

Total and specific IgE in nasal polyps is related to local eosinophilic inflammation

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Background: Nasal polyps (NPs) are characterized by eosinophilic inflammation and often coexist with asthma. However, the role of atopy and IgE in NP pathogenesis is unclear. **Objective:** We sought to determine whether there is an association between total and specific IgE to a variety of allergens in polyp and nonpolyp tissue and markers of eosinophilic inflammation or skin test results.

Methods: Homogenates were prepared from nasal tissue of 20 patients with NPs and 20 patients without NPs and analyzed for concentrations of IL-5, IL-4, eotaxin, leukotriene (LT) C4/D4/E4, sCD23, and histamine (ELISA). Eosinophil cationic protein (ECP), tryptase, and total and specific IgE for inhalant allergens and *Staphylococcus aureus* enterotoxins were measured (ImmunoCAP).

Results: The concentrations of total IgE, IL-5, eotaxin, ECP, LTC4/D4/E4, and sCD23 were significantly higher in NP tissue compared with nonpolyp tissue. Total IgE was significantly correlated to IL-5, ECP, LTC4/D4/E4, and sCD23 and to the number of eosinophils in NPs. On the basis of the presence of specific IgE antibodies in tissue, 3 NP groups were defined. NP group 1 demonstrated no measurable specific IgE, and NP group 2 selected specific IgE. The third group demonstrated a multiclonal specific IgE, including IgE to *S aureus* enterotoxins, a high total IgE level, and a high prevalence of asthma. **Conclusions:** These studies suggest that there is an association between increased levels of total IgE, specific IgE, and eosinophilic inflammation in NPs, which may be of relevance in the pathophysiology of nasal polyposis. Similarly, the presence of specific IgE to staphylococcal enterotoxins A and B also points to a possible role of bacterial superantigens. (J Allergy Clin Immunol 2001;107:607-14.)

Key words: Nasal polyps, eosinophils, atopy, IL-5, total IgE, specific IgE, sCD23, eotaxin, *Staphylococcus aureus* enterotoxins, superantigens

Clinically, nasal polyps (NPs) are characterized by edematous masses in the nasal and paranasal cavities, leading to nasal obstruction, secretion, loss of smell,

Abbreviations used

ECP: Eosinophil cationic protein
HSA: Human serum albumin
IQR: Interquartile range
LT: Leukotriene
NP: Nasal polyp
SEA: Staphylococcal enterotoxin A
SEB: Staphylococcal enterotoxin B

headache, and reduced general well-being. Nasal polyposis is believed to be a multifactorial disease that is frequently associated with asthma and aspirin sensitivity, but the mechanisms underlying the cause of this disease are thus far ill defined.^{1,2}

Although an allergic cause of nasal polyposis had been presumed since the early 1930s,³ this suggestion was challenged in the 1970s, when a retrospective study by Settiple and Chafee⁴ demonstrated that more NPs were found in the nonatopic group than in the atopic group, and subsequent studies demonstrated that multiple positive skin test responses were less common in patients with NPs compared with responses in the general population.⁵ However, tissue IgE concentrations have been found to be increased irrespective of skin test results, suggesting a possible local IgE production.^{5,6} Remarkably, studies of patients with seasonal allergy with NPs have demonstrated that symptoms and markers of eosinophilic inflammation are not influenced by the season.^{5,7} Thus the relationship between NPs, IgE, and allergy is not clearly understood.

A drawback in elucidating the cause and pathologic mechanisms of this disease is the lack of a widely accepted classification that includes clinical history and histology to differentiate between the various forms of nasal polyposis. Stammberger⁸ has recently proposed a classification for NPs and suggested that bilateral polyps are frequently linked to asthma and aspirin sensitivity. Indeed, bilateral polyps are the most predominant type of NPs, covering 80% to 90% of polyp disease in Europe and the United States, and are associated with tissue eosinophilia in most cases.⁹

A key to understanding polyp pathophysiology is the regulation of recruitment, activation, and survival of eosinophils, as well as their effect on polyp formation and growth.¹⁰ We have demonstrated that synthesis of IL-5 and survival of eosinophils is significantly increased

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in NP tissue compared with nonpolyp control tissue.^{11,12} Additionally, ex vivo studies demonstrated that eosinophil survival was decreased by incubation with anti-IL-5–neutralizing mAbs, suggesting a functional role for IL-5 in the regulation of eosinophil survival.¹²

In the current study we aimed to investigate the possible effect of atopy (skin prick test positivity) and local IgE on eosinophilic inflammation. Therefore total and specific IgE levels to common inhalant allergens were measured in NP and nonpolyp tissue homogenates. Because *Staphylococcus aureus* enterotoxins have been shown to modify atopic dermatitis^{13,14} and unstable asthma,^{15,16} we also investigated the nasal tissues for the presence of specific IgE to these enterotoxins to elucidate whether these may also play a role in the pathophysiology of nasal polyposis.

METHODS

Patients

Nasal tissue was obtained from 20 patients with bilateral NPs and 20 patients without NPs outside the pollen season at the Department of Otorhinolaryngology, Ghent University Hospital. Approximately 0.5-cm³ tissue strips were collected from the surface of each inferior turbinate (turbinatectomy, 0.2–0.5 g of tissue) or bilateral NP (0.2–2.0 g of tissue) during routine septal and sinus surgery, respectively.

Bilateral polyposis was diagnosed on the basis of history, clinical examination, nasal endoscopy, and sinus computed tomography scanning, according to the classification of Stammberger.⁸ A history of asthma was reported in 4 patients without NPs and 11 patients with NPs, with 2 subjects in the NP group also demonstrating a history of aspirin sensitivity. The atopic status of all patients was evaluated by using skin prick tests with a standard panel of allergens, according to the guidelines of the European Academy of Allergology and Clinical Immunology.¹⁷ The reaction to a skin prick test was considered positive if the wheal area caused by allergen was greater than 7 mm² (diameter >3 mm). The panel of allergens was composed of the following: grass pollen mix (*Dactylis glomerata*, *Festuca elatior*, *Lolium perenne*, *Phleum pratense*, and *Poa pratensis*); mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Tyrophagus putrescentiae*, *Acarus siro*, and *Lepidoglyphus destructor*); molds (*Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, and *Penicillium notatum*); and *Curvularia spicifera* (ALK-Abelló, Denmark). Negative and positive controls (10 mg/mL histamine solution) were also included with each skin prick test. Patients treated with oral corticosteroids within the last 4 weeks before surgery were excluded. The ethical committee of the Ghent University Hospital approved the study, and informed consent was obtained from all subjects.

Measurement of cytokines, mediators, and IgE in tissue homogenates

All (n = 40) freshly obtained tissue specimens were weighed, and 1 mL of 0.9% NaCl solution was added per every 0.1 g of tissue. The tissue was then homogenized with a mechanical homogenizer (B. Braun Melsungen, Germany) at 1000 rpm for 5 minutes on ice, as described previously.^{11,18} After homogenization, the suspensions were centrifuged at 3000 rpm for 10 minutes at 4°C, after which the supernatants were separated and stored at –80°C until analysis. All supernatants were assayed for IL-5, IL-4, eotaxin, sCD23, histamine (R&D System), and leukotriene (LT) C₄/D₄/E₄ (Amersham Pharmacia Biotech) by means of ELISA with commercially available kits. Eosinophil cationic protein (ECP), tryptase,

and total and specific IgE levels were measured by using the UniCAP system (Pharmacia & Upjohn).^{19,20} Specific IgE was determined for grass pollen mix (*Dactylis glomerata*, *Festuca elatior*, *Lolium perenne*, *Phleum pratense*, and *Poa pratensis*), house dust mix (Hollister-Stier Labs; *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Blattella germanica*), mold mix (*Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, *Penicillium notatum*, *Candida albicans*, and *Helminthosporium halodes*), *S aureus* enterotoxins A and B, and *Curvularia spicifera* Bipolaris. ImmunoCap coated with human serum albumin (HSA) or glycine were used to evaluate any nonspecific binding of IgE.

Immunohistochemistry

Samples were fixed in 4% formaldehyde (phosphate buffered 6.8–7.2, Klinipath) and embedded in paraffin wax before cutting into 5-μm sections and mounting on poly-L-lysine-coated slides. After deparaffinization in parasolve (Prosan), the sections were hydrated through graded ethanol and stained (Pappenheim) for standard histomorphologic analysis. For mast cell staining, tissue sections were treated with trypsin (0.1%, Sigma-Aldrich) for 20 minutes at 37°C (to enhance immunohistochemical reactivity) and then incubated with mouse anti-human mast cell tryptase clone AA1 (1:500, Dako) for 1 hour before staining by means of the standard alkaline phosphate–antialkaline phosphate technique.^{21,22} Sections were counterstained with hematoxylin.

All tissue sections were examined with an Olympus light microscope by 2 independent observers blinded to the experimental conditions. The numbers of eosinophils and mast cells were counted in the epithelium and in the adjacent lamina propria in 10 randomly selected fields (final magnification, 400×), and the results were expressed as the mean number of positive cells per field.

Statistical analysis

Data are expressed as median and interquartile range (IQR). When comparisons were made between groups, significance in between-group variability was first established by using the Kruskal-Wallis test. The Mann-Whitney *U* test was then used for between-group comparison. The Spearman rank correlation coefficient (*r*) was used to assess the relationships between the parameters. *P* values of less than .05 were considered statistically significant.

RESULTS

Protein concentrations and immunohistochemistry in nonpolyp versus NP tissue

Analysis of total IgE, IL-5, ECP, LTC₄/D₄/E₄, eotaxin, and sCD23 in supernatants prepared from tissue homogenates demonstrated that the concentrations of these mediators were significantly higher in NP tissue compared with nonpolyp tissue (Table I). In contrast, no significant differences were found in the levels of IL-4, histamine, and tryptase.

Similarly, immunohistochemical analysis of whole NP and nonpolyp tissue samples demonstrated that the numbers of eosinophils in both the epithelium and in the lamina propria were also significantly higher in NP tissue compared with nonpolyp tissue (Table I). Contrary to the findings for eosinophils, however, significantly higher numbers of mast cells were found in the lamina propria of nonpolyp tissue compared with NP tissue, and there were no differences in numbers of epithelial mast cells.

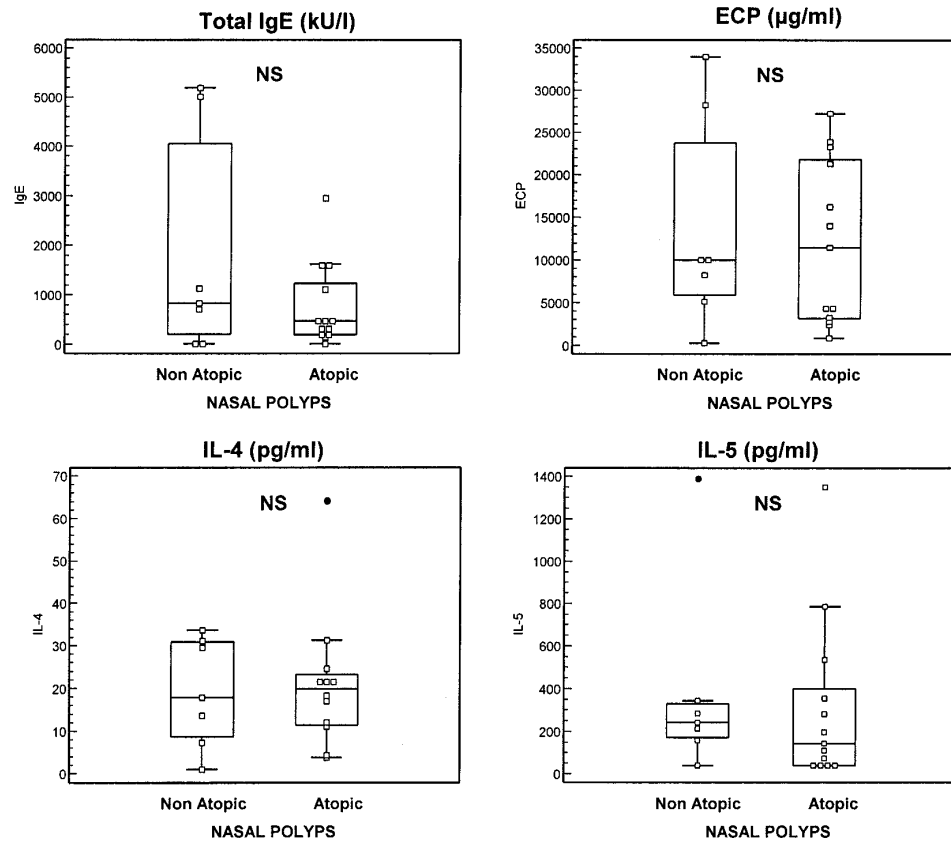


FIG 1. Comparison of IgE, IL-4, IL-5, and ECP concentrations between nonatopic and atopic patients with NPs, showing no significant differences between the groups. The *box-and-whisker plot* represents the median, the lower to upper quartile, and the minimum to the maximum value, excluding outside and far out values, which are displayed as separate points. Statistical analyses were performed by using the Mann-Whitney *U* test. *NS*, Not significant.

TABLE I. Statistical comparisons between nonpolyp and NP tissue

	Inferior turbinates (n = 20, median [IQR])	Mann-Whitney <i>U</i> test	NPs (n = 20, median [IQR])
ELISA			
Total IgE (kU/L)	22.3 (6.6-142.4)	<i>P</i> < .001	479.6 (199.7-1479.0)
sCD23 (U/mL)	All BDL	<i>P</i> < .001	5 BDL; 17.5 (5.5-32.0)
IL-5 (pg/mL)	19 BDL	<i>P</i> < .001	5 BDL; 205.2 (47.5-353.3)
IL-4 (pg/mL)	17.1 (12.7-33.9)	<i>P</i> = .578	18.3 (11.1-29.6)
LTC4/D4/E4 (pg/mL)	2932.5 (1387.2-3713.4)	<i>P</i> = .025	4594.7 (3405.4-6011.6)
ECP (µg/mL)	539.8 (118.4-899.6)	<i>P</i> < .001	10,077.5 (3518.7-22,740.7)
Eotaxin (pg/mL)	16 BDL	<i>P</i> < .001	1 BDL; 1516.7 (461.6-3534.1)
Histamine (mmol/L)	20.4 (9.0-43.2)	<i>P</i> = .055	31.2 (20.7-67.8)
Tryptase (mg/mL)	11.1 (5.4-15.7)	<i>P</i> = .197	6.7 (3.5-11.2)
Immunohistochemistry			
Eosinophils in epithelium	0.1 (0-0.2)	<i>P</i> = .017	0.8 (0.1-2.9)
Eosinophils in lamina propria	4.2 (1.8-15.4)	<i>P</i> = .003	52.5 (9.6-76.0)
Mast cells in epithelium	0.6 (0.2-1.9)	<i>P</i> = .853	0.7 (0.2-1.4)
Mast cells in lamina propria	7.8 (5.7-18.8)	<i>P</i> = .003	3.9 (1.9-6.2)

The concentrations of total IgE, sCD23, IL-5, IL-4, LTC4/D4/E4, ECP, eotaxin, histamine, and tryptase were measured in homogenates of nonpolyp (inferior turbinate) and NP tissue. The number of eosinophils and mast cells were counted on Papanheim- and tryptase-stained paraffin slides. Statistical analyses were performed by the Mann-Whitney *U* test. *P* values of less than .05 were considered statistically significant.

BDL, Below detection level.

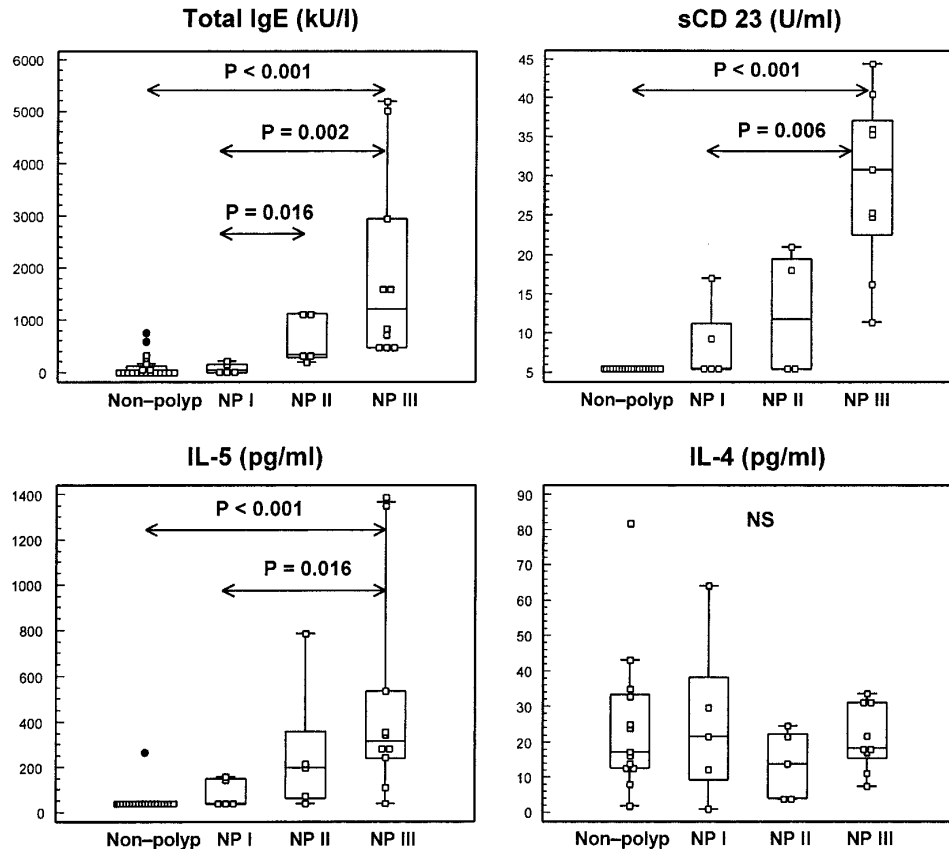


FIG 2. Measurement of IgE, sCD23, IL-5, IL-4, ECP, eotaxin, histamine, and tryptase tissue concentrations in inferior turbinates (nonpolyp) and NP groups: NP group 1, undetectable specific IgE; NP group 2, selected specific IgE; and NP group 3, multiclonal IgE). The box-and-whisker plot represents the median, the lower to upper quartile, and the minimum to the maximum value, excluding outside and far out values, which are displayed as separate points. Statistical analyses were performed by using the Mann-Whitney *U* test. NS, Not significant.

Total IgE in atopic versus nonatopic subjects

In 10 of 20 patients without NPs and in 13 of 20 patients with NPs, the skin prick test response was positive for at least one allergen. In the nonpolyp group 5 patients with positive skin prick test responses and symptoms to grass pollens or house dust mite showed elevated total IgE and corresponding elevated specific IgE concentrations for grass pollens or house dust mite in tissue homogenates. The median (IQR) IgE concentrations in nonpolyp tissue were 11.9 kU/L (4.7-38.4 kU/L) in nonatopic subjects and 45.9 kU/L (16.0-389.4 kU/L) in atopic subjects ($P < .05$).

Comparison between atopic and nonatopic patients within the NP group did not show any significant differences for any of the above-mentioned parameters. In NP tissue of nonatopic and atopic patients, the total IgE concentrations were found to be 836.0 kU/L (49.5-5011.1 kU/L) and 467.0 kU/L (203.9-1354.5 kU/L), respectively (Fig 1). Additionally, there was no correlation between the levels of IgE and skin prick test positivity in these individuals.

However, assessment for any correlations between IgE and other indices of inflammation demonstrated that in

NP tissue the concentration of total IgE was significantly correlated with concentrations of sCD23 ($r = 0.737$, $P < .001$), ECP ($r = 0.457$, $P < .05$), LTC4/D4/E4 ($r = 0.588$, $P < .01$), IL-5 ($r = 0.676$, $P < .001$), and numbers of eosinophils in both the epithelium ($r = 0.731$, $P < .001$) and the lamina propria ($r = 0.497$, $P < .05$). In contrast, total IgE in nonpolyp tissue was correlated with histamine ($r = 0.654$, $P < .05$) and tryptase ($r = 0.538$, $P < .05$).

NP groups based on specific IgE in nasal tissue

A positive ImmunoCap response to inhalant allergens was detectable in tissue homogenates of 15 of 20 patients with NPs. In 2 of 9 samples tested against ImmunoCap with either nonallergenic protein (HSA) or no protein (glycine), positive reactions were obtained. The lack of correlation with total IgE supports the hypothesis of a specific response. The reaction with HSA of the atopic patient with a skin test response positive to guinea pig could be due to allergenic similarities. IgE antibody to carbohydrate matrix of the ImmunoCap could explain the other reaction.

On the basis of the presence of specific IgE antibodies in tissue homogenates, we were able to arbitrarily distin-

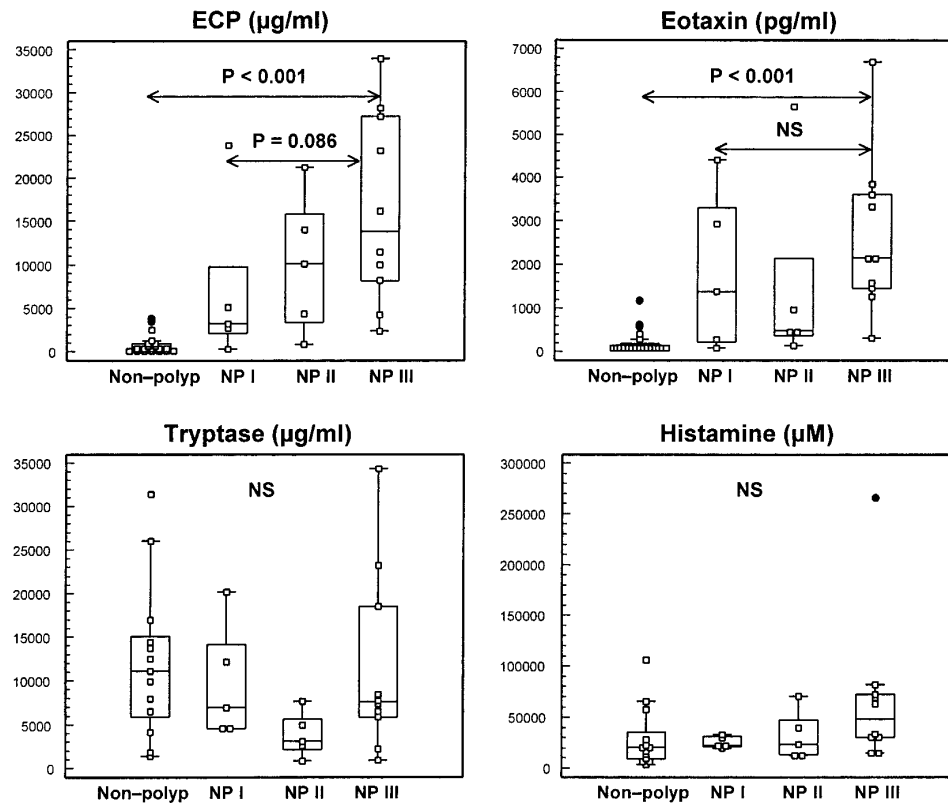


FIG 2. Continued

TABLE II. NP groups based on the presence of specific IgE in NP tissue

NP groups	Skin prick test	Asthma	Total IgE (kU/L)	Specific IgE (kU _A /L)					Dummy caps		
				gx1	hx2	mx2	SEA, SEB	C Bip	Glycine	HSA	
NP group 1	Nonatopic	Negative	–	8.2	BDL	BDL	BDL	BDL	BDL	/	/
		Negative	–	49.5	BDL	BDL	BDL	BDL	BDL	/	/
	Atopic	hdm, mx	–	212.3	BDL	BDL	BDL	BDL	BDL	/	/
		gx	–	9.7	BDL	BDL	BDL	BDL	BDL	/	/
NP group 2	Nonatopic	hdm	–	140.6	BDL	BDL	BDL	BDL	BDL	/	/
		Negative	–	1131.8	BDL	4.7	BDL	BDL	BDL	/	/
	Atopic	hdm, gx	Asthma	195.5	31.0	BDL	BDL	BDL	BDL	/	/
		hdm	Asthma	343.2	BDL	BDL	12.4	BDL	BDL	/	/
		hdm	Asthma	317.6	BDL	16.3	BDL	BDL	BDL	/	/
		hdm	–	1114.2	BDL	7.6	BDL	BDL	BDL	BDL	BDL
NP group 3	Nonatopic	Negative	–	5011.1	11.0	9.7	7.9	9.8	6.1	BDL	BDL
		Negative	Asthma	710.7	6.4	6.9	5.6	6.5	4.4	BDL	BDL
		Negative	–	836.0	3.8	4.7	5.2	5.7	3.0	BDL	BDL
		Negative	APA	5189.9	5.1	5.8	6.8	4.8	4.0	BDL	BDL
	Atopic	gx	Asthma	488.6	11.1	19.0	10.0	15.4	9.8	BDL	BDL
		gx	Asthma	2948.4	4.4	5.2	4.9	5.7	2.6	2.3	9.8
		hdm	Asthma	467.0	17.5	9.4	6.5	36.1	BDL	/	/
		hdm, gx	Asthma	1594.7	75.9	40.1	76.6	4.1	7.4	BDL	BDL
		hdm, gx	APA	470.7	9.6	10.9	8.2	7.0	4.4	/	/
		hdm	Asthma	1612.0	4.2	4.3	4.1	3.7	2.6	1.4	2.3

Patients with NPs are grouped on the basis of the presence of specific IgE in NP tissue: NP group 1, undetectable specific IgE; NP group 2, selected specific IgE; and NP group 3, multiclonal IgE. Atopic status was evaluated by using skin prick tests to common inhalant allergens: grass pollen mixture, mites, molds, and *Curvularia spicifera* Bipolaris. Skin prick tests for *Staphylococcus aureus* were not available and therefore not performed. Polyp total IgE concentrations and specific IgE were determined for grass pollen mix, house dust mix, mold mix, *S aureus* enterotoxins (SEA and SEB) and *Curvularia spicifera* Bipolaris. Specific IgE to HSA and glycine was determined to exclude unspecific binding. Data from each individual are given separately.

gx1, Grass pollen mixture; hx1, house dust mix; mx2, mold mix; C Bip, *Curvularia spicifera* Bipolaris; /, not tested; BDL, below detection level; APA, patients with the triad of aspirin sensitivity, polyposis, and asthma.

guish 3 NP groups (Table II). NP group 1 was characterized by no measurable specific IgE and a low total IgE concentration. In NP group 2 selected specific IgE levels directed to house dust mite mix, grass pollen, or mold mix were measurable, and total IgE was increased. NP group 3 demonstrated a multiclonal IgE level and high total IgE tissue concentrations (>450 kU/L). sIgE to staphylococcal enterotoxin A (SEA) and staphylococcal enterotoxin B (SEB) was also measured consistently in this group of patients, whereas these specific antibodies were not detectable in any of the other specimens.

Whereas in NP group 1 no patient had asthma, 8 of 10 patients in NP group 3 had a history of asthma, and 2 patients reported a clinical history of aspirin sensitivity. Furthermore, the number of eosinophils in the tissue and the concentrations of total IgE, sCD23, ECP, LTC₄/D₄/E₄, eotaxin, and IL-5, but not histamine, tryptase, or IL-4, were significantly higher in NP group 3 compared with concentrations in the nonpolyp control group and NP group 1 subjects (Fig 2).

DISCUSSION

This is the first report to describe a relationship between concentrations of total and specific IgE and the severity of eosinophilic inflammation in human NP tissue. Remarkably, these findings are unrelated to skin prick test results and symptoms, differing from a typical atopic disease, such as allergic rhinitis. We could demonstrate a multiclonal specific IgE level in 50% of NP samples. The presence of specific IgE antibodies to SEA and SEB in these samples points to a possible role of bacterial superantigens as disease modifiers.

In line with previous studies,^{11,12,18,23-25} we were able to demonstrate a significant upregulation of IL-5 protein in NPs, showing a firm correlation to ECP protein. It is widely accepted that IL-5 is an important cytokine for mature eosinophil activation.²⁶ The important functional role of IL-5 in nasal polyposis has been demonstrated by experiments showing the induction of programmed cell death by neutralizing mAbs (anti-IL-5 mAb).¹² In addition, our study has also demonstrated that the increased concentration of eotaxin was correlated to ECP, suggesting a key role of this C-C chemokine for eosinophil recruitment in collaboration with IL-5.

Upregulated total IgE concentrations were paralleled by an increase of the soluble low-affinity IgE receptor sCD23. Membrane-bound CD23 on B cells was described to downregulate IgE formation on binding to IgE,²⁷ and the soluble receptor could interfere by capturing IgE and preventing binding to the receptor. Thus a high concentration of sCD23 would be consistent with elevated total IgE concentrations.

We further analyzed specific IgE to common inhalant allergens and selected molds in comparison with skin prick test results in nonpolyp mucosa from the inferior turbinate of atopic and nonatopic patients. As expected, increased total IgE and specific IgE in the inferior turbinates of subjects allergic to inhalant allergens were

found in correspondence with the skin prick test results. In marked contrast, atopy based on positive skin prick test responses to inhalant allergens was not related to total or specific IgE in NP homogenates. Contrary to other reports,²⁸ no effect of atopy could be found on any of the mediators or cytokines in the polyp group, questioning the role of common allergens in NP pathophysiology.

On the basis of the finding of specific IgE, we were able to differentiate 3 groups of patients with nasal polyposis: NP group 1 with undetectable specific IgE and low total IgE (5-220 kU/L); NP group 2 with selected specific IgE antibodies and increased total IgE (190-1150 kU/L); and NP group 3 with multiclonal specific IgE and high total IgE (450-5200 kU/L) concentrations.

In the last group, representing 50% of the patients with NPs in this study, all polyps demonstrated specific IgE responses to SEA and SEB, which were not found in any other subject. After the classification of patients into these 3 groups of polyps, we could demonstrate that total IgE, sCD23, IL-5, and ECP all follow a common pattern, with significantly increased concentrations in NP group 3 compared with either nonpolyp control or NP group 1 samples. This is the first study to show that total IgE is related to IL-5 and ECP protein concentrations and thus possibly to eosinophilic inflammation. Interestingly, 8 of 10 patients in this group had asthma, indicating not only a more severe local, but also systemic, disease in these patients.

In contrast to other publications,^{5,29,30} we could not find increased histamine or tryptase levels within NPs compared with nonpolyp tissue, questioning the role of mast cells in the pathogenesis of mature NPs. In line with our finding, however, significantly lower numbers of mast cells were found in the lamina propria of NP tissue compared with nonpolyp tissue. Although it could be speculated that mast cells in NPs were undetectable by means of immunohistochemistry because of degranulation, the lack of increased histamine and tryptase concentrations in NP tissue does not support this view.

The high IgE protein concentrations could be preferentially derived from the serum because an extravasation and deposition of serum proteins in polyp tissue has been shown.³¹ However, allergen-induced heavy-chain switching to IgE occurs locally within the nasal mucosa of patients with seasonal allergic rhinitis,³¹ and increased local IL-4 mRNA, IgE heavy chain (C ϵ), and IgE heavy chain promoter (I ϵ) RNA³² has been demonstrated after allergen exposure. Thus a local IgE production also seems possible in NPs. Interestingly, although IL-4 has been shown to be necessary for IgE synthesis, we could not demonstrate increased IL-4 protein concentrations in NP tissue with high total IgE concentrations compared with nonpolyp tissue. This, however, confirms our previous findings,¹² in which IL-4 mRNA expression in NP samples was also found to be low and not significantly different from that found in control samples. On the other hand, it has been demonstrated that only a small quantity of IL-4 is necessary to induce IgE synthesis in the presence of

high IL-5 concentrations^{33,34} and that IL-13 may replace IL-4.³⁵ Furthermore, Leung et al have demonstrated an increased IgE production induced by *S aureus* superantigen in lymphocytes from patients with seasonal rhinitis in the absence of exogenous IL-4.^{36,37}

Although the demonstration of specific IgE to *S aureus* superantigen within polyp tissue in the present study proves former contact to enterotoxins, the exact role of specific IgE needs further clarification. IgE to *S aureus* superantigen has been demonstrated to mediate basophil degranulation, and *S aureus* superantigens are thought to act as superantigens through unconventional interaction with the T-cell receptor.^{16,38} There is recent evidence that *S aureus* superantigen may also play an important role in atopic dermatitis.¹³ Anti-SEB IgE titers have been shown to correlate with the severity of disease in patients with mild-to-severe atopic dermatitis.¹⁴ The majority of T cells found in lesional skin expressed a T-cell receptor V β repertoire that corresponded to the *S aureus* superantigen produced by the colonizing *S aureus* strain.³⁹ However, enterotoxins may also function as classic antigens through antigen-presenting cells, resulting in specific sensitization, because *S aureus* superantigens also induce the synthesis of chemokines in a human epithelial cells⁴⁰ and may thus recruit T cells and eosinophils to the site of infection. Furthermore, SEB has also been shown to induce lymphocyte-dependent airway inflammation, including the recruitment of eosinophils, in mice.¹⁶

It is unclear whether the different groups of NPs defined in the present study represent different disease entities or rather an evolution from group 1 NP to group 3 NP. Thus far, we have been unable to relate specific IgE to the age of the patient or duration of disease. Furthermore, it has to be elucidated whether *S aureus* superantigens represent causative or only modulating factors, being dependent on a former damage of the mucosa by unrelated pathomechanisms.

In summary, our studies have demonstrated that in marked contrast to allergic rhinitis, specific IgE in NPs is unrelated to skin prick test positivity, and total IgE correlates to markers of eosinophilic inflammation, although not to mast cell activation markers. In 50% of bilateral eosinophilic NPs, multiclonal IgE, including specific IgE to SEA and SEBB, has been demonstrated, suggesting a possible role of superantigens as disease modifiers. We suggest that NPs may have pathophysiologic principles in common with atopic dermatitis and asthma with respect to the role of *S aureus* superantigens. Furthermore, we have developed a concept to differentiate bilateral NPs into a further 3 subgroups on the basis of our findings for the presence of specific IgE antibodies within polyp tissue.

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Correction

The following change applies to the article "Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast" (Nelson HS, Busse WW, Kerwin E, Church N, Emmett A, Rickard K, Knobil K. 2000;106:1088-95). Figs 1 and 2 both reflect the "mean change from baseline," not the "mean percent change from baseline," as originally published.