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Lifetime Allergy Symptoms in IgG4-Related Disease: A Case-Control Study

Samantha Sanders, MD, MBA[1], **Xiaoqing Fu, MS**[2,3], **Yuqing Zhang, DSc**[1,2,3,4,5], **Cory A. Perugino, DO**[1,3,5], **Rachel Wallwork, MD**[3,5], **Emanuel Della-Torre, MD, PhD**[6], **Liam Harvey, BS**[3], **Tyler Harkness, BS**[2,3,4], **Aidan Long, MD**[1,3,5], **Hyon K. Choi, MD, DrPH**[1,2,3,4,5], **John H. Stone, MD, MPH**[1,3,5], **Zachary S. Wallace, MD, MSc**[1,2,3,4,5]

[1]Harvard Medical School, Massachusetts General Hospital in Boston, MA

[2]Clinical Epidemiology Program, Massachusetts General Hospital in Boston, MA

[3]Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital in Boston, MA

[4]Mongan Institute, Massachusetts General Hospital in Boston, MA

[5]Department of Medicine, Massachusetts General Hospital in Boston, MA

[6]Unit of Immunology, Rheumatology, Allergy, and Rare Diseases, IRCCS-San Raffaele Scientific Institute, Milan, Italy.

Abstract

Objective: The etiology of IgG4-related disease (IgG4-RD) is unknown and there has been controversy over the significance of allergic conditions in IgG4-RD. We examined the prevalence of lifetime allergy symptoms in IgG4-RD and the association between these and IgG4-RD.

Methods: We identified IgG4-RD patients and non-IgG4-RD controls without autoimmune conditions seen at a single center. IgG4-RD patients were classified using the ACR/EULAR classification criteria. Allergy symptoms were ascertained by questionnaire. We assessed the association of IgG4-RD features with allergy symptoms. We compared the proportion of cases and controls with allergy symptoms using conditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) after matching cases and controls 1:1 by age and sex.

Results: Lifetime allergy symptoms were reported by 165 (71%) of 231 IgG4-RD cases. Aero-allergen symptoms were most commonly reported (135, 58%) followed by skin allergy symptoms (97, 42%) and food allergy symptoms (47, 20%). IgG4-RD cases with a history of allergy symptoms were more likely to have head and neck involvement (OR 2.0 [95% CI: 1.1–3.6]) and peripheral eosinophilia (OR 3.3 [95% CI: 1.2–9.0]) than those without allergy symptoms. The prevalence of any allergy symptoms was similar between cases and controls (OR 0.7 [95% CI: 0.4–1.1]); this remained consistent after stratifying by head and neck involvement.

Corresponding Author: Zachary S. Wallace, MD, MSc, Clinical Epidemiology Program, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, 100 Cambridge Street, 16th Floor, Boston, MA 02114, Phone: 617-724-2507, Fax: 617-643-1274, zswallace@mgh.harvard.edu, @zach_wallace_md.

Conclusion: Lifetime allergy symptoms are common in IgG4-RD but are not reported more often in IgG4-RD compared to non-IgG4-RD patients without autoimmune conditions. These findings suggest that allergies are not uniquely associated with the pathogenesis or presentation of IgG4-RD.

INTRODUCTION

IgG4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory condition characterized by tumorous lesions, often with an elevated serum IgG4 concentration (1, 2). The etiology remains poorly understood and there has been controversy over the significance of allergic conditions and T-helper type 2 (Th2) cells in the pathogenesis and presentation (3).

Th2 cells and allergies were hypothesized to be important in the pathogenesis and presentation of IgG4-RD following several clinicopathologic observations. First, allergic symptoms, especially allergic rhinitis, have been reported to be common in IgG4-RD, especially among those with manifestations in the head and neck (e.g., sialoadenitis, dacryoadenitis, and orbital disease) (2, 4). Second, elevated peripheral IgE concentrations, peripheral eosinophilia, and tissue infiltrating eosinophils are often observed in IgG4-RD patients, as they are in many patients with allergic conditions (4, 5). Third, cytokines typically associated with Th2 cells have been reported to be present at high concentrations in tissues affected by IgG4-RD (6–8).

Despite these observations, however, mounting evidence suggests that Th2 cells are unlikely to play a pathogenic role IgG4-RD (3). Indeed, a previous study found that circulating Th2 memory cells appear to be restricted to a subset of patients with atopy (9, 10). The same Th2-associated cytokines previously used to infer Th2 cell tissue infiltration, such as IL-4, are also produced by a specific subset of follicular helper T cells, which have been shown to accumulate in tissues affected by IgG4-RD (11). Moreover, upon rigorous quantification of CD4+ T cells infiltrating tissue, Th2 cells were found to account for only 5–10% of all CD4+ T cells on average, including salivary gland tissues and tissues from patients with IgG4-RD and concurrent atopy (12). Although the pathogenic role of Th2 cells in IgG4-RD has been called into question, there remains a lack of clarity regarding the burden and potential significance of allergic symptoms in IgG4-RD patients.

Previous studies of allergy symptoms in IgG4-RD have been limited to Asian populations, did not rely on standardized assessments of allergy symptoms, and/or did not include a reference population for comparison (2, 4, 13, 14, 15, 16, 17). Here, we sought to overcome these limitations by examining the characteristics and distributions of lifetime allergy symptoms in a US-based IgG4-RD cohort with diverse manifestations using a standardized allergy questionnaire and by measuring the association between allergy symptoms and the odds of having IgG4-RD using a case-control design.

PATIENTS AND METHODS

IgG4-RD cohort:

The Massachusetts General Hospital (MGH) Center for IgG4-RD, a part of the Rheumatology Unit, maintains a database of all patients referred for evaluation in the center. The inclusion of patients with IgG4-RD was based on the classification criteria approved by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) (18). We included patients who fell into one of three categories: (1) Definite IgG4-RD, (2) Probable IgG4-RD, and (3) Atypical IgG4-RD. Patients in the definite category fulfilled the published classification criteria. Patients who were considered probable fulfilled two parts of the ACR/EULAR Classification Criteria (i.e., had clinical involvement of a typical organ and were rigorously evaluated to ensure that they did not meet any exclusion criteria) but did not reach the threshold of 20 inclusion points according to the criteria (frequently retroperitoneal fibrosis in a typical pattern because no biopsy could be safely obtained or the biopsy was not informative). Of the 34 patients with probable IgG4-RD, 31 had ACR/EULAR Classification Criteria scores ≥ 8, which correspond to a specificity of ≥ 85% for IgG4-RD. The remaining three patients with probable IgG4-RD had typical pachymeningeal (2 patients) and bile duct (1 patient) involvement. Patients who were considered atypical met the previously established pathological and immunostaining criteria for diagnosing IgG4-RD but presented with involvement of an atypical organ (e.g., breast, prostate) that was not considered in the ACR/EULAR Classification Criteria (19).

We included all IgG4-RD patients who were seen between January 19, 2012 and September 12, 2019 and completed an allergy questionnaire. Some of the clinical and laboratory features of cases included in this study have been reported previously (9, 20–24). However, this cohort's allergic histories have not been investigated using a standard questionnaire and compared to a reference population before, and the analyses pertaining to allergy symptoms reported herein are novel.

Data pertaining to demographics and IgG4-RD manifestations were collected from the Center's database. Laboratory results were extracted from the electronic health record. Age at IgG4-RD onset (index date) refers to the age at which the patient first developed symptoms ultimately attributed to IgG4-RD or the time at which the disease was first diagnosed (whichever was earlier) (20).

Control subjects:

We identified controls from a sample of patients without IgG4-RD seen in the Massachusetts General Hospital rheumatology clinic between June 1, 2016 and March 30, 2020. We chose to include patients without autoimmune diseases as controls because some autoimmune rheumatic diseases, including eosinophilic granulomatosis with polyangiitis and rheumatoid arthritis, may be associated with a history of allergy symptoms (25). Accordingly, we limited our control group to patients seen in our clinic because of non-inflammatory joint disease (e.g., osteoarthritis), crystalline arthritis, fibromyalgia, or osteopenia/osteoporosis. One control was matched to each case by sex and the age (± 5 years) at which the controls completed the survey relative to the age of cases at the index date. Between June 1, 2016

and July 31, 2018, potential controls were invited to participate at the time of a routine clinic visit. Beginning August 1, 2018, potential controls were invited to participate electronically. The change in recruitment from an in-person to electronic methodology was made after our study group established electronic recruitment as a viable option to facilitate recruitment and limit the in-person resources needed for recruitment. To recruit electronically, we identified eligible patients who had been seen in clinic, obtained permission from their provider, and invited those for whom we had permission by a standardized method through our electronic patient messaging system. The proportion of patients with allergies was similar among cases recruited via in-person vs electronic methods suggesting that this change did not impact our results.

Allergy ascertainment:

We administered an allergy questionnaire to all patients following an initial visit and asked 34 questions about a lifetime history of allergy symptoms, including history of aero-allergen symptoms (e.g., hay fever-type allergy symptoms), food allergy symptoms, skin allergy symptoms (atopic dermatitis, skin reactions, and urticaria), and anaphylaxis (Supplemental Material). This questionnaire had similar questions to those administered in the 2005–2006 National Health and Nutrition Examination Survey (26).

Statistical analysis:

Categorical variables are reported as N (%). Continuous variables are reported as mean (± standard deviation [SD]) or median (interquartile range [IQR]) depending on their distribution. First, we examined the distribution of allergy symptoms among IgG4-RD patients. Among IgG4-RD patients, we assessed the association between reported allergy symptoms and select IgG4-RD features and manifestations using unadjusted and age- and/or sex-adjusted logistic regression. Second, we assessed for the association between allergy symptoms and the odds of having IgG4-RD. For these analyses, we used conditional logistic regression to first evaluate the association between any allergy symptom and the odds of having IgG4-RD. We then used conditional logistic regression to evaluate the independent association between each type of allergy symptom and the odds of having IgG4-RD. Associations were reported using odds ratios (OR) and 95% confidence intervals (CI). We evaluated the association between allergy symptoms and IgG4-RD overall and after stratifying according to whether or not cases had head and neck involvement given previous reports of an association between head and neck manifestations and allergy symptoms among patients with IgG4-RD (2, 4). In a sensitivity analyses, we evaluated whether our findings persisted when we restricted the definition of allergies to those reported to be diagnosed by a physician. For all analyses, two-sided P-values < 0.05 were considered significant.

IRB Approval:

This study was approved by the Partners HealthCare Institutional Review Board prior to the enrollment of any patients.

RESULTS

IgG4-RD Cohort Description:

There were 231 patients in the IgG4-RD cohort on the date of data accession (Table 1). The mean age was 60 (±14) years and the majority were male (150, 65%) and white (173, 75%). Of the 231 patients, 179 (78%) had definite IgG4-RD, 34 (15%) had probable IgG4-RD, and 18 (8%) had IgG4-RD with atypical organ involvement. The most common IgG4-RD manifestations included the head or neck (137, 59%), particularly sialoadenitis and/or dacryoadenitis (113, 49%). A minority (11 [5%]) of patients with head and neck involvement had IgG4-RD involvement of the nasal cavities or sinuses. Other commonly affected organs included the pancreato-hepatobiliary system (78, 34%), lymph nodes (63, 27%), and kidneys (47, 20%). The serum IgG4 concentration was elevated at any point in a patient's available medical history in 168 (73%) patients.

Features of IgG4-RD Patients According to Allergy Symptoms:

Lifetime allergy symptoms were reported by 165 (71%) IgG4-RD patients, the details of which are reported in Table 2. The proportion of patients reporting allergy symptoms was similar across those with definite (73%), probable (66%), and atypical (83%) IgG4-RD. Of the lifetime allergy symptoms reported, aero-allergen symptoms were most common (135, 58%) followed by skin allergy symptoms (97, 42%) and food allergy symptoms (47, 20%). A history of anaphylaxis was reported in 20 (9%) subjects. Aero-allergen symptoms, food allergies, and skin allergies predated the onset of IgG4-RD in 99%, 94%, and 98% of patients, respectively, typically by many years (Supplementary Table 1). The majority of IgG4-RD patients (61%) with a history of allergy reported no change in their allergy symptoms following a diagnosis of IgG4-RD (Table 2). Only six patients reported increasing their use of antihistamines since being diagnosed with IgG4-RD.

Among patients with IgG4-RD, there were associations (Table 3) between those with allergy symptoms having head and neck involvement (aOR: 2.02 [95% CI: 1.12–3.62]) and having peripheral eosinophilia (aOR: 3.27 [95% CI: 1.19–9.02]), compared to those without head and neck involvement and without peripheral eosinophilia, respectively. The association between head and neck disease with allergy symptoms was strongly driven by the subgroup of patients with sialoadenitis and/or dacryoadenitis (aOR: 1.92 [95% CI: 1.06–3.48]) when compared to those without these manifestations. The association between allergy symptoms and head and neck involvement by IgG4-RD persisted when we specifically examined the association between aero-allergen symptoms and these manifestations (aOR: 2.24 [95% CI: 1.30–3.86]) compared to those without head and neck involvement. We did not observe associations between allergy symptoms and having elevated IgG4 or IgE concentrations, having elevated inflammatory markers, or being hypocomplementemic. When we stratified patients with IgG4-RD according to prior glucocorticoid exposure, there was no difference in the proportion reporting a history of any allergy among those who had used glucocorticoids versus those who had not (72% vs 69%, P=0.7).

Case-control analysis:

Of 788 potential controls invited to complete the allergy questionnaire, 208 (26%) completed the questionnaire. We matched 201 IgG4-RD cases to 201 controls with rheumatic diseases that are not associated with autoimmunity (Table 4). The cases and controls were well-matched with regard to age (mean 60.2 [±12.5] vs. 60.7 [±13.3] years, respectively) and sex (121 [60%] vs. 121 [60%] male, respectively). The control population included patients with gout/pseudogout (67, 33%), osteoarthritis (65, 32%), fibromyalgia (20, 10%), other mechanical/degenerative disease (19, 9%), osteoporosis/osteopenia (12, 6%), and other conditions (18, 9%).

A similar proportion of cases and controls (Table 5, Supplementary Table 2) reported any lifetime allergy symptoms. Any allergies were reported by 142 (71%) cases vs 158 (79%) controls (OR 0.7 [95% CI: 0.4–1.1]). The prevalence of aero-allergen symptoms (OR 0.7 [95% CI: 0.5–1.1]) and skin allergy symptoms (OR 1.0 [95% CI: 0.6–1.5]) was similar in cases and controls. These observations remained consistent after stratifying cases according to the presence or absence of head and neck manifestations of IgG4-RD. Our findings remained unchanged after matching cases and controls on race (data not shown) and when restricting the definition of allergy symptoms (Supplementary Table 3) as those reported to have been diagnosed by a physician.

Significantly fewer cases than controls reported food allergy symptoms (39 [19%] of cases vs 68 [34%] of controls; OR 0.5 [95% CI: 0.3–0.9]), although this association was significantly attenuated after stratifying cases according to head and neck IgG4-RD involvement and did not persist when restricting the definition of food allergy to those diagnosed by a physician (26 [13%] of cases vs 23 [11%] of controls; OR 1.1 [95% CI: 0.6–2.1]).

DISCUSSION

In this case-control study, the first of its kind in IgG4-RD, we found that lifetime allergy symptoms are common in IgG4-RD. The development of allergies did not seem to be temporally related to the presence of IgG4-RD, as allergic symptoms were typically present for many years prior to the development of IgG4-RD. Among patients with IgG4-RD, those with allergy symptoms, especially aero-allergen symptoms, were more likely to have sialoadenitis and/or dacryoadenitis than those without allergy symptoms. While the prevalence of allergy symptoms in IgG4-RD patients was high, allergy symptoms were reported by IgG4-RD patients at a similar frequency to non-IgG4-RD controls, even among those with head and neck involvement by IgG4-RD. Our epidemiologic observations of allergy symptoms in IgG4-RD and controls complement those made in previous laboratory-based studies suggesting that allergic, Th2 mediated responses are unlikely to be pathogenic drivers of IgG4-RD or unique features of IgG4-RD presentations (3).

There is limited data on the lifetime prevalence of allergy symptoms in the general population, in part because symptoms may be managed by patients using over the counter medications without a physician diagnosis or prescription. In our study, the prevalence of lifetime allergy symptoms reported by both cases and controls are similar to a prevalence of

58% reported in a recent study (25). Compared to that study, we found a higher proportion of patients reporting any history of allergy but these differences may have to do with differences in geography distribution of survey respondents, demographic differences of participants, and survey design.

Our study overcomes many limitations of prior studies that have evaluated allergy symptoms in IgG4-RD. These studies enrolled only Asian patients, did not systematically evaluate allergy symptoms, and/or did not use a reference population to compare the frequencies in IgG4-RD versus a control population (2, 4, 13, 14, 15, 16, 17). Our findings confirmed previous observations that allergy symptoms are commonly reported in IgG4-RD with previous studies reporting prevalence rates for aero-allergen symptoms between 25% and 63% (2, 4, 13, 14, 27, 15, 16, 17). We also found that allergy symptoms are more frequently reported in patients with head and neck involvement, particularly dacryoadenitis and/or sialoadenitis (2, 14, 16). To our knowledge, our study is the first to report an association between self-reported allergy symptoms and peripheral eosinophilia in IgG4-RD which may be related to our more rigorous study design, including standardized assessments of allergy symptoms and a larger sample size than some prior studies (2, 28). While this observation is not necessarily surprising, it raises the question of whether IgG4-RD patients with allergy symptoms are more likely to relapse given previous studies describing an association between peripheral eosinophilia and higher risk of IgG4-RD relapse (23, 28), as well as a previous study demonstrating an association between allergy symptoms and a higher risk of relapse (15).

The difference in organ involvement among those with and without allergy symptoms might suggest etiologic heterogeneity among patients with IgG4-RD such that the onset in some patients is related to immune system dysfunction that is also contributing to allergy symptoms (31). There are several possible explanations as to why IgG4-RD patients with head and neck manifestations more often had self-reported allergy symptoms. First, it is possible that patients with head and neck disease are more likely to report allergy symptoms due to recall bias given that allergies often affect the head and neck. However, this is less likely to explain our findings given that allergy symptoms (e.g., itchy eyes, rhinitis) are likely distinguishable from IgG4-RD symptoms in the head and neck (e.g., proptosis, sialoadenitis) and few patients had IgG4-RD affecting the sino-nasal cavities. Second, allergen exposure could lead to a generalized activation of the immune system in the head and neck, manifesting in predisposed individuals as IgG4-RD involving the head and neck. If this were the case, we would expect those with head and neck disease to be more likely to have allergy symptoms than control patients but our ability to detect this may have been obscured by a smaller sample size. Future studies might further investigate the association between allergy symptoms and IgG4-RD manifestations in the head and neck, which has now been replicated across cohorts of diverse ethnic makeups, by confirming allergic diagnoses, evaluating specific allergens, considering the role of local mucosal immunity and the oral microbiome, and comparing the eosinophilic infiltrate across organs (2, 14). Although a mild to moderate eosinophil infiltrate is frequently commented on in association with IgG4-RD, this component of the immune response has not been well investigated, especially in the head and neck (19).

In our study, we found that food allergy symptoms were more commonly reported to have ever occurred in controls than in IgG4-RD. However, this trend did not persist when we restricted our analysis to allergies reported to have been diagnosed by a physician. A potential negative association between these allergy sub-types and IgG4-RD would be somewhat surprising given our understanding of the pathogenesis of IgG4-RD. Accordingly, these observations should be interpreted cautiously but confirm our hypothesis that specific allergy symptoms are not more commonly reported by patients with IgG4-RD. Further research is needed to investigate why these allergy types may be less frequently reported by IgG4-RD patients.

Our study has several strengths which include its sample size, use of a standardized questionnaire, and case-control design. Moreover, this is among the first studies to apply the recently defined ACR/EULAR Classification Criteria in an epidemiologic study. While classification criteria are not meant for diagnostic purposes, they can have an important role in observational studies such as this one for identifying patients for inclusion. Our identification of three groups (definite, probable, and atypical) using the entry, exclusion, and inclusion criteria of the ACR/EULAR Classification Criteria may be of use for future observational studies in IgG4-RD and reflects the realities of clinical practice where some patients will not fulfill definite criteria because of the organ distribution (e.g., breast, pancreas, retroperitoneum) but are accepted to have IgG4-RD based on histopathology and/or clinical assessment by expert providers.

Our study has certain limitations. First, as with any survey study, recall bias is possible. In this instance, patients may have been more likely to recall allergy symptoms given that they were asked to complete the survey in the context of medical care. Additionally, patients may have been more likely to recall certain allergy symptoms (e.g., aero-allergen symptoms) if they were administered the survey during allergy season for aero-allergens. However, both IgG4-RD patients and controls were asked to complete the survey under similar circumstances and our survey asked about lifetime allergy symptoms. Therefore, any recall bias would be expected to be similar between cases and controls. Second, allergy symptoms were based on patient-reported symptoms and medical history. However, similar methods have been used to estimate the burden of allergic conditions in the US population through national health surveys (26). Future studies might define allergic conditions more stringently using an evaluation by an allergist with or without formal allergy testing. Third, our study did not account for the severity of the allergy disease in cases and controls, which future studies could measure. Fourth, it is possible that sinus or nasal cavity IgG4-RD involvement may have been reported as allergies; nonetheless, this most likely did not affect our outcomes given the qualitatively different nature of allergy symptoms and IgG4-RD manifestations and the low proportion of patients with sinus or nasal cavity involvement (5%). Fifth, subgroup analyses (e.g., by manifestations, laboratory results) were limited by smaller sample sizes and we cannot rule out the possibility that associations might exist if studied in larger IgG4-RD cohorts. Sixth, our control recruitment methodology switched from in-person to electronic recruitment during the study period. However, the proportion of controls reporting allergy symptoms was similar regardless of the recruitment method suggesting that this did not impact our findings. Finally, our study was performed at a tertiary referral center and in a cohort composed of patients who self-identified as White.

Therefore, the generalizability of our findings may be limited but we note the wide range of manifestations represented in our cohort as well as its size despite the rarity of this condition.

In conclusion, lifetime allergy symptoms are frequently reported in IgG4-RD, especially among those with head and neck involvement, but not at a higher rate than in controls without autoimmune conditions. We found a similar or lower prevalence of lifetime allergy symptoms among IgG4-RD patients when compared with age- and sex-matched controls without autoimmune conditions; these observations persisted after stratifying cases by head and neck disease involvement. This supports the hypothesis that allergies are unlikely to play a unique role in the pathogenesis or presentation of IgG4-RD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE AND INNOVATIONS

- Lifetime allergy symptoms are common in IgG4-related disease, particularly among patients with head and/or neck involvement
- In contrast to hypothesized associations, allergy symptoms are not reported more frequently in patients with IgG4-related disease than in patients without IgG4-RD or other autoimmune diseases, regardless of whether they have head and neck involvement or not
- These observations suggest that allergies are unlikely to play a unique role in the pathogenesis or presentation of IgG4-RD.

Table 1:

Demographics and Features of the IgG4-Related Disease Cohort

	Overall
N	231
Age at Diagnosis (mean, SD)	59.5 (13.7)
Male (N, %)	150 (65%)
Race	
White	173 (75%)
Asian	32 (14%)
Black	10 (4%)
Native-American	1 (<1%)
Unknown / Other	15 (6%)
Ethnicity	
Non-Hispanic	185 (80%)
Hispanic	29 (13%)
Unknown / Other	17 (7%)
Selected Organ Involvement	
Head and Neck	137 (59%)
Dacryo- or Sialoadenitis	113 (49%)
Lacrimal glands	50 (22%)
Salivary glands	98 (42%)
Orbital (non-lacrimal)	34 (15%)
Other head and neck	109 (47%)
Lymph nodes	63 (27%)
Pulmonary	44 (19%)
Aorta	21 (9%)
Retroperitoneum	41 (18%)
Pancreato-hepatobiliary	78 (34%)
Renal	47 (20%)
Laboratory Results (median, IQR)	
IgG4 Concentration (n=228)	142.4 (53.2, 390.8)
% Ever Elevated[^]	168 (73%)
Eosinophil Concentration (n=193)	0.20 (0.10, 0.40)
% Elevated[^]	40 (21%)
IgE Concentration (n=192)	104.0 (25.0, 284.5)
% Elevated[^]	98 (51%)
Erythrocyte Sedimentation Rate (n=159)	24.0 (10.0, 45.0)
% Elevated[^]	66 (42%)
C-Reactive Protein (n=161)	3.8 (1.3, 9.1)
% Elevated[^]	53 (33%)
C3 (n=191)	115.0 (85.0, 145.0)

	Overall
% Low C3	23 (12%)
C4 (n=193)	23.0 (12.0, 31.0)
% Low C4	32 (17%)

^ Elevated refers to serum IgG4 concentration > the assay's upper limit of normal, serum IgE concentration ≥ 100 IU/mL, eosinophils ≥ 0.5 10^9/L, ESR > 30 mm/hr, and CRP > 7 mg/L

Table 2:

Characteristics of Lifetime Allergy Symptoms in IgG4-Related Disease

Features of Allergy Symptoms	Frequency
Any Allergy Symptoms (N, %)	165 (71%)
Aero-Allergen Symptoms	
History of Aero-Allergen Symptoms	135 (58%)
Self-reported allergy symptoms	129 (56%)
Occurred in the last 12 months[†]	86 (41%)
Physician-diagnosed allergies	87 (38%)
Self-reported and physician-diagnosed allergies	81 (35%)
Underwent Aero-Allergen Sensitization Testing	101 (44%)
Reported Allergen	
Seasonal allergens (e.g., grass, pollen)	32 (14%)
Pet dander (e.g., cats, dogs)	18 (8%)
Mold	10 (4%)
Dust mites	17 (7%)
Other	28 (12%)
Food Allergy Symptoms and Hypersensitivities (N, %)	
History of Food Allergy Symptoms/Hypersensitivities	47 (20%)
Self-reported allergy symptoms	43 (19%)
Physician-diagnosed allergies	32 (14%)
Self-reported and physician-diagnosed allergies	28 (12%)
Underwent Food Allergen Testing	36 (16%)
Reported Allergen/Hypersensitivity	
Dairy/lactose	1 (< 1%)
Nuts	3 (1%)
Shellfish	3 (1%)
Other	12 (5%)
Skin Allergy Symptoms (N, %)	
History of Skin Allergy Symptoms	97 (42%)
Self-reported contact dermatitis symptoms	47 (20%)
Self-reported eczema symptoms	39 (17%)
Any physician-diagnosed allergy	59 (26%)
Self-reported and physician-diagnosed allergies	32 (14%)
Attributed Causes of Contact Dermatitis[*]	
Latex	12 (5%)
Chemicals/perfumes	8 (3%)
Plants/trees	4 (2%)
Nickel/other metals	1 (< 1%)
Other	17 (7%)
Anaphylaxis (N, %)	20 (9%)
Allergy Symptoms Following IgG4-RD Onset (N, %)	

Features of Allergy Symptoms	Frequency
Improved	31 (19%)
No Change	101 (61%)
Worsened	16 (10%)
Other or Not Reported	17 (10%)

[*] % of self-reported contact dermatitis

[†] Data missing in 20 subjects

Table 3:

The Association of Select IgG4-Related Disease Manifestations with Any Allergy Symptoms

	Overall (N=231)	Any Allergy Symptoms (N=165)	No Allergy Symptoms (N=66)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)
Head/Neck Disease					
Yes	137	106 (64%)	31 (47%)	**2.03 (1.14–3.62)**	**2.02 (1.12–3.62)**
No	94	59 (36%)	35 (53%)	**Ref**	**Ref**
Dacryo- or Sialoadenitis					
Yes	113	88 (53%)	25 (38%)	**1.87 (1.05–3.36)**	**1.92 (1.06–3.48)**
No	118	77 (47%)	41 (62%)	**Ref**	**Ref**
IgG4 Concentration Elevated					
Yes	168	121 (73%)	47 (71%)	1.11 (0.59–2.10)	1.31 (0.67–2.54)
No	63	44 (27%)	19 (29%)	Ref	Ref
IgE Concentration Elevated					
Yes	96	76 (54%)	22 (43%)	1.54 (0.81–2.94)	1.58 (0.81–3.08)
No	94	65 (46%)	29 (57%)	Ref	Ref
Peripheral Eosinophilia					
Yes	40	35 (25%)	5 (10%)	**3.10 (1.14–8.42)**	**3.27 (1.19–9.02)**
No	153	106 (75%)	47 (90%)	**Ref**	**Ref**
ESR Elevated					
Yes	66	45 (39%)	21 (47%)	0.75 (0.37–1.49)	0.89 (0.42–1.87)
No	93	69 (61%)	24 (53%)	Ref	Ref
CRP Elevated					
Yes	53	37 (32%)	16 (34%)	0.89 (0.43–1.83)	0.90 (0.43–1.88)
No	108	78 (68%)	30 (65%)	Ref	Ref
C3 Hypocomplementemia					
Yes	23	17 (12%)	6 (12%)	0.97 (0.36–2.63)	1.01 (0.37–2.78)
No	168	125 (88%)	43 (88%)	Ref	Ref
C4 Hypocomplementemia					
Yes	32	21 (15%)	11 (22%)	0.63 (0.28–1.42)	0.67 (0.29–1.54)
No	161	121 (85%)	40 (78%)	Ref	Ref

*Age-and sex-adjusted

Table 4:

Demographic Features of IgG4-RD Cases and Matched Controls

	IgG4-Related Disease Cases	Age-and Sex-Matched Controls
N	201	201
Age (mean, SD)	60.2 (12.5)	60.7 (13.3)
Male (%)	121 (60)	121 (60)
Race(%)		
White	155 (77)	189 (94)
Asian	24 (12)	0 (0)
Black	9 (4)	6 (3)
Unknown / other	13 (7)	6 (3)

Table 5:

The Association Between Lifetime Allergy Symptoms and IgG4-RD

	IgG4-Related Disease Cases OR (95% CI)	Age-and Sex-Matched Controls
All Cases Included		
Model 1:		
Any Allergy Symptoms	0.67 (0.43, 1.05)	1.0 (Ref)
Model 2:*		
Aero-Allergen Symptoms	0.72 (0.46, 1.11)	1.0 (Ref)
Food Allergy Symptoms	0.52 (0.30, 0.88)	1.0 (Ref)
Skin Allergy Symptoms	0.96 (0.63, 1.48)	1.0 (Ref)
Head and Neck Cases		
Model 1:		
Any Allergy Symptoms	0.72 (0.39, 1.32)	1.0 (Ref)
Model 2:*		
Aero-Allergen Symptoms	0.90 (0.49, 1.65)	1.0 (Ref)
Food Allergy Symptoms	0.63 (0.34, 1.17)	1.0 (Ref)
Skin Allergy Symptoms	0.97 (0.53, 1.78)	1.0 (Ref)
Non-Head/Neck Cases		
Model 1:		
Any Allergy Symptoms	0.63 (0.33, 1.19)	1.0 (Ref)
Model 2:*		
Aero-Allergen Symptoms	0.57 (0.28, 1.13)	1.0 (Ref)
Food Allergy Symptoms	0.81 (0.33, 1.98)	1.0 (Ref)
Skin Allergy Symptoms	0.93 (0.45, 1.93)	1.0 (Ref)

*In Model 2, each allergy symptom was included in the model to evaluate the independent association between each symptom and the odds of having IgG4-RD.