

Correlation of Symptoms, Clinical Signs, and Biomarkers of Inflammation in Postsurgical Chronic Rhinosinusitis

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Abstract

Objective: The study aimed to evaluate symptoms described by patients with chronic rhinosinusitis with polypoid changes/nasal polyps and their correlation with computed tomography (CT), nasal endoscopy, and intranasal biomarkers.

Study Design: Prospective multicenter study symptom data from postsurgical adult chronic rhinosinusitis study participants with recurrent disease refractory to medical therapy were analyzed in comparison with objective data.

Methods: Using logistic regression analysis, participant-rated 16-question surveys from 258 participants were assessed for correlation with nasal endoscopy scores, CT percentage of sinus occlusion, and intranasal biomarkers of fungal antigens (*Alternaria* and *Aspergillus*), eosinophilic inflammation (eosinophil-derived neurotoxin [EDN] and major basic protein [MBP]), and inflammatory cytokines (interleukins 5 and 13).

Results: Study participant assessments revealed increased CT occlusion in participants presenting with greater inability to smell ($P < .019$). Mucosal inflammation identified on nasal endoscopy was positively correlated with congestion ($P < .028$), runny nose ($P < .002$), and ear pain ($P < .007$). Elevated EDN was positively correlated in patients with bothersome congestion ($P < .031$) and runny nose ($P < .011$). Sneezing was positively correlated with multiple markers: *Alternaria* ($P < .024$), interleukin-13 ($P < .027$), MBP ($P < .034$), and interleukin-5 ($P < .019$).

Conclusion: Nasal endoscopy, not CT imaging, has the strongest correlation with the 2 cardinal symptoms of congestion and runny nose in CRS patients; these correlate with biomarkers of eosinophilic inflammation.

Keywords

chronic rhinosinusitis, biomarker, CT scan, nasal endoscopy, nasal polyposis

Introduction

Chronic rhinosinusitis (CRS) is a condition diagnosed by clinical symptoms that arise as a result of inflammation of the nasal and paranasal sinus mucosae. It was the primary diagnosis at approximately 11.5 million office visits throughout the US in 2009 and for which universally effective treatment continues to be elusive.^{1,2} Patients with CRS experience impaired quality of life due to the myriad of symptoms faced throughout the course of the disease, including congestion, facial pain and pressure, anosmia, headaches, mucus production, and increased susceptibility to acute bacterial infection of the paranasal sinuses. To be diagnosed, the symptoms must persist continuously for greater than 12 weeks and include an objective sign of mucosal inflammation via computed tomography (CT) or nasal endoscopy (NE). These “signs of inflammation” are referred within the guidelines as “polyps, edema, or purulent mucus.”³

The use of NE provides direct visualization of the nasal cavities and paranasal sinus ostia while CT scans provide a comprehensive view of the opacification within the paranasal

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sinuses as well as the nasal cavities. Computed tomography scans in particular have been referred to by the Joint Council of Allergy, Asthma, and Immunology as the ideal technique in which to evaluate the nasal cavity and paranasal sinuses.² Recently, the use of a coronal 2D single slice image through the osteo-meatal complex (OMC) has been shown to be a valid representation of mucosal thickening in patients with CRS as this slice correlates well to 3D CT scans representing all the sinuses of the same patients.⁴

Mucosal inflammation, which characterizes CRS and is behind much of the clinical symptomatology, has been previously associated with the release and deposition of eosinophil-derived major basic protein (MBP) in the nasal mucus.⁵ The presence of toxic levels of MBP may contribute to damage of the mucosa from the luminal side and be a factor in the continuous nature of CRS symptoms. In fact, MBP in the nasal mucus was suggested as a potential biomarker of CRS, and subsequent validation for its use has been demonstrated.^{5,6} The catalyst of eosinophil migration and degranulation has been suggested to be the presence of nonpathogenic fungus within the sinus mucus.⁷⁻⁹

In the current literature, there is a paucity of information regarding the correlation of biomarker presence or objective inflammation with patient symptomatology.¹⁰⁻¹²

Due to the paucity of biomarkers for CRS, in this study, we evaluated which objective measure of inflammation, among CT scans and NE, exhibited greater correlative ability to clinically experienced symptomatology and biomarkers in recurrent postsurgical CRS patients.

Methods

This study analyzed prospectively collected multicenter data on postsurgical chronic rhinosinusitis patients in 59 centers in the US who previously failed traditional medical and surgical therapy and were subsequently enrolled in a phase 3 clinical trial. Participants included adults over age 18 who were able to speak English and had provided informed consent. Institutional Review Board (IRB) approval was obtained from either the participating center's IRB or a central IRB.

The minimum enrollment criteria defined subjects as females and males between ages 18 and 85 with the diagnosis of recurrent postsurgical CRS after sinus surgery for CRS greater than 6 months prior. Enrollees had to meet diagnostic criteria for CRS via international criteria with objective measurements of a minimum 5 mm mucosal thickening in at least 1 maxillary sinus assessed via CT and polyps or polypoid mucosal thickening identified via NE.³

Those candidates with an acute upper or lower respiratory infection or systemic antibiotic use within the prior month were excluded. Further exclusion criteria included: immunosuppressed patients receiving disease-modifying agents, participants who began use or had a dose change of

nasal corticosteroids within 3 months, or individuals receiving oral or intravenous steroids to treat any condition other than asthma within the previous month. Candidates who used intranasal and/or systemic antifungal therapy within 3 months as well as those who had an acute asthma exacerbation within 3 days were not enrolled. Patients with anatomic abnormalities blocking access to the sinuses and preventing specimen collection, including a clinically significant deviated nasal septum not remedied by surgery, nasal passage obstruction (ie, concha bullosa), or nasal cavities with stage 4 nasal polyposis, were excluded. Candidates were not enrolled if found to have cystic fibrosis or a cancer history other than treated squamous cell or basal cell carcinoma of the skin in full remission for at least 5 years. Lastly, candidates who had a positive pregnancy test or used any investigational products within the past 30 days were also excluded.

Patient symptom data were analyzed from participant-completed 16-symptom questionnaires that were developed with CRS patients prior to the study. The terms asked focused on congestion, cough, facial pain, facial pressure, dry mouth, ear pain, ear pressure, fever, headache(s), inability to smell, postnasal drip, runny nose, sneezing, sore throat, fatigue, and watery eyes. These were scored on a 6-point Likert scale from 0 (absent) to 5 (most bothersome possible).

The questionnaires used in this study were developed using patient-described symptoms and included symptoms in "layman's language" from the Rhinosinusitis Disability Index and SNOT-20. These questionnaires were not used exclusively as the goal was to include symptoms from both tools as well as ask patients about symptoms in a way they would describe their symptoms. For example, the SNOT-20 does not include *congestion*. Figure 2 (in the Results section) illustrates the response rate to the questionnaire, and the high overall prevalence of each symptom was expected. The goal was to identify the most commonly reported symptoms that could be considered the "cardinal symptoms" of CRS. These cardinal symptoms were then correlated to the objective measurements of inflammation and the measurement of nasal mucus biomarkers.

Computed tomography of the paranasal sinuses was judged by a local radiologist, for inclusion purposes, to determine whether a minimum of 5 mm mucosal thickening was present in at least 1 of the maxillary sinus cavities. Images from candidates meeting this criterion were transmitted to Perceptive Informatics (Waltham, Massachusetts, USA) for centralized and independent review. The CT images were standardized by using a single 2D coronal plane view demonstrating the maxillary and ethmoid sinuses with distinctive bony landmarks for the middle meatus (Figure 1). Perceptive Informatics' image analysis software, ALICE, was used to measure the area of mucosal thickening (MT) and air (A). The mucosal thickening

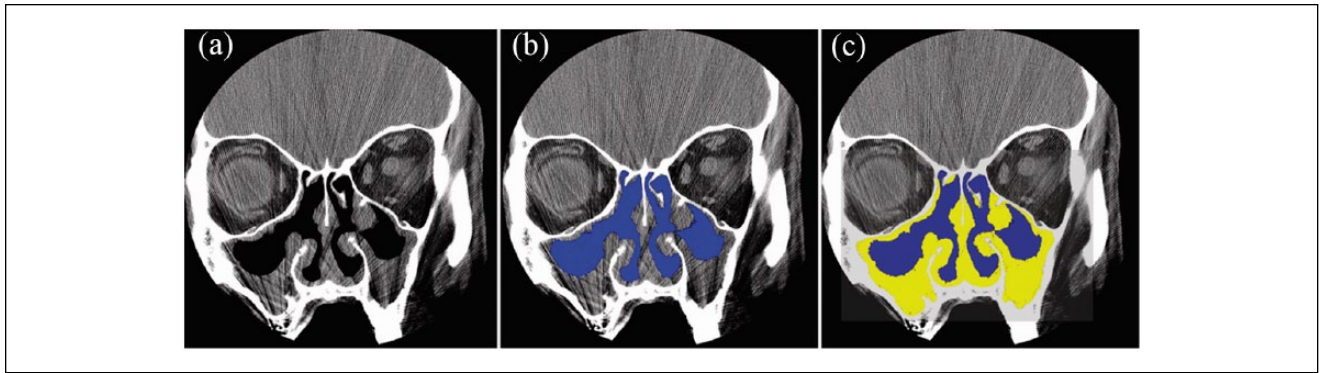


Figure 1. An example of the single slice 2D computed tomography (CT) scan used to assess mucosal thickening is shown to illustrate the process of measuring mucosal thickening (MT) and air (A). (a) Original CT scan of patient with signs of thickening in ethmoidal and maxillary sinuses. (b) Based on the density pattern in the scan, the area that A occupies was measured. (c) The area between the ones of the sinuses and the air was identified and measured as MT. The percentage of MT was calculated using $MT/(MT + A)$.⁴

percentage of the whole area (MT + A) defined the opacified area (Figure 1).

A staff physician at each center blinded to responses on symptom questionnaires at the time of evaluation performed nasal endoscopy and subsequent scoring. Nasal endoscopy of each nasal cavity was graded between 0 and 4 based on modified Rasp classification system:¹³

Stage 0: No evidence of disease.

Stage 1: Inflammatory mucosal changes confined to the middle meatus superior to the lower edge of middle turbinate.

Stage 2: Inflammatory mucosal changes between the lower edge of middle turbinate and the root of inferior turbinate.

Stage 3: Inflammatory mucosal changes between the root of inferior turbinate and the lower edge of inferior turbinate.

Stage 4: Inflammatory changes below the lower edge of inferior turbinate or in anterior nasal cavity.

Nasal Mucosal Biomarkers

Middle meatus nasal secretion specimens were concurrently obtained during NE using a sinus secretion collector (Xomed Surgical Products, Jacksonville, Florida, USA). No nasal decongestants or anesthetics were permitted prior to examination or collection of specimens to avoid dilution. There were instances in which insufficient mucus was obtained. In this setting, specific biomarker testing was prioritized (MBP, *Aspergillus*, and *Alternaria*).

Symptom questionnaires were evaluated for potential correlation with objective NE scores, MT percentage from facial CT imaging, and nasal mucus concentrations of *Aspergillus* (ASP) and *Alternaria* (ALT) antigens, eosinophil major basic protein, eosinophilic-derived neurotoxin

(EDN), and interleukin-5 (IL-5) and -13 (IL-13). Concentrations of MBP in the specimen supernatants were quantitated by ELISA (IMMCO Diagnostics, Inc, Buffalo, New York, USA), and nasal mucus concentrations of EDN, *Aspergillus* and *Alternaria* antigens, along with IL-5 and IL-13 were measured by a microarray (IMMCO Diagnostics, Inc) developed and verified for this study.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) Version 13.0 (SPSS, Chicago, Illinois, USA) was used to analyze the association between specific clinical symptoms and CT scores and NE scores. A *P* value of <.05 was considered to be statistically significant for all analyses. The symptom severity scores were grouped as none to mild (0-2) or moderate to severe (3-5). The CT scores were categorized based on the area of occlusion as 0% to 25%, 25% to 50%, 50% to 75%, and greater than or equal to 75%. The efficacy of CT imaging in illustrating patient symptoms was evaluated by calculating the sensitivity, specificity, and predictive values across all symptoms and CT occlusion areas. Further, logistic regression analysis (with 95% confidence intervals) was used to evaluate the association between the categorized CT scores and the patient symptom severity categories. Similarly, endoscopy score was graded as mild (less than 3 unilaterally or 4 total for both sides) versus moderate to severe (greater than or equal to 3 unilaterally or 4 total) for comparison with patient symptom severity survey scores. The categorized CT scores were compared to endoscopy scores by the chi-square test. Due to the large amount of data within this trial, it was decided to transfer continuous variables into categorical data to facilitate statistical testing.

The biomarker values were categorized based on their percentile distribution (25th, 50th, 75th, or greater than 75th percentile) based on standard deviation from the mean.

Table 1. Study Participant Demographics (n = 258).

Age, y		
Mean (SD)	50.9	(12.3)
Median	51.0	
Range	23-83	
Ethnicity		
	n	%
Asian	4	2
Black	18	7
White	228	89
Other	7	3
Female gender	143	56

Logistic regression analysis was used to evaluate the relationship of nasal biomarkers and symptom scores.

Results

Study Participants

Two hundred ninety-nine study volunteers were enrolled in the multicenter study during a period of 12 months; however, 39 individuals were excluded who had less than 5 mm mucosal thickness on independent CT review. Two additional study volunteers were excluded due to the absence of more than 1 symptom score, thus limiting our analysis to 258 study participants (Table 1). Participant data were retrieved from a secure database housed at the Gromo Sinus Institute (Buffalo, New York, USA).

Subjective Questionnaires

Symptom questionnaires demonstrated prevalence of greater than 50% for 15 of 16 complaints, as illustrated in Figure 2. The most common symptoms reported are congestion (100%), being tired (96.5%), headache (95.8%), postnasal drip (94.9%), facial pressure (92.2%), and runny nose (90.7%). These symptoms were all reported as predominantly moderate-severe.

Computed Tomography and Nasal Endoscopy

Opacified MT percentages from CT imaging indicated that nearly one-half of CRS study participants experienced greater than 50% occlusion of the nasal cavity and paranasal sinuses. The NE scores also demonstrated moderate mucosal inflammation with an average unilateral NE score of 2 and bilateral (total) NE score of 4 (Table 2).

Based on mean CT opacification, analysis of the presence of each symptom with the corresponding CT opacification score failed to demonstrate reliable positive predictive value (PPV). "Inability to smell" or anosmia yielded the largest PPV of only 48.37% (95% CI,

42.26%-54.48%), with all remaining symptoms reflecting poorer results when correlated with CT imaging ($P > .05$). Further subgroup analysis of none to mild (0-2) versus moderate to severe (3-5) symptom scores also had poor PPV of 50.6% (95% CI, 44.50%-56.72%). Analysis by logistic regression curves, however, indicated an increased likelihood of CT opacification above the mean for CRS patients presenting with moderate to severe anosmia ($P < .019$; OR = 1.86; 95% CI, 1.10-3.15).

Nasal endoscopy scores consistently paralleled CT imaging assessment of opacification at the maxillary sinus ostium (Figure 3). Logistic regression modeling was used to evaluate the association between symptom severity scores and corresponding unilateral and total NE scores. Our results demonstrated advanced inflammatory changes found on NE were associated with an increased likelihood of reported congestion ($P < .028$; OR = 2.33; 95% CI, 1.08-5.02), runny nose ($P < .002$; OR = 2.23; 95% CI, 1.34-), and ear pain ($P < .007$; OR = 2.08; 95% CI, 1.21-3.56) (Figure 4).

Nasal Mucus Biomarker Quantification

Laboratory quantification of nasal mucus markers yielded wide-ranging values with significant deviation from statistical means (Table 3). Logistic regression analysis to evaluate the association between stratified biomarker data and study participant symptoms demonstrated that higher nasal mucus EDN was associated with a statistically significant increased likelihood of reporting bothersome congestion ($P < .031$; OR = 4.09; 95% CI, 1.21-13.79) and runny nose ($P < .011$; OR = 3.614; 95% CI, 1.44-9.09). Sneezing was significantly associated with moderate ALT ($P < .024$; OR = 2.86; 95% CI, 1.29-6.32) and IL-13 ($P < .027$; OR = 2.63; 95% CI, 1.17-5.91) in addition to high MBP ($P < .034$; OR = 2.71; 95% CI, 1.18-6.22) and IL-5 ($P < .019$; OR = 2.82; 95% CI, 1.19-6.70).

Discussion

Patients who suffer from CRS with or without nasal polyps present to physicians with a wide variety of symptoms. Optimally, for diagnostic purposes, having an objective measure that closely correlates with clinical severity would be advantageous in improving the management of patients based on disease severity. The 2 objective modalities assessed in this study included NE and previously validated 2D CT scan slices including the OMC. The described CT scan provides a convenient and noninvasive objective inquiry, but unsurprisingly, our study reveals that nasal endoscopy results more closely parallel cardinal patient symptoms. Additionally, our results show the most frequently reported symptoms at this time and in previous reports were found to be associated with an increased likelihood in testing positive for nasal mucus biomarkers of eosinophilic inflammation.¹⁴

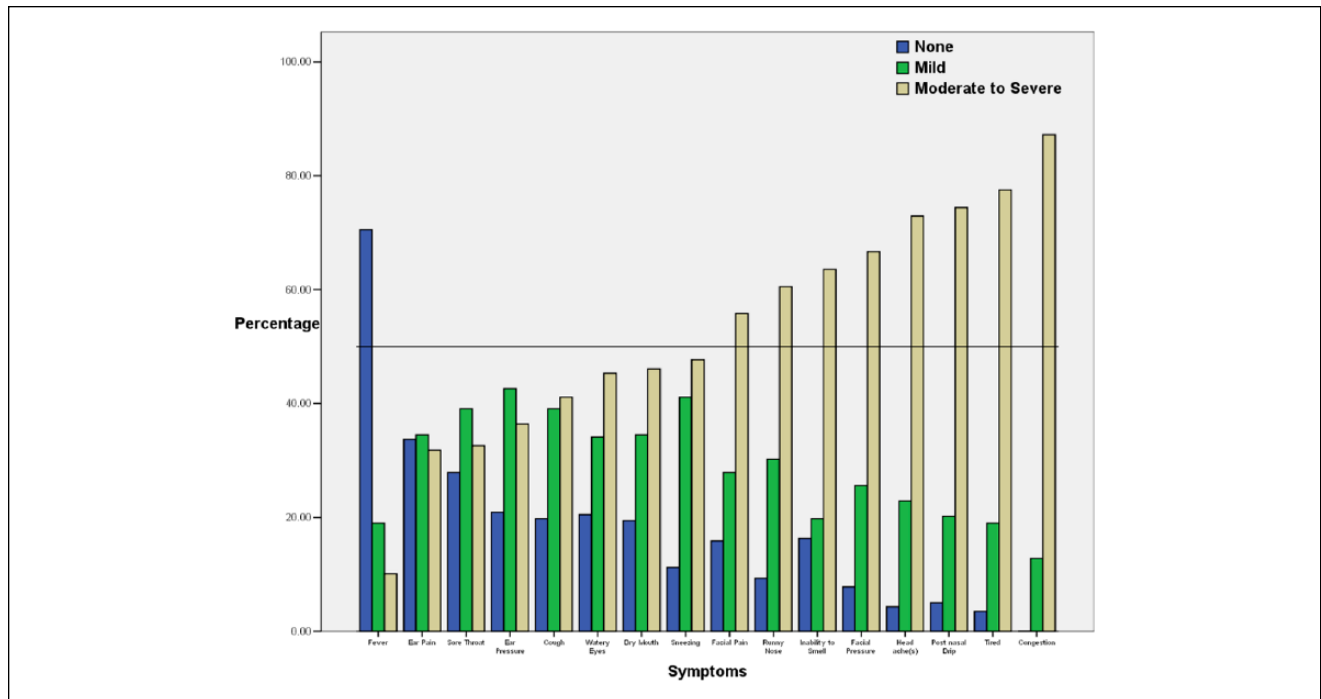


Figure 2. Percentage of patients responding regarding disease severity for 16 complaints via survey. Eight symptoms were significant in that greater than 50% of those surveyed rated symptoms as moderate to severe. Conversely, fever stood out for being the only symptom with over 50% of patients reporting no severity.

Table 2. Computed Tomography (CT) Occlusion Area Percentage and Total Nasal Endoscopy (NE) Scores.

	Mean	SD	Median	Mode	Range
CT occlusion (%), n = 258	49.3	20.1	46.6	31.4	13.1-94.5
Total NE score, n = 256	4	1	4	2	1-6

The pivotal role of CT imaging of the paranasal sinuses was recognized during the 1970s; further advancement in imaging modalities and the introduction of endoscopic sinus surgery has led to a compelling role for CT in the preoperative assessment of patients with CRS.^{16,17} Advancements in CT during the past 4 decades have continued to improve the multidimensional imaging of the anatomy of the paranasal sinuses, including 3D CT images. Our study utilized a specific 2D anatomical slice obtained via CT, which has shown significantly greater correlation with 3D volumetric evaluation as well as significantly greater sensitivity to change compared to the Lund-Mackay system.^{4,18}

These CT images demonstrated a PPV with only 1 symptom, anosmia, assessed via questionnaire. As anosmia was associated with mucosal thickening, it would be pertinent in the future to investigate whether this symptom may be predictive of mucosal thickening. This appears to indicate a limitation in the use of CT image results to accurately reflect the subjective nature of the severity of CRS.

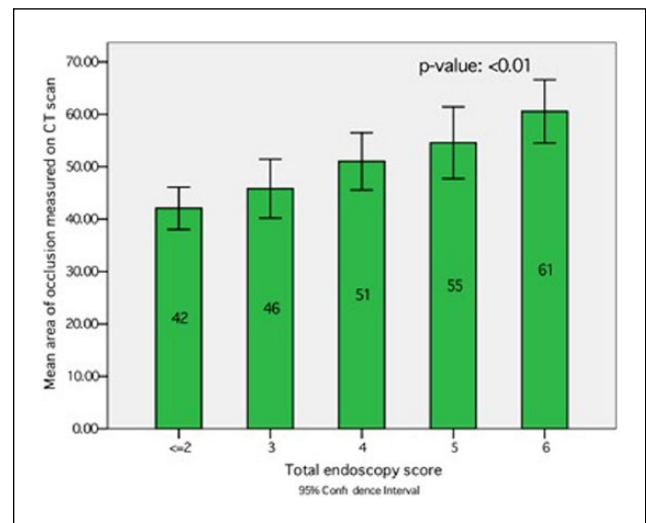


Figure 3. Correlation between mean area of occlusion measured on computed tomography (CT) scans and total endoscopy score based on the Rasp classification system. The results indicate a positive correlation: When the mean areas of mucosal thickening increase, the total endoscopy scores for the same patients increase as well.

Our patient survey results indicate that the local complaints of “congestion” and “runny nose” are the most common complaints found in patients with CRS (Figure 2). This is

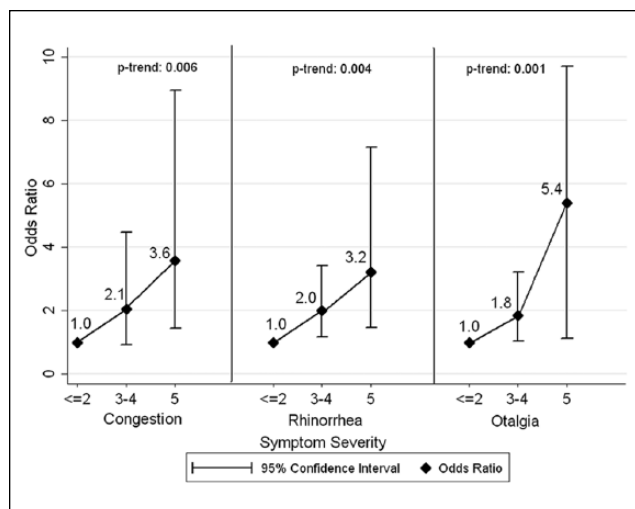


Figure 4. Laboratory quantification of nasal mucus markers yielded wide-ranging values with significant deviation from statistical means (Table 3). Logistic regression analysis to evaluate the association between stratified biomarker data and study participant symptoms demonstrated that higher nasal mucus eosinophil-derived neurotoxin (EDN) was associated with a statistically significant increased likelihood of reporting bothersome congestion ($P < .031$; OR = 4.09; 95% CI, 1.21-13.79) and runny nose ($P < .011$; OR = 3.614; 95% CI, 1.44-9.09). Sneezing was significantly associated with moderate *Alternaria* antigen (ALT) ($P < .024$; OR = 2.86; 95% CI, 1.29-6.32) and interleukin-13 (IL-13) ($P < .027$; OR = 2.63; 95% CI, 1.17-5.91) in addition to high major basic protein (MBP) ($P < .034$; OR = 2.71; 95% CI, 1.18-6.22) and IL-5 ($P < .019$; OR = 2.82; 95% CI, 1.19-6.70).

similar to previous surveys that have also identified “congestion” and “nasal discharge” as being the most frequent complaints of patients with CRS with nasal polyps.^{14,15} In particular, Thompson et al¹⁵ reported an association between ECF (eosinophilic chemotactic factor) and the symptoms of nasal congestion, anosmia, and sneezing. These are similar to our results and indicate a continued trend that eosinophilic markers are associated with the cardinal symptoms of CRS.

The symptoms of congestion and nasal discharge are descriptive issues associated with overall airflow obstruction and consistent drainage of the nasal passages specifically. This is despite the positive correlation observed between thickening of the nasal mucosa on CT scans and the NE score in similar patients (Figure 3). It remains possible that in CRS it is not how much inflammation is present but where that inflammation is localized that matters more in regards to quality of life. The NE score provides a good assessment of disease severity within the nasal passage where the majority of reported symptoms originate from.

This result is retrospectively unsurprising as the NE classification system assesses nasal inflammation on a continuum with a higher number indicating a higher

degree of involvement of the nasal cavity. Congestion caused in part by nasal polyp obstruction would be an expected finding within severely affected patients. This provides reasoning for the greater symptom specificity for NE over CT imaging in regards to objective measurement of inflammation in CRS. Further, nasal endoscopy allows the examiner the ability to visualize nasal mucosa, assess stage and extent of inflammatory mucosal thickening, and obtain nasal mucus for evaluation of cellular and various biomarker content. However, given our result and the positive features associated with NE, the limited view of NE does not provide detailed information about the extent of disease within the paranasal sinuses as afforded by CT imaging. This potentially allows CT imaging to remain the primary assessment modality of the state of the paranasal sinuses in the management and preoperative evaluation of a CRS patient refractory to medical therapy.

The discovery that eosinophils degranulate and release MBP into the mucus as opposed to the tissue revealed the importance of the nasal mucus in establishment and progression of the disease process. These studies identified toxic MBP deposition in the nasal mucus as a potential catalyst of nasal mucosa damage, and further work validated that MBP as a biomarker within the nasal mucus be streamlined as a diagnostic tool for CRS.^{5,19}

Our study demonstrated correlation of several eosinophilic inflammatory biomarkers with the most common symptoms of CRS. Specifically, EDN, MBP, IL-5, IL-13, and ALT antigen were all found to be statistically significant with at least 1 reported symptom (Figure 4). The ALT antigen in particular has been shown previously to be involved in migration, activation, and degranulation of eosinophils.⁷⁻⁹ Conceptually, this ALT-driven cascade could be self-perpetuating as EDN has been shown to be a stimulator of the Th-2 immune cascade resulting in the production of cytokines including IL-5 and IL-13. IL-5 is a potent stimulator of eosinophils, and its production may serve to increase the eosinophils within the nasal mucus.^{20,21}

In fact, CRS with nasal polyps has recently been shown to be associated with Th-2 type inflammatory mediators including IL-5 and IL-13.²² All these events could be behind the overall deposition of MBP, which has been shown to be detrimental to the nasal mucosal lining.²³ The association of EDN with bothersome congestion and runny nose is understandable as the damage induced by end products of eosinophil degranulation to the nasal mucosae would lead to a reduction in mucociliary clearance. In addition, the association of IL-5, IL-13, MBP, and ALT to sneezing might lead to the speculation that the presence of eosinophils and their degranulation products in the nasal cavity may be related to the symptom of sneezing.

The association of these markers with the cardinal subjective symptoms gives credence to the further assessment and incorporation of these biomarkers into a diagnostic and

Table 3. Nasal Mucus Biomarkers.

	N	Mean	SD	Median	Mode	Range
ALT antigen (ng/ml)	172	65.8	259.8	10.0	5	5-2292
ASP antigen (ng/ml)	172	303.0	2325.1	59.5	20	20-30389
MBP (ng/ml)	172	1365.4	4694.8	159.5	20	20-52210
EDN (ng/ml)	171	19781.3	92939.1	2203.5	96	96-1146505
IL-5 (pg/ml)	169	3144.4	7747.6	204.0	60	47-46471
IL-13 (pg/ml)	171	319.1	602.6	165.5	60	59-4124

Abbreviations: ASP, Aspergillus; ALT, Alternaria; EDN, eosinophilic-derived neurotoxin; IL, interleukin; MBP, major basic protein.

targeted therapeutic approach of severe and refractory CRS.

Conclusion

While both NE and CT imaging are valid objective tools in the evaluation of CRS patients, NE has a stronger correlation with the 2 cardinal symptoms of congestion and anterior rhinorrhea in CRS patients. The association of eosinophilic and fungal (ALT) biomarkers responsible for the recruitment and activation (IL-5, IL-13) of eosinophils, as well as the products of eosinophil degranulation, namely, EDN and MBP, suggest a potential for each to be clinically useful as a panel for CRS diagnosis.

Authors' Note

This study was awarded the third-place poster prize by the American Academy of Otolaryngology—Head and Neck Surgery at the Annual Meeting in October 2009 (San Diego, California, USA).

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The Mayo Foundation for Medical Education and Research owns intellectual property rights, including United States Patent No. 6416955, which lists J.U.P., D.A.S., and H.K. as inventors who are receiving royalty payments from licensing agreements between the Mayo Foundation and Immco Diagnostics Inc.

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