Original Article

Clinical Characteristics of Patients with Chronic Rhinosinusitis with Nasal Polyps, Asthma, and Aspirin-Exacerbated Respiratory Disease

Whitney W. Stevens, MD, PhD[a], Anju T. Peters, MD[a], Annemarie G. Hirsch, PhD, MPH[b], Cara M. Nordberg, MPH[b], Brian S. Schwartz, MD, MS[c,d], Dione G. Mercer, BS[b], Mahboobeh Mahdavinia, MD, PhD[a], Leslie C. Grammer, MD[a], Kathryn E. Hulse, PhD[a], Robert C. Kern, MD[e], Pedro Avila, MD[a], and Robert P. Schleimer, PhD[a,e] *Chicago, Ill; Danville, Pa; and Baltimore, Md*

What is already known about this topic? Aspirin-exacerbated respiratory disease (AERD) is characterized by the clinical triad of asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and an intolerance of medications that inhibit the cyclooxygenase 1 enzyme.

What does this article add to our knowledge? Before this study, the prevalence of AERD among patients with CRSwNP was not well defined. This study created one of the largest cohorts of patients with CRSwNP to date and more extensively characterized the clinical features of patients with AERD compared with patients with CRSwNP.

How does this study impact current management guidelines? Understanding the clinical characteristics of AERD will assist physicians in the appropriate medical management of this subgroup of patients with severe upper and lower airway disease.

BACKGROUND: Aspirin-exacerbated respiratory disease (AERD) comprises the triad of chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, and intolerance to inhibitors of the cyclooxygenase-1 (COX-1) enzyme. The prevalence of AERD remains unclear, and few studies have compared the clinical characteristics of patients with AERD to those with CRSwNP alone, asthma alone, or both CRSwNP and asthma.

OBJECTIVE: To determine the prevalence of AERD within a tertiary care setting, and to identify unique clinical features that could distinguish these patients from those with both CRSwNP and asthma or with CRSwNP alone.

METHODS: Electronic medical records of patients at Northwestern in Chicago, Illinois, were searched by computer algorithm and then manual chart review to identify 459 patients with CRSwNP alone, 412 with both CRSwNP and asthma, 171 with AERD, and 300 with asthma only. Demographic and clinical features including sex, atopy, and sinus disease severity were characterized.

[a]Division of Allergy-Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Ill

[b]Center for Health Research, Geisinger Health System, Danville, Pa

[c]Departments of Environmental Health Sciences and Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Md

[d]Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Md

[e]Department of Otolaryngology, Northwestern University Feinberg School of Medicine, Chicago, Ill

This work was supported by the Parker B. Francis Fellowship Program, the American Partnership for Eosinophilic Disorders/American Academy of Allergy, Asthma and Immunology HOPE Pilot Grant Award, the National Institutes of Health (grant nos. U19 AI106683-01 [Chronic Rhinosinusitis Integrative Studies Program], T32 AI083216, K12 HD055884, R37 HLO68546, RO1 HL0788860, and R01 AI104733), and the Ernest Bazley Foundation.

Conflicts of interest: W.W. Stevens has received research support from Parker B. Francis Fellowship Program, American Partnership for Eosinophilic Disorders/American Academy of Allergy, Asthma and Immunology HOPE Pilot Grant Award. A.T. Peters has received lecture fees from Greer and received research support from AstraZeneca and Sanofi. A.G. Hirsch has received research support from the National Institutes of Health. C.M. Nordberg has received research support from the National Institutes of Health (grant funding from the National Institute of Allergy and Infectious Diseases [grant no. U19 AI106683] for work on chronic rhinosinusitis epidemiology). B.S. Schwartz, D. Mercer, K.E. Hulse, and P. Avila have received research support from the National Institutes of Health. L.C. Grammer has received research and travel support from the National Institutes of Health; has received the Bazley Foundation grant; has received consultancy fees from Astellas Pharmaceuticals; is employed by Northwestern University and Northwestern Medical Faculty Foundation; has received research support from the Food Allergy Network; has received lecture fees from the American Academy of Allergy, Asthma & Immunology and Mount Sinai New York; and receives royalties from Lippincott, UpToDate, BMJ, Elsevier, and Kluwers Wolter. R.P. Schleimer has received research support from the National Institutes of Health; has received consultancy fees from Intersect ENT, GlaxoSmithKline, Allakos, Aurasense, Merck, BioMarck, Sanofi, AstraZeneca/Medimmune, Genentech, Exicure, Inc, and Otsuka, Inc; and has stock/stock options in Allakos, Aurasense, BioMarck, and Exicure, Inc. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 8, 2016; revised November 28, 2016; accepted for publication December 20, 2016.

Available online ■■

Corresponding author: Whitney W. Stevens, MD, PhD, Division of Allergy-Immunology, 211 E Ontario St, Ste 1000, Chicago, IL 60611. E-mail: whitney-stevens@northwestern.edu.

2213-2198

http://dx.doi.org/10.1016/j.jaip.2016.12.027

Abbreviations used

AERD- aspirin-exacerbated respiratory disease
COX-1- cyclooxygenase 1
CRS- chronic rhinosinusitis
CRSwNP- chronic rhinosinusitis with nasal polyps
CRSwNP + Asthma- chronic rhinosinusitis with nasal polyps and asthma
CT- computed tomography
EDW- Enterprise Database Warehouse
OR- odds ratio
PNIF- peak nasal inspiratory flow

RESULTS: The prevalence of AERD among patients with CRSwNP was 16%. Patients with AERD had undergone 2-fold more sinus surgeries ($P < .001$) and were significantly younger at the time of their first surgery (40 ± 13 years) than were patients with CRSwNP (43 ± 14 years; $P < .05$). Atopy was significantly more prevalent in patients with AERD (84%) or asthma (85%) than in patients with CRSwNP (66%, $P < .05$). More patients with AERD (13%) had corticosteroid-dependent disease than patients with both CRSwNP and asthma (4%, $P < .01$) or asthma (1%, $P < .001$).

CONCLUSIONS: AERD is common among patients with CRSwNP; even though patients with AERD have CRSwNP and asthma, the clinical course of their disease is not the same as of patients who have CRSwNP and asthma but are tolerant to COX-1 inhibitors. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *AERD; CRS; CRSwNP; Asthma; Samter's disease; Sinus*

Chronic rhinosinusitis (CRS) is characterized by chronic inflammation of the sinonasal mucosa and is estimated to affect 31 million Americans.[1,2] This disease is associated with a significant financial burden on the US health care system, with direct and indirect costs approximating $22 billion annually.[3] Only a fraction of patients with CRS develop nasal polyps, benign inflammatory outgrowths of the epithelial lining of the sinonasal mucosa.[4] However, patients with chronic rhinosinusitis with nasal polyps (CRSwNP) on average have greater severity of clinical disease and impairment of quality of life when compared with patients with CRS without nasal polyps.[5-9]

It is estimated that 48% of patients with CRSwNP have comorbid asthma, which is thought to impact disease severity.[1,10] In one study of 106 patients with CRS undergoing sinus surgery, those with asthma had significantly worse sinonasal inflammation and nasal polyps than did those without asthma.[11] In addition, in a cohort of patients with asthma, those with severe lung disease were more likely than patients with mild disease to undergo sinus surgery for nasal polyps.[12] Given these associations, further studies are needed to more directly address how asthma may impact CRSwNP and vice versa.

A subset of patients with CRSwNP and asthma is also intolerant of medications that inhibit the cyclooxygenase-1 (COX-1) enzyme. Over the years, patients with this clinical triad have been defined as having Samter's disease, Samter's triad, Widal's triad, aspirin-exacerbated respiratory disease (AERD), or nonsteroidal anti-inflammatory drug—exacerbated respiratory disease.[13-15] In the present study, we use the term AERD to refer to those patients with CRSwNP and asthma who specifically develop upper and/or lower respiratory tract reactions to COX-1 inhibitors. Importantly, the true prevalence of AERD among patients with CRSwNP is not well defined, although AERD is thought to place an even higher clinical and financial burden on affected individuals.[16]

Numerous groups have advanced the understanding of the underlying mechanisms contributing to the pathogenesis of CRSwNP and AERD. In particular, AERD is uniquely characterized by a dysregulation in arachidonic acid metabolism, reflecting diminished levels of the anti-inflammatory prostanoid prostaglandin E2 and increased levels of 5-lipoxygenase products leukotriene C4, leukotriene D4, and leukotriene E4.[17-19] Low expression levels of the prostaglandin E2 receptor, EP2, as well as aberrant downstream receptor signaling and induction of the IL-1 receptor, is also thought to be important.[20-23] Aspirin challenges further reduce protective prostaglandin E2 and dramatically elevate leukotrienes from mast cells, eosinophils, and other cells as well as prostaglandin D2 derived from mast cells.[24-26] Clinically, the development of a respiratory reaction to COX-1 inhibitors remains the major feature differentiating patients with AERD from those with CRSwNP. However, patients with AERD typically avoid taking aspirin and nonsteroidal anti-inflammatory drugs of their own accord. This leads to the question of whether, in the absence of COX-1 inhibitor use, there are other clinical or demographic differences between patients with AERD and patients with CRSwNP alone. Because all patients with AERD have asthma but not all patients with CRSwNP do, this study controlled for the presence of asthma by including a separate cohort of patients who had both CRSwNP and asthma (CRSwNP + Asthma).

By searching an electronic medical database of patients within our tertiary care facility, we assembled one of the largest cohorts of patients with CRSwNP available to date, encompassing 1059 unique patients. Within this cohort we identified patients with AERD and estimated the prevalence of this disease among patients with CRSwNP. Finally, we investigated various clinical characteristics to determine whether and how patients with AERD, in the absence of COX-1 inhibitor treatment, differ from patients with CRSwNP with or without comorbid asthma. Knowledge about how these conditions differ could provide important insights into the etiology or pathophysiology of these conditions, which could help inform prevention and treatment strategies.

METHODS

Identification of subjects

We identified patients with CRSwNP, asthma, and AERD using a mix of automated and manual chart reviews as described below. Additional details on our methods are described in this article's Online Repository at www.jaci-inpractice.org. The Northwestern University Internal Review Board approved this study.

To identify subjects with CRSwNP, we first conducted an automated search of the Northwestern University Enterprise Database Warehouse (EDW) to identify patients with acute or chronic sinusitis. Then, we manually reviewed the medical records of all patients identified with an *International Classification of Diseases,*