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HTLV-1 decreases Th2 type of immune response in patients with strongyloidiasis

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SUMMARY

Eosinophils, immunoglobilin (Ig)E and cytokines have important roles in defence mechanisms against helminths. In this study, the influence of HTLV-1 infection, characterized by a Th1 type of immune response, was evaluated on the cytokine pattern and parasitic specific IgE response in patients with strongyloidiasis. Patients were divided into four groups: strongyloidiasis without HTLV-1 infection, strongyloidiasis with HTLV-1, HTLV-1 without strongyloidiasis and controls without either helminth infection or HTLV-1. The cytokine profile was determined in supernatants of mononuclear cells stimulated with Strongyloides stercoralis *crude antigen and the parasite specific IgE was measured by ELISA. Patients coinfected with HTLV-1 had higher levels of interfron (IFN)-γ and interleukin (IL)-10 ($P < 0{\cdot}05$) and lower levels of IL-5 and IgE ($P < 0{\cdot}05$) than patients with strongyloidiasis without HTLV-1. There was an inverse relationship between IFN-γ and IL-5 ($P = 0{\cdot}01$; $r_s = -0{\cdot}37$) and between IFN-γ and parasite specific IgE ($P = 0{\cdot}01$; $r_s = -0{\cdot}39$), and a direct relationship between IFN-γ and IL-10 ($P = 0{\cdot}04$; $r_s = 0{\cdot}35$). These data show that coinfection with HTLV-1 decreases IL-5 and IgE responses in patients with strongyloidiasis consistent with a relative switch from Th2 to Th1 response. Immunological responses such as these are important in the control of this helminthic infection.*

Keywords *HTLV-1, strongyloidiasis, IgE,* S. stercoralis

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INTRODUCTION

An association between strongyloidiasis and HTLV-1 infection has been documented in areas where these infections are endemic (1–4). While there is no agreement that HTLV-1 increases the prevalence of strongyloidiasis, there are strong data indicating that HTLV-1 has important clinical and immunological implications in this helminthic infection. For example, a high rate of therapeutic failure with thiabendazol and, consequently, chronic *Strongyloides stercoralis* infection has been documented in patients infected by HTLV-1 (5), and a severe form of disease with larval dissemination has been reported in patients coinfected with these two agents (6–9). Additionally, there is an inverse correlation between interferon (IFN)-γ levels and total immunoglobulin (Ig)E in patients with HTLV-1 and strongyloidiasis (10).

Individuals infected with HTLV-1 have spontaneous T cell proliferation (11–13) and high levels of IFN-γ (10), which are immunological functions asssociated with a Th1 type of immune response. The immune response in strongyloidiasis is not completely understood. Considering that helminthiases usually have a Th2 type immune response (14–18) and that levels of IgE in serum and interleukin (IL)-4 in cell supernatant fluids of patients with strongyloidiasis are elevated (10,19,20), it appears that these patients have a predominantly Th2 type of immune response. This type of immune response may be important in controlling hyperinfection due to *S. stercoralis*, since both IgE and IL-4 participate in killing or expulsion of helminths from the host (21–24). Moreover, since IL-4 and IL-13 share receptor components (25), it is posible that there also is participation of IL-13 in the defence mechanisms against helminths. The aim of the present study was to determine the cytokine profile in patients with

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strongyloidiasis either coinfected or uninfected with HTLV-1 and to evaluate whether the increased IFN-γ production observed in patients coinfected with HTLV-1 and *S. stercoralis* may modulate the production of IL-5, IL-10, IL-13 and antigen specific IgE responses.

MATERIALS AND METHODS

Patients

Participants of the present study included HTLV-1 positive seroreactors from blood banks, and patients who lived in a rural endemic area for *S. stercoralis* near Salvador, state of Bahia, Brazil, with positive faecal examinations for *S. stercoralis* infection. A clinical history was taken and physical examination performed. The labouratory analysis included serology (IgE) for *S. stercoralis*, confirmation of HTLV-1 by Western blot and determination of cytokines (IFN-γ, IL-5, IL-10 and IL-13) in supernatant fluids of *S. stercoralis* antigen stimulated peripheral blood mononuclear cells (PBMC). Subjects were divided into four groups based on serology for HTLV-1 and *S. stercoralis* infection: group I comprised 20 individuals with negative serology for HTLV-1 and infected with *S. stercoralis*, group II comprised 20 patients coinfected with *S. stercoralis* and HTLV-1, group III comprised 20 individuals with positive serology for HTLV-1 and three negative stool examinations by the method of Baermann and group IV comprised 15 healthy subjects with negative serology and absence of helminths in the stool examination. The mean ages of patients in group I, group II group III and in group IV were 39 ± 9 years, 26 ± 16 years, 21 ± 3 and 20 ± 4, respectively, and the male/female ratio was 2·3 : 1, 4 : 1, 3 : 1 and 1·4 : 1, respectively. All the patients were asymptomatic in relation to strongyloidiasis. The criterion for a diagnosis of strongyloidiasis was a positive faecal examination (Baermann technique). After blood collection, all patients were treated with cambendazol (5 mg/kg weight). Informed consent was obtained and the human experimentation guidelines of the Hospital Universitário Prof. Edgard Santos were followed in the conduct of this clinical research.

Immunological studies

Antigen

Antigen for serology was prepared from infective larval stage 3 (L3) of the parasite recovered from faecal specimens of infected monkeys, after being allowed to develop at 25°C in charcoal cultures. Larvae were separated from the charcoal by the Baermann procedure and washed repeatedly by centrifugation. They were then exposed to 0·25% chlorox (sodium hypoclhorite) for 3–5 min for surface sterilization followed by multiple cycles of centrifugation in RPMI medium (Gibco, Grand Island, NY, USA) containing 100 μg per ml gentamicin. A soluble supernatant of sonicated larvae provided the somatic antigen used in the ELISA test.

Serum specific-IgE assays

S. stercoralis specific serum IgE was measured by ELISA on microtitre plates (Immulon 2; Dynatech Laboratories, Chantilly, VA, USA) as previously described (10). Sera were first depleted of IgG by treatment with Gamma Bind G Sepharose (Pharmacia Biotechnology, Uppsala, Sweden) before reaction with antigen overnight at 4°C. Detection of antibody was performed with goat antihuman IgE conjugated to alkaline phosphatase (Sigma, St Louis, MO, USA); the substrate was *p*-nitrophenylphosphate (Sigma) and the results are expressed as international units (IU).

Cytokine determination

Cytokine levels (IFN-γ, IL-5, IL-10 and IL-13) in supernatants of mononuclear cells were measured by ELISA. Briefly, peripheral blood mononuclear cells were obtained by density gradient centrifugation using lymphocyte separation media (LSM; Organon Teknika Coorporation, Durham, NC, USA). After washing in saline, the cells were adjusted to 3×10^6/ml in RPMI 1640 (Gibco) supplemented with 10% AB + sera containing 100 U penicillin/G and 10 μg/ml of streptomycin. The cells were either unstimulated or stimulated with *S. stercoralis* antigen (1 μg/ml). All cultures were incubated at 37°C in 5% CO_2 for 72 h. Supernatant fluids were collected and stored at − 20°C. IFN-γ (Genzyme Corp., Cambridge, MA, USA), IL-5, IL-10 and IL-13 (PharMingen, San Diego, USA) levels were measured by ELISA sandwich technique (26) and the results were expressed in pg/ml based on a standard curve generated using recombinant cytokines. Values represent the difference between the value of stimulated cultures minus the values of unstimulated cultures. Because we found that IFN-γ levels in subjects infected with HTLV-1 were similar in unstimulated or antigen stimulated cultures, for these groups of patients, the IFN-γ data presented correspond to the values observed in unstimulated cultures.

Serology for HTLV-1

HTLV-1 serology was performed by ELISA test (Cambridge Biotech, Cambridge, MA, USA). Positive ELISA tests were confirmed by Western blot (HTLV Blot 2·4, Genelabs, Singapore).

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Statistical analysis

The correlations were analysed by Spearman correlation test. The Rank Sum Test was used to compare the means.

RESULTS

With the aim of determining the cytokine profile in patients with strongyloidiasis, coinfected or not with HTLV-1, the levels of IFN-γ, IL-5, IL-10 and IL-13 were determined in supernatants from *S. stercoralis* antigen stimulated lymphocyte cultures (Figure 1). The mean ± SD of IFN-γ levels in patients only infected with *S. stercoralis* was 20 ± 46 pg/ml (0–192 pg/ml) and the mean in supernatants of patients coinfected with *S. stercoralis* and HTLV-1 was 919 ± 944 pg/ml (0–3470 pg/ml) ($P = 0{\cdot}01$). Although there was a tendency for the IFN-γ levels be higher in subjects only infected with HTLV-1 without strongyloidiasis (2063 ± 2499 pg/ml with variation of 15–9675 pg/ml) than in patients with HTLV-1 and strongyloidiasis 919 ± 944 pg/ml (0–3470 pg/ml), this diference was not statisticaly significant. The mean ± SD of IL-5 levels in patients only infected with *S. stercoralis* was 727 ± 554 pg/ml (0–1683 pg/ml). This value was higher than that observed in patients coinfected with *S. stercoralis* and HTLV-1 (173 ± 168 pg/ml with variation of 0–488 pg/ml) ($P < 0{\cdot}0001$) and in subjects without HTLV-1 and without *S. stercoralis* infection (2 ± 2 pg/ml). There was also a tendency for higher IL-13 levels in patients with strongyloidiasis without HTLV-1 (220 ± 361 pg/ml) than in patients coinfected with HTLV-1 (43 ± 45 pg/ml) ($P = 0{\cdot}41$). Although the levels of IL-5 and IL-13 in subjects only infected with *S. stercoralis* were higher than that observed in subjects coinfected with *S. stercoralis* and HTLV-1, there was a higher production of IL-10 in this last group. The mean ± SD of IL-10 levels in first group was 5 ± 11 pg/ml (0–37 pg/ml) and in the group II was 35 ± 53 pg/ml (0–532 pg/ml) ($P = 0{\cdot}02$). The level of IL-10 in patients only infected with HTLV-1 was 141 ± 115 pg/ml (0–390 pg/ml).

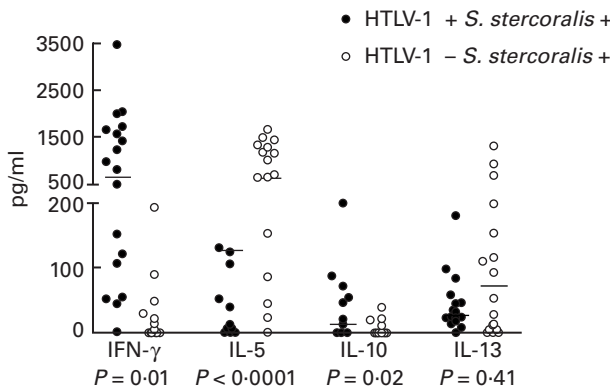

Figure 1 Cytokine profile in patients with strongyloidiasis coinfected or not with HTLV-1. Data for IFN-γ and IL-5 were obtained from all 40 patients. IL-10 levels were documented in 17 blood donors only infected with *S. stercoralis* and in 15 blood donnors coinfected with *S. stercoralis* and HTLV-1. IL-13 levels were documented in 17 blood donnors only infected with *S. stercoralis* and in 20 blood donnors coinfected with *S. stercoralis* and HTLV-1. Values of IL-5, IL-10 and IL-13 represent the differences between the values of stimulated cultures minus the values of unstimulated cultures. The IFN-γ data presented correspond to the value observed in unstimulated cultures.

Parasite specific IgE levels in patients only infected with *S. stercoralis* were higher than in patients coinfected with HTLV-1 and *S. stercoralis* ($P = 0{\cdot}01$). The mean ± SD in the group I was 251 ± 437 IU and in the group II was 74 ± 94 IU.

The relationship between IFN-γ production in supernatants of lymphocyte cultures and IL-5, IL-13 and serum specific IgE levels in 40 patients with strongyloidiasis, with or without HTLV-1 coinfection, is shown in Table 1. An inverse relationship between IFN-γ and serum specific IgE ($P = 0{\cdot}01$; $r_s = -0{\cdot}39$) and between IFN-γ and IL-5 ($P = 0{\cdot}01$; $r_s = -0{\cdot}37$) was observed by Spearman analysis. When IL-5 production in supernatants of lymphocyte cultures was related to parasite specific IgE levels and to IL-13 in the same subjects, there was a direct relationship ($P = 0{\cdot}0001$; $r_s = 0{\cdot}57$ and $P < 0{\cdot}0001$; $r_s = 0{\cdot}75$, respectively). A direct relationship was also found between IFN-γ and IL-10 levels in supernatants of lymphocyte cultures ($P = 0{\cdot}04$; $r_s = 0{\cdot}35$). However, IL-10 levels were so low that it was difficult to interpret the results.

DISCUSSION

The present study shows that the cytokine profile in patients with strongyloidiasis is characterized by a predominance of IL-5 in relation to IFN-γ and that high levels of antigen specific IgE antibodies against *S. stercoralis* are observed. Coinfection with HTLV-1 changes this immunological

Table 1 Correlations between IFN-γ, IL-5, IL-13 and specific IgE levels in patients infected with strongyloidiasis with or without HTLV-1 coinfection

Variables	*r*	*P*
IFN-γ and IgE	− 0·39	0·01
IFN-γ and IL-5	− 0·37	0·01
IFN-γ and IL-13	− 0·04	0·92
IL-5 and IL-13	0·75	< 0·0001
IL-5 and IgE	0·57	0·0001

response leading to a decrease of IL-5 and specific IgE antibodies against *S. stercoralis.*

The documentation that $CD4^+$ T cells are a heterogeneous population formed by Th1 and Th2 cells has contributed to our understanding of the modulation of the immune response and the pathogenesis of several diseases. CD4 Th1 cells secrete predominantly IL-2, IFN-γ and TNF-α, while Th2 cells produce mainly IL-4, IL-5 and IL-10 (27). A predominant Th1 type response suppresses Th2 cell differentiation (28) and Th2 cytokines such as IL-4 and IL-10 downregulate IFN-γ Th1 functions (29). We have previously documented that HTLV-1 infection decreases IL-4 synthesis and total IgE levels in patients with strongyloidiasis (10). In this study, we extend these observations showing that coinfection with HTLV-1 leads to a decrease in levels of IL-5 and specific IgE antibodies against *S. stercoralis*.

IL-10 is a cytokine produced predominantly by macrophages, B cells and CD4 Th2 cells (30,31). IL-10 has an important modulatory effect in the immune response, mainly suppressing macrophage function (32,33), lymphocyte proliferation (34) and IFN-γ synthesis (29). In comparison to IL-5 that was reduced in patients coinfected with HTLV-1 and *S. stercoralis*, there was a direct relationship between IFN-γ and IL-10. Because high IFN-γ levels decrease Th2 cell function, it is likely that, in patients coinfected with HTLV-1 and *S. stercoralis*, the source of IL-10 was not CD4 Th2 cells. In these cases, it is possible that the increased levels of IL-10 observed in coinfected patients may be a host attempt to modulate the high levels of IFN-γ production.

The majority of subjects infected with *S. stercoralis* have an asymptomatic or mild infection. When autoinfection occurs on a large scale, severe disease with parasitic dissemination is observed. Although the defence mechanism against *S. stercoralis* is not completely understood, based on histopathological findings in strongyloidiasis and on observations in other helminthic infections, cytokines, IgE, eosinophils and mast cells participate in helminthic expulsion and killing. IL-4 is the major cytokine that differentiates B cells to produce IgE, and both IL-4 and IL-13 increase the intestinal fluid content, a phenomenon that may contribute to parasite rejection (25,35). IL-5 is an important cytokine for differentiation, activation and proliferation of eosinophils (36,37), which are cells that are involved in the killing of helminths (37). Mast cell degranulation mediated by IgE and parasite antigens is also involved in the expulsion of parasites (38). A reduction in numbers of eosinophils has been observed in patients with disseminated strongyloidiasis (39) and decreased total IgE antibody levels have been observed in patients with severe strongyloidiasis associated with HTLV-1 infection (3,7,40). Additional recent evidence for HTLV-1 as an important factor for disseminated strongyloidiasis has been reported from Peru (9). Our data showing decreases of IL-5, IL-13 and specific IgE in patients coinfected with HTLV-1 and *S. stercoralis,* suggest that a decrease in the Th2 type immune response mediated by high levels of IFN-γ may be the immunological basis for the increased susceptibility of the coinfected patients to develop disseminated strongyloidiasis.

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