

Objective measures of allergic disease in children with human immunodeficiency virus infection

Bruce K. Bacot, MD, Mary E. Paul, MD, Maritza Navarro, MD,
Stuart L. Abramson, MD, PhD, Mark W. Kline, MD, I. Celine Hanson, MD,
Howard M. Rosenblatt, MD, and William T. Shearer, MD, PhD *Houston, Tex.*

Background: Available information suggests that IgE levels are elevated in adults infected with human immunodeficiency virus (HIV), and that increased IgE levels correlate with allergic disease, with decreased CD4 counts, and with a poor prognosis. Data with respect to these factors in children are scant.

Objective: We investigated whether serum IgE levels are elevated in children with HIV and, if so, whether the serum IgE level correlates with the degree of immunodeficiency and/or objective indicators of allergic disease.

Methods: Serum IgE levels, CD4 counts, absolute eosinophil counts, and immediate hypersensitivity skin test (IHST) results were collected from 43 children with symptomatic HIV infection (mean age 7.2 years). Associations between serum IgE levels, CD4 counts, and eosinophil counts were investigated by multiple stepwise linear regression analysis. Data were stratified according to IHST positivity, and analysis of variance was used to compare mean values for age, CD4 counts, IgE levels, and eosinophil counts between the two groups.

Results: Serum IgE values were elevated more than 2 SDs above control age-matched mean values in 17 of 43 patients (40%). IHST results were positive in 12 of 43 patients (28%). CD4 counts were less than 200/mm³ in 17 of 43 patients (40%). Stepwise linear regression failed to demonstrate any correlation between serum IgE levels and either CD4 or eosinophil counts. With data divided into two groups according to IHST results (positive vs negative), analysis of variance failed to reveal significant differences between means for patient age, CD4 counts, IgE levels, or eosinophil counts.

Conclusions: Our findings confirm that serum IgE levels are increased in children infected with HIV, just as in adults.

However, an elevated serum IgE level did not correlate with allergic disease as measured by IHST results and eosinophil

Abbreviations used

AIDS:	Acquired immunodeficiency syndrome
HIV:	Human immunodeficiency virus
IHST:	Immediate hypersensitivity skin testing
INF- γ :	Interferon- γ
IVIG:	Intravenous IgG
T _{H1} /T _{H2} :	T helper cells

counts, nor with the degree of immune dysfunction as approximated by CD4 counts. The mechanism and significance of elevated serum IgE levels remain unclear in children with HIV, and warrant further investigation. (*J Allergy Clin Immunol* 1997;100:707-11.)

Key words: Pediatric human immunodeficiency virus, serum IgE, allergy, skin test reactivity, eosinophil count

Adults infected with the human immunodeficiency virus (HIV) develop clinical symptoms of allergy at a greater frequency than is expected in the general population.¹ However, mechanisms that could account for the development of allergic disease in individuals infected with HIV are poorly understood. Current information suggests that allergy represents an abnormal immune response to environmental agents, and that the predisposition to develop allergic disease reflects underlying genetic control of the immune response. The observation that the incidence of allergic disease is increased in patients with HIV infection invites the hypothesis that the immune dysregulation caused by HIV impairs normal allergy control mechanisms, thereby allowing enhanced clinical expression of allergic disease.

Data in adults with HIV infection implicate defective T cell immunity in the appearance of hyperallergic conditions associated with recurrent infections such as sinusitis.¹⁻⁷ Although conflicting data exist, most published studies report markedly elevated serum IgE levels in adults with HIV infection, and correlate these elevated IgE levels with the degree of immunodeficiency.^{1,8} Available data document that the extent of IgE elevation correlates inversely with both CD4 and CD8 T lymphocyte numbers.^{1,5} Interestingly, in a recent study by Israel-Biet et al.,⁵ no apparent link was noted between elevated serum levels of IgE and atopic disease in patients infected with HIV. However, in that study,

From Baylor College of Medicine and Texas Children's Hospital Houston, Texas.

Supported by National Institute of Allergy and Infectious Diseases AIDS Clinical Training Grant Award No. AI 07456 (B.K.B.), Underserved Minority Investigator Award No. AI 32466-0351 (M.N.), General Clinical Research Center Grant No. RR 00188, Centers for AIDS Research Grant No. AI 36211, and the Immunology Research Fund, Texas Children's Hospital.

Received for publication Aug. 23, 1996; revised June 27, 1997; accepted for publication July 1, 1997.

Reprint requests: Mary E. Paul, MD, Texas Children's Hospital, MC 1-3291, 6621 Fannin St., Houston, TX 77030.

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0091-6749/97 \$5.00 + 0 1/1/84505

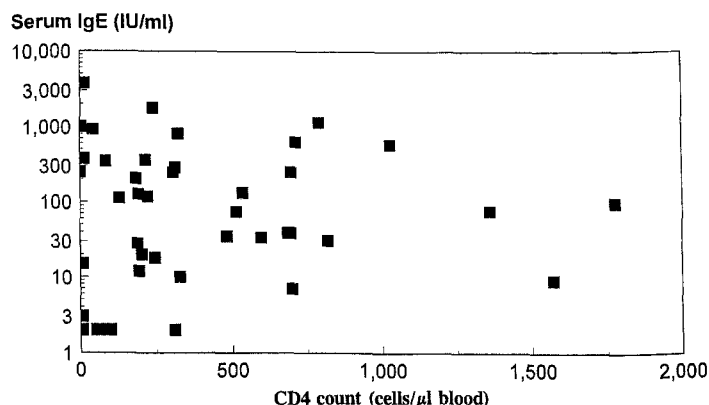


FIG. 1. Serum IgE level vs CD4 count (coefficient of determination = 0.02). Elevation of serum IgE level does not correlate with decreased CD4 count.

elevated IgE values defined a group of patients with a particularly poor prognosis.⁵ Most of the currently published data regarding the elevation of serum IgE levels and allergy in patients with HIV are derived from adult studies. Several recent publications support the observation that serum IgE levels are elevated in children with HIV infection.^{9, 10}

Our experience suggests that the incidence of allergic disease in children infected with HIV is greater than in their uninfected peers. Severe allergy in children with HIV may contribute to the increased incidence of upper respiratory infections such as otitis media, sinusitis, and pharyngitis. We hypothesized that allergy in children with HIV may result in substantial morbidity, and noted that data with respect to allergic disease and its possible correlation with the degree of immune impairment in such children are lacking. We undertook the current study to define the incidence of allergy, elevated serum IgE levels, and eosinophilia in pediatric patients with HIV infection and to determine whether these factors correlate with worsening immunodeficiency as measured by absolute CD4 T lymphocyte counts.

METHODS

Forty-three pediatric patients more than 3 years of age were enrolled in the study, which was approved by the Institutional Review Board for Human Subject Research at Baylor College of Medicine. Immediate hypersensitivity skin testing (IHST) with a panel of locally relevant aeroallergens was performed by the epicutaneous prick method. Skin test positivity was defined as two or more antigens producing 2 mm or more induration in excess of the negative control. We obtained a concomitant complete blood cell count from which the absolute eosinophil count was calculated. Lymphocyte phenotyping was performed by flow cytometric analysis to obtain CD4 counts. We obtained serum for measuring IgE levels, which were determined fluorometrically by a sandwich immunoassay with mouse monoclonal anti-human IgE antibody. Data were tabulated and analyzed by stepwise linear regression (Microstat and SigmaPlot software) to determine if correlations existed between serum IgE levels, CD4 counts, and eosinophil counts.

Finally, data were stratified according to IHST positivity and

analysis of variance was used to determine any significant differences in mean values for IgE level, absolute eosinophil count, and CD4 lymphocyte count between children who had positive skin test results and those who did not. CD4 counts at enrollment were compared with results obtained approximately 1 year later by the use of a paired *t* test to determine any significant change in this measure of immune dysfunction. A *p* value of 0.05 or greater was considered significant. Medical records were reviewed to collect information regarding demographic data, documented drug allergy, clinical status, HIV transmission risk, survival, and treatment with intravenous IgG (IVIG).

RESULTS

The 43 patients in the study ranged in age from 3 to 20 years (mean, 8.0 years; SD, 3.6 years). In this group, 58% were male, 42% were female, 69% were Black, 12% were Hispanic, and 19% were White. Two patients were infected with HIV as a result of blood product transfusions, one as the result of sexual exposure, and the remainder (93%) acquired HIV perinatally. Clinical status was determined by the 1994 revised classification system. Seven of 43 patients were asymptomatic (Category N), whereas 36 of 43 had HIV-related symptoms, with 9 of 43 having a documented acquired immunodeficiency syndrome (AIDS)-defining condition. Five patients had received monthly infusions of IVIG for more than 1 year at the time of evaluation, four as part of an ongoing clinical protocol and one after splenectomy. Only five patients (11.6%) had ever experienced an allergic reaction to any medication (responsible agents included trimethoprim-sulfamethoxazole, amoxicillin/clavulanate, and erythromycin). Two of 43 patients died during the 1-year evaluation period, both of whom had an AIDS-defining condition.

IHST results were positive in 12 of 43 patients (28%). Four of these patients experienced a significant reaction to dust mite antigen, three patients to both dust mite and pollen, and seven patients to various pollens. Serum IgE levels were elevated (>200 IU/ml) in 17 of 43 patients (40%). IgE values were elevated more than 2 SDs above

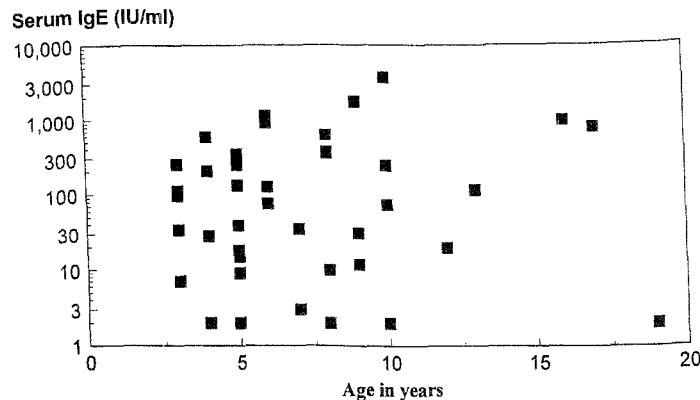


FIG. 2. Serum IgE level vs age (coefficient of determination = 0.05). Elevation of serum IgE level does not correlate with age.

age-matched control mean values in 17 of 43 patients (40%). Eosinophilia was not a notable feature of our patients, and no patient had an absolute eosinophil count greater than $470/\text{mm}^3$. Profound immunodeficiency was present in 17 of 43 patients (40%), with CD4 counts less than $200/\text{mm}^3$. CD4 counts did not change significantly as evaluated by paired *t* test over the 1 year studied.

Stepwise linear regression failed to demonstrate any significant correlation between serum IgE levels and either CD4 counts, absolute eosinophil counts, or patient age ($p > 0.05$ in all cases). These data are presented in Figs. 1 to 3. Increasing serum IgE and eosinophil numbers tended to correlate with increasing age; however, these trends were not statistically significant.

Patients were divided into two groups according to IHST results (positive vs negative). Analysis of variance was applied to determine whether significant differences existed between the means for ages, CD4 counts, IgE levels, or eosinophil counts for the two groups. No statistically significant differences were found between the IHST positive and negative groups for any of these four variables.

DISCUSSION

Evidence suggests that serum IgE levels are significantly elevated in adults with HIV infection, and that the degree of elevation correlates with markers of immune dysfunction as well as with the development of allergic disease.¹ Specifically, several studies have shown that serum IgE levels correlate inversely with CD4 counts. However, several studies have found that the elevated serum IgE levels in patients with HIV do not correlate with atopic disease.^{7,11} In other words, whereas serum IgE values may be elevated compared with normal ranges, levels are comparable in both atopic and non-atopic individuals with HIV. It also appears that increased levels of serum IgE protein are not related to atopic allergens.¹²

The main cellular target of HIV is the CD4 receptor,

an adhesion protein expressed predominantly by class II major histocompatibility complex restricted helper T lymphocytes. Infection with HIV eventually causes distinct alterations in immune function, even before profound decreases in the numbers of CD4 T helper cells are evident. A loss of T helper cell function can be demonstrated even when CD4 counts remain greater than $500/\text{mm}^4$. Other alterations in immune function include increased B cell activity, polyclonal B cell activation, and hypergammaglobulinemia.¹¹ Also, perturbations in immunoregulatory cytokine profiles follow HIV infection. These perturbations may contribute to the increased expression of allergic disease.

Murine models suggest the presence of several distinct subsets of T helper cells that are defined by the cytokine profile they produce.¹¹ T_{H1} cells elaborate γ -interferon (IFN- γ) and IL-2 and direct cell-mediated immune responses. T_{H2} cells produce IL-4, IL-5, IL-6, and IL-10. The T_{H2} profile of cytokines drives a humoral immune response and is proinflammatory. IL-4 is required to enable isotype switching of B cells for IgE synthesis. IL-6 increases nonspecific, polyclonal IgE production and is directly induced by HIV antigens.¹³ IL-5 enhances eosinophil production, activates resting eosinophils, and prolongs eosinophil survival. A shift to the T_{H2} profile of cytokine production after HIV infection would provide a viable theoretical mechanism for increased IgE levels and allergic symptoms in these patients.¹¹ T_{H1} and T_{H2} clones have been isolated from humans. A number of studies have been performed in adults examining the association of increased IgE, allergic rhinitis, sinusitis, and IHST positivity among patients with HIV.^{2,8,14} Most currently available information suggests that IgE levels and allergic symptoms increase as immune dysfunction increases in patients infected with HIV.

Our study supports the observation that serum IgE levels are often markedly elevated in patients with HIV infection and extends this observation to the pediatric population. Definitions of an abnormally elevated serum IgE value are inconsistent, with cutoffs ranging from 20

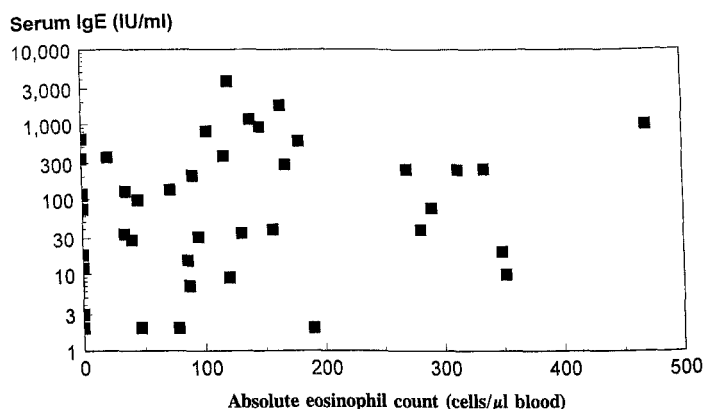


FIG. 3. Serum IgE level vs eosinophil count (coefficient of determination = 0.02). Elevation of serum IgE level does not correlate with increased absolute eosinophil count.

to 200 IU/ml in the literature. We chose to identify results as elevated if they measured more than 2 SDs above age-matched control mean values. Age-matched mean values were used because normal ranges for serum IgE change with age in pediatric patients. With this conservative criterion, 40% of our 43 enrolled patients had elevated serum IgE levels.

We were unable to correlate the degree of IgE elevation with immunodeficiency as reflected by CD4 lymphocyte counts. A qualitative deficiency such as loss of memory cells, defects in antigen processing and presentation, or cytokine imbalances such as deficient IL-12 and IFN- γ production may exist even when absolute numbers of CD4-positive T helper cells are normal.¹¹ These qualitative deficiencies in T cell help may be more critical in children than in adults, and this may explain why we observed no relationship between elevation of serum IgE level and CD4 counts in our patients.¹¹

Several possibilities must be considered to explain the character of the IgE produced by children with HIV who have elevated IgE levels. First, one could presume that nonspecific, polyclonal production of IgE accounts for the observed elevation. This would be consistent with the premise that derangements in immune regulation are responsible for increased IgE production. However, some information from adult studies suggests that elevated serum IgE levels represent specific, functional production of IgE directed against extrinsic allergens.²

Our study, limited to pediatric patients, reveals a 28% prevalence of IHST positivity based on previously noted criteria. This prevalence is greater than in the general population, where large epidemiological studies reveal a prevalence range of 17% to 22%.¹⁵⁻¹⁷ Prevalences reported in children are somewhat lower, between 3% and 10% for children under the age of 14 years.¹⁸⁻²⁰ Whereas some portion of the increased IgE levels in patients with HIV may be specific for common aeroallergens, some of this IgE must be HIV specific. Histamine is released in 80% of adult patients with AIDS in direct response to HIV antigen.²¹ The production of IgE as a significant component of the immune response to HIV could relate

to poor prognosis as observed in some adult studies. It could also help explain the lack of observed correlation between elevated serum IgE levels and either IHST positivity or CD4 counts.

Immune dysregulation and a shift to the T_{H2} pattern of cytokine production has been proposed as a mechanism for clinical deterioration in adult patients with HIV.¹¹ This factor may be even more important in children. Viral respiratory infection in childhood frequently results in elevated serum IgE levels and manifestations of allergy. Respiratory syncytial virus, parainfluenza virus, and rhinovirus have all been implicated in such a phenomenon. The presumed mechanism involves a genetic predisposition to direct a humoral response to the virus along T_{H2} lines. Patients who develop elevated IgE levels in response to these viral infections often have a more severe and prolonged clinical course than those who do not.

The immunological aspects of pediatric respiratory syncytial virus infection have been the subject of extensive investigation, and clearly children who mount a significant IgE response to the virus are subject to more severe illness and to complications that may persist for years.^{22,23} The same may be true for pediatric HIV infection, in which elevated serum IgE levels may not necessarily reflect the extent of immunodeficiency, but rather an inherent tendency to respond to viral infection with a T_{H2} cytokine profile and IgE antibody. In this case, we would expect a significant portion of serum IgE antibody in these pediatric patients to be directed against epitopes of HIV itself.

Our data support the reported lack of correlation between serum IgE levels and the clinical manifestations of atopic disease in patients with HIV. Our group of pediatric patients with HIV and positive IHST results demonstrated no significant differences in CD4 counts, serum IgE levels, or absolute eosinophil counts compared with patients with negative IHST results. We propose that elevated serum IgE levels in pediatric patients do not appear to be directed against common aeroallergens, but rather could reflect HIV-specific IgE

or nonspecific polyclonal IgE production after HIV infection. Recently, recombinant HIV glycoprotein 120 and tumor necrosis factor- α have been shown synergistically to stimulate polyclonal immunoglobulin production in normal B cells in vitro, possibly explaining some of these clinical observations.²⁴

In summary, our data extend to the pediatric population the observation that the serum IgE level is often elevated in patients with HIV infection. We were unable to define any correlation between serum IgE level and either CD4 count or eosinophilia. Mean values for CD4 counts, IgE, age, or eosinophil counts did not differ significantly between patients with HIV grouped according to IHST results. We conclude that, whereas the IgE level is elevated compared with normal values, it does not correlate with either immunodeficiency as measured by CD4 counts or allergy as measured by eosinophilia and IHST results.

Further studies in the pediatric population are necessary to clarify these issues. Specific points that need to be addressed include assessing abnormalities in T helper cell function in patients with relatively preserved CD4 counts, as well as attempting to define better the specificities of IgE in patients with elevated serum IgE levels. Studies investigating the administration of IFN- γ to pediatric patients with HIV are currently underway, and may provide some coincidental insight with respect to IgE production in children with HIV. Elevation of serum IgE levels in children infected with HIV would seem to correlate more with underlying immune dysregulation than with overt symptoms or objective indicators of allergic disease. If this is true, then it may be possible to modify this immune imbalance and decrease morbidity related to HIV infection.

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