# IgG4-related disease in patients with idiopathic orbital inflammation syndrome: data from the French *SIOI* prospective cohort

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**ABSTRACT.**

***Purpose:*** **To better characterize IgG4-related disease (RD) in the setting of idiopathic orbital inflammation syndrome (IOIS).**

***Methods:*** **National, multicentre, prospective, observational cohort study. Among the patients consecutively included in the French multicentre *SIOI* cohort, we selected those who underwent orbital and/or adnexal biopsy. Clinical, morphological and pathological findings at diagnosis were blindly analysed. Serum IgG4 levels at inclusion were measured and all available biopsy specimens were immunostained for IgG4 and IgG. Biopsy samples with more than 10 IgG4-positive plasma cells per high-power field and a IgG4+/IgG+ plasma cell ratio above 40% were scored as positive. IgG4-positive patients were then screened for comprehensive diagnostic criteria for IgG4-RD.**

***Results:*** **Of the 87 patients included, 35 had histologically documented IOIS. Thirteen patients (37%) with a mean age at onset of 27 years (range 21–78) had IgG4-positive biopsies, among which 10 patients (77%) and 3 (23%, with IgG4 serum levels >1.35 g/L) were considered as having probable and definite IgG4-RD, respectively. The latter 13 patients more frequently fulfilled histological criteria for IgG4-RD (including plasmacytic infiltrate ($p = 0.006$), fibrosis ($p = 0.0025$) and periphlebitis ($p = 0.075$)) than IgG4-negative patients. Storiform fibrosis was exclusively found in orbital tissues from IgG4-positive patients ($n = 3$, 23%). Eosinophilia associated with recurrent sinusitis or asthma was a prominent feature in patients with definite IgG4-RD.**

***Conclusions:*** **More than one-third of patients with biopsy-proven IOIS satisfied criteria for IgG4-RD, but only a few had a definite type.**

**Key words:** idiopathic orbital inflammatory syndrome – IgG4-related disease – IgG4-related ophthalmic disease – inflammatory orbital pseudotumour

*A complete list of members of the French Orbital Inflammation Study Group (GFEOI) and collaborators is provided in the Acknowledgements section.

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# Introduction

Idiopathic orbital inflammatory syndrome (IOIS), previously known as orbital pseudotumour, is a heterogeneous group of disorders characterized by orbital inflammation with no identifiable local or systemic cause (Jacobs & Galetta 2002; Yuen & Rubin 2003; Swamy et al. 2007). Since low-grade lymphoma and systemic diseases can mimic its clinical presentation, IOIS remains a diagnosis of exclusion, thereby justifying tissue biopsies when in doubt (Mombaerts et al. 2016). The 2017 IOIS pathological nomenclature suggests that two histological patterns predominate, namely a lymphoplasmacytic infiltrate or fibrous and/or hyalinized connective tissue (Mombaerts et al. 2017). Conversely, the presence of granulomas, vasculitis or necrosis generally excludes the diagnosis of IOIS (Mombaerts et al. 2017).

IgG4-related disease (IgG4-RD) is a systemic fibro-inflammatory disorder characterized by lymphoplasmacytic infiltration and IgG4 tissue deposits in involved organs (Kamisawa et al. 2015). Recently, IgG4-RD has been reported as a possible cause of scleritis and features of IgG4-RD have been evidenced in orbital tissues of patients with IOIS, suggesting that IOIS might be part of the spectrum of IgG4-RD (Plaza et al. 2011; Karim et al. 2017). Yet, due to the retrospective design of all IOIS studies published to date and their inherent limitations (e.g. absence of IgG4 immunostaining, missing baseline IgG4 levels, losses to follow-up...), the true prevalence of IgG4-RD among patients with IOIS is unclear. Moreover, it is of paramount interest to determine baseline serum IgG4 levels in IOIS patients who satisfy histological criteria for IgG4-RD since high IgG4 levels are associated with extra-ophthalmological disease features in IgG4-RD with orbital involvement (Wallace et al. 2014).

In 2012, a French prospective multicentre cohort of patients with IOIS (hereafter referred to in French as the *SIOI* cohort) was set up in order to better decipher the clinical course and outcome of IOIS and its possible subentities. The first aim of the *SIOI* cohort was to assess the prevalence and characteristics of patients with biopsy-proven IOIS who also satisfied the criteria for IgG4-RD.

# Materials and Methods

The *SIOI* cohort (ClinicalTrials.gov number, NCT01443000) was a national, multicentre, prospective, observational cohort study. Written informed consent was obtained from all the patients before enrolment. The study protocol complied with the Declaration of Helsinki and was approved in June 2010 by a local ethics committee (Comité de protection des personnes Ile de France VI, approval number 09SAD-cohorteSIOI_AvisFavCPP_20100610).

### Study participants

This study was conducted between March 2012 and July 2015 in 12 university hospitals (Avicenne, Quinze-Vingts, Caen, Rennes, Fondation A. de Rothschild, Reims, Nancy, Nantes, Nice, Limoges, Pitié-Salpétrière and Cochin) with expertise in the field of orbital inflammatory diseases. The study included ≥18-year-old patients with orbital inflammation (≥3 months duration) and no identifiable local or systemic cause (including lymphoma) despite an extensive workup. Patients fulfilling classification criteria for an autoimmune disease (e.g. Graves' disease, autoimmune thyroiditis, sarcoidosis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, systemic lupus erythematosus and Sjögren syndrome) were excluded, as were patients with an underlying infectious disease (e.g. HIV, *Mycobacterium tuberculosis* or parasitic infection). For the purposes of the present study, only patients from the *SIOI* cohort who underwent orbital and/or adnexal biopsy were selected.

### Clinical, biological and radiological data collected

Clinical data were retrieved from medical charts using a standardized anonymous form, including age at disease onset, gender, country of birth and a complete medical history. Sinusitis was considered in patients with sinus pain or discharge, and/or abnormal sinus radiographic findings. The type and duration of immunosuppressive therapy (i.e. corticosteroids and/or conventional immunosuppressive drugs and/or biologics) administered from diagnosis to inclusion were recorded for each patient.

Data from magnetic resonance imaging or computerized tomography of the orbit were blindly reviewed by a neuroradiologist with expertise in the field (FH). For each patient, the following locations and their laterality were screened in order to specify the anatomic structure(s) involved in the inflammatory process: lacrimal gland, extraocular muscles, orbital fat, globe or sclera, apex and optic or infraorbital nerve.

The results of workup for autoimmune diseases were extracted from medical charts: positivity for antinuclear antibody (ANA), thyroid autoantibodies and antineutrophil cytoplasmic antibodies (ANCA) was recorded.

Additionally, blood samples were prospectively collected at inclusion, and serum aliquots were stored at −20°C. IgG subclass measurements were performed in a centralized laboratory (AA and PA). Serum IgG subclass levels were measured by using a competitive ELISA with selected monoclonal antibodies, after thawing the serum aliquots from patients with biopsy-proven IOIS (Aucouturier et al.1984, 1985). Serum total IgG levels were measured by immunonephelometry (IMMAGE immunochemistry systems, Beckman).

### Pathological analysis

All biopsy specimens obtained at diagnosis were blindly analysed by two unrelated pathologists (AM and NC). In case of discrepancies, the biopsies were re-examined by both experts until a consensus was found. In addition to ocular adnexal biopsy, salivary gland biopsies, when available, were also reviewed. Histopathologic findings were based on haematoxylin and eosin staining.

In accordance with the grading system used by Andrew et al., the magnitude of the following histopathologic features was graded from 0 to 3: sclerosis, lymphoplasmacytic or histiocytic infiltrations, and follicular hyperplasia, which was defined as a lymphoid infiltrate organized in germinal centres (Andrew et al. 2015). Sclerosis was categorized as 'collagenous' when it had a lamellar architecture and as 'storiform' when it formed a whirling pattern. The presence (1) or absence (0) of phlebitis (obliterative or nonobliterative) was also recorded. The grading system was standardized by defining the characteristics indicative of each score and by using a series of reference photomicrographs against which cases were judged (Fig. 1).

Histopathologic patterns were initially classified following Mombaerts' description (Mombaerts et al. 1996). The presence of multinucleated giant cells in the orbital tissue was the hallmark of a granulomatous subtype of idiopathic orbital inflammation whereas patients with evidence of vasculitis in the wall of small vessels were considered as having a vasculitic pattern. In the absence of both features of granuloma and vasculitis, patients with a sclerosis score of 1 or less were classified as having a classic pattern of IOIS (cIOIS) and those with a score above 1 as having a sclerosing pattern (sIOIS). In agreement with the 2017 consensus (Mombaerts et al. 2017), only patients with cIOIS or sIOIS patterns were considered as having a non-specific orbital inflammation and thereby were included in the current study.

For the purpose of the study, two adjacent 3-$\mu$m-thick, formalin-fixed, paraffin embedded sections with the highest intensity lymphoplasmacytic infiltrate were selected for additional immunohistochemical staining. The Benchmark XT automated immunohistochemistry slide staining system (Ventana Medical Systems, Tucson, AZ, USA) was used to stain one slide for IgG (rabbit polyclonal anti-IgG antibody, Dako, Santa Clara, USA, diluted at 1/5000 with the Ventana CC1 protocol) and the other for IgG4 (rabbit monoclonal anti-human IgG4 antibody, clone EP4420, GeneTex, Irvine, USA, diluted at 1/2000 with the CC1 protocol). Both slides were treated with the ultraview detection kit (Ventana Medical Systems) followed by haematoxylin 2 (Ventana Medical Systems) and bluing reagent (Ventana Medical Systems). The average number of IgG4-positive plasma cells within three fields with the highest number of IgG4+ plasma cells (magnification $\times$40) was used to estimate the density of the IgG4-positive inflammatory infiltrate (Deshpande et al. 2012). Tissue specimens with more than 10 IgG4-positive plasma cells per high-power field (hpf) and with a ratio of IgG4+/IgG+ plasma cells of more than 40% were scored as positive. Patients with positive orbital tissue were considered IgG4-positive.

### IgG4-RD diagnosis

Serum IgG4 levels were considered elevated when higher than 1.35 g/l. According to the 2012 comprehensive clinical diagnostic criteria for IgG4-RD (Umehara et al. 2012), IgG4-RD was considered as a definite diagnosis when patients fulfilled clinical, biological and pathological criteria, and as a probable diagnosis when serum IgG4 levels were normal despite pathological staining for IgG4. As previously suggested, an orbital localization of IgG4-RD was referred to as IgG4-related ophthalmic disease (IgG4-ROD; Stone et al. 2012a).

### Statistical analysis

Patient characteristics are reported as the number and percentage for categorical variables and as the mean $\pm$ SD for continuous variables. We differentiated patient subsets based on their status for IgG4 immunostaining. For these subsets, quantitative variables were compared using Student's *t*-test, and categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. All statistical analyses used the SAS software package version 9.4 (SAS Institute Inc, Cary, NC, USA). p Values below 0.05 were considered to denote significant differences.

## Results

Of the 87 patients included in the *SIOI* cohort, 49 (56%) underwent orbital or adnexal biopsy, and 14 were subsequently excluded (unavailable biopsy specimens, $n = 5$; inconclusive pathological analysis, $n = 6$; granulomatous pattern (Fig 1, A1), $n = 3$). Hence, 35 (40%) patients were included in the final analysis (Fig. 2). All of the latter patients had non-specific orbital inflammation and were thus considered as having biopsy-proven IOIS.

Of the 35 patients with histologically characterized IOIS, 13 (37%) patients satisfied IgG4 immunostaining criteria among which 10 (77%) and 3 (23%) fulfilled criteria for probable and definite IgG4-RD, respectively.

### Epidemiologic features

IgG4-positive patients were predominantly Europeans (54%), with no gender predominance (M/F: 7/6). Mean age at diagnosis was 53 $\pm$ 17.8 years (range 31–78 years) while mean age at the onset of IOIS was 50.7 $\pm$ 19.1 years (range 21–78 years; Table 1).

### Histopathologic features

Of the 35 patients with biopsy-proven disease, 30 (86%) were treatment (whether corticosteroids, immunosuppressants and/or biologics) naïve prior to biopsy. A biopsy was performed in the five remaining cases (patients 6, 15, 16, 25 and 28) after corticosteroids had been stopped 24 $\pm$ 34 months before (range 3–84 months).

The 13 IgG4-positive biopsies involved orbital fat, lacrimal gland and extraocular muscles in respectively 69%, 38.5% and 31% of cases. None of them was performed in the case of pure myositic involvement. Three (23%) of the 13 IgG4-positive patients had more than 100 IgG4-positive plasma cells/hpf (patients 18, 21 and 22; Table S1). Such a level of IgG4 plasma cell infiltration was described purely in fat or lacrimal gland in patients 18 (Fig. 1, A2) and 22, and in heterogenous orbital tissue admixing lacrimal gland, fat and extraocular muscles in patient 21. IgG4

immunostaining was positive in 3 (21.5%) of the 14 cIOIS patients and 10 (48%) of the 21 sIOIS patients, but inconclusive in a single patient of the latter subgroup (Table 2).

A diffuse lymphocytic infiltrate was exclusively found in orbital tissue from IgG4-negative patients with IOIS (Figs. 1, A3 and A4) while storiform fibrosis (Fig 1, A5) was exclusively found in orbital tissues from IgG4-positive patients ($n$ = 3, 23%). IgG4-positive patients differed from IgG4-negative patients owing to the presence of marked plasmacytic infiltrate (Fig 1, A6; 100% versus 57%, p = 0.006) and orbital fibrosis (predominantly of the collagenous type, Fig 1, A7) on biopsy specimen (77% versus 57%, p = 0.0025). Presence of periphlebitis tended to be more frequent in IgG4-positive than in IgG4-negative cases (84.5% versus 52%, p = 0.075). Of note, periphlebitis was never obliterative (Fig 1, A8). Based on these findings, all IgG4-positive patients were considered as fulfilling pathological criteria for IgG4-RD (Table 3).

### Orbital site involvement

Most of IgG4-positive patients (77%) had orbital fat involvement but less than one-half of them (46%) had bilateral disease. The proportion of patients with infraorbital nerve involvement tended to be higher in IgG4-positive than in IgG4-negative cases (40% versus 6.25%, p = 0.055), while patients in the two subgroups did not differ with regard to other disease anatomic involvements (Table 1).

### Systemic features

Of the 13 IgG4-positive patients, three (23%) had elevated serum IgG4 levels associated with polyclonal hypergammaglobulinaemia on standard serum protein electrophoresis (Table S2). Hence, less than one-quarter of the patients met the criteria for definite IgG4-RD (patients 18, 21 and 24). The

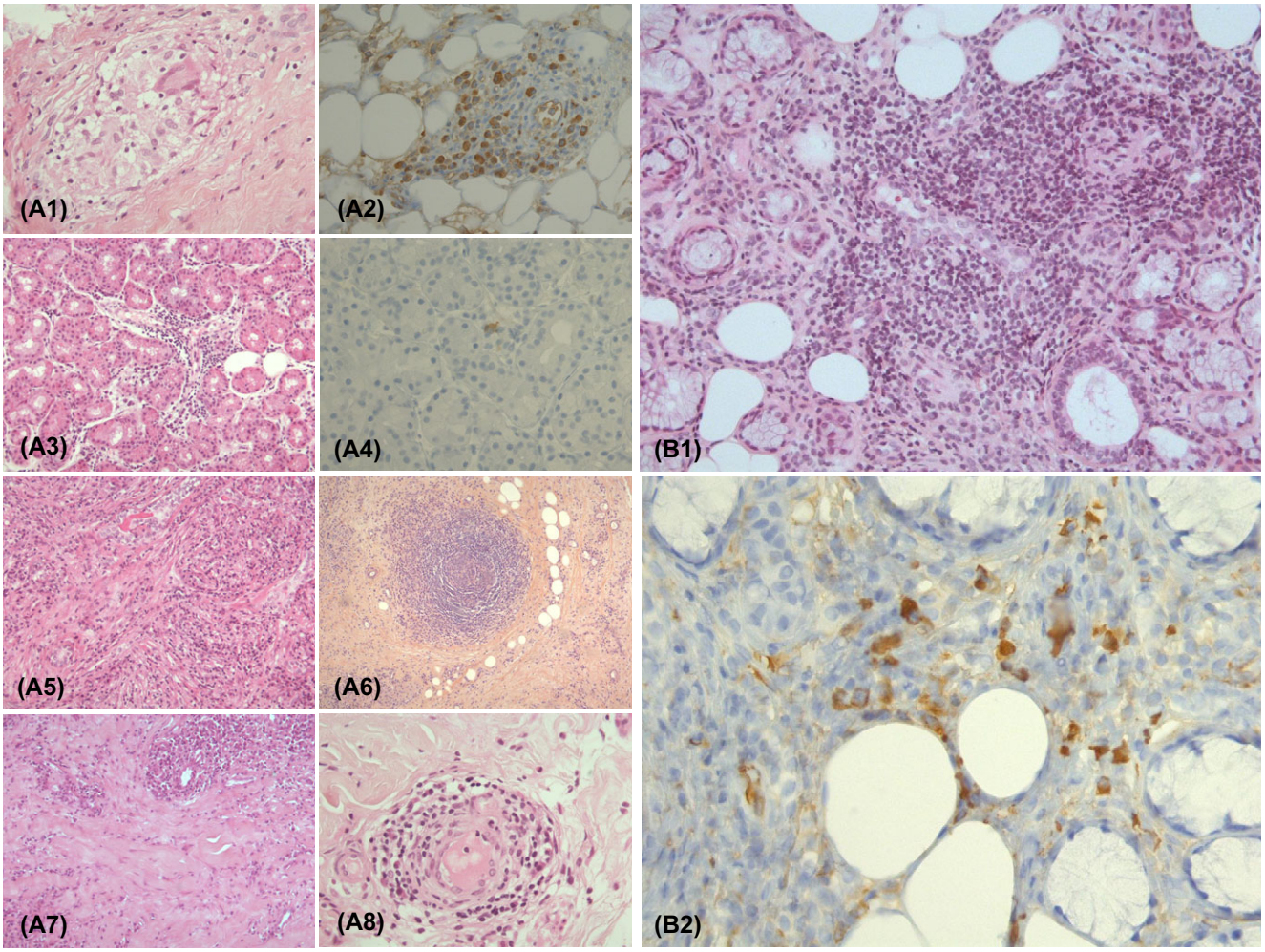


**Fig. 1.** Histopathologic classification system for patients with idiopathic orbital inflammation syndrome (A1–A8). For each patient, the intensity of fibrosis, lymphoplasmacytic or histiocytic infiltration and follicular hyperplasia were scored from 0 to 3 using photographs taken from some of our patients as reference and listed hereinafter: (A1; HES X400) dense histiocytosis infiltrate (score 3) organized in non-caseating granuloma, (A2; patient 18, immunostaining X400) lymphoplasmacytic infiltrate (score 3) with increased number of IgG4-positive plasma cells (100 IgG4-positive plasma cells/hpf) in a patient with definite IgG4-RD, (A3; patient 5, HES X40) slight lymphocytic infiltrate (score 1) without fibrosis or histiocytes (score 0), (A4; patient 5, immunostaining X400) diffuse lymphocytic infiltrate with negative-IgG4 immunostaining, (A5; patient 22, HES X200) storiform fibrosis scored as 2, (A6; patient 18, HES X200) plasmacytic infiltrate score of 3, (A7; patient 15, HES X200) collagenous fibrosis scored as 3, (A8; patient 21, HES X400) presence of nonobliterative phlebitis. Histopathologic findings from biopsy of minor salivary gland (B1, B2): (B1; patient 18, HES X400) follicular lymphoid hyperplasia and plasma cell infiltration, (B2; patient 18, immunostaining X400) IgG4 immunostaining was strongly positive on plasma cells in patients with definite IgG4-RD.

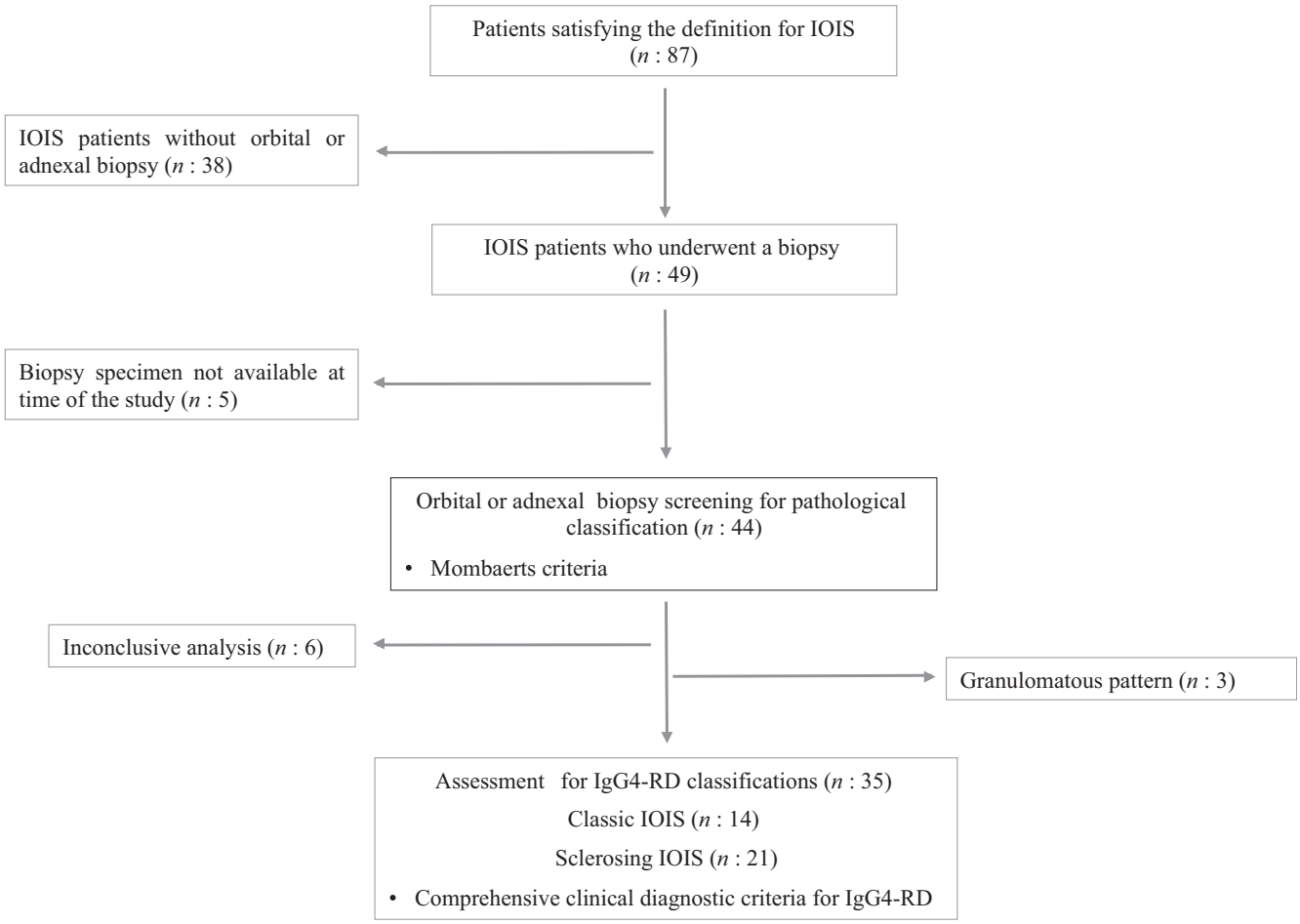


**Fig. 2.** Flow diagram of the study cohort.

10 remaining IgG4-positive patients (77%) did not meet any serologic criteria (missing data in patients 3 and 19) and were therefore considered as having probable IgG4-RD. Of note, four of the latter patients had previously been treated with corticosteroids that had been discontinued 50.5 ± 42.5 (range 6–96) months before inclusion while a single patient (patient 23) was still under treatment with corticosteroids at study entry.

Albeit not reaching statistical significance, the comparison of pathologic data between IgG4-positive and IgG4-negative patients showed a trend towards a higher proportion of IgG4-positive patients with sinusitis (46% versus 14%, p = 0.056; Table 1). All three patients who satisfied criteria for definite IgG4-RD had infraorbital nerve involvement. Of note, both patients with eosinophilia >10% and asthma or recurrent sinusitis had definite IgG4-RD (patients 18 and 24, respectively; Table 4). Such patients also had sialadenitis, which is an additional feature of IgG4-RD according to Umehara's criteria (Figs. 1, B1 and B2). Yet, at study inclusion, none of the IgG4-positive patients had other systemic (i.e. extra-ophthalmological) feature suggestive of IgG4-RD (Table 4).

# Discussion

As previous pathological studies have suggested a strong link between idiopathic orbital inflammation and IgG4-RD (Plaza et al. 2011; Deschamps et al. 2013; Andrew et al. 2015; Sa et al. 2015), we performed IgG4 immunostaining (blindly analysed by two unrelated pathologists with expertise in the field of IOIS and IgG4-RD) and measured serum IgG4 levels at study inclusion (in a central laboratory) in all patients from the *SIOI* cohort with available tissue biopsies in a search for IgG4-RD criteria. Hence, in this prospective multicentre cohort study, we show that more than one-third of patients with biopsy-proven IOIS satisfied disease criteria for IgG4-RD, but only a few had a definite type.

In line with prior histopathologic studies (Deschamps et al. 2013; Andrew et al. 2015), more than one-third of our patients (37%) with non-specific orbital inflammation fulfilled Umehara's immunostaining criteria for IgG4-RD and met the pathological criteria for IgG4-RD. Concordant with the study by Deschamps et al., a higher level of plasmacytic infiltration and nonobliterative phlebitis was observed in IgG4-positive patients (Deschamps et al. 2013). Moreover, in agreement with a recent meta-analysis of all published cases of IgG4-ROD cases (Wu et al. 2015), obliterative phlebitis, a major histopathologic criterion associated with IgG4-RD (Deshpande et al. 2012), was never found herein, highlighting the fact that obliterative phlebitis is not a salient diagnostic criterion for IgG4-ROD. As expected, IgG4-positive patients frequently exhibited orbital fibrosis, predominantly of lamellar pattern (collagen type

**Table 1.** Epidemiological, ophthalmologic, systemic and serological data according to IgG4 immunostaining in patients with biopsy-proven IOIS

| | IgG4 + n: 13 | IgG4−n: 21 | Totaln: 34 | p* |
|---|---|---|---|---|
| **Epidemiological characteristics** | | | | |
| Mean age years (SD, Range) | | | | |
| At onset | 50.7 (19.2, 21–78) | 48.8 (12.4, 24– | 49.5 (15, 21–78) | / |
| At dignosis | 53.1 (17.8, 31–78) | 49.7 (12, 24–69) | 50.5 (14.3, 24–78) | / |
| Sex ratio (M/F) | 7/6 | 10/11 | 17/17 | / |
| Origin, # | | | | |
| European | 7 | 15 | 22 | / |
| North African | 3 | 3 | 6 | / |
| Black African | 3 | 2 | 5 | / |
| Asian | 0 | 1 | 1 | / |
| **Ophthalmologic locations,** n† | | | | |
| Lacrimal gland | 8 | 10 | 18 | 0.43 |
| Extraocular muscles | 4 | 5 | 9 | 0.7 |
| Globe/sclera | 2 | 4 | 6 | 1 |
| Orbital fat | 10 | 13 | 23 | 0.46 |
| Apex | 4 | 4 | 8 | 0.68 |
| Optic nerve | 4 | 9 | 13 | 0.7 |
| Infraorbital nerve | 4† | 1† | 5 | 0.055 |
| Bilateral presentation | 6 | 5 | 11 | 0.26 |
| **Systemic manifestations,** n† | | | | |
| Asthma | 1 | 0 | 1 | 0.38 |
| Sinusitis | 6 | 3 | 9 | 0.056 |
| Pulmonary nodules | 1 | 5 | 6 | 0.37 |
| Eosinophilia > 10% | 2 | 0 | 2 | 0.13 |
| **Serum IgG4 at inclusion** ≥1.35 g/l, n† | | | | |
| Patients treated with ISD within the last 6 month follow-up | | | | |
| No | 2 | 0§ | / | / |
| Yes | 1£ | 1€ | / | / |
| Total | 3£ | 1§€ | / | / |
| **ANCA at diagnosis,** n† | | | | |
| MPO positivity | 0 | 1‡ | / | / |
| PR3 positivity | 0 | 1‡ | / | / |
| **Other data at diagnosis**, n† | | | | |
| ANA | 3 (n : 11§) | 2 | / | / |
| Anti-Ro and anti-La antibodies | 0 (n: 9§) | 0 (n: 20§) | / | / |
| Thyroid autoantibodies | 0 (n: 10§) | 0 (n: 18§) | / | / |

* p values are based on the chi-square test or Fisher's exact test, as appropriate. p values below 0.05 were considered to denote significant differences.
† Imaging analysis was inconclusive for three IgG4-positive patients and five IgG4-negative patients.
‡ ANCA serology was not available at diagnosis for one patient (#8) among the 21 IgG4-negative patients.
§ Immune serologies at diagnosis lacking in some patients.
Serum collection at inclusion lacked for two IgG4-positive patients (#3 and 19)£ and two IgG4-negative patients (#13€ and 30$).
ISD = Immunosuppressive drugs; ANCA = Antineutrophil cytoplasmic antibodies; MPO = Myeloperoxidase; PR3 = Proteinase-3; ANA = Anti-nuclear antibodies.

**Table 2.** Pathological classification according to IgG4 immunostaining in biopsy-proven IOIS

| | IgG4 immunostaining | | | |
|---|---|---|---|---|
| | IgG4+n : 13 | IgG4−n: 21 | IgG4 NDn: 1 | Totaln: 35 |
| **Pathologic pattern of IOIS***, n | | | | |
| Classical form | 3 | 11 | 0 | 14 |
| Sclerosing form | 10 | 10 | 1 | 21 |

* According to Mombaerts' classification.
ND = Not determined.

fibrosis). Noteworthy, storiform fibrosis, a hallmark of IgG4-RD (but yet very seldom reported in patients with IgG4-ROD; Wu et al. 2015), was exclusively seen in IgG4-positive patients.

Contrary to the literature (Plaza et al. 2011; Deschamps et al. 2013; Andrew et al. 2015; Sa et al. 2015), even though half of IgG4-positive patients had lacrimal involvement, there was no significant difference between IgG4-positive and IgG4-negative subgroups. A plausible explanation to these discrepancies could be that most of IgG4-positive patients had widespread disease within the orbit, leading to heterogenous tissue specimens involving mostly orbital fat, lacrimal gland and sometimes extraocular muscles. As previously shown by others (Takano et al. 2014; Wu et al. 2015), infraorbital nerve involvement was more frequent in patients with IgG4-ROD than in controls and was associated with higher serum IgG4 and extra-ophthalmologic involvement (e.g. sialadenitis) in the cases of definite IgG4-ROD.

A meta-analysis showed that the prevalence of extra-orbital involvement ranges from 22% to 50% in patients with probable or definite IgG4-ROD (Andrew et al. 2013). Yet, and contrary to our cohort, patients included were highly heterogenous, making it difficult to clearly identify patients with primarily localized orbital disease who satisfied criteria for IgG4-ROD.

From a pathophysiological viewpoint, since two (66%) patients satisfying criteria for definite IgG4-ROD also shared histological (e.g. dense histiocytic infiltrate) and systemic (e.g. sialadenitis, recurrent rhinosinusitis, asthma and/or mild eosinophilia) features of adult-onset asthma and periocular xanthogranuloma syndrome (AAPOX; Cavallazzi et al. 2009), our findings suggest that both conditions might be part of the same disease spectrum (London et al. 2015; McKelvie et al. 2017). In this line, a retrospective study of 16 cases of widespread xanthogranulomatous diseases evidenced that eight (50%) of the latter patients also fulfilled stringent criteria for IgG4-ROD, including the only two patients with genuine AAPOX. Besides ophthalmological manifestations, these two patients had features of bronchial hyperreactivity,

**Table 3.** Comparison of histological findings according IgG4 immunostaning in patients with biopsy-proven IOIS

| | cIOS | | sIOIS | | Total | | |
|---|---|---|---|---|---|---|---|
| Histologic features | IgG4 + n: 3 | IgG4−n: 11 | IgG4 + n: 10 | IgG4−n: 10 | IgG4 + n: 13 | IgG4−n : 21 | p* |
| **Number cells/hpf**, n | | | | | | | **0.001** |
| 0–9 | 3 | 0 | 10 | 1 | 0 | 19 | |
| 10–29 | 3 | 0 | 3 | 1 | 6 | 2 | |
| 30–99 | 0 | 0 | 4 | 0 | 4 | 0 | |
| ≥100 | 0 | 0 | 3 | 0 | 3 | 0 | |
| **IgG4/total IgG ratio,** n | | | | | | | **0.001** |
| <10 | 0 | 7 | 0 | 7 | 0 | 14 | |
| <40 | 0 | 11 | 0 | 10 | 0 | 21 | |
| ≥40 | 3 | 0 | 10 | 0 | 13 | 0 | |
| ≥80 | 0 | 0 | 2 | 0 | 2 | 0 | < |
| ≥100 | 0 | 0 | 0 | 0 | 0 | 0 | |
| **Lymphocytic infiltrate,** n | | | | | | | 0.13 |
| Nodular | 3 | 10 | 10 | 9 | 13 | 19 | |
| Diffuse | 0 | 1 | 0 | 1 | 0 | 2 | |
| Score | | | | | | | |
| 0–1 | 0 | 2 | 0 | 3 | 0 | 5 | |
| 2–3 | 3 | 9 | 10 | 7 | 13 | 16 | |
| **Plasmacytic infiltrate,** n | | | | | | | **0.006** |
| Score | | | | | | | |
| 0–1 | 0 | 6 | 0 | 3 | 0 | 9 | |
| 2–3 | 3 | 5 | 10 | 7 | 13 | 12 | |
| **Histiocytic infiltrate,** n | | | | | | | 0.54 |
| Score | | | | | | | |
| 0–1 | 3 | 11 | 8 | 9 | 11 | 20 | |
| 2–3 | 0 | 0 | 2 | 1 | 2 | 1 | |
| **Background fibrosis,** n | | | | | | | **0.0025** |
| Collagen | 3 | 2 | 7 | 10 | 10 | 12 | |
| Storiform | 0 | 0 | 3 | 0 | 3 | 0 | |
| No fibrosis | 0 | 9 | 0 | 0 | 0 | 9 | |
| Score | | | | | | | |
| 0–1 | 3 | 11 | 0 | 0 | 3 | 11 | |
| 2–3 | 0 | 0 | 10 | 10 | 10 | 10 | |
| **Periphlebitis,** n | | | | | | | 0.075 |
| Obliterative | 0 | 0 | 0 | 0 | 0 | 0 | |
| Non obliterative | 2 | 3 | 9 | 8 | 11 | 11 | |
| None | 1 | 8 | 1 | 2 | 2 | 10 | |
| **Follicular hyperplasia,** n | | | | | | | 0.347 |
| Score | | | | | | | |
| 0–1 | 3 | 9 | 7 | 10 | 10 | 19 | |
| 2–3 | 0 | 2 | 3 | 0 | 3 | 2 | |

* p-values are based on the chi-square test or Fisher's exact test, as appropriate. p-values below 0.05 (in bold) were considered to denote significant differences.

but none presented with IgG4-RD systemic manifestations (Verdijk et al. 2014). Moreover, since most of IOIS patients of the present series who otherwise met the criteria for definite IgG4-RD also had allergic manifestations (e.g. asthma, recurrent sinusitis, eosinophilia), the data presented herein suggest a potential link between IgG4 positivity and Th2 immune response. The same trend has previously been reported in large published case series of adult patients with IOIS. In the work by Plaza et al. (2011), five (45%) IgG4-positive patients (contrasting with only one (10%) IgG4-negative patient) had asthma, and recurrent sinusitis was exclusively seen in IgG4-positive patients ($n$ = 3, 27%). Sa et al. (2015) reported on sinusonasal involvement in five (45%) IgG4-positive patients but in none of the 13 IgG4-negative patients. In Deschamps' series, eosinophilia was more frequent when tissue biopsy was positive for IgG4 ($n$ = 3, 30% versus $n$ = 1, 6%; Deschamps et al. 2013). Moreover, in prior series of IgG4-RD patients atopic Th2-driven disease features (including bronchial asthma, rhinitis and/or peripheral blood eosinophilia) have been reported in up to 40% of the cases (Masaki et al. 2009; Stone et al. 2012b; Martínez-Valle et al. 2017). Most of these patients originated from Asia or North America and had primarily orbital disease (Masaki et al. 2009; Kubota & Moritani 2012), just as our patients did. Taken together, these findings should prompt physicians to search for IgG4-RD in patients with IOIS and a history or symptoms of allergy.

Our work has some limitations. Since guidelines regarding when to perform tissue biopsies were lacking at the time of diagnosis (Mombaerts et al. 2017) and that a substantial (approximately 40%) proportion of patients from the SIOI cohort did not undergo tissue biopsies, this might have

**Table 4.** Systemic features and IgG4-RD status of patients with biopsy-proven IOIS

| | Orbital IgG4 immunostaining | | |
|---|---|---|---|
| | IgG4 + n: 13 | IgG4−n: 21 | Totaln: 34 |
| **IgG4-related disease**[£], n | | | |
| Definite (including serum IgG4 ≥ 1.35 g/l) | 3*#**18**,***21***,**24** | 0* | 3* |
| Probable | 8*#1,2,15,16,17,20,22,*23* | 0* | 9* |
| **IgG4-related disease**[$], n | | | |
| ≥100 cells/hpf | 2#**18**,***21***,22 | 0 | 2 |
| **Systemic features**, n | | | |
| Combined features listed below | 2 | 3#29(13 IU/ml) | 5 |
| Pulmonary nodules + pANCA anti-PR3 (≥10 IU/ml) | 0 | | 1 |
| Sinusitis + pulmonary nodules | 0 | #6,*8* | 2 |
| Asthma + eosinophilia > 10% | #**18** | 0 | 1 |
| Reccurent sinusitis + pulmonary nodules + eosinophilia > 10% | #**24** | 0 | 1 |
| Isolated features listed below | 5 | 4** | 9** |
| Sinusitis | #3,16,***19***,20,***21*** | #27 | 6 |
| Pulmonary nodules | 0 | #4,10 | 2 |
| pANCA anti-MPO (≥10 IU/ml) | 0 | #*11*(54 IU/ml) | 1 |
| Other manifestations | 0 | 0 | 0 |

[£] IgG4-RD was considered as definite when patients fulfilled all Umehara's criteria (in bold).
[$] Histopathological features were considered highly suggestive of IgG4-RD when IgG4-positive plasma cell infiltration reached the cutoff of 100 cells per high-power field (/hpf) from the consensus statement on the pathology of IgG4-RD.
* IgG4 serum unavailable at inclusion for IgG4-positive patients #3 and 19, IgG4-negative patients #13 and 30.
** ANCA serology unavailable at diagnosis for IgG4-negative patient #8.
Patients who received immunosuppressive treatment within the last 6 months before inclusion are shown in italics.
ANCA = Antineutrophil cytoplasmic antibodies; MPO = Myeloperoxidase; PR3 = Proteinase-3.

led to a selection bias. Next, a single IgG4-positive patient with a normal IgG4 serum level was still under treatment with glucocorticoids at the time of blood collection, possibly leading to a slightly underestimation of the prevalence of definite IgG4-RD (23%). Yet, all of the remaining patients were weaned of corticosteroids a long time before inclusion (50.5 ± 42.5 months, range 6–96). Noteworthy, the rate of definite IgG4-RD herein was equivalent to that of patients with 100 IgG4-positive plasma cells/hpf (23%), a highly suggestive threshold of IgG4-RD according to international pathological criteria (Deshpande et al. 2012).

In conclusion, in a large multicentric prospective cohort of biopsy-proven patients with IOIS, our data suggest that more than one-third of patients with IOIS meet pathologic criteria for IgG4-RD. Yet, patients with definite IgG4-RD are scarce and most of them had recurrent sinusitis, asthma or eosinophilia, suggesting a potential link between IgG4-ROD and Th2-mediated allergic manifestations. During the ongoing prospective phase of the study, we aim to determine whether patients with IgG4-ROD, and especially those with definite IgG4-ROD, further develop manifestations of other Th2-mediated diseases.

# References


Andrew N, Kearney D & Selva D (2013): IgG4-related orbital disease: a meta- analysis and review. Acta Ophthalmol **91**: 694–700.

Andrew NH, Sladden N, Kearney DJ & Selva D (2015): An analysis of IgG4-related disease (IgG4-RD) among idiopathic orbital inflammations and benign lymphoid hyperplasias using two consensus-based diagnostic criteria for IgG4- RD. Br J Ophthalmol **99**: 376–381.

Aucouturier P, Danon F, Daveau M, Guillou B, Sabbah A, Besson J & Preud'homme JL (1984): Measurement of serum IgG4 levels by a competitive immunoenzymatic assay with monoclonal antibodies. J Immunol Methods **74**: 151–162.

Aucouturier P, Mounir S & Preud'homme JL (1985): Distribution of IgG subclass levels in normal adult sera as determined by a competitive enzyme immunoassay using monoclonal antibodies. Diagn Immunol **3**: 191–196.

Cavallazzi R, Hirani A, Vasu TS, Sergott RC, Bilyk JR, Eagle RC & Weibel S (2009): Clinical manifestations and treatment of adult-onset asthma and periocular xanthogranuloma. Can Respir J J Can Thorac Soc **16**: 159–162.

Deschamps R, Deschamps L, Depaz R et al. (2013): High prevalence of IgG4-related lymphoplasmacytic infiltrative disorder in 25 patients with orbital inflammation: a retrospective case series. Br J Ophthalmol **97**: 999–1004.

Deshpande V, Zen Y, Chan JK et al. (2012): Consensus statement on the pathology of IgG4-related disease. Mod Pathol **25**: 1181–1192.

Jacobs D & Galetta S (2002): Diagnosis and management of orbital pseudotumor. Curr Opinion Ophthalmol **13**: 347–351.

Kamisawa T, Zen Y, Pillai S & Stone JH (2015): IgG4-related disease. Lancet **385**: 1460–1471.

Karim F, de Hoog J, Paridaens D, Verdijk R, Schreurs M, Rothova A, van Hagen M & van Laar J (2017): IgG4-related disease as an emerging cause of scleritis. Acta Ophthalmol **95**: e795–e796.

Kubota T & Moritani S (2012): Orbital IgG4-RD: clinical features and diagnosis. ISRN Rheumatol **2012**: 412896.

London J, Martin A, Soussan M et al. (2015): Adult onset asthma and periocular xanthogranuloma (AAPOX), a rare entity with a strong link to IgG4-related disease: an observational case report study. Medicine (Baltimore) **94**: e1916.

Martínez-Valle F, Fernández-Codina A, Pinal-Fernández I, Orozco-Gálvez O & Vilardell-Tarrés M (2017): IgG4-related disease: evidence from six recent cohorts. Autoimmun Rev **16**: 168–172.

Masaki Y, Dong L, Kurose N et al. (2009): Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. Ann Rheum Dis **68**: 1310–1315.

McKelvie P, McNab AA, Hardy T & Rathi V (2017): Comparative study of clinical, pathological, radiological, and genetic features of patients with adult ocular adnexal xanthogranulomatous disease, erdheim-

chester disease, and IgG4- related disease of the orbit/ocular adnexa. Ophthal Plast Reconstr Surg **33**: 112–119.

Mombaerts I, Goldschmeding R, Schlingemann RO & Koornneef L (1996): What is orbital pseudotumor? Surv Ophthalmol **41**: 66–78.

Mombaerts I, Rose GE & Garrity JA (2016): Orbital inflammation: biopsy first. Survey Ophthalmol **61**: 664–669.

Mombaerts I, Bilyk JR, Rose GE et al. (2017): Consensus on diagnostic criteria of idiopathic orbital inflammation using a modified delphi approach. JAMA Ophthalmol **135**: 769–776.

Plaza JA, Garrity JA, Dogan A, Ananthamurthy A, Witzig TE & Salomão DR (2011): Orbital inflammation with IgG4-positive plasma cells: manifestation of IgG4 systemic disease. Arch Ophthalmol **129**: 421–428.

Sa HS, Lee JH, Woo KI & Kim YD (2015): IgG4-related disease in idiopathic sclerosing orbital inflammation. Br J Ophthalmol **99**: 1493–1497.

Stone JH, Khosroshahi A, Deshpande V et al. (2012a): Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. Arthritis Rheum **64**: 3061–3067.

Stone JH, Zen Y & Deshpande V (2012b): IgG4-related disease. N Engl J Med **366**: 539–551.

Swamy BN, McCluskey P, Nemet A, Crouch R, Martin P, Benguer R, Ghabriel R & Wakefield D (2007): Idiopathic orbital inflammatory syndrome: clinical features and treatment outcomes. Br J Ophthalmol **91**: 1667–1670.

Takano K, Yajima R, Seki N, Abe A, Yamamoto M, Takahashi H & Himi T (2014): A study of infraorbital nerve swelling associated with immunoglobulin G4 Mikulicz's disease. Mod Rheumatol/Jpn Rheum Assoc **24**: 798–801.

Umehara H, Okazaki K, Masaki Y et al. (2012): Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol **22**: 21–30.

Verdijk RM, Heidari P, Verschooten R, van Daele PL, Simonsz HJ & Paridaens D (2014): Raised numbers of IgG4-positive plasma cells are a common histopathological finding in orbital xanthogranulomatous disease. Orbit Amst Neth **33**: 17–22.

Wallace ZS, Deshpande V & Stone JH (2014): Ophthalmic manifestations of IgG4- related disease: single-center experience and literature review. Semin Arthritis Rheum **43**: 806–817.

Wu A, Andrew NH, McNab AA & Selva D (2015): IgG4-related ophthalmic disease: pooling of published cases and literature review. Curr Allergy Asthma Rep **15**: 27.

Yuen SJ & Rubin PA (2003): Idiopathic orbital inflammation: distribution, clinical features, and treatment outcome. Arch Ophthalmol **121**: 491–499.

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# Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

**Table S1.** Histological findings and immunostaining in patients with biopsy-proven IOIS.

**Table S2.** Serological findings in patients with biopsy-proven IOIS at inclusion.