	Lymphadenitis colli	--
Nervus opticus atrophie	Submandibular lymphadenitis	--
Nervus opticus swelling	Submandibular lymphadenitis	--

Note: In the groups of IgG4-ROD: lymphadenopathy occurrs in 29%, autoimmune pancreatitis in 14%, gall bladder inflamation in 5%, thyreopathy in 5%, chronical rhinosinusitis in 1%.

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abdominal pain, xerostomia, xeropthalmia, or lymphadenopathy [13]. Other studies have suggested that IgG4-related lymphadenopathy should be listed in the differential diagnosis of benign reactive lymph nodes, particularly when perifollicular granuloma and plasmacytosis coexist [39].

Orbital soft tissue and lacrimal glands are usually the first to show signs of IgG4-RD. It is well-established that IgG4 can be involved in more than one-third of idiopathic inflammation of orbital tissue. It has been shown that higher systemic manifestations of IgG4-RD can be observed in impaired adnexal involvement [11]. These can include changes in immunological and biochemical parameters. However, further development of new diagnostic steps allowing precise diagnosis is needed [38]. In addition, orbital soft tissue and periorbital structures with intact lacrimal glands with clinical signs of proptosis can be affected. An international symposium (Boston, 2011) concluded that the combination of histopathological and immunohistochemical findings were significant in the diagnosis of IgG4-RD. However, the full correlation between clinical manifestations in individual patients needs to be taken into consideration [40]. When determining IgG4-RD, diagnostic biopsy should involve three major histopathologic manifestations: 1) dense lymphoplasmacytic infiltration with predominant T lymphocytes; 2) fibrotic signs arranged at least in storiform patterns; and 3) obliterating phlebitis. The IgG4-RD is defined by simultaneous occurrence of at least two of these characteristics. Other findings should also be taken into consideration such as phlebitis without obliteration, histiocytosis of sinuses, increased amount of eosinophils, or ratio of IgG4/IgG plasmatic cells above 40%. However, none of these can 100% guarantee that it is a case of IgG4-RD. The findings mentioned above can be also found in lymphoma, rheumatoid arthritis, and in histiocytosis of sinuses with massive lymphadenopathy (Rosai-Dorfman disease) [40]. We can assume these diseases to have close connections to IgG4-RD, and can be associated with the formation of idiopathic inflammatory eye problems or with additional cancerous diseases, congenital malformations, or systemic orbital inflammation [15].

Long term experiences with treating IgG4-RD came mostly from Japanese and American authors, and their findings still do not offer unequivocal results. Therefore, new types of treatment and new medications are constantly considered, aiming to reach remission and to block relapse. Aggressive and timely treatment is necessary, as any delay might result in damage or even failure of affected organs [8,13-15]. However, treatment immediately after diagnosis is usually not required. Our own experience has shown that it is better to postpone treatment until the final diagnosis is fully verified by laboratory and clinical results, as spontaneous regression of IgG4-RD has been known to occur.

The first choice in medications are glucocorticoids [40]. In literature, one can find significant differences in medical procedures, particularly between Japanese and American physicians. Japanese groups recommend starting daily doses of prednisone around 0.6-1 mg/kg for 2-4 weeks [1,8,14,17,21] followed by gradual lowering of the dose during the next 3-6 months based on clinical response to 5 mg/day and subsequent long-term treatment with 2.5-5 mg/day for next 3 years. Treatment recommended by the Mayo Clinic starts with 40 mg/day of prednisone for 30 days followed by gradual decrease of the dose by 5 mg for next 2 months and ending the treatment after 11-12 weeks [16].

Neither treatment stops relapses, which are rather common, particularly in cases of extrapancreatic forms of this disease. The main criteria for success of treatment with glucocorticoid is gradual decrease of plasmatic IgG4 levels, therefore followup evaluations of these levels in 3-month intervals is recommended, particularly during the first year of treatment.

Ebbo's group described positive effects of azathioprine (75% effective), rituximab (67% effective), and methotrexate (50% effective) [13,14]. Some studies even found rituximab treatment to be 100% effective [13]. Other studies found similar effects for radiotherapy and for combination of prednisone and azathioprine [1]. Rituximab therapy leads to specific IgG4 reduction together with apparently very effective disease control, even in steroid refractory cases [36]. Radiotherapy can be recommended in patients with documented resistance to steroids or in patients where these drugs cannot be used (such as tuberculosis) [38]. Combination of steroids and mycophenolate is also used [40]. It is important to note, however, that long term medical effects of these drugs are currently not known, as the number of studies evaluating the patients for an extended period is very limited.

Conclusion

IgG4-associated disease remains an overlooked clinical challenge, and our knowledge slowly growing. Fifteen years after the first clear definition, we have seen improvements in diagnostics as well as expansion of adequate medical treatments. However, this rather new type of problem resulting from dysregulation of immune system needs to be evaluated and monitored in close cooperation of several medical sectors.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	MZ	JR	VV	IL
Research concept and design	✓	✓	--	✓
Collection and/or assembly of data	✓	✓	--	✓
Data analysis and interpretation	✓	✓	✓	✓
Writing the article	✓	✓	✓	✓
Critical revision of the article	✓	✓	✓	✓
Final approval of article	✓	✓	✓	✓

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