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Brief Report

Association Between Staphylococcal Enterotoxin-Specific IgE and House-Dust-Mite-Specific IgE in Brazilian Patients with Chronic Rhinosinusitis with Nasal Polyps

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Abstract: Chronic Rhinosinusitis (CR) is a common inflammatory condition with complex pathophysiology involving multiple interleukins. In times of precision medicine, it is mandatory to cluster our patients to offer the best tailored treatment with the lowest cost possible. Therefore, some triage markers can be used towards this goal, without raising much financial burden. The aim of this study was to identify the association of staphylococcal enterotoxin (SE)-specific IgE of types A, B, C, and TSST-1 (toxic shock syndrome toxin-1); and total IgE (tIgE) and specific IgE for *Dermatophagoides pteronyssinus* (DP), *Dermatophagoides farinae* (DF), and *Blomia tropicalis* (BT) in Brazilian patients with CRSwNP. Thirty-six patients with CSRwNP were analyzed for serum IgE levels: tIgE and specific IgE for: DP, DF, BT, and SE types A, B, C, TSST-1 by ImmunoCAP®. The mean value of tIgE in SE-specific IgE-positive patients was 767 IU/mL and in house-dust-mite (HDM)-positive patients, the mean tIgE was 319 IU/mL ($p < 0.005$). A total of 86% of patients who had high tIgE levels but were SE-specific IgE-negative had positive specific IgE for at least one of the HDMs tested. The Fisher exact test statistic value for this association was significant ($p < 0.05/p = 0.014$). We found an association between high levels of tIgE and SE-specific IgE in patients with CRSwNP, possibly related to local and peripheric polyclonal IgE production. The mean value of tIgE—with a suggested cutoff point of tIgE levels of 767 IU/mL—can be used as a triage biomarker for positive SE-specific IgE in CRSwNP patients.

Keywords: Chronic Rhinosinusitis with Nasal Polyps; staphylococcal enterotoxin; House-Dust-Mite; IgE

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1. Introduction

Chronic Rhinosinusitis (CR) is a prevalent inflammatory disorder affecting the nasal and paranasal sinuses, persisting for 12 weeks or longer. Diagnosis requires at least two of the following symptoms: nasal obstruction or discharge, facial pain or pressure, and a reduction or loss of smell. Additionally, the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020) emphasizes the necessity of objective evidence of sinonasal inflammation through nasal endoscopy or computed tomography (CT) imaging [1].

CR significantly impacts global health, leading to increased healthcare utilization and reduced productivity [2]. The condition is categorized into primary and secondary types

based on etiology, with further classification into unilateral or bilateral presentations [1]. This study focuses on primary bilateral CR, specifically, Chronic Rhinosinusitis with Nasal Polyps (CRSwNP). In pediatric cases, nasal polyps are uncommon; when present, genetic disorders such as cystic fibrosis should be considered as potential underlying causes [2].

Assessing CR control involves evaluating symptoms' presence and their impact on quality of life. Validated questionnaires, such as the 22-item Sinonasal Outcome Test (SNOT-22), are employed to measure the disease-specific quality of life [3,4]. SNOT-22 assesses the severity of sinonasal symptoms over the preceding four weeks, with scores ranging from 0 (best) to 110 (worst). It encompasses various domains, including nasal symptoms, sleep function, and emotional consequences [4].

Objective measures, like the Lund–Kennedy Endoscopic Scoring System (LKESS), are also utilized to evaluate disease severity [5]. The LKESS assesses factors such as edema, polyps, scarring, crusting, and discharge in each nostril, with scores ranging from 0 (best) to 10 (worst). While widely used in clinical practice, some studies have reported a poor correlation between endoscopic findings and subjective symptoms [5].

The pursuit of precision medicine in CRSwNP has led to the identification of potential molecular targets correlated with prognosis and treatment resistance [6]. Biomarker testing, though financially burdensome, plays a crucial role in this endeavor [6]. CRSwNP, characterized by a complex interplay of multiple interleukins, has become a focal point in the era of biologics. The cost-effectiveness of targeted interventions depends on factors such as test accuracy and the costs of testing and personalized treatment [6]. Therefore, it is essential to balance the search for precision medicine approaches with the consideration of cost-effective triage tests and analyses [6].

Staphylococcal enterotoxins (SEs) are a group of high-molecular-weight superantigens implicated in various respiratory diseases, including rhinitis, asthma, and CRSwNP. SEs can trigger the production of specific IgE antibodies and are associated with elevated total IgE levels and eosinophilic inflammation [7–9]. Through the activation of T cells, SEs induce the release of interleukins such as IL-4, IL-5, and IL-13, promoting class switching to IgE and enhancing eosinophilic inflammation [10,11]. Additionally, *Staphylococcus aureus* can damage epithelial cells, leading to the release of alarmins, which activate type 2 innate lymphoid cells (ILC2), further contributing to eosinophilic inflammation and airway remodeling via IL-5 and IL-13 synthesis [10,11].

Severe CRSwNP is predominantly characterized by a Th2-skewed immune response, with up to 50% of patients exhibiting IgE antibodies against *S. aureus* enterotoxins [9]. The presence of these superantigens is associated with increased disease severity and resistance to standard treatments [9,12]. Understanding the role of SEs in the pathogenesis of CRSwNP is crucial for developing targeted therapeutic strategies aimed at modulating the immune response and improving patient outcomes.

This study aimed to identify a possible correlation between the positivity of SE-specific IgE of types A, B, C, TSST-1 (toxic shock syndrome toxin-1), tIgE, and specific IgE for *Dermatophagoides pteronyssinus* (DP), *Dermatophagoides farina* (DF), and *Blomia tropicalis* (BT) in Brazilian patients with CRSwNP.

2. Materials and Methods

This was an observational study carried out in Rio de Janeiro, Brazil in one health unit aimed at education, research, assistance, and technological development. Thirty-six patients with CSRwNP, defined by 2012-EPOS (European Position Paper on Rhinosinusitis) criteria and submitted to nasal endoscopy and CT scan of paranasal sinuses for diagnosis confirmation, were analyzed for serum IgE levels: total IgE and specific IgE for DP, DF, BT, and SE types A, B, C, and TSST by ImmunoCAP® method. The patients were also

evaluated for LKESS, presence or absence of asthma, and SNOT-22, validated for Brazilian Portuguese questionnaire [3]. The exclusion criteria were based in the classification of the patient with any type of CRS other than CRSwNP, or if the patient did not complete all above-mentioned tests and questionnaires. All patients signed an informed consent to undertake these procedures and permit data use. The data were stored in an Excel database, and statistical analysis was performed using SPSS software, version 23. The Mann–Whitney U tests were carried out to establish the relation between total IgE levels and LKESS; presence or absence of asthma; and SNOT-22. Categorical variables were presented as numbers and percentages and analyzed using Pearson's chi-squared test or Fisher's exact test, as appropriate; p values of <0.05 were considered statistically significant.

3. Results

The average age of the patients was 51.8, and 52% of them were women. The mean value of tIgE in SE-specific IgE-positive patients was 767 IU/mL, and in house-dust-mite (HDM)-positive patients, it was 319 IU/mL (Figure 1).

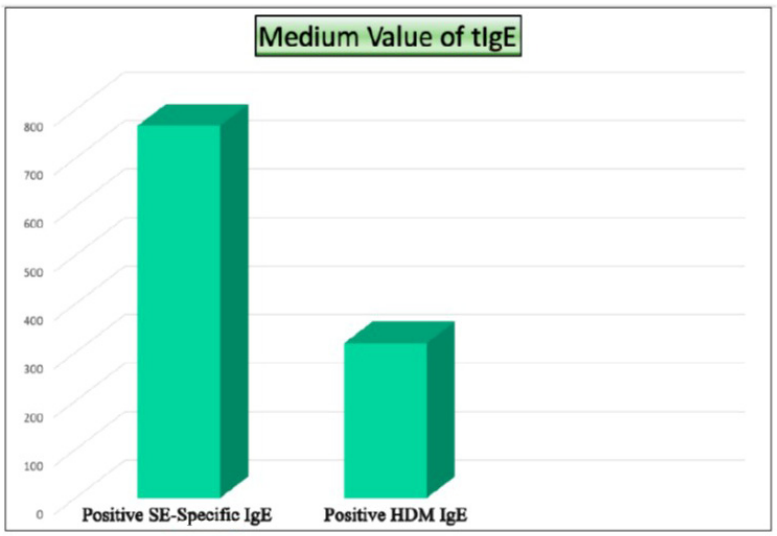

Figure 1. Medium total IgE.

Twenty-five patients (69.5%)—(Tables 1–3) were negative for SE-specific IgE. Of these, 72% also had low tIgE (<100 IU/mL). This relationship between low tIgE and negative SE-specific IgE was proved significant by the Mann–Whitney test, with $p < 0.005$ (Figure 2).

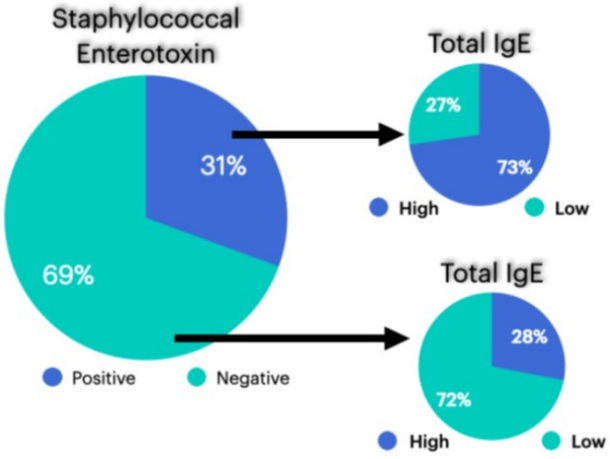

Figure 2. Staphylococcal enterotoxin IgE vs. total IgE.

Table 1. Profile of patients with low or normal total IgE (t-IgE) levels, combined with negative SE-specific IgE and negative HDM-specific IgE—Y (yes)/N (no).

Patient	Sex	t-IgE	Age	Asthma	Previous Surgeries	AERD	Lund–Kennedy Score	SNOT-22
1	F	5,3	76	Y	N	N	04	31
2	M	16	62	N	Yes, 1	N	06	40
3	M	15	63	Y	Yes, 1	N	02	08
4	M	13	45	Y	Yes, 1	Y	04	26
5	M	66	25	N	N	N	02	12
6	F	10	68	N	N	N	03	23
7	F	8,0	68	Y	N	N	02	30
8	M	65	51	N	N	N	02	12
9	F	24	34	N	N	N	03	19
10	M	87	56	N	N	N	04	27
11	F	9,0	46	N	N	N	02	21
12	F	6,4	55	Y	N	N	03	13
13	F	33	25	N	N	N	01	09

Table 2. Profile of patients with low or normal total IgE (t-IgE) levels, combined with negative SE-specific IgE and positive for at least one of HDM-specific IgE—Y (yes)/N (no).

Patient	Sex	t-IgE	Age	Asthma	Previous Surgeries	AERD	Lund–Kennedy Score	SNOT-22
14	M	25	20	N	N	N	02	28
15	M	68	73	Y	N	N	03	32
16	M	86,3	59	N	N	N	04	46
17	M	25	40	Y	N	N	03	36
18	M	60	39	Y	N	N	02	29

Table 3. Profile of patients with high total IgE (t-IgE) levels, combined with negative SE-specific IgE and positive for at least one of HDM-specific IgE—Y (yes)/N (no).

Patient	Sex	t-IgE	Age	Asthma	Previous Surgeries	AERD	Lund–Kennedy Score	SNOT-22
19	M	305	44	Y	Yes, 5	Y	02	37
20	F	360	14	N	Yes, 5	N	01	32
21	F	249	54	Y	Yes, 1	Y	03	10
22	F	214	40	N	N	N	02	20
23	F	234	50	N	N	N	02	31
24	F	544	58	Y	N	N	01	27
25	M	325	64	N	N	N	02	32

Of SE-specific IgE positive patients (11 patients, Tables 4–6), 73% of them had increased tIgE; this means that SE-specific IgE-positive patients had a prevalence ratio (PR) of 2.6 times increased tIgE than that of the population with negative SE-specific IgE. As shown in Figure 2, 85.7% of patients who had high tIgE levels but were SE-specific IgE-negative had positive specific IgE for at least one of the HDMs tested. The Fisher's exact test statistic value for this association also proved to be significant ($p < 0.05/p = 0.014$). The

Mann–Whitney U test showed that high total IgE levels (>100 IU/mL) had a correlation with higher scores of SNOT-22, above 25 points (U = 77,500; $p < 0.005$), with a risk ratio of 1.4 (40% higher chance of higher scores of SNOT-22 if the tIgE level is above 100 IU/mL). We found no correlation between higher scores of SNOT-22 and high scores in LKESS or presence of asthma and AERD. We also found that the chance of AERD presence was 2.1 times superior in patients with higher levels of total IgE (>100 IU/mL) than that in patients with low levels of it, independent of presence or absence of specific IgE measures for HDMs or SE-specific IgE.

Table 4. Profile of patients with high total IgE (t-IgE) levels combined with positive SE-specific IgE and positive for at least one of HDM-specific IgE—Y (yes)/N (no).

Patient	Sex	t-IgE	Age	Asthma	Previous Surgeries	AERD	Lund–Kennedy Score	SNOT-22
26	F	487	40	Y	Yes, 1	N	05	65
27	M	165	55	N	N	N	04	41
28	F	914	26	N	N	N	04	55

Table 5. Profile of patients with high total IgE (t-IgE) levels combined with positive SE-specific IgE and negative HDM-specific IgE—Y (yes)/N (no).

Patient	Sex	t-IgE	Age	Asthma	Previous Surgeries	AERD	Lund–Kennedy Score	SNOT-22
29	M	173	62	Y	Yes, 6	Y	08	73
30	M	149	43	N	Yes, 2	N	06	68
31	F	3040	58	Y	Yes, 1	N	04	71
32	F	1030	32	N	N	N	02	41
33	F	180	60	N	N	N	02	35

Table 6. Profile of patients with low or normal total IgE (t-IgE) levels combined with positive SE-specific IgE and negative HDM-specific IgE—Y (yes)/N (no).

Patient	Sex	t-IgE	Age	Asthma	Previous Surgeries	AERD	Lund Kennedy Score	SNOT-22
34	F	92	65	N	Yes, 1	Y	06	43
35	M	84	56	N	N	N	04	48
36	F	53	44	Y	N	N	04	27

The Pearson correlation coefficient (PCC) showed a positive association between the SNOT-22 score and higher total IgE levels (p: 0.003) and LKESS (p: 0.00), with a moderate and strong concordance in variation, respectively (PCC: 0.488; PCC: 0.677).

4. Discussion

The findings of this study highlight the significant relationship between Staphylococcal enterotoxin-specific IgE and total IgE levels in Brazilian patients with CRSwNP. Our results corroborate the existing literature that suggests SEs contribute to a heightened TH2 response, a hallmark of severe CRSwNP [13,14]. The marked elevation of tIgE levels in patients with positive SE-specific IgE underscores the potential role of these superantigens in exacerbating the inflammatory pathways associated with chronic airway diseases. We also showed a positive correlation between high IgE levels in AERD patients which is corroborated by many studies such as that by Van Zele Thibaut et al. that found significantly higher total IgE compared with that of other CRSwNP patients and control groups [7].

The striking prevalence ratio of 2.6 for increased tIgE levels among patients with positive SE-specific IgE supports the belief that sensitization to SEs is a critical factor in the immunological landscape of CRSwNP, such as data formerly published [10,11].

With these findings, we could suggest the cutoff point of tIgE levels of 767 IU/mL for the possible sensitization of Staphylococcal enterotoxin in CRSwNP patients, since above this value, all of our patients were sensitized only to SE and not HDM.

The observation that 85.7% of high tIgE levels in SE-negative patients were associated with positive specific IgE to at least one house dust mite indicates a complex interplay between multiple allergens, suggesting that patients may exhibit poly-sensitization. This poses a challenge for managing CRSwNP, as targeting only SE-specific IgE might not fully address the respiratory burden posed by other allergens such as house dust mites (HDM).

Furthermore, the presence of high tIgE levels in patients with negative SE-specific IgE suggests possible sensitization to unidentified aeroallergens. This could indicate a need for more extensive allergenic testing to identify additional potential triggers that could be contributing to chronic inflammation observed in this patient population [15]. Moreover, the relationship between alarmins released by epithelial cell damage and the activation of type 2 ILCs further emphasizes the roll of intricate mechanisms in CRSwNP, potentially resulting in progressive airway remodeling and loss of function.

The implications of these findings are profound, as they suggest that successful management of CRSwNP may require a multifaceted approach that considers both SE and HDM sensitivities. Immunotherapy targeting both superantigens and common allergens may be necessary to achieve better clinical outcomes.

Additionally, our results indicate the importance of individualized patient assessment in managing CRSwNP. As patients may present varying patterns of sensitization, personalized treatment plans that incorporate allergen avoidance and allergen-specific immunotherapy should be prioritized. This would enhance the potential for improved quality of life and alleviation of symptoms.

On top of that, considering the increasing complexity of precision medicine interventions that results in higher levels of uncertainty about the incremental cost-effectiveness ratio of these new tests [6], we are quite aware of the cost that ImmunoCap® testing is nowadays (about GBP 62.28 per person, for eight allergens tested) [15]. This knowledge improves the power of decision in clustering patients for better results not only towards treatment but also regarding proper financial health.

Concerning our limitations, due to the small study group, this paper has a low level of strength of evidence; the number of subjects enrolled in the study was not large enough to represent CRSwNP patients having various phenotypes. Additionally, this was a single-center study conducted at a tertiary care university hospital, in a single-demographic area of Brazil [16]. In addition, for more valuable data we could have measured eosinophil-activation markers, such as eosinophil cationic protein and eosinophil-derived neurotoxin [17].

5. Conclusions

In conclusion, our study emphasizes the correlation between SE-specific IgE and increased tIgE levels in CRSwNP, highlighting the need for comprehensive allergen testing and tailored therapeutic strategies with low-cost testing. Continuing to explore the complex interactions of multiple allergens and superantigens may pave the way for more effective interventions in managing this challenging condition without severe burdens in financial health.

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