Original Article

Symptom-Based Clustering in Chronic Rhinosinusitis Relates to History of Aspirin Sensitivity and Postsurgical Outcomes

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What is already known about this topic? Patients with chronic rhinosinusitis (CRS) with aspirin sensitivity have a higher disease burden and poorer postsurgical outcomes. Without a clear history of aspirin reaction, there are no good clinical tools to predict a history of aspirin sensitivity.

What does this article add to our knowledge? Patients with CRS exhibit a heterogeneous symptom burden with varying emphasis on individual 22-item SinoNasal Outcome Test symptoms. This heterogeneity was associated with history of aspirin sensitivity and was related to treatment outcomes.

How does this study impact current management guidelines? The study result facilitates the recognition of symptom heterogeneity in CRS, which should aid in the workup of CRS and in the prediction of aspirin sensitivity and which relates to response to treatment such as surgery.

BACKGROUND: Symptoms burden in chronic rhinosinusitis (CRS) may be assessed by interviews or by means of validated tools such as the 22-item SinoNasal Outcome Test (SNOT-22). However, when only the total SNOT-22 scores are used, the pattern of symptom distribution and heterogeneity in patient symptoms is lost.

OBJECTIVES: To use a standardized symptom assessment tool (SNOT-22) on preoperative symptoms to understand symptom heterogeneity in CRS and to aid in characterization of distinguishing clinical features between subgroups.

METHODS: This was a retrospective review of 97 surgical patients with CRS. Symptom-based clusters were derived on the basis of presurgical SNOT-22 scores using unsupervised analysis and network graphs. Comparison between clusters was performed for clinical and demographic parameters, postsurgical symptom scores, and presence or absence of a history of aspirin sensitivity.

RESULTS: Unsupervised analysis reveals coclustering of specific symptoms in the SNOT-22 tool. Using symptom-based clustering, patients with CRS were stratified into severe overall (mean total score, 90.8), severe sinonasal (score, 62), moderate sinonasal (score, 40), moderate nonsinonasal (score, 37) and mild sinonasal (score, 16) clusters. The last 2 clusters were associated with lack of history of aspirin sensitivity. The first cluster had a rapid relapse in symptoms postoperatively, and the last cluster demonstrated minimal symptomatic improvement after surgery.

CONCLUSION: Symptom-based clusters in CRS reveal a distinct grouping of symptom burden that may relate to aspirin sensitivity and treatment outcomes. © **2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:934-40)**

Key words: *Chronic rhinosinusitis; Aspirin sensitivity; CRS symptoms; SNOT-22; Aspirin exacerbated respiratory disease*

Chronic rhinosinusitis (CRS) is defined as 12 weeks or longer of 2 or more symptoms of mucopurulent drainage, nasal obstruction, facial congestion or pressure, or decreased sense of smell and objective documentation of inflammation by mucopurulent drainage, presence of polyps in nasal cavity, and/or radiographic imaging showing inflammation of paranasal sinuses.[1] Because the criteria for defining CRS emphasizes

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Conflicts of interest: R. Divekar is employed by Mayo Clinic and has received revenue from Google.com for an unrelated Web blog. J. Hagan has received research support from the National Institute of Allergy and Infectious Diseases, National Heart, Lung, and Blood Institute, GlaxoSmithKline, and AstraZeneca. H. Kita has received research support from the NIAID and the NHLBI and receives royalties from IMMUCO. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used
AT- aspirin tolerant
CRS- chronic rhinosinusitis
CT- Computerized tomography
H-AS- history of aspirin sensitivity
IQR- interquartile range
LM- Lund-Mackay
SNOT-22- 22-item SinoNasal Outcome Test

symptoms, measuring and comparing individual or groups of symptoms in CRS is important in assessing disease severity and treatment outcomes. Addition of 2 questions, impairment of taste/smell and blockage or congestion of the nose, to the well-validated CRS 20-item SinoNasal Outcome Test questionnaire[2] has provided an additional measure of sinonasal disease burden and has also been validated (22-item SinoNasal Outcome Test [SNOT-22]).[3] Previous studies have used overall SNOT-22 scores,[4,5] individual scores,[6] or *predefined* combinations of symptoms[7,8] and have documented differences in *a priori*—defined CRS subtypes (including aspirin sensitivity) in regard to symptom burden.[3] Cluster analysis of symptoms to define such subgroups has recently been attempted,[9,10] but pretherapy and posttherapy differences using unsupervised methods have not been extensively studied. In this article, we obtained preoperative SNOT-22 scores of patients who underwent endoscopic sinus surgery for CRS, used *unsupervised learning* to model symptom-based patient clusters, and studied differences between these clusters for select clinical parameters, including history of aspirin intolerance and surgical outcomes.

METHODS

Study design

This was a retrospective study of adults with physician-confirmed CRS seen in the Department of Otorhinolaryngology and the Division of Allergic Diseases at Mayo Clinic, Rochester, Minnesota, from 2012 to 2014. The study was approved by the institutional review board, and clinical data from patients' medical record were used in the study.

Study population and data collection

This was a retrospective review of patients who met criteria for CRS based on symptoms and objective findings for more than 12 weeks.[1] All patients underwent endoscopic sinus surgery in the Department of Otorhinolaryngology. Ninety-seven consecutive patients who had consented previously to participation in research at the Mayo Clinic were included. Exclusion criteria included the presence of secondary causes of recurrent or chronic sinusitis including cystic fibrosis, primary ciliary dyskinesia, or primary immune deficiency. The study was approved by the institutional review board. The median interval for presurgical score was 26 days (interquartile range [IQR], 7-41).

Follow-up SNOT-22 scores were obtained at an initial postoperative period (median day 21 IQR, 14-36) and at a subsequent second visit (median day 97 IQR, 58-198) after surgery. Additional clinical data were gathered (listed in Table I). Upon further review, 14 of 22 patients who reported a history of aspirin sensitivity underwent a challenge/desensitization postsurgery in the Division of Allergic Diseases.

Clinical and laboratory testing

Vitamin D_3 and serum IgE assessment was done at Mayo Medical Laboratory. Eosinophil count before surgery and the highest eosinophil count in the medical record were recorded. The allergy status of the participants was determined using a standard panel by skin prick testing congruent with their geographic location.

Network graphs and clustering

SNOT-22 scores for each question item were converted into a format suitable for use with Gephi 0.8.2 (www.Gephi.org), an open-source, interactive visualization and exploration tool.[11] Weighted degree centrality, which is the cumulative measure of quantity and weight of connections made with a node, was calculated and represented by a node size set between 12 and 60. Force-directed algorithm (such as Force-Atlas),[12] was applied to the resultant network to reveal patterns of association. Hierarchical agglomerative clustering was applied to standardized data to reveal cluster membership and boundaries.

Statistical analysis

The χ^2 test was used to assess for significance in categorical data. Means and ANOVA were used for assessing significance in continuous data, with significant difference between all pairs calculated using the Tukey HSD test or the Wilcoxon rank sum test. A P value of less than .05 was considered statistically significant. Analysis was performed using JMP software (v10, SAS institute Inc, Cary, NC) and Microsoft Office (2010 Microsoft corporation, Redmond, Wash).

RESULTS

Characteristics of the subjects in the study

Table I presents basic characteristics of subjects included in the study. Thirty-three percent of the subjects were women (n = 32 of 97), and the mean age of the subjects was 51 years. Among the subjects, approximately 23% (n = 22) reported an "allergic reaction" with aspirin and approximately 61% (n = 59 of 97) carried a diagnosis of physician-diagnosed asthma. For the purpose of the study, the patients who had a history of reactions to aspirin were designated as "history of aspirin sensitivity" (H-AS) whereas those who did not were designated as "aspirin tolerant" (AT). Among those with H-AS, 45% were women, whereas among those who did not endorse such history, 29% were women (P = .19). The mean age of patients in the 2 groups was different, with those with H-AS being younger (mean, 45.7 years) than those in the AT group (mean, 52.5 years; P = .04).

Select laboratory parameters and clinical variables between these 2 groups of patients (Table I) are also shown as part of baseline comparison. Presurgical peripheral eosinophil count was similar between the H-AS group (mean, 463 cells/mm^3) and the AT group (437 cells/mm^3; P = .74). The highest recorded eosinophil count was greater in the H-AS group (mean, 916 cells/mm^3) compared with the AT group (mean, 574 cells/mm^3; P = .002). The mean level of vitamin D in patients with H-AS was 25.7 ng/mL compared with 33.9 ng/mL in the AT group (P = .11). There were no significant differences between total serum IgE levels or atopic status between the 2 groups. All patients in the H-AS group had nasal polyps (100%; n = 22) compared with 80% in the AT group (P = .01). The mean Lund-Mackay (LM) computerized tomography (CT) score for sinus disease was 15.7 ± 0.9 in the H-AS group compared with 13.7 ± 0.5 in