

Evidence of Maxillary Sinus Inflammation in Seasonal Allergic Rhinitis

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Abstract

Objective. Allergic rhinitis has been frequently associated with both acute and chronic sinusitis. Previous studies have shown an influx of eosinophils into the maxillary sinus after nasal challenge with allergen. The objective of this study was to determine, in humans, if the development of seasonal allergic inflammation, secondary to natural allergen exposure, leads to similar inflammation within the maxillary sinus.

Study Design. Prospective, longitudinal study.

Setting. Academic medical center and research laboratory.

Subjects and Methods. Eighteen subjects were evaluated in and out of the ragweed allergy season using subjective measures (nasal symptoms, quality of life), nasal secretory response to methacholine challenge, and evaluation of biomarkers in nasal and sinus lavages.

Results. The subjects became symptomatic during the season and reported worse quality of life and increased nasal reactivity to methacholine. The total number of eosinophils obtained by nasal lavage during the season (median = 35,691) was significantly higher compared with out of season (median = 2811, $P \leq .02$). Similarly, there were significantly more eosinophils, albeit to a lesser magnitude, in the maxillary sinus during the season (median = 4248) compared with the out-of-season samples (median = 370, $P \leq .02$).

Conclusion. The authors provide evidence that natural exposure to pollen during an individual's allergy season leads to both nasal and sinus inflammation, strengthening the association between allergic rhinitis and sinusitis. The mechanism of this inflammatory response needs to be elucidated.

Keywords

allergic rhinitis, nose, maxillary sinus, eosinophils, methacholine reactivity

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Rhinosinusitis is a common medical disease affecting millions of Americans and resulting in a large expenditure of health care resources and a significant negative impact on quality of life.^{1–3} Although no well-conducted, prospective studies exist to address the coexistence of allergic rhinitis and rhinosinusitis, multiple studies suggest a correlation between these 2 entities. This applies to both acute⁴ and chronic rhinosinusitis.^{5–8} Furthermore, Lane and colleagues⁹ have shown that failure to address allergic rhinitis in patients with chronic rhinosinusitis diminishes the probability of success of endoscopic sinus surgery. Although many of these studies are limited by patient selection biases, they do suggest that allergic rhinitis might be involved in the pathophysiology of rhinosinusitis.

Most individuals believe that allergic inflammation in the nose causes swelling, which obstructs the ostium of the sinuses, leading to changes within the sinuses. We have observed in a mouse model of allergic rhinitis and acute sinusitis that allergic rhinitis can augment sinusitis without anatomically obstructing the ostia.¹⁰ This observation led us to seek another mechanism in humans by which allergic rhinitis could affect the sinuses without causing obstruction of the ostia.

We had previously performed a nasal allergen challenge and sampled the maxillary sinus by lavage in allergic subjects. We showed that, in addition to the nasal eosinophilic response after an allergen challenge, an inflammatory eosinophilic response was also seen within the maxillary sinus.¹¹ Specifically, we demonstrated an increase in vascular permeability and an influx of eosinophils into the ipsilateral maxillary sinus after subjects were intranasally challenged with allergen out of season and speculated, among other mechanisms, that a neurogenic reflex could be responsible for these findings. The purpose of the current study was to investigate the effect of the ragweed allergy season, often a milder allergic stimulation of the nose than a

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laboratory challenge, on inflammation within the maxillary sinus. We hypothesized that allergic subjects in season would have an eosinophilic influx not only into the nose but also in the maxillary sinus compared with when they were out of season. We used symptom scores, quality-of-life questionnaires, and a nasal challenge with methacholine to document a positive nasal allergic response during the season and also hypothesized that these parameters would show a larger response in season than out of season.

Methods

Study Design

Eighteen otherwise healthy subjects with seasonal allergic rhinitis to ragweed were studied during and after their ragweed allergy season. The study was conducted during 2 ragweed allergy seasons, 2001 and 2002. In all subjects, the initial visit was performed during the ragweed allergy season in Chicago (September) and the second visit several months after the season (between November and January). During each visit, symptoms were recorded and a mini rhinoconjunctivitis quality-of-life questionnaire (RQLQ) was completed. Subjects had a nasal methacholine challenge performed and then had blood drawn for peripheral eosinophils. Subjects underwent a nasal lavage and had a maxillary sinus catheter placed to perform a maxillary sinus lavage. The catheter was always placed in the same maxillary sinus for the 2 visits. The protocol was approved by the Institutional Review Board of the University of Chicago, and all participants read and signed the informed consent form prior to their participation in the study. The study was completed before mandatory registration in clinicaltrials.gov.

Subjects

All 18 subjects had a history of symptoms of seasonal allergy during the ragweed season for at least the previous 2 years and a positive skin prick test to ragweed allergen. All subjects had active allergy symptoms during the seasonal visit and no active allergy symptoms at the time of the second, out-of-season visit. Subjects with an upper respiratory tract infection within the previous 2 weeks, nasal polyps, or severe septal deviation were excluded. Subjects were otherwise healthy except for mild asthma controlled with as-needed bronchodilators (3/18 subjects had mild asthma and required bronchodilators a few times a year). Subjects were recruited using advertisements.

Symptoms

Subjects recorded their symptoms (reflective over the previous 12 hours) at each visit. Symptoms included sneezing, runny nose, stuffy nose, and itchy nose/throat and were scored on a scale from 0 to 3, with 0 = no symptoms, 1 = mild, 2 = moderate, and 3 = severe symptoms.

Quality of Life

Subjects filled out a mini RQLQ at each visit that reflected how they felt over the previous week.¹² The domains evaluated were activity, practical, nose, eye, other symptoms, and

overall. Scores were based on a scale of 0 to 6, with 0 being not troubled and 6 being extremely troubled. The overall domain was the average of all the individual domain scores.

Methacholine Challenge

Localized disc challenge with methacholine was performed as previously described using filter paper discs placed on the anterior nasal septum to apply the challenge solutions and collect generated secretions.¹³ Subjects were challenged with 0.9% NaCl (diluent for the methacholine solutions) and the following increasing doses of methacholine: 0.02, 0.06, and 0.19 mg. The outcome of the test was weight of generated nasal secretions.

Nasal and Sinus Lavages

After the methacholine challenge was completed, subjects had their nasal cavities lavaged (2.5 mL warm Lactated Ringer's [LR] on each side) as previously described, and the lavages were transferred to plastic tubes and placed on ice until processing.¹⁴ Next, a maxillary sinus catheter was placed by puncture through the inferior meatus as previously described.¹⁵ The sinus catheter was connected to a syringe that was used to lavage the maxillary sinus antrum. At the end of the experiment, the catheter was pulled out of the sinus and firm pressure applied to that nostril for 5 minutes to prevent any bleeding. The maxillary sinus cavity was lavaged with 15 mL saline, and the fluid was transferred to plastic tubes and placed on ice for processing.

Eosinophil Counts

Lavages collected from subjects were initially shaken to break up mucus and centrifuged at 5000 rpm for 15 minutes, and the supernatant was decanted and stored at -20°C for mediator measurements. The cell pellets were then suspended in 9 mL distilled water to lyse the red blood cells, and then 1 mL of $10\times$ phosphate-buffered saline (PBS) was added to bring the samples back to an isotonic solution. Total cells were then counted in these samples, and the sample was again centrifuged and the supernatant discarded. The cell pellet was suspended in LR and cytopun on slides. Pilot experiments showed that the percentage of recovered cells was not affected by this processing technique.¹¹ These slides were evaluated for eosinophil numbers by a single trained observer blinded to treatment protocols and study visits. Two hundred cells were evaluated on slides (when possible), and we enumerated eosinophils, neutrophils, and mononuclear cells. We thus obtained a percentage of eosinophils in the lavage samples. Because the total number of cells was known, the total number of eosinophils was calculated. Low cells in the cytopun slides occurred because of low total cell counts or technical difficulties during the process of preparing the smears. From our previous experience using this technique, a large sampling error can occur when the total number of cells evaluated in the smear is less than 50. Because of the paucity of cells in some of the specimens, we made some assumptions relating to eosinophil number. The lowest total number of eosinophils obtained from slides with adequate cells counted and evaluable total cell counts was 25. This number

was assigned to specimens in the following situations: (1) when the number of cells evaluated in the smear was less than 50 and (2) when the number of eosinophils and thus percentage of eosinophils obtained from examining the differential count was zero. Exceptions to this assumption were patients who had a large number of total cells ($>60,000$) and where the resultant smears had fewer than 50 cells to evaluate. These samples were considered technically inadequate and not included in data analysis. Including the sinus and nasal count for both in- and out-of-season samplings in 18 subjects, the total number of samples was 72 (18 subjects $\times$ 2 nasal samples $\times$ 2 sinus samples). Seven of 72 samples were technically inadequate.

Assays

Human serum albumin was measured using an enzyme-linked immunosorbent assay (ELISA) sensitive to 1 ng/mL albumin.¹⁶ Eosinophil cationic protein (ECP), a marker of eosinophil activation, was measured by a commercially available double-antibody radioimmunoassay (Pharmacia AB, Uppsala, Sweden) sensitive to 2 μ g/L. Concentrations below the limits of detection were assigned a value half that of the corresponding sensitivity.

Statistical Analysis

The data for the methacholine challenges and quality of life were normally distributed. Analysis of variance (ANOVA) was first performed within each methacholine challenge to examine differences between challenge doses, and post hoc analysis was performed using a Fisher test. To compare in- and out-of-season methacholine challenges, we compared the net change over diluent within each visit using a paired Student *t* test. A paired *t* test was also performed to compare the diluent and each methacholine challenge between in and out of season individually. Quality-of-life measures were compared using parametric statistics, and scores in and out of season were compared with the Student *t* test.

Symptom scores, which are usually not normally distributed, were compared between in- and out-of-season time points using the Wilcoxon signed ranks test. The same analysis was performed for mediator levels and numbers of eosinophils. Spearman rank correlations were used. All statistical tests were performed using a Macintosh computer (Apple Computer, Cupertino, California) and Statview II statistical software (Abacus Concepts, Piscataway, New Jersey).

Results

The 2001 and 2002 ragweed allergy seasons were typical for the Chicagoland area. Ragweed counts were obtained from the local reporting station that documents the counts as low, moderate, or high for each day of the season. During the 2001 season, there were 21 days with low counts, 15 days with moderate counts, and 10 days with high counts. During the 2002 season, there were 16 days with low counts, 14 days with moderate counts, and 7 days with high counts. For comparison, the average number of days with the specific pollen counts for the 3 years after the study (2003-2005) was pretty similar: 17 days with low counts, 9 days with moderate

counts, and 9 days with high counts. Of our 18 subjects, 10 were men and 8 were women with a median age of 29.9 years (range, 22-41 years). There were 4 African Americans, 12 whites, and 2 of Hispanic descent. Three had mild asthma and used bronchodilators as needed a few times a year.

All subjects had significantly more sneezes and worse runny nose, stuffy nose, itchy nose/throat, and overall symptoms during the season ($P < .001$ for all; **Figure 1**). Similarly, quality of life (QOL) was significantly worse during the ragweed season ($P < .0001$ for overall and individual domains; **Figure 2**).

Compared with the diluent response, challenge with methacholine led to significant increases in collected secretions in both in- and out-of-season visits (ANOVA $P = .0001$ and $P < .05$ for all methacholine doses vs diluent in both in- and out-of-season visits; **Figure 3**). When the net change over diluent was compared between in- and out-of-season visits, no significant difference was found ($P = .16$). However, there were significant differences between in- and out-of-season secretion weights for the following challenges: diluent ($P = .036$), 0.02 mg methacholine ($P = .003$), and 0.19 mg methacholine ($P = .017$) (**Figure 3**).

There was a significant eosinophilic influx in both the nose and maxillary sinus during the season compared with outside the pollen season ($P \leq .02$). The total numbers of eosinophils increased more than 10-fold in both the nose and sinus (**Figure 4**). In the circulation, the percentage of eosinophils was significantly higher during the season (median [range], 2.5% [1%-8%]) compared with out of season (2% [1%-5%]; $P = .02$). There was no correlation between the percentage of circulating eosinophils and the percentage of eosinophils in the nose or sinus during the allergy season. There was also no correlation between the total number of eosinophils in the nasal and sinus cavities during the season.

There was a significant increase in ECP levels in nasal lavage during the season when compared with the levels outside the season ($P = .05$). The ECP levels were not significantly different in sinus lavages when comparing the out-of-season with the in-season levels (**Figure 5**). It is of note that many samples from the sinus lavage had nondetectable levels of ECP commensurate with the lower number of eosinophils in the sinus during the season compared with the nasal cavity. As expected, there were strong correlations between the number of eosinophils in lavages and levels of ECP during the season in both the nose ($r_s = 0.9$, $P < .01$) and the maxillary sinus ($r_s = 0.47$, $P < .05$).

Because the speculated mechanism of the eosinophil influx into the maxillary sinus might be related to a neural reflex, we correlated the number of sneezes during the season (a reflection of neural reflexes in the nose) with the number of eosinophils in the sinus cavity. There was a significant positive correlation with $r_s = 0.53$, $P < .05$.

Albumin levels in nasal lavages were significantly higher in the nose during the season compared with the out-of-season lavage levels ($P = .001$). Although there was a numeric increase in the levels of albumin in sinus lavages during the season, this did not reach statistical significance ($P = .20$;

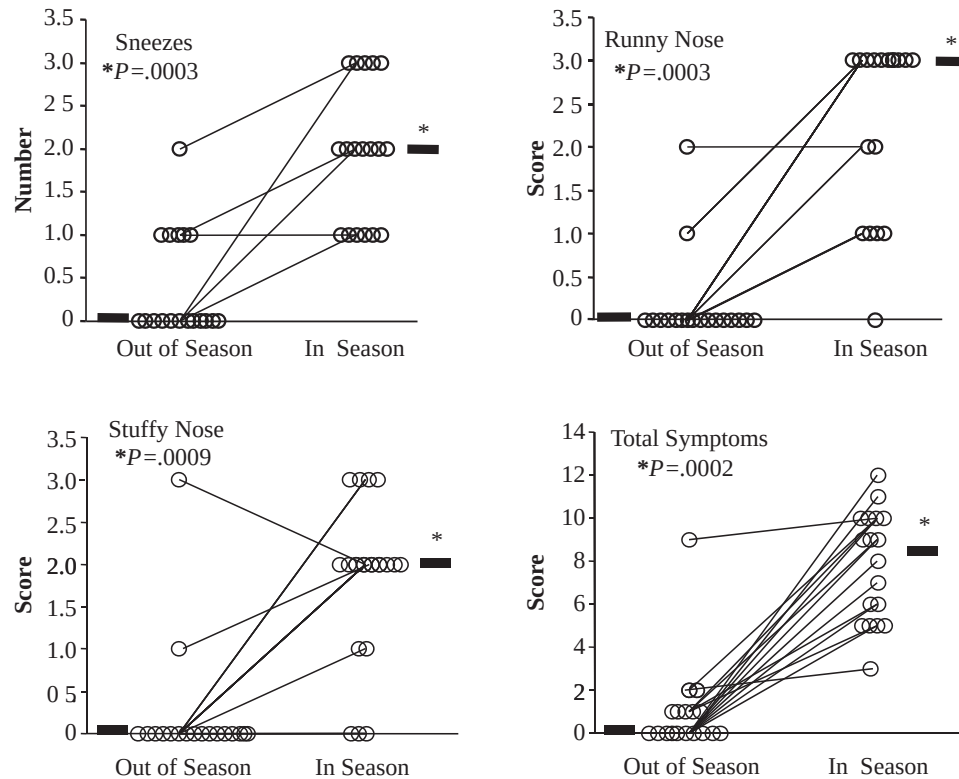


Figure 1. Nasal symptoms. Symptoms were worse during the ragweed season. The in- and out-of-season data are shown for sneezes, runny and stuffy nose, and total symptoms. *Denotes a significant difference between in- and out-of-season scores with *P* values shown. Solid bars indicate median values.

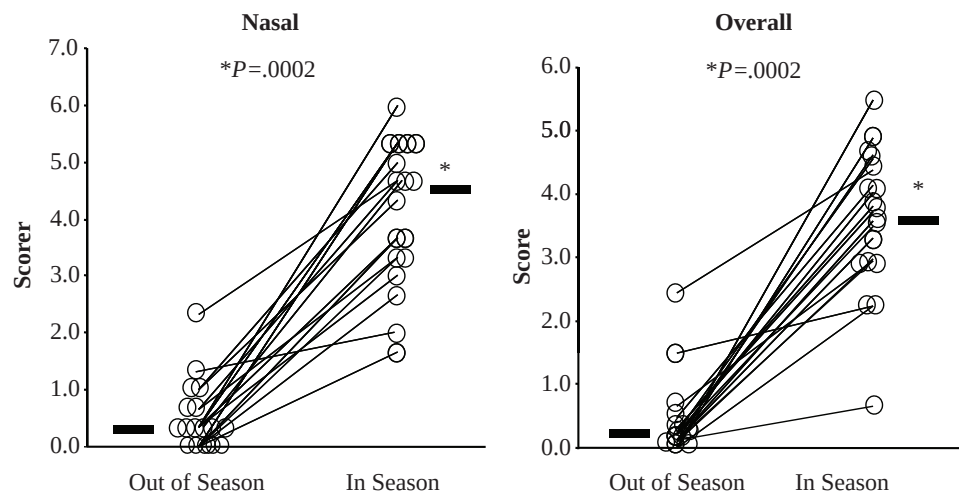


Figure 2. Quality of life was adversely affected during the ragweed season. Only data for nasal and overall domains are shown here, but similar results were seen for all other domains, including activity, practical, eye, and other symptoms. *Denotes a significant difference between in- and out-of-season scores with *P* values shown. Solid bars indicate median values.

Figure 6). During the season, albumin levels in the nose correlated with the levels in the maxillary sinus ($r_s = 0.59$, $P = .01$).

Discussion

In our previous work, we showed an increase in vascular permeability and an eosinophilic influx into the ipsilateral maxillary

sinus after nasal challenge with allergen, suggesting that an allergic reaction in the nose could cause inflammation in the sinuses. In the current study, we set out to extend those findings to seasonal disease. Our subjects reacted like typical ragweed allergic individuals. They became symptomatic and decreased their quality of life during the allergy season. Nasal nonspecific hyperresponsiveness increased during the

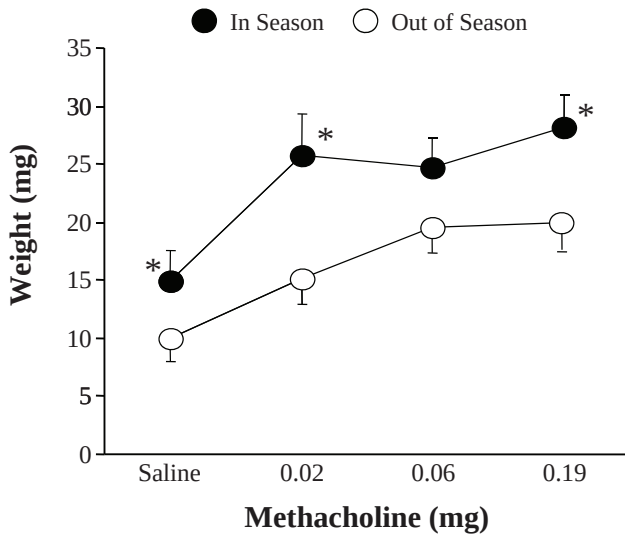


Figure 3. Nasal responsiveness to methacholine. There were significant increases in secretion weights after methacholine challenges when compared with diluent challenge for both in- and out-of-season visits. As shown, there was an increased responsiveness to diluent, 0.02 mg methacholine, and 0.19 mg methacholine during the season. * $P < .04$ between in- and out-of-season weights.

season, as indicated by a significant increase in the amount of secretions produced in response to a diluent challenge as well as to the lowest and highest doses of methacholine. This increase in baseline response to diluent negated our ability to show a net increase in the change over baseline for the doses of methacholine. We have previously reported similar findings following nasal challenge with antigen and during the season.¹⁷ Typical of allergic individuals, the percentage of circulating eosinophils was higher in season compared with out of season.

Accompanying the symptomatic change during the season, subjects showed increased nasal inflammation. During the season, the total number of eosinophils present in nasal lavages was significantly higher. In addition, there were significantly higher levels of albumin and ECP in the nose during the ragweed season.

During the ragweed season, the lavage of the maxillary sinus showed an increase in the number of eosinophils, suggesting an inflammation in the sinus caused by the allergic reaction in the nose. The maxillary sinus levels of ECP for both in- and out-of-season visits were frequently below the limit of detection, so we had measureable value for only a few samples. The levels of ECP, however, correlated with the number of eosinophils in the sinuses. Although there were higher levels of albumin in the maxillary sinus during the season, the difference did not reach statistical significance as it did in our previous nasal challenge with antigen study. This could be related to the fact that seasonal challenge is less vigorous than an experimental challenge in a laboratory setting.

The possibility exists that bleeding into the maxillary sinus could account for the significant increase in eosinophil numbers seen in the maxillary sinus during the season. The maxillary sinus punctures were all done by the principal investigator (F.B.), and most of the initial sinus lavages were grossly bloodless. For these clean punctures, we estimate that less than 1/20 of a drop of blood, or approximately 1 μ L, was in each sinus lavage. The median number of circulating eosinophils was 180/ μ L, which equates to 180 eosinophils in each lavage. The median number of eosinophils during the season in the maxillary sinus was 4248, more than 10-fold higher than that circulating in the periphery.

As to the mechanism by which nasal inflammation leads to sinus maxillary involvement, one possibility is that a reflex occurs between the nose and the maxillary sinus. Acetylcholine and vasoactive intestinal peptide are released from postganglionic parasympathetic fibers, which have been mapped to the nasal mucosa and submucosal glands. Vasoactive intestinal

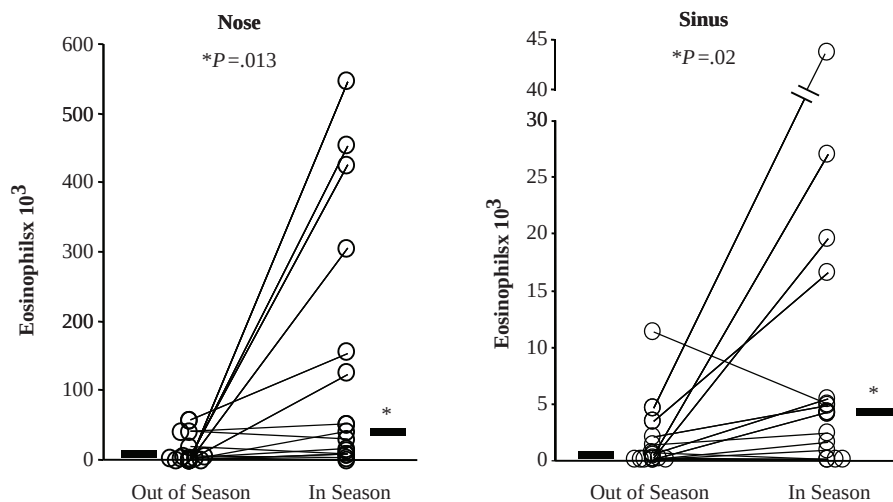


Figure 4. In- and out-of-season data for nasal and maxillary sinus eosinophil counts. There were significantly more eosinophils in both the nose and maxillary sinus during the ragweed season. *Denotes a significant difference between in- and out-of-season scores with P values shown. Solid bars indicate median values.

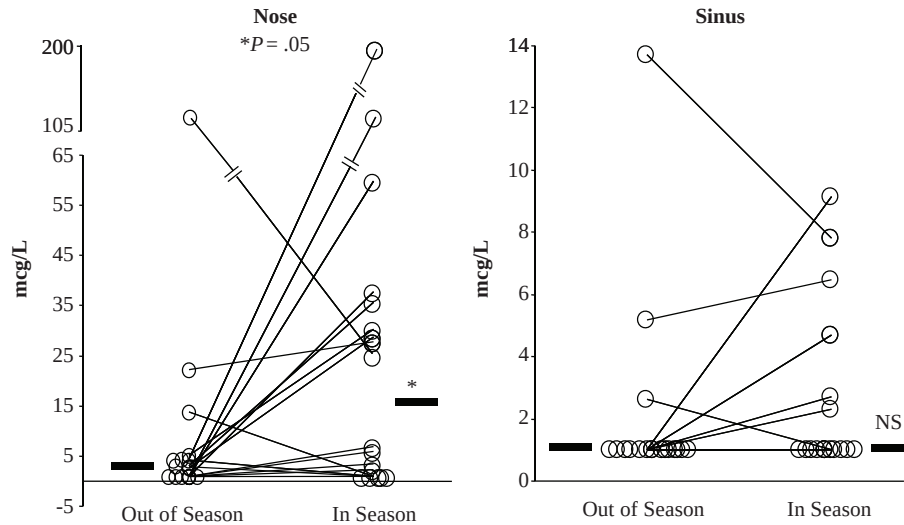


Figure 5. In- and out-of-season data for nasal and maxillary sinus eosinophil cationic protein (ECP) levels. The ECP levels were significantly higher in the nose during the season, but there was no significant difference in the maxillary sinus. *Denotes a significant difference between in- and out-of-season scores with *P* values shown. Solid bars indicate median values.

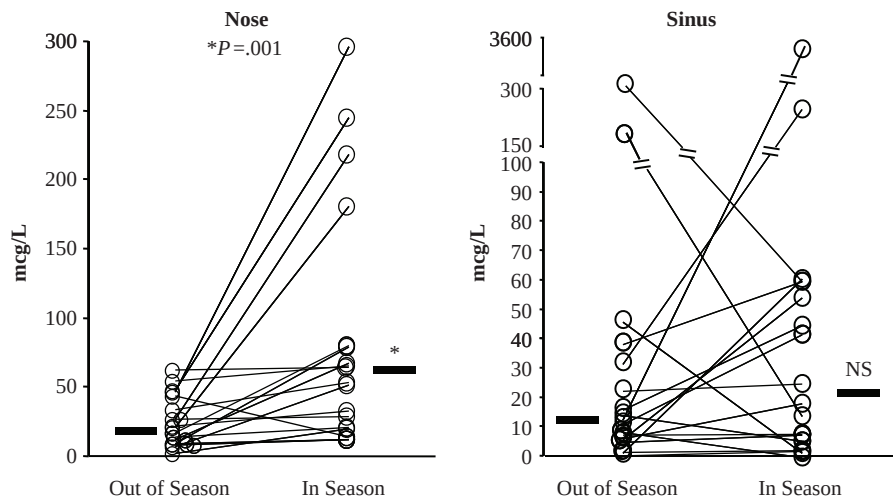


Figure 6. In- and out-of-season data for nasal and maxillary sinus albumin levels. Albumin levels were significantly higher in the nose during the season, but there was no significant difference in the maxillary sinus. *Denotes a significant difference between in- and out-of-season scores with *P* values shown. Solid bars indicate median values.

peptide is a potent vasodilator and secretagogue. It has also been postulated to stimulate T cells to release interleukin-5 (IL-5).¹⁸ Interleukin-5 is a TH2 cytokine involved in the late-phase allergic response, as demonstrated from nasal mucosal biopsies of allergic patients after allergen challenge.¹⁹ It is thought to upregulate the production and release of eosinophils from the bone marrow.^{20,21} Interleukin-5 acts as a chemotactic agent for eosinophils and activates and promotes their survival in tissues. Allergic inflammation stimulates sensory fibers, which leads to a reflex parasympathetic response in the nose; a cascade effect may therefore be initiated via the release of IL-5 that recruits eosinophils not only to the site of allergen exposure but also to adjacent sites, such as the maxillary sinus, connected through neural pathways. In support of the neural mechanism of sinus inflammation in

response to seasonal nasal allergic inflammation is the fact that the number of sneezes reported in the nose during the season, an essentially nerve-mediated symptom, correlated strongly and significantly with the number of eosinophils in the maxillary sinus. As to the correlation between the eosinophils in the nose and those in the sinuses, if one considers that the sinus response might be a reflex, then the magnitude of the nasal and sinus responses might not be equivalent and need not be necessarily correlated.

Our findings could also be explained by a generalized systemic inflammatory response to allergen exposure. As stated above, this response would recruit inflammatory cells, including eosinophils, to the site of exposure but also to separate sites such as the maxillary sinus. Nasal congestion and obstruction of the sinus ostia could also occur as a result of

seasonal allergic inflammation, but this does not really explain the increased eosinophils measured in the sinus cavity.

Although many studies in humans describe an association between allergic rhinitis and both acute and chronic sinusitis, limited studies have examined the development of sinus inflammation following allergic nasal inflammation. We¹¹ and Pelikan and Pelikan-Filipek²² have used nasal challenge with antigen and shown evidence of inflammation in the sinus. Slavin et al²³ used imaging techniques of the sinuses during the ragweed season and found no changes in the sinuses. We present here the first evidence of the development of maxillary sinus inflammation during an allergy season.

Author Contributions

Fuad M. Baroody, conception, design, acquisition and analysis of data, drafting the article and approving final version; **Samantha M. Mucha**, acquisition and analysis of data, drafting the article and approving final version; **Marcy deTineo**, acquisition of data, revising article for intellectual content; **Robert M. Naclerio**, conception, design, revising article for intellectual content and approving final version.

Disclosures

Competing interests: Fuad M. Baroody has received speaker honoraria from Merck and GlaxoSmithKline. Robert M. Naclerio has received speaker honoraria from Sundovian and Merck; has received a research grant from Merck, GlaxoSmithKline, Nasoneb, SinuNeb, and NcNeal; and is a consultant for Sundovian, Teva, Kalypsos, Regeneron, Meda, and SinuNeb.

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