

Immunoglobulin E to Staphylococcal and Streptococcal Toxins in Patients with Chronic Sinusitis/Nasal Polyposis

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Background: The role of infectious agents and their contribution to the inflammation in chronic sinusitis/nasal polyposis (CS/NP) is not clear. Staphylococcal and streptococcal toxins have superantigen activity and have been implicated in inflammatory conditions such as atopic dermatitis, psoriasis, and asthma. **Objective:** We investigated the presence of immunoglobulin (Ig)E antibodies to staphylococcal and streptococcal toxins in the serum of individuals with CS/NP. **Method:** IgE antibodies to staphylococcal exotoxins, A, B, and toxic shock syndrome toxin-1 and streptococcal pyrogenic exotoxin A, B, and C were measured in 23 individuals with CS/NP before functional endoscopic sinus surgery and in controls (7 atopic and 6 nonatopic) individuals without chronic sinusitis. Presence of IgE to the toxins was also correlated with disease severity on sinus computed tomography (CT) scans. **Results:** Staphylococcal and streptococcal toxin specific IgE antibodies were detected in 18 of 23 (78%) and 7 of 21 (33.3%) patients, respectively. None of the controls had IgE to the staphylococcal or streptococcal toxins ($P < .0001$). There was no association between radiographic severity of sinus disease and the presence of IgE antibody to the toxins. **Conclusion:** A significantly greater proportion of CS/NP patients had IgE to staphylococcal or streptococcal toxins. Evidence of IgE antibodies directed against staphylococcal and streptococcal toxins in the sera of patients with CS/NP suggests a potential role of these toxins with established superantigen effects in the pathogenesis of CS/NP. **Key**

Words: Chronic sinusitis, sinonasal polyps, superantigens, staphylococcal toxins.

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INTRODUCTION

Chronic rhinosinusitis (CRS) is one of the most common health care problems in the United States and affects almost 15% of the population.¹ Historically, research on CRS has been hampered by the lack of consensus on a precise definition. The Sinus and Allergy Health Partnership recently defined CRS as a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 consecutive weeks duration.² CRS is, therefore, currently viewed as a broad spectrum of diseases with variable clinical courses and responses to treatment. The most severe forms of CRS exhibit nasal polyposis, with a high rate of symptomatic recurrence despite optimal medical and surgical care.^{3,4} The etiology of chronic sinusitis with nasal polyposis (CS/NP) remains poorly understood; however, it is believed to be multifactorial, with infection, noninfectious inflammation, anatomic, and genetic abnormalities implicated in selected patients.²

The dominant role of bacterial pathogens in acute sinusitis is well established, with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* the most common agents. Analysis of both human and animal sinus tissue in this setting reveal bacterial tissue invasion with a predominantly neutrophilic response and a TH1 cytokine profile.² In contrast, the role of infectious agents and their contribution to inflammation in CRS with and without polyps is not clear, despite the observation that *Staphylococcus aureus* (*S. aureus*) often colonizes the nasal passages of these patients.⁵ Histologic analysis of the sinus mucosa of CRS fails to reveal signs of tissue invasion, demonstrating a predominantly eosinophilic and lymphocytic response, with a mixed TH1/TH2 cytokine profile in most cases.³ Despite the lack of clear scientific evidence for bacterial infection in CRS, antimicrobial ther-

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apy has remained the most common treatment for this disorder, with definite efficacy in some cases.²

Staphylococcus organisms cultured from nasal passages of patients with CRS have, in some cases, been shown to produce toxic shock syndrome toxin (TSST)-1.⁶ TSST-1 is one of an expanding class of virulence factors produced primarily by *Staphylococcal* and *Streptococcal* organisms known as superantigens (SAGs).⁴ SAGs are in some cases 10⁴ more potent than conventional antigens, triggering a massive T-cell response with resultant cytokine release.⁴ The association of a SAG response in human disease has been suggested for rheumatoid arthritis, diabetes mellitus, rheumatic fever, and Kawasaki's disease.⁷ Furthermore, evidence is emerging that staphylococcal and streptococcal SAGs may play a role in the pathogenesis of diseases such as allergic rhinitis, asthma, atopic dermatitis (AD), psoriasis, and possibly CRS.^{8–17} Specific immunoglobulin (Ig)E antibodies directed against staphylococcal exotoxins A and B (SEA, SEB) were detected in the nasal polyp tissue of 10 of 20 patients with CRS.⁸ Tissue concentrations of eosinophils, eosinophil cationic protein, LTC4/D4/E4, eotaxin, and interleukin-5 were higher in these patients compared with nonpolyp controls. Although the exact mechanism is not known, these findings suggest an association between the IgE antibodies to staphylococcal toxins and the eosinophilic inflammation seen in some individuals with polyps. Although 50% of the polyp patients still failed to demonstrate IgE to SEB or SEA, this study was limited to these two SAGs despite the possible presence of other bacterial toxins with known SAG capacity.⁸

In the current study, we have evaluated the presence of a systemic IgE antibody reaction directed against six staphylococcal and streptococcal toxins with established SAG capacity in patients with nasal polyps. The goals of this pilot study were to determine the prevalence of serum IgE antibodies against staphylococcal and streptococcal toxins in these patients and to compare the extent of radiographic disease on sinus computed tomography (CT) scans in patients with and without IgE to the toxins.

METHODS

Twenty-three consecutive patients with CS/NP (7 males, 16 females) who were scheduled for functional endoscopic sinus surgery were included in this study. All 23 had chronic sinusitis based on the guidelines established by the Sinus and Allergy Health Partnership for defining adult CRS along with confirmatory findings of mucosal inflammation on sinus CT scans.² All patients failed medical therapy for the control of symptoms and had bilateral nasal polyps on office endoscopy. Specifically, patients with an isolated antrochoanal polyp or unilateral nasal polyps were excluded from the study. Blood was collected from these individuals before the surgical procedure. The 13 control patients included seven atopic and six nonatopic volunteers without CRS. Details of patients' characteristics are included in Table I. None of the individuals had AD. All individuals were skin tested to pollens (tree, grass, and ragweed), dust mites, cat, dog, and molds with Hollister-Stier Canada Company (Toronto, Ontario) extracts. A positive skin test response was defined by a wheal of 3 mm or greater in size than that produced by the saline control. Histamine was used as a positive control. Allergic rhinitis individuals had at least one positive skin reaction with the prick-

TABLE I.
Clinical Characteristics of Subjects with Chronic Sinusitis/Nasal Polypsis.

Patient	Age	Allergic Rhinitis	Asthma	Aspirin Sensitivity
1	28	Yes	Yes	Yes
2	28	Yes	Yes	No
3	58	Yes	Yes	Yes
4	30	Yes	No	No
5	54	Yes	Yes	No
6	69	Yes	Yes	Yes
7	34	Yes	Yes	No
8	36	Yes	Yes	Yes
9	45	Yes	Yes	No
10	48	Yes	Yes	No
11	34	Yes	Yes	No
12	58	Not tested	No	No
13	60	No	Yes	No
14	28	Yes	Yes	No
15	51	Yes	No	No
16	50	Yes	Yes	No
17	28	Not tested	Yes	No
18	27	Yes	No	No
19	32	Yes	Yes	No
20	37	No	Yes	No
21	21	Yes	Yes	No
22	29	Yes	No	No
23	23	Yes	No	No

puncture technique to the extracts. Serum was obtained from all the patients before the surgical procedure as well as from the controls. IgE to staphylococcal exotoxins (SEA, SEB, and TSST-1) and streptococcal pyrogenic exotoxins A, B, and C (SPEA, SPEB, and SPEG) was determined by Toxin Technology Inc. (Sarasota, FL), as previously reported.^{18–22}

Preoperative sinus CT scans without contrast were staged by the radiologist who was blinded to each patient's clinical history and physical examination. The Lund-MacKay scoring system (0–24 point scale) was used to grade the severity of sinus disease.²³ Informed consent was obtained from the patients before the procedure, and the study was approved by the Institutional Review Board of Northwestern University Feinberg School of Medicine.

Statistical Analysis

The proportion of CS/NP versus control patients having IgE to either SEB or TSST-1 was compared with Fisher's exact test. The mean Lund-MacKay score was compared between patients "with" versus "without" IgE to SEB or TSST-1, and also between patients "with" versus "without" IgE to SPEA, using t test for independent groups.

RESULTS

As shown in Table II, IgE to SEB was detected in the serum from 14 of 23 (60.9%) patients with CS/NP (95% confidence interval [CI] = 40.9%–80.8%). Nine (39.1%) CS/NP patients had IgE antibody to TSST-1 (95% CI = 19.2%–59.1%), and five (21.8%) had IgE antibody to both SEB and TSST-1 (95% CI = 4.9%–38.6%). In contrast,

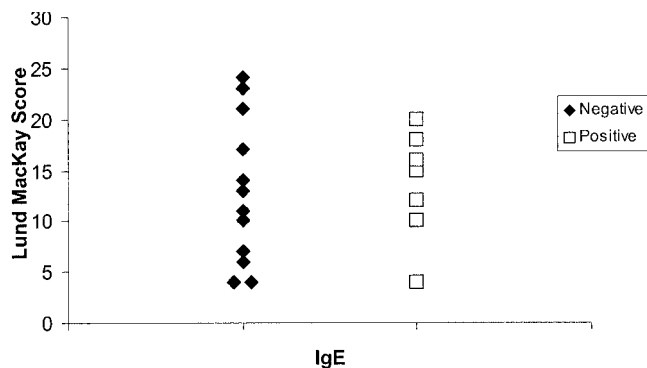


Fig. 2. Lund-Mackay score versus presence of Immunoglobulin (IgE) antibody to streptococcal pyrogenic exotoxins (streptococcal pyrogenic exotoxins A and C).

levels did not correlate with the presence of toxin specific IgE. The presence of IgE to the toxins, however, did not correlate with increased radiographic severity of CS/NP in this study.

The etiology and pathogenesis of CS/NP is the subject of considerable debate, and the role of bacterial toxins or IgE sensitivity to these toxins in this process remains uncertain.² Recent studies have identified fungi as well as bacteria colonizing or infecting the sinonasal mucosa of CS/NP patients; however, it remains unclear how these organisms could incite the lymphocytic and eosinophilic tissue response observed in most cases of this disorder.² Bacterial toxins provide a mechanism with the potential to generate these histopathologic changes, however. If present in the nose, bacterial toxins could trigger the inflammatory profile seen in CS/NP patients in at least two ways. First, staphylococcal and streptococcal toxins are known to act as SAGs capable of extensive, semispecific T-cell activation.^{9,10} In comparison with conventional antigens, SAGs do not require processing by antigen presenting cells (APC) but rather bind directly to the major histocompatibility complex (MHC) II.⁷ In addition, SAGs will also bind to the T-cell receptor (TCR) outside of the typical antigen binding site, resulting in an effective "clasp" between the T cell and the APC.⁷ SAGs bind the TCR in the V β region of the receptor and, given the limited variability of these sites, activation of up to 30% of the all T cells can occur in response to given SAG.⁷ This has the potential to generate a massive release of TH1 and TH2 cytokines at the site of the exposure. Second, bacterial toxins may also act as typical allergens, stimulating the production of IgE to these proteins.⁸ Repetitive exposure to these toxins in the nose has the potential to generate both a SAG and a chronic allergic response. Theoretically, the additive effect of these two processes should favor a lymphocytic and eosinophilic tissue infiltration characteristic of severe CS/NP.⁸

The current report demonstrates that a high percentage of CS/NP patients have evidence of a systemic IgE response to one or more staph or strep toxins with established SAG capacity. Although these results indicate a high incidence of exposure and sensitization to the toxins, specific evidence of involvement in the pathogenesis of

CS/NP is minimal. In AD and asthma, however, disorders that share many immunologic and histologic features with CS/NP, significant evidence has been developed. In AD, greater than half of the patients have skin colonization with *S. aureus* strains that are capable of secreting toxins with SAG activity.^{24–26} Furthermore, patients with AD often mount a systemic IgE immune response against these exotoxins that correlates with disease severity.^{22,27,28} In asthma, SEB exposure in mice airways is associated with increased upper airway hyper-responsiveness.¹⁴ Recently, a higher prevalence of T cells with restricted V β motifs to *S. aureus* SAGs has been demonstrated in the bronchoalveolar lavage of patients with severe asthma when compared with those with only mild disease.¹³ The selective proliferation of characteristic V β motifs is considered diagnostic of a SAG response.⁷ A recent preliminary study has identified similar V β clonal proliferation in the polyp lymphocytes of three CS/NP patients.²⁹ Taken together, it is reasonable to hypothesize that bacterial toxins may contribute to the pathogenesis of CS/NP as well, acting locally as both conventional allergens and SAGs triggering an eosinophilic and lymphocytic tissue infiltration.⁸ Further studies confirming this clonal proliferation in polyp lymphocytes, as well as demonstration of the actual toxins in the nose in CS/NP, are necessary to extend this hypothesis.

The incidence of IgE to staph was much higher than strep toxins in this study of CS/NP patients. This is consistent with the high incidence of toxin secreting *Staph aureus* noted in earlier studies.^{6,29} The incidence of toxin secreting streptococcal species in the nose is unknown, and their role, if any, in CS/NP remains uncertain. SAG streptococcal pyrogenic exotoxins have been implicated in the pathogenesis of psoriasis, a T-cell-mediated inflammatory skin disease often preceded by streptococcal throat infection.¹⁶ Because T cells and infections play a role in CRS, we investigated the presence of IgE to streptococcal toxins in these patients. We found evidence of IgE to streptococcal pyrogenic exotoxins in some patients; however, the significance needs to be further studied. With respect to individual staph toxins, the current study did not find evidence of IgE to SEA in the sera of any patients with CS/NP (0/23). This is in apparent contrast with Bachert et al.⁸ who detected IgE to both SEA and SEB in the polyp tissue of 50% of CS/NP patients (10/20) in that study. This variation may reflect regional differences in toxin expression that are believed to exist.³⁰ Both studies, however, had relatively small numbers, and the current study investigated systemic IgE, whereas Bachert et al. reported local IgE in the polyp tissue. In addition, Bachert et al. report positive findings for SEA and SEB together, so it is difficult to discern the percentage of each individual toxin in that study.

In conclusion, this report provides support for the hypothesis that bacterial toxins, particularly staph toxins, may play a role in the etiology and pathogenesis of CS/NP. These toxins have the capacity to act as both traditional allergens and SAGs, thereby possessing the theoretical ability to stimulate the lymphocytic/eosinophilic profile observed in the tissue of most CS/NP patients. Further studies are necessary to identify bacterial toxins in the

nose and to correlate the presence of these toxins with the clonal expansion of T cells in nasal polyp tissue.

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