

ALLERGIC RHINITIS IN HIV-INFECTED PATIENTS

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Infection with the human immunodeficiency virus (HIV) has been known to render persons more susceptible to allergic, as well as infectious disorders. As the number of HIV-infected persons increases, it has been noted by many practitioners that chronic nasal symptoms, sinusitis, and otitis are quite common problems.¹⁶ It is a matter of debate which percentage of these nasal symptoms are truly allergic in nature.

The etiology of rhinitis is broadly classified into allergic or nonallergic forms, including chronic infectious rhinitis, mucociliary disturbances such as cystic fibrosis,⁹ and immune deficiency, predisposing to chronic infection.²³ Seasonal or perennial allergic rhinitis may be caused by different pollens, mold spores, animal dander, dust mite, and other allergens.

The pathophysiology of allergic rhinitis results from the development of both humoral and cellular immune reactions to airborne allergens, with symptoms of sneezing, rhinorrhea, nasal blockage, and itching, owing to IgE-dependent mast cell activation in the nasal mucosa with the release of numerous inflammatory mediators.¹² An increase in vascular permeability, glandular secretion, and secretion of cytokines results, leading to chronic inflammation.¹³ Additional mediators from an influx of inflammatory cells are chemoattractants for neutrophils, eosinophils, T lymphocytes, and basophils,¹² which have been shown to induce the release of histamine from mononuclear cells from patients with allergic rhinitis.⁵

An increase in the basal levels of α interleukin (IL)-1 in mononuclear

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cells obtained from allergic rhinitis patients have been demonstrated in the laboratory of these authors. Nasal α IL-1 levels in allergic rhinitis patients following grass and ragweed *in vivo* nasal provocation were demonstrated to diminish during the late-phase inflammatory reaction after 1 month of antihistamine treatment.⁶ We have also reported the release of soluble intercellular adhesion molecules by cytokine-activated human tracheal epithelial cells.²⁴

Activation of allergen-specific Th2 lymphocytes can induce a cascade of events with secretion of IL-4, IL-5, IL-13. An increase in nasal IL-8 levels during the late-phase inflammatory reaction after grass and ragweed nasal provocation has been reported in patients with allergic rhinitis from our center.¹⁴

THE CLINICAL EVALUATION AND DIFFERENTIAL FINDINGS

The important fundamentals in the diagnostic evaluation of rhinitis are the clinical history, physical examination, and nasal smear. Physical examination shows a pale bluish edematous nasal turbinate with thin, clear secretions, typical features of allergic rhinitis with a normal or eosinophil predominance on nasal cytology. In vasomotor rhinitis, the mucosal appearance is normal with clear secretions; in infectious rhinitis, yellow-green secretions with a considerable number of neutrophils and bacteria are seen. Infraorbital "shiners" caused by venous engorgement and periorbital edema, scleral or conjunctival inflammation, or middle ear otitis may be present, along with sinusitis or nasal polyps.¹²

Skin testing with appropriate allergens by the prick-puncture method is the most sensitive and useful procedure to confirm allergy and suspected sensitivity. This is less expensive than *in vitro* measurements of allergen-specific IgE and can even be performed on infants under 1 year of age to determine if food antigens or indoor allergens (e.g., house dust mite) are the possible trigger of rhinitis or eczema.¹² Although nasal provocation with suspected allergens is still considered a research tool, it has yielded a great deal of information on nasal mediators of inflammation.^{6, 14, 17, 41}

COMPLICATIONS

Serous otitis media is a significant complication of allergic rhinitis especially in children in whom eustachian tube dysfunction is common. Mucoïd effusions secondary to recurrent infection may ensue.¹² Chronic sinusitis as a comorbid factor for allergic rhinitis can trigger asthma. Both serous otitis media and chronic sinusitis are frequently present in HIV disease.⁷ In adults, pain, headache, fever, and purulent nasal discharge are the most frequently recognized signs and symptoms of rhinosinusitis.¹²

On physical examination discoloration beneath the eyes with edema owing to engorged vasculature may be present. An inflamed nasal mucosa with purulent discharge beneath the middle turbinate may also be evident.¹² The possibility of other underlying conditions that predispose to the development of sinusitis should be considered, such as cystic fibrosis, common variable immune deficiency, IgG subclass or IgA deficiency, vasculitis, or HIV infection.¹²

THERAPY FOR ALLERGIC RHINITIS

The treatment of allergic rhinitis for HIV-infected and uninfected patients is generally the same. Environmental control to avoid exposure to both indoor and outdoor allergens is often helpful. The institution of appropriate pharmacologic intervention with single or a combination of agents or of allergen immunotherapy are other useful considerations. The immunologic effects of allergen immunotherapy include an increase in specific IgG antibodies and a gradual reduction in both allergen-specific and seasonal increases in IgE, late-phase allergic reactions, and inflammatory mediator production. In addition, the generation of allergen-specific T cells has been reported, and our laboratory has noted that Th1 responses characterized by increased interferon gamma levels improved, whereas Th2 responses characterized by interleukin-10 generation were suppressed after 3 and 6 months of immunotherapy.³⁸

Pharmacotherapy for allergic rhinitis consists of both intranasal and/or oral medications.¹² One type of intranasal spray contains corticosteroids aimed at decreasing the inflammatory reaction. These medications must be used regularly over time before a beneficial response is seen. The most commonly prescribed oral medications for rhinitis include various antihistamines and decongestants. They may be used alone or in combination with the nasal sprays for relief of allergic rhinitis symptoms.¹² The first-generation antihistamines were developed many decades ago and have been classified into six different groups based on chemical composition properties. All of the classes, however, are associated with a significant sedative effect. The second-generation antihistamines, such as terfenadine, astemizole, and cetirizine, were developed to overcome the problem of sedation. It is important to bear in mind that astemizole and terfenadine have been shown to have significant metabolic crossreactivity when used in combination with macrolide antibiotics or antifungal agents, potentially leading to QT interval prolongation or cardiac arrhythmias. Thus, in HIV-infected patients treated with antifungal drugs, it would be safer to use one of the newer antihistamines such as loratidine, cetirizine, or fexofenadine.

Future directions in the therapy of allergic rhinitis may include selective immunologic modulation, control of IgE synthesis with soluble IL-4, inhibition of IgE binding to its receptor, synthetic IgE fragments, IgG blocking antibodies, high-potency newer topical corticosteroids, po-

tent topical antihistamines, adhesion molecule antagonists, and other novel anti-inflammatory agents.

EVIDENCE FOR ATOPY IN HIV DISEASE

Allergic rhinitis, asthma, and atopic dermatitis have been evaluated in adults with HIV disease.^{11, 20, 28, 35} An elevation of IgE in HIV-infected adults has been shown to be a marker of poor prognosis in late-stage HIV infection.¹¹ Israel-Biet and colleagues evaluated 315 HIV seropositive and 100 HIV-seronegative subjects for concentrations of IgE and other immunoglobulins.¹¹ Although no skin testing or specific IgE determinations were performed, subjects with AIDS appeared to have a worsening of preexisting symptoms of allergy.¹¹ IgE levels were significantly higher in HIV-infected subjects compared with seronegative controls and a strong inverse relationship occurred between IgE levels and CD4 cell counts. Total IgE levels were not related to atopy as previously reported by Wright and co-workers.⁴³ The authors postulated that the elevation in IgE concentrations could be due to the polyclonal immunoglobulin synthesis observed in HIV¹⁶ infection and described for other immunoglobulin classes.¹⁸

Elevated IgD levels have been observed in both atopic dermatitis and in immunodeficiencies. In a study at our center investigation of circulating IgE and IgD in HIV-infected patients was performed.³¹ We investigated the relationship of previously reported elevated serum IgD in AIDS and serial IgE in the same patients.³⁰ The predominance of IgD-positive reactions in AIDS is an interesting finding that could also be the result of polyclonal B-cell activation or because of a faster turnover of IgD-bearing B lymphocytes.³⁰ Thirteen patients with AIDS, nine with opportunistic infections, and four with Kaposi's sarcoma, and 13 age- and sex-matched control donors were serologically evaluated for IgE using a monoclonal immunoenzymetric assay.³¹ Elevated IgE was observed in 5 of 13 patients, or 38%, primarily with those with opportunistic infections, with a mean of 325.5 ± 108 IU/ml. The mean IgE level in the control patients was 65.4 ± 30.7 IU/ml. Thus, a possible relationship was suggested to exist between IgE and IgD in AIDS.³¹ Figure 1 illustrates a hypothetical scheme of the relationship of IgE and IgD in HIV disease.

Mazza et al assessed total IgE levels in 36 HIV-infected adults using an allergy questionnaire, T- and B-cell markers, and measurements of specific IgE to eight environmental allergens (e.g., oak, grass, *Cladosporium*, *Alternaria*, dog and cat dander, and short ragweed).²⁵ A subgroup of patients had marked increases in serum IgE that were not associated with any detectable antigen-specific IgE to any allergen or any significant change in lymphocyte markers.²⁵ These authors concluded that acquired dysregulation of IgE synthesis occurs with elevated circulating IgE protein that is not attributable to specific allergens or changes in lymphocyte

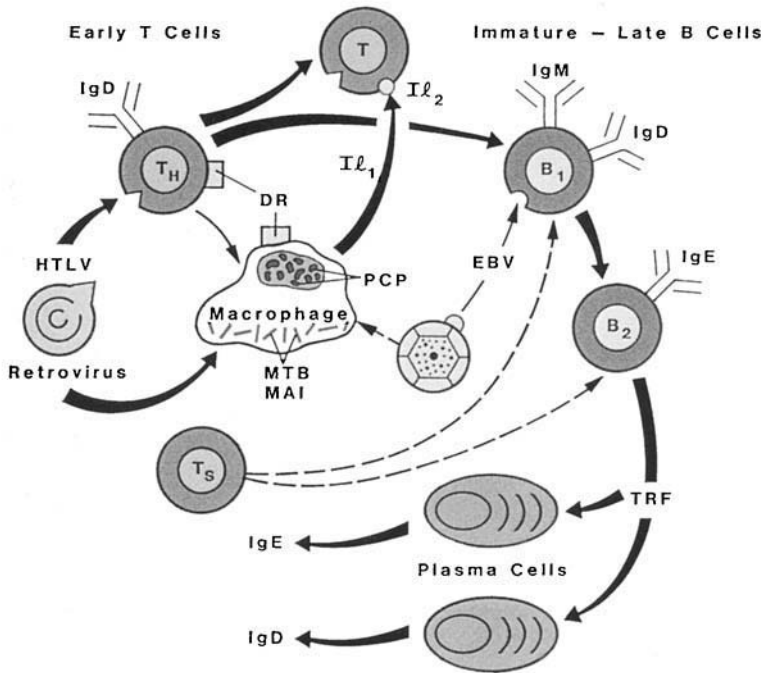


Figure 1. Hypothetical scheme of the relationship of IgE and IgD in HIV disease. Regulation by T cells, macrophages and factors. HTLV = human T cell leukemia virus; EBV = Epstein Barr virus; DR = HLA-DR Class II Ag; IL = interleukins, T_H/T_S = T helper T suppressor cells; PCP = *Pneumocystis carini* pneumonia; MTB, MAI = *Mycobacterium tuberculosis* or *avium intracellulare*; TRF = T-cell replacement factor.

markers. This phenomenon may be possible owing to production of lymphokines or other factors.²⁵

Similarly, Pagnelli et al evaluated 9 adult patients with AIDS, 51 HIV-positive patients without hyper IgE syndrome, and 3 patients affected by the primary hyper IgE syndrome. Lymphocyte subpopulations, immunoglobulins and subclasses, eosinophil cationic protein, soluble CD23 levels, in-vitro IgE synthesis, and specific IgE to pollens (ryegrass, Parietaria, mugwort), house dust mites, cat dander, and *Candida albicans* were measured.²⁹ Spontaneous in-vitro synthesis of IgE was confirmed in both hyper IgE conditions, along with elevated levels of circulating eosinophil cationic protein. Serum-soluble CD23 was similar to that of normal controls in the HIV-positive patients with hyper IgE. The authors concluded that a hyper IgE-like syndrome represents a distinct aspect of the clinical features of HIV infection, and immunologic mechanisms appear to differ from those known in primary hyper IgE syndrome since CD4⁺ Th2 cells are markedly depleted in HIV-positive patients.²⁹ The IgE system is a complex network involving many cell types, cytokines,

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Figure 2. The IgE system illustrating a complex network of cells, cytokines, and receptors. Cells and interleukins (IL) cooperate in IgE induction. High and low affinity IgE receptors (Fce R1/R2) trigger further release of mediators. (From Vercelli D: Regulation of IgE Synthesis. Current Views in Allergy Immunology, March 1995, with permission.)

and receptors. IgE binds to the high- and low-affinity IgE receptors on different cells (Fig. 2). This binding results in the release of chemical mediators that produce the allergic symptoms.

INCIDENCE OF RHINOCONJUNCTIVITIS IN HIV INFECTION

The incidence of allergic rhinitis and conjunctivitis increased two-fold after HIV seroconversion in 28 HIV patients with secondary infections, and 10 HIV patients with cancer.³⁵ Elevated serum concentrations of IgE to environmental antigens (by means of modified RAST for Bermuda grass, timothy, common ragweed, English plantain, oak, cat and dog dander, *Alternaria*, house dust, and *Dermatophagoides farinae*) were observed in these HIV-seropositive male homosexual patients.³⁵ Of the total group of HIV-infected men, 41% had a history of allergic rhinitis, allergic conjunctivitis, urticaria or extrinsic asthma, and 19% had been skin tested for allergies by a physician before onset of HIV infection.³⁵ Nasal eosinophilia and positive RAST results were more common in patients with cancer. Thus, the increased incidence of newly acquired allergic disease in association with elevated serum levels of IgE to environmental antigens suggested that some control of specific IgE production in these subjects remained. Therefore some of the increased frequency of immediate hypersensitivity type reactions to certain medications might be due to IgE-dependent mechanisms.

Asthma and related atopic disorders including rhinitis were evaluated in outpatients attending an adult urban HIV clinic.²¹ Seventeen percent and 15% of patients claimed to have asthma and allergic rhinitis, respectively. There was no association between rhinitis symptoms and CD4-cell depletion. Recurrent sinusitis and otitis were significantly associated with current rhinitis with or without chronic nasal symptoms. Current rhinitis showed significant univariate association with family history of rhinitis and current asthma, but not with inhaled drug abuse.²¹ The proportion of patients reporting current asthma and rhinitis in various risk strata is shown in Figure 3. The data from this study suggested that further studies should focus on the role of chronic rhinitis and family atopy as risk factors for the development of paranasal disease such as sinusitis and otitis media, which occur commonly in HIV infection.²¹

Immunologic studies in pediatric HIV disease show patterns that are similar in some respects to adult HIV disease.²⁰ Common complications of chronic rhinitis, which affects 20% of the general population, such as sinusitis and otitis media, are also quite common in children



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Figure 3. Patients reporting current asthma and rhinitis with respect to CD4 counts in different risk categories. CD4 $\leq$ 200/dL (*dotted bar*) and CD4 $\geq$ 200/dL (*hatched bar*). (From Lin RY: Ann Allergy Asthma Immunol, 74:510, 1995, with permission.)

infected with HIV. In a study by Koutsonikolis et al, the relationship between HIV infection in children and IgE levels was evaluated.¹⁶ Specific IgE levels were determined by RAST to *Dermatophagoides pteronyssinus*, American cockroach, Bahia grass, short ragweed, cat dander, and oak pollen. In 29 infected children, 57 total IgE and 342 specific IgE levels were measured. In contrast to Sample et al suggesting a correlation among total IgE, specific RAST to environmental antigens and clinical atopy,³⁶ there was no detectable specific IgE to any aeroallergen or correlation between IgE, and absolute CD4 number or CD4-to-CD8 ratio.²¹ Skin-prick testing may have provided additional information, and the possibility that there may be IgE specific to antigens not tested also remains. In another study of 58 children infected vertically with HIV and 35 children with seroconversion aged 4 months to 11 years, serum IgE levels, CD4 cell counts, and skin prick to common airborne and food allergens were performed.²² IgE dysfunction in this population was similar to that seen in the adult HIV-infected population, suggesting that IgE over production is a marker of disease progression with a switch from the Th1 to Th2 cytokine profile.²⁸

RHINOSINUSITIS IN HIV INFECTION

Sinusitis is a comorbid feature of rhinitis. Several studies have reported on increased incidence of allergic sinusitis in HIV patients. Figures in the various studies range from 10% to 17%, to 30% to 68%.^{34, 36, 37, 39} In a study conducted in 1992 by Small et al, a correlation between increased IgE levels, allergic reactivity, and sinusitis in HIV-positive patients was noted. Skin-prick testing was performed on 32 HIV-positive rhinosinusitis patients and on 37 HIV-negative rhinosinusitis patients, as well as on 32 normal controls.³⁹ Dust mites were the most common allergen in both HIV-positive and HIV-negative subjects, whereas other allergens such as ragweed were less common in both groups (Fig. 4). Allergic reactivity was very high in both groups of HIV-positive patients, with 72% (23/32) exhibiting at least two positive skin test results. Only 24% (5/21) of the HIV-negative rhinosinusitis patients, and 12.5% (2/16) of the nonatopic normal controls had more than 2 positive skin test results. The difference between the HIV+ and negative subjects was highly significant ($P<0.05$).

Numerous other studies have shown that allergic disorders other than sinusitis are common in HIV. It has been documented that multiple-drug allergies, especially to antibiotics like TMP-SMX, are common (mentioned elsewhere in this issue). There is also an increased incidence of contact dermatitis, asthma, eosinophilic vasculitis and pustular folliculitis.

It has been suggested that the frequent occurrence of sinusitis in HIV-positive patients is not purely infectious in origin but may be due to the acquired atopic state.³⁹ Patients may develop allergies that result in allergic nasal inflammation, blockade of the sinus ostia, and secondary

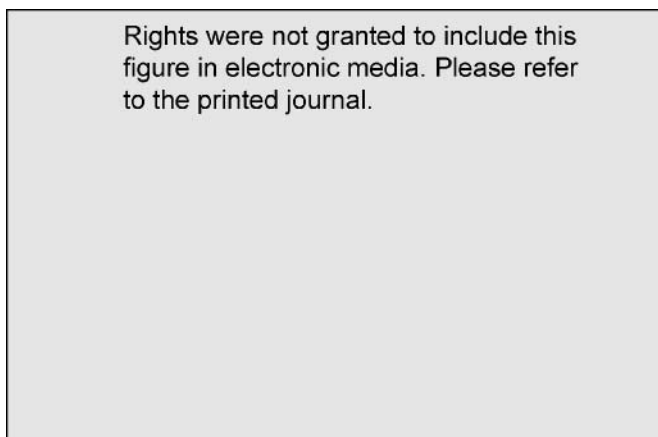


Figure 4. Pattern of reactivity to common aeroallergens in HIV-positive and negative subjects. HIV (+) = 32 HIV-infected patients; HIV(−) = 37 HIV-negative patients without atopic history; HIV(−) atopic = 32 HIV-negative atopic rhinosinusitis patients. Vertical bars indicate the percentage of skin test reactivity to allergens listed on horizontal axis. Solid bar = HIV(−); Medium shaded bar = HIV(+); Light shaded bar = HIV(−) atopic. (Modified from: Small, et al. J Inf Dis 167:283, 1993 with permission.)

bacterial infection. When such patients were treated with medications aimed at reducing allergic inflammation such as intranasal corticosteroids, in addition to conventional therapy with antibiotics, the response was found to be good. It is clear, however, that the anti-inflammatory effects of corticosteroids encompass nonallergic inflammation as well.

IMMUNOTHERAPY IN HIV

Allergen immunotherapy is the process by which gradually increasing doses of an allergen are injected subcutaneously to reduce or prevent allergic symptoms in a sensitive subject. Immunologically, it has been shown that there is an increase and later a fall in allergen-specific IgE antibodies with a rise in the specific IgG antibodies that have been termed *blocking* in nature. This may be one of the mechanisms involved in a successful response to immunotherapy although better markers of efficacy of this treatment regimen are currently being sought. Other mechanisms, such as a reduction in late-phase allergic responses, decreases in mediator and lymphokine production, and the generation of allergen-specific T cells have also been associated with allergen immunotherapy.

In the HIV patient, the immune system is activated and targeted by the virus, resulting in immunologic dysregulation. Currently, the general

practice is to refrain from administering immunotherapy to the HIV-positive patient, as it is not known what effect this could have on the already compromised immune system. Studies are underway in various institutions to evaluate whether such therapy would be of benefit to the HIV patient with allergic rhinitis symptoms.

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