

The role of allergy in sinusitis in adults

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Allergic sinus disease in adults has not been definitively established. On the other hand, sinusitis is more common in allergic individuals than control subjects. Nasal provocation studies with allergens produce clinical findings and radiographic evidence suggestive of allergic sinusitis. Studies that use single-photon emission computerized tomography do not confirm direct entry of pollens into the sinuses. Fungal sinusitis typically occurs in patients with allergic rhinitis and nasal obstruction for many years. Patients often have an elevated specific IgE and total IgE with positive skin tests to the fungus involved. The diagnosis is confirmed by computed tomographic scan or magnetic resonance imaging of the sinuses. There is no direct fungal invasion. Many patients who have chronic severe sinusitis, asthma, and frequently aspirin idiosyncrasy appear to have immunologic reactions in the sinuses (and bronchial tissue). Histologic findings of the sinus mucosa show infiltration with plasma cells and eosinophils. Immunofluorescent stains show IgE dispersed throughout the tissue possibly in plasma cells. An intense linear stain for IgD is found along the epithelial side of the basement membrane. (J ALLERGY CLIN IMMUNOL 1992;90:518-20.)

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The very existence of allergic sinusitis has been questioned by investigators. If it indeed exists, are the immunologic reactions present in the paranasal sinuses based on IgE or non-IgE mechanisms? Before the question is addressed, another question is also pertinent.

IS ALLERGY MORE COMMON IN PATIENTS WITH ACUTE OR CHRONIC SINUSITIS?

Savolinen¹ studied 224 patients who had both radiologically and aspiration-verified *acute* maxillary sinusitis determined by means of an allergy questionnaire, skin testing, and nasal smears. The criteria for allergy were met in 56 patients (25%) and considered probable in 14 patients (6.5%). The corresponding percentages in the control group were 16.5% and 3%, respectively. The difference between the sinusitis group and controls was statistically significant; the prevalence in the control group was comparable with that found in the Finnish population of similar age range.

Earlier studies had linked *chronic* maxillary sinusitis with allergic rhinitis.^{2,3} According to these studies, allergy was an underlying factor in 40% to 67% of

Abbreviation used

SPECT: Single-photon emission computerized tomography

patients with chronic sinusitis and in as many as 80% of patients with bilateral sinusitis.⁴

CLASSIC IgE MEDIATED SINUSITIS: WHAT IS THE EVIDENCE?

Allergic rhinitis is the most common allergic problem seen by physicians, with approximately one of every five individuals affected. In view of this high prevalence, one might expect that allergic sinusitis would accompany allergic rhinitis in many individuals. In practice marked allergic rhinitis does not usually occur with an accompanying abnormal sinus x-ray film. This could mean that the radiograph of the paranasal sinuses is not a very sensitive measure of an allergic reaction, or it may mean that the nose may actually protect the paranasal sinuses from contact with an allergen. Attempts to clarify the role of allergens in producing sinusitis are not easy, because the sinus is not very accessible to the usual type of challenge, such as provocative challenge done on an experimental basis. This is contrasted with the wealth of data obtained by provocative challenges in the nose or lungs.⁵ Nasal reactions are typically accompanied by swollen turbinates, clear secretions, eosinophilia,

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and release of chemical mediators. The patient may experience various symptoms such as sneezing, runny nose, itching of the nose or palate, and nasal stuffiness.

Perhaps the best studies to implicate allergic reactions in the paranasal sinuses experimentally are those of Pelikan et al.⁶ These investigators performed 73 nasal provocation challenges in 37 patients and followed them with rhinomanometry as well as maxillary sinus x-ray films before and after the challenges. There were 41 positive nasal provocation tests in 29 patients. Thirteen of the patients had immediate reactions only, 18 had late reactions only, and 10 had dual reactions. Of these, 32 patients had x-ray film changes compatible with an allergic reaction occurring in the sinuses, with increased mucosal edema or opacification. Patients also had clinical evidence of a sinus problem, that is, a feeling of increased pressure in the maxillary sinus, acute headache, and otalgia. The increased thickening of the mucosal membrane compared with baseline was defined as thickening (edema) of greater than 3 mm, usually 5 to 8 mm at 2, 6, or 12 hours after the allergen challenge. If isolated immediate nasal responses or a negative nasal response occurred, an additional radiograph was performed 24 hours after the allergen challenge and again at 48 hours in the case of a late nasal response. No significant radiographic changes in the maxillary sinuses or in nasal symptoms were recorded in 37 control challenges with saline solution. Slavin et al.^{7,8} approached the issue of allergic sinusitis in a different way. In fact this group was probably the first to suggest a cause-and-effect relationship between allergen exposure and changes in the paranasal sinuses. Their studies (published in abstract form) used SPECT to determine metabolic activity and dynamic physiology. Radioactive tracer was injected first into the paranasal sinuses, and a computer then analyzed small sections. The uptake of the isotope during the initial minutes measured the blood pool activity and focal hyperemia. The imaging after 2 hours showed relative bone metabolic activity. In the first study three patients who had strong positive ragweed skin test and allergic rhinitis were studied during the ragweed season.⁷ Nasal mucosa was markedly edematous, and sinus x-ray films were normal. SPECT showed significant hyperemia of the sinuses, with delayed imaging demonstrating marked increase in bone uptake around the sinuses. SPECT performed after the ragweed season showed normal bone uptake. Thus this first SPECT study suggested the presence of an allergic process in the sinuses during the season.

In a second study a patient who had a positive skin test and clinical sensitivity to ragweed was studied

out of the ragweed season.⁸ Ragweed pollen was insufflated into one nostril, which caused subjective and objective signs of rhinitis. Injection of technetium 99m intravenously and imaging with SPECT revealed hyperemia and increased metabolic activity in the maxillary sinus on the same side. In a nonallergic patient, pollen was seen in the region of the turbinates but not the sinuses. The implication of this study is that pollen does not directly enter the sinuses.

IgE-RELATED FUNGAL SINUSITIS

An IgE mechanism has also been implicated in certain patients with allergic fungal sinusitis. In a case study and review article of allergic fungal sinusitis published in 1983,⁹ patients who had a fungal problem had an elevated specific IgE and total IgE with positive skin tests to the fungus involved. Fungal sinusitis typically occurred in patients who had allergic rhinitis and nasal obstruction for many years. The diagnosis was often confirmed by a computed tomographic scan of the paranasal sinuses, and there typically was no evidence of invasion. There was an associated inflammatory polypoid disease of the sinuses, with mucus containing necrotic eosinophils in the form of Charcot-Leyden crystals. Infected mucus appeared dark, yellow to brown. A biopsy specimen showed eosinophilia and fungal hyphae without invasion. The treatment of choice was surgical debridement or steroids.

The term "allergic fungal sinusitis" was proposed when it was found that fungi other than *Aspergillus* were grown out of the sinuses.¹⁰ Thus in a recent study, bipolaris fungus was discovered in three patients, all of whom were young, atopic, and immunocompetent.¹¹ All patients had pansinusitis, nasal polyps, and a history of multiple surgical procedures. Two had bony erosion but no direct fungal invasion. The pathologic findings of bipolaris sinusitis were similar to those found with other fungi. There was an eosinophilic exudate, Charcot-Leyden crystals, and hyphae. Patients typically had positive immediate skin tests, positive precipitants, and increased specific IgE and IgG antibody along with an elevated total IgE.

The role of the eosinophil in mediating injury to the bronchial epithelium has been evaluated in other situations in which no apparent fungal pathogens were present. Harlin et al.¹² assessed the role of eosinophils obtained from tissues and patients with sinusitis that had undergone surgery. Patients typically had chronic asthma or allergic rhinitis. The histopathologic findings of the sinus tissue were similar to those found in bronchial tissue, which suggests that eosinophils play an important role in both. The immunofluorescent tissues show an associated extracellular deposition of

major basic protein proportionate to the amount of damage to the sinus mucosa.

SINUSITIS WITH OTHER IMMUNOLOGIC MECHANISMS

For many years, we have been interested in the histologic findings and immunofluorescence of sinusitis in patients with chronic severe sinusitis, many of whom have aspirin idiosyncrasy.¹³ We noted the similarity between bronchial tissue and sinus tissue (a comment also made by Harlin et al.). Typically, the submucosa was edematous and infiltrated with plasma cells, lymphocytes, eosinophils, and polymorphonuclear leukocytes in descending order of frequency. Immunofluorescent staining for IgG was generally patchy and of low intensity. The most striking observation was the intense staining for IgE in all tissues examined. Numerous cells in each section were apparently filled with IgE. However, it is not clear if these were cells synthesizing IgE or containing phagocytized IgE protein. In any case the cells appeared to be plasma cells. Another striking finding was the fairly intense immunofluorescent line of IgD along with the epithelial edge of the basement membrane. There was no significant evidence of IgD elsewhere. IgA and IgM occurred in a somewhat patchy manner in both an intracellular and extracellular location. The intensity varied but was generally higher than what was seen for IgG and considerably lower than that for IgE. When nasal polyps were examined, they showed similar changes to those found in sinus tissues, but it was not clear if the immunologic changes occurred after the disease process had been established by a different mechanism or if the immunologic reaction was responsible for the disease.

In summary, there is evidence that immunologic reactions can and do occur in the paranasal sinuses. Their significance and frequency have yet to be determined.

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DISCUSSION

Dr. Kaliner. We look for immunoglobulins in the mucosa. IgG is the overwhelming immunoglobulin. IgA and IgE are really found localized within cells. It turns out that IgE is localized almost exclusively within mast cells. IgD turns out to be the second most prevalent immunoglobulin that we see. Data suggest that patients who are IgA deficient compensate in part by producing IgE or IgM.

Dr. Slavin. Your comments about IgD were fascinating. Did you do these in just allergic people or what are your data referring to in terms of the IgD work?

Dr. Kaliner. There are 150 lymphocytes/ml of basement membrane. When you look and quantitate the number of IgE-positive cells, it is about six to eight per mm basement membrane and those are all mast cells. If you look at IgD-positive cells, it is also about six to eight.

Dr. Gwaltney. I agree with what Dr. Kaliner said and that is you have inflammation, swelling, obstruction, and then the bacteria that are in their noses and become trapped in the sinus and cannot escape, and then you may get infectious sinusitis. It seems to me it is also reasonable to think you have an allergic disease that causes swelling and symptoms, and you can have a pure allergic sinusitis. So I can easily visualize that you have two diseases of the sinuses: one infectious and one noninfectious, both associated with allergy.

Dr. Spector. What seems obvious is that whatever the mechanism is, pure allergy or allergy followed by infection afterward, I think it is all of our clinical impression that when you give antiallergic treatment, like nasal steroid aerosols, that people do better, and when you see the histology of it, it makes sense.