Elevation of IgE in HIV-infected children and its correlation with the progression of disease

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Background: According to recent data, a switch from a Tm1 to a Tm2 pattern of cytokines might be a critical step in the progression of human immunodeficiency virus (HIV) infection. Previous studies have demonstrated a disturbance in IgE synthesis in HIV-infected adults.

Methods: Fifty-eight children infected vertically with HIV and 35 children with seroreversion, aged 4 months to 11 years, were evaluated for IgE serum level, CD4+ cell count, skin prick test responses to common airborne and food allergens, individual and family history of atopy, and presence of opportunistic infections. In thirty of the 58 HIV-infected children serum interleukin-4 and interferon-γ levels were assessed. Thirty-three of the 58 HIV-infected children had a follow-up of 1 year for IgE levels, CD4+ cell count, and occurrence of opportunistic infections and recurrent bacterial infections.

Results: Both IgE concentration and the percentage of children with IgE elevation were markedly increased (with no correlation to skin prick test responses or opportunistic infections) in the group of 58 HIV-infected children as compared with the 35 children with seroreversion (p < 0.05). The same parameters were higher in children with acquired immunodeficiency syndrome as compared with children with asymptomatic or mildly symptomatic disease (p < 0.05). Serum interleukin-4 and interferon-γ levels do not account for IgE hyperproduction. There was a significant association between persistent IgE elevation and severe decline (≥30% over 1 year) in CD4+ counts, as well as increased susceptibility to bacterial infections.

Conclusions: Our study demonstrates a spectrum of IgE dysfunction in children, which is similar to that observed in adults. A persistent IgE hyperproduction appears to be associated with a severe decline in CD4+ cell count, suggesting that this clinical test is a useful marker of disease progression. (J ALLERGY CLIN IMMUNOL 1995;95:627-32.)

Key words: IgE hyperproduction, vertical HIV infection, children, markers of progression

In the last few years great progress has been achieved in our knowledge of the cellular and molecular signals responsible for the regulation of human IgE synthesis. In the mouse, and possibly in human beings, IgE production is controlled by T cells of two subtypes: Tm1 and Tm2 cells, which produce interferon-γ (IFN-γ) and interleukin-4 (IL-4), respectively.1,2 It has been suggested that imbalances between IFN-γ and IL-4 production may result in disordered IgE secretion.3

Recent data have indicated that a switch from a Tm1 to a Tm2 pattern of cytokines may be a critical step in the progression of human immunodeficiency virus (HIV) infection.4-6 We can therefore also expect that the regulation of IgE synthesis would be severely disturbed in this disease. Previous studies demonstrated a correlation between IgE elevation and HIV infection in adults.7,8 The increase in IgE levels did not appear to be related to an increased prevalence of atopic disease or to the presence of opportunistic infections (OIs).7-9 Moreover, IgE levels increase with the severity of immunodeficiency and have proven to be a discriminating marker of progression toward acquired
immunodeficiency syndrome (AIDS). Our study was performed to determine whether an IgE elevation similar to that reported in adults could be identified in HIV-infected children and to correlate the possible existence of IgE elevation with the progression of immunodeficiency and the susceptibility to infections.

**METHODS**

**Study population**

Fifty-eight HIV-infected children and 35 children with seroreversion, aged 4 months to 11 years, were studied. All of the 58 infected children had vertically transmitted HIV infection. Children older than 18 months of age were considered to be HIV-positive on the basis of positive serum anti-HIV IgG antibodies as determined by ELISA and Western blot. Children younger than 18 months of age were considered to be HIV-positive on the basis of positive p-24 antigen or HIV proviral sequences. They were subdivided according to the Centers for Disease Control (CDC) definition into three groups: 29 patients with asymptomatic infection (P-1B), 14 patients with mildly symptomatic illness (P-2A), and 15 patients with AIDS (P-2B to P-2F alone or in combination). All patients with AIDS and at stage P-2A were receiving antiretroviral therapy, intravenous immunoglobulin, and aerosol pentamidine prophylaxis at the time of this study. The 35 subjects with seroreversion include children born to HIV-positive mothers who have been documented to be HIV-negative by 18 months of age and who have no other laboratory and clinical evidence of HIV infection.

**Subject evaluation**

All of the HIV-infected children and those with seroreversion were concomitantly evaluated for IgE serum level, CD4+ cell count, skin prick test responses to common airborne and food allergens, and individual and family history of atopy. A subject was defined as atopic if he or she had symptoms of asthma or occasional bronchospasm, allergic rhinitis, sinusitis or dermatitis and a history of drug hypersensitivity. All of the HIV-infected children were also evaluated for the presence of OIs at the time of IgE assessment. Thirty of the HIV-infected children were also evaluated for IL-4 and IFN-γ serum concentrations.

Of the 58 HIV-infected children, 33 were followed up for 1 year. They were monitored for IgE levels and CD4+ cell counts every 3 months and for the occurrence of OIs and recurrent bacterial infections (BIs) throughout the study period. Patients were classified as being free of infections if they had no OIs or no more than one BI. Patients were classified as having infections if they had experienced at least one BI or more than one BI during that period. OIs were considered as those required for the CDC P-2D classification of children with HIV infection and included either persistent oropharyngeal or esophageal candidiasis, Pneumocystis carinii pneumonia, diarrhea caused by Cryptosporidium organisms, atypical mycobacterial infection, cytomegalovirus infection, severe herpetic stomatitis, and recurrent or persistent varicella-zoster infection. The BIs were either microbiologically documented or clinically defined. Focal infections (e.g., pneumonia, sinusitis, and otitis media) and systemic infections (septicemia) were considered in this definition.

**IgE assay**

Total serum IgE levels were measured by immunocapture (Pharmacia CAP System IgE RIA; Pharmacia, Uppsala, Sweden). Our references for normal IgE values during childhood are in accordance with previously published data. IgE values are expressed as Kilo International Units per liter (KIU/L). The interassay and intraassay coefficients of variation were less than 10%.

**IL-4 and IFN-γ determinations**

Serum levels of IL-4 were measured with commercial Quantikine Human IL-4 Immunoassay (R & D Systems, Minneapolis, Minn.). Serum levels of IFN-γ were measured with the commercial IFN-γ EIA kit (Medgenix, Brussels, Belgium). The assays were performed according to the manufacturers’ instructions. The interassay and intraassay coefficients of variation were less than 10%. In our study, the sensitivities of the assays were 4.0 pg/ml and 0.01 IU/ml for IL-4 and IFN-γ, respectively.

**Statistical procedures**

IgE data were analyzed after conversion into their neperian logarithmic values, because they are not normally distributed. Comparisons between groups were made with Student’s t test and analysis of variance. Newman-Keuls multiple comparison procedures were applied to assess differences among the groups. The chi square test with Yates’ correction was performed to compare proportions between two groups. The statistical model applied for hypothesis testing of person-months data was the binomial distribution. All statistical tests...
Table I. Demographic, laboratory, and clinical characteristics of children with HIV infection with seroreversion

<table>
<thead>
<tr>
<th>Stage of disease*</th>
<th>SR (n = 35)</th>
<th>P-1B (n = 29)</th>
<th>P-2A (n = 14)</th>
<th>AIDS (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) Mean (SD)</td>
<td>4.4 (2.0)</td>
<td>5.3 (3.3)</td>
<td>4.7 (2.1)</td>
<td>5.0 (2.9)</td>
</tr>
<tr>
<td>Range</td>
<td>2.5-7</td>
<td>0.3-11</td>
<td>0.7-7</td>
<td>0.4-11</td>
</tr>
<tr>
<td>CD4+ count (cells/mm3) Mean (SD)</td>
<td>1400 (425)</td>
<td>777 (496)</td>
<td>765 (558)</td>
<td>585 (628)</td>
</tr>
<tr>
<td>Range</td>
<td>1000-1800</td>
<td>108-2589</td>
<td>50-1847</td>
<td>1-1660</td>
</tr>
<tr>
<td>No. with positive SPT results</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No. with atopic disease</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No. with OIs</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

SR, Seroreversion; SPT, skin prick test.
*Disease stage was determined according to the CDC classification system.10

Table II. Serum IgE levels and stages of HIV infection

<table>
<thead>
<tr>
<th>Stage of disease*</th>
<th>SR (n = 35)</th>
<th>P-1B (n = 29)</th>
<th>P-2A (n = 14)</th>
<th>AIDS (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE (KIU/L) Mean (SEM)</td>
<td>32 (18)</td>
<td>151 (61)</td>
<td>102 (52)</td>
<td>501 (180)</td>
</tr>
<tr>
<td>Range</td>
<td>2-472</td>
<td>2-1210</td>
<td>2-902</td>
<td>2-2000</td>
</tr>
<tr>
<td>No. (%) with IgE value elevated for age</td>
<td>4 (11)</td>
<td>14 (48)</td>
<td>6 (41)</td>
<td>11 (73)</td>
</tr>
</tbody>
</table>

SR, Seroreversion.
*Disease stage was determined according to CDC classification system.10

RESULTS

The demographic, laboratory, and clinical features of the study population are given in Table I. The HIV-infected and seroreversion groups were similar with regard to age and prevalence of atopic disease. Skin prick test results were negative in all children included in the study. CD4+ cell counts were lower in HIV-infected patients than in those with seroreversion; the differences between the symptom-free patients and those who had symptoms were not significant. With regard to OIs, only two patients, both with AIDS, had such infections at the time of IgE evaluation. One had diarrhea caused by Cryptosporidium organisms, and the other had diarrhea as a result of a Mycobacterium avium-intracellulare infection.

The IgE levels and the percentages of children with IgE elevated for age are shown in Table II. In HIV-infected children at any stage of the infection, IgE levels were significantly increased compared with IgE levels of the seroreversion group (p < 0.05). With respect to clinical setting, children with AIDS exhibited higher IgE levels than children in either the P-1B or P-2A group (p < 0.05). P-1B and P-2A groups showed similar IgE values.

The percentage of children with IgE values elevated for age was 15%, 48%, 41%, and 73% in seroreversion, P-1B, P-2A, and AIDS groups, respectively. These percentages were higher in the HIV-infected children at any stage of the infection than in the children with seroreversion (p < 0.05). With respect to clinical setting, the percentage of children with IgE values elevated for age was higher in patients with AIDS than in patients in the P-1B or P-2A group (p < 0.05). P-1B and P-2A groups showed similar percentages of children with IgE values elevated for age.

With respect to the degree of immunodeficiency, as assessed by the CD4+ cell counts, IgE levels and
Table III. Correlation between change in CD4\(^+\) cell count and IgE profile in HIV-infected children

<table>
<thead>
<tr>
<th>IgE profile*</th>
<th>Change in CD4(^+) cell count over 1 year</th>
<th>No</th>
<th>%</th>
<th>Decrease (\geq 30%)</th>
<th>No change or decrease</th>
<th>(\geq 30%)</th>
<th>No.</th>
<th>%</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE elevation ((n = 19))</td>
<td>14</td>
<td>74</td>
<td>5</td>
<td>26</td>
<td>0.002</td>
<td>Normal IgE ((n = 14))</td>
<td>2</td>
<td>14</td>
<td>12</td>
</tr>
</tbody>
</table>

*IgE profile: IgE levels were determined every 3 months for 1 year.

CD4\(^+\) cell counts were not significantly correlated (Spearman's \(r = 0.17\); data not shown).

IgE follow-up of 33 HIV-infected children, every 3 months for 1 year, demonstrated two different IgE profiles: 19 and 14 subjects showed IgE levels that were persistently elevated for age or always normal, respectively. The 19 subjects with persistent IgE elevation included five in the P-1B group, seven in the P-2A group, and seven in the AIDS group. Of the seven patients with AIDS, three had progressive encephalopathy (P-2B), two had a history of OI (P-2D), and one had progressive encephalopathy and cardiomyopathy (P-2BF). The 14 subjects with always normal IgE levels included five in the P-1B group, five in the P-2A group, and two patients with AIDS. Patients with AIDS were classified as P-2B and P-2D, respectively. The time course of CD4\(^+\) cell counts in these 33 children is shown in Table III. The proportion of subjects who exhibited a decrease in CD4\(^+\) cells equal to or greater than 30% was higher in patients with persistent IgE elevation (14 of 19) than in those with normal IgE levels (2 of 14) \((p = 0.002)\).

The incidence of BI and OI over 1 year of clinical observation in children with elevated or normal IgE profiles has also been compared (Table IV). Twenty-seven episodes of BI and six episodes of OI occurred in six (2 P-2A, 4 AIDS) of the 19 children with IgE elevation compared with only seven episodes of BI and one episode of OI in three (2 P-2A, 1 AIDS) of the 14 children with normal IgE levels. All 34 BIs were respiratory tract infections (pneumonia, sinusitis, and otitis media) requiring recurrent courses of antibiotics. The seven OIs included five cases of persistent oral candidiasis, one case of Cryptosporidium-induced diarrhea, and one case of disseminated infection with Mycobacterium avium-intracellulare. The incidence of BIs throughout the study period was higher in children with IgE levels that were continuously elevated (12 BIs per 100 child-months of observation) than in children with normal IgE (4 BIs per 100 child-months of observation) \((p < 0.01)\).

To determine whether serum levels of IFN-\(\gamma\) and IL-4 may account for differences in IgE levels in HIV-infected children, the amounts of these cytokines in the serum of 14 and 16 subjects with IgE values that were normal or elevated for age were determined (Table IV). Serum levels of IFN-\(\gamma\) and IL-4 were barely detectable and we did not find any difference between children with normal IgE values or IgE values elevated for age.

**DISCUSSION**

Previous adult studies found a correlation between IgE elevation and HIV infection.\(^7,8\) Both the IgE concentration (60 to 143 KIU/L) and the percentage of patients with IgE elevation (27% to 52%) markedly increase during progression of the disease from the asymptomatic stages to the AIDS stage.\(^9\) Our study demonstrates a spectrum of IgE dysfunction in children, which is similar to that observed in adults. Both the IgE concentrations and the percentage of children with IgE levels elevated for age increase along with the severity of HIV infection. These findings do not appear to be related to atopy or to the presence of OIs. However, children show a higher IgE concentration (151 to 501 KIU/L from P-1B to AIDS), and a higher proportion of children have IgE elevation (48% to 73% from P-1B to AIDS) than adults at a similar stage of the disease.

The abnormal IgE synthesis observed during HIV infection may be explained by the switching from a T\(_m\) to a T\(_h\) cytokine profile as the disease progresses. In fact, Clerici et al.\(^{13}\) found that IL-4 production increases, whereas IL-2 production decreases during the course of HIV infection and that AIDS develops in a higher percentage of patients with a weak IL-2 response than those with a strong IL-2 response. The above-mentioned difference in IgE synthesis between children and adults could be due to an earlier and more pronounced T\(_m\) dysfunction in the pediatric patients.

In contrast to adults, in children, we did not find a relationship between IgE levels and CD4\(^+\) cell counts. However, recent findings indicated that
Table IV. Correlation between incidence of infections and IgE profile in HIV-infected children

<table>
<thead>
<tr>
<th>IgE profile</th>
<th>No. of BIs/ OIs/</th>
<th>Ratea</th>
<th>p Value</th>
<th>No. of BIs/ OIs/</th>
<th>Ratea</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE elevation</td>
<td>(n = 19)</td>
<td>27/6</td>
<td>11.8</td>
<td>0.01</td>
<td>6/4</td>
<td>2.6</td>
</tr>
<tr>
<td>Normal IgE</td>
<td>(n = 14)</td>
<td>7/2</td>
<td>4.2</td>
<td>—</td>
<td>1/1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

IgE levels were determined every 3 months for 1 year.

*aRates shown are the number of infections per 100 child-months of observation.

loss of Th function can occur in HIV-infected adults and children independently of CD4+ cell counts.14-17

Follow-up at 1 year allowed us to identify children with IgE levels that were persistently elevated or normal. These two groups of patients include subjects in either the asymptomatic or symptomatic stage of the disease. A severe decline in CD4+ cell counts and an increased susceptibility to BIs are both strongly correlated with a persistent IgE hyperproduction. It is well known that a more rapid decline in CD4+ cell counts,18 a higher incidence of BI and OI,16 and a more rapid progression to AIDS are all associated with a defect in Th function. A defect in Th function in turn is independent of clinical stages of HIV infection.14 Thus it is likely that the persistent IgE hyperproduction detected in our pediatric patients may reflect the loss of Th function.

It is well established that IL-4 and INF-γ are the main regulatory cytokines of IgE production, with opposite effects on the synthesis of this immunoglobulin class.1 Imbalances between IL-4-producing and IFN-γ-producing helper T cells seem to be responsible for polyclonal IgE production in patients with hyperimmunoglobulinemia E syndrome, atopic disease, and parasitic infections.19 In our pediatric patients serum IL-4 and IFN-γ levels were nearly undetectable, and they do not account for IgE hyperproduction. These findings may be due to the short half-life of these cytokines or to the fact that they are locally released and immediately processed by blood cells or serum components.

This study demonstrates an abnormal IgE synthesis in HIV-infected children and an increase in IgE values as the disease progresses. Persistent IgE hyperproduction appears to be associated with AIDS-related events such as a severe decline in CD4+ cell counts and an increased susceptibility to BI. These findings suggest that IgE hyperproduction is a marker of disease progression and that it may be an indirect indication of the switch from Th1 to Th2 cytokine profile. Sequential monitoring of serum IgE levels might be a relatively inexpensive and simple clinical tool for the monitoring of the progression of HIV infection in children.

We thank Samantha Airaghi of the Endocrine Unit, L. Sacco Hospital, Milan, Italy, for the assessment of IgE values.

Table V. Serum IFN-γ and IL-4 concentrations according to IgE values in 30 HIV-infected children

<table>
<thead>
<tr>
<th>Children</th>
<th>IgE values elevated for age (n = 16)</th>
<th>Normal IgE values (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE (KIU/L)</td>
<td>Mean (SEM)</td>
<td>452 (136)</td>
</tr>
<tr>
<td>IFN-γ (IU/ml)</td>
<td>Mean (SEM)</td>
<td>0.82 (0.42)</td>
</tr>
<tr>
<td>IL-4 (pg/ml)</td>
<td>Median (range)</td>
<td>0 (&lt;4-100)</td>
</tr>
<tr>
<td>below threshold (&lt;4 pg/ml)</td>
<td>Median (range)</td>
<td>9/16</td>
</tr>
</tbody>
</table>

REFERENCES

4. Clerici M, Shearer GM. A TH1→TH2 switch is a critical