Characteristics of IgG4-related Disease Complicated With Allergic Rhinitis or Chronic Rhinosinusitis: A Large Cohort Study in China

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Abstract

Objective

Patients of IgG4-related disease (IgG4-RD) often present nasal symptoms that could be diagnosed as allergic rhinitis (AR) or chronic rhinosinusitis (CRS). In this study, demographic, clinical and laboratory characteristics of IgG4-RD patients complicated with AR/CRS were investigated.

Methods

We retrospectively analyzed 756 IgG4-RD patients who were recruited in five medical centers from 2009 to 2021. We divided 756 IgG4-RD patients into 2 groups: the case group included IgG4-RD patients complicated with AR/CRS, and the control group included IgG4-RD patients without AR/CRS.

Results

411 patients were diagnosed as AR/CRS among the 756 patients. Patients in the case group showed longer disease duration and interval between symptom onset and diagnosis. Multiple organs involvement(≥3) and allergic disease were more common in the case group. The most frequently involved organs in the case group were lung, salivary gland and lacrimal gland. Patients in the case group had a higher level of serum IgG4, IgE and ESR. High IgE level and complication of allergic disease were risk factors for patients in the case group. In the case group, most patients had nasal manifestations before the diagnosis of IgG4-RD. The median time interval from nasal symptoms appearance to IgG4-RD diagnosis was -120 and -90 months for patients complicated with AR and CRS, respectively.

Conclusion

This study revealed the clinical characteristics of IgG4-RD patients complicated with AR/CRS. Our findings may be conducive to determine a new clinical entity of IgG4-RD and suggest underlying association of pathogenesis of IgG4-RD and AR/CRS.

Introduction

IgG4-related disease (IgG4-RD) is an immune-mediated systemic disorder that is typified by sclerosing lesions in multiple organs(1, 2). The characteristic pathological features of IgG4-RD are lymphocyte and plasmacyte infiltration, storiform fibrosis, and obliterative phlebitis(1, 3-5). IgG4-RD was recognized as isolated entities incipiently and was first described in pancreas in a cohort of Japanese patients in 2001(6). Subsequent studies found that it was a systemic condition and could affect nearly any anatomic site(7, 8).

Sinusitis was first recognized as a complication of extra-pancreatic lesions of autoimmune pancreatitis in 2011(9). However, studies about the nasal complications of IgG4-RD was scarce and mainly focused on chronic rhinosinusitis (CRS) (9-13). In clinical practice, we found that many patients diagnosed as

IgG4-RD had nasal symptoms, such as nasal obstruction and rhinorrhea, that could be diagnosed as allergic rhinitis (AR)(14) or CRS(15) accordingly, and were sensitive to glucocorticoid therapy. In this study, we retrospectively analyzed the demographic, clinical and laboratory disparities in the 756 IgG4-RD patients. To our knowledge, this is the largest cohort study comparing the two phenotypes of IgG4-RD with and without CRS/AS. Confirming the characteristics of these two groups could contribute to identify risk factors and comprehend underlying differences in pathogenesis.

Methods

Patients

We retrospectively analyzed 756 IgG4-RD patients fulfilled 2020 revised comprehensive diagnostic criteria for IgG4-RD(16), and 479 (63.4%), 96 (12.7%) and 181 (23.9%) cases were diagnosed as definite, probable and possible IgG4-RD in all enrolled patients, respectively. All the patients were recruited in 5 medical centers from 2009 to 2021. AR was diagnosed according to the clinical manifestations, medical history, examinations and investigations(14). CRS was diagnosed on the basis of clinical manifestations, endoscopic findings and radiographic imaging results(15). The clinical diagnosis of AR or CRS was made by otolaryngologists. Patients diagnosed as IgG4-RD was categorized into the case group if they met the diagnostic criteria of AR(14) and/or CRS(15). The control group included IgG4-RD without AR or CRS (**Table 1**).

Demographic features like age and gender, and clinical characteristics including clinical manifestation, disease duration and organ involvement were recorded. The time interval from disease onset to diagnosis was defined as the time interval from extra-nasal symptoms (such as enlargement of salivary gland) onset to the diagnosis of IgG4-RD.

Laboratory studies, image features and histological examinations

Laboratory tests were recorded comprising serum IgG4 level, serum IgG4/IgG ratio, serum IgE level, complement, eosinophilia, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and autoantibodies (including RF and ANAs).

All patients underwent radiological examinations comprising of ultrasonography, Computed Tomography (CT), or Magnetic resonance imaging (MRI); and some patients underwent 18 F-fluorodeoxyglucose PET/CT.

Tissue biopsy samples were fixed in formalin and embedded in paraffin wax, then stained with haematoxylin and eosin (H&E) and immunocytochemistry (IHC). IHC was performed using antibodies against CD3, CD20, IgG, IgG4, CD138 and CD38.

Statistical analysis

All statistical analyses were performed by GraphPad Prism 8.0 using descriptive methods, with standard summary statistics including mean (S.D.), median, interquartile range (IQR), and proportions. Student's *t* test was used for differences for continuous, normally distributed data; Mann-Whitney test was used for differences for continuous, non-normally distributed data. Categorical variables were processed by X^2 or Fisher's exact tests. Logistic regression analysis with enter method was performed to compare the patients in the case group and control group. Factors with $P<0.05$ and clinical significance in the univariate analysis were included in the multivariate analysis. *P*-value < 0.05 was deemed as statistically significant.

Results

Demographic characteristics

Demographic characteristics of a total of 756 patients diagnosed as IgG4-RD were listed in **Table 1**. A total of 408 patients (53.97%) were categorized into the case group for complication of AR or CRS. The rest of 348 patients (46.03%) without AR or CRS were categorized into the control group.

Patients in the case group had longer time interval from onset to diagnosis (24 months vs 12 months, $p=0.0089$), longer disease duration (24 months vs 12 months, $p=0.0096$) and longer follow-up period (51.5 months vs 41 months, $p=0.0107$) compared with patients in the control group (**Table 2**).

Clinical features

In general, the proportion of number of involved organs≥3 in the case group was higher than that in the control group (65.5% vs 35.4%, $p<0.0001$) as shown in **Table 2**. Patients in the case group showed more lymph node (41.12 vs 26.96, $p<0.0001$), lung (29.93 vs 14.78, $p<0.0001$), salivary gland (63.26 vs 42.32, $p<0.0001$), lacrimal gland (52.07 vs 24.93, $p<0.0001$) and parotid gland (35.52 vs 19.13, $p<0.0001$) involvement than the control group. The most frequently involved organs in the case group were salivary gland (63.26%), lacrimal gland (52.07%) and lymph node (41.12%). In contrast, salivary gland (42.32%), pancreas (27.54%) and lymph node (26.96%) were the most frequently involved organs in the control group.

Laboratory findings

Patients in the case group had higher level of serum IgG4 (650 vs 385, p<0.0001), serum IgE (347 vs 98, $p<0.0001$) and ESR (14 vs 12, $p=0.0481$) than control group, as shown in **Table 2**. Eosinophilia (17.76% vs 5.51%, $p<0.0001$) and hypocomplementemia (38.93% vs 20.87%, $p<0.0001$) were more common in the case group, too.

Clinical nasal manifestations of patients in the case group

The main clinical nasal manifestations of patients in Group A were sneezing (29.04%), nasal obstruction (27.47%), nasal itching (20.57%) and rhinorrhea (20.09%) as shown in **Figure 1**. The main clinical nasal

manifestations of patients in Group B were nasal obstruction (35.32%), decreased sense of smell (24.26%), mucopurulent drainage (20.85%) and facial pain-pressure-fullness (11.49%), which were consistent with previous study(10).

Risk factors for the patients in the case group

In univariate analysis, disease duration, complication of allergic disease, number of involved organs≥3, lymph node involvement, salivary gland involvement, thyroid gland involvement, lung involvement, biliary system involvement, gallbladder involvement, salivary gland involvement, lacrimal gland involvement, parotid gland involvement, higher level of serum IgG4, higher level of serum IgE, higher level of ESR, eosinophilia and hypocomplementemia were associated with higher rate of IgG4-RD complicated with AR or CRS (**Table 3**).

In multivariate analysis, only IgE and complication of allergic disease were associated with complication of AR or CRS (**Figure 2**).

Time interval between complication of AR/CRS and disease diagnosis in the case group

The time interval was calculated between the time of complication of AR or CRS and the time of IgG4-RD diagnosis. Positive or negative results meant the complication of AR or CRS occurred after or before IgG4-RD diagnosis, respectively. The time relationship of complication of AR or CRS and IgG4-RD diagnosis was divided into 3 groups including: complication of AR or CRS occurred before IgG4-RD diagnosis, complication of AR or CRS occurred after IgG4-RD diagnosis and complication of AR or CRS occurred simultaneously with IgG4-RD diagnosis (defined as the time interval between complication of AR or CRS and IgG4-RD diagnosis was no more than 12 months).

As shown in **Figure 3**, the percentage of each group in Group A was 84.83% (complication of AR or CRS occurred before IgG4-RD diagnosis), 12.32% (complication of AR or CRS occurred simultaneously with IgG4-RD diagnosis) and 2.84% (complication of AR or CRS occurred after IgG4-RD diagnosis), respectively. The percentage of each group in Group B was 78.41% (complication of AR or CRS occurred before IgG4-RD diagnosis), 17.05% (complication of AR or CRS occurred simultaneously with IgG4-RD diagnosis) and 4.55% (complication of AR or CRS occurred after IgG4-RD diagnosis), respectively. The median time interval of each group in Group A was 144 months (IQR: 96-306; complication of AR or CRS occurred before IgG4-RD diagnosis), 9 months (IQR: 2-12; complication of AR or CRS occurred simultaneously with IgG4-RD diagnosis) and 54 months (IQR: 39-69; complication of AR or CRS occurred after disease IgG4-RD diagnosis), respectively. The median time interval of each group in Group B was 120 months (IQR: 60-360; complication of AR or CRS occurred before IgG4-RD diagnosis), 12 months (IQR: 6-12; complication of AR or CRS occurred simultaneously with IgG4-RD diagnosis) and 35.5 months (IQR: 32.25-57; complication of AR or CRS occurred after IgG4-RD diagnosis), respectively.

Discussion

In the present study, we described the clinical manifestations of IgG4-RD patients complicated with AR or CRS in a large cohort. Moreover, we compared the demographic, clinical and laboratory disparities of 408 IgG4-RD patients complicated with AR or CRS and 348 IgG4-RD patients without AR or CRS. The chronological relationship of complication of AR or CRS and IgG4-RD disease diagnosis was analyzed. To our current knowledge, this is the first and largest cohort study focusing on the complication of both AR and CRS of IgG4-RD, and exploring the differences of IgG4-RD with AR or CRS and IgG4-RD without AR or CRS phenotypes.

IgG4-RD is an immune-mediated systemic disorder that is typified by sclerosing lesions in multiple organs. Organs in the head and neck region are commonly involved in IgG4-RD, such as salivary gland, lacrimal gland and parotid gland(17, 18). However, few studies have discussed nasal involvement in IgG4-RD, which is mainly because there is no classification diagnostic criterion for IgG4-related rhinitis or IgG4-related rhinosinusitis. Clinical symptoms of exocrine gland involvement are common in IgG4-RD patients(8) and secretory gland is a major part of the nasal membrane, which indicates that the nasal membrane may be theoretically involved in IgG4-RD(13). Moreover, patients with IgG4-RD do have a higher proportion of being complicated with AR or CRS based on previous study(9) and our clinical practice experiences. Therefore, this study retrospectively analyzed the demographic, clinical and laboratory characteristics of IgG4-RD patients complicated with AR or CRS, which could be conducive to determine a new clinical entity of IgG4-RD and better understanding of the pathogenesis of IgG4-RD.

The percentage of complication of AR or CRS in the present study was 54.0%, which was higher than previous studies (43.5%(11), 37.0%(10) and 32.3%(9)). The different inclusion criteria may explain for the discrepancy. IgG4-RD patients complicated with AR or CRS seemed to have longer time interval from disease onset to diagnosis. Multiple organs involvement (≥3 organs) was more common in patients complicated with AR or CRS than patients without AR or CRS, and the distribution of involved organs were also different, suggesting different underlying pathogenesis.

IgG4-RD patients complicated with AR or CRS had higher serum IgG4 level and serum IgE level. Complication of allergic disease and eosinophilia were also more common in these patients because many IgG4-RD patients with AR or CRS had an allergic constitution. IgG4-RD patients complicated with AR or CRS presented more elevated ESR level and hypocomplementemia that indicated high disease activity, which was correlated with more multiple organs involvement.

Higher serum IgE level and complication of allergic disease were risk factors for complication of AR or CRS in IgG4-RD patients. Both factors suggest the existence of allergic disease, which is a known risk factor for AR(19), and AR was a common concomitant disease of IgG4-RD patients with CRS(9). We found that most patients in the case group had nasal symptom onset years earlier before IgG4-RD diagnosis, which may be due to the ignorance of underlying relationship of IgG4-RD and AR/CRS.

The relationship of AR/CRS and IgG4-RD is unclear based on previous studies and there is no unified definition of IgG4-related nasal lesions. However, many patients diagnosed as IgG4-RD were complicated with AR/CRS in the present study, which was consistent with previous studies(9-13). Therefore, patients

with AR/CRS should be followed-up to observe if they have complicated with IgG4-RD in the future because most patients had AR/CRS months before the diagnosis of IgG4-RD in our study.

In our opinion, IgG4-RD patients with AR/CRS may be considered as a new clinical entity, which is supported by several findings: 1) 54.0% patients (408) in our study had AR or CRS (34.0% for AR, 15.3% for CRS and 4.7% for both), which was higher than the morbidity of general population(20, 21); 2) IgG4-RD patients with AR/CRS showed different demographic, clinical and laboratory characteristics than patients without AR/CRS; 3) IgG4-RD patients with AR/CRS in our study were sensitive to glucocorticoid therapy and their nasal symptoms alleviated or disappeared after treatment, while CRS alone is insensitive to glucocorticoid therapy. Although AR alone is sensitive to glucocorticoid therapy, IgG4-RD patients complicated with AR had outstanding allergic symptoms and showed different laboratory characteristics than patients with IgG4-RD alone. Therefore, we consider AR may be related to IgG4-RD. To further explore the relationship of AR/CRS with IgG4-RD, pathological findings of nasal lesions are necessary in future study.

There are several limitations of this study. First, although most cases underwent general examinations, its retrospective nature made some involved organs neglected. Second, due to the long time-interval of complication of AR or CRS and IgG4-RD diagnosis, the nasal manifestations of IgG4-RD patients with AR/CRS may be inaccurate because of recall bias.

Conclusion

In the present study, we compared the demographic, clinical and laboratory differences between IgG4-RD patients with AR/CRS and IgG4-RD patients without AR/CRS. IgG4-RD patients with AR/CRS had longer time interval from onset to diagnosis. Complication of allergic disease and multiple organs involvement were more common in these patients. IgG4-RD patients with AR/CRS showed higher levels of serum IgG4 and IgE, and higher percentages of ESR elevation, eosinophilia and hypocomplementemia. Physicians should pay attention to the medical history of AR/CRS because AR and CRS occurred several years earlier than IgG4-RD diagnosis in the present study. These findings may be conducive to determine a new clinical entity of IgG4-RD and suggest underlying association of pathogenesis of IgG4-RD and AR/CRS.

Abbreviations

IgG4-RD, IgG4-related disease; AR, allergic rhinitis; CRS, chronic rhinosinusitis; CT, Computed Tomography; MRI, Magnetic resonance imaging; H&E, haematoxylin and eosin ; IHC, immunocytochemistry.

Declarations

Ethical Approval and Consent to participate: This study was approved by all Medical Ethics Committees of the five medical centers that carried out this study (Peking University People's Hospital; Beijing

Friendship Hospital, Capital Medical University; People's Hospital of Hebei Province; Handan First Hospital; and Tengzhou Central People's Hospital).

Consent for publication: All authors of this study have their consent for publication.

Availability of supporting data: The datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Tables

Table 1 Demographic and clinical characteristics of 756 IgG4-RD patients

	Case group: IgG4-RD complicated with AR/CRS				Control group:
Characteristics	Total	Group A	Group B	Group C	IgG4-RD without AR/CRS
Number of cases, n	408	257	116	35	348
Definite diagnosis, n (%)	257 (62.99%)	153 (59.53%)	82 (70.69%)	22 (62.86%)	222 (63.79%)
Probable diagnosis, n (%)	39 (9.56%)	28 (10.89%)	8 (6.90%)	3 (8.57%)	57 (16.38%)
Possible diagnosis, n (%)	112 (27.45%)	76 (29.57%)	26 (22.41%)	10 (28.57%)	69 (19.83%)
Median age at disease onset, years (IQR)	56 (46-62)	55 (46-62)	55 (45-61)	54 (45.5-61)	56 (46-64)
Median age at diagnosis, years (IQR)	57.5 (50-64)	56 (48-65)	57 (50-64)	57 (49.5-63)	58 (48-65)
Median time from onset to diagnosis, months (IQR)	24 (12-60)	12 (0-36)	18 (0-48)	12 (0-48)	12 (6-36)
Gender (Male: Female)	1.34:1	1.22:1	1.56:1	1.69:1	1.46:1
Complication of allergic disease, n (%)	216 (52.55)	\	85 (56.29)	\	43 (12.36)
Organ involvement, n (%)					
1 organ involved	77 (18.87)	63 (24.51)	13 (11.21)	1 (2.86)	138 (39.66)
2 organs involved	74 (18.14)	47 (18.29)	23 (19.83)	4 (11.43)	67 (19.25)
3 organs involved	69 (16.91)	34 (13.23)	26 (22.41)	9 (25.71)	56 (16.09)
≥4 organs involved	188 (46.08)	113 (43.97)	54 (46.55)	21 (60.00)	1. (25.00)

a. IgG4-RD, IgG4-related disease; b. IQR, interquartile range; c. AR, allergic rhinitis; d. CRS, chronic rhinosinusitis; e. Group A included IgG4-RD patients complicated with AR, Group B included IgG4-RD patients complicated with CRS and Group C included IgG4-RD patients complicated with AR and CRS; f. The rate of complication of allergic disease in Group A and Group C was 100% and marked as “\”

Table 2 Differences of demographic, clinical and laboratory characteristics between IgG4-RD patients complicated with AR/CRS (case group) and without AR/CRS (control group)

Characteristics	ALL (n=756)	Case group (n=408)	Control group (n=348)	*P*-value
Demographics				
Age at disease onset, years, median (IQR)	56 (46-63)	56 (46-62)	56 (46-64)	0.4380
Age at diagnosis, years, median (IQR)	57.5 (49-65)	57.5 (50-64)	58 (48-65)	0.5078
Time from onset to diagnosis, months, median (IQR)	24 (12-48)	24 (12-60)	12 (6-36)	0.0089*
Follow-up period, months, median (IQR)	48 (26-71.5)	51.5 (33-72)	41 (24-70)	0.0107*
Disease duration, months, median (IQR)	24 (12-48)	24 (12-60)	12 (6-36)	0.0096*
Gender (Male: Female)	1.39:1	1.34:1	1.46:1	0.6838
Clinical features n (%)				
Complication of allergic disease	341 (45.11)	216 (52.55)	125(36.23)	<0.0001*
Number of involved Organs≥3	391 (51.7)	269 (65.5)	122(35.4)	<0.0001*
Lymph node	262 (34.66)	169 (41.12)	93 (26.96)	<0.0001*
Thyroid gland	46 (6.08)	30 (7.30)	16 (4.64)	0.1273
Lung	174 (23.02)	123 (29.93)	51 (14.78)	<0.0001*
Kidney	113 (14.95)	64 (15.57)	49 (14.20)	0.5590
Liver	28 (3.70)	17 (4.14)	11 (3.19)	0.4919
Pancreas	217 (28.70)	122 (29.68)	95 (27.54)	0.5156
Biliary system	96 (12.70)	52 (12.65)	44 (12.75)	0.9667
Gallbladder	67 (8.86)	43 (10.46)	24 (6.96)	0.0911
Retroperitoneal fibrosis	124 (16.40)	61 (14.84)	63 (18.26)	0.1020
Mesentery	7 (0.93)	4 (0.97)	3 (0.87)	0.8822
Aorta	17 (2.25)	13 (3.16)	4 (1.16)	0.0642
Prostate	35 (4.63)	20 (4.87)	15 (4.35)	0.7355

Salivary gland	406 (53.70)	260 (63.26)	146 (42.32)	<0.0001*
Lacrimal gland	300 (39.68)	214 (52.07)	86 (24.93)	<0.0001*
Parotid gland	212 (28.04)	146 (35.52)	66 (19.13)	<0.0001*
Laboratory findings				
Serum IgG4 (mg/dL), median (IQR)	502 (248-1360)	650 (312-1520)	385 (185-1136)	<0.0001*
Serum IgG4 (mg/dL)/IgG (mg/dL), median (IQR)	0.28 (0.14-0.49)	0.32 (0.19-0.53)	0.21 (0.12-0.38)	<0.0001*
Serum IgE (IU/ml), median (IQR)	246 (72-655)	347 (153-958)	98 (39-288)	<0.0001*
CRP (mg/dl), median (IQR)	1.83 (0.68-6.40)	1.98 (0.74-6.87)	1.63 (0.61-6)	0.5607
ESR (mm/h), median (IQR)	13 (7-36)	14 (7-42)	12 (6-28)	0.0481*
Elevated CRP, n (%)	117 (15.48)	67 (16.30)	50 (14.50)	0.4934
Elevated ESR, n (%)	228 (30.16)	142 (34.55)	86 (24.93)	0.0041*
Eosinophilia, n (%)	92 (12.17)	73 (17.76)	19 (5.51)	<0.0001*
C3 (g/L) mean (SD)	0.89 (0.74-1.08)	0.84 (0.73-1.04)	0.97 (0.81-1.12)	<0.0001*
C4 (g/L), median (IQR)	0.19 (0.15-0.26)	0.19 (0.14-0.24)	0.21 (0.16-0.28)	<0.0001*
ANA (+), n (%)	94 (12.43)	51 (12.41)	43 (12.46)	0.9818
RF (+), n (%)	97 (12.83)	56 (13.63)	41 (11.88)	0.4758
Hypocomplementemia, n (%)	232 (30.69)	160 (38.93)	72 (20.87)	<0.0001*

a. IgG4-RD, IgG4-related disease; b. IQR, interquartile range; c. AR, allergic rhinitis; d. CRS, chronic rhinosinusitis; e. Case group included IgG4-RD patients complicated with AR or CRS, and the control group included IgG4-RD patients without AR or CRS; f. * means *P*-value <0.05

Table 3 Univariate analysis of logistic regression of risk factors for IgG4-RD patients complicated with AR or CRS (Case group)

Characteristics	Univariate analysis		
	P-value	OR	95%CI
Demographics			
Age at disease onset, median (IQR)	0.438	0.996	0.985, 1.006
Age at diagnosis, median (IQR)	0.507	1.004	0.993, 1.014
Disease duration, months, median (IQR)	0.011*	1.006	1.001, 1.010
Female, n (%)	0.684	0.941	0.704, 1.259
Clinical features			
Complication of allergic disease, n (%)	0.001*	5.093	3.389, 7.655
Organ involvement, n (%)			
≥3 organs	0.001*	3.827	2.823, 5.189
Lymph node	0.001*	2.856	2.058, 3.962
Thyroid gland	0.040*	2.011	1.032, 3.919
Lung	0.001*	3.071	2.073, 4.548
Kidney	0.214	1.315	0.853, 2.027
Liver	0.328	1.512	0.660, 3.466
Pancreas	0.202	1.237	0.892, 1.713
Biliary system	0.027*	1.672	1.060, 2.636
Gallbladder	0.017*	2.013	1.134, 3.573
Retroperitoneal fibrosis	0.916	0.979	0.657, 1.458
Mesentery	0.548	1.686	0.307, 9.258
Aorta	0.076	2.785	0.900, 8.620
Prostate	0.736	1.125	0.567, 2.233
Salivary gland	0.001*	2.347	1.751, 3.146
Lacrimal gland	0.001*	3.272	2.396, 4.467
Parotid gland	0.001*	2.329	1.665, 3.258
Laboratory examinations			

Serum IgG4 (mg/dL), median (IQR)	0.001*	1.000	1.000, 1.001
Serum IgG4 (mg/dL)/IgG (mg/dL) , median (IQR)	0.001*	8.545	2.804, 26.036
Serum IgE (IU/ml), median (IQR)	0.001*	1.002	1.001, 1.002
CRP (mg/dl), median (IQR)	0.428	1.004	0.994, 1.015
ESR (mm/h), median (IQR)	0.001*	1.024	1.003, 1.045
Eosinophilia, n (%)	0.001*	4.509	2.068, 9.831
ANA (+), n (%)	0.115	0.639	0.366, 1.115
RF (+), n (%)	0.937	1.024	0.573, 1.828
Hypocomplementemia, n (%)	0.018*	1.754	1.100, 2.796

a. IgG4-RD, IgG4-related disease; b. IQR, interquartile range; c. AR, allergic rhinitis; d. CRS, chronic rhinosinusitis; e. * means *P*-value <0.05

Figures

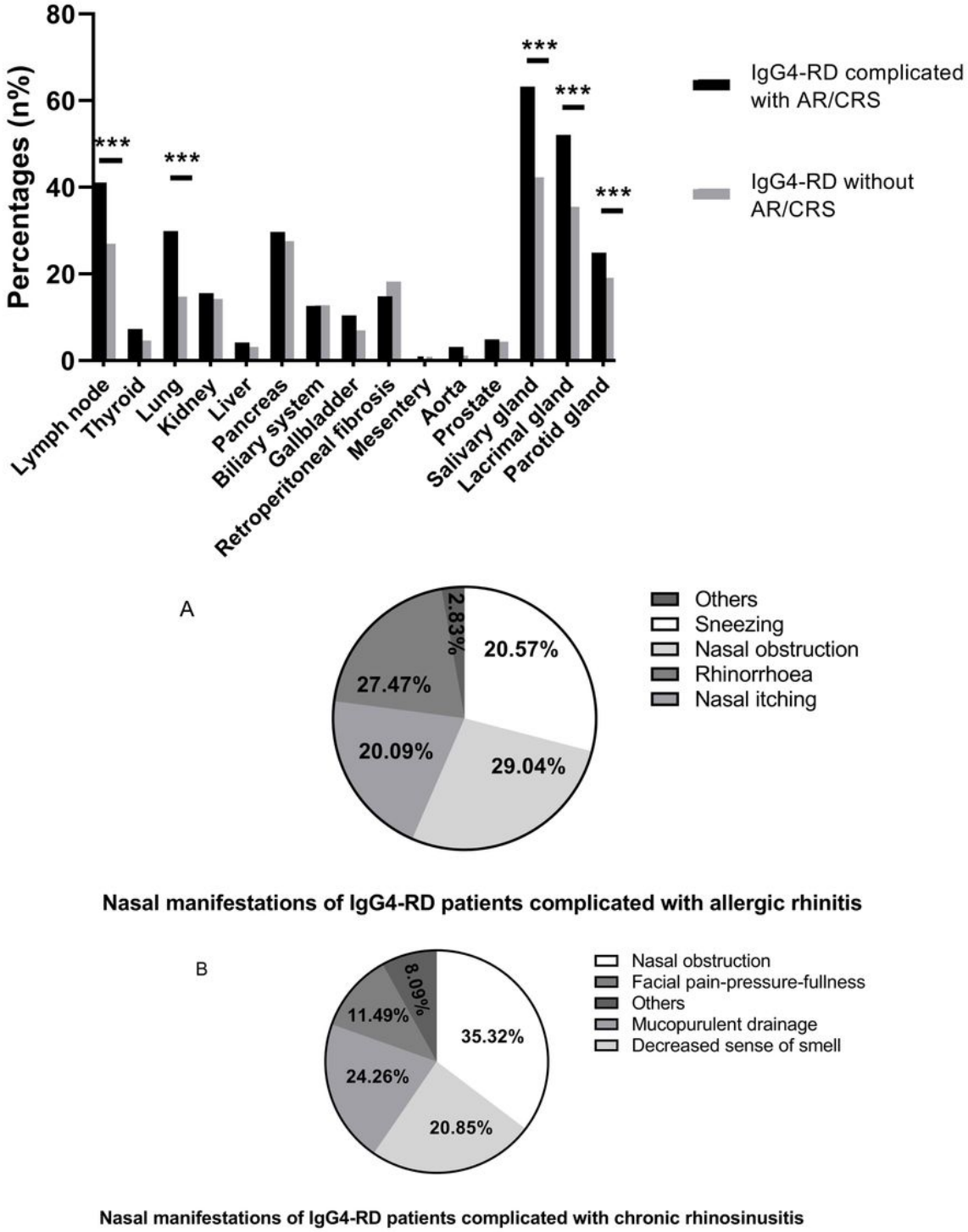

Figure 1

Nasal manifestation of IgG4-RD patients complicated with AR (Group A) and CRS (Group B) A: Patients complicated with AR showed sneezing, nasal obstruction, nasal itching and rhinorrhea most commonly. B: Patients complicated with CRS showed nasal obstruction, decreased sense of smell, mucopurulent drainage and facial pain-pressure-fullness most commonly. IgG4-RD, IgG4-related disease; AR, allergic rhinitis; CRS, chronic rhinosinusitis

Varibles	OR (95%CI)	*P*-value
IgE	1.003 (1.001, 1.005)	0.002*
Complication of allergic disease	3.196 (1.146, 8.908)	0.026*

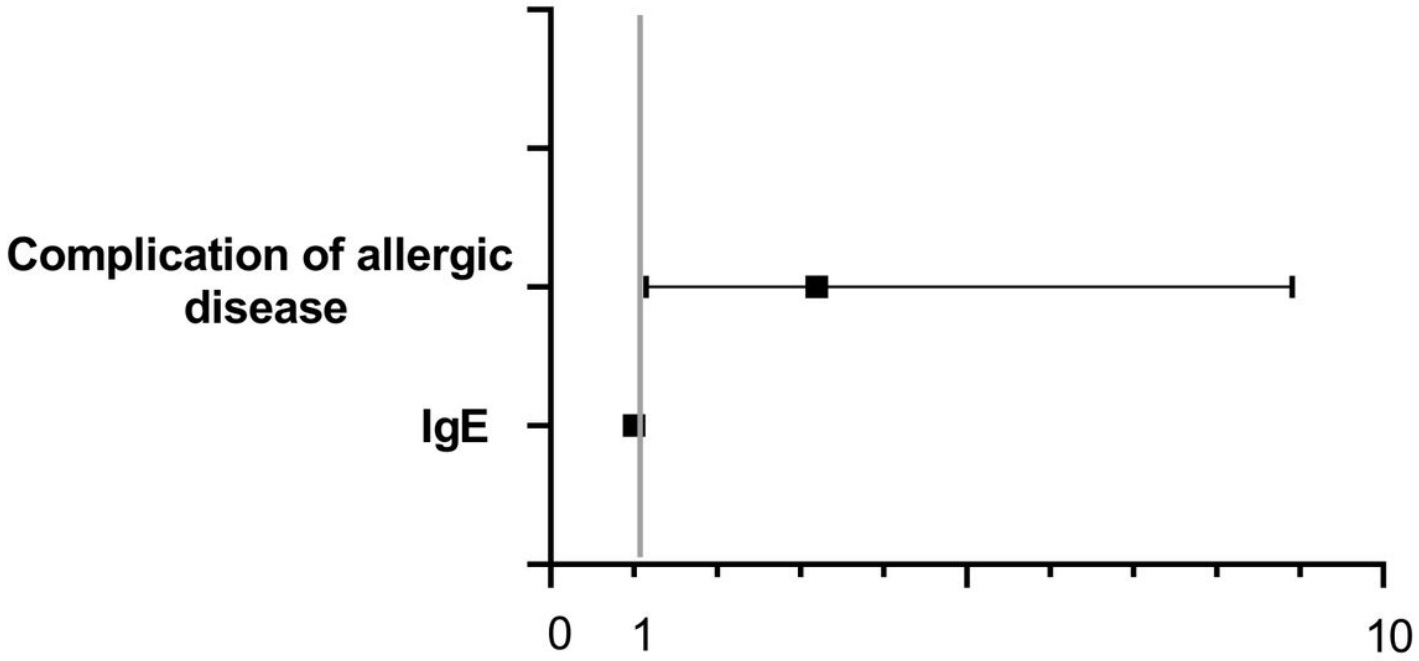

Figure 2

Multivariate analysis of logistic regression of IgG4-RD patients complicated with AR or CRS (Case group) High IgE level and complication of other allergic disease were risk factors for patients complicated with AR/CRS. IgG4-RD, IgG4-related disease; AR, allergic rhinitis; CRS, chronic rhinosinusitis; * means P-value <0.05

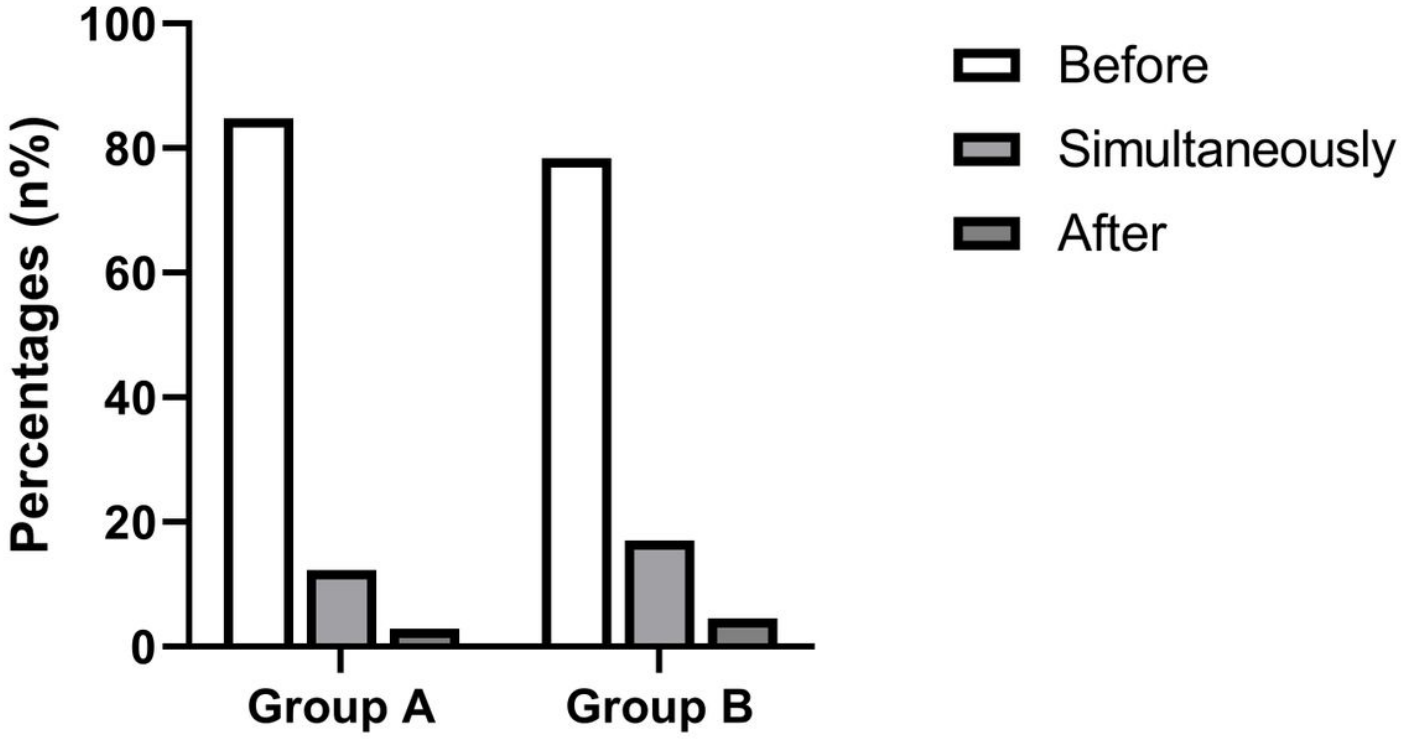

Figure 3

Chronological relationship of complication of AR/CRS and IgG4-RD diagnosis in IgG4-RD patients. In Group A (IgG4-RD complicated with AR), 84.83% patients had nasal symptoms before IgG4-RD diagnosis. In Group B (IgG4-RD complicated with CRS), 78.41% patients had nasal symptoms before IgG4-RD diagnosis. IgG4-RD, IgG4-related disease; AR, allergic rhinitis; CRS, chronic rhinosinusitis