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# Correlation of Total and Specific Serum Immunoglobulin E Levels with the Severity of Chronic Sinusitis in Children

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**SUMMARY** **Chronic sinusitis is frequently associated with allergy and asthma. Previous studies have shown that serum immunoglobulin E (IgE) levels correlate with allergy and asthma in adults. Because the role of allergic inflammation in the severity of chronic sinusitis remains controversial in children, we set out to determine whether a correlation exists between serum levels of total and specific IgE and the severity of chronic sinusitis in children. Forty-four children with chronic sinusitis were enrolled in the study. Computed tomographic scans were reviewed and scored for the severity of sinusitis. All children were mite-sensitive. Serum samples were assayed for total IgE and specific IgE antibodies to mite allergen using a fluoroimmunoassay. Fourteen subjects had extensive sinus disease. There was no significant difference in the average of total and specific IgE between the subjects with extensive and limited disease ($p$ = 0.562 and 0.755, respectively). Thirty-four subjects were diagnosed with asthma. The subjects with extensive sinus disease had a higher prevalence of moderate to severe asthma than the subjects with limited disease ($p$ = 0.006), but there was no significant difference in the average of total and specific IgE between the subjects with different severities of asthma. ($p$ = 0.833 and 0.425, respectively). The data suggests that levels of total or specific IgE do not correlate with severity of chronic sinusitis in children. Nonetheless, the severity of chronic sinusitis and asthma correlate well with each other irrespective of total and specific IgE.**

Sinusitis is characterized by inflammation of the paranasal sinus associated with purulent nasal discharge, postnasal drip, cough, headache, fever, facial pain, etc.[1-3] Acute sinusitis is manifested by signs and symptoms of upper respiratory tract infection (URI) persisting for more than 7-10 days and is usually bacterial. The term chronic sinusitis is generally used when symptoms persist for longer than 3 months. It has been estimated that 5-13% of the general population may have experienced sinusitis during childhood, but the exact incidence of sinusitis in children is not known.[1,2] Because children have an average of six to eight URIs per year, sinusitis is more common in the pediatric population than in the adult population.[1,3] The most commonly associated factors with sinusitis in children are URI and allergy. One study reported that sinus disease prevalence was found to be 63% in atopic children with chronic respiratory disease symptoms.[3] Various other studies have supported a concordance of allergy and sinusitis between 25% and 70%.[3,4]

Atopic disease is often associated with rhinitis and asthma.[5] Approximately 80% to 90% of those who have asthma are sensitized to at least one common allergen.[6] Chen *et al.* reported that abnormal sinus radiographs were found in 54.7% of asthmatic children in Taiwan.[7] Sinusitis has been described as one of the severe aggravating factors of chronic asthma in both adults and children.[3,7-9] Baroody *et al.*[10] proposed that the link between IgE levels and asthma may be a shared pattern of inheritance. Lee *et al.*[11] proposed that measurement of serum eosinophil

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cationic protein (sECP), one of the major proteins of eosinophils, may be a useful parameter in the evaluation of the severity of the asthma in children. Sugai *et al.*[12] suggested that sECP levels would be a more useful marker than eosinophil counts for making analyses and estimating treatment efficacy in pediatric patients with allergic disease. Sinusitis is a chronic inflammatory disease with similarities to asthma characterized by the infiltration of eosinophils and lymphocytes, which cause the normally thin mucosa lining to thicken. Some studies have reported a correlation between the severity of sinusitis and the levels of total and specific IgE.[10,13,14]

Computed tomography (CT) is currently the image modality of choice in evaluating sinus diseases. The coronal plane shows details of the ostiomeatal complex (OMC) and ethmoid sinus, which are considered to be of primary importance in the pathophysiology of sinusitis. CT scans provide an accurate display of regional anatomy and establish the extent of mucosal disease.[15,16]

We focused on children with atopy and chronic sinusitis. The objective of this study was to compare the levels of total and specific IgE with the severity of sinus disease because there was no similar study reported in children. In addition, we tried to determine whether the severity of asthma, sECP, sex, and age were associated with the severity of sinusitis.

## MATERIALS AND METHODS

### Patients

We retrospectively reviewed patients who had visited the Pediatric Allergy Clinic at Chang Gung Children's Hospital in Taiwan. A total of forty-four children with chronic sinusitis were enrolled in the study consecutively between September 1996 and January 1997. They had at least a 3-month history of symptoms consistent with chronic sinusitis including radiographic evidence of mucosal hyperplasia or opacification of the paranasal sinuses after adequate medical therapy for prolonged or recurrent symptoms of sinusitis. The mean age of these patients was 9.5 years old with a range of 3.6 years old to 14 years old. There were thirty-eight male patients. Computed tomographic scans were routinely performed for all of these patients. All children were mite-sensitive in terms of having a positive history of asthma or rhinitis attack during house cleaning and a positive skin test response and mite immunoCAP result. We collected the patient's blood to measure the total IgE, specific IgE and sECP using a fluoroimmunoassay. Thirty-four patients were diagnosed with asthma on the basis of family history, clinical symptoms, and lung function test. The diagnosis and classification of clinical severity of asthma was made according to the National Asthma Educational and Prevention Program.[17]

### Coronal CT scans

Patients were scanned in a prone direct coronal position. The extent of the examination was adjusted to include the nasal cavity and paranasal sinuses. Slice thickness was 3 mm. Data were reconstructed with a bone algorithm (120-140 kV and 200 mA/sec).[7,16]

CT scans were interpreted by an experienced radiologist and an allergologist blinded to the clinical conditions and data results. We designed a scoring system to quantify the extent of disease, which was modified from two scoring systems that have been used by Newman *et al.*[13] and April *et al.*,[10] respectively. In this scoring system, the area of the soft tissue disease was first divided into the nasal passages, the ostiomeatal complexes (OMCs), and the paranasal sinuses with the exception of the sphenoid sinuses under the consideration of cost and amount of radiation. Based on the degree of obstruction present relative to one normal sinus CT, 0 to 3 points were awarded for each unit of the nasal passages, the OMC units, and the developed paranasal sinuses (Table 1). If the sinus was not developed enough to be read, we arbitrarily assigned a value of 0.

### Skin-prick test and immunoassays

Skin-prick test was done using extracts of mite (*Dermatophagoides pteronyssinus* [DP]). A positive skin test was defined as response greater than 2+ (wheal > 10 mm by intracutaneous route with mite extract at a concentration of $10^{-6}$ g/ml). Total IgE and sECP were determined with a fluoroimmunoassay, based on immunoCAP technology, purchased from Pharmacia & Upjohn (Uppsala, Sweden). If levels of some total IgE and sECP samples were above the detection limits, we diluted these serum samples and sent for further quantification. Specific IgE levels were determined for mite allergen (DP). Serum-specific IgE antibody was measured 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 sample was extrapolated from the standard curve. Patients were considered atopic if they had

a specific IgE level of greater than or equal to ≥ 0.7 $kU_A/l$ for mite allergen.

### Spirometry

A pulmonary function test was performed using a Vitolograph Compact II Spirometer. The results of forced expiratory volume in 1 second (FEV1) or peak expiratory flow (PEF) were expressed as a percent of predicted.[16] FEV1 or PEF were recorded for 44 subjects on the charts.

All the subjects had CT scans of the sinuses performed on the same day as skin-prick test and the immunofluorescent measurements including total and specific IgE and sECP. In addition, the lung function test was performed within 1 to 2 months of IgE determination.

### Statistical analysis

Wilcoxon rank sum test (a nonparametric test) or two-sample unpaired *t*-test were used to determine whether age, total IgE, specific IgE, and sECP, respectively, differed between these subjects with extensive and limited diseases. Chi-square test or Fisher's exact test, where appropriate, was used to determine whether sex and severity of asthma differed between these subjects with extensive and limited diseases. Kruskal-Wallis test was used to determine whether total IgE, specific IgE, and sECP, respectively, were affected by different severities of asthma. All reported *p*-values were two-sided. Statistical significance was defined as *p*-value ≤ 0.05.

**Table 1** Scoring system for sinus computed tomographic scans

| **Maximum score, 30 points as follows:** | | |
|---|---|---|
| Nasal passages (2 units) | 6 points | [1]0-3 points, each |
| [2]OMCs (2 units) | 6 points | [1]0-3 points, each |
| Sinuses | 18 points, total | [1]0-3 points, each |
| Frontal (2 units) | 6 points | |
| Maxillary (2 units) | 6 points | |
| Ethmoidal (2 units) | 6 points | |

[1]The degrees of obstruction were graded as follows: 0 = the same as a normal sinus CT, 1 = involvement of 1/3 or less of each unit; 2 = involvement of 1/3 to 2/3 of each unit; 3 = involvement of 2/3 or more of each unit.
[2]OMCs: ostiomeatal complexes

**Table 2** A comparison of the averages of total and specific IgE and sECP between the subjects with extensive and limited diseases[1]

| **Group** | **N** | **Total IgE** (kU/l) mean ± SD | **Specific IgE** (kU/l) mean ± SD | **sECP** (μg/l) mean ± SD |
|---|---|---|---|---|
| **Limited** | 30 | 1,043.9 ± 836.6 | 113.2 ± 82.0 | 12.2 ± 15.1 |
| **Extensive** | 14 | 885.3 ± 841.5 | 104.5 ± 91.9 | 9.4 ± 7.3 |

[1]The CT scan scores ranged from 0 to 30. We divided these subjects into extensive disease (CT score ≥ 12) and limited disease (CT score 0 –11).
*p*-value = 0.562, 0.755, and 0.412, respectively.

## RESULTS

### CT findings

The CT scan scores ranged from 1 to 30 with a mean of 10.2. The scores were not normally distributed; therefore, we divided these subjects into extensive disease (CT score ≥ 12, n = 14, mean = 21) and limited disease (CT score, 0–11; n = 30; mean = 4.2).

### Comparisons with the severity of sinusitis

#### *Sex and age*

There was no significant difference in terms of predisposal to extensive disease between boys and girls (31.6 % *vs* 33.3 %; $p = 0.530$), but boys (n = 38) outnumbered girls (n = 6) in the prevalence of chronic sinusitis. There was a significant difference in the average age between the subjects with extensive and limited disease (8.5 *vs* 10.1 years old; $p = 0.0066$).

### Total IgE, specific IgE, and sECP

We compared the average of total and specific IgE and sECP in the subjects with the severity of their disease (Table 2). There was no significant difference in the average of total IgE, specific IgE to DP and sECP between the subjects with extensive and limited disease ($p = 0.562$, 0.755, and 0.412, respectively).

**Table 3** Comparing the severity of chronic sinusitis in the subjects with the different severities of asthma

| Severity of sinusitis | | [1]Severity of asthma | | |
|---|---|---|---|---|
| | | [2]No | Mild | Moderate to severe |
| Limited | N (%) | 8 (80.0) | 20 (80.0) | 2 (22.2) |
| Extensive | N (%) | 2 (20.0) | 5 (20.0) | 7 (77.8) |

[1]Using "Guidelines for the Diagnosis and Management of Asthma (EPR-II)"(1997)[17] divided the severity of asthma.
[2]No = no asthma.
*p*-value = 0.006 by Fisher's exact test and 0.012 by Chi-square test.

**Table 4** A comparison of total and specific IgE and sECP between the subjects with different severities of asthma

| Group | N | Total IgE (kU/l) mean ± SD | Specific IgE (kU/l) mean ± SD | sECP (μg/l) mean ± SD |
|---|---|---|---|---|
| [1]No | 10 | 958.4 ± 984.9 | 79.1 ± 73.8 | 19.9 ± 23.5 |
| Mild | 25 | 1019.9 ± 809.4 | 121.8 ± 90.2 | 9.1 ± 6.5 |
| [1]MS | 9 | 847.8 ± 718.1 | 113.6 ± 77.4 | 8.2 ± 7.2 |

[1]No: no asthma; MS: moderate to severe asthma.
*p*-value = 0.833, 0.425, and 0.473, respectively

**Table 5** Evaluation as specific IgE classes

| Specific IgE class | Value less than | Value greater than or equal to |
|---|---|---|
| 6 | | 100 |
| 5 | 100 | 50 |
| 4 | 50 | 17.5 |
| 3 | 17.5 | 3.5 |
| 2 | 3.5 | 0.7 |
| 1 | 0.7 | 0.35 |
| 0 | 0.35 | |

The values of specific IgE are expressed in $kU_A/l$.

## Asthma

We divided the 44 subjects into groups with no asthma, mild asthma, and moderate to severe asthma (Table 3). The subjects with extensive disease had a higher predisposition to moderate to severe asthma than the subjects with limited disease ($p$ = 0.006 and 0.012 by Fisher's test and Chi-square test, respectively).

## Analysis for different variables

To estimate whether the total and specific IgE and sECP were affected by the severity of asthma in our study, we compared the average of total and specific IgE and sECP in these subjects with the severity of their diseases (Table 4). There was no significant difference between the subjects with different severities of asthma ($p$ = 0.833, 0.425, and 0.473, respectively).

## DISCUSSION

Chronic sinusitis is more common in allergic subjects than in control subjects.[3,4,13,14,18] Some studies have shown that allergic children with symptoms of rhinitis and/or asthma have a high frequency of sinusitis.[3,4] Atopy is the production of abnormal amounts of specific IgE antibodies in response to contact with aeroallergens. Higher levels of serum total IgE in atopic individuals than in non-atopic individuals have also been noted.[10,12,13,19] Various studies have been reported comparing the levels of total and specific IgE with the severity of sinusitis, but mostly restricted to adults. Baroody *et al.*[8] showed that there was a significant positive correlation between total IgE levels and CT score. 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. Newman *et al.*[11] reported that allergic individuals were at increased risk for extensive sinus disease, but the severity of chronic sinusitis did not correlate with total serum IgE. Indeed, among the patients who had a CT score of at least 12 and no positive RAST result, the mean total serum IgE was 101 μg/l.

Our study focused on children, with all subjects having allergic reaction to mite (*Dermatophagoides pteronyssinus*), which was not the case in previous studies. We divided these subjects into extensive disease (CT score ≥ 12, n = 14, mean = 20.2) and limited disease (CT score 0-11, n = 30, mean = 4.3) because the scores were not normally distributed. Fourteen subjects (14/44 = 31.8 %) had extensive disease. There was no significant difference in the average of total IgE, specific IgE and sECP between the subjects with extensive and limited disease ($p$ = 0.562, 0.755, and 0.412, respectively). Many studies have reported that chronic sinusitis correlates well with asthma.[1,3,4,13,14] Sinusitis might cause or aggravate asthma. Similarly, the association between chronic sinusitis and asthma was strong only in the group with extensive disease. Our study also showed that the subjects with extensive disease had a higher prevalence of moderate to severe asthma ($p$ = 0.006). In addition, there was no significant difference in the average of total and specific IgE and sECP between the subjects with different severities of asthma ($p$ = 0.833, 0.425, and 0.473, respectively). Thus these results suggest that the severity of chronic sinusitis and asthma correlates well irrespective of the levels of serum total and specific IgE and sECP.

We focused on these children sensitive to mite (*Dermatophagoides pteronyssinus*) due to its higher prevalence (> 90 %) than all non-mite allergens in Taiwan. We also measured other serum-specific antibodies using the same Pharmacia CAP system. Among the subjects with atopy, sensitivity to *Dermatophagoides farinae* (DF) (one of the mite allergens) was detected in 100% (44 of 44), to cat dander in 9.1% (4 of 44), to dog dander in 13.6% (6 of 44), to *Candida albicans* in 11.4% (5 of 44), and to cockroach in 31.8 % (14 of 44). Furthermore, to estimate the overall severity of allergic disease, the fluorescence measurements of specific IgE to all allergens were then translated into classes (Table 5) and totalized. As with the previous results, there was no significant difference in the two groups ($9.6 \pm 6.1$ *vs* $11.7 \pm 4.9$, $p$ = 0.2154). With the exception of DP and DF, low prevalence, low specific IgE levels (mostly < 3.5 kU/l), and symmetric distribution in all subjects for all allergens were noted in our study. Besides, among 4 children without atopy, there were 3 children with severe sinus disease (all CT scores ≥ 21, data not shown). These results suggest there is little evidence in support of a serum IgE-mediated and multi-allergen mechanism for predisposal to extensive disease.

Hoover *et al.*[12] reported that atopy correlated with chronic sinusitis, and it was more pertinent in younger individuals. This suggests that atopy may have a causative role in the initiation of chronic sinusitis. Regardless, other risk factors need to be considered for aggravating chronic sinusitis in children, such as cystic fibrosis, immune deficiency, asthma, immotile cilia syndrome, tumors, foreign bodies, septal deviation, polyps, trauma, tooth infections, etc.[1,4] This may explain why there was a significant difference in the average age between the subjects with extensive and limited disease in our study (8.47 *vs* 10.13 years old, $p$ = 0.0066). Younger children appear to be even more at risk for sinusitis, perhaps because of small anatomical structures, more frequent viral infections, and more exposure to indoor allergens and irritants.

Chronic sinusitis manifests as symptomatic inflammation of the paranasal sinuses associated with mucosal thickening, polyp formation, etc. It is an unusual diagnosis in infancy, but it may increase in frequency as the child experiences more upper respiratory tract infections and allergic rhinitis. In our study, there was one limit that no non-atopic patient was enrolled in our study. We have excluded four children without atopy to the above allergens due to fewer samples. We may need more non-atopic children enrolled in our study to compare atopy and non-atopy and their severity of sinusitis as objective as possible. Nevertheless, we found that total and specific IgE did not correlate well with the severity of chronic sinusitis. We hypothesize that the elevation of total and specific IgE may cause an increase in the prevalence of chronic sinusitis, but some other factors may participate in exacerbating the severity of sinusitis in children. These possible correlations require further studies.

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