

Chronic Sinusitis with Nasal Polyps: Staphylococcal Exotoxin Immunoglobulin E and Cellular Inflammation

David B. Conley, M.D.,* Anju Tripathi, M.D.,# Anne M. Ditto, M.D.,# Kathryn Reid, Ph.D.,§ Leslie C. Grammer, M.D.,# and Robert C. Kern, M.D.*

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ABSTRACT

Background: The etiology of chronic sinusitis with nasal polyposis (CS/NP) remains enigmatic. Frequently, *Staphylococcus aureus* is present in the nose of CS/NP patients, although the significance is unclear. Recent reports have suggested the hypothesis that these bacteria may secrete exotoxins triggering the inflammatory mucosal changes seen in CS/NP. This mechanism of immunopathology has been established in other diseases associated with *Staphylococcus* colonization and exotoxin secretion such as atopic dermatitis. In atopic dermatitis, the exotoxins incite a local superantigen response in which clonal T-cell activation and massive cytokine release occur in the affected skin. Second, these exotoxins can act as traditional allergens, stimulating a typical immunoglobulin E (IgE) response in the serum, which has been correlated with disease severity. This study is designed to begin the assessment of the hypothesis that a similar mechanism takes place in CS/NP.

From the *Department of Otolaryngology—Head and Neck Surgery, #Division of Allergy and Immunology, Department of Medicine, and §Center for Sleep and Circadian Biology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Address correspondence and reprint requests to David B. Conley, M.D., Department of Otolaryngology—Head and Neck Surgery, Northwestern University Feinberg School of Medicine, 303 East Chicago Avenue, Searle 12-561, Chicago, IL 60611

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Methods: Serum was drawn from patients with CS/NP undergoing endoscopic sinus surgery as well as 13 atopic and nonatopic control subjects without sinusitis. IgE levels to *S. aureus* exotoxins A (SEA), SE exotoxins B (SEB), and toxic shock syndrome toxin 1 were measured using enzyme-linked immunosorbent assay. Tissue eosinophilia and the presence of lymphocytes on hematoxylin and eosin-stained sections of polyps were scored by a blinded pathologist and correlated to presence of toxin IgE in the serum.

Results: Staphylococcal exotoxin (SE)-specific IgE was found in the serum of 5/10 (50%) of the patients with CS/NP. In contrast, 0/13 control patients had IgE to the exotoxins ($p = 0.031$). Polyp eosinophil, lymphocyte, and mononuclear cell counts were compared in IgE exotoxin-positive and -negative subjects. A trend toward increased eosinophil counts in patients with SE IgE (SE IgE⁺) was present, but not statistically significant.

Conclusion: These results indicate that a high percentage of CS/NP patients show a systemic IgE response to *S. aureus* exotoxins in comparison with controls without CS/NP. Although these results are consistent with the actions of *Staphylococcus* toxins in other diseases, additional work is necessary to establish a local superantigen response in the nasal mucosa of CS/NP patients. (American Journal of Rhinology 18, 273–278, 2004)

The etiology and pathogenesis of chronic sinusitis (CS) is poorly understood and multiple factors likely contribute to this frequently reported chronic disease. Subsets of patients with CS have nasal polyps, in general comprising the groups most recalcitrant to treatment, given the high

recurrence rate despite aggressive medical and surgical therapy. These patients have been classified as having "chronic hyperplastic sinusitis/nasal polyposis (CS/NP)" or "hyper-trophic sinusitis" with the histological hallmark of dense eosinophilic infiltration.¹ Infection, noninfectious inflammation, and anatomic abnormalities are the main factors considered to contribute to CS in general and CS/NP in particular. Recent studies have highlighted the possible role of the eosinophil as the key mediator of tissue damage in CS.²⁻⁴

The role of infectious agents and their contribution to CS/NP is not clear, although reports have suggested that fungi may play a critical role.⁵ Alternatively, chronic bacterial colonization and/or infection, in particular with *Staphylococcus aureus*, also has been suggested as an etiologic agent.⁶ Frequently, this organism is cultured from the nasal passages of patients with polyps, but infection alone appears unlikely to be responsible for the type of inflammation seen in CS/NP.⁷ *S. aureus* cultured from nasal passages of patients with CS has been shown to produce exotoxins.⁸ Both *in vitro* and *in vivo* studies have established that many of these staphylococcal exotoxins have superantigen (SAg) activity.⁹ SAg's have the capacity to bypass the classic specificity restrictions inherent in the immune response resulting in 1000- 10,000-fold greater potency than conventional antigens in triggering T-cell proliferation and cytokine release.¹⁰ This classic SAg response has been implicated in the pathogenesis of chronic inflammatory diseases such as asthma and atopic dermatitis.¹¹⁻¹⁴ A recent preliminary report now has provided the first evidence of an SAg response to staphylococcal exotoxins in CS/NP.¹⁵

The host response to SAg exposure is extremely complex, controlled by the specific toxin, the site of exposure, the concentration of the toxin, and the genetics of the host among other factors.¹⁶ These variables make a direct systematic analysis of SAg effects in nasal polyp tissue problematic, particularly given that these substances are biologically active in picogram per milliliter concentrations.¹⁰ In atopic dermatitis (AD), the disease associated most closely with staphylococcal exotoxins with the best-characterized SAg response, toxins mediate a classic T-cell reaction in the exposed skin.¹⁷ In addition, SAg's act as typical allergens in the most severe cases of AD, generating a measurable serum immunoglobulin E (IgE) response to one or more staphylococcal toxins.¹⁸ In CS/NP, preliminary studies have shown IgE antibodies to staphylococcal exotoxins in the polyp tissue of 5/10 patients.⁶ These findings further suggested an association between the presence of IgE antibodies to staphylococcal toxins and the intensity of eosinophilic inflammation.

In this study, we have evaluated the serum of CS/NP patients for the presence of IgE antibodies directed against the three best-characterized staphylococcal toxins (*S. aureus* exotoxin A [SEA], *S. aureus* exotoxin B [SEB], and toxic shock syndrome toxin [TSST] 1). These toxins have established SAg effects in AD.¹⁹ The goals of this pilot

study are to determine the prevalence of serum IgE to SAg's in CS/NP patients and to attempt to correlate this with the intensity and cellular profile of the local inflammatory response in the polyp tissue. Ultimately, this research is designed to not only provide additional evidence for an SAg response in CS/NP, but also to explore the potential for the use of a straight-forward serum test to characterize the nature of the inflammation in an individual patient.

MATERIALS AND METHODS

Ten patients with CS/NP underwent endoscopic sinus surgery by and were sequentially included in the study. CS was defined based on guidelines established by The Sinus and Allergy Health Partnership.²⁰ All patients also had obvious nasal polyps on office endoscopic examination, positive sinus CT scans, and failed to gain adequate control of their symptoms with medical therapy. To be a candidate for surgery, patients received a minimum of 4 weeks of broad-spectrum oral antibiotics and nasal steroids. All patients received oral steroids consisting of 30-50 mg of prednisone per day for 4-5 days before surgery. Blood and nasal lavage were collected from these patients before the surgical procedure. Controls included seven atopic and six nonatopic individuals without CS. Clinical details are included in Table I. Allergic rhinitis was defined by at least one positive skin reaction with the prick-puncture technique to extracts of common allergens such as tree, grass, ragweed, house-dust mites, cat or dog dander, or molds. A positive skin test response was defined by a wheal of ≥ 3 mm in size than that was produced by a saline control. Histamine was used as a positive control. Serum was obtained from all patients before the surgical procedure as well as from the controls. Presence or absence of serum IgE to staphylococcal exotoxins (SEA, SEB, and TSST-1) was determined by Toxin Technology as previously reported.^{17,21-24} Surgical polyp specimens were collected during endoscopic sinus surgery and tissue was processed in formalin and paraffin embedded. Four-micron sections were stained with hematoxylin and eosin and scored for eosinophil density. Additional sections were stained with CD4, CD8, CD14, and CD20 antibodies: CD4 AB-8 (clone 4B12; NeoMarkers, Fremont, CA), anti-human CD8 (clone C8/114B; DAKO, Glostrup, Denmark), CD14 Ab-2 (clone 14C02; same as 7; NeoMarkers), anti-human CD20cy, B cell (clone L26; DAKO). CD4 is the standard immunohistochemical marker for T-helper cells, CD8 is standard for cytotoxic T cells, CD14 is standard for myelomonocytic cells, and CD20 is standard for B cells. Microscopic evaluation was performed at 400 $\times$ (high-power field) in the lamina propria of the polyp in both randomly selected high-power fields as well as selected high-power fields where dense cellular infiltration was present. Positively stained cells were counted over 20 high-power fields and the number was divided by two with data reported as "cells per 10 high-power fields (cells/10 hpf)." Statistical analysis

TABLE I

Clinical Characteristics and Serum IgE Status of Subjects

Patient	Age (yr)	Allergic Rhinitis	Asthma	Aspirin Sensitivity	Anti-SEB	Anti-TSST
1	60	Yes	No	No	—	—
2	28	Yes	Yes	No	—	+
3	28	Yes	Yes	Yes	—	—
4	51	Yes	No	No	—	—
5	27	Yes	No	No	—	—
6	30	Yes	No	No	—	—
7	54	Yes	Yes	No	+	+
8	48	Yes	Yes	No	+	—
9	50	Yes	Yes	No	+	—
10	28	Not tested	Yes	No	+	—

Clinical characteristics (age, AR, asthma, aspirin sensitivity) of subjects with CS/NP who underwent endoscopic sinus surgery and status of anti-staphylococcal toxin IgE antibodies (anti-SEB and anti-TSST).

AR = allergic rhinitis.

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was performed using a nonparametric assessment (two-tailed Mann–Whitney *U*-Wilcoxon rank sum *W* test) of the cell counts in the two groups of patients. Informed consent was given by patients before the surgery and the study was approved by the Institutional Review Board of Northwestern University Medical School.

RESULTS

IgE to SEB and TSST-1

IgE to SEB or TSST-1 was present in the serum of 5/10 (50%) of the patients with CS/NP. No patient showed IgE to SEA in this study. In the control group, 0/13 control patients had IgE to the exotoxins (Table I). This difference between CS/NP patients and controls is statistically significant at $p = 0.031$ by Fisher's exact test.

Eosinophils

Eosinophils were counted in randomly selected high-power fields as well as high-power fields selected for areas of increased cellular infiltrate.

Randomly Selected Fields

The mean eosinophil density for staphylococcal exotoxin IgE antibody-negative patients (–IgE SE) was 66.4 cells/10 hpf $\pm$ 123.2 SD. For staphylococcal exotoxin IgE antibody-positive patients (+IgE SE), there were 109 cells/10 hpf $\pm$ 52.3 SD. These groups were not statistically different by a two-tailed Mann–Whitney *U*-Wilcoxon rank sum *W* test ($p = 0.12$) but a trend was present with higher eosinophil counts in the +IgE SE group (Table II).

Fields Selected for Dense Cellular Infiltrate

The mean eosinophil density for –IgE SE patients was 141.8 cells/10 hpf $\pm$ 216.7 SD. For +IgE SE patients, there were 398.4 cells/10 hpf $\pm$ 185.9 SD. These groups were not statistically different by a two-tailed Mann–Whitney *U*-Wilcoxon rank sum *W* test ($p = 0.07$) but a trend was present with higher eosinophil counts in the +IgE SE group (Table II).

Lymphocytes and Mononuclear Cells

Lymphocytes and mononuclear cells were counted in fields selected for dense cellular infiltrate. The mean CD4 density for –IgE SE was 403.2 cells/10 hpf $\pm$ 115.1 SD and +IgE SE was 502.4 cells/10 hpf $\pm$ 119.7. The mean CD8 density for –IgE SE was 527.4 cells/10 hpf $\pm$ 227.6 SD and +IgE SE was 776.4 cells/10 hpf $\pm$ 186.2. The mean CD14 density for –IgE SE was 123.2 cells/10 hpf $\pm$ 108.5 SD and +IgE SE was 337.8 cells/10 hpf $\pm$ 241.7. The mean CD20 density for –IgE SE was 334.2 cells/10 hpf $\pm$ 159.5 SD and +IgE SE was 728.8 cells/10 hpf $\pm$ 514.4 (Table III). None of these means was statistically different (–IgE SE group in comparison with +IgE group) using Mann–Whitney *U*-Wilcoxon rank sum *W* test: CD4 ($p = 0.35$), CD8 ($p = 0.07$), CD14 ($p = 0.17$), and CD20 ($p = 0.25$).

DISCUSSION

This study identifies the presence of serum IgE antibodies to staphylococcal exotoxins in 5/10 CS/NP patients as opposed to 0/13 controls. This difference is statistically significant and does not appear related to atopic status because seven of the controls were defined as having classic atopy based on positive skin testing to common allergens. The study further attempted to correlate the pres-

TABLE II

Mean Eosinophil Counts in Patients with and without IgE to Staphylococcal Enterotoxins

Fields Selected Randomly			Fields Selected for High Density		
	IgE SE–	IgE SE+		IgE SE–	IgE SE+
	1	195		1	691
	14	104		77	406
	4	108		21	421
	27	82		86	235
	286	56		524	239
Mean	66.4	109	Mean	141.8	398.4
SD	123.1799	52.345	SD	216.683	185.938

Mean eosinophil counts/10 hpf for each subject sorted by the absence or the presence of IgE to SEB or TSST-1 (IgE SE– or +). Fields are either chosen randomly or by identification of areas of dense cellular infiltrate. The difference between means 66.4 and 109 in the randomly selected fields is not statistically significant by two-tailed Mann-Whitney U–Wilcoxon rank sum W test ($p = 0.12$). The difference between means 141.8 and 398.4 in the densely selected fields is not statistically significant by two-tailed Mann-Whitney U–Wilcoxon rank sum W test ($p = 0.07$).

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TABLE III

Lymphocyte and Mononuclear Cell Densities

IgE SE		Subject					Mean	SD
		1	2	3	4	5		
Absent	CD4	309	503	305	550	349	403.2	115.1
Absent	CD8	195	459	735	747	501	527.4	227.6
Absent	CD14	20	246	5	137	208	123.2	108.5
Absent	CD20	184	154	460	366	507	334.2	159.5
Present	CD4	702	630	601	251	328	502.4	199.7
Present	CD8	1010	859	829	535	649	776.4	186.2
Present	CD14	497	639	360	78	115	337.8	241.7
Present	CD20	962	804	1426	168	284	728.8	514.4

Lymphocyte and mononuclear cell counts/10 hpf for each subject sorted by the absence or presence of IgE to SEB or TSST-1. The differences between CD subsets were not significant by two-tailed Mann-Whitney U–Wilcoxon rank sum W test: CD4 ($p = 0.35$), CD8 ($p = 0.07$), CD14 ($p = 0.17$), CD20 ($p = 0.25$).

ence or absence of serum IgE to staphylococcal exotoxins with a density of inflammatory cell types in the polyps. No difference was seen in CD4, -8, -14, or -20 expressing cells. A trend toward increased polyp eosinophilia was apparent in patients with serum IgE directed against staphylococcal toxins, but this did not reach statistical significance. Nevertheless, these results support and extend earlier findings where IgE directed against staphylococcal exotoxins was identified directly within the polyp tissue of 50% of CS/NP patients.⁶ This earlier study was able to establish a correlation between the presence of IgE to staphylococcal toxins in polyps and tissue eosinophilia.⁶ Overall, these two studies indicate that a high proportion of CS/NP patients will show an IgE response to staphylococcal exotoxins, suggesting a potential link between allergy and infection in this disease.

Furthermore, these studies support the hypothesis that staphylococcal exotoxins, with known SAg activity, contribute to the pathogenesis of CS with NP.

Staphylococci are cultured frequently in CS and a recent study, using multiple cultures per patient, indicated a 100% incidence of staphylococcal species in 10 CS/NP patients.¹⁵ Furthermore, 5/10 patients were toxigenic strains of *S. aureus* that produced SEA, SEB, or TSST-1 *in vitro*.¹⁵ If these bacteria also produced these toxins in the nose, multiple host reactions are possible. First, because these toxins are foreign proteins, they will be processed as typical antigens by antigen-presenting cells. This results in the presentation of peptide fragments of the toxin in conjunction with major histocompatibility complex (MHC) class II molecules on the surface of the antigen-presenting cells. T-helper cells

possessing specific T-cell receptors (TCRs) that bind the antigen then will be stimulated and the normal protective immune response will occur. Second, these toxins also have the capacity to act as SAg's in that they can directly bind the MHC class II proteins and the TCR outside the peptide binding groove, without the normal constraints of antigen processing, presentation, or specificity.¹⁰ The SAg will act as a "clamp," binding the variable portion of the β -chain (V β) of the TCR to the MHC class II molecule, resulting in a 1000- to 10,000 greater response than typically processed antigens.¹⁰ Because the number of different V β -regions is limited (<50 in the human) and most SAg's can bind more than one, up to 30% of a patient's T cells can be activated by a given SAg.¹⁶ Each SAg is associated with a characteristic "V β -signature" so that only T cells bearing particular V β -segments will be stimulated by a given SAg. Preliminary evidence of a V β -signature recently has been shown in the polyp tissue of three patients with CS/NP.¹⁵ In the classic SAg response, T-cell proliferation will occur, with the release of cytokines including interleukin (IL)-3, IL-4, IL-5, and granulocyte macrophage-colony-stimulating factor; eosinophils also will be recruited and activated.²⁵ The third potential host response to staphylococcal toxin is to treat the protein as a typical allergen, with a systemic and local IgE response and histamine release on repeat toxin exposure.¹⁹ As mentioned previously, one recent study showed IgE directed against staphylococcal toxins in nasal polyps.⁶ This study is the first demonstration of serum IgE directed against staphylococcal toxins in CS/NP patients. If bacteria secreting these toxins are present in the nose of sensitized patients such as those identified in this study, one would anticipate the potential for chronic allergic stimulation with subsequent recruitment of eosinophils, characteristic of the late phase of the allergic response.

Evidence for involvement of staphylococcal toxins in CS/NP is only preliminary. This study provides evidence for a systemic IgE response to these toxins in a high proportion of CS/NP patients; however, no claims can be made regarding direct pathogenic effects in the nose from these results alone. Staphylococcal toxins have been implicated in the pathogenesis of other chronic inflammatory diseases, which share similarities to CS/NP, such as AD and asthma. In asthma, a V-signature has been identified in the bronchoalveolar lavage fluid of severe asthmatic patients as compared with well-controlled patients.¹³ In addition, airway exposure in mice to staphylococcal exotoxin B induced lymphocytic airway inflammation and increased airway responsiveness.¹⁴ Studies of AD have identified skin colonization with *S. aureus* that secrete SAg's in >50% of patients.²⁶⁻³⁰ Furthermore, patients with the most severe forms of AD generate IgE to these toxins.¹⁸ The presence of IgE to these toxins has been shown to correlate with disease severity and dermal T-cell infiltration in AD.²⁶ The typical allergic pathway appears to combine with the local SAg response in patients with the most severe forms of AD.

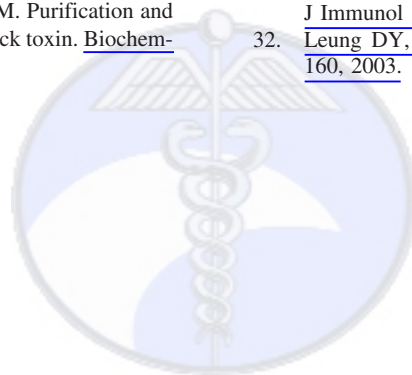
CS/NP is an inflammatory disorder characterized by tis-

sue infiltration of lymphocytes and eosinophils in its most severe forms.²⁰ Inflammatory triggers in CS/NP remain a subject of debate but this study, together with the earlier work mentioned previously, supports the hypothesis that staphylococcal toxins may play a role in some patients. In the further testing of this hypothesis, it should be kept in mind that the response to these toxins is controlled genetically. The capacity to generate an SAg response by a given individual is determined by the specific MHC class II alleles expressed generating a spectrum of susceptibility in a population.³¹ Second, the tendency to mount an IgE response to a given toxin also is, in part, genetically determined but by different loci.³² By analogy with AD, we would hypothesize that the most severe forms of CS/NP would have the genetic capacity to respond to staphylococcal toxins as both an allergen and an SAg. Additional studies are necessary to assess the validity of these hypotheses.

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