

Original article

Subjects with allergic rhinitis show signs of more severely impaired paranasal sinus functioning during viral colds than nonallergic subjects

Background: Viral cold is thought to be the major contributing factor in the pathogenesis of sinusitis, as it causes ostiomeatal obstruction. The aim was to evaluate whether paranasal sinus functioning during viral colds is similar in subjects with and without allergic rhinitis.

Methods: Forty-eight volunteers were examined during an early (2–4 days) natural cold and again 3 weeks later. The examinations included computed tomography (CT) scans, nasal mucosal biopsies, and viral and bacterial specimens. Subjects with positive skin prick tests and persistent or intermittent rhinitis were considered to have allergic immunoglobulin E (IgE)-mediated rhinitis. In addition, specific IgE antibodies to staphylococcal enterotoxin B (SEB) were measured.

Results: Nine subjects (19%) had allergic rhinitis. The allergic subjects were significantly more often IgE sensitized to SEB than the nonallergic subjects (33% vs 3%, $P = 0.02$). Viral etiology of the cold was identified in 32 (67%) subjects. The subjects with allergic rhinitis had significantly higher CT scores compared with nonallergic subjects during the colds (median (range) scores 16 (6–22) vs 6 (0–17), $P = 0.004$). In both groups, the median scores declined markedly during convalescence, but the difference remained significant ($P = 0.009$). Among the allergic subjects, those who were IgE sensitized to SEB tended to have the highest CT scores [median (range) 16 (16–22)]. Total serum IgE and the nasal subepithelial eosinophil counts correlated with the CT scores during the cold ($r_s = 0.38$, $P = 0.008$ and $r_s = 0.46$, $P = 0.001$, respectively).

Conclusions: Subjects with allergic IgE-mediated rhinitis had more severe paranasal sinus changes in CT scans than nonallergic subjects during viral colds. These changes indicate impaired sinus functioning and may increase the risk of bacterial sinusitis.

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Viral cold is thought to be the major contributing factor in the pathogenesis of bacterial sinusitis, as it causes ostiomeatal obstruction with consequent impairment of sinus ventilation and mucociliary clearance (1). Several other factors, such as allergic rhinitis, anatomic variants and immunologic defects, may also increase the risk of sinusitis (2–4). Allergic rhinitis has been shown to be frequent in patients with acute and chronic sinusitis (5, 6), and correspondingly, patients with allergic rhinitis have been demonstrated to have a high prevalence of sinus disease (7). However, data on how allergic rhinitis affects the pathomechanism of sinusitis are still scarce.

Allergic rhinitis is an inflammation of the nasal mucosa in which eosinophils and the damaged airway epithelium are in a key role by releasing cytokines and other proinflammatory proteins. Recently it has been shown

that dermal and nasal carriage of *Staphylococcus aureus* and sensitization to staphylococcal enterotoxins may enhance the inflammatory reaction in atopic dermatitis and allergic rhinitis (8, 9). This mucosal inflammatory reaction may directly obstruct sinus drainage and enhance bacterial sinusitis, as it has been shown in mice (10).

We hypothesized that allergic immunoglobulin E (IgE)-mediated rhinitis could also enhance the risk of sinusitis by impairing sinus functioning during viral colds. During viral infections, some sinus abnormalities have been reported in 30–87% of healthy adults, but the possible effect of allergic rhinitis on these findings is not known, as allergic subjects have been excluded from these studies (11, 12). To assess sinus functioning in subjects with and without allergic IgE-mediated rhinitis and/or IgE

sensitization to staphylococcal enterotoxin B (SEB) during viral colds, we recruited adult volunteers with natural colds of 2–4-day duration. The viral etiology was examined and IgE sensitization to common inhalant allergens was assessed by skin prick tests and that to SEB by serological methods. Sinus functioning was evaluated with computed tomography (CT) imaging. Moreover, the amounts of eosinophils, neutrophils and T- and B-lymphocytes in the nasal mucosa, which have been shown to be the most important cells in allergic rhinitis and bacterial sinusitis (13, 14), were quantitated.

Methods

Subjects

Forty-eight subjects were recruited during two periods between February 1 and May 15, 1996, and August 15 and December 31, 1996, by solicitations for adult volunteers with an acute community-acquired cold by advertising in a newspaper distributed in Oulu, a city in Finland with about 120 000 inhabitants. The inclusion criteria were: duration of symptoms of acute common cold for 2–4 days, presence of nasal symptoms, no nasal polyps, and no ongoing antibiotic treatment. The Ethical Committee of the University of Oulu found the study protocol ethically acceptable, and written informed consent was obtained from all subjects.

The subjects were examined at enrolment (acute phase) and again 21 days later (convalescent phase). Background variables were recorded on a questionnaire. The subjects rated the following 10 symptoms on a scale from 0 (not present) to 10 (very severe): runny nose, nasal stuffiness, sneezing, sore throat, facial pain, cough, fatigue or lethargy, muscle aches, chills and headache. The sum of the individual scores was used as the total symptom score.

The viral etiology of the cold was evaluated by antigen detection from nasal mucus and virus isolations and rhino-polymerase chain reaction from nasopharyngeal swabs (15, 16). Specimens for aerobic bacterial cultures were taken from the nasopharynx.

Allergic parameters

The questionnaire included questions about allergic symptoms and possible triggering factors, history of wheezing or asthma, current medications, and other chronic respiratory symptoms.

Skin prick tests (Prick-Lancet; Ewo Care AB, Gislaved, Sweden) were performed as described earlier (17) with the following common inhalants: dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), cat, dog, cow and horse hair, birch and alder, grass (*Phleum pratense*, *Festuca pratensis*, *Poa pratensis*, *Alopecurus pratensis*), *Artemisia vulgaris* plant, latex and moulds (*Penicillium expansum*, *Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*). The subjects who had at least one positive (≥ 3 mm) skin prick test and persistent or intermittent rhinitis were considered to have allergic IgE-mediated rhinitis (18).

Specific IgE for SEB was measured from the sera using the UniCAP system (Pharmacia & Upjohn, Woerden, The Netherlands) according to the manufacturer's instructions. Values of at least 0.70 kU/l were regarded as positive.

Total serum IgE was measured with the QuantiCLONE Total IgE Kit (Kallestad Diagnostics, Inc., Chaska, MN). Patients with a total eosinophil count of at least $0.3 \times 10^9/l$ were considered to have peripheral eosinophilia.

Computerized tomography scoring

Computed tomographic scans of the nasal passages and all the paranasal sinuses were taken during the cold and 3 weeks later (Sytec 3000 Plus or HiSpeed Advantage scanner; General Electric Medical Systems, Milwaukee, WI). Two experienced radiologists and one ENT specialist evaluated the CT scans independently from a hard copy. In cases of disagreement, the two groups reassessed the findings jointly to reach consensus. The reviewers were blinded to all the other parameters.

Each sinus group was graded as 0 (no abnormality), 1 (partial opacification), or 2 (total opacification). The ostiomeatal complex was scored as 0 (not occluded) or 2 (occluded) (19). The total score could range from 0 to 24, and each side could be considered separately (0–12).

Nasal inflammatory cells

Nasal mucosal biopsies were taken in the acute and convalescent phases from the inferior turbinate following local application of 4% lidocaine. The specimens were fixed in formalin and embedded in paraffin, and 4 μ m thick sections were stained with Hematoxylin–Eosin and immunohistochemical methods as described previously (20). In brief, for CD3 staining, rabbit polyclonal antiserum (Code A 0452; Dako, Glostrup, Denmark) was used after boiling the sections in 10 ml/l citrate buffer for 20 min. For CD20 detection, the sections were incubated with monoclonal antibodies (Clone L26; Dako). Bound antibodies were detected using the avidin–biotin method (Dako). For negative control stainings, the primary antibody was replaced with phosphate-buffered saline.

All histological analyses were performed by an investigator who was blinded to all the other information. Eosinophilic and neutrophilic granulocytes and T- and B-lymphocytes in the lamina propria were counted in a minimum of three consecutive fields and expressed as cells/mm². To assess the repeatability of the cell count, ten randomly selected classes were counted twice blindly, and a good intraclass correlation coefficient of 0.8 was obtained.

Statistical analysis

Summary statistics are expressed as medians and ranges. To analyze the associations between two categorical and continuous variables, Fisher's exact test and Mann–Whitney *U*-test were used, respectively. Correlation coefficients were calculated using Spearman's rank correlation.

Results

Of the 48 patients, nine (19%) were found to have allergic IgE-mediated rhinitis. The background characteristics of the subjects with and without allergic rhinitis were similar, except that the allergic subjects were significantly younger than the nonallergic ones. (Table 1).

Five (56%) of the subjects suffering from allergic rhinitis had intermittent symptoms and four (44%) persistent symptoms (Table 2). Only three (8%) of the nonallergic subjects had chronic nasal symptoms. The most common findings in the skin prick tests were sensitization to birch and alder, cat or dog hair, and grass. The subjects with allergic rhinitis were significantly

Table 1. Background characteristics of 48 adult volunteers with viral colds according to their allergy findings

	Nonallergic subjects (n = 39)	Subjects with allergic rhinitis* (n = 9)	P-value†
Mean (SD) age in years	37 (11)	27 (10)	0.007
Women (%)	30 (77)	6 (67)	0.52
Low occupational status (%)	24 (62)	7 (78)	0.36
Current smokers (%)	11 (28)	5 (56)	0.12
Recurrent sinusitis history (%)	19 (49)	4 (44)	0.82
Median (range) no of common colds per year	3 (1, 7)	2 (1, 10)	0.84

*Defined as positive skin prick tests to inhalant allergens and persistent or intermittent rhinitis.

†Tested with the Mann–Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables.

Table 2. Details of the allergic characteristics of 48 adult volunteers with viral colds

	Nonallergic subjects (n = 39)	Subjects with allergic rhinitis* (n = 9)	P-value†
Chronic rhinitis	3 (8)	9 (100)	<0.001
Intermittent rhinitis	1 (3)	5 (56)	
Persistent rhinitis	2 (5)	4 (44)	
Asthma	2 (5)	1 (11)	0.50
Positive skin prick tests	0	9 (100)	<0.001
Birch and alder		6	
Grass		4	
<i>Artemisia vulgaris</i> plant		1	
Cat or dog hair		5	
Dust mites		2	
Specific IgE antibodies to <i>Staphylococcus aureus</i> enterotoxin B	1 (3)	3 (33)	0.02
Peripheral blood eosinophilia (>0.3 × 10 ⁹ /l)	10 (26)	3 (33)	0.69
Median (range) total S-IgE (μg/l)	21 (1, 790)	98 (18, 1444)	0.003

* Defined as positive skin prick tests to inhalant allergens and persistent or intermittent rhinitis.

† Tested with the Mann–Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables.

more often IgE sensitized to SEB than the nonallergic subjects (33% vs 3%, $P = 0.02$). The allergic subjects had significantly higher overall S-IgE values than the nonallergic subjects.

The viral etiology of the cold was verified in 32 (67%) of the subjects, the most frequent virus being rhinovirus. The viral etiologies were similar in the two groups (Table 3). Similarly, pathogenic bacteria (*Streptococcus pneumoniae*, *Haemophilus Influenzae*, *Moraxella Catarrhalis*) was found equally in the nasopharynx in both the allergic and nonallergic subjects. The allergic subjects tended to have higher nasal eosinophil counts during their viral colds than the nonallergic subjects ($P = 0.07$). The median symptom

Table 3. Details of the cold episodes of 48 adult volunteers according to their allergy findings

	Nonallergic subjects (n = 39)	Subjects with allergic rhinitis* (n = 9)	P-value†
Proven viral infection (%)	26 (67)	6 (67)	1.0
Rhinovirus	13	4	
Enterovirus	3	1	
Adenovirus	4		
Parainfluenzae 1 and 3	3		
Respiratory syncytial virus	2		
Two viruses	1	1	
Median (range) CT scores§			
Acute phase	6 (0, 17)	16 (6, 22)	0.004
Convalescent phase	2 (0, 17)	10 (0, 17)	0.009
Nasopharyngeal pathogenic bacteria (%)‡	11 (28)	1 (11)	0.42
Median (range) nasal inflammatory cells			
Neutrophils	0 (0, 41)	0 (0, 20)	0.91
Eosinophils	0 (0, 61)	20 (0, 82)	0.07
T-lymphocytes	256 (31, 939)	215 (82, 760)	0.72
B-lymphocytes	112 (5, 388)	133 (0, 495)	0.89

* Defined as positive skin prick tests to inhalant allergens and persistent or intermittent rhinitis.

† Tested with the Mann–Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables.

‡ *Streptococcus pneumoniae*, *Haemophilus Influenzae*, *Moraxella Catarrhalis*

§ Each sinus group was graded as 0 (no abnormality), 1 (partial opacification), or 2 (total opacification). The ostiomeatal complex was scored as 0 (not occluded) or 2 (occluded) (19).

scores were similar between the allergic and nonallergic subjects [140 (range 31–259) vs 143 (29–375), respectively, $P = 0.75$].

The subjects with allergic rhinitis had significantly higher CT scores compared with the nonallergic subjects during their colds [median (range) scores 16 (6–22) vs 6 (0–17), $P = 0.004$] (Table 3). In both allergic and nonallergic subjects, the median scores declined markedly at convalescence, but the difference remained significant ($P = 0.001$). Among the allergic subjects, those who were IgE sensitized to SEB tended to have the highest CT scores [median (range) 16 (16–22)]. The total S-IgE and the nasal subepithelial eosinophil counts correlated with the CT scores during the colds ($r_s = 0.38$, $P = 0.008$ and $r_s = 0.46$, $P = 0.001$, respectively).

Discussion

We found that the subjects with allergic IgE-mediated rhinitis had significantly poorer paranasal sinus functioning, as demonstrated with CT imaging, during viral colds than the nonallergic subjects. The significant correlations found between serum IgE levels and nasal subepithelial eosinophil counts, and the CT scores further emphasize the role of allergy in the paranasal sinus findings. As

impairments of sinus ventilation and mucociliary clearance have been regarded as the key factors in the development of bacterial sinusitis (21), our results suggest that the subjects with allergic rhinitis may be at a greater risk of developing bacterial sinusitis as a complication of viral cold than nonallergic subjects. However, at least during the early phase of the viral colds (2–4 days of symptoms) the allergic subjects often had equal pathogenic bacteria in their nasopharynx than the nonallergic subjects.

We are not aware of previous studies addressing the significance of allergic rhinitis in paranasal sinus changes shown in CT scans during viral colds, as allergic subjects have been excluded from the earlier studies evaluating paranasal sinus findings (11, 12). In chronic sinusitis, however, total IgE levels and positive IgE antibodies to inhalant antigens associate with extensive sinus changes on CT scans (6, 22). The possible mechanism of how allergies could increase the risk of sinusitis include direct ostial obstruction or deterioration of sinus function during viral colds. Blair et al. have shown that allergic inflammation enhances bacterial sinusitis in mice without viral infection (10).

As the difference in the CT scores between the allergic and the nonallergic subjects persisted 3 weeks after the cold, we do not know whether the dissimilar sinus findings prevail all the time or are caused by different temporary reactions provoked by the viruses in the two groups. That is, the different CT findings during the colds could be explained in two ways: either the virus-induced changes were additional to the chronic allergic mucosal changes or the allergies modified the virus infections. Active allergic inflammation may worsen viral colds by switching the response to a respiratory virus from a T_H1 to a T_H2 pattern (23) or by increasing the expression of intercellular adhesion molecule 1 on nasal epithelial cells (24). The results of clinical studies are conflicting as to whether allergic subjects have a different immune response to colds compared with nonallergic subjects (25, 26). Similarly, the opinions of whether or not there are marked chronic radiological changes in the paranasal sinuses in allergic rhinitis vary (7, 27). However, in view of the end result, namely the risk of bacterial sinusitis, it does not matter which mechanism has caused the sinus functioning to be deteriorated.

Shiomori et al. have shown that nasal carriage of *S. aureus* is more common in patients with allergic rhinitis and that this carriage may aggravate allergic rhinitis (9). Several *S. aureus* toxins may act as antigens, resulting in sensitization. Sensitization to SEB has been related to the

severity of skin lesions in patients with atopic dermatitis (8). In agreement with this, we found that the subjects with allergic rhinitis were significantly more often IgE sensitized to SEB than the nonallergic subjects and that among the allergic subjects, those who were IgE sensitized to SEB tended to have the highest CT scores. Our findings suggest that *S. aureus* or its enterotoxins may play a role in the pathological inflammatory process in the nose in natural colds especially in allergic subjects.

We used a prospective case series design and were able to verify an acute viral cold in two-third of the cases. The subjects were not recruited during the worst period of seasonal allergies (from the end of May to the beginning of August), to avoid having allergy symptoms confound the cold symptoms. Moreover, results from the questionnaire revealed that all volunteers had symptoms compatible with a respiratory infection that either disappeared or lessened during follow-up so that almost all of the subjects were free of symptoms at the time of the control visit. We had a group of volunteers as our sample, but the selection process was similar for all subjects and the allergy status was assessed after enrolment. The viral etiology of the cold and the distributions of the background variables did not differ between the allergic and nonallergic subjects, except that the allergic subjects were younger than the nonallergic ones. Each clinical, histopathological and radiological variable was measured blindly to all the other variables. Nasal inflammatory cells were counted instead of those in the sinuses, because these have been shown to correlate well with each other, although the inflammatory response seems to be more pronounced in the nose than in the maxillary sinus (28). We had a relatively small sample, which involved a limited power to detect effects. Still, the associations we found were so strong as to be obvious even in our small sample.

In conclusion, we found that subjects with allergic IgE-mediated rhinitis had more severe paranasal sinus changes than nonallergic subjects during viral colds and that these changes associated with both serum IgE levels and nasal subepithelial eosinophil counts.

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