

## Increased immune reactivity to house dust mites in adults with chronic rhinosinusitis

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### Summary

Sixty-three adults with symptomatic chronic rhinosinusitis had computerized tomographic (CT) scans of the paranasal sinuses, which were used to quantify disease severity. These patients were divided into three closely age- and sex-matched groups: a CT scan-negative group (chronic rhinitis only), a mild sinusitis group and a severe sinusitis group. Serum dust mite-specific IgG levels were found to be significantly elevated in the sinusitis patients compared with a matched group of asymptomatic normal individuals. Levels were highest in the more severe sinusitis group, in which the mean titre was 559 U/ml and the incidence of titres greater than 400 U/ml was 48%, as compared with a mean titre of 139 U/ml and only a 10% incidence of titres greater than 400 U/ml in the normal subjects ( $P < 0.005$  and  $< 0.01$ ). In contrast, although the frequency of immediate hypersensitivity to dust mite, as assessed by intradermal skin tests, tended to be higher in patients with sinusitis, it was not significantly different from normal individuals. The association between mite IgG and disease was most striking in the patient sub-group with negative mite skin tests. In this group, mite IgG levels were significantly higher than normal, even in those patients with only chronic rhinitis. These findings demonstrate that increased serum levels of IgG against dust mites are strongly associated with chronic rhinosinusitis, especially in the sub-group of patients who are not allergic to mites.

*Clinical and Experimental Allergy*, Vol. 23, pp. 669–677. Submitted 20 November 1992; revised 4 February 1993; accepted 5 March 1993.

### Introduction

Rhinosinusitis is one of the most common chronic conditions in the developed world [1]. The constellation of symptoms in this condition is often similar whether disease is confined to the nose (chronic rhinitis) or if it extends to the sinuses (chronic sinusitis), and includes nasal congestion, posterior rhinorrhea (post nasal drip) and facial discomfort. Extension of disease to the sinuses often begins with inflammation and blockage of the osteomeatal unit, the region of the nasal cavity adjacent to the sinus orifices. This blockage results in decreased sinus drainage, increased mucous stasis, decreased oxygen concentration in the sinus cavities and secondary overgrowth of bacteria. The combination of inflammatory obstruction and low-grade bacterial infection leads to chronicity and explains why, once established, chronic

disease in the sinuses is difficult to eradicate without therapeutic intervention.

The aetiology of chronic rhinosinusitis is not well understood. An important role of inhaled allergens in the sub-group of rhinosinusitis patients who are allergic (skin-test positive) was suggested by the studies of Pelikan and Pelikan-Filipek [2] demonstrating that nasal inhalation of allergens can reproduce clinical and radiographic signs of maxillary sinusitis [2]. However, immediate hypersensitivity (i.e. IgE-mediated) does not appear to be involved in the majority of adults with this problem. For instance, Slavin *et al.* [3,4] reported that the incidence of reactive skin tests in adult patients with radiographic evidence of sinusitis and co-existing asthma was less than 40%.

The cause of chronic inflammation in these non-atopic, chronic rhinosinusitis patients is poorly understood. Recently, we have described an association between elevated mite allergen-specific IgG antibodies and upper

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chronic inhalation of dust mite antigens induces production of increased amounts of mite-specific IgG, and that interaction between mite-specific antibodies and dust mite antigens in the nose produce the nasal inflammation that progresses to osteomeatal unit blockade and sinusitis. The incidence of chronic sinusitis peaks between the third and fourth decades [1], which is consistent with the idea that prolonged inhalation of mite antigens is necessary to develop elevated mite IgG levels and disease.

The final pathway for inflammation would presumably be mediated through some effector cell. Eosinophils and neutrophils have receptors for IgG and cross-linking of bound IgG by antigen induces their degranulation and the release of inflammatory cellular constituents [16]. Increased numbers of eosinophils and eosinophil products are found in the sinus mucosa of non-allergic patients with sinusitis and asthma [17] and in nasal polyps [18,19]. Neutrophils are also present, especially in non-allergic patients with chronic rhinitis [20]. Thus, IgG-mediated neutrophil or eosinophil degranulation could lead to local tissue damage and set into motion a cycle of inflammation leading to chronic rhinosinusitis. Although such a hypothesis is attractive, at present it remains only speculative since there is relatively little supportive evidence for it that is directly related to rhinosinusitis. One potentially useful experiment for testing this hypothesis would be to evaluate the response of mite IgG-positive patients to nasal challenge with mite antigen but, to our knowledge, none has yet been reported.

A related but alternative possibility is that mite-specific serum IgG may simply be a marker for increased mite antigen exposure and the presence of some other form of mite immunity. For instance, allergen-specific IgA is found in the nasal mucosa after exposure to pollen allergens and might therefore also be induced by mite antigen [21,22]. Of particular interest in this regard is the fact that IgA is the most potent immunoglobulin inducer of eosinophil degranulation [23,24], making this a potentially attractive hypothesis and worthy of further exploration.

There are several other less likely explanations for the association between increased mite IgG and rhinosinusitis. One is that the increase in mite IgG is merely a marker for increased mite exposure in rhinosinusitis patients and that the disease is caused by some other, presumably non-immunological, mechanism. For this to be true, dust mite antigens would have to be irritating, which has never been shown. Alternatively, it has been suggested that the increase in mite IgG may only be secondary to nasal or sinus disease. According to this hypothesis, deposition of mite antigen on the inflamed nasal or sinus mucous membranes would induce the production of larger amounts of mite-specific IgG than would normally occur.

Finally, it has been suggested that chronic rhinosinusitis patients might be immunologically hyperresponsive, so that they produce increased amounts of IgG to many different stimuli. However, in a previous study, we demonstrated that chronic rhinosinusitis patients had normal levels of all immunoglobulin classes, which argues against this point [5]. Although there is very little evidence to support any of these latter three hypotheses, they cannot be completely disproven at the present time.

In conclusion, this study demonstrates that increased serum levels of mite-specific IgG are strongly associated with chronic rhinosinusitis, especially in non-mite-allergic patients. Determining the exact reasons for the increase in mite IgG levels will require additional experimentation. However, if mite exposure proves to be involved in the pathogenesis of chronic rhinosinusitis, its ubiquity would help to explain the prevalence of this problem, its delayed onset and its chronicity. Furthermore, it would suggest that in order to be maximally efficacious, therapy of this condition should include drugs that decrease inflammation, such as intranasal corticosteroids, in addition to the more usual regimen of antibiotics and decongestants. A recent study has confirmed the advantage of this approach [25]. Finally, if this hypothesis is correct, environmental elimination of house dust mites might prove beneficial in the prevention and treatment of chronic rhinosinusitis and recurrent nasal polyps, even in those patients who are not allergic to mites.

### Acknowledgments

We are indebted to John Tu, Joan Gorman and Judy Carlucci for their technical assistance. This work was supported in part by funding from the Saul and Lola Kramer Foundation, the National Institutes of Health grant no. AI-29871 and the Albert Einstein College of Medicine Cancer Core Grant no. P30-CA13330.

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