

Predictors of atopy in HIV-infected patients

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Background: Some studies have reported an increase of atopy in HIV-infected (HIV+) patients, but the cause still remains unclear.

Objective: To determine the prevalence of atopy in HIV+ patients and to investigate its predictors.

Methods: Seventy-four HIV+ hospitalized patients (46 of them with AIDS) were studied prospectively for the presence of atopy, based on immediate hypersensitivity to common allergens by prick test. Serum immunoglobulins, specific IgE, lymphocyte subsets, and the expression of low affinity IgE receptor (CD23) on B cells were determined.

Results: Thirty-one percent of patients presented IgE values greater than 150 ku/L (39% of patients without AIDS and 26% of AIDS patients; $P = .23$) and 47% showed an increase ($\geq 2\%$) in the percentage of CD23+ B cells. Non-AIDS patients had higher IgE values than AIDS patients (346 ± 605 versus 175 ± 276 ; $P = .16$). Atopy prevalence was higher in non-AIDS than in AIDS patients (28% versus 11%; $P = .06$). Specific IgE agreed with positive prick test in 58% of cases. Multivariate analysis showed that a personal history suggestive of allergic disease and IgE > 150 ku/L were predictors of atopy, while gender, risk group, CD4+ T cells, CD23 expression on B cells, and AIDS were not associated.

Conclusions: HIV+ patients present a higher prevalence of atopy in early stages of HIV infection than general population. Since allergic reactions could accelerate HIV-infection by increasing type 2 cytokines, it is important to evaluate the atopic state in HIV+ patients with IgE > 150 ku/L or with suggestive allergic history in order to prevent it.

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INTRODUCTION

HIV-infected (HIV+) patients present immunologic alterations characterized by cellular immunodeficiency (as a consequence mainly of CD4+ T cell depletion) and polyclonal B cell activation.¹ This immunologic impairment is presented at clinical level mainly by opportunistic infections and neoplasms.

Polyclonal activation of B cells results in increased concentrations of serum immunoglobulins, mainly IgG and IgA.^{2,3} Elevated IgE levels and allergic diseases associated with HIV-infection have been reported in different studies,

sometimes with discrepancies in relation to the prognostic value of IgE in the evolution of AIDS^{4–6} and in the role that IgE plays in the development of allergic diseases.^{7–9}

An imbalance in the immunoregulatory cytokine network has been reported in HIV+ subjects in progression to AIDS, characterized by a decrease in type 1 cytokines (IL-2 and IFN- γ) and an increase in type 2 cytokines (IL-4 and IL-13).^{10,11} This alteration could explain the increase in IgE levels observed in some of these patients. Furthermore, type 2 cytokines also up-regulated the expression of the low affinity IgE receptor (Fc ϵ R/CD23), which can contribute together with high IgE levels to the development of an allergic response.

The purpose of this study was to assess whether the immunologic dysregulation presented by HIV+ subjects

influences on IgE production and induces an atopic state that leads to an increase in the prevalence of atopy. Another goal of the study was to evaluate which factors were predictors of atopy in these patients.

PATIENTS, MATERIAL AND METHODS

Patients

A cross-sectional study was performed with 74 HIV+ patients hospitalized at the Infectious Diseases Service. HIV-infection had been confirmed by the presence of HIV antibody determined by ELISA and Western blot methods. All patients were at least 18 years old and an informed consent was obtained in order to participate in the study. Treatment with antihistamines, corticoids, or inhibitors of mediator release was stopped for at least 72 hours before the tests were done. The presence of parasitic infection excluded the patient from the study.

A medical history was taken with emphasis on the HIV-infection process and on individual and family symptoms suggestive of allergic diseases presented before or after HIV diagnosis. A complete physical examination was performed.

Skin Tests

Skin tests were done by prick method to 20 common environmental allergens (various grass, tree and weed pollens, molds, dust mites, cockroach, cat, and dog dander) and other allergens to which clinical history suggested hypersensitivity (CBF-LETI, Barcelona, Spain). Histamine (1%) and glycerine physiologic solutions were used as positive and negative control respectively. Prick test was considered positive if ratio between the diameter of the allergen wheal and the diameter of the histamine wheal was greater than 0.5, in absence of wheal in negative control.

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Laboratory Tests

A blood sample was obtained in order to evaluate the following four parameters.

- Differential blood cell count.
- Total serum immunoglobulins (IgG, IgA, and IgM) and IgG subclasses. Concentrations were measured by immunonephelometric methods (Behring Diagnostic, Marburg, Germany).
- Total and specific IgE were determined by CAP-System (Pharmacia, Uppsala, Sweden). Total IgE was measured in all patients, whereas specific IgE was determined only in patients with positive prick test. According to the values obtained in nonatopic HIV-negative population, levels of IgE > 150 ku/L and specific IgE > 0.70 ku/L were considered elevated.
- Lymphocyte subsets were analyzed with double immunofluorescent method by flow cytometry (FacScan device Becton-Dickinson, Mountain View, USA), using conjugated FITC or PE-monoclonal antibodies: Leu-3a (CD4+ T cells), Leu-2a (CD8+ T cells), Leu-16 (CD20+ B cells). The expression of low-affinity IgE receptor on B cells was analyzed in the same way, using monoclonal antibody Leu-20 (anti-CD23) in 60 patients, calculating the percentage of CD23+ B cells (CD20+CD23+ cells).

Definitions

AIDS. AIDS was defined according to 1993-Europe definition.¹² The presence of AIDS-defining diseases presented previously or during hospitalization was considered.

Atopy. Patients with positive prick test were considered atopic.

Statistical Analysis

Data were analyzed by means of statistical package SPSS (Chicago, IL). Chi-square test with Yates' correction was performed to compare qualitative variables. Non-parametric tests were used to compare quantitative data and Pearson correlation to assess the significance of association between variables. Multivariate analysis (logistic regression with stepwise procedure) was performed with Egret program (Seattle, Washington) in order to evaluate which factors were predictors for atopy. The following variables were included: gender, risk group, individual history suggestive of allergic disease, CD4+ T cells, CD23 expression on B cells, AIDS diagnosis, and IgE values. Odds ratio (OR) and 95% confidence interval (CI) were calculated. Results were expressed as the mean $\pm$ standard deviation of the mean.

RESULTS

Among 74 HIV+ patients studied, 46 had AIDS. By risk group, 53% of patients were intravenous drug users

(IVDU), 19% heterosexuals, 15% IVDU and homosexuals, 9% were homosexuals and in 4% transmission mechanism was unknown. Characteristics of both groups AIDS and non-AIDS HIV+ patients are shown in Table 1.

According to normal laboratory values, concentrations of IgG (>1800 mg/dL), IgM (>150 mg/dL), and IgA (>450 mg/dL), were elevated in 70%, 62%, and 47% of the patients, respectively. High IgG values were due mainly to an increase in IgG1, and IgG3 subclasses. We did not observe statistically significant differences in these values between AIDS and non-AIDS HIV+ patients except for IgA which was higher in AIDS patients than in non-AIDS patients ($P = .004$). These results are shown in Table 2.

Forty-seven percent of patients presented higher percentage of CD23+ B cells than observed in normal non-atopic population (normal values $\leq 2\%$).¹³

In non-AIDS patients, we observed a negative correlation between IgA levels and the percentage and total number of CD4+ T cells ($r = 0.4894$; $P = .008$; $r = 0.4357$; $P = .02$ respectively) and a positive correlation with the percentage of CD8+ T cells ($r = 0.4074$; $P = .031$). In the group of AIDS patients IgG and IgM showed positive correlation with the percentage and total number of CD8+ T cells (IgG: $r = 0.3188$; $P = .031$ and $r = 0.5236$; $P = .001$ respectively; IgM: $r = 0.3095$; $P = .036$; $r = 0.4256$; $P = .003$, respectively) and age correlated positively with the percentage and total number of eosinophils ($r = 0.3320$; $P = .024$; $r = 0.3617$; $P = .014$, respectively).

Fifteen of the 74 HIV-infected patients (20%) gave a personal history suggestive of allergic disease. Nine of them related respiratory symptoms (rhinoconjunctivitis in eight patients and asthma in one patient) and six patients, skin alterations (urticaria and dermatitis). In four patients the symptoms had started after HIV+ diagnosis. Only in one patient an allergologic study by means of prick test had been

Table 1. Characteristics of HIV Positive Patients According to AIDS Diagnosis

	No AIDS (N = 28)	AIDS (N = 46)	P Value
Gender			
Male	25	33	.07
Female	3	13	
Age (yr)	28 $\pm$ 6	35 $\pm$ 8	<.0001
CD4+ T cells			
Total	273 $\pm$ 258	83 $\pm$ 108	.0003
Percentage	17.7 $\pm$ 11.1	9.3 $\pm$ 10.1	.0019
CD8+ T cells			
Total	817 $\pm$ 592	555 $\pm$ 399	.026
Percentage	61.4 $\pm$ 13.4	63.3 $\pm$ 16.4	NS
CD20+ B cells			
Total	89 $\pm$ 75	64 $\pm$ 47	NS
Percentage	7.7 $\pm$ 4.1	10.4 $\pm$ 9.8	NS

NS = not significance.

Table 2. Immunologic Parameters in HIV-Infected Patients According to AIDS Diagnosis

	No AIDS (N = 28)	AIDS (N = 46)	P Value
IgG (mg/dL)	2312 ± 738	2220 ± 868	NS*
IgG1 (mg/dL)	1167 ± 429	1132 ± 528	NS
IgG2 (mg/dL)	343 ± 161	371 ± 206	NS
IgG3 (mg/dL)	157 ± 100	141 ± 64	NS
IgG4 (mg/dL)	33 ± 33	35 ± 29	NS
IgA (mg/dL)	359 ± 253	581 ± 346	.004
IgM (mg/dL)	374 ± 229	332 ± 201	NS
IgE (ku/L)	346 ± 605	175 ± 275	NS
%CD20+ CD23+ cells	3.4 ± 2.8	5.1 ± 6.6	NS

* NS = not significance.

performed previously with a positive result. This test was also positive in the present study.

Prick test was carried out in 73 patients, due to the refusal of one patient to continue the study. Thirteen patients (18%) showed positive prick tests. According to AIDS diagnosis, eight patients without AIDS (28%) and five patients with AIDS (11%) were atopic ($P = .06$). Nine patients were mono-sensitized (four patients showed hypersensitivity to dust mites, three patients to pollen, and two patients to molds) and four patients were polysensitized (two patients to dust mites and molds; one patient to dust mites, molds and pollen; and one patient to dust mites, pollen, and dander). We did not observe statistical differences in the diameter of the histamine-produced wheal between atopic and nonatopic patients or in patients without or with AIDS.

Among the fifteen patients with individual history suggestive of allergic disease, six showed positive prick test (40%), while seven patients with positive prick test did not clearly relate previous or actual allergic disease. There was a statistical significance between diagnosis of atopy and the personal history of possible allergy ($P = .03$). There was no relation between positive prick test and the presence of disease of possible allergic etiology after HIV infection.

Comparison of parameter values between atopic and nonatopic HIV+ patients are showed in Table 3. We did not observe statistical differences except for IgE.

Thirty-one percent of HIV+ patients had IgE values greater than 150 ku/L (39% of patients without AIDS and 26% of patients with AIDS). Patient distribution according to IgE values were as follows: 51 patients (69%) had IgE values lower than 150 ku/L, 13 patients (18%) between 150 to 500 ku/L, 6 patients (8%) showed IgE levels between 501 to 1000 ku/L and 4 patients (5%) between 1001 to 2175 ku/L. AIDS patients had lower IgE values (175 ± 276 ku/L) than non-AIDS patients (346 ± 605 ku/L) but without statistical significance ($P = .167$).

We did not find any relation between IgE levels and AIDS or CD4+ T cells count.

Atopy was more frequent in patients with IgE values higher than 150 ku/L ($P = .003$). There was no relation between atopy and CD4+ T cell count

higher or lower than 200 ($P = .5$). The frequency of atopic patients according CD4 values were as follows: CD4 < 50, 12.5% (4/32); CD4 50 to 100, 16.6% (2/12); CD4 101 to 300, 17.6% (3/17); and CD4 > 300, 30.7% (4/13). Specific IgE showed concordance with positive prick test in 58% of cases.

In the AIDS group, IgE levels showed positive correlation with the percentage and total number of eosinophils ($r = 0.6595$; $P = .0001$ and $r = 0.6978$; $P = .0001$, respectively), IgA values ($r = 0.3569$; $P = .015$), and percentage of CD20+ CD23+ cells ($r = 0.3569$; $P = .013$).

Multivariate analysis showed that the predictor factors for atopy were a personal history suggestive of allergic diseases and IgE levels higher than 150 ku/L, while gender, risk group, CD4+ T cells, CD23 expression on B cells and AIDS had no influence (Table 4).

DISCUSSION

In our study, 31% of HIV+ patients showed high IgE levels (>150 ku/L) but contrary to other reports^{4,5,9,14,15} they were not related with more advanced stages of AIDS. Thus AIDS patients showed even lower IgE values than non-AIDS patients. In this sense, four patients of the study had IgE values greater than 1000 ku/L, but only one of them presented AIDS diagnosis (he suffered a *Pneumocystis carinii* pneumonia). According to recent re-

Table 3. Patients Characteristics According to Diagnosis of Atopy

	No atopy (N = 60)	Atopy (N = 13)	P Value
Gender			
Male	45	12	NS*
Female	15	1	
Age (yr)	33 ± 8	31 ± 8	NS
CD4+ T cells			
Total	136 ± 176	245 ± 284	NS
Percentage	11.7 ± 11	16.2 ± 11.5	NS
CD8+ T cells			
Total	623 ± 449	801 ± 671	NS
Percentage	62.7 ± 15.2	61.9 ± 15.9	NS
CD20+ B cells			
Total	72 ± 60	79 ± 64	NS
Percentage	10.1 ± 8.8	6.5 ± 4.1	NS
IgE (ku/L)	206 ± 419	399 ± 490	.047
CD23+ B cells: percentage	4.9 ± 5.9	2.8 ± 2.5	NS

* NS = not significance.

sults reported in HIV-infected children, we have not observed in adult patients a correlation between high IgE levels and decreased CD4 cells count.¹⁶

As a consequence of immunologic alterations, HIV+ patients show high immunoglobulin levels^{2,4} and some studies have reported an association between high IgA levels and the progression of infection.^{3,4} The patients studied presented hypergammaglobulinemia, but only IgA levels were more elevated in AIDS patients than in non-AIDS patients. This, as well as the results obtained in correlation analysis, suggest that there are similar regulatory mechanisms for IgG and IgM synthesis, but different for IgA and for IgE.

In our study HIV+ patients showed an increase of CD23 expression on B cells. The low affinity IgE receptor or CD23 regulates IgE response acting as T-B cell adhesion molecule¹⁷ and improving antigen presentation to T cells.¹⁸ CD23 expression on lymphocytes is induced by type 2 cytokines, which also induce IgE synthesis. The results obtained suggest that in the course of HIV infection there is a type 2 cytokines predominance, in agreement with the hypothesis of Clerici et al.¹⁰ However according to our results this predominance would not be closely related with the progression of the disease, since AIDS patients did not show higher IgE levels and higher percentage of CD23+ B cells than HIV+ patients without AIDS. This could be explained by the fact that HIV is replicated preferentially in TH2 clones which decrease in advanced stages of infection.¹⁹

The high IgE levels and the increase in the percentage of CD23+ B cells that present in these patients, could favor the development of allergy. The increase of allergic diseases in HIV+ patients has been reported in some studies but with contradictory results due to different criteria used in the diagnosis.^{4,5,7,20} In some of them, the prevalence of atopy is based in high levels of specific IgE^{5,7,21} while in others, the diagnosis is based in the pres-

Table 4. Predictive Factors of Atopy in HIV-Infected Patients

Variable	P Value	Odds-Ratio	95% Confidence Interval
Allergy antecedents	.04	4.2	1.01–17.40
IgE > 150 ku/L	.006	6.8	1.73–26.69

Not associated with gender, risk group, CD4+ T cells, CD23 expression on B cells and/or AIDS diagnosis.

ence of suggestive symptoms of allergic diseases.^{4,7,9} Other studies, besides IgE increase, do not observe a rise in atopic diseases.^{5,8,9,14,21}

These discrepancies could be explained because many HIV+ patients show in the course of infection, rhinosinusal symptoms, which can suggest an IgE-mediated disease. On the other hand the severe infections that present in these patients can mask an allergic disease (we found patients with positive prick test who did not relate allergic symptoms).

Our results show that HIV+ patients (with or without AIDS diagnosis) presented a higher prevalence of atopy than general population from a similar geographic area²² (18% versus 8%; $P = .001$). This prevalence is higher in the early stages of HIV-infection (HIV-infected patients without AIDS presented a prevalence of 28% versus 8% of general population; $P < .001$) than in patients with AIDS diagnosis (with a prevalence of 11%). In this sense, Goetz et al also reported that aeroallergen-specific IgE expression becomes less prevalent with HIV progression.²³

It is possible that the immunologic dysregulation induces in the early stages of HIV-infection, in patients with an atopic genetic background, an increase in allergic diseases. But this prevalence could decrease with the progression of infection, since certain immunocapacity would be necessary to respond to allergens and to develop an allergic reaction. This hypothesis would be corroborated by the discrepancy in these patients between the positive prick test and positive specific IgE (possibly because serum IgE has a shorter life than IgE bound to mast cells) and by the fact that the frequency of atopy is lower in patients with low

number of CD4+ T cells. These data agree with the results of Rancinan et al²⁴ which showed that HIV+ patients with CD4+ T cells number lower than 50 present lower frequency of allergic diseases than patients with a high number of CD4+ T cells.

We were not able to show a clear relation between atopy and CD4+ T cells number, but we observed a lower prevalence of atopy in AIDS patients than in non-AIDS patients. This would indicate that the functional capacity of the immunologic system to respond to allergen is more significant than the CD4+ T cells number.

Other hypothesis, based in works that show that HIV replication happens in cell clones with a pattern of type 2 cytokines,¹⁹ is that allergic patients (with a type 2 cytokines predominance) would be more inclined to the progression of HIV infection. This could also explain the increase of prevalence of atopy in early stages of symptomatic HIV infection.

According to the results obtained, we consider it important to evaluate the atopic state in early stages of HIV-infection in patients with IgE > 150 ku/L or with possible allergic history in order to prevent the development of allergic reactions which could accelerate the evolution of HIV-infection.

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