

Allergic sensitization does not predispose to sinus inflammation in externalized paranasal sinuses

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ABSTRACT

Background: Chronic rhinosinusitis (CRS) has a multifactorial etiology, with a debate about the role of inhalant allergy in the pathogenesis of CRS.

Objective: This study assessed the impact of allergy status on externalized paranasal sinuses after tumor resection to determine if a predisposition to inhalant allergy brought about additional inflammation after sinus surgery.

Methodology: A case-control study was performed on patients who had no history of CRS who underwent paranasal sinus tumor resection. Allergic sensitization was defined by a positive serum ImmunoCAP test result. Outcomes were measured at least 6 months after surgery by using the modified Lund-Mackay endoscopic score and the 22-item Sino-Nasal Outcome test, with rhinitis, sleep, psychological, ear and/or facial, and sinus subscores to assess the impact of allergy status on mucosal inflammation.

Results: A total of 103 patients (53.44 ± 17.46 years; 46% women) were assessed. Of these, 61.17% were allergically sensitized at the time of surgery. Postsurgery endoscopic assessment was similar [the modified Lund-Mackay endoscopic score allergic sensitized 0.5 (1.7) versus nonallergic sensitized 0.0 (0.9); $p = 0.15$]. Sinonasal symptoms were also similar between the groups' 22-item Sino-Nasal Outcome test scores, allergic sensitized versus allergic nonsensitized, (allergic 28.9 ± 20.8 versus nonallergic 33.5 ± 19.7; $p = 0.31$), rhinitis score (5.9 ± 5.5 versus 6.4 ± 4.7; $p = 0.66$), sleep score (6.9 ± 5.9 versus 7.7 ± 4.8; $p = 0.50$), ear and/or facial symptom score (3.4 ± 3.6 versus 4.3 ± 3.3; $p = 0.22$), psychological score (6.9 ± 6.0 versus 8.3 ± 6.7; $p = 0.29$), and of nasal symptom score (6.4 ± 5.2 versus 7.0 ± 5.3; $p = 0.61$).

Conclusions: Externalization of the sinuses in patients with inhalant allergy did not bring about significant additional inflammation in patients after tumor surgery.

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The etiology of chronic rhinosinusitis (CRS) is multifactorial, with allergic rhinitis, viral infection, cigarette smoke, anatomic defects, bacterial infection, air pollutant, antibody deficiencies, stress, and ciliary dysmotility all believed to be factors in the pathogenesis.^{1–3} Allergic inflammation is thought to be a precursor to rhinosinusitis, and a similar profile of allergy is noted between adults and children.^{4–6} Many studies assessed prognostic factors that influence success after functional endoscopic sinus surgery (FESS), specifically allergy status.⁷ There is no doubt that patients with CRS and with inhalant allergy have a greater symptom burden, but debate exists on the impact of allergy sensitization in the development of CRS. From animal models, allergic inflammation can augment bacterial infection with an enhanced inflammatory response.¹

Huang⁸ compared 413 patients with perennial allergic rhinitis and patients with seasonal allergic rhinitis, and found that the incidence of sinusitis was more common in winter when patients with perennial allergic rhinitis were compared with patients with seasonal allergic rhinitis. They also found that the patients with perennial allergic rhinitis and with mold allergy had a relative risk of 2.49 of developing acute sinusitis.⁸ However, chronicity and the disease entity of CRS was similar between the groups. Although previous studies looked at

factors that predict CRS development in patients who are allergy sensitized⁹ and the accumulative risk with additional lung disease,¹⁰ few case-control studies provide a definitive link between allergy sensitization and the development of CRS. There are several studies that demonstrate an association of disease severity and influence of treatment outcomes^{11–16}; however, data that demonstrate a causal relationship have not been established.

The wide opening of sinuses for the purposes of delivering topical therapy, removal of tumors, or orbital surgery has raised the speculation that such exteriorization of the sinus cavity may expose the paranasal sinuses to a greater “environmental” burden. This postulated burden should be greater in patients who are allergically sensitized. Although there are no perfect animal models to assess the impact on allergic sensitization on externalized mucosa without the presence of CRS, clinical experience indicates that the most widely open sinus cavities in the setting of tumor and orbital surgery result in stable noninflamed mucosal systems. Chronic sinonasal inflammation and the establishment of CRS are not common events in this subgroup. This study evaluated the influence of inhalant allergen sensitization as a potential contributor to the inflammatory burden in normal sinuses that underwent externalization after tumor resection.

METHODS

A case-control trial was conducted of patients who attended a tertiary rhinology practice in Sydney, Australia. Patients were included if they underwent a paranasal sinus tumor resection and had at least 6 months of follow-up. The follow-up timeline was based on the work of Jo *et al.*,¹⁷ which showed healing 3 months after tumor resection. The study had approval of the local St Vincent's Human Research ethics committee (09/083). The patients provided informed consent for research data collection.

Population

Consecutive patients were included if they underwent a paranasal sinus tumor resection and had perioperative blood taken for allergy assessment. Asthma status was defined with a previous spirometry that demonstrated a 15% improvement on forced expiratory volume in the first second of expiration with a bronchodilator, 15% worsening of forced expiratory volume in the first second of expiration on methacholine chal-

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Table 1 Breakdown of allergic sensitized and nonsensitized patient groups

	Allergy Status		p Value
	Allergy Sensitized (n = 55)	Not Allergy Sensitized (n = 48)	
Age, mean $\pm$ SD, y	50.2 $\pm$ 17.42	57.1 $\pm$ 16.94	0.05*
Women, % (no.)	46.3 (25)	45.8 (18)	0.96
With asthma, % (no.)	31.4 (16)	7.1 (3)	<0.01*
Smokers, % (no.)	7.4 (4)	4.4 (2)	0.82
Treatment factors, % (no.)			
Radiotherapy	16.7 (9)	18.8 (8)	0.78
Olfactory resection	16.7 (9)	16.7 (8)	1.00
Dura resection	64.8 (35)	79.2 (38)	0.11
Flap formation	67.3 (37)	79.2 (38)	0.18

SD = Standard deviation.

*p = 0.99.

Table 2 Impact of allergy status in terms of subjective functional outcome measure by using subdomains of SNOT-22

	Allergy Status, mean $\pm$ SD		p Value
	Allergy Sensitized (n = 42)	Not Allergy Sensitized (n = 39)	
SNOT-22 overall score	28.9 $\pm$ 20.75	33.5 $\pm$ 19.73	0.31
Rhinitis score	5.9 $\pm$ 5.48	6.4 $\pm$ 4.68	0.66
Sleep score	6.9 $\pm$ 5.92	7.7 $\pm$ 4.81	0.50
Ear and/or facial symptom	3.4 $\pm$ 3.55	4.3 $\pm$ 3.26	0.22
Psychological score	6.9 $\pm$ 6.00	8.3 $\pm$ 5.68	0.29
Nasal symptom score	6.4 $\pm$ 5.18	7.0 $\pm$ 5.32	0.61

SNOT-22 = 22-Item Sino-Nasal Outcome Test; SD = standard deviation.

lenge or if they were actively using reliever and/or preventative medication. Smoking status was defined as any tobacco use or a patient with regular use who had ceased within the past 12 months. Patients with a history of CRS, surgery for CRS, or septal or turbinate surgery were excluded.

Allergy Status

Allergy status, or aeroallergen sensitization, was defined by serologic assessment. On the day of surgery, the patient had a 10-mL EDTA blood collection, which was analyzed via ImmunoCAP (Phadia AB, Uppsala, Sweden). Serum specific immunoglobulin E to four allergen mixes was evaluated (dust mite, mold, animal, and grass). House-dust allergen mix tested for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blattella germanica*; mold mix for *Penicillium chrysogenum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Alternaria alternata*; epithelial mix for cat dander, horse dander, cow dander, dog dander; and grass mix for *Cynodon dactylon*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*, *Sorghum halepense*, and *Paspalum notatum*. Serum specific immunoglobulin E results of >0.35 mU/mL for any four of the mixed airborne antigen was considered positive. This provided the separation into two separate populations based on evidence of inhalant allergen sensitization.

Endoscopic Evaluation

Objective postoperative outcomes were measured by using the endoscopy score. The last available nasoendoscopy video and images, which were from at least 6 months after the operation, were blindly reviewed retrospectively by two otorhinolaryngologists (H.P.B. and Anna Kinsley) and were scored by using the modified Lund-Mackay endoscopic score as defined by Snidvongs *et al.*¹⁸ This score has three components: mucosa, discharge, and purulence. The mucosa component is assessed on a seven-point ordinal scale, which assesses mucosal inflammation, which ranges from normal mucosa to polyp beyond the cavity. The discharge score is assessed on a three-point ordinal scale of normal mucosa, thin discharge, or thick discharge, whereas the purulence score is a two-point ordinal scale of absent or

present purulent discharge (Table 1). The total endoscopy score was reported as the average of all opened cavities because the number of sinuses opened was dependent on the nature of the disease and differed among individuals. The individual assessments of mucosa, discharge, and purulence were reported as the highest value across all cavities.

Patient-Reported Outcome Measures

The last available 22-item Sino-Nasal Outcome Test (SNOT-22) score that is at least 6 months after the operation is used to assess subjective patient outcome measures and is reported as a total score from 0 to 110.¹⁹ Previous sinonasal symptoms were distorted by the presence of tumor-related sinonasal dysfunction and were not used as discriminating factors. The subdomains of the SNOT-22, which were derived from Browne *et al.*,²⁰ was also analyzed. The rhinitis subdomain covers five questions regarding the following: need to blow nose, sneezing, runny nose, postnasal discharge, and thick nasal discharge. The ear and facial pain subdomain covers four questions regarding the following: ear fullness, dizziness, ear pain, and facial pain and/or pressure. The third subdomain covers sleep function, with three questions regarding the following: difficulty falling asleep, waking up at night, and lack of a good night's sleep. The fourth component was the psychological score, which included six questions regarding the following: reduced productivity, reduced concentration, fatigue, frustration and/or restlessness and/or irritability, sadness, and embarrassment. An additional subdomain of nasal symptoms, developed by Baguley *et al.*,²¹ and Barham *et al.*²² was also analyzed. It included previously mentioned questions regarding nasal obstruction, thick discharge, need to blow nose, smell loss, and facial pain. All the questions were on a six-point ordinal scale, which ranged from 0 (no problem) to 5 (a problem as bad as it can be).

Statistical Analysis

Data were analyzed by using SPSS 22 (SPSS Inc., Chicago, IL). The demographic and treatment factor differences between patients who

Table 3 Impact of allergic status on CRS symptoms

Symptoms	Allergy Status, % (no.)*		p Value
	Allergy Sensitized	Not Allergy Sensitized	
Nasal obstruction	26.1 (11)	23.1 (9)	0.79
Thick discharge	14.6 (6)	18.0 (7)	0.77
Need to blow nose	30.9 (13)	23.1 (9)	0.81
Postnasal discharge	17.0 (7)	23.1 (9)	0.57
Smell loss	26.1 (11)	30.8 (12)	0.37
Facial pain	7.2 (3)	12.9 (5)	0.17
Sneezing	7.2 (3)	12.9 (5)	0.07
Runny nose	9.6 (4)	5.1 (2)	0.35

CRS = Chronic rhinosinusitis.

*Percentages in the highest three categories.

Table 4 Comparison of allergy status on endoscopic score as measured by the MLMES*

	Allergy Status, % (no.)		p Value
	Allergy Sensitized	Not Allergy Sensitized	
Highest mucosa score			0.07
Normal mucosa	36.0 (9)	62.5 (15)	
Mild edema	36.0 (9)	20.8 (5)	
Severe edema	20.0 (5)	12.5 (3)	
Mild polypoid	0.0	0.0	
Severe polypoid	8.0 (2)	4.2 (1)	
Polyp within cavity	0.0	0.0	
Polyp beyond cavity	0.0	0.0	
Highest discharge score			0.63
No discharge	68.0 (17)	75.0 (18)	
Clear, thin discharge	24.0 (6)	16.7 (4)	
Thick, purulent discharge	8.0 (2)	8.3 (2)	
Highest purulent score			0.31
Absent	96.0 (24)	100.0 (24)	
Present	4.0 (1)	0.0 (0)	
MLMES average	0.5 (1.7)	0.0 (0.9)	0.15

MLMES = Modified Lund-Mackay endoscopy score.

*From Ref. 15.

were allergy sensitized and patients who were not sensitized were tested by using the independent Student's *t*-test (for continuous data) and the Pearson χ^2 test for (for nominal data). The endoscopy score difference between the two populations was tested by using the Mann-Whitney *U* test because it was nonparametric, whereas the Kendall τ_b was used to analyze the ordinal endoscopy subdomains of mucosa, discharge, and purulence. SNOT-22 and its subdomain were assessed between the two populations by using the independent Student's *t*-test, and specific symptoms were analyzed by using the Kendall τ_b test. The *p* values of <0.05 were considered significant.

RESULTS

One hundred and three patients (mean [standard deviation (SD)] age, 53.4 ± 17.46 years; 46.1% women) were assessed. This group consisted of 53.4% who were sensitized based on ImmunoCAP testing. Asthma was prevalent in 20.4% ($n = 19$) of the population, and 6.1% (6) were active smokers and 4.0% (4) were ex-smokers. As part of their surgery, 16.7% ($n = 17$) had olfactory resection, 71.6% (73) had dura resection, and 72.8% (75) had a nasoseptal flap harvested for reconstructive purposes. Radiotherapy was given to 17.7% (18). Not all the patients had both endoscopy and patient-reported outcome measures available at the time of data collection, but 103 patients as a group were analyzed by allergy status, with 53.4% who demonstrated allergic sensitization. Patients who were allergy sensitized were sim-

ilar with regard to age (mean [SD] age, 50.2 ± 17.42 years versus 57.1 ± 16.9 years; $p = 0.05$), female sex (46.3 versus 45.8%; $p = 0.96$), and smoking status (7.4 versus 4.4%; $p = 0.82$). As expected, patients who were allergy sensitized were more likely to have asthma compared with patients who were not sensitized (31.4 versus 7.1%; $p < 0.01$). There was no difference in dura resection (64.8 versus 79.2%; $p = 0.11$) and nasoseptal flap reconstruction (67.3 versus 79.2%; $p = 0.18$). Importantly, there was no difference in olfactory apparatus resection (16.7 versus 16.7%; $p > 0.99$) or postoperative radiotherapy (16.7 versus 18.8%; $p = 0.78$) because these two factors might influence posttumor sinonasal function (Table 1).

The patient-reported outcome measures were similar between the two groups (Table 2). The patients who were allergy sensitized had a similar mean SNOT-22 score versus the nonallergic group (28.9 ± 20.8 versus 33.5 ± 19.7 ; $p = 0.31$); similarly, there was no difference observed for the mean scores of the rhinitis score (5.9 ± 5.5 versus 6.4 ± 4.7 ; $p = 0.66$), sleep score (6.9 ± 5.9 versus 7.7 ± 4.8 ; $p = 0.50$), ear and/or facial symptom score (3.4 ± 3.6 versus 4.3 ± 3.3 ; $p = 0.22$), psychological score (6.9 ± 6.0 versus 8.3 ± 6.7 ; $p = 0.29$), and nasal symptom score (6.4 ± 5.2 versus 7.0 ± 5.3 ; $p = 0.61$). There was no difference between the patients who were allergy sensitized and those who were not sensitized to individual symptom scores of nasal obstruction, thick discharge, need to blow nose, postnasal discharge, smell loss, facial pain, sneezing, and runny nose (Table 3).

Endoscopic assessment *via* the modified Lund-Mackay endoscopic score demonstrated no significance difference between patients who were allergy sensitized and patients who were not sensitized (0.5% ($n = 1.7$) versus 0.0% ($n = 0.9$); $p = 0.15$). The subdomains of the endoscopy score showed no significant difference between patients who were allergy sensitized versus patients who were not sensitized; the mucosa score (28.0 versus 16.7% with more than mild edema; $p = 0.07$), discharge score (32.0 versus 25.0% with either thin or thick discharge; $p = 0.63$), and purulence score (4.0 versus 0.0% with any purulent discharge; $p = 0.31$).

DISCUSSION

This study investigated the effect of externalization of the sinuses, without previous CRS, to exclude confounding variables. There was no difference between either subjective (SNOT-22 and subdomains) or objective scores (endoscopic scores) between those patients who had previous allergic sensitization and those without previous allergic sensitization (Tables 2 and 4). After endoscopic sinus surgery, Benninger¹¹ found that 65% of the patients had worsening sinus symptoms with seasonal allergic exacerbations but that 93% of patients who were allergy sensitized still had good postsurgical outcomes. Similarly, Ramadan¹² had a 74% success rate after FESS in patients who were allergy sensitized compared with 71% in patients without allergy. However, Dursun *et al.*¹³ found that the allergy status was a prognostic indicator of poor outcomes after FESS, with a relative risk of 5.29 (2.11–13.26), and, similarly, Kennedy¹⁴ found environmental allergies to be risk factors for poor objective outcome. Despite these studies, there are equivocal studies that indicate that allergy status does not impact outcome. Even though Senior *et al.*¹⁵ showed a marginally significant relationship between allergy and more-extensive disease, the rate of revision surgery in patients who were allergy sensitized was not significant. Smith *et al.*²³ also found that allergy status did not have an impact on objective measures because patients had similar computed tomography and endoscopy scores. The impact of allergy status on patient outcome in CRS may have more to do with the accumulative symptom burden. Kim *et al.*²⁴ demonstrated that, if allergy was identified and treated, it did not impact on the outcome after FESS, with an odds ratio of 2.3 (95% confidence interval, 0.1–149.5; $p = 0.38$).

There is no perfect model for assessing the impact of allergen exposure to the paranasal sinuses. It would be unethical to externalize normal sinuses because, such as in this study, patients with a paranasal sinus were used as surrogates for normal sinuses. Although this approach had limitations to extrapolating our data to patients with CRS, it showed that simply opening the sinuses in patients with inhalant allergy did not bring about excessive inflammation nor did allergen sensitization predispose to the development of CRS. Instead, recovery after externalization of sinuses was similar, regardless of previous allergy sensitization. The mean age of this study's population was higher than those classically affected by CRS and could potentially limit the findings of this study.^{7,13,23,25–27} However, the baseline characteristics of allergy sensitization seemed to reflect accurate characterization of our populations because the patients with allergy were both younger and with a higher incidence of asthma. The origins of mucosal inflammation in CRS are likely to be broader than simple inhalant immunoglobulin E-mediated allergy.

CONCLUSION

In patients without a history of CRS who underwent tumor surgery, externalizing the sinuses in patients with inhalant allergy did not bring about significant additional inflammation.

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