

Sinusitis and asthma: Entering the realm of evidence-based medicine

The sinuses are among the most poorly comprehended organs of the body, and this confusion has extended to our understanding of the causes and treatment of their disorders. A failure to properly diagnose sinusitis, confounded by a poor comprehension of the pathophysiologic character of sinus disorders, has led to the inadequacies of current therapeutic interventions for our patients. One of the more important outcomes of the study by ten Brinke et al,¹ which appears in this issue of *The JACI*, is to further establish the impossibility of either diagnosing the presence or quantifying the severity of sinusitis through use of clinical criteria. Historically, the diagnosis of sinusitis has been based on the presence of such symptoms as purulent nasal discharge, posterior pharyngeal drainage, periorbital edema, headache, facial pain, toothache, earache, sore throat, halitosis, cough, and worsening asthma.² However, none of these clinical criteria is specific for sinusitis; rather, they are more reflective of the presence of nasal disease, bronchial diseases including asthma, dental and ocular diseases, and the full spectrum of causes of frontal headaches. The predictive value of these parameters in the diagnosis of sinusitis has never been established, and as shown in the current study, these criteria might be little better than random in predicting presence or severity of this disorder. This has led to the paradox of subjects presenting with what were considered to be "classic" symptoms of sinusitis who were then labeled as having sinusitis and involved in various medical and surgical interventions but in whom objective evidence for actual sinus disease might have been completely absent! This absence of proper criteria by which to correctly diagnose, quantify, and objectively follow up interventions has polluted much of the sinusitis literature and raises doubts about the conclusions drawn by investigators who used clinical criteria either to make the diagnosis of sinusitis or to assess efficacy of an intervention. Insofar as standard radiography of the sinuses is similarly not useful in the diagnosis or quantification of sinusitis, the only valid technique for diagnosing and quantifying sinusitis is provided by the CT scan, which, as these investigators note,

Abbreviation used

CHS: Chronic hyperplastic eosinophilic sinusitis

"is a more or less obligatory diagnostic procedure."³ In contrast to clinical criteria, the current study does provide supportive evidence for rhinoscopic findings, including signs of pharyngeal drainage, nasal secretions, nasal polyps, and a deformed middle meatus, in the diagnosis of sinusitis. However, the data provided suggest that rhinoscopy is neither sufficiently sensitive nor sufficiently specific to be useful in screening patients or performing appropriate outcome studies.

A link between sinusitis and asthma has been suspected since perhaps even the time of Galen.⁴ When adults with asthma are evaluated by means of CT scanning, approximately 74% to 90% have some degree of mucosal hyperplasia,⁵⁻⁷ which is often asymptomatic. The current work by ten Brinke et al¹ confirms this association; more importantly, however, it takes advantage of a validated scoring system using the CT scan to correlate severity of sinusitis with parameters of asthma severity and inflammation.⁵ Whereas a subject with chronic disease of the sinuses might have an immune inflammatory disorder, an infectious disease, or even allergic fungal sinusitis, the sinusitis typically associated with asthma has been termed *chronic hyperplastic eosinophilic sinusitis* (CHS). CHS, which is often present in association with nasal polyposis, is a proliferative disorder characterized by the accumulation of eosinophils, fibroblasts, mast cells, and goblet cells.⁸ However, it is the accumulation of activated eosinophils that is considered to be the primary hallmark of this condition.^{9,10} The sinusitis tissue demonstrates a marked increase in cells expressing mRNA for cytokines responsible for allergic inflammation. As with asthma, this disorder is associated with the activation of T_H2-like lymphocytes characterized by the production of IL-3, IL-4, IL-5, IL-13, eotaxin, and GM-CSF.^{8,11-13} Eosinophils are an additional source of these cytokines, suggesting that CHS can become a disease of unregulated accumulation of eosinophils—with eosinophils themselves providing, in an autocrine fashion, the growth factors necessary for their own recruitment, proliferation, and activation. The production of growth factors by activated eosinophils and these other cells might contribute to the proliferation of fibroblasts and deposition of connective tissue seen in CHS. Indeed, CHS should perhaps best be understood as "asthma of the upper airways."

Several hypotheses can be proposed for a linkage between sinusitis and asthma. Earlier theories, including

From the Asthma and Allergic Disease Center, University of Virginia Heath System.

Received for publication January 9, 2002; revised January 11, 2002; accepted for publication January 17, 2002.

Reprint requests: Larry Borish, MD, Asthma and Allergic Disease Center, University of Virginia Heath System, Box 801355, Charlottesville, VA 22908.

J Allergy Clin Immunol 2002;109:606-8.

Copyright © 2002 by Mosby, Inc.

0091-6749/2002 \$35.00 + 0 1/39/123024

doi:10.1067/mai.2002.123024

direct aspiration of mediators from the upper to lower airway,¹⁴ are considered unlikely, given the absence of evidence of aspiration in radionuclide studies in human beings.¹⁵ A sinobronchial neurologic reflex mediated by the cholinergic pathway is supported by some data⁴ but is unlikely to explain what is predominantly an inflammatory disease of the lower airway; for example, it would be difficult to explain on the basis of a neurologic reflex the linkage described in the current paper between sinusitis severity and increased levels of eosinophils, both in the peripheral circulation and in induced sputum, as well as the linkage between sinusitis and an increase in exhaled NO. In contrast, these observations support the concept that the influence of upper respiratory disease on asthma is mediated through the circulation.^{16,17} Patients with CHS have an intense and immunologically mediated inflammatory process of the upper airways. The generation of cytokines, T helper lymphocytes, eosinophil precursors, and inflammatory mediators in the sinuses leads to increased production of eosinophils, mast cells, and basophils in the bone marrow and ultimately to the selective recruitment of these cells and mediators into the lungs, where they exacerbate the airways inflammation characteristic of asthma. The absence of relevant adhesion molecules or other "homing" molecules in the healthy lung would explain the ability of sinusitis to develop in the absence of asthma. In contrast, the presence of asthma in the absence of any radiographic evidence for sinusitis is more difficult to explain. In the current study, only 23.6% of the subjects had no evidence of sinus disease. Interestingly, despite having what is described as "severe bronchial asthma," many of the subjects in this study also demonstrated an absence of circulating or sputum eosinophils and vanishingly low exhaled NO concentrations. Although this might reflect influences of corticosteroids, the study of Newman et al¹⁸ suggests that corticosteroids do not completely eliminate eosinophilia from asthmatic subjects and suggests that many of these subjects without sinus disease might in fact be suffering from vocal cord dysfunction. The role for sinus radiography in the evaluation of vocal cord dysfunction is an important area for further research.

It should also be appreciated that it is plausible that there is no causal influence of sinusitis on the presence or severity of asthma. The concept that sinusitis exacerbates asthma is based on often uncontrolled studies involving clinical diagnostic criteria or standard radiography that frequently failed to either quantify severity of sinusitis or document improvement in the sinus disease after intervention. Reports that treatment of sinusitis has beneficial influences on asthma are tempered by the absence of a properly controlled study, the lack of evidence that these interventions (eg, the Caldwell-Luc procedure) could even mitigate the sinus disease, and the likelihood that these studies merely report the coincidental-but-not-causally-related improvement in asthma. It is therefore reasonable to speculate that there is no exacerbating influence of sinus disease on asthma and that these represent 2 conditions of similar pathology and etiology

developing and evolving independently in the upper and lower respiratory tracts. According to this model, the inflammation in the sinuses does not exacerbate the lung disease; however, it does provide an opportunity to better understand the inflammatory processes occurring in the asthmatic lung.

This concept that chronic hyperplastic sinusitis represents "asthma of the upper airways" has several implications for the treatment of this disorder. Although acute sinusitis might frequently complicate CHS, insofar as CHS is not an infectious disease, antibiotics have little, if any, role in this condition. Similarly, although surgery might play an important role in the treatment of chronic infectious or allergic fungal sinusitis, it is unlikely to provide more than short-term relief for what is primarily a hyperplastic inflammatory disorder. Arguably, surgery is as likely to be as beneficial for CHS as it would be for asthma! Again, in the absence of controlled trials with objective quantification of the severity of sinusitis, it is difficult to judge the efficacy of any of our current therapeutic interventions.

A final novel outcome of this study was the demonstration of a linkage between sinus severity and the physiologic changes in the lung of increased functional residual capacity and diminished diffusing capacity. It is crucial that studies be performed—including, most importantly, examination of the small airways and alveoli—to determine the pathologic basis for these findings. One implication for these physiologic changes is the presence of irreversible airway remodeling with air trapping, subepithelial fibrosis, and perhaps other inflammatory and structural changes extending into the small airways and alveoli. Interestingly, these subjects represent a unique phenotype with adult onset asthma that was present for a comparatively shorter duration and was frequently characterized by the presence of aspirin intolerance. Aspirin intolerance is a disease caused in part by overexpression of the enzyme leukotriene C4 synthase and constitutive overproduction of cysteinyl leukotrienes.¹⁹ Given the influences of cysteinyl leukotrienes on myofibroblast proliferation and collagen deposition, it is intriguing to speculate that this might explain the rapid progression of the physiological changes described by these investigators.²⁰ As confirmed in the current study, aspirin intolerance is associated with particularly severe hyperplastic disease of the sinuses and nasal polyps. This mechanism would therefore similarly explain this severity of the upper respiratory disease and suggest that CHS and nasal polyposis represent a particularly aggressive "remodeling" of the upper airway. These observations invite further investigations into sinus disease as a tool for better understanding asthma.

Larry Borish, MD
Charlottesville, Va

REFERENCES

1. ten Brinke A, Grootendorst DC, Schmidt JT, de Bruïne FT, van Buchem MA, Sterk PJ, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol* 2002;109:621-6.

2. Shapiro GG, Rachelefsky GS. Introduction and definition of sinusitis. *J Allergy Clin Immunol* 1992;90:417-8.
3. Zinreich SJ. Functional anatomy and computed tomography imaging of the paranasal sinuses. *Am J Med Sci* 1998;316:2-12.
4. McFadden ER Jr. Nasal-sinus-pulmonary reflexes and bronchial asthma. *J Allergy Clin Immunol* 1986;78:1-3.
5. Newman LJ, Platts-Mills TAE, Phillips CD, Hazen KC, Gross CW. Chronic sinusitis: relationship of computed tomographic findings to allergy, asthma, and eosinophilia. *JAMA* 1994;271:363-7.
6. Pfister R, Lutolf M, Schapowal A, Glatte B, Schmitz M, Menz G. Screening for sinus disease in patients with asthma: a computed tomography-controlled comparison of A-mode ultrasonography and standard radiography. *J Allergy Clin Immunol* 1994;94:804-9.
7. Bresciani M, Paradis L, Des Roches A, Vernhet H, Vachier I, Godard P, et al. Rhinosinusitis in severe asthma. *J Allergy Clin Immunol* 2001;107:73-80.
8. Hamilos DL, Leung DYM, Wood R, Bean DK, Song YL, Schotman E, et al. Eosinophil infiltration in nonallergic chronic hyperplastic sinusitis with nasal polyposis (CHS/NP) is associated with endothelial VCAM-1 upregulation and expression of TNF- α . *Am J Respir Cell Mol Biol* 1996;15:443-50.
9. Harlin SL, Ansel DG, Lane SR, Myers J, Kephart GM, Gleich GJ. A clinical and pathologic study of chronic sinusitis: the role of the eosinophil. *J Allergy Clin Immunol* 1988;81:867-75.
10. Demoly P, Crampette L, Mondain M, Campbell AM, Lequeux N, Enander I, et al. Assessment of inflammation in noninfectious chronic maxillary sinusitis. *J Allergy Clin Immunol* 1994;94:95-108.
11. Hamilos DL, Leung DYM, Wood R, Cunningham L, Bean DK, Yasruei Z, et al. Evidence for distinct cytokine expression in allergic versus non-allergic chronic sinusitis. *J Allergy Clin Immunol* 1995;96:537-44.
12. Bachert C, Wagenmann M, Hauser U, Rudack C. IL-5 synthesis is upregulated in human nasal polyp tissue. *J Allergy Clin Immunol* 1997;99:837-42.
13. Minshall EM, Cameron L, Lavigne F, Leung DY, Hamilos D, Garcia-Zepeda EA, et al. Eotaxin mRNA and protein expression in chronic sinusitis and allergen-induced nasal responses in seasonal allergic rhinitis. *Am J Resp Cell Mol Biol* 1997;17:683-90.
14. Bardin PG, Van Heerden BB, Joubert JR. Absence of pulmonary aspiration of sinus contents in patients with asthma and sinusitis. *J Allergy Clin Immunol* 1990;86:82-8.
15. Brugman SM, Larsen GL, Henson PM, Honor J, Irvin CG. Increased lower airways responsiveness associated with sinusitis in a rabbit model. *Am Rev Respir Dis* 1993;147:314-20.
16. Denburg JA, Sehmi R, Saito H, Pil-Seob J, Inman MD, O'Byrne PM. Systemic aspects of allergic disease: bone marrow responses. *J Allergy Clin Immunol* 2000;106:S242-S246.
17. Jarjour NN, Gern JE, Kelly EAB, Swenson CA, Dick CR, Busse WW. The effect of an experimental rhinovirus 16 infection on bronchial lavage neutrophils. *J Allergy Clin Immunol* 2000;105:1169-77.
18. Newman KB, Mason UG III, Schmaling KB. Clinical features of vocal cord dysfunction. *Am J Respir Crit Care Med* 1995;152:1382-6.
19. Cowburn AS, Sladek K, Soja J, Adamek L, Nizankowska E, Szczeklik A, et al. Overexpression of leukotriene C4 synthase in bronchial biopsies from patients with aspirin-intolerant asthma. *J Clin Invest* 1998;101:834-46.
20. Panettieri RA Jr, Tan EML, Ciocca V, Luttmann MA, Leonard TB, Hay DWP. Effects of LTD4 on human airway smooth muscle cell proliferation, matrix expression, and contraction in vitro: differential sensitivity to cysteinyl leukotriene receptor antagonists. *Am J Respir Cell Mol Biol* 1998;19:453-61.

Bound volumes available to subscribers

Bound volumes of The Journal of Allergy and Clinical Immunology are available to subscribers (only) for the 2002 issues from the Publisher, at a cost of \$107.00 for domestic, and \$128.00 for international subscribers for Vol. 109 (January-June) and Vol. 110 (July-December). Shipping charges are included. Each bound volume contains a subject and author index, and all advertising is removed. The binding is durable buckram with the journal name, volume number, and year stamped in gold on the spine. *Payment must accompany all orders.* Contact Mosby, Subscription Customer Service, 6277 Sea Harbor Dr, Orlando, FL 32887; phone (800) 654-2452 or (407) 345-4000.

Subscriptions must be in force to qualify. Bound volumes are not available in place of a regular journal subscription.