

Total IgE Levels and Peripheral Eosinophilia

Correlation With Mucosal Disease Based on Computed Tomographic Imaging of the Paranasal Sinus

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Objective: To evaluate the relationship among peripheral eosinophilia, total IgE, and paranasal sinus mucosal disease based on computed tomography (CT) of the sinus.

Design: Retrospective review of a large medical information database from a tertiary referral medical center.

Setting: Tertiary referral medical center specializing in respiratory disorders.

Patients: Consecutive patients having total IgE and peripheral eosinophil levels and sinus CT imaging available for review. Patients 18 years or older were included; subjective or objective evidence of chronic rhinosinusitis was not used as selection criteria. A total of 303 patients were found to have peripheral eosinophil levels and CT imaging for review; 288 patients had total IgE levels and CT imaging.

Main Outcome Measures: Linear regression analysis was used to evaluate (1) the correlation between pe-

ripheral eosinophil level and CT stage of sinus disease and (2) the correlation between total IgE level and CT stage of sinus disease. The CT scans were graded using the Lund-MacKay scoring system.

Results: There was a significant positive correlation between sinus CT stage and peripheral eosinophil levels ($r=0.60$, $P<.05$). Eighty-nine percent of the abnormal eosinophil counts (>550 cells/ μ L) were associated with CT scores higher than 12. Total IgE did not correlate with CT stage of disease ($r=0.05$, $P>.05$).

Conclusions: The presence of peripheral eosinophilia indicates a high likelihood of mucosal sinus disease based on CT imaging. No correlation was noted between total IgE levels and CT stage of mucosal disease. These data support a link between eosinophilia and the presence of paranasal sinus mucosal inflammation.

Arch Otolaryngol Head Neck Surg. 2007;133(7):701-704

CHRONIC RHINOSINUSITIS (CRS) remains one of the most common chronic diseases and affects millions of patients. The pathogenesis of CRS remains ill defined and seems to be multifactorial. Altered eosinophil function and IgE-mediated disease processes are 2 factors that have been implicated in the pathogenesis of CRS.

The eosinophil comprises approximately 2% to 5% of granulocytes in a person without allergies. There has been increasing awareness of the role of the eosinophil in several physiologic and pathologic processes. Activated eosinophils have been found to play a role in allergy, asthma, parasitic diseases, granulomatous disorders, fibrotic conditions, and several malignant tumors. Tissue eosinophilia in the upper and lower airway mu-

cosa seems to be an important factor in the development of CRS and asthma.¹⁻³ Eosinophils contain and release a number of toxic proinflammatory mediators, including major basic protein, eosinophil cationic protein, reactive oxygen species, lipid mediators, and cytokines. The pathways triggering or regulating eosinophil function and mediator release in vivo, however, remain unclear. Eosinophil progenitors are released from the bone marrow into the circulation and are chemically attracted to the site of action by chemotactic factors. In addition, development and maturation of eosinophils can occur in situ within peripheral sites of inflammation.

Eosinophilic chronic hyperplastic rhinosinusitis represents a subtype of CRS that has been closely linked to tissue eosinophilia.⁴ This phenotype of CRS is associated with the accumulation of acti-

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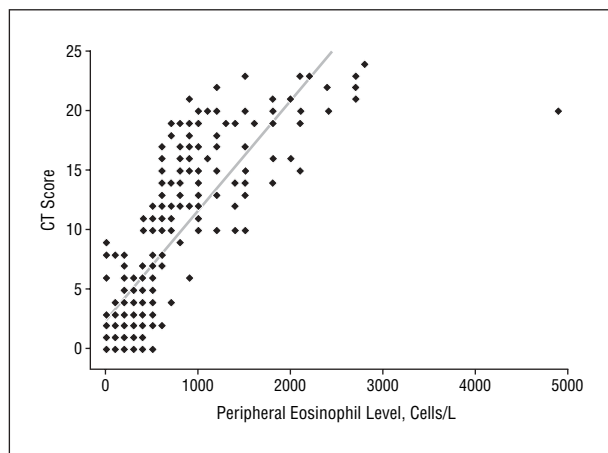


Figure 1. Linear regression analysis of the correlation between peripheral eosinophil count and sinus computed tomographic (CT) score using the Lund-MacKay scoring system; $r=0.60$, $P<.05$.

vated eosinophils in sinonasal tissue, the development of nasal polyposis, and asthma. The release of a variety of proinflammatory mediators from the activated eosinophils is believed to contribute to mucosal inflammation, edema, and tissue injury. This tissue response may then lead to secondary bacterial infection with the development of chronic mucosal hyperplasia, hyperreactive mucosa, and airway remodeling. Although the precise causal relationship remains to be defined, the eosinophil seems to be an important player in the development of airway inflammation.

The relationship between IgE-mediated hypersensitivity and CRS remains poorly defined. Although many authors suggest a clinical association between allergic upper airway disease and CRS, the precise mechanism of how allergy predisposes an individual to rhinosinusitis, or affects the course of rhinosinusitis, is unclear.⁵⁻⁷ Inflammatory cells, especially eosinophils, mast cells, and T lymphocytes, seem to be major effector cells in both allergic rhinitis and CRS.⁸ Hypotheses to explain the link include tissue edema and vascular congestion causing obstruction of sinus drainage, direct entry of allergens into the sinuses, an exaggerated response in patients with allergies, allergic inflammation inducing systemic host responses, and finally allergic nasal inflammation that may induce neurogenic responses within the sinuses.⁸

The purpose of this investigation was to evaluate the relationship among peripheral eosinophilia, total IgE levels, and the presence of mucosal disease present on sinus CT imaging.

METHODS

The laboratory medical record database for March 2004 to February 2005 at the National Jewish Medical and Research Center (hereinafter, NJ) was reviewed in a retrospective fashion for patients with peripheral eosinophil level and serum total IgE level. The medical records found to have these laboratory values were then cross-referenced with the NJ radiology database for those patients also having CT sinus imaging available for review within 60 days of the time of serum evaluation. A total of 303 patients were found to have peripheral eosinophil lev-

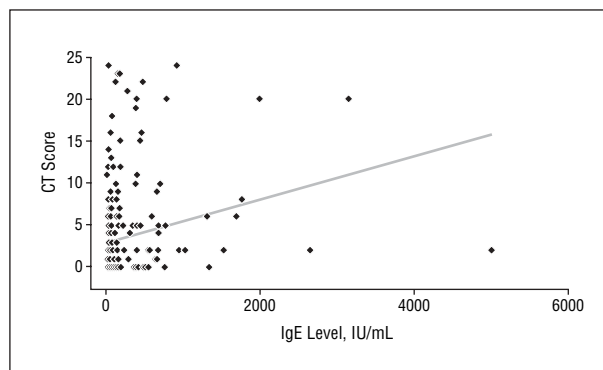


Figure 2. Linear regression analysis of the correlation between total IgE count and sinus computed tomographic (CT) score using the Lund-MacKay scoring system; $r=0.05$, $P>.05$.

els and CT imaging for review. Total IgE levels and CT imaging were found for 288 patients. These patients were not selected based on the presence of subjective or objective evidence of CRS. Thus, this cohort represents a group of consecutive patients presenting to a tertiary medical center regardless of the diagnosis of CRS.

The CT scans were reviewed in a blinded fashion. The scans were graded using the Lund-MacKay scoring system.⁹ This system grades each paranasal sinus (maxillary, frontal, sphenoid, anterior ethmoids, and posterior ethmoids) as follows: 0, no abnormality; 1, partial opacification; and 2, total opacification. The ostiomeatal complex is scored as 0 when there is no opacification and 2 when it is obstructed. The total score possible with this system ranges from 0 to 24. A score higher than 12 is considered abnormal.

Linear regression analysis (using SigmaPlot software [Systat Software Inc, San Jose, California]) was used to assess statistical significance. The correlation coefficient, r , represents the degree to which the 2 variables correlate: $r \geq 0.5$ represents a strong positive correlation; $r=0$ indicates no correlation; and $r < 0$ shows a negative correlation. The confidence interval was set at 95%, which corresponds to $P < .05$.

The NJ laboratory considers an IgE level greater than 100 IU/mL and an eosinophil count higher than 550 cells/ μ L to be abnormal values for these respective tests. Thus, for purposes of calculating positive and negative predictive values, we used the following cutoff points: for IgE, 100 IU/mL; for eosinophilia, 550 cells/ μ L; and for CT, a Lund-MacKay score of 12.

RESULTS

Peripheral eosinophil level and CT imaging were found in 303 patients. The mean eosinophil level was 660 cells/ μ L (range, 0-4900 cells/ μ L). The mean CT score was 8.4 (range, 0-24). There was a significant positive correlation between CT stage and peripheral eosinophil levels ($r=0.60$, $P < .05$) (**Figure 1**). The positive predictive value for peripheral eosinophilia indicating mucosal disease on CT scan was 89%. The negative predictive value was 99%.

A total of 288 patients had total IgE levels and CT scans for review. The mean IgE level was 192 (range, 0-5000). The mean CT score was 3.3 (range, 0-24). The total IgE did not correlate with CT stage of disease ($r=0.05$, $P > .05$) (**Figure 2**). Sixty-two percent of abnormal IgE levels were associated with CT scan scores higher than 12. The positive predictive value was 17%.

Chronic rhinosinusitis is a considerable problem that results in patient morbidity and large expenditures of health care dollars. Despite the prevalence of CRS, its pathophysiologic characteristics, staging, and treatment still attract controversy in the literature. The advent of CT scanning and nasal endoscopy has improved diagnostic capabilities considerably; however, these objective measures do not seem to correlate with subjective parameters. New efforts are focused on defining the cellular and molecular characteristics of CRS.⁴

Recent investigations have focused on the eosinophil as the characteristic and predominant cell in CRS. Histopathologic studies of the sinus mucosa of most adult patients with CRS demonstrate eosinophilic tissue infiltration, as well as elevated levels of interleukin 5, granulocyte and macrophage colony stimulating factor, and interleukin 3, all of which support eosinophilic inflammation.² Harlin et al¹⁰ demonstrated infiltration of sinus mucosa by eosinophils in patients with CRS. Eosinophilia was significantly greater when the CRS was accompanied by asthma or allergic rhinitis than when CRS was the only manifestation. Bryson et al¹¹ showed that the proportion of eosinophils in diseased tissue from patients with CRS with or without polyps was significantly greater than the proportion in nasal mucosa from the middle turbinates of controls. There was, however, no difference between the 2 clinical groups.

In relation to peripheral eosinophilia and sinus disease, Newman et al⁷ initially demonstrated extensive disease on CT imaging in 39% of patients undergoing functional endoscopic sinus surgery, which was found to correlate with the presence of asthma and peripheral eosinophilia. Sixty-five percent of patients with extensive mucosal disease had eosinophilia vs only 7% of those with a CT score lower than 12. In a study conducted by Zadeh et al,¹² a higher proportion of patients with serum eosinophilia had a history of asthma, polyp disease, or allergic fungal sinusitis. These authors also reported a significant correlation between eosinophilia and recurrent postoperative infection, the development of polyposis, increased need for anti-infective therapy, and a greater incidence of revision surgery.

Kountakis et al⁴ recently presented the molecular and cellular parameters associated with CRS in a cohort of patients undergoing endoscopic sinus surgery. They demonstrated a significant correlation between peripheral eosinophilia and the presence of asthma, nasal polyps, and severity of disease based on CT stage. Interestingly, they did not find any correlation between eosinophilia and preoperative symptom scores or the presence of allergy. Kountakis et al⁴ also explored the relationship between sinus tissue eosinophilia and several clinical parameters. They found elevated sinus mucosal eosinophilia to correlate with a higher incidence of asthma and higher CT scores, and higher preoperative and postoperative endoscopy scores. These data emphasize the importance of the eosinophil in the pathogenesis of CRS.

The current study involved the correlation of peripheral eosinophilia with mucosal disease noted on CT imaging in a cohort of patients not selected on the basis of the presence or diagnosis of CRS. Eighty-nine percent of our patients with peripheral eosinophilia had abnormal CT imaging. By contrast, 99% of patients with normal CT imaging had normal serum eosinophil levels. Also, the blood eosinophil count increased as severity of mucosal disease increased. This indicates a strong correlation between CT evidence of mucosal disease and peripheral eosinophilia, suggesting that this laboratory measurement may serve as a marker for paranasal sinus inflammation.

Our data did not show a correlation between serum total IgE levels and CT imaging. This again brings into question the role of allergy and CRS. Emanuel and Shah⁵ studied allergy testing in 200 patients with CRS who had undergone functional endoscopic sinus surgery. Eighty-four percent of the patients tested positive for allergies. Moreover, 60% of all patients had significant allergic sensitivity, and 52% had multiple allergen sensitivities. Interestingly, there was a predominance of perennial allergens, especially dust mites. Gutman et al⁶ showed similar results in their cohort of 48 patients with CRS and recurrent acute rhinosinusitis. Fifty-seven percent had a positive allergy test. Ninety-two percent of these patients demonstrated sensitivity to perennial allergens, in particular, molds and dust mites.

Pelikan and Pelikan-Filipek¹³ reported that 75% of their patients with allergies showed an increase in maxillary mucosal thickening on sinus radiographs after nasal allergen challenge. Naclerio et al¹⁴ reported a 60% prevalence of mild sinus mucosal changes on CT imaging in symptomatic patients with allergies during ragweed season. These changes did not resolve after treatment. Berrettini et al¹⁵ reported abnormalities on CT imaging in 67.5% of patients with perennial allergic rhinitis compared with 33.4% of controls.

Previous studies directly reviewing total serum IgE levels have been inconclusive. Baroody et al¹⁶ studied CT imaging and IgE levels in 300 patients. In contrast to our data, they demonstrated a positive correlation between severity of disease based on CT imaging and IgE levels. Newman et al⁷ reported a positive correlation between the severity of sinusitis according to CT imaging and both tissue and peripheral blood eosinophilia but did not find a correlation between CRS and total IgE levels. Hoover et al¹⁷ also did not find an association between mucosal disease and IgE. Although the clinical association between allergic rhinitis and CRS seems real, the causative mechanisms underlying this association have not been clarified. Further studies examining this association are warranted.

Weaknesses of this study include the retrospective method used to identify patients and gather data. We did not select study patients based on a diagnosis of CRS. This was intentional and an effort to look for correlations that were independent of the presence of this diagnosis. The NJ is a tertiary referral center specializing in respiratory disease; thus, the likelihood of these patients having upper airway disease is higher than in the general population. This fact could introduce a

selection bias. In addition, the impact of concurrent medical treatment on these laboratory values and the associated CT findings cannot be established with the methods used. Finally, correlating these objective measures with subjective data (patient symptoms) would be ideal but is not possible with this study design.

In conclusion, we have shown that serum eosinophil levels may be useful as a predictor of paranasal sinus mucosal disease. Our patient population demonstrated that if findings from preliminary work-up with serum eosinophil levels are within the reference range, the likelihood that mucosal disease will be found in sinus CT imaging is extremely low (negative predictive value 99%). Conversely, we did not find a significant correlation between total IgE levels and CT evidence of mucosal disease.

Submitted for Publication: October 12, 2006; final revision received January 10, 2007; accepted February 21, 2007.

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Author Contributions: Drs Poznanovic and Kingdom had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Poznanovic and Kingdom. *Acquisition of data:* Poznanovic. *Analysis and interpretation of data:* Poznanovic and Kingdom. *Drafting of the manuscript:* Poznanovic and Kingdom. *Critical revision of the manuscript for important intellectual content:* Poznanovic and Kingdom. *Statistical analysis:* Poznanovic. *Administrative, technical, and material support:* Poznanovic. *Study supervision:* Kingdom.

Financial Disclosure: None reported.

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