

IgE and atopy in perinatally HIV-infected children

Bowser CS, Kaye J, Joks RO, Charlot C-A, Moallem HJ. IgE and atopy in perinatally HIV-infected children.
Pediatr Allergy Immunol 2007.

© 2007 The Authors

Journal compilation © 2007 Blackwell Munksgaard

Elevated serum immunoglobulin E (IgE) and increased prevalence of atopy is reported in patients infected with human immunodeficiency virus (HIV). The elevated serum IgE may be attributed to polyclonal stimulation of B cells or IgE production against allergens, viruses, fungi and bacteria. This study investigates the prevalence of atopy in perinatally HIV-infected children, and the relationships between serum IgE (and other serum immunoglobulins) with atopy, CD4+ cell count and HIV-disease stage. Serum immunoglobulin levels, epicutaneous skin test for common aeroallergens, clinical Centers for Disease Control and Prevention (CDC) classification, CD4+ cell counts and allergy history were extracted from the charts of perinatally HIV-infected children on highly active antiretroviral therapy. The prevalence of atopy (52%) and the pattern of aeroallergen sensitivity were comparable with the US pediatric population. Serum IgE levels did not correlate with clinical disease stage. However, in non-atopic patients, serum IgE levels increased with disease progression ($p = 0.02$). There was an inverse relationship between the prevalence of elevated serum IgE levels and atopy with progression of disease ($p = 0.019$). Serum IgE did not correlate with atopy, CD4+ cell count, or duration of HIV infection or levels of serum immunoglobulins. This is the first study to show no increased prevalence of atopy in perinatally HIV-infected children compared with the general population. In advanced stages of HIV, elevated serum IgE may be specific for antigens other than those known as allergens.

Corinna S. Bowser, Jean Kaye, Rauno O. Joks, Cascy-Arnoux Charlot and H. Jack Moallem

Division of Allergy and Immunology, Department of Pediatrics and Medicine, SUNY Downstate Medical Center, Brooklyn, NY, USA

Key words: human immunodeficiency virus (HIV); AIDS; IgE; atopy; allergy; immunoglobulin; CD4+ T cell; children; immediate hypersensitivity skin testing

Jack Moallem, SUNY Downstate Medical Center, Box 49, 450 Clarkson Ave, Brooklyn, NY 11203, USA
Tel.: 718 270 4178
Fax: 718 270 1985
E-mail: hj.moallem@downstate.edu

Accepted 27 October 2006

Increased prevalence of atopy is reported in human immunodeficiency virus (HIV)-infected adults and children (1–4). However, there is a higher incidence of sinusitis, which often causes symptoms similar to allergic rhinitis (1, 5). Drug allergies are more common in HIV-infected individuals, but it is unclear if HIV-positive patients truly have more immunoglobulin E (IgE)-mediated allergy (6, 7). Elevated serum IgE is reported in patients with HIV infection by some researchers; however, controversy remains if elevated serum IgE correlates with atopy, HIV disease stage or CD4+ cell counts, and whether it can be used as an indicator of disease progression (3, 4, 8). Increased serum IgE levels in HIV-infected patients may be secondary to polyclonal stimulation of B-cells or IgE production against

either environmental antigens (allergens and viruses) or HIV antigen itself (7, 9, 10).

This study investigates the prevalence of atopy and sensitization to common aeroallergens in HIV-infected children compared with HIV-negative populations. It also evaluates if elevated serum IgE and atopy are associated with the clinical progression of HIV-related disease in a perinatally infected pediatric cohort.

Methods

We conducted a chart review focused on the allergy history of perinatally HIV-infected children. All children were born to HIV-positive mothers, and for each individual child, HIV

infection was confirmed by at least two positive enzyme-linked immunosorbent assays (ELISA) and Western Blot on two separate peripheral blood specimens obtained from different days after 18 months of age or a plasma HIV RNA value of greater than 10,000 copies/ml.

The subjects were clinically categorized using the Centers for Disease Control and Prevention (CDC) classification for HIV (11). Thirty-one patients were enrolled. All patients were undergoing treatment with highly active antiretroviral therapy (HAART) and two fulfilled criteria for AIDS (11). The total serum IgM, IgG and IgA levels were measured by nephelometry. Total serum IgE was determined by immunofluorescence, and T-cell studies were performed by flow cytometry (Epics, Beckman-Coulter, Fullerton, CA, USA). All values were compared with age-related normal values. All selected subjects had undergone immediate hypersensitivity skin testing for evaluation of various complaints, such as cough, sinusitis and symptoms of rhinitis with glycerinated extracts of the following common aeroallergens: *Alternaria alternata*, *Cladosporium herbarium*, 10 trees mix (alder, ash, elm, beech, birch, maple, hickory, oak, poplar, sycamore), English plantain, five grasses mix (timothy, orchard, red top, june, sweet vernal), Timothy grass, mix of giant and short ragweed, American cockroach, cat pelt, dog hair, mouse epithelia, histamine and saline control (Alk Abello, Port Washington, NY, USA), *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* mix (Hollister Stier, Spokane, WA, USA). The test was read after 15 minutes. None of the individuals was taking oral antihistamines or leukotriene antagonists for at least 1 wk before the date of the test. Atopy was defined as a wheal at least 3 mm larger than the saline control for at least one allergen.

Statistics

Spearman correlation coefficients were determined to evaluate the relationship between IgE and total IgM, IgG, IgA, CDC classification and duration of HIV infection.

Binomial exact test and Fisher's exact test were employed to compare the prevalence of atopy and sensitivity to specific allergens with the general population and a selected pediatric asthmatic population from our hospital, respectively. Fisher-Freeman-Halton exact test was used to examine the trend of prevalence of elevated IgE and atopy vs. CDC class. Cochran-Armitage exact test of trend was used to evaluate the relationship of the trends.

Table 1. Demographics of pediatric human immunodeficiency virus (HIV)+ subjects

Ethnicity	African American	23 (74%)
	Hispanic	8 (26%)
Gender	Female	13 (42%)
	Male	18 (58%)
CDC category	A	8 (26%)
	A1	5 (16%)
	A2	3 (10%)
	A3	0 (0%)
	B	16 (52%)
	B1	9 (29%)
	B2	5 (16%)
	B3	2 (6%)
	C	7 (23%)
	C1	3 (10%)
	C2	2 (6%)
	C3	2 (6%)

Results

Thirty-one patients with perinatally acquired HIV infection were enrolled in the study (Table 1). The patients' ages ranged from 10 to 20 yr, mean 15.1 ± 3.1 yr, median 15 yr. All patients were on HAART, but three patients admitted to be non-compliant with the regimen.

Thirteen patients (42%) had been diagnosed with allergy-related diseases, four with asthma (13%), two with allergic rhinoconjunctivitis (6%), two with atopic dermatitis (6%), one with angioedema (3%), two with chronic sinusitis (6%) and two with drug allergies (6%). Twenty-two (72%) patients complained of constant allergic symptoms, including nasal pruritus, generalized pruritus, throat clearing and cough, of whom 16 (52%) complained of constant sneezing. Thirteen (42%) subjects had boggy, pale turbinates on physical examination. Two patients were taking medication for their allergies on a regular basis; one patient was on cetirizine and the other was on fluticasone propionate nasal spray. Table 2 depicts the immunologic parameters of our patient population.

Table 2. Immunologic parameters of pediatric human immunodeficiency virus (HIV)+ subjects

	Mean $\pm$ s.d.	Median	Normal range
CD4+ cell %	25.2 ± 11.5	27	25–57
CD4+ cell ($\times 10^6/l$)	505 ± 345	486	400–2100 (10–16 yr*) 300–1400 (>16 yr)
IgE (U/ml)	368 ± 1111	46	2.1–195 (14 yr) 1.5–114 (17 yr)
IgG (mg/dl)	1638.9 ± 566.7	1620	639–1349
IgM (mg/dl)	136.8 ± 109.8	101	56–352
IgA (mg/dl)	298 ± 202.9	266	70–312
Years with HIV	15.1 ± 3.1	15	–

*yr, years.

Ig, immunoglobulin; s.d., standard deviation.

Table 3. Results of epicutaneous skin testing in human immunodeficiency virus (HIV)+ pediatric patients in comparison with the general US population (12)

	HIV+ subjects* (%) (n = 31)	General population (%)	p value
Atopy total	52 (16)	56	0.9
Dust mite	23 (7)	28	0.7
Cockroach	26 (8)	26	0.8
Cat	13 (4)	17	1.0
Ragweed	6 (2)	26	0.04

*Values expressed as percentage (total number of study subjects).

Table 4. Result of epicutaneous skin testing of 31 human immunodeficiency virus (HIV)+ patients, in comparison with asthmatic children at our institution (13)

Allergen	Atopic HIV+ subjects* (%) (n = 16)	Asthmatic children (%)	p value
Dust mite	44 (7)	49	0.8
Cockroach	50 (8)	42	0.6
Alternaria	25 (4)	28	1.0
Cladosporium	25 (4)	31	0.8
Ten trees	19 (3)	44	0.1
Five grasses	25 (4)	34	0.6
Ragweed	13 (2)	40	0.04

*Values expressed as percentage (total number of study subjects).

Atopy

The overall prevalence of atopy was 52% (16 of 31 patients) in our cohort, similar to the prevalence in the general US population (12) of 54% (56% for teenagers 10- to 19-yr old) ($p = 0.9$). The prevalence of hypersensitivity to both indoor and outdoor (29%), only indoor (16%) or only outdoor (6%) allergens in our study cohort did not differ significantly from the general US population (indoor and outdoor 22%, $p = 0.26$; only indoor 14%, $p = 1.0$; only outdoor 10%, $p = 0.82$) (12). The prevalence of sensitization to various aeroallergens among HIV-infected children was similar to the general population except for ragweed (6% vs. 26%, $p = 0.043$) (Table 3). Among atopic HIV-infected patients, hypersensitivity to aeroallergens followed a similar pattern as a population of asthmatic children from our hospital (13), and differed only in the sensitivity to ragweed (13% vs. 40%, $p = 0.044$) (Table 4).

IgE

In the entire group studied (atopic and non-atopic patients), there was no significant correlation between serum IgE and CDC classification (Spearman coeff. 0.309, $p = 0.11$). In the

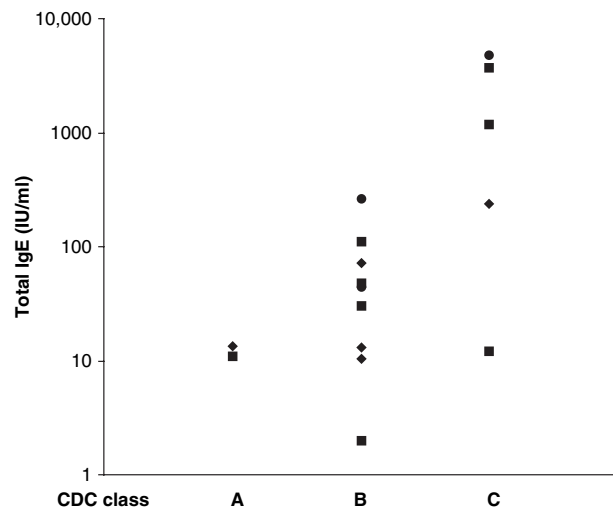


Fig. 1. Serum IgE correlates with clinical CDC class in non-allergic HIV patients ($R = 0.54$, $n = 16$, $p = 0.02$).

non-atopic HIV-positive patients, serum IgE increased with disease progression based on clinical CDC classification (A, B, C) (Spearman coeff. 0.507, $p = 0.02$) (Fig. 1). Serum IgE did not correlate with prevalence of atopy, CD4+ cell count, immunologic CDC class (1, 2 or 3) duration of HIV infection (age) or serum levels of IgG, IgM or IgA.

IgE, atopy and progression of HIV infection

In our cohort, the prevalence of elevated serum IgE increased with progression of HIV disease, from 0% in CDC class A, to 19% in class B, to 47% in class C ($p = 0.027$). However, there was a trend for decrease in the prevalence of atopy with advanced HIV disease (75% in class A, 31% in class B and 29% in class C; $p = 0.093$). There was a significant inverse relation between elevated serum IgE levels and atopy with progression of disease (Cochran–Armitage exact test of trend: $p = 0.019$) (Fig. 2).

Discussion

Many studies have investigated the association between atopy and elevated serum IgE in patients infected with HIV (2–4, 8, 14). The majority of studies in adults and children revealed an increased prevalence of atopic disease in HIV-infected patients compared with the general population (2, 4, 14). In the present study, the prevalence of atopy and specific allergen sensitization patterns did not differ from the general population (12, 13). This controversy may be explained by differing definitions of atopy and selection of HIV-negative

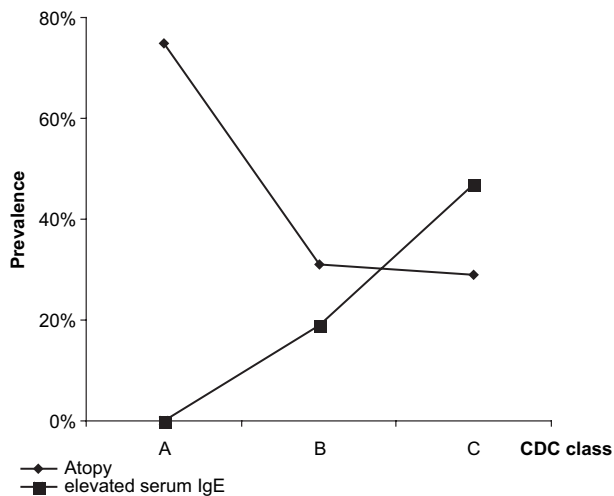


Fig. 2. Inverse trend between prevalence of atopy and elevated IgE with progression of HIV-related disease (Cochran-Armitage test, $p = 0.019$).

control groups. Some studies used elevated serum IgE as a marker for atopy (8), while others utilized allergen skin testing (2, 14) or the presence of allergic symptoms (9). Although HIV-infected patients have a high incidence of sinusitis, no correlation between rhinosinusitis and atopic disease has been found in HIV-infected patients, suggesting that sinusitis may be of infectious origin in a large part of cases (5). In a pediatric study in 1997 (2), prevalence of atopy was 28% in HIV-infected patients, which is higher than the prevalence of the control group-based studies completed more than 23 years earlier (1966–1976) (15–17). A study of adult HIV patients (14) compared the prevalence of atopy to a population-based study 7 years earlier (18). However, the prevalence of allergies and atopy has been constantly rising in the industrialized world, even doubling over a time frame of 10 years in some studies (19,20).

In this study, we used a recent large population-based study (12) and a group of asthmatics from our institution (13) as controls, and did not find increased prevalence of atopy in our HIV-infected group. The pattern of aeroallergen sensitization was similar to the non-HIV-infected asthmatic group in our institution, indicating an expected local pattern of allergic reactions in the atopic HIV-infected group. In contrast to the asthmatic children from our hospital and the general population, HIV-positive patients had a lower prevalence of ragweed sensitization. This cannot be explained by different aeroallergen exposure pattern, as the asthmatic children and the HIV-positive patients live in the same geographic area. It could however be a result of

the small sample size of this study and selection bias.

Total serum IgE in our patients did not correlate with atopy, which is in accordance with previous studies (2, 8). Correlation of serum IgE and CD4+ cell counts is an area of controversy. Bacot found higher serum IgE levels in AIDS vs. non-AIDS patients (8). Israel-Biet demonstrated a significant increase of serum IgE with drop in CD4+ cell counts, and suggested that serum IgE could be a surrogate marker for HIV disease progression (4). HIV replication was shown to occur more in Th2 clones, leading to deterioration of disease in patients with Th2 predominance (14, 21).

Other authors suggest that elevated serum IgE in more advanced HIV disease may be protective against further progression, and may be directed against HIV itself (9, 10, 22). In many studies, a direct correlation between serum IgE and CD4+ cell counts was not found, but the highest serum IgE levels were detected among long-term HIV survivors with advanced disease (9, 22). In this study, we did not observe a correlation of serum IgE and CD4+ cell count and immunologic CDC classification. In contrast to previous studies, all of our patients were on HAART therapy, and fewer patients had symptomatic HIV infection. CD4+ cell counts give a better picture of the present disease status, but do not draw into account previous HIV-related changes in the immune system. The CDC classification for pediatric and adult HIV-infected patients is based on clinical symptoms, and reflects overall immune status of the HIV-infected patient over time (11). We found a significant correlation between clinical, but not immunologic CDC category and serum IgE level in non-atopic patients, suggesting that serum IgE is not exclusively allergy related in our cohort. In fact, with HIV disease progression, it seemed less likely that serum IgE was related to atopy. Based on similar observations in the past (2, 3), it was postulated that the elevation of serum IgE could be a consequence of polyclonal B-cell stimulation (8). In our study, there was no correlation between serum IgM, G, A and IgE, suggesting that serum IgE may also be independently elevated and not necessarily be a consequence of polyclonal B-cell stimulation. The elevated serum IgE may be directed against bacteria, parasites, viruses (including HIV) or fungi (23–26). Patients with opportunistic infections have been shown to have very elevated serum IgE levels, with the highest level in disseminated cytomegalovirus infection (3). However, other investigators found higher serum IgE in patients

with advanced HIV disease without opportunistic infections, suggesting that the serum IgE may be protective against the progression of HIV disease and opportunistic infections (9). Several studies have found serum IgE antibody directed against HIV itself (9, 10, 22, 27). *In vitro* studies have shown that IgE inhibits the replication of HIV virus in lymphocyte culture (10). The mechanism of inhibition is not clear, and may represent an alternative immune response in advanced HIV disease. It remains unknown what elements or conditions trigger the production of high levels of serum IgE in HIV-infected patients, and why it may be protective in some but not others.

This is the first study to reveal no increased prevalence of atopy in perinatally HIV-infected children compared with the general population. By comparing clinical disease stage (rather than CD4+ cell counts) with serum IgE levels and atopy, we have found that with disease progression, there is an increase of non-atopy-related IgE. This infers that IgE may be directed against opportunistic pathogens or HIV itself. It remains unclear if increased IgE reflects a protective mechanism, an altered immune response to HIV infection, or poor prognosis of HIV disease. The study is limited owing to the relatively small cohort of patients. Information obtained about clinical allergic symptoms (such as sinusitis and cough) may not actually be of allergic origin, but may stem from infections. With a retrospective approach, such as chart review, the difference may be difficult to determine. Further evaluation of the antigen driving the generation of IgE in advanced HIV is warranted.

Acknowledgments

We thank Dr. J. Weedon for statistical help and Andrew D. Bowser for editorial support.

References

1. WRIGHT DN, NELSON RP, LEDFORD DK, FERNANDEZ-CALDAS E, TRUDEAU WL, LOCKEY RF. Serum IgE and human immunodeficiency virus (HIV) infection. *J Allergy Clin Immunol* 1990; 85: 445–52.
2. BACOT BK, PAUL ME, NAVARRO M, et al. Objective measures of allergic disease in children with human immunodeficiency virus infection. *J Allergy Clin Immunol* 1997; 100: 707–11.
3. ELLAURIE M, RUBINSTEIN A, ROSENSTREICH DL. IgE levels in pediatric HIV-1 infection. *Ann Allergy Asthma Immunol* 1995; 75: 332–6.
4. ISRAEL-BIET D, LABROUSSE F, TOURANI J, SORS H, ANDRIEU JM, EVEN P. Elevation of IgE in HIV infected subjects: a marker of poor prognosis. *J Allergy Clin Immunol* 1992; 89: 68–75.
5. GARCIA-RODRIGUEZ JF, COROMINAS M, FERNANDEZ-VILADRICH P, MONFORT JL, DICENTA M. Rhinosinusitis and atopy in patients infected with HIV. *Laryngoscope* 1999; 109: 939–44.
6. MORENO-ANCILLO A, LOPEZ-SERRANO MC. Hypersensitivity reactions to drugs in HIV-infected patients. Allergic evaluation and desensitization. *Clin Exp Allergy Suppl* 1997; 4: 57–60.
7. MARSHALL GD. AIDS, HIV-positive patients, and allergies. *Allergy Asthma Proc* 1999; 20: 301–4.
8. KOUTSONIKOLIS A, NELSON RP, FERNANDEZ-CALDAS E, et al. Serum total and specific IgE levels in children infected with human immunodeficiency virus. *J Allergy Clin Immunol* 1996; 97: 692–7.
9. SECORD EA, KLEINER GI, AUCI DL, et al. IgE against HIV proteins in clinically healthy children with HIV disease. *J Allergy Clin Immunol* 1996; 98: 979–84.
10. PELLEGRINO MG, BLUTH MH, SMITH-NOROWITZ T, et al. HIV type 1-specific IgE in serum of long-term surviving children inhibits HIV type 1 production *in vitro*. *AIDS Res Human Retroviruses* 2002; 18: 363–72.
11. National Center for Infectious Diseases Division of HIV/AIDS, CASTRO KG, WARD JW, et al. 1993. Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS among adolescents and adults. Available from: <http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm>
12. ARBES S, GERGEN PJ, ELLIOTT L, ZELDIN DC. Prevalences of positive skin test responses to 10 common allergens in the US population. Results from the Third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 2005; 116: 377–83.
13. ACKERMAN M, VALENTINE-MAHER S, RAO M, et al. Allergen sensitivity and asthma severity at an Inner City Asthma Center. *J Asthma* 2003; 40: 55–62.
14. COROMINAS M, GARCIA JF, MESTRE M, FERNANDEZ-VILADRICH P, BUENDIA E. Predictors of atopy in HIV-infected patients. *Ann Allergy Asthma Immunol* 2000; 84: 607–11.
15. HAGY GW, SETTIPANE GA. The frequency of allergy and positive skin tests among college students. *J Allergy* 1966; 37: 107–8.
16. GREENBERG M, MILNE JF, WATT A. A survey of workers exposed to dust containing *Bacillus subtilis*. *Br Medical J* 1970; 2: 629–33.
17. BARBEE RA, LEBOWITZ MD, THOMPSON HC, BURROWS B. Immediate skin-test reactivity in a general population sample. *Ann Intern Med* 1976; 84: 129–33.
18. CAMPOS A, ALAMAR R, CASTELLO JV, ENGUIDANOS M. The Projecte ORBA: 1983–1993. Changes in the prevalence of asthma, rhinitis, urticaria and drug allergy in Valencia. *Allergol Immunol Clin* 2002; 17: 151–8.
19. PEARCE N, DOUWES J, BEASLY R. The rise and rise of asthma: a new paradigm for the new millennium? *J Epidemiol Biostat* 2000; 5: 5–16.
20. VON MUTIUS E. The rising trends in asthma and allergic disease. *Clin Exp Allergy* 1998; 28: 45–9, discussion 50–1.
21. MAGGI E, MAZZETTI M, RAVINA A, et al. Ability of HIV to promote a Th1 to Th0 shift and to replicate preferentially in Th2 and Th0 cells. *Science* 1994; 265: 244–8.
22. SEROOGY CM, WARA DW, BLUTH MH, DORENBAUM A, WHITE C, DURKIN HG, ELDER ME. Cytokine profile of a long-term pediatric HIV survivor with hyper-IgE syndrome and a normal CD4 T-cell count. *J Allergy Clin Immunol* 1999; 104: 1045–51.
23. PEDERSEN M, PERMIN H, JENSEN C, STAHL SKOV P, NORN S, FABER V. Histamine release from basophil

- leukocytes induced by microbial antigen preparations in patients with AIDS. *Allergy* 1987; 42: 291.
24. PEDERSEN M, NIELSEN PB, PERMIN H, et al. Type I reactions directed against *Pneumocystis carinii* in AIDS patients. *APMIS* 1089; 97: 120.
 25. MAGGI E, MAZZETTI M, RAVINA A, et al. Increased production of IgE protein and IgE antibodies specific for fungal antigens in patients with the acquired immunodeficiency syndrome. *RIC Clin Lab* 1989; 19: 45.
 26. WEBER B, BRAUN W, TYRALLA B, DOERR HW. Human cytomegalovirus (HCMV)-specific immunoglobulin E as a serologic marker for HCMV infection in immunocompromised patients. *Clin Invest* 1992; 70: 497.
 27. PEDERSEN M, NIELSEN C, PERMIN H, NORN S. HIV antigen stimulates basophil leucocytes from AIDS patients to release histamine due to type I allergy. *Agents Actions* 1989; 27: 55.