

Staph's Toxins IgE Antibodies and Its Relation to the Severity of Allergic Rhinitis

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Background: Specific IgE against *Staphylococcus* can be found in approximately 40% of patients with allergies, also in patients without allergies because they may be sensitized. These antibodies are functional, and they can induce histamine release contributing to chronic pruritus which can worsen disease severity. The objective of this study was to compare levels of specific IgE against *S. aureus* toxins in those populations.

Methods: A cross-sectional, comparative non-blinded survey was made at the Regional Center for Allergy and Clinical Immunology. Ninety-nine adults between 18 and 70 years of age with allergic rhinitis (AR) and without allergic rhinitis (wAR) were recruited. A clinical history and demographic data, and allergic sensitization patterns to 35 aeroallergens were obtained, and participants were classified according to their severity using the Allergic Rhinitis and Its Impact on Asthma (ARIA) classification. Specific IgE levels were determined using ImmunoCAP™ 100 platform.

Results: The median age (IQR) of the participants was 23 (20–33.7); 56.2% were women. The most frequent comorbidities were asthma and obesity. Of the patients with AR, 46.7% were classified as mild intermittent and 25% as moderate persistent. IgE levels against staph toxins A, B, and TSST were significantly higher in the AR group vs the wAR group [median IQR 0.01 (0.01–0.03) vs. 0.01 (0–0.02), $p = 0.01$; 0.02 (0.01–0.03) vs. 0.01 (0–0.02), $p = 0.02$; 0.04 (0.02–0.09) vs. 0.01 (0–0.04), $p = 0.002$, respectively]. A significant difference was found in serum IgE levels against Staph B toxin between severity subgroups.

Conclusion: People with AR have higher IgE levels against staph toxins A, B and TSST than wAR subjects. However, it is not possible to declare that the IgE titers were related to disease severity.

Keywords: allergic rhinitis, ARIA, IgE, *Staphylococcus aureus*, staphylococcal superantigens

Introduction

A significant increase in allergic diseases has been observed globally in the last two decades. According to the World Health Organization, these conditions are among the most frequent diseases in pediatric and adult populations.^{1,2} It is estimated that 30 to 50% of the world population lives with one or more allergic diseases, of which 10–25% suffer from allergic rhinitis (AR).³ There is evidence that these diseases cause significant personal deterioration such as emotional problems, sleep disorders, and dysfunction in social activities.⁴ They also have a negative impact on the socioeconomic wellness of society.^{5,6}

Staphylococcus aureus is considered a bacterium of the human microbiota. Approximately 25% of the population are *S. aureus* carriers.⁷ However, although *S. aureus* infection can be a symbiosis, it can also be a life-threatening condition at the expense of staphylococcal superantigens (SS) that induce an inflammatory immune response.⁸

Specific IgE against *S. aureus* can be found in approximately 40% of patients with allergies, also in patients without allergies because they may be sensitized.^{9–11} Specific antibodies against *S. aureus* are functional as they bind with high affinity to their respective receptors on mast cell membranes, inducing histamine release and contributing to chronic pruritus.^{9,10,12} In allergic disease, SS increase antigen sensitivity and decrease the T-cell response to steroids, which can worsen disease severity.^{8,13} Nevertheless, it remains elusive if in individuals with and without AR differ the levels of specific IgE against *S. aureus toxins*, and its possible relation between the production of specific IgE and allergic respiratory severity. Our study aims to find the relationship, if any, between the IgE against *S. aureus toxins* levels and allergic respiratory severity.

Materials and Methods

Study Design

The present cross-sectional comparative survey recruited 99 Mexican patients with (n=64) and without (n=35) AR. All subjects, including healthy volunteers, were subjected to skin “prick” test (SPT) for aeroallergens. Diagnosis of AR was based on ARIA guidelines.¹⁴ Patients without AR were recruited through preventive campaigns and were referred to the Regional Center for Allergy and Clinical Immunology clinic (CRAIC) at the Hospital Universitario “Dr. José Eleuterio González”.

For study inclusion, subjects had to be over 18 years of age. Subjects with uncontrolled arterial hypertension, pregnant and/or breastfeeding, subjects who had suffered an upper respiratory tract infection four weeks before study entry, and patients who were taking antibiotics for any reason were excluded. Similarly, subjects who did not complete the evaluations and who withdrew informed consent were eliminated. Same exclusion criteria were applied to control group, additionally if the skin prick test was positive, the subject was excluded.

A 2:1 sample size calculation (cases: control) was performed, ensuring a power of 80% and a bilateral 95% confidence, to detect an elevation difference in IgE levels of 27%⁹ between the groups of patients without allergic rhinitis (control) and those with allergic rhinitis. A minimum sample of 60:30 participants respectively per group was needed.

Measurements

A complete medical history with an emphasis on personal and family history of allergic diseases was obtained. Demographic information for each patient and the skin prick tests to 35 aeroallergens (intramural and extramural) prevalent in our population were collected.

ARIA Classification

The severity of allergic rhinitis was determined according to the Allergic Rhinitis and its Impact on Asthma (ARIA) classification determining AR as mild and moderate and subdivided into persistent or intermittent, according to the level of symptoms.¹⁴

IgE Measurements

Serum measurements of specific IgE against *S. aureus* toxins, Staph A, Staph B, Staph C and Toxic Shock syndrome toxin (TSST) were performed using a fluor-enzymatic immunoassay autoanalyzer, the ImmunoCAP 100 platform (ThermoFisher), according to the manufacturer’s instructions. The measurements were carried out with a peripheral blood sample from the anterior fossa of the forearm.^{15,16}

Quality of Life

The self-applicable Spanish version of the rhinoconjunctivitis quality of life questionnaire (RQLQ) was used with all patients.¹⁷ This questionnaire assesses the domains of activity limitations, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems, and emotional function.

Ethical Considerations

This study was approved by the Research Ethics and the Research Committees of the Facultad de Medicina and Hospital Universitario, Universidad Autónoma de Nuevo León (Registration number AL14-003). All patients were informed of the objectives of the study and signed written informed consent.

Statistical Analysis

Descriptive statistics were applied to determine the frequency and proportions of demographic (gender) and clinical variables (allergic diseases and aeroallergens). For continuous quantitative variables (age and anti-*Staphylococcus* IgE levels) after a normality assessment (measured by asymmetry and kurtosis and the Kolmogorov Smirnov test), the median and the interquartile range (IQR) were used as a measure of central tendency and dispersion. IgE levels of the AR participants vs the controls were compared using the Mann Whitney *U*-test. The Kruskal–Wallis test was used to compare the severity subgroups. Significant differences between groups were represented by $p < 0.05$. *P* value thresholds were Bonferroni-corrected for multiple comparisons.¹⁸ SPSS version 23.0 statistical software (IBM Corp. Armonk, NY) was used for data processing.

Results

Demographic Data

Ninety-nine adults between 18 and 70 years of age with and without allergic rhinitis were recruited. Of these, 10 were eliminated for not having responded to the evaluation or withdrawing their consent (Figure 1). The median age and interquartile range of all participants was 23 years (20–33.7), 31.5 (22.4–40.7) for the allergic rhinitis group, and 20 (18–20.5) for the control group. Women represented 56.2%, of which 51.7% and 65.5% were in the AR and control groups, respectively (Table 1).

The most frequent comorbidities in the AR group were asthma, obesity, gastroesophageal reflux disease (GERD), and food allergy. On the other hand, the main allergens demonstrated by the skin “prick” tests in the AR population were *Dermatophagoides pteronyssinus* (71.7%), *Dermatophagoides farinae* (68.3%), *Fraxinus americana* (26.7%), *Cynodon*

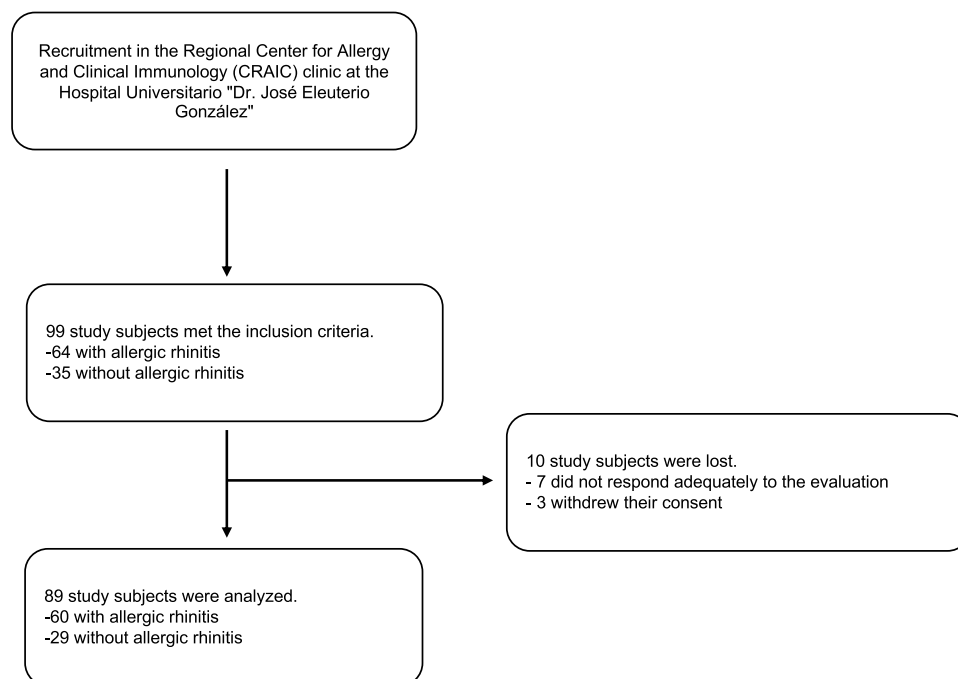


Figure 1 Study flow diagram.

Table 1 Demographic Characteristics

Characteristics	Total n=89	AR n=60	Control n=29	p-value
Sex, Women, n (%)	50 (56.2)	31 (51.7)	19 (65.5)	0.21
Age, years, median (IQR)	23 (20–33.7)	31.5 (22.2–40.7)	20 (18–20.5)	≤.001 ^a
Comorbilidades, n(%)				
Acute sinusitis	2 (2.2)	2 (3.3)	0 (0)	0.99
AERD	1 (1.1)	1 (1.7)	0 (0)	0.99
Allergic conjunctivitis	1 (1.1)	1 (1.7)	0 (0)	0.99
Anxiety disorder	3 (3.3)	2 (3.3)	1 (3.4)	0.99
Arterial hypertension	1 (1.1)	1 (1.7)	0 (0)	0.99
Asthma	16 (18)	16 (26.7)	0 (0)	0.001
Atopic dermatitis	3 (3.3)	3 (5)	0 (0)	0.54
Contact dermatitis	1 (1.1)	1 (1.7)	0 (0)	0.99
Food Allergy	5 (5.6)	5 (8.3)	0 (0)	0.16
GERD	9 (10.1)	7 (11.7)	2 (6.9)	0.71
Hypothyroidism	1 (1.1)	1 (1.7)	0 (0)	0.99
Keratosis pilaris	1 (1.1)	1 (1.7)	0 (0)	0.99
Nasal polyps	2 (2.2)	2 (3.3)	0 (0)	0.99
Nodular scleritis	1 (1.1)	1 (1.7)	0 (0)	0.99
Obesity	13 (14.6)	8 (13.3)	5 (17.2)	0.75
OCD	1 (1.1)	1 (1.7)	0 (0)	0.99
Pressure urticaria	1 (1.1)	1 (1.7)	0 (0)	0.99
Type 2 diabetes	1 (1.1)	1 (1.7)	0 (0)	0.99

Notes: ^ap-value, obtained by the Mann Whitney U-Test comparing AR against control. p-value, obtained by Fisher's exact test for 2×2 tables.

Abbreviations: AR, Allergic rhinitis; IQR, Interquartile range; GERD, Gastroesophageal reflux disease; AERD, Aspirin Exacerbated Respiratory Disease; OCD, Obsessive Compulsive Disorder.

dactylon (23.3%), *Periplaneta americana* (21.7%), and *Phleum pratense* (13.3%). All healthy volunteers (control) showed no reaction in response to these allergens (Table 2).

Proportion of Positive Specific IgE

The proportion of specific IgE against any of the 4 staphylococcal toxins, 79.3% for the control group and 83.3% for the AR group is compared in Table 3. When comparing positivity for toxins in isolation between these groups, no significant difference was found.

Table 2 Intramural and/or Extramural Aeroallergens Evaluated and Its Proportion in AR Patients

Allergens	Species
Dust	<i>Dermatophagoides farinae</i> (68.3%) and <i>Dermatophagoides pteronyssinus</i> (71.7%)
Fungi	<i>Alternaria alternata</i> (5%), <i>Aspergillus fumigatus</i> (1.7%), <i>Helminthosporium sativum</i> (5%), <i>Hormodendrum cladosporioides</i> (3.3%), <i>Penicillium chrysogenum</i> (1.7%), <i>Rhizopus nigricans</i> (1.7%)
Pastures	<i>Bromus</i> spp (10%), <i>Cynodon dactylon</i> (23.3%), <i>Holcus lanatus</i> (5%), <i>Lolium perene</i> (6.7%), <i>Phleum pratense</i> (13.3%), <i>Sorghum halepense</i> (13.3%)
Trees	<i>Fraxinus americana</i> (26.7%), <i>Juglans regia</i> (10%), <i>Juniperus sabinoide</i> (3.3%), <i>Ligustrum Vulgare</i> (3.3%), <i>Populus alba</i> (3.3%), <i>Prosopis</i> spp (6.7%), <i>Quercus</i> spp (15%)
Weeds	<i>Amaranthus palmeri</i> (10%), <i>Ambrosia elatior</i> (6.7%), <i>Artemisia ludoviciana</i> (6.7%), <i>Atriplex canescens</i> (21.7%), <i>Chenopodium amb</i> (8.3%), <i>Helianthus annus</i> (6.7%), <i>Salsola Kali</i> (1.7%)
Insects	<i>Periplaneta americana</i> (21.7%)
Others	<i>Canis familiaris</i> (3.3%), <i>Cotton</i> (1.7%), <i>Blatella germanica</i> (5%), <i>Felis domesticus</i> (5%), <i>Tobacco</i> (3.3%), <i>Wool</i> (0%).

Table 3 Presence of IgE Antibodies

Antibody	Total n (%) n=89	AR n (%) n=60	Control n (%) n=29	p-value
IgE (+)	73 (82)	50 (83.3)	23 (79.3)	0.76
IgE vs Staph A	62 (69.7)	43 (71.1)	19 (65.5)	0.62
IgE vs Staph B	65 (73)	44 (73.3)	21 (72.4)	0.99
IgE vs Staph C	61 (68.5)	42 (70)	19 (65.5)	0.80
IgE vs TSST	71 (79.8)	49 (81.7)	22 (75.9)	0.57

Notes: IgE (+). The presence of IgE was considered positive for any of the 4 toxins. p-value obtained by Fisher's exact test for 2×2 tables.

Abbreviations: AR, Allergic rhinitis; TSST, toxic shock syndrome toxin.

ARIA Classification and Specific IgE Levels

Of the 60 patients with AR, 46.6% were classified as mild intermittent (MiAR), 20% mild persistent (PMiAR), 8.3% moderate intermittent (MoIAR), and 25% moderate persistent (PMoAR). The IgE levels against toxins Staph A, Staph B, and TSST were significantly different, with higher values in subjects from the AR group compared to the control group. No difference was found between the IgE levels vs staph C toxin between the groups (Table 4).

When comparing the specific IgE serum levels against staphylococcal toxins in patients with AR classified by severity, a significant difference was found in serum IgE levels just against Staph B toxin between the subgroups. This difference was found between MiAR and PMiAR [median IQR 0.02 (0.0125–0.0575) vs. 0.01 (0–0.01), $p = 0.029$] (Table 5).

A comparison was made between the severity classifications of AR and the different domains evaluated by the RQLQ. In the seven domains of the RQLQ, the 28 patients classified with MiAR indicated less involvement compared to the rest of the subgroups. Statistically, a difference was found between the groups in 4 out of 7 domains: sleep, practical problems, nasal, and emotional symptoms. However, in the post hoc analysis with the Bonferroni correction just the 'nasal symptoms' domain was statistically significant between MiAR and MoPAR [median IQR 1.25 (0.56–1.75) vs. 3.25 (1.75–4.25), $p = 0.11$] (Table 6).

Discussion

In this study, we sought to correlate the sensitivity of IgE against *Staphylococcus aureus* in patients diagnosed with allergic rhinitis and compare the severity with the RQLQ developed by Junipper et al. A difference was found in the presence of IgE antibodies to staphylococcal toxins between the AR and control groups. Additionally, there was a difference between IgE immunoglobulins against Staph B toxin when subdivided, based on severity. On the other hand, in the different domains of the RQLQ, lower values were found in the mild intermittent allergy rhinitis group.

This leads us to infer that there is a relationship between the presence of antibodies and the presence of AR, but our data is not enough to support that this relationship were associated on severity. Meanwhile, the RQLQ reinforce that a classification of greater symptom severity has a greater impact on the different aspects of quality of life.

Table 4 Comparison of IgE Levels Against Staphylococcal Toxins Between the Allergic Rhinitis Group and the Control Group

IgE vs Toxin	AR n=60 Median (IQR)	Control n=29 Median (IQR)	p-value
Staph A	0.01 (0.01–0.03)	0.01 (0–0.02)	0.01
Staph B	0.02 (0.01–0.03)	0.01 (0–0.02)	0.02
Staph C	0.02 (0–0.03)	0.01 (0–0.05)	0.55
TSST	0.04 (0.02–0.09)	0.01 (0–0.04)	0.002

Note: p-value obtained by Mann Whitney U-test.

Abbreviations: AR, allergic rhinitis; IQR, Interquartile range; TSST, toxic shock syndrome toxin.

Table 5 Comparison of IgE Levels Against Staphylococcal Toxins in Patients with RA Between ARIA Classification Groups

IgE vs Toxin	MiIAR Median (IQR) n= 28	PMiAR Median (IQR) n= 12	MolIAR Median (IQR) n= 5	PMoAR Median (IQR) n= 15	p
Staph A	0.02 (0.01–0.045)	0.01 (0.0025–0.02)	0 (0–0.145)	0.02 (0.01–0.02)	0.285
Staph B	0.02 (0.0125–0.0575) ^a	0.01 (0–0.01) ^b	0.05 (0.01–0.075) ^{a,b}	0.02 (0.01–0.03) ^{a,b}	0.023
Staph C	0.025 (0.01–0.065)	0.01 (0–0.03)	0.01 (0.005–0.1)	0.02 (0.01–0.02)	0.293
TSST	0.05 (0.0225–0.11)	0.025 (0.012–0.08)	0.05 (0.025–0.13)	0.03 (0.02–0.1)	0.574

Notes: Data are median (IQR). Mild intermittent allergic rhinitis (MiIAR), Persistent mild allergic rhinitis (PMiAR), Moderate intermittent allergic rhinitis (MolIAR), and Persistent moderate allergic rhinitis (PMoAR); IQR, Interquartile range; TSST, toxic shock syndrome toxin. p-value obtained by the Kruskal–Wallis test. P value thresholds were Bonferroni-corrected for multiple comparisons. ^{a,b}Each superscript letter indicates a subset of groups whose column medians do not differ significantly from each other at level 0.05.

Table 6 Comparison of AR Classifications Between the Dimensions Evaluated by the RQLQ

Dimension	MiIAR n=28	PMiAR n=12	MolIAR n=5	PMoAR n=15	p-value
Daily activity	1.16 (0.66–1.91)	2.66 (0.66–2.66)	3.00 (0.83–4.16)	2.66 (1.00–3.00)	0.13
Sleep	0.33 (0.00–1.33)	0.66 (0.00–3.00)	2.00 (0.16–3.00)	2.33 (1.00–3.33)	0.02
General symptoms	0.85 (0.42–1.71)	1.28 (0.28–5.14)	2.14 (0.64–3.21)	1.85 (0.57–3.14)	0.15
Practical problems	1.00 (0.00–1.91)	2.00 (0.66–5.33)	2.33 (1.50–5.16)	2.66 (1.00–3.66)	0.01
Nasal symptoms	1.25 (0.56–1.75) ^a	2.50 (0.50–4.25) ^{a,b}	2.75 (1.62–3.87) ^{a,b}	3.25 (1.75–4.25) ^b	0.003
Eye symptoms	0.62 (0.25–1.68)	1.75 (0.25–4.00)	1.25 (0.37–2.75)	2.00 (0.50–3.00)	0.15
Emocional	0.50 (0.00–1.25)	1.50 (0.50–5.00)	2.00 (0.87–3.25)	2.25 (1.00–3.75)	0.005

Notes: Data are median IQR Mild intermittent allergic rhinitis (MiIAR), Persistent mild allergic rhinitis (PMiAR), Moderate intermittent allergic rhinitis (MolIAR), and Persistent moderate allergic rhinitis (PMoAR); IQR, Interquartile range; TSST, toxic shock syndrome toxin. p-value obtained by the Kruskal–Wallis test. P value thresholds were Bonferroni-corrected for multiple comparisons. Each superscript letter indicates a subset of groups whose column medians do not differ significantly from each other at level 0.05.

Some studies, as Rossi et al¹⁹ found an association between *S. aureus* superantigens and exacerbations in patients with allergic diseases. Interestingly, we could not be corroborated this finding; the specific IgE serum levels against staphylococcal toxins in patients with AR classified by severity did not differ. On the other hand, Shiomori et al²⁰ reported that allergic rhinitis makes it easier for patients to be *S. aureus* nasal carriers and that this factor seems to be detrimental in the disease. In our study, we did find a major proportion of *S. aureus* in AR patients but we could not associate it with disease severity.

The present study is subject to some limitations. Although participants of different ages and sexes were included to maintain representativeness, the control group was significantly younger. However, as stated by John Bradley in his review,²¹ the presence of IgE antibodies once exposed to *S. aureus* does not differ significantly once adulthood is reached, so we consider that it does not generate a major problem in our patients' results. In addition, each of the study participants underwent a skin prick test, ensuring that the control participants did not present reactivity to the 35 most common aeroallergens in our community, which, although in a small control group, ensures comparability between the groups.

With respect to IgE sensitization in patients with AR, some consideration should be highlighted. Future studies, with longer follow up periods should investigate the correlation between IgE sensitization with number of exacerbations and poor symptoms control despite treatment. If this association can be proven, clinicians could implement a more intense and individualized treatment approach, focused on antigen-IgE desensitization in order to reach an adequate symptom control.

Conclusions

The present study reinforces the hypothesis that subjects diagnosed with allergic diseases, in our case with AR, have higher specific IgE immunoglobulin levels against Staph A, B and TSST toxins compared to healthy subjects. However,

we did not have enough evidence to declare that IgE titles are related to the level of disease severity. More studies with a different methodological design are needed to assess whether there is an association between IgE levels and the occurrence of allergic diseases such as AR.

Disclosure

Rosa Ivett Guzmán-Avilán and Sandra Nora González-Díaz are co-first authors for this study. The authors report no conflicts of interest in this work.

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