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IGG-4RELATEDDISEASEINOPHTHALMOLOGY

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SUMMARY
IgG4 related disease (IgG4-RD) is a distinct entity that frequently occures in an ophthalmic location. IgG4 – RD is not limited to the orbit but may also involve other anatomical structures in and around the eye. A high level of suspicion for the diagnosis can be derived from careful clinico-radiologic examination, the use of immunohistological examination in the context of characteristic histopathologic features. Serum IgG4 levels are neither sensitive nor specific for the diagnosis of IgG4-RD and should not relieved upon solely. Careful evaluation of histologic and immunophenotipic features and clinical correlation are required to distinguish orbital IgG4-RD from other inflammatory lesions in the orbit. Glucocorticoids are the first-line drugs for therapy of IgG4-RD. Azathioprine or mycofenolat mofetil can be used as a second possibility. Rituximab can be effective in the patients with relapse IgG4-RD.

Key words: IgG4-RD, diagnosis eye, therapy

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INTRODUCTION

In 1892 Johan von Mikulicz – Radecki described the clinical course of a disease in a patient with symptoms of symmetrical swelling of the lachrymal, parotid and submandibular glands, with massive infiltration of the affected glands by mononuclear cells [16, 28]. Subsequent descriptions of further patients with the same clinical symptoms were then termed Mikulicz's disease. After the clinical course of Sjogren's syndrome was identified in 1953, a discussion took place about the linkage of these pathologies. In 2001 a connection was found between Mikulicz's disease and high values of IgG4, which decreased significantly together with the remission of the disease following glucocorticoid therapy [16, 17, 21, 22, 26, 28]. Subsequent descriptions of further pathologies connected with an increased level of IgG4 defined a new clinical unit, linked to systemic fibro-inflammatory disorder with the presence of lesions with a viscous lymphoplasmacytic infiltrate rich in IgG4 positive plasmatic cells with storiform fibrosis, frequently but not always with a linkage to increased values of plasmatic IgG4 and with a good therapeutic response to corticoids [2, 3, 8, 9, 11, 13, 15, 17, 21, 22, 26, 28, 32]. In 2001 Hamano et al. described not only an increase in IgG4 in autoimmune pancreatitis, but also found characteristic histopathological manifestations accompanying retroperitoneal fibrosis, and thus prepared the bases for distinguishing multi-organ affliction, a unit newly defined as IgG4–RD (Related disease) [17]. In 2012 a uniform classification of IgG4-RD syndrome was published, and in the same year the criteria for the diagnosis of this disease were stipulated by Japanese authors [23, 29].

Diagnosis: The algorithm for the diagnosis of IgG4-RD uses extensive diagnostic criteria, and in combination with organ -specific criteria is based on an evaluation of the affected organ (enlargement, nodular lesion, dysfunction of organs) (table 1). Its is further based on values of IgG4 in a concentration higher than 1.35 mg/ml, histological findings with lymphoplasmacytic infiltrate, fibrosis, obliterative phlebitis or eosinophilic infiltrate. For IgG4-RD vascular pathology is highly specific and exceptional in diseases interchangeable with IgG4-RD [21, 22, 23, 27, 28, 29]. In the case of certain pathological findings it is essential to take into account the limits of fine needle aspiration biopsy, which do not always provide a sufficient sample of tissue necessary for diagnosis. Detection of low IgG4 values plays a significant role in differential diagnosis of orbital lymphoproliferative disorders [18]. In the case of certain clinical manifestations of IgG-4-RD, practical histological demonstration is not available. For patients who meet the organ-specific criteria for IgG-4-RD, diagnosis is definitive [29]. From the perspective of both specificity and sensitivity, quality of diagnosis is improved by an observation of the values of the level of IgG4/IgG. This level higher than 0.08 is valuable for determining the diagnosis of the disease [4, 5]. For this evaluation our centre uses a higher value of index 0.10 – 0.12. This index markedly increases both the specificity and sensitivity of determination of IgG4-RD [4]. In the case of clinical manifestations where histological verification is excluded, the distinct level of IgG4 is applied – at our centre we use the limit of IgG-4-RD 2.0 mg/ml of serum. However, even this is not always unequivocal for diagnosis, because we find increased values of IgG4 in a range of other pathologies (autoimmune, cancers, cystic fibrosis, interstitial pneumontis, vasculitis, allergic disorders, sarcoidosis etc.) [9, 14, 17, 36]. Maculopathy has been described following the application of topiramate with induction of IgG4-RD [7]. Discontinuation of treatment upon induction of topiramate-associated maculopathy is prevention against the risk of irreversible damage or loss of

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Table 1. Guidelines for diagnosis of IgG4-RD [3, 7, 8, 11, 12, 13, 16, 19, 20, 24, 25, 26, 27, 28, 32]

• Clinical features highly suggestive of IgG4-RD
- Symmetrical swelling of lacrymal, parotid, submandibular glands
- Autoimmune pancreatitis
- Inflammatory pseudotumour
- Suspicion of Castelman'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%
- Blood plasmablasts
• Laboratory data highly suggestive of IgG4-RD
- Unilateral swelling of at least one lachrymal, parotid or submandibular gland
- Orbital pseudotumour
- Sclerosing cholangitis
- Prostatitis
- Interstitial pneumonitid
- Thyroiditis / hypo function of thyroid
• Laboratory data suggestive of IgG4-RD
- Hypergammaglobulinemia
- Immune complex
- Hypocomplementemia

vision. Polyclonal increase of IgG4 values for numerous food and animal allergens supports the hypothesis of an impairment of the regulatory mechanisms of the immune system [6]. It is necessary to point out that we may encounter IgG-4-RD without increased values of this immunoglobulin [25, 32]. Even despite advances in the diagnosis of this disease, a question remains with regard to complete and reliable diagnostic criteria [23, 29]. Further possible examinations are sought which would increase the specificity and sensitivity of diagnosis of IgG4-RD. A very promising test is observation of the values of plasmablasts in peripheral blood. It is stated that this test may be independent of higher levels of IgG4 [33] and may respond to treatment [1]. Plasmablasts (CD19-, CD20neg, CD38+, CD27+) are becoming a significant diagnostic criterion for the diagnosis of IgG4-RD. Of other possible observed diagnostic criteria, the possibility of measuring free light chains is being considered. We find increased values of these not only in the case of IgG4-RD, but also in other, primarily autoimmune disorders [12]. This diminishes the significance of this demanding diagnostic criterion. A further clinical contribution to the diagnosis of the disease is the index of IgG4-RD. Its advantage lies partially in the possibility of observation without neglecting the finding of possible multi-organ affliction, and partially also in monitoring the clinical course of the disease depending on treatment or spontaneous remission [5].

Clinical manifestations: The discovery of a systemic pathology with a finding of high IgG4 values accompanied by changes of cellular substrate led to changes in diagnostic and therapeutic approaches in a range of clinical disciplines. IgG4-RD may influence any cellular systems of various organs, and affliction of the eye is in first place in the profile of clinical manifestations of this disease [3, 15, 19]. In table 1 we present the main directions of diagnosis of IgG4-RD. The literature describes a range of clinical manifestations appearing in various frequency, and often not isolated but in connection with the affliction of other organs (thyroid gland, lungs, kidneys, salivary glands etc.) (table 2). Clinical manifestations in patients with suspected IgG4-RD may be accompanied by a range of symptoms such as ataxia, weight loss, pains in the abdominal cavity, xerostomia, xerophthalmia, lymphadenopathy and others [8].

Soft tissues of the orbit and lachrymal gland are often the first manifestations of IgG4-RD. IgG4 may be linked with more than one third of idiopathic inflammations of the orbit. A higher incidence of systemic manifestations of IgG-4-RD can be observed in affliction of the ocular adnexa [2]. At present a range of clinical manifestations classified within this category are specified by changes of biochemical and immunological indicators, but further specification of the diagnosis requires the discovery of new diagnostic procedures which would definitively determine the disease [19]. Tissues of the orbit and periorbital structures may be afflicted, with intact lachrymal glands with clinical manifestations of proptosis. An international symposium held in Boston in 2011 defined the main currents for ultimate diagnosis of IgG4-RD with the statement that a combination of histopathological findings and immunohistochemical stainings could be a decisive contribution for determination of IgG4-RD, but that it remained necessary to take into account the correlation with clinical manifestations of the disease in individual patients for determination of a definitive diagnosis [20]. A diagnostic biopsy for determination of diagnosis should incorporate three histopathological manifestations determining IgG4-RD: 1) viscous lymphoplasmacytic infiltrate with predominance of T-lymphocytes, 2) fibrotic manifestations arranged in deposits of woolly patterns and 3) obliterative phlebitis. A minimum of two of these criteria define the disease. Further significant findings may be added to these, for example phlebitis without obliteration, increased number of eosinophils, proportion of IgG4/IgG plasmatic cells in a ratio of > 40 % and others. However, even these delineated diagnoses are not absolutely unequivocal for IgG4-RD. The above findings may be present in lymphomas, rheumatoid arthritis, histiocytosis of the sinuses with massive lymphadenopathy (Rosai-Dorfman disease) [20]. Nevertheless, we may assume that the above-stated pathologies may be closely connected with IgG4-RD, and are closely linked with the incidence of idiopathic inflammatory afflictions of the eye, together with a range of cancerous diseases of congenital malformations and systemic inflammations of the orbit [11].

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Table 2. IgG4-ROD (Related Orbital Disease) – clinical involvement of other organs*

Ocular 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	Tubointerstitial nephritis	
Idiopathic orbital inflammation	Lymphadenitis	
Idiopathic orbital inflammation	Dacryoadenitis	
Graves orbitopathy	Thyroiditis	
Graves orbitopathy	Lymphadenitis colli	
Nervus opticus atrophia	Submandibular lymfadenitis	
Nervus opticus swelling	Submandibular lymfadenitis	

*Note: In the groups of IgG4-ROD: lymphadenopathy occurs in 29%, autoimmune pancreatitis 14%, gall bladder inflammation 5%, thyreopathy 5%, chronic rhinosinusitis 1% - see prevalence according to the available literature, the findings are affected by the small number of individuals described

Treatment: Ten-year experiences with the treatment of IgG4 primarily from Japanese and American authors still have not produced unequivocal results, and new therapeutic procedures are constantly being added, together with the selection of new preparations, with the aim of achieving remission of the disease and preventing its recurrence. Aggressive and timely therapy is essential, since delay may lead to a disorder of the affected organs, resulting in their failure [8, 9, 11, 22]. However, in the case of timely diagnosis, quick treatment is not generally essential, according to our experiences it may be of benefit to await confirmation of the diagnosis, above all through verification of the laboratory and clinical findings, because it is known that spontaneous regression of the disease occurs in a small proportion of patients with IgG4-RD. On the other hand, in a number of the observed individuals relapse may occur, with the affliction of further organs.

The medication of first choice in the treatment of IgG4-RD is glucocorticoids [20]. The therapeutic schema of the Japanese authors is different from the approach of the American doctors. The Japanese recommend Prednisone in an initial dose of 0.6 – 1 mg/kg of weight per day for a period of 2-4 weeks [9, 15, 16, 22, 23], with a progressive reduction of the dose within 3-6 months according to the clinical response to 5 mg per day, and subsequent long-term treatment with a dose of 2.5 – 5 mg for a total period of three years. The therapeutic approach recommended by the Mayo clinic begins with a dose of 40 mg of Prednisone daily, after one month reduction of the dose by 5 mg for a period of two months, with termination of treatment after 11 – 12 weeks [13].

Relapses of the disease are relatively frequent in the aforementioned therapeutic procedure, primarily in the case of affliction of extra-pancreatic forms of the disease. The criterion for a beneficial therapeutic approach by corticoids is a progressive reduction of the values of plasmatic IgG4. For these reasons we recommend observing values of IgG4 in the first year, at three-monthly intervals.

Medications of further choice have a lesser effect in a range of cases, though further experiences shall be necessary for us to evaluate these therapeutic approaches. Ebbo [2, 10] states a therapeutic effect of azathioprine in 75% of cases, rituximab in 67% and metotrexate in 50%. At present the best therapeutic results are stated upon treatment with rituximab, Ebbo states a 100% therapeutic effect [9]. Similarly beneficial effects are stated following radiotherapy or following a combination of prednisone and azathioprine [16]. Beneficial therapeutic results in the case of refractory IgG4-RD, with a finding of an influence of plasmablasts through binding to CD 19+ B cells and CD 19+ CD 38 high are described by Alegria et al. [1]. Radiotherapy is useful for patients with a demonstrated resistance to steroids or for patients with contraindications for their use (TBC) [19]. A combination of steroids and mycophenolate mofetil is also used today [20]. However, it is necessary to point out that the long-term therapeutic effect of the above-stated preparations is not yet known, due to the fact that to date only a small number of studies have been published observing patients over a longer period.

Conclusion: IgG4-related disease remains an overlooked clinical unit, even though awareness and knowledge of the pathology is increasing. Fifteen years since the first definition of this disease, its diagnosis is improving and adequate therapeutic procedures are being disseminated. However, this remains a new clinical unit, ensuing from a dysregulation of the immune system, which requires observation in close inter-disciplinary co-operation. From our experiences and tho-

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se of foreign centres, it ensues that it is essential for a doctor who determines a diagnosis in a particular field to co-operate with an immunologist and immunohistologist, and in the case of affliction of other organs, consultation co-operation with a corresponding specialist is essential. The commencement of treatment of the disease is essential after the determination of a definitive diagnosis, which is given by fulfilment of the criteria for diagnosis of IgG4-RD (in ophthalmology, in accordance with isolated reports, we recommend use of the term IgG4-ROD - Related Orbital Disease).

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