

INCREASED PRODUCTION OF IgE PROTEIN AND IgE ANTIBODIES SPECIFIC FOR FUNGAL ANTIGENS IN PATIENTS WITH THE ACQUIRED IMMUNODEFICIENCY SYNDROME •

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The acquired immunodeficiency syndrome (AIDS) has firmly established itself as one of the most devastating acquired diseases of the human immune system⁵. While T cell-mediated immunity is consistently depressed^{4,5}, abnormalities of humoral immunity in AIDS appear to be more heterogeneous. Concomitant to a depression of primary antibody responses, an overreactivity of the B cell compartment has been reported, based on the demonstration of elevated levels of serum immunoglobulins, mainly of IgG and IgA classes⁶, circulating immune complexes⁸ and increased spontaneous immunoglobulin secretion by individual B lymphocytes⁶. Mechanisms responsible for paradoxical B cell hyperreactivity in patients with AIDS are still controversial. Polyclonal activation of B cells has been related to Epstein-Barr virus infection⁶, stimulation by human immunodeficiency virus (HIV) itself¹⁰ or enhanced activity of residual helper T cells⁷.

In the present study we have measured IgE levels in the serum samples from a large number of seropositive patients. We have found increased serum IgE levels in a proportion of patients with constitutional symptoms or full-blown disease. The enhanced IgE response in these patients was polyclonal and it can be at least partially related to the production of IgE antibodies specific for fungal antigens.

Key-words: Acquired immunodeficiency syndrome; Fungal antigens; Human immunodeficiency virus; IgE antibodies; IgE protein.

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MATERIALS AND METHODS

Patients - A total number of 511 subjects at risk for HIV infection coming to the Florence Centre for AIDS were examined. They included intravenous drug-users, homosexual men and hemophiliacs. All subjects displaying seropositivity for HIV were grouped according to the Center for Disease Control (CDC) classification criteria¹.

Detection of serum antibodies against HIV structural proteins - Antibodies against HIV proteins were detected in all serum samples by either two commercial enzyme-linked immunosorbent assay (ELISA) kits (Vironostika, Organon and Wellcozym, Wellcome) or the Western blot technique (DuPont).

Measurement of serum IgE protein and IgE antibodies - Levels of IgE protein were evaluated in all the serum samples by a commercial radioimmunoassay (RIA) kit (IgE-RIA, Pharmacia). IgE levels higher than 150 IU/ml (the mean value $\pm$ 5 SD found in 80 healthy non-allergic donors) were considered as abnormally elevated. IgE antibodies specific for a panel of 8 different allergenic extracts (*Dermatophagoides pteronyssinus*, grass pollen, *Parietaria* pollen, cat dander, and spores of *Alternaria*, *Penicillium*, *Aspergillus* and *Candida*) were detected by the radioallergosorbent (RAST) assay (IgE-test, Phadebas). Serum samples showing a RAST score >2 were considered as positive¹¹.

Statistical analysis - A pooled Student's *t*-test and the χ^2 statistical analysis were used.

RESULTS

Increased levels of serum IgE protein in patients with group IV disease - Sera from 400 out of 511 subjects at risk for HIV infection showed the presence of antibodies against HIV. Of these, 180 were included in group II, 108 in group III, 64 in group IVa and 48 in group IVb-e disease according to the CDC classification criteria. The proportion of sera showing IgE levels higher than 150 IU/ml was significantly higher in groups IVa and IVb-e than in seronegative controls. The mean values of IgE in the sera of these two groups

subjects	n ^a of cases	cases with IgE levels >150 IU/ml		mean ($\pm$ SE) serum IgE levels (IU/ml)
		n ^a	(%)	
HIV-seropositive				
group II	180	18	(10)	96 $\pm$ 19
group III	108	16	(15)	71 $\pm$ 8
group IVa	64	24	(37)*	278 $\pm$ 64**
group IVb-e	48	16	(33)*	214 $\pm$ 62**
HIV-seronegative***	111	20	(17)	78 $\pm$ 11

Values which appeared to be significantly different according to the *t* (*) and the χ^2 (**) test, respectively; *** serum samples were obtained from subjects showing the same risk factors for HIV infection (male homosexuals, intravenous drug-users and hemophiliacs).

Tab. 1 - Enhanced production of IgE in HIV-infected individuals.

antigenic extract	subjects showing IgE antibodies			
	HIV-seropositive (n ^a = 35)		HIV-seronegative (n ^a = 19)	
	n ^a	(%)	n ^a	(%)
<i>Dermatophagoides pteronyssinus</i>	9	(25)	3	(16)
grass pollen	11	(31)	7	(36)
<i>Parietaria</i>	11	(31)	6	(31)
cat dander	14	(40)	7	(36)
<i>Alternaria tenuis</i>	10	(28)	2	(10)
<i>Aspergillus fumigatus</i>	9	(25)	3	(16)
<i>Penicillium</i>	12	(34)	3	(16)
<i>Candida albicans</i>	15	(43)	1	(5)

Tab. 2 - Increased prevalence of IgE antibodies specific for fungal antigens in HIV-infected individuals showing high levels of serum IgE.

of patients were also significantly higher than in seronegative subjects or in seropositive patients with group II or group III disease (tab. 1).

Increased prevalence of IgE antibodies specific for fungal antigens in the serum of patients with group IV disease - Table 2 summarizes the results obtained by testing the sera from 35 HIV-infected and 19 uninfected individuals showing IgE titres higher than 150 IU/ml for the presence of IgE antibodies specific for constituents of a panel of 8 different antigenic extracts (*Dermatophagoides pteronyssinus*, grass and *Parietaria* pollens, cat dander, spores of *Alternaria*, *Aspergillus*, *Penicillium* and *Candida*). The proportion of sera displaying IgE antibodies specific for the 4 non-fungal allergenic extracts was not significantly different between HIV-seronegative and -seropositive subjects. In contrast, the percentage of sera containing IgE antibodies specific for fungal antigens was markedly higher in seropositive than in seronegative subjects. Among the former, the proportion of sera showing IgE antibodies specific for fungal antigens was higher in patients with group IVa and IVb-e disease than in other groups, except for IgE antibody against *Candida* that were frequently found in serum samples from patients belonging to the group III as well (tab. 3).

diagnosis	n ^a of cases	patients showing IgE antibodies specific for							
		<i>Alternaria</i>		<i>Aspergillus</i>		<i>Penicillium</i>		<i>Candida</i>	
		n ^a	(%)	n ^a	(%)	n ^a	(%)	n ^a	(%)
group II	8	2	(25)	2	(25)	2	(25)	2	(25)
group III	7	3	(43)	0	–	0	–	0	–
group IVa	9	4	(44)	6	(66)	5	(55)	5	(55)
group IVb-e	11	6	(54)	6	(54)	5	(45)	5	(45)

Tab. 3 - Increased prevalence of IgE antibodies specific for fungal antigens in HIV-infected patients with group IV disease.

DISCUSSION

It has been shown that in contrast to depression of the T cell compartment, patients with AIDS paradoxically have hypergammaglobulinemia predominantly of IgG and IgA classes⁶. The present study demonstrates that a proportion of HIV-infected patients with group IV disease can also have elevated serum levels of IgE. This finding is consistent with the results of previous studies reporting frequent occurrence of allergic reactions during full-blown AIDS¹¹; it is also in line with our previous results showing that T cell clones obtained from residual CD4⁺ peripheral blood T cells of AIDS patients, as well as their supernatants (SUPs), displayed increased helper activity for IgG and IgE synthesis in comparison with control CD4⁺ T cell clones⁷. Preliminary studies devoted to better elucidate this point suggest that the enhanced ability of T cell clone SUPs to induce IgE synthesis may be due to either their high interleukin-4 (IL-4) or their low interferon- γ (IFN- γ) content (MAGGI et al., manuscript in preparation). Recently, indeed, it has been shown that IL-4 and IFN- γ reciprocally regulate the IgE synthesis in both mice and humans^{2,3}.

Another interesting finding emerging from this study is that the enhanced IgE production in AIDS patients appears to be polyclonal and at least partially directed against fungal antigens. The reason why a noticeable proportion of AIDS patients produce IgE antibodies against fungal antigens is at present unclear. One possibility may be that when the HIV-induced T helper cell damage results in an imbalance between IFN- γ - and IL-4-producing lymphocytes B cells from these patients synthesize not only IgG and IgA, but also IgE, in response to different microorganisms. The mechanisms responsible for the selective depletion in a proportion of AIDS patients of helper T cells displaying a negative regulatory role on IgE synthesis are now being investigated in our laboratory. Experiments are also in progress to ascertain whether B cells from patients with AIDS show an enhanced production of IgE antibodies specific for protozoan, viral and bacterial antigens as well.

SUMMARY

Levels of IgE protein and IgE antibodies specific for 8 different allergenic extracts were measured in the serum of a large series of patients infected by the human immunodeficiency virus (HIV) and in HIV-seronegative subjects belonging to the same risk groups (intravenous drug-users, homosexual men and hemophiliacs). The proportion of subjects showing elevated IgE levels was higher among HIV-infected patients with group IV disease than among HIV-infected patients with group II-III diseases or seronegative individuals. In addition, many HIV-infected patients with elevated IgE levels showed the presence in their serum of IgE antibodies specific for fungal antigens.

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