Rapid communications

Total IgE serum levels correlate with sinus mucosal thickness on computerized tomography scans

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Background: Sinusitis involves an inflammatory response with similarities to asthma.
Objective: We sought to determine whether a correlation exists between total IgE and the sinus mucosal thickening as assessed by computed tomography (CT) scans.
Methods: We screened the charts of 300 otolaryngology patients who had total and specific serum IgE determinations in 1994 and from this group selected all patients who had also undergone a sinus CT scan close to the time of serum evaluation (n = 86). Severity of disease on CT scan was graded by two investigators blinded to IgE levels.
Results: There was a significant positive correlation between severity of disease on CT scans and IgE (r_s = 0.37, p = 0.0007). Furthermore, patients with a more advanced disease stage had higher IgE levels. There was also a positive correlation between severity of disease and the sum of specific IgE grades (r_s = 0.29, p = 0.007).
Conclusion: The data suggest that IgE levels or a linked genetic parameter may contribute to the mucosal inflammation in the paranasal sinuses. (J Allergy Clin Immunol 1997;100: 563-8.)

Key words: Sinusitis, total IgE, CT scans, mucosal thickening

Sinusitis, inflammation of the paranasal sinuses, adversely affects the quality of life of millions of Americans.[1] Although the pathophysiology of this disease is not fully understood, it most likely represents a multifactorial, heterogeneous problem with both genetic and environmental influences. Inflammation of the sinus mucosa by activation of eosinophils and lymphocytes characterizes the disease and causes the normally thin mucosal lining to thicken. This thickened mucosa can be detected by computed tomography (CT) scan.[2-5]

Interest in understanding the genetic component of asthma has focused on the observation that IgE levels correlate with asthma and airway hyperresponsiveness.[6-8] The correlations with IgE remained after corrections known to affect total IgE levels such as age, sex, smoking, and allergic status were made. IgE levels are controlled by both cognate and noncognate interactions. The noncognate interactions relate to IL-4 and other cytokines (e.g., IL-13). The genes for these cytokines map within the "IL-4 cytokine-gene cluster" in chromosome 5q31.1, or within the 5q31.2-5q33 region.[9] Evidence suggests that this region might contain a candidate gene that causes susceptibility to asthma.[10] Thus the link between IgE levels and asthma may be a shared pattern of inheritance.

Abbreviations used
CT: Computed tomography
OMC: Ostiomeatal complex

Because sinusitis is a chronic inflammatory disease with similarities to asthma,[11] we hypothesized that there would be a correlation between serum IgE levels and the severity of sinus mucosal inflammation as assessed by CT scans. We retrospectively reviewed patients seen in an outpatient otolaryngology clinic over the course of 1 year who had both a total IgE level determination and a sinus CT scan.

METHODS

Subjects

Three hundred patients attending the Otolaryngology–Head and Neck Surgery Clinic of the University of Chicago in 1994 had total IgE level determinations and RASTs as part of their evaluation for nasal complaints. Eighty-six of these patients had CT scans of the sinuses performed within 1 to 2 months of the IgE determination. The patients were referred for CT scanning because of chronic sinus complaints and were treated with antibiotics with or without intranasal steroids before imaging was performed. The median age of the subjects was 44.5 years with a range from 6 to 85 years. There were 51 female and 35 male subjects (a female to male ratio of 1.5:1).

CT scan evaluation

CT scans were performed at The University of Chicago with the method described by Zinreich et al.[12] Severity of disease documented by the CT scans was rated according to two published scoring systems by two investigators who were blinded to the IgE results. Both systems rate the severity of mucosal disease because observations suggest that the degree of mucosal disease relates to the surgical outcome (i.e., the more severe the disease on CT scan, the poorer the prognosis). The

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first of these systems, described by April et al,[13] scores the extent of soft tissue disease in each of the developed paranasal sinuses (maxillary, frontal, sphenoid, anterior, and posterior ethmoids) as follows: 0 = none, 1 = involvement of 25% or less of the sinus, 2 = involvement of 25% to 75% of the sinus, 3 = involvement of 75% or more of the sinus, and 4 = total opacification. The total score possible for both sides with this system ranges from 0 to 40. The second system, developed by Lund and Mackay,[14] grades each paranasal sinus (maxillary, frontal, sphenoid, anterior, and posterior ethmoids) as follows: 0 = no abnormality, 1 = partial opacification, and 2 = total opacification. The ostiomeatal complex (OMC) is scored as 0 = not obstructed or 2 = obstructed. The total score possible with this system ranges from 0 to 24 or 0 to 20 when the OMC is excluded from the score.

Another way to categorize the severity of sinus disease is to stage it. We staged the disease with four independently described staging systems, because there is no currently accepted gold standard.[15-18] These staging systems all grade disease from stage 0 (normal CT scan) to stage IV (diffuse sinonasal polyposis). They vary somewhat in their handling of unilaterality and bilaterality of sinus disease, as well as the presence of anatomic abnormalities.

IgE determination

IgE was determined with a RAST fluoroimmunoassay, based on ImmunoCAP technology, purchased from Pharmacia & Upjohn (Uppsala, Sweden). Levels of total IgE are reported in international units/per milliliter. The sensitivity of the assay is less than 1 IU/ml. We converted absolute levels of IgE into a log scale, and log total IgE levels (IU/ml) are reported in the Results section. Levels of IgE lower than the detection limit were arbitrarily assigned a value of 0.5 IU/ml (i.e., a log IgE value = −0.3 IU/ml). Serum-specific IgE antibody was measured by using the same system. Reference serum with known amounts of IgE was run in parallel with the experimental samples, and the amount of IgE in the experimental samples was extrapolated from the standard curve. The fluorescence measurements were then translated into classes from 0 to 6. Specific IgE levels were determined for the following antigens: white ash, *Dermatophagoides farinae,* timothy grass, giant ragweed, *Aspergillus fumigatus, Alternaria alternata, Helminthosporium* species, cat, milk, and *Candida albicans*. Patients were considered to have allergic rhinitis if they had a RAST class of 2 or greater for one or more allergens and were considered nonallergic if the RAST class to all of the allergens was less than 2. According to these criteria, our study group included 44 subjects with allergy and 42 subjects without allergy. Among the subjects with allergy, sensitivity to white ash was detected in 13.6% (6 of 44), to *D. farinae* in 45.5% (20 of 44), to timothy grass in 22.7% (10 of 44), to giant ragweed in 38.6% (17 of 44), to molds in 40.9% (18 of 44), to cat in 50% (22 of 44), and to milk in 13.6% (6 of 44). Many subjects had multiple sensitivities. There was no pattern of specific allergies in patients with more severe disease as determined by CT scan compared with those who had milder disease, and the sensitization to the above allergens was evenly and randomly distributed among all the subjects. To rank the overall severity of allergic disease, the specific IgE classes for each patient were arbitrarily summed.

Chart review

The clinic charts of the patients were reviewed, and information on age, sex, smoking history, and history of asthma was obtained when available. Because some charts lacked part of the information, all analyses do not have the same number of data points. Four patients had total IgE levels greater than two standard deviations from reported norms. None of these patients had the clinical signs and symptoms of dermatitis and recurrent staphylococcal abscesses diagnostic of hyper-IgE syndrome.[19] Information on the concomitant use of intranasal steroids was available in 69 patients. All patients who were taking intranasal steroids were using intranasal sprays.

Statistical analysis

The data were analyzed by using nonparametric statistics with Statview II (Abacus Concepts, Berkeley, Calif.) and Systat (Systat Inc.) software packages run on a Macintosh computer (Apple Computers, Cupertino, Calif.). Correlations were determined with the Spearman rank test (r_s).[20] When multiple variables were compared, Kruskall-Wallis analysis of variance was performed to assess for the existence of overall significant differences and post hoc analysis was carried out with the Mann-Whitney U test. Comparisons between different groups of patients were also performed with the Mann-Whitney U test. A stepwise multiple regression was also performed to evaluate the relative contributions of the different variables to the correlation of IgE levels and CT sinus scores. Two-tailed p values less than 0.05 were considered significant.

RESULTS

Correlations of IgE and severity of disease on CT scan

CT scan scores obtained by the two different scoring systems[13, 14] were correlated. There was a strong correlation between the April scoring system and the Lund system including OMC evaluation (r_s = 0.97, p = 0.0001). There was also a strong correlation between the April scoring system and the Lund system excluding OMC evaluation (r_s = 0.98, p = 0.0001). We then correlated total IgE levels with CT scan severity scores obtained with each of the evaluation systems. There was a significant positive correlation between total IgE levels and CT score as evaluated by the April technique (r_s = 0.36, p = 0.001), by the Lund technique excluding OMC evaluation (r_s = 0.37, p = 0.0007), and by the Lund technique including OMC evaluation (r_s = 0.34, p = 0.002) (Fig. 1).

There was a significant positive correlation between the sum of specific IgE levels and CT score as evaluated by the April technique (r_s = 0.29, p = 0.007), by the Lund technique excluding OMC evaluation (r_s = 0.29, p = 0.007), and by the Lund technique including OMC evaluation (r_s = 0.29, p = 0.009).

Comparison of total and specific IgE in different stages of sinusitis

We compared the levels of total and specific IgE in the patients with the severity of their disease on the basis of the different staging systems described above. When the severity of disease documented by CT scan was staged with the Kennedy system (A0 to AIV), levels of total IgE increased from 1.37 IU/ml (range, −0.3 to 1.95 IU/ml) in patients with stage A0 (n = 11) to 2.29 IU/ml (range, 1.98 to 2.49 IU/ml) in patients with stage AIV (n = 4)

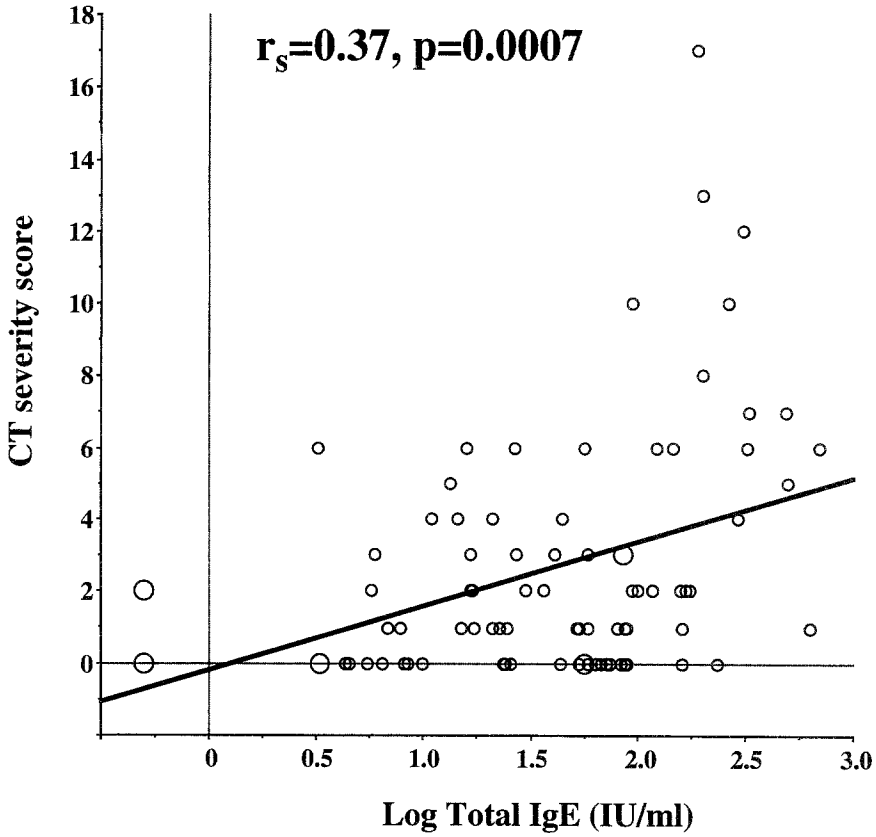

FIG. 1. Correlation between severity of sinus disease as assessed by CT scan score (with the Lund system excluding evaluation of the ostiomeatal complex) and log total serum IgE levels. *Large circles* represent overlap of more than one data point.

(Fig. 2). There was an overall significant difference in total IgE levels between the different stages (analysis of variance: $p = 0.006$), with stages AIII and AIV having significantly higher total IgE levels than stage A0 on post hoc analysis ($p = 0.02$ and $p = 0.004$, respectively). Because of the small numbers of subjects in stages AIII and AIV, we also combined the subjects in these two stages into a single category (AIII/IV). The combined group had 12 subjects and a median log total IgE of 2.3 IU/ml (range, 0.5 to 2.69 IU/ml). There was an overall significant difference between the groups ($p = 0.003$), and there was a significant difference in total IgE levels between the A0 group and the combined group (AIII/IV) ($p = 0.002$).

When the same comparison was performed for the sum of specific IgE classes and stage of disease by using the Kennedy staging system, the sum of specific IgE classes increased from 0 (range, 0 to 16) in patients with stage A0 to 2 (range, 0 to 14) for stage AI ($n = 36$), 3 (range, 0 to 40) for stage AII ($n = 27$), 6 (range, 0 to 18) for stage AIII ($n = 8$), and 9.5 (range, 2 to 13) for stage AIV. There was an overall significant difference between the different stages (analysis of variance: $p = 0.04$); and stages AI, AII, AIII, and AIV had significantly higher total IgE levels than stage A0 on post hoc analysis ($p = 0.05$, $p = 0.03$, $p = 0.02$, and $p = 0.02$, respectively). The same overall trend was preserved when total IgE and the sum of specific IgE classes were examined in relation to stage of sinus disease when evaluated with the three other staging systems.

Analysis for different variables

Because several variables are known to affect IgE levels, we corrected for them by performing a multiple regression analysis and by repeating the correlations after grouping the patients according to these variables (Table I). The CT scan scores used for these comparisons were those obtained by the Lund technique excluding OMC evaluation. Patients were considered to have allergic rhinitis if they had a RAST class of more than or equal to 2 for one or more allergens and were considered to be nonallergic if the RAST class to all of the allergens was less than 2. There were no significant differences in IgE levels between the different subgroups, with the exception of subjects with allergy who had higher levels than subjects without allergy. Male subjects and subjects with allergy had more severe disease as documented by CT than female subjects and subjects without allergy, respectively, and a similar trend for more severe disease was seen in smokers. Some of

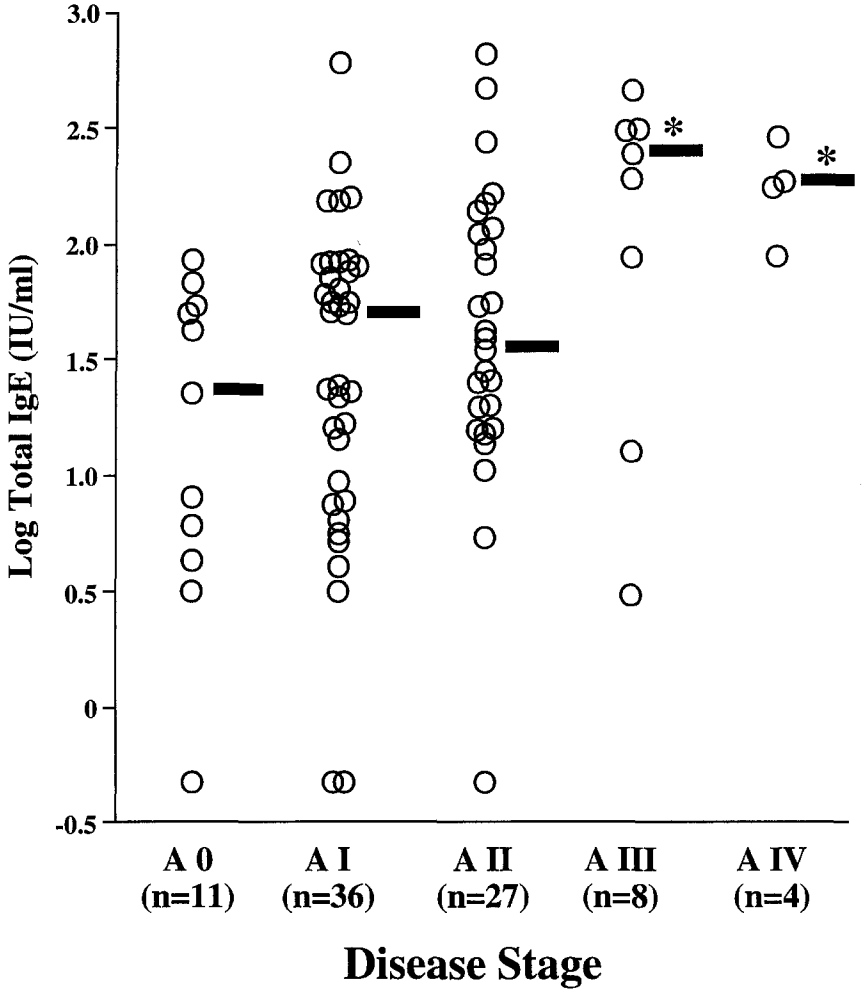

FIG. 2. Levels of serum log total IgE in patients with different stages of severity of sinusitis as classified by the Kennedy system from A0 to AIV. Individual data points are shown. *Solid bars* represent respective median values. Higher IgE levels were found in patients with more severe disease. *$p < 0.05$ versus A0.

the correlations were not significant after the groups were subdivided, and this might be related to small numbers after subgrouping.

To assess the relative contribution of the different variables to IgE level, a stepwise multiple regression analysis was performed. This yielded a correlation coefficient ($r = 0.38$), with the only significant contributor to the correlation being the CT scan score ($p = 0.006$). The next most important, but not statistically significant, contributor to the correlation was allergy status ($p = 0.2$). This was followed by sex ($p = 0.37$), history of asthma ($p = 0.59$), smoking ($p = 0.66$), and age ($p = 0.93$). This correlation stresses the importance of the correlation between severity of sinusitis, as assessed by CT score, and total IgE levels and assures us that the correlation is not simply the result of one or more of the other variables that are known to influence total IgE levels and may be linked to sinusitis.

DISCUSSION

Current definitions of chronic sinusitis require the patient to have persistent symptoms despite medical treatment and to have an imaging study such as a CT scan that documents mucosal thickening. The nature of symptoms and the type of medical treatment that classify a patient as having chronic sinusitis are not adequately defined.

Chronic sinusitis is undoubtedly the clinical end point of several different pathophysiologic processes. The disease probably involves multiple factors. To date, the contributions of anatomy and infection have been emphasized. The role of genetics clearly contributes to sinusitis in patients with cystic fibrosis. Because the results of this study show a significant correlation between the extent of sinus disease as determined by CT scan and serum levels of total IgE, they raise the hypothesis that another factor might be the inflammatory response to precipitating events such as viral or

TABLE I. Analysis by different variables

Factor	*n*	Log total IgE (IU/ml)*	CT score*	r_s	*p* Value
Sex					
Female	51	1.57 (−0.3-2.85)	1 (0-13)	0.47	0.0008
Male	35	1.77 (−0.3-2.69)	2 (0-17)†	0.25	0.15
Age					
<15 yr	4	1.37 (0.8-1.75)	5 (0-6)	0.95	0.1
15-34 yr	18	1.75 (−0.3-2.85)	1 (0-17)	0.46	0.06
35-54 yr	40	1.73 (−0.3-2.7)	1 (0-12)	0.46	0.004
>55 yr	24	1.77 (−0.3-2.8)	2 (0-13)	0.00	1.0
Smoking status					
Smoker	8	1.8 (0.51-2.3)	3.5 (0-13)‡	0.19	0.6
Nonsmoker	60	1.59 (−0.3-2.85)	1 (0-12)	0.32	0.01
History of asthma					
Positive	23	1.75 (−0.3-2.85)	2 (0-10)	0.3	0.16
Negative	33	1.72 (0.52-2.81)	1 (0-10)	0.26	0.14
Allergy status					
Allergic	44	1.92 (−0.3-2.81)†	2 (0-17)†	0.4	0.009
Nonallergic	42	1.37 (−0.3-2.85)	1 (0-10)	0.25	0.1
Intranasal steroids					
Yes	34	1.76 (−0.3-2.85)	2.0 (0-12)	0.51	0.004
No	35	1.64 (−0.3-2.7)	2.0 (0-10)	0.24	0.16

Total numbers less than 86 imply that the data was missing for some of the subjects.
*Data reported as median (range).
†$P < 0.05$.
‡$P = 0.07$.

bacterial infections or IgE-mediated allergic reactions. As expected in a multifactorial disease, this factor probably contributes in a small but significant percentage of cases. The correlation does not appear to be caused by simultaneous interactions with a third variable that affects both (e.g., age, sex, history of asthma, allergy, or smoking) because correcting for these factors did not affect our observations.

In addition to correlating with asthma, total IgE levels have previously been shown to correlate with sinusitis in two instances. First, high levels of total IgE have been shown to occur in fungal sinusitis, and the level of total IgE has been proposed as a marker of disease activity.[21] None of our patients had CT scans suggestive of fungal sinusitis. Because patients did not necessarily undergo surgery, we do not have histologic or culture evidence to rule out fungal disease. The incidence of fungal sinusitis is less than 10% in patients undergoing surgery for treatment of chronic sinusitis. Second, sinusitis occurs frequently in patients with HIV infection, and in these patients IgE levels correlate with sinus disease severity and stage of HIV infection.[22]

Newman et al[4] reported a positive correlation between the severity of sinusitis as documented by CT scan and both tissue and peripheral blood eosinophilia but did not find a correlation between chronic sinusitis and total IgE levels in their study. There are two major differences between their study and ours. First, their study population had chronic sinusitis that required surgical intervention, whereas our population had nasal symptoms that were further investigated by a total IgE level determination and a sinus CT scan. Thus our patients had a greater spectrum of sinus involvement, including those without evidence of mucosal disease. Excluding these patients from our data did not change the significance of the correlation ($r_s = 0.35, p = 0.009, n = 58$). Second, we used different CT scan scoring systems. Our choice was based on previously published results.[13, 14] We excluded scores for obstruction of the sinus ostia and focused solely on mucosal changes within the sinuses. The scans were viewed as a continuum and were not arbitrarily divided into limited and extensive disease. We also staged sinusitis on the basis of four published staging systems and reached the same conclusion.

Our method of selecting patients may have biased our selection of individuals with allergy because patients first seen with nasal and sinus complaints (which constituted the patients in our study) are more likely to have allergies than those without such complaints. Despite that potential bias, our population consisted of 44 subjects with allergy and 42 subjects without allergy. IgE may be directly involved in sinusitis. This involvement could result from allergic inflammation, as suggested by the correlation of our ranking of the severity of allergic disease and the severity and staging of sinusitis documented by CT scan. Furthermore, IgE and CT scores correlated significantly in patients with allergy, and these

patients had a significantly higher CT score compared with subjects without allergy. The mechanisms by which allergic inflammation increases the risk of sinusitis are unknown.

Alternatively, the level of total IgE could serve as a phenotypic marker for a candidate gene or genes associated with an exaggerated inflammatory response of the sinus mucosa. Genes for several cytokines with the ability to regulate IgE levels by noncognate mechanisms (IL-4, IL-13) are located on chromosome 5q31.1. Genes for other cytokines such as IL-5 map within the "IL-4 gene cluster."[9] These cytokines can influence eosinophils and can be produced by T helper cells, both of which are components of the inflammatory response in the sinus mucosa that enlarges in sinusitis and is visualized by CT scan. Thus our findings of a correlation between IgE and sinus CT combined with theoretical support from the literature leads to the hypothesis that the genetic control of the host inflammatory response may be a contributor to sinusitis.

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