

## Laboratorial atopy markers in children with human immunodeficiency virus

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*Changes in immune system functions are one of the most important consequences of human immunodeficiency virus (HIV) infection. Studies have reported a higher prevalence of disease mediated by immunological hypersensitivity mechanisms in HIV-positive patients. This study aims to observe how immunological changes in HIV-infected children interfere in atopy determinants. Fifty-seven HIV-positive children were studied between June 2004-August 2005 to evaluate the possible modifications in atopy diagnosis from prick test environmental allergen reactivity. Patients were subjected to two evaluations: on both occasions, atopic and non-atopic groups were correlated with immunological (CD4<sup>+</sup> and CD8<sup>+</sup> lymphocyte concentrations and serum levels of IgA, IgM, IgG and IgE) and viral parameters (HIV viral load). The percent atopy was 20.05 in the first and 29.82 in the second evaluation and atopy was diagnosed in patients without immunosuppression or with moderate immunosuppression. Six patients changed from a negative to a positive atopy profile. One patient with a decreased CD4<sup>+</sup> T lymphocyte concentration failed to demonstrate prick test positivity between evaluations. Multivariate analysis showed that the variables associated with atopy diagnosis included a personal history of allergic diseases as well as elevated IgE for age and elevated IgE levels. Atopy development in HIV-infected children seems to be modulated by genetic and environmental factors as well as immunological condition.*

Key words: HIV - child - immunoglobulin E - allergy

Beginning in the 1980s, with the first descriptions of AIDS and the later identification of the human immunodeficiency virus (HIV) as the causal agent, knowledge of immunological alterations that occur in the disease's evolution has been improving constantly.

HIV-infected patients present complex immunological alterations due to CD4<sup>+</sup> T lymphocyte depletion and changes in the function of different immune effectors cells, such as polyclonal B cell activation and the consequent increase in immunoglobulin production (Rosenberg & Fauci 1988). These immunological alterations are represented clinically by recurring bacterial infections, opportunistic infections and neoplasias (Luzuriaga & Sullivan 2000, Starr 2003).

However, other factors have been identified in the disease's physiopathology such as an imbalance in cytokine immunoregulation, characterized by a reduction in Type 1 and an increase in Type 2 cytokines (Romagnani & Maggi 1994, Clerici et al. 1997).

Different studies have suggested a possible increase in the prevalence of allergic diseases, such as IgE-mediated Type 1 hypersensitivity, in these patients who, paradoxically, have been evolving toward immunosuppression (Lin & Lazarus 1995, Corominas et al. 2000). Recently, this contradictory effect has been attributed to functional

and quantitative alterations in regulatory T cells (Kinter et al. 2004, Eggena et al. 2005). These observations suggest that immunological alterations secondary to HIV infection alter the normal allergy control mechanisms, thus permitting an increase in the clinical expression of allergic diseases (Bacot et al. 1997).

However, the epidemiology and clinical and laboratory manifestations of atopy have been monitored preferentially in transverse studies in the adult infected population (Sample et al. 1990, Small et al. 1993, Corominas et al. 2000). This study was developed to evaluate prospectively whether immunological alterations and their evolution during the course of HIV infection in children influence the development and prevalence of atopic diseases.

### PATIENTS, MATERIALS AND METHODS

*Study design* - This was a longitudinal, prospective and descriptive study performed between June 2004-August 2005 involving children with confirmed HIV infection followed in outpatient clinics at a tertiary reference hospital. HIV infection was defined according to Centers for Disease Control and Prevention (CDC 1994). Children between 1-13 years old were included randomly. This group was followed regularly in the ambulatory care clinic and their parents or legal guardians had consented. Exclusion criteria were applied for those children who used drugs that could interfere in laboratory exam results, such as corticosteroids, anti-histamines and hyperimmune gamaglobulin.

A total of 68 patients was initially included in the study. All underwent clinical evaluation, complementary laboratory exams and the prick test. Demographic and medi-

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cal history data were collected from medical records with emphasis on personal history suggestive of allergic diseases. Patients were evaluated twice between 6-12 months, with a mean of 10 months. Of the original 68 patients participating in the first evaluation, 57 were selected for the second. Eleven patients did not undergo the second evaluation; the reasons for this were that 10 did not attend the routine consultation on the planned date or did not provide samples for the laboratory exams. In the other case, the second prick test was not authorized by the parents.

**Laboratory exams** - The following laboratory exams were performed at both evaluations: CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocyte concentrations (μL) by flow cytometry, HIV viral load (number of viral copies) by RT-PCR, serum levels of IgA, IgM and IgG by nephelometry, serum levels of immunoglobulin E by radioimmunoassay and complete hemogram. IgE, IgG, IgM and IgA levels were evaluated using reference tables related to age group (Adelman et al. 2002, Adkinson et al. 2003).

Patient immunodeficiency levels were based upon CD4<sup>+</sup> T lymphocyte counts from each evaluation using the immunological classification table adopted by the CDC (1994).

Prick tests were performed with environmental allergens (domestic dust, grasses, mites, fungi, cat hair and cockroaches), 10 mg/mL histamine as a positive control and 0.9% saline solution as a negative control. All extracts and positive controls were obtained from IPI ASAC BRASIL<sup>®</sup>. Patients were advised not to use anti-histamines for seven days prior to the prick test.

The prick test was considered positive when the presence of papules with a mean orthogonal diameter of ≥3 mm was observed. Patients were then classified as either atopic (patients with a positive prick test to one or more of the tested allergens) or non-atopic (patients displaying negative results to all extracts).

**Statistical analysis** - The data were analyzed using JMP 5.1<sup>®</sup> statistics software. The Student's *t* test and the Mann-Whitney, Wilcoxon and Kruskal-Wallis non-parametric tests were used to compare continuous variables between groups. The chi-squared and Fisher exact tests were used for two or more nominal variables. Logistic regression with the stepwise forward procedure was performed to identify variables associated with a diagnosis of atopy and included factors such as personal history of allergic disease, CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocyte counts, viral load, IgE, IgG, IgM and IgA levels, their classification as normal or elevated for age group and absolute count and percentage of eosinophils. The minimum significance level was set at 5%.

**Ethics** - This study was approved by our institution's Human Research Ethical Committee.

## RESULTS

The average ages varied between 1.30-13.34 years with a mean of  $7.36 \pm 3.33$  years from the initial sample. Females predominated (63.16%; 36 patients). The median time from HIV infection diagnosis was 4.27 years, varying from 0.49-11.32 years. All patients acquired HIV infection by vertical transmission.

Median serum immunoglobulin values were 91.20 UI/mL for IgE, 1640 mg/dL for IgG, 134.50 mg/dL for IgM and 178 mg/dL for IgA. According to age reference tables, concentrations of IgE, IgG, IgM and IgA were elevated in 24 (42.10%), 17 (30.35%), 37 (66.07%) and 20 (35.71%) patients, respectively.

Prick test results at first evaluation showed 12 (21.05%) patients as being atopic. Of those 12 children, seven reacted to only one extract, two to two extracts, one to three extracts, one to four extracts and one to five of the six allergen extracts tested. Immediate hypersensitivity was mainly to mite and domestic dust extracts.

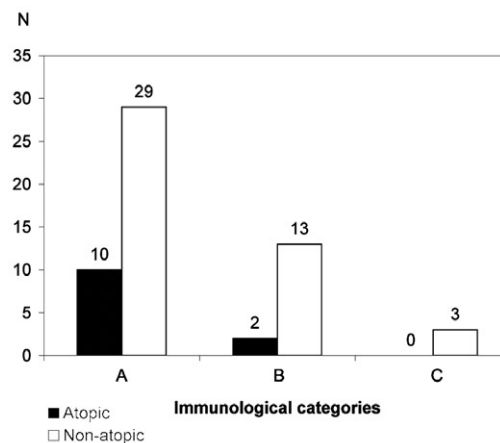
Comparing atopic and non-atopic group patients, personal histories of allergic diseases showed that six (50%) of the 12 atopic group children had reported at least one atopic symptom of some kind. In the non-atopic group, 42 (93.33%) denied having clinical symptoms ( $p = 0.0015$ ).

Atopic patients had a median IgE of 237.5 UI/mL, which was higher than non-atopic patients (78.2 UI/mL,  $p = 0.0328$ ). Medians of IgA, IgM and IgG were similar between groups (Table I).

Comparing the two groups for elevated immunoglobulin levels for their age group, we observed that 75% of atopic patients and 33.33% of non-atopic patients were considered to have elevated levels ( $p = 0.0187$ ). The proportion of patients with elevated IgG, IgM and IgA levels were similar between groups.

Absolute count and percentages of eosinophils were similar between groups, with a median of 138.30 cells/μL and 1.5% for atopic as compared with 204 cells/μL and 3% for non-atopic patients ( $p = 0.4448$  and  $p = 0.4470$ , respectively) (Table I). There was no difference between groups for CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocyte counts and viral load (Table I).

Regarding CD4<sup>+</sup> T lymphocyte counts from the first evaluation, 10 of the 12 HIV-positive atopic patients did not have immunosuppression and two patients had moderate immunosuppression (Figure).



Immunological classification of atopic and non-atopic groups according to CD4<sup>+</sup>T lymphocyte count at first evaluation.  $n = 57$ ;  $p = 0.2883$ ; A: absence of immunosuppression; B: moderate immunosuppression; C: strong immunosuppression.

TABLE I  
Comparison between atopic and non-atopic groups for IgE, IgG, IgM and IgA levels, CD4<sup>+</sup>, CD8<sup>+</sup> T lymphocyte counts and viral load at first and second evaluations

Count (median)	First evaluation			Second evaluation		
	Atopic	Non-atopic	p value	Atopic	Non-atopic	p value
IgE (UI/mL)	237.50	78.20	0.0328	410	59.05	0.0002
IgG (mg/dL)	1465	1660	0.3327	1775	1630	0.7953
IgM (mg/dL)	123.50	138.50	0.2550	124.50	130	0.5974
IgA (mg/dL)	191	173.50	0.8967	180.50	160	0.4418
Eosinophils (cell/ $\mu$ L)	138.30	204	0.4448	517	215.40	0.0037
CD4 <sup>+</sup> (cell/ $\mu$ L)	991	750	0.6526	870	801	0.2188
CD8 <sup>+</sup> (cell/ $\mu$ L)	1063	1286	0.1128	1198	1280	0.7272
Viral load (copies/mL)	1430	6340	0.1202	12000	23550	0.4732
Viral load (log)	3.15	3.80	0.1202	4.07	4.36	0.4732

Logistic regression analysis showed factors associated with atopic diagnosis at first evaluation. These factors were personal history of allergic diseases ( $p = 0.0003$ ) and proportion of patients considered to have elevated IgE levels for their age ( $p = 0.0111$ ).

In the second phase of the study, the prick test showed a change in atopy profile. Seventeen (29.82%) of the 57 children were diagnosed as atopic. From the 45 non-atopic patients from the first evaluation, six had at least one positive prick test and were considered atopic in the second assessment. Of the 12 atopic patients identified at the first evaluation, one presented a negative prick test at the second evaluation, having therefore become non-atopic.

In the group of six patients whose prick test profile changed from negative to positive, at the first examination the mean age was 7.41 years, SD = 2.58 years varying between 4.4-11.06 years. In the second evaluation, the average was 8.15 years with a SD of 2.7, varying between 5.2-12 years.

CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocyte levels and viral load were similar in both groups at the second evaluation. Atopic patients had higher IgE levels than non-atopic ( $p = 0.002$ ) patients, as well as proportion of patients with elevated IgE for their age ( $p < 0.001$ ). In contrast with the first evaluation, the second revealed a higher percentage and absolute eosinophil counts in atopic (medians of 5.50% and 517 cells/ $\mu$ L) than in non-atopic patients (medians of 3% and 215.40 cells/ $\mu$ L). The atopic group and the non-atopic group showed a significance of  $p = 0.0278$  and  $p = 0.0037$ , respectively (Table I).

Factors associated with a diagnosis of atopy in the second evaluation by logistic regression analysis included a personal history of allergic diseases ( $p = 0.0034$ ), IgE serum levels ( $p = 0.0436$ ) and the proportion of patients with elevated IgE for their age ( $p = 0.0085$ ).

Table II shows the evolution of 18 patients with a positive prick test in some phase of the study. Factors such as CDC immunological classification according to CD4<sup>+</sup> T lymphocyte counts, IgE levels and eosinophil levels were found at both phases.

Seventeen patients maintained their immunological status in the second evaluation. Only one patient, who showed worsening immune responses from the first-second evaluation in accordance with the CDC classification, changed the profile from atopic to non-atopic. Six patients whose prick tests changed from negative to positive between evaluations had no immunological alterations (Table II). Any changes that were seen were observable in the specificity response to cutaneous extracts between the analysis phases. The unique exception was the number of patients that recognized the extracts. The mean orthogonal papule diameter was different in patients who were negative at evaluation one and positive at evaluation two for mite mix and domestic dust extracts ( $p = 0.049$  and  $p = 0.006$ , respectively).

At first evaluation, the six patients had higher mean IgE levels than the patients with negative prick tests, with measure results of 322 UI/mL and 69 UI/mL, respectively ( $p = 0.0886$ ).

## DISCUSSION

Studies using different methodologies suggest a higher prevalence of atopy in HIV-infected patients. However, most of these studies are focused on adults with only one diagnostic test and a single evaluation. Some have considered personal history of allergic diseases as a diagnosis (Wright et al. 1990, Ellaurie et al. 1995, Lin & Lazarus 1995, Secord et al. 1996), whereas others have used laboratory techniques, such as the prick test, or studied specific IgE for environmental allergens (Nissen et al. 1999, Corominas et al. 2000). This study was based on a group of infected children using environmental allergen prick test results as the criterion for defining the presence or absence of atopy. We demonstrated that allergic reaction against these environmental allergens could change. Prospective analysis of the results suggests that immune alterations due to the evolution of HIV infection in children interfere with the development and prevalence of atopic diseases.

The frequency of a positive prick test in the study population was 21% at the first evaluation and 30% at

TABLE II  
Laboratory characteristics of the 18 patients presenting at least one positive Prick test (atopic) at some time in the study

Patient code	Atopic		Immunosuppression grade		IgE		IgE for age group		Eosinophils (%)	
	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
3	+	+	1	1	> 2000	1786	E	E	0	15
12	-	+	1	1	> 2000	> 2000	E	E	3	2
16	+	+	1	1	1173	1234	E	E	9	-
17	-	+	1	1	25,6	14,4	N	N	1	2
19	+	+	1	1	162	310	E	E	3	14
20	+	+	1	1	215	822	E	E	5	5
22	+	+	1	1	27	110	N	E	1	5
27	-	+	1	1	535	254	E	E	7	7
29	+	+	2	2	466	334	E	E	0	4
31	-	+	1	1	89	410	N	E	2	4
37	+	+	1	1	1007	991	E	E	1	8
38	+	+	1	1	260	220	E	E	1	2
58	+	+	1	1	> 2000	1240	E	E	20	6
59	+	+	1	1	156	468	E	E	6	4
62	+	+	2	2	141	84	N	N	2	6
64	-	+	1	1	1497	> 2000	E	E	11	6
67	+	-	1	2	2	11	N	N	1	4
68	-	+	2	2	109	89	E	N	7	10

E: elevated; IgE values expressed in UI/ml; N: normal; 1: absence of immunosuppression; 2: moderate immunosuppression; 3: strong immunosuppression.

the second. This was higher than those rates observed by Corominas et al. (2000) in infected adults (18%) and similar to children (28%) (Bacot et al. 1997).

The results suggest that there are special characteristics in this population that correlate with the development of this type of hypersensitivity and immunological reconstitution. The majority of the atopic patients in this study had normal CD4<sup>+</sup> T values for their age. Carvalho et al. (2008) showed an association between Type 1 hypersensitivity-mediated dermatitis in HIV-positive children with improved immune responses. Lin and Lazarus (1995) correlated asthma in HIV-positive adults with lower level immunosuppression. A higher prevalence of atopy was observed in patients with increased CD4<sup>+</sup> T lymphocyte levels in relation to those with advanced disease (Corominas et al. 2000). In the same way, a separate study (Goetz et al. 1997) reported that aeroallergen-specific IgE was less prevalent with disease in progress.

Most patients whose prick test response changed to negative from positive presented CD4<sup>+</sup> levels compatible with immunocompetence and they maintained these levels in both evaluations. The opposite result occurred in one patient with worsening immune responses. This patient had a CD4<sup>+</sup> T cell reduction and became negative at the second prick test. These findings suggest that the CD4<sup>+</sup> level influences skin test results. As suggested by Corominas et al. (2000), these immunological changes that can occur in the early stages of HIV infection or during im-

mune reconstruction could induce an increased prevalence to allergic diseases in patients genetically predisposed to develop atopy. However, laboratory and clinical expression could decrease along with disease progression once their immunological capacity is available to respond to allergens and trigger an allergic reaction - an effect that is lost in the high immunosuppression phases.

Recent reports have suggested that the immune changes in HIV-infected individuals could be linked to alterations in T lymphocyte regulators, known as Tregs (CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup>). In the initial phase, higher Treg activity induces a paradoxical effect of stabilized CD4<sup>+</sup> levels by reducing CD8<sup>+</sup> T activity (Kinter et al. 2004, Eggena et al. 2005). Therefore, the progressive reduction in Tregs results in an increased Th2 CD4<sup>+</sup> T lymphocyte response to environmental allergens. This leads to an increased prevalence of atopy that decreases when immunosuppression develops (Xystrakis et al. 2006). However, during immunological reconstruction, CD4<sup>+</sup> T lymphocyte levels gradually increase and there is a possible slower recuperation of T lymphocyte regulators. As a result, the atopic response returns.

In non-infected individuals, Th2 lymphocyte clones that react with environmental antigens are activated constantly due to permanent exposure (Roberts et al. 2005). In the HIV-infected patient, this sensitivity seems to disappear with disease progress (Goetz et al. 1997), presumably due to the destruction of memory clones that occurs with

the progressive loss of CD4<sup>+</sup> T lymphocytes. This is the same phenomenon that occurs in the case of lost responses to antigen-based vaccines (Douek et al. 2000, Feeney et al. 2003, De Milito et al. 2004, Rosenblatt et al. 2005). Since immunoglobulin production is T lymphocyte-dependent, a reduction in Th2 CD4<sup>+</sup> lymphocyte clones decreases B lymphocyte stimulation, thus resulting in reduced IgE levels. As IgE half-life in tissue is at a maximum at 14 days (Hamilton 2001), there is a progressive disappearance of the prick test response in these patients.

Immune restoration after introducing anti-retroviral therapy allows new cell clones to appear from the thymus (Douek et al. 2000, Johnston et al. 2001, Resino et al. 2003, Touloumi et al. 2004, Ye et al. 2004). These new cells could be stimulated quickly by environmental allergens, resulting in the production of IL-4-type inducer cytokines and IgE by allergen-specific B lymphocytes. When this happens, prick positivity can be re-established in the genetically predisposed individuals.

Upon analyzing the six patients whose prick test profile changed from negative to positive, the results demonstrate that nearly all variables were similar in patients who were atopic at both evaluation times and they were different in non-atopic patients. In these six patients, we could not detect laboratorial alterations common to atopy at this point. However, fully clinical development occurred at the immune restoration phase, which was quantitatively and functionally associated with a Th2 clone expression improvement.

This study shows an elevated prevalence of atopy in HIV-infected children and demonstrates a change in the atopic sensitivity profile in this population. The data suggest that the development of atopy in HIV-infected children is modulated by genetic and environmental factors as well as immunological condition. The loss of follow-up of 16% of the initial sample represented a limitation of the study. Therefore, we believe that studies with larger populations and longer follow-up may corroborate our findings in this present paper.

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