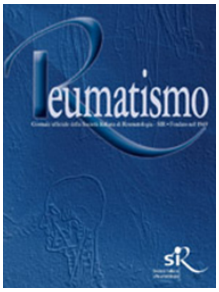

Reumatismo - The Italian Journal of Rheumatology

https://www.reumatismo.org/reuma

eISSN 2240-2683

Please cite this article as:

Rincón-Riaño DN, Rodríguez-Ariza DE, Pacheco C, et al. **IgG4-related disease: findings from a retrospective cohort in Colombia**. *Reumatismo* doi: 10.4081/reumatismo.2025.1887

Submitted: 12-03-2025
Accepted: 01-07-2025

IgG4-related disease: findings from a retrospective cohort in Colombia

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Key words: epidemiology, IgG4-related disease, mikulicz disease.

Contributions: all authors contributed to the study conception and design. DNRR, FAT, CP, LFG, DERA, material preparation, data collection, and analysis; DNRR, first draft of the manuscript; all authors commented on previous versions of the manuscript. All co-authors take full responsibility for all aspects of the study and the final manuscript. The authors express the originality of the conceptualization of the work, the interpretation of the data and the elaboration of the conclusions, stating that those intellectual contributions of other authors have been duly referenced in the text of said work.

Conflict of interest: the authors do not have any potential conflicts of interest for this manuscript.

Ethics approval and consent to participate: all procedures performed in this study were according to the ethical standards of the Research Ethics Committee of Artmedica IPS (Approval No. 2021001), followed by the 1964 Helsinki Declaration and its later amendments and national ethical standards (Resolution 8430 of 1993). The Artmedica's Research Ethics Committee reviewed and approved the study and the use of the medical records under the data privacy laws for clinical studies and scientific publications.

Informed consent: the research does not involve human or animal participants, and informed consent is not required because it was a survey for physicians. The work was approved by the Research Committee of the institution.

Patient consent for publication: the research does not involve human or animal participants, and informed consent is not required because it was a survey for physicians.

Availability of data and materials: data and materials are available from the corresponding author upon request.

Funding: the authors no received financial support for the prepraration, research, authorship and publication of this manunscript.

Summary

Objective. IgG4-related disease (IgG4-RD) is a recently described fibroinflammatory disorder. The most common presentations include salivary and lacrimal gland hypertrophy, orbitary disease, autoimmune pancreatitis, retroperitoneal fibrosis, and tubulointerstitial nephritis. Lymphoplasmacytic infiltration, fibrosis, IgG4+ cell hyperplasia, and elevated IgG4 serum levels are the primary pathophysiological findings related to the disease. We described for the first time the epidemiology and clinical manifestations in our country.

Methods. A descriptive study of patients from a retrospective cohort based on clinical records of adults with IgG4-RD treated between 2014 and 2021 in a high-complexity national center.

Results. 23,381 patients with IgG4-RD diagnosis from 12 centers nationwide until December 2021 provided demographical data. We limited the search through ICD-10 coding: M358, M359, and M368, other specified systemic involvement of connective tissue; L948, other specified localized connective tissue disorders; D472, monoclonal gammopathy; K861, other chronic pancreatitis; H051, H059, and H063, chronic inflammatory disease of orbit; and C488, malignant neoplasm of overlapping sites of retroperitoneum and peritoneum. Thirty-three patients were identified with IgG4-RD based on comprehensive diagnostic criteria. A definitive diagnosis was obtained in 48.48% of patients, a probable diagnosis in 27.7%, and a possible diagnosis in 24.24%. A total of 21 patients were female, with a male/female ratio of 1/1.75. The median age at diagnosis was 53.87 years (interquartile range of 27.06), the minimum age of diagnosis was 11.53 years, and the maximum was 79.18. Regarding clinical presentation at diagnosis, ocular/orbitary affectation was present in 16 patients (48.48%), followed by head and neck in 10 patients (30.30%), and biliary tract/gastrointestinal in 9 (27.27%). A single-organ compromise was identified in 15 patients (45.45%), and 18 patients (54.55%) had two or more organs affected, with lymphatic and ocular/orbitary being the most commonly reported.

Conclusions. Epidemiologic and demographic data on IgG4-RD in our country are similar to those in world medical literature. The higher frequency of the disease in males above 65 years and females under 65 years suggests distinct pathophysiologic factors related to sex and age. This work has a limitation of subreports or misreports, which physicians can make when registering ICD-10 codes in clinical records. Nonetheless, it is the legal record in Colombia and requires an analysis like the one made in this study.

Introduction

IgG4-related disease (IgG4-RD) is a recently described fibroinflammatory systemic disease, which groups different conditions formerly considered as individual entities: Mikulicz disease (lacrimal and salival gland involvement), Kuttner tumor (isolated submandibular glands), autoimmune pancreatitis, sclerosing cholangitis, hypertrophic pachymeningitis, hypophysitis, tubulointerstitial nephritis, aortic aneurysms, Ormond's disease (retroperitoneal fibrosis), and sclerosing mediastinitis among others. A dense lymphoplasmocitary infiltrate with a high rate of IgG4 plasmacells, storiform fibrosis, obliterating phlebitis, and frequent tissue eosinophilia characterize the disease, leading to the development of sclerotic masses and fibrosis, affecting synchronic or meta-chronically almost any organ (1). Epidemiology is underestimated due to diagnosis difficulties. Most of the reports have been made in Japan, where an incidence between 0.8 to 3.1 cases per 100,000 persons and a prevalence among 1/600.000 habitants is estimated. However, the disease has been described in different ethnic groups (2). The highest peak of incidence is the fifth and seventh life decades, with a marked male predominance, which varies between 1.6:1 for head and neck manifestations and 4:1 for aortic/retroperitoneal involvement (3). Most frequently reported clinical presentations are sialoadenitis, dacryoadenitis, lymphadenopathy, type 1 autoimmune pancreatitis, tubulointerstitial nephritis, lung disease, biliary tract disease, retroperitoneal fibrosis, and orbitary disease. Histopathological examination of the affected organ provides the best diagnostic test with positive IgG4 plasmacells, organ fibrosis, and obliterating venulitis, all in the context of high IgG4 serum levels in approximately 80% of cases (4). Due to its low prevalence, information about this disease is based on reports and case series. For this reason, this study aims to describe the characteristics and treatment of patients with IgG4-RD evaluated in a specialized center of autoimmune diseases. This study included patients diagnosed with IgG4-RD according to comprehensive diagnostic criteria (3).

Materials and Methods

A descriptive and unicentric study from a retrospective cohort based on clinical records of adults treated in Artmedica, a clinic of autoimmune/autoinflammatory diseases with 12 centers in Colombia, including Medellín and Bogota (the biggest cities in our country). We searched clinical records in a database of patients from the rheumatology program (23,381 patients) between 2014 and 2021. The search included to ICD-10 codes M358, M359, and M368, other specified systemic involvement of connective tissue; L948, another specified localized connective tissue disorders; D472, monoclonal gammopathy; K861, another chronic pancreatitis; H051, H059, H063, chronic inflammatory disease of the orbit; C488, malignant neoplasm of overlapping sites of retroperitoneum and peritoneum. Clinical records were revised, and 33 patients with IgG4-RD based on comprehensive diagnostic criteria (CDC) de Umehara-Okazaki (3) were identified, these criteria consist of three major components: clinical examination with evidence of characteristic organ involvement, serological finding with elevated serum IgG4 concentration, generally defined as >135mg/dL and histopathological features.

The registry of variables was performed in an Excel program. Analyzed variables were grouped into sociodemographic, clinical, paraclinical, and treatment categories. Statistical analysis was performed with the SPSS program, version 26th. Basic descriptive statistics were used for continuous variables (median with 1 and 3 quartiles) and categoric variables (frequencies and percentages) for patient characterization. Bivariate analysis by Chi-square or Fisher exact method was made (depending on event number less than 5) to document the association between variables: sex, IgG4 serum levels, number of organs involved, and target organ compromise (lymphadenopathy, ocular/orbitary, retroperitoneum, salival gland, pancreas, and lacrimal gland).

All patients included had signed consent for personal information handling. Data acquired were labeled with a consecutive number as identification. The data from the clinical records were taken to analyze and register in the database designed anonymously.

According to the Helsinki Declaration, all patients gave informed consent to the study. All procedures performed in this study were according to the ethical standards of the Research Ethics Committee of Artmedica IPS (Approval No. 2021001), followed by the 1964 Helsinki Declaration and its later amendments and national ethical standards (Resolution 8430 of 1993). The Artmedica's Research Ethics Committee reviewed and approved the study and the use of the medical records under the data privacy laws for clinical studies and scientific publications.

Results

1193 clinical records were revised, and 33 patients diagnosed with IgG4-RD were finally selected based on comprehensive diagnostic criteria (CDC) de Umehara-Okazaki (3). Definite diagnosis was obtained in 48.5% of patients, probable in 27.7%, and possible in 24.2%. Twenty-one patients were female, with an M/F ratio = 1/1.75. The median age to diagnosis was 53.87 years (interquartile range of 27.06), the minimum age of diagnosis was 11.5 years, and the maximum was 79.2 years. Regarding clinical presentation at diagnosis, ocular/orbitary involvement was present in 16 patients (48.5%), followed by head and neck in 10 patients (30.3%) and biliary tract/gastrointestinal in 9 (27.3%) (Table 1).

Organ involvement was observed by imaging, such as computed tomography and magnetic resonance, or biopsies. We found 15 (45.5%) patients with single organ involvement and 18 (54.6%) with two or more compromised organs. Lymphatic and ocular/orbitary were the most commonly reported (Table 2). Histologic diagnosis was obtained in 25 (75.8%) patients, and IgG4 serum levels were normal in 43.3% (Table 3). The data collection included a search for supplementary test results, though these were not available for the entire cohort. Rheumatoid factor was positive in one patient (n=19), antinuclear antibodies (ANA) in 4 patients (n=25), and anti-neutrophil cytoplasmic antibodies (ANCA) by indirect immunofluorescence assay (IFI) in one patient (n=16). Positivity for ANCA, antibodies to extractable nuclear antigens, and ELISA assay for anti-PR3 (n=15) was not observed.

The treatment is described in Table 4. Regarding the number of organs compromised, we did not find an association with IgG4 serum levels or sex (p: 0.918 and p: 0.895, respectively). In addition, we did not observe a relation between sex and specific-organ involvement (Table 5 and Figure 1).

Discussion

IgG4-RD poses multiple diagnostic challenges. The initial presentation may be nonspecific or confused with other frequent conditions. However, data from different cohorts allowed for a better characterization of four phenotypes: pancreato-biliary, retroperitoneal/aortitis, head and neck limited, and Mikulicz/systemic. Data collected in this study are the first described in Colombia, using comprehensive diagnostic criteria (CDC) de Umehara-Okazaki (3) and allowing us to compare our population with other cohorts worldwide. Results of this study showed a lower age and more frequent female representation in all phenotypes. The most frequently involved organs were similar to those reported in the different series: lymph nodes, pancreas, lacrimal and salival glands, and retroperitoneum. Infrequent manifestations like pachymeningitis, scleritis, ichthyosis, and sub-glottic stenosis are also described. IgG4-RD is a global disease described in different populations: Asian cohorts including 403 (5), 346 (6), and 235 (7) patients, followed by a multicentric Latin American study of 148 patients (8), and a multiethnic US cohort of 125 patients (9). The disease has also been studied in France (10), Italy (11), and Spain (12). Differences observed in the different studies could derive from an ethnic effect on the disease presentation. Most heterogeneity is observed in age at diagnosis, predominance for males, organ involvement, and response to glucocorticoids.

Age at diagnosis varies between different cohorts, being older in Japan (median of 67 years), followed by Italy and France with a median of 62 and 58 years, respectively. In America, IgG4-RD starts earlier with an age median between 50 and 55 years (6,7). Findings in our cohort corroborate these differences.

Different series described a male sex predominance with a male: female ratio up to 4:1 (7). However, Latin American cohorts do not show this tendency, presenting similarities between both sexes. For example, our study reported a higher frequency of female sex (only cohort with this characteristic) with a male: female rate close to 1:2. Furthermore, an association between sex and organ involvement has been described with male sex associated with periaortitis and female sex with sialoadenitis and dacryoadenitis (7). This difference has been analyzed and was not documented in our study, possibly due to the over-representation of females in our cohort, as shown in Asian cohorts.

Clinical manifestations are variable and depend on involved organs. Our series holds similarities with other American and Latin American cohorts, where head and neck limited phenotype is predominant and differs principally from Japanese and European series, where the pancreato-biliary phenotype is the most frequent. Multiorgan involvement in our study is up to 54%, similar to the mentioned cohorts; however, this percentage is lower than the French cohort that reported a higher multiorgan involvement (92%) (10). Also, we did not demonstrate a relationship between IgG4 serum levels and multiorgan involvement (we described eight patients with normal IgG4 serum levels of whom 5 with an isolated lesion, and 3 with multiorgan involvement) as suggested by Wallace, who evidenced higher organ damage, higher IgE levels, eosinophilia, and low complement levels in patients with high IgG4 serum levels (7). These findings suggest a lower disease burden in our population and support the question raised in worldwide literature about the diagnostic and prognostic value of IgG4 levels, especially in people different from Asians. IgG4 concentrations have been related to higher pancreatic involvement, which wasn´t confirmed in our cohort (13).

Relating to treatment, initial therapy in different case series is based on glucocorticoids, although response and flares differ among studies. Differences in predominant phenotype, multiorgan involvement frequency, and aortitis likely explain these findings. Moreover, we described clinical response with lower glucocorticoid doses (25 mg/day prednisone) than those used in other series (up to 60 mg/day). For this reason, a combination with cs-DMARD (azathioprine, methotrexate, and mycophenolate mofetil) seems enough to prevent flares, limit organ damage, and lower long-term adverse effects associated with glucocorticoids. In Colombia, only a case series has been reported (4 patients with sub-glottic stenosis, autoimmune pancreatitis, retroperitoneal fibrosis, and systemic involvement); all of them had elevated IgG4 levels and histological confirmation with complete response to glucocorticoids, which points to an optimal response to this therapy and, possibly, to lower disease severity in our population (14). Regarding other autoantibodies measured in this study, we didn´t find a relationship with the positivity of RF, ANA, ANCA by IFI, or MPO/PR3 antibodies as mentioned in other studies, although almost half of the patients presented multiple organ involvement and elevated IgG4 levels (15). These abnormal levels of IgG4 are usually associated with hypocomplementemia, elevated IgE, eosinophilia, and immune complex formation (7). Other autoimmune diseases or IgG4-RD mimicking conditions weren´t observed during follow-up.

The main limitations of this study are its retrospective nature and the possible underreporting related to the entry of the ICD-10 coding. Another limitation is the referral bias due to the registry from a tertiary care center. However, this cohort is one of the largest in South America and describes a racially diverse population.

Conclusions

This study presented demographic and epidemiological information on IgG4-RD in our country. The data are similar to those reported by the medical literature of South America but differ in organ involvement according to age and sex. Unlike other ethnic groups, our population is more represented by women with compromise of head and neck, with few systemic symptoms and retroperitoneal-aortitis manifestations. The present study is limited by underreporting or wrong registration when entering the

ICD-10 code in medical records. However, it is data that is legally registered in Colombia and deserves an analysis, as we carried out in the present study.

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Table 1. Clinical and sociodemographic variables (n=33).

Variable	n (%); Median (percentile 25, 75)
Sex	
Male	12 (36.36)
Female	21 (63.63)
Age at first symptom (years)	53,08 (37.09-64.15)
Age at diagnosis (years)	53,87 (40.14-65.57)
Time to diagnosis (years)*	1,42 (0.72-6.07)
Follow-up time (years)	1,48 (0.51-3.39)
BMI (kg/m^2)	26.19 (22.98-27.95)
Initial symptoms	
Ocular/orbitary	16 (48.48)
Proptosis	7 (43.75)
Eye pain	6 (37.50)
Reduced visual acuity	6 (37.50)
Diplopia	5 (31.25)
Lacrimal gland hypertrophy	4 (25.00)
Dry eye	2 (12.50)
Red eye	2 (12.50)
Enophthalmos	1 (6.25)
Papilledema	1 (6.5)
Head and neck	10 (30.30)
Lymphadenopathy	5 (50.00)
Submandibular glands hypertrophy	4 (40.00)
Parotid hypertrophy	3 (30.00)
Gastrointestinal/Biliary tract	9 (27.27)
Abdominal pain	9 (100.00)
Diarrhoea	2 (22.22)
Upper respiratory airway	7 (21.21)
Rhinorrhea	2 (28.47)
Nasal obstruction	2 (28.47)
Xerostomy	1 (14.29)
Salivary glands hipertrophy	1 (14.29)
Neurologic	6 (18.18)
Headache	6 (100.00)
Urinary tract	
Obstructive urinary symptoms	3 (9.09)
Lower respiratory airway	2 (6.06)
Dyspnea	1 (50.00)
Chest pain	1 (50.00)
Cough	1 (50.00)
Arterial - Thickening, thrombosis of Aorta	3 (30.00)
Medical history	
Hypertension	7 (21.21)
Thyroid disease	5 (15.15)
Prediabetes or diabetes	2 (6.06)
Thromboembolic disease	1 (3.03)
Chronic kidney disease	1 (3.03)
Dyslipidemia	2 (6.06)
Asthma	1 (3.03)
Turbinate hypertrophy	1 (3.03)
Urolithiasis	1 (3.03)
Vasospastic angina	1 (3.03)
Hodgkin lymphoma	1 (3.03)
No previous medical history	7 (21.21)

BMI, body mass index; kg/m^2: kilograms per square meter. *Time between symptom onset and definite diagnosis.

Table 2. Frequency of organic manifestation as isolated or multiple lesions.

Variable		**n (%)**
Single organ involvement		15 (45.5)
2 organ involvement		14 (42.4)
3 organ involvement		3 (9.1)
5 organ involvement		1 (3.0)
Compromised organs (number of events 57)	Lymphadenopathy (cervical, mediastinal or abdominal)	11 (33.3)
	Ocular/Orbit	9 (27.3)
	Retroperitoneum	7 (21.2)
	Salival gland	7 (21.2)
	Lacrimal gland	6 (18.2)
	Pancreas	5 (15.2)
	Arterial	3 (9.1)
	Lung	2 (6.1)
	Meninges	2 (6.1)
	Parotid gland	1 (3.0)
	Upper airway	1 (3.0)
	Neck	1 (3.0)
	Heart	1 (3.0)
	Hepatobiliary	1 (3.0)
	Mediastinum	1 (3.0)
	Skin	1 (3.0)
	Ear	1 (3.0)

Table 3. IgG4-related disease diagnosis.

		n (%)
IgG4-related disease associated diagnosis	Lymphadenopathy (cervical, mediastinal or abdominal)	11 (33.3)
	Ocular pseudotumor	8 (24.2)
	Retroperitoneal fibrosis	7 (21.2)
	Pancreatitis	5 (15.2)
	Sialoadenitis	4 (12.1)
	Dacrioadenitis	4 (12.1)
	Vasculitis	3 (9.1)
	Meningitis	2 (6.1)
	Submaxilar mass	2 (6.1)
	Lacrimal gland infiltration	2 (6.1)
	Right auricular mass	1 (3.0)
	Ichthyosis with hyperkeratosis and lipomatous infiltration of the skin	1 (3.0)
	Retro-glottic mass	1 (3.0)
	Extraocular muscles infiltration	1 (3.0)
	Pulmonar mass	1 (3.0)
	Pulmonary nodes	1 (3.0)
	Nasal chondritis	1 (3.0)
	Parotiditis	1 (3.0)
	Submaxilar gland hypertrophy	1 (3.0)
	Mediastinal fibrosis	1 (3.0)
	Biliar tract disease	1 (3.0)
	Chronic otomastoiditis	1 (3.0)
	Lung infarction	1 (3.0)
	Vascular thrombosis	2 (6.1)
Biopsies performed (n=25), localization	Orbit	5 (20.0)
	Lacrimal gland	5 (20.0)
	Retroperitoneum	3 (12.0)
	Parotid gland	2 (8.0)
	Mediastinal lymph nodes	2 (8.0)
	Meninges	2 (8.0)
	Lung	1 (4.0)
	Auricular mass	1 (4.0)
	Nasal cartilage	1 (4.0)
	Salival gland	1 (4.0)
	Larynx	1 (4.0)
	Pancreas	1 (4.0)
Histologic findings (n=25)*	Highly suggestive histology	17 (68.0)
	Probable histology	8 (32.0)
IgG4 serum levels (n=24)	Positive (>135 mg/dL)	16 (66.7)
	Value (mg/dL) (Median(Q1-Q3))	795 (292.3-1108.0)

IgG4, immunoglobulin G4; Q1, quartile 1; Q3, quartile 3. *Classification based on Consensus statement on the pathology of IgG4-related disease (4)

Table 4. Therapy received in IgG4-related disease (n=33).

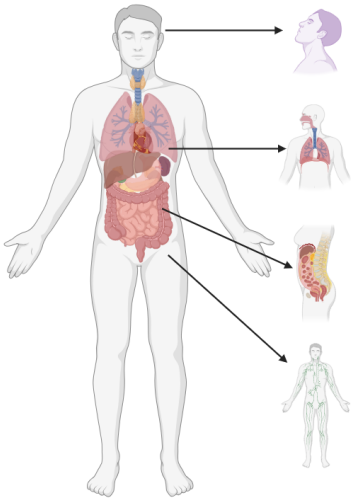
Pharmacologic therapy	n (%); Median (Q1-Q3)
Glucocorticoids	31 (93.9)
Dose (mg/day) *	25 (10-40)
Non-biologic immunomodulator	27 (81.8)
Azathioprine	23 (85.2)
Methotrexate	7 (25.9)
Mycophenolate mofetil	6 (22.2)
Cyclophosphamide	3 (11.1)
Biologic therapy (rituximab)	3 (9.1)

Q1, quartil 1; Q3, quartil 3. *Prednisolone equivalent dose.

Table 5. Association between IgG4 serum levels, sex and number of involved organs.

	Total	Isolated lesion	Multiple lesion*	p**
IgG4 serum level				
≤135 mg/dL	8 (33.3)	3 (30.0)	5 (35.7)	0.918
between 135 y 270 mg/dL	4 (16.7)	2 (20.0)	2 (14.3)	
>270 mg/dL	12 (50.0)	5 (50.0)	7 (50.0)	
Sex				
Female	21 (63.6)	10 (66.7)	11 (61.1)	0.741
Male	12 (36.4)	5 (33.3)	7 (38.9)	

IgG4, immunoglobulin G4. *Defined as two or more organs; **p with significant value less than 0.05.



Association between principal compromised organs and sex

Organic compromise	Total	Female	Male	p**
Adenomegalies (cervical, mediastinal or abdominal)	11	6 (54,6)	5 (45,5)	0,775
Ocular/orbit	9	7 (77,8)	2 (22,2)	0,301
Retroperitoneal fibrosis	7	6 (85,7)	1 (14,3)	0,171
Salival gland	7	4 (57,1)	3 (42,9)	0,687
Pancreas	5	2 (40,0)	3 (60,0)	0,233
Arterial	3	3 (100,0)	0 (0,0)	0,170

**p: with significant value less than 0,05

Figure 1. Association between principal compromised organs and sex.