Self-Reported Allergies in IgG4-Related Disease: A Case-Control Study

Self-Reported Allergies in IgG4-Related Disease: A Case-Control Study

by

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Submitted in Partial Fulfillment of the Requirements for the M.D. Degree with Honors in a Special Field at Harvard Medical School

February 10, 2020

Abstract

Objective: IgG4-related disease (IgG4-RD) is an immune-mediated condition of unknown etiology. There has been controversy over the significance of allergic conditions in IgG4-RD. We examined the prevalence of allergy symptoms in IgG4-RD and the association between allergy symptoms and IgG4-RD in a case-control study.

Methods: We identified IgG4-RD patients and non-IgG4-RD controls 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 (e.g., age of onset, organ involvement) with self-reported allergy symptoms. We compared the proportion of cases and controls with allergic symptoms using conditional logistic regression to estimate odds ratios and 95% confidence intervals after matching cases and controls 1:1 by age and sex.

Results: Allergic symptoms were reported by 165 (71%) of 231 IgG4-RD cases who completed the questionnaire. Compared to those without allergies, IgG4-RD cases with allergies were more likely to have head and neck involvement (adjusted odds ratio 2.0 [95% CI: 1.1-3.6]) and more likely to have peripheral eosinophilia (adjusted odds ratio 3.3 [95% CI: 1.2-9.0]). The prevalence of allergic symptoms among IgG4-RD cases was not different from that of the controls with other rheumatic conditions (110 [72%] vs. 114 [75%], OR 0.9 [95% CI: 0.5-1.5]).

Discussion: Allergic symptoms are common in IgG4-RD but are reported with a similar frequency by patients with IgG4-RD and patients with other rheumatic conditions. These findings suggest that allergic conditions are not uniquely linked to the pathogenesis of IgG4-RD.

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Acknowledgements

This thesis is dedicated to my wonderful advisor, Dr. Zachary Wallace. I am immensely grateful for his constant guidance and encouragement. Throughout our research process, he taught me about IgG4-related disease and core epidemiological concepts, but my learnings from him stretch beyond these topics. I also learned several intangible lessons from our time working together, such as the exhilaration of performing cutting-edge research on a newly discovered disease, the importance of keeping the patient in mind throughout the research process, and the power of outstanding mentorship. Over the past two years, Dr. Wallace has embodied the qualities of what I think a mentor should be. I will never forget his support and kindness, and I hope that one day I can mentor a medical student the way he has mentored me.

I also want to thank Dr. Jennifer Potter of Castle Society, who has also been an incredible mentor to me. I have always been able to turn to her for personal and professional advice, and I have been amazed by her depth of caring and empathy over the past several years. She has also served as one of my biggest cheerleaders throughout medical school. For example, Dr. Potter encouraged me to apply to the Honors in a Special Field Program, and I would not be submitting this thesis without her support.

Thanks also to the Rheumatology Unit at MGH, who all helped to nurture my love of rheumatology and my interest in research. A special thank you to Dr. Eli Miloslavsky, who initially connected me with Dr. Wallace. Dr. Miloslavsky is an exceptional educator, and it has been a true privilege to learn from him since my first year of medical school.

Finally, thank you to my wonderful family and friends, as well as the rest of my mentors and advisors at HMS. It takes a village to get through medical school, and I am lucky to have people in my life who are steadfast, compassionate, and unconditionally supportive.

Statement of Research

This thesis is almost entirely based on a manuscript we recently submitted to the journal *Rheumatology.* This manuscript is currently under review, and I have included a copy of it with my thesis submission. Its full citation is as follows:

Sanders S, Fu X, Zhang Y, Perugino CA, Wallwork R, Della-Torre E, Long A, Choi HK, Stone JH, Wallace ZS. Self-Reported Allergies in IgG4-Related Disease: A Case-Control Study. Rheumatology. Submitted 2020.

With regards to funding, Dr. Wallace received funding in the form of a Scientist Development Award from the Rheumatology Research Foundation and by the NIH/NIAMS (K23-AR073334 and L30-AR070520). Dr. Perugino received funding from a Rheumatology Research Foundation Scientist Development Award and a Sponsored Research Agreement with UCB. Drs. Stone, Wallace, and Perugino are funded by the National Institute of Allergy and Infectious Diseases (Autoimmune Disease Center of Excellence, UM1 AI144295).

Glossary

Abbreviations and definitions

IgG4-RD – IgG4-related disease

IgG4 – Immunoglobulin G4, which is the least common subclass of Immunoglobulin G. Its role is not well-understood, and it has features that make it a poor activator of the immune system, such as half molecule exchange and poor Fcγ binding.[1]

Th2 cells – T-helper type 2 cells. These lymphocytes are essential in the immune response to extracellular parasites such as helminths, and they are also responsible for the development of asthma and allergic inflammatory diseases.[2]

EULAR – European League Against Rheumatism

ACR – American College of Rheumatology

SD – Standard deviation

IQR – Interquartile range

OR – Odds ratio

aOR – Adjusted odds ratio

CI – Confidence interval

IgE – Immunoglobulin E

ESR – Erythrocyte Sedimentation Rate

CRP – C-Reactive Protein

[1] Davies AM, Rispens T, Ooijevaar-de Heer P, Gould HJ, Jefferis R, Aalberse RC, Sutton BJ. Structural determinants of unique properties of human IgG4-Fc. *J Mol Biol*. 2014 Feb 6;426(3):630-44.
[2] Zhu J. T helper 2 (Th2) cell differentiation, type 2 innate lymphoid cell (ILC2) development and regulation of interleukin-4 (IL-4) and IL-13 production. *Cytokine*. 2015 Sep;75(1):14-24.

Organ manifestations of IgG4-related disease[3]

Dacryoadenitis – Enlargement of the lacrimal glands, which is typically painless and bilateral. Associated with dry eye and pseudoproptosis (i.e., the appearance of proptosis in the absence of orbital disease).

Sialoadenitis – Enlargement of the submandibular or parotid glands, which is typically painless and bilateral. Associated with dry mouth.

Orbital (non-lacrimal) – Inflammation of the orbital apex, which typically results in proptosis. Extra-ocular muscles may also be involved and demonstrate myositis.

Lymph nodes – Lymphadenopathy, which may be solitary or multifocal in nature.[4]

Pulmonary – Peri-bronchovascular and septal thickening in the lung. Also presents with thoracic paravertebral soft tissue mass.

Aorta – Aortitis, which typically shows multiple regions of aortic involvement.[5]

Retroperitoneum – Fibrosis resulting in soft tissue encasement of the abdominal aorta, most frequently involving the infrarenal arteries. Fibrosis can also result in hydronephrosis secondary to encasement of the ureters.

Pancreato-hepatobiliary – Chronic pancreatitis, which can present asymptomatically. It is associated with diffuse pancreatic enlargement noted on imaging as well as endocrine and

[3] Many organ manifestation definitions listed here were adapted from Wallace ZS, Naden RP, Chari S Members of the ACR/EULAR IgG4-RD Classification Criteria Working Group, et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. Annals of the Rheumatic Diseases 2020;79:77-87.

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exocrine insufficiency. Mass-like lesions also could be noted in pancreas or liver. Biliary involvement typically entails steroid-responsive sclerosing cholangitis.

Renal – Manifestations include tubulointerstitial nephritis or membranous nephropathy. May also see mass-like lesions in renal cortex.

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 (3).

Th2 cells were hypothesized to be important in the pathogenesis 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). This association has been hypothesized to relate to the proximity of these anatomic sites to mucosal surfaces that may be exposed to allergens, such that a regional immune response may affect nearby glands (2). 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). Moreover, 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). Although the pathogenic role of Th2 cells 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 allergic 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, 12, 13). Here, we sought to overcome these limitations by examining the characteristics and distributions of allergy symptoms in a US-based IgG4-RD cohort with diverse manifestations using a standardized allergy questionnaire and by measuring the association between allergies and the risk of IgG4-RD using a case-control design.

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 diagnosis of IgG4-RD was based on the classification criteria approved by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) (14). 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 had clinical involvement of a typical organ and did not meet any exclusion criteria but did not reach the threshold of 20 inclusion points according to the criteria (frequently because no biopsy was available or the biopsy was not informative). Patients who were considered atypical met the pathological and immunostaining definition of IgG4-RD but presented with involvement of an atypical organ (e.g., breast, prostate) (15).

We included all IgG-RD patients who were seen between January 19, 2012 and September 12, 2019 and completed a detailed allergy questionnaire. Some of the clinical and laboratory features of cases included in this study have been reported previously (9, 16-20). However, the cohort's allergic histories have not been investigated using a standard questionnaire and compared to a reference population, and the analyses pertaining to allergies 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) (16).

Control subjects: We identified controls among a convenience sample of patients without IgG4-RD seen in the Massachusetts General Hospital rheumatology clinic between June 1, 2016 and January 30, 2019. 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 following his or her visit. To achieve a control group composed of a majority of male patients (given the distribution of sex in IgG4-RD), males were preferentially invited during electronic enrollment. 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. The distribution of allergy symptoms among the various conditions represented in the control population was similar (range among largest subgroups 71% to 82%; p=0.2). Moreover, the proportion of patients with any self-reported allergy in the control group was similar to that reported in similar populations in other studies (21).

Allergy ascertainment: We administered an allergy questionnaire to all patients following an initial visit and asked 34 questions about a lifetime history of allergic symptoms, including history of aero-allergen symptoms (e.g., hay fever-type allergic symptoms), food allergies, skin allergies (atopic dermatitis, skin reactions, and urticaria), and anaphylaxis (**Supplemental Material**). This questionnaire had similar questions to that administered in the 2005-2006 National Health and Nutrition Examination Survey (22).

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. Statistical significance of differences was determined by Fisher's exact test,

unpaired t-test, Wilcoxon Rank Sum Test, and logistic regression, as appropriate. First, we examined the distribution of allergic symptoms among IgG4-RD patients. Among IgG4-RD patients, we assessed the association between allergy status and select IgG4-RD features and manifestations using unadjusted and age- and/or sex-adjusted logistic regression. Second, we compared the proportion of cases and controls with allergic symptoms using conditional logistic regression. Associations were reported using odds ratios (OR) and 95% confidence intervals (CI). In addition to overall associations between any allergy symptom and IgG4-RD, we also assessed the association of specific allergies (e.g., air, contact, food) with IgG4-RD as well as the association of self-reported and physician-reported allergies, respectively, with IgG4-RD. 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, 172 (75%) had definite IgG4-RD, 41 (18%) had probably IgG4-RD, and 18 (8%) had atypical IgG4-RD. The most common IgG4-RD manifestations in this cohort involved the head or neck (137, 59%), particularly sialoadenitis and/or dacryoadenitis (113, 49%). Other commonly affected organs included the pancreato-hepatobiliary system (78, 34%), lymph nodes (63, 27%), and renal system (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 Allergic Symptoms: One hundred sixty-five (71%) patients reported having any allergy symptoms, the details of which are reported in **Table 2**. The proportion of patients reporting allergies was similar across those with definite (73%), probable (66%), and atypical (83%) IgG4-RD. Aero-allergen symptoms were most commonly reported (135, 58%) followed by skin allergies (97, 42%) and food allergies (47, 20%). A history of anaphylaxis was reported in 20 (9%) subjects.

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]). 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]). The association between allergies 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]). We did not observe associations between allergy symptoms and having elevated IgG4 or IgE concentrations, having elevated inflammatory markers, or being hypocomplementemic.

Case-control analysis: Of 1,253 potential controls invited to complete the allergy questionnaire, 291 (23%) completed the questionnaire. We matched 152 IgG4-RD cases to 152 controls with other rheumatic diseases (**Table 4**). The cases and controls were well-matched with regard to age (mean 56.9 [±13.7] vs. 60.3 [±15.3] years, respectively) and sex (95 [63%] vs. 95 [63%] male, respectively). Controls represented a diversity of rheumatic conditions, including inflammatory arthritis (69, 45%), vasculitis (26, 17%), non-inflammatory musculoskeletal conditions (20, 13%), and others.

As reported in **Table 5**, a similar proportion of cases and controls had any reported allergic symptoms (110 [72%] vs. 114 [75%], OR 0.9 [95% CI: 0.5-1.5]), aero-allergen symptoms (91 [60%] vs. 99 [65%], OR 0.8 [95% CI: 0.5-1.3]), skin allergies (63 [41%] vs. 56 [37%], OR 1.2 [95% CI: 0.8-1.9]), and food allergies (33 [22%] vs. 48 [32%], OR 0.6 [95% CI: 0.4-1.0]). Among those with head and neck disease, there was also no association found between allergies and IgG4-RD (OR 1.1 [95% CI: 0.6-2.2]). Our findings remained unchanged when we compared the proportion of cases and controls with allergy diagnoses reported to have been made by a physician (data not shown).

Discussion, Conclusions, and Suggestions for Future Work

In this case-control study, the first of its kind in IgG4-RD, we found that allergic symptoms are common in IgG4-RD. The frequency with which they are reported, however, is similar to that observed in other rheumatic conditions. Among patients with IgG4-RD, those with allergic symptoms, especially aero-allergen symptoms, were more likely to have sialoadenitis and/or dacryoadenitis than those without allergies. Our observations of allergic symptoms in IgG4-RD and controls complement those made in previous studies suggesting that Th2 cells are unlikely to be pathogenic drivers of IgG4-RD (3). Collectively, this growing body of evidence suggests that allergic responses are unlikely to play a specific role in the pathogenesis of IgG4-RD.

Our study overcomes many limitations of some of the prior studies that have evaluated allergies 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, 23). Our findings confirmed previous observations that allergies are commonly reported in IgG4-RD with previous studies reporting prevalence rates for aero-allergen symptoms between 40% and 60% (2, 4, 13, 23, 24). We also found that allergy symptoms are more frequently reported in patients with head and neck involvement, particularly dacryoadenitis and/or sialoadenitis (2, 13). 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 study design, including standardized assessments of allergy symptoms and a larger sample size than some prior studies (2, 25). 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 (19, 25).

A recent study suggested that rheumatoid arthritis may be associated with a history of allergies, particularly food allergies (21). In our study, we evaluated associations between food allergies as well as aero-allergies and skin allergies with IgG4-RD individually and found no differences compared to our control group which included patients with diverse rheumatic conditions. A potential association between allergic symptoms and autoimmune conditions would be somewhat surprising because of our understanding of the different pathogenic mechanisms responsible for these categories of disease. If true, one might hypothesize that IgE auto-antibodies generated during an autoimmune response could potentiate the activation of infiltrating mast cells and amplify sub-clinical allergic symptoms. IgE auto-antibodies specific to galectin-3 have been reported in IgG4-RD and IgE rheumatoid factor has been observed in seropositive rheumatoid arthritis (26, 27). Given that the expression of Fcε receptors is restricted to mast cells, basophils and eosinophils, it is not yet clear what role such IgE isotype auto-antibodies have in autoimmune conditions such as IgG4-RD and other rheumatic conditions.

The difference in organ involvement among those with and without allergic 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 allergic symptoms (28). There are several possible explanations as to why IgG4-RD patients with head and neck manifestations more often had self-reported allergies. First, it is possible that patients with head and neck disease are more likely to report allergies due to recall bias given that allergies often affect the head and neck. However, this is less likely to explain our findings given that allergic symptoms (e.g., itchy eyes, rhinitis) are easily distinguishable from IgG4-RD symptoms in the head and neck (e.g., proptosis, sialoadenitis). 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 similar phenomenon occurring in patients with rheumatoid arthritis, as recently reported (21). Future studies might further investigate the association between allergic 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, 13). 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 (15).

Our study makes several novel contributions to the literature, including its sample size, use of a standardized questionnaire, and case-control design. Moreover, this is the first study 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.

Our study has certain limitations. First, as with any survey study, recall bias is possible but unlikely since both IgG4-RD patients and controls were asked to complete the survey in the context of medical care. 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 (22). Future studies might define allergic conditions more stringently using an evaluation by an allergist with or without formal allergy testing. Third, 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. Finally, our study was performed at a tertiary referral center and 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. Future studies might use a multi-center design to further study the association between IgG4-RD, other immune-mediated conditions, and allergic conditions.

In conclusion, allergic symptoms, especially aero-allergen symptoms, are frequently reported in IgG4-RD but at a similar rate as in controls with other immune-mediated conditions. Among IgG4-RD patients, allergic symptoms are more common among those with head and neck disease, particularly sialoadenitis and/or dacryoadenitis. We found a similar prevalence of allergies among IgG4-RD patients and age- and sex-matched controls, supporting the hypothesis that allergies are unlikely to play a unique role in the pathogenesis of IgG4-RD.

Summary and Key Messages

- Allergic symptoms are common in IgG4-related disease, particularly among patients with head and/or neck involvement
- Allergic symptoms are reported with a similar frequency by patients with IgG4-related disease and patients with other rheumatic conditions.
- It is unlikely that allergies play a unique role in the pathogenesis of IgG4-RD.

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Tables and Figures

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

^ Elevated refers to serum IgG4 concentration ≥ 135mg/dL, serum IgE concentration ≥ 100 IU/mL, eosinophils ≥ 0.5 10^9/L, ESR > 30 mm/hr, and CRP > 7 mg/dL

Table 2: Characteristics of Allergic Conditions in IgG4-Related Disease

Features of Allergic Conditions	Frequency
Any Allergy (N, %)	165 (71%)
Aero-Allergen Symptoms	
History of Aero-Allergen Symptoms	135 (58%)
Self-reported allergies	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 Allergies and Hypersensitivities (N, %)	
History of Food Allergies/Hypersensitivities	47 (20%)
Self-reported allergies	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 Allergies (N, %)	
History of Skin Allergies	97 (42%)
Self-reported contact dermatitis	47 (20%)
Self-reported eczema	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, %)	
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 Allergies

	Overall (N=231)	Allergy (N=138)	No Allergy (N=51)	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

	Cases*	Controls
N	152	152
Age (mean, SD)	56.9 (13.7)	60.3 (15.3)
Male (%)	63	63
Race (%)		
White	72	86
Asian	15	4
Black	5	5
Unknown / other	8	6
Primary Condition (N, %)		
IgG4-RD	130 (100%)	--
Inflammatory Arthritis	--	69 (45%)
Vasculitis	--	26 (17%)
Non-inflammatory MSK	--	20 (13%)
Connective Tissue Disorder	--	10 (7%)
Myositis-Spectrum Disease	--	2 (1%)
Osteoporosis	--	1 (1%)
Other	--	24 (16%)

MSK: musculoskeletal conditions; *Not all cases could be matched with a control

Table 5: The Association Between Allergies and IgG4-RD

	Cases	Controls	Odds Ratio (95% CI)
N	152	152	
Any Allergy			
Yes	110 (72%)	114 (75%)	0.87 (0.52-1.46)
No	42 (28%)	38 (25%)	Ref
Aero-Allergies			
Yes	91 (60%)	99 (65%)	0.78 (0.48-1.27)
No	61 (40%)	53 (35%)	Ref
Aero-Allergies in Last 12 Months			
Yes	53 (40%)	57 (43%)	0.88 (0.54-1.44)
No	81 (60%)	77 (57%)	Ref
Food Allergies			
Yes	33 (22%)	48 (32%)	0.63 (0.39-1.04)
No	119 (78%)	104 (68%)	Ref
Skin Allergies			
Yes	63 (41%)	56 (37%)	1.2 (0.77-1.89)
No	89 (59%)	96 (63%)	Ref

Figure 1: Allergy Questionnaire Administered to Patients

FAMILY HISTORY		
Are you aware of cases of allergy in your family (1st degree relatives)?	Yes	No
Hay Fever		
Asthma		
Eczema		
Food Allergy		
Stinging insect allergy		
Medication allergy		
AIR ALLERGENS (POLLENS)		
Have you ever experienced hay fever-type allergic symptoms (red and itchy eyes, runny nose, sneezing, asthma, hives) after exposure to seasonal pollens, dust, cats, dogs, molds or other environmental factors, in the absence of a cold or flu?	Yes	No
If YES, are those symptoms seasonal or year-round?	Seasonal	Year-Round
Has a doctor or other health professional ever told you that you have hay fever or allergies?	Yes	No
How old were you when you were first told you had hay fever or allergy?	Years: _____	
Have you ever undergone allergy skin testing, allergy blood testing (specific IgE blood measurement) or an allergy evaluation?	Yes	No
If YES, do you remember the results of those tests?	_____	
During the past 12 months, have you had any symptoms suggestive of respiratory allergy (conjunctivitis and/or nasal allergies)?	Yes	No
FOOD ALLERGENS		
Have you ever experienced allergic symptoms after exposure to a particular food (itching, tingling, swelling of the lips mouth, throat or tongue, abdominal cramping, abdominal pain, nausea, vomiting, diarrhea, red and itchy eyes, runny nose, sneezing, asthma, hives)?	Yes	No

Has a doctor or other health professional ever told you that you have allergies to foods?	Yes	No
How old were you when you were first told you had food allergies?	Years: _____	
Have you ever undergone allergy skin testing or allergy blood tests (specific IgE blood measurement) for possible food allergy?	Yes	No
If YES, do you remember the results of those tests?	_____	
During the past 12 months, have you had any allergy symptoms in relation to foods?	Yes	No

ATOPIC DERMATITIS, SKIN REACTIONS AND URTICARIA

Has a doctor or other health professional ever told you that you have atopic dermatitis, eczema or urticaria/hives?	Yes	No
Have you ever experienced allergic symptoms (hives, skin itchy rash) after contact with a specific substance (latex, chemicals, perfumes, etc)?	Yes	No
If YES, which substance?	_____	
Have you ever had an itchy rash that waxed and waned for at least 6 weeks?	Yes	No
Have you had this itchy rash at any time in the last 12 months?	Yes	No
Have you ever been stung by a bee or insects?	Yes	No
If YES, have you had an allergic reaction such as generalized rash, and/or swelling, asthma symptoms, faintness or even loss of consciousness after an insect sting?	_____	
Has a doctor or other health professional ever told you that you have atopic dermatitis, eczema or uritcaria/hives?	Yes	No
At what age did this itchy rash first occur?	Years: _____	

Have you ever undergone specific IgE blood measurement for enquiring about skin allergy?	Yes	No
If YES, do you remember the results of those tests?	_____	

ANAPHYLAXIS

Have you ever experienced anaphylaxis (severe generalised allergic reaction) or anaphylactic shock (drop in blood pressure, faintness or loss of consciousness)?	Yes	No
If YES, did you require epinephrine?	Yes	No

DRUG HISTORY

Are you taking any medications for allergic symptoms?	Yes	No
If YES, which medications (antihistamines, topical steroids inhalers or nasal sprays or other)?	_____ _____	
Are the symptoms improving after taking those medications?	Yes	No
Have you ever had allergy shots or allergen immunotherapy through subcutaneous injections or oral pills?	Yes	No
If YES, when and were they effective?	_____ _____	

IgG4-RELATED DISEASE

Since developing symptoms related to IgG4-RD or being diagnosed with IgG4-RD, how have your allergic symptoms been?	Improved	No Change	Worsened
Have you increased the use of antihistamines since the diagnosis of IgG4-related disease?	Yes		No