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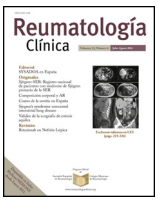

Review Article

IgG4-related Disease: A Concise Review of the Current Literature☆

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ABSTRACT

IgG4-related disease is the term used to refer to a condition characterized by a lymphoplasmacytic infiltrate, fibrosis and an increased number of IgG4+ cells present in tissue, in most cases, with an elevated serum IgG4 level. This disease frequently affects the pancreas, salivary glands and lymph nodes, but can involve almost any tissue. Its etiology and the exact role of the different inflammatory cells in the damage to the target organ is still unclear. As yet, there is no international consensus about diagnostic criteria for the disease, but there are important advances in its treatment and in the quest to achieve remission. We include a review of the history, possible pathogenesis, clinical manifestations, diagnostic approach and available therapeutic approaches.

Enfermedad relacionada con IgG4: revisión concisa de la literatura

Palabras clave:
Inmunoglobulina G4
Enfermedad de Mikulicz
Pancreatitis autoinmune
Enfermedad relacionada con IgG4

RESUMEN

La enfermedad relacionada con IgG4 (ER-IgG4) es una entidad recientemente nominada para definir diversas enfermedades caracterizadas por infiltración linfoplasmocítica, fibrosis, presencia de un número aumentado de células IgG4+ y, en gran parte de los casos, niveles aumentados de IgG4 sérica, afectando frecuentemente el páncreas, las glándulas salivales y los ganglios linfáticos pero pudiendo comprometer casi cualquier estructura de la anatomía humana. Aunque su etiología se desconoce, se han realizado avances en el conocimiento de sus bases fisiopatológicas e inmunológicas, al igual que del rol de las células inflamatorias en el desarrollo de daño del órgano blanco. No existe hasta la fecha un consenso internacional sobre su diagnóstico, lo que no ha impedido avances terapéuticos muy importantes en su control y búsqueda de remisión. Se hace una revisión acerca de la historia, hipótesis sobre la etiología de la enfermedad, sus manifestaciones clínicas, abordaje diagnóstico y terapéutico.

Methodological Review

We conducted a nonsystematic review of the literature in English and Spanish in the PubMed and SciELO databases, for the purpose of defining basic aspects of IgG4-related disease (IgG4-RD): the initial historical description of the disease and its course, pathophysiological and immunological bases, clinical manifestations, diagnosis and current therapeutic approach. In both databases, we selected articles published within the last 10 years. In PubMed, we used a search strategy (Immunoglobulin g4 [MeSH] related disease) that yielded a total of 132 results. In SciELO, we used the combination (Igg4 related disease), and found no pertinent results to add to those obtained in PubMed. We did a detailed search for the historical references mentioned in the articles found using the first strategy, as well as the articles of interest mentioned in the respective reference lists. In all, we included 49 references: 42 from the initial search and 7 obtained from the bibliographies.

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Introduction and Historical Details

IgG4-related disease is the name that was given within the last decade to a condition characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive cells, storiform fibrosis and, frequently, but not always, elevated serum IgG4 levels.[1] The first reports of disease processes compatible with this disorder are from 1892, when Johann von Mikulicz-Radecki described a 42-year-old patient, a farmer, without sicca symptoms, who had "symmetrical edema of the lacrimal, parotid and submandibular glands, with their massive infiltration by mononuclear cells." He died a year after that description, allowing Dr. Mikulicz to perform the autopsy.[2] In it, he confirmed the enlargement of those glands, as well as lymphadenopathy and microscopic evidence of a mononuclear infiltrate. The drawing of what he saw with the microscope is very similar to mucosa-associated lymphoid tissue (MALT) lymphoma but, at the present time, it is impossible to confirm one diagnosis or the other (or the development of the lymphoma in the presence of IgG4-RD), meaning that modern clinicians must always consider malignancy as a differential diagnosis.[3]

Mikulicz' syndrome is characterized by swelling of the parotid glands and perhaps the submandibular glands. In 1953, it was included as a possible clinical manifestation of Sjögren's syndrome.[4] Years later, in the decade of the 1960s, cases were reported of another condition referred to as "chronic sclerosing pancreatitis".[5] Some of the patients had what was described as a lymphoplasmacytic infiltrate in the affected structure, with a diffuse increase in the size of the organ, but of unknown cause.[6] In 1995, the concept of autoimmune pancreatitis was proposed, based on the report of cases of pancreatitis with hypergammaglobulinemia in patients who were autoimmune-positive and responded to corticosteroids.[7] However, it was not until 2001, when elevated serum IgG4 levels were recorded in patients with sclerosing pancreatitis, thus separating a new nosological entity.[8] In 2004, the documentation of elevated IgG4 concentrations in patients with Mikulicz' disease established it definitely within the IgG4-RD spectrum.[9] The current nomenclature of IgG4-RD was proposed in 2010 and was accepted in 2011 during the first international symposium on this condition, held in Boston. Since then, the annual number of publications on this subject has increased progressively, including, in 2012, the first international consensus on the pathological findings that define it at the present time.[10]

Incidence, Prevalence and Affected Organs

Three histopathological findings characterize the disease in the affected organ: (1) the presence of a storiform pattern of sclerosis; (2) a dense lymphoplasmacytic infiltrate; and (3) an increased proportion of IgG4-positive cells with respect to IgG-positive cells according to immunohistochemical evidence. The average of this proportion is an IgG4+/IgG+ plasma cell ratio >40%, but the criteria varies depending on the organ affected.[10] Using these histological findings, it was estimated that the prevalence of IgG4-RD in Japan is 2.63–10.2 cases per million population, with an incidence of 336–1300 new cases each year. To date, the findings in 5 patient cohorts have been published, providing information on the presentation and natural history of the disease (Table 1).

This condition is generally diagnosed between the sixth and seventh decades of life. It most frequently affects the pancreas, but cases have been reported involving nearly every component of our anatomy, as well as the pediatric population.[11–14] Macroscopic and imaging evidence confirm the increase in the size of the affected organ and the presence of fibrosis, a reason why, prior to the era of immunohistochemical diagnosis, different manifestations of the same disease were attributed to different entities and were referred to in terms of the organ involved. Today, Riedel's thyroiditis (fibrous thyroiditis), Küttner tumor (enlargement of the submandibular glands with fibrosis), Ormond's disease (retroperitoneal fibrosis) and Mikulicz' disease are classified within the IgG4-RD spectrum.

Table 1
Cohorts Reporting Patients With IgG4-related Disease.

Author(ref)	Country	Patients (n)	Average patient age in years (range)[a]	Male sex	Most common manifestations and/or organs affected (%)	Patient outcome[b]
Ebbo et al.[22]	France	25	58 (24–83)	72%	Lymphadenopathy (76), sclerosing pancreatitis (52), sialadenitis (44), interstitial nephritis (44), sclerosing cholangitis (32)	92% treated with corticosteroids, clinical improvement in 90%. 48% with corticosteroid dependence or secondary effects of them. One death.
Chen et al.[23]	China	28	51 (24–73)	64.2%	Sialadenitis (79), dacryoadenitis (46) lymphadenopathy (43), pancreatitis (32), cholangitis (29)	93% received prednisone. 68% received other immunosuppressive agents. Treatment efficacy 90%. No deaths.
Fernández-Codina et al.[47]	Spain	55	53	69.1%	Retroperitoneum (27), orbital pseudotumor (22), salivary glands (16), pancreas (16%), lacrimal glands (16)	85% received corticosteroids and 34% other immunosuppressive agents. 46% had complete response and 50% partial. One death from pneumonia.
Inoue et al.[15]	Japan	235	67 (35–86)	80.4%	Pancreas (60), salivary glands (34), kidney (23), lacrimal glands (23), aorta (20)	78% received treatment with corticosteroids and all achieved remission. Other immunosuppressive agents were not used. 24% had relapses.
Wallace et al.[16]	USA	125	55 (24–83)	60.8%	Submandibular glands (28), lymph glands (27), orbit (22), pancreas (19), retroperitoneal fibrosis (18)	51% received corticosteroids, with response in 86% of them, but relapse in 77%. 85% with active disease and 68% without treatment at time of registry.

[a] Age range for Spanish cohort unknown.
[b] Retrospective data on treatment in United States cohort.