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Review Article

Epidemiological and clinical interaction between HTLV-1 and *Strongyloides stercoralis*

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SUMMARY

Strongyloides stercoralis *is the most common human parasitic nematode that is able to complete a life cycle and proliferate within its host. The majority of patients with strongyloidiasis have an asymptomatic infection or mild disease. However, when autoinfection occurs, a high number of infecting larvae can gain access to the bloodstream by penetrating the colonic mucosa leading to a severe hyperinfection and the development of disseminated strongyloidiasis.*

The human T cell lymphotropic virus type 1 (HTLV-1) predominantly infects T cells and induces spontaneous lymphocyte proliferation and secretion of high levels of type 1 cytokines. Strongyloides stercoralis *patients with HTLV-1 co-infection have a modified immunological responses against parasite antigens and co-infection has clinical implications for strongyloidiasis. The high production of IFN-γ observed in patients co-infected with HTLV-1 and* Strongyloides stercoralis *decreases the production of IL-4, IL-5, IL-13 and IgE, molecules that participate in the host defence mechanism against helminths. Moreover, there is a decrease in the efficacy of treatment of* Strongyloides stercoralis *in patients co-infected with HTLV-1. Alterations in the immune response against* Strongyloides stercoralis *and the decrease in the efficacy of anti-parasitic drugs are responsible for the increased prevalence of* Strongyloides stercoralis *among HTLV-1 infected subjects and make HTLV-1 infection the most important risk factor for disseminated strongyloidiasis.*

Keywords *helminths and HTLV-1, HTLV-1, human T cell lymphotropic virus type 1,* Strongyloides stercoralis*, strongyloidiasis*

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INTRODUCTION

Strongyloides stercoralis is an intestinal nematode with world-wide distribution that is specifically common in tropical and subtropical regions. It is estimated that 50–100 million individuals are infected with *Strongyloides stercoralis*, with a high prevalence in tropical regions of Africa, Asia and South America (particularly Brazil and Colombia). The rainfall of the area is important, since transmission is favoured by high humidity. Marked faecal contamination of the environment contributes to the high prevalence of the infection in endemic areas, (1) in migrants, (2) in patients in mental institutions, (3) and in former prisoners of war (4).

Although the majority of infections are asymptomatic, a severe form of the disease characterized by parasite dissemination has a high death rate. *Strongyloides stercoralis* is recognized as an opportunistic agent causing severe infections in patients receiving corticosteroid or cytotoxic drugs (5,6). Recently, it has also been shown that concurrent infection of *Strongyloides stercoralis* in persons infected with human T lymphotropic virus type 1 (HTLV-1) is highly associated with parasite dissemination and development of severe strongyloidiasis (7–10).

The life cycle of *Strongyloides stercoralis* is complex and involves two stages – one as a free organism and the other as a parasite. The former occurs in humid soil in hot regions, where the male and female rhabditiform larvae (L1, L2) have a favourable environment. Under these conditions, they copulate, release eggs in the soil and, within a few hours, the rhabditiform larvae emerge. When the soil conditions are not favourable, the rhabditiform larvae transform into infective larvae, also called filariform larvae (L3). When they come into contact with the host the filariform larvae penetrate the skin and spread haematogenously through capillaries. At the lungs they cross the alveolar membrane, migrating into the alveolar space, reach the epiglottis and are swallowed. In the mucosa of the small intestine they

became adult worms. It is here that the parthenogenetic female lays eggs that release the rhabditiform larvae. The rhabditiform larvae migrate to the intestinal lumen and, in stages L1 and L2, are excreted in stool. However, particularly in the colon, the L2 larvae may become infective larvae. In this case, the filariform larvae gain access to the bloodstream by penetrating the colonic mucosa. This particular route of infection is called autoinfection, and is responsible for the perpetuation of the parasite even after a long period without infestation (11,12). Autoinfection occurs continuously. However, in immunosupressed individuals this process is enhanced, larval dissemination occurs, and the patient develops severe strongyloidiasis. Conditions such as malnutrition, malignancies, corticosteroid and immunosuppressive therapy impair host resistance and are recognized as risk factors for development of severe strongyloidiasis. Recently, however, the major factor related to severe strongyloidiasis has been recognized as HTLV-1 infection (8,13).

HTLV-1 is a retrovirus that was first isolated from a patient with adult T cell leukaemia lymphoma (ATLL). HTLV-1 is endemic in Africa, Japan, the Caribbean, and in South America. It is estimated that 10–20 million individuals are infected by HTLV-1 world-wide (14). The virus can be transmitted by breast feeding, by sexual contact, or by contaminated blood products, syringes or needles. In contrast to human immunodeficiency virus (HIV), maternal–foetal spread of HTLV-1 occurs via breast feeding. HTLV-1 predominantly infects T cells, although B cells, macrophages, dendritic cells, and endothelial cells can also be infected (15–17) The majority of the individuals infected with HTLV-1 are asymptomatic, and less than 5% will develop the two most important diseases associated with HTLV-1: ATLL and HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP).

INTERACTION OF HTLV-1 WITH THE IMMUNE SYSTEM

Retroviruses are single-stranded RNA viruses, with reverse transcriptase activity that leads to transcription of viral DNA and integration into the host genome. In this way, the virus is able to persist by escaping immune surveillance.

The HTLV-1 genome contains elements that are common to all known replication component retroviruses, as well as a region encoding gene products unique to HTLV-1. Common to all retroviruses are the group-specific antigen (gag), protease (pro), polymerase (pol), and envelope (env) genes. Other functionally distinct proteins unique to HTLV-1 are encoded within the PX region of the genome. Several factors, either host-derived or viral-specific, may regulate gene expression from the integrated provirus and may potentially impact the course of disease progression during and after the primary infection. The viral protein Tax, encoded within the PX region, has been demonstrated to be a critical factor with respect to genomic activation and viral gene expression. Tax increases the expression of several cytokines and receptors involved in T cell growth and proliferation, such as IL-2, IL-15, GM-CSF, and IL-2 receptor (18–20). IL-15 mRNA expression is elevated in lymphocytes obtained from HAM/TSP patients when compared with those of normal donors, and contributes to the maintenance of lymphocyte proliferation and cytokine synthesis, as well as to preventing apoptosis (18,21,22). IL-15 plays a major role in the persistence of Tax-specific CD8 cells in HAM/TSP, and IL-15 is a critical cytokine for the maintenance of memory-phenotype CD8 cells (22). There is a larger number of viral-specific CD8 cells in these patients, a state that is associated with the inflammatory response in the central nervous system. Blocking IL-15 action decreases the number of virus-specific CD8 cells. This decrease is followed by both inhibition of proliferation and induction of apoptosis in these cells. Addition of Abs directed toward IL-15 and IL-2, or toward their receptors, partially inhibits lymphocyte proliferation in HTLV-1 patients (23). Tax has also been shown to repress the expression of cellular genes involved in apoptosis. This increase in growth-inducing factors, combined with the decrease in repair and apoptotic factors in HTLV-1 infected cells, provides an environment that supports T cell proliferation and spontaneous secretion of cytokines.

HTLV-1 infected T cells can induce activation of uninfected T cells via T cell–T cell interaction mediated by the CD2–LFA3 (CD58) pathway (24–26). This could potentially induce IL-2 production from the uninfected cells, leading to a more generalized activation of the immune system, acceleration of the spread of the virus, and a basis for some of the disease associated with HTLV-1. Additionally, cell–cell contact is required for efficient transmission of HTLV-1. HTLV-1 T cell cloning occurs independently of CD80 or CD86 co-stimulation for proliferation and for IL-15 and IFN-γ secretion (24).

IMMUNOLOGICAL RESPONSES IN PATIENTS CO-INFECTED WITH HTLV-1 AND *STRONGYLOIDES STERCORALIS*

The immunological response in HTLV-1 infected patients is characterized by a marked T cell activation, with spontaneous T cell proliferation and secretion of cytokines. Although both Th1 and Th2 cells are activated during HTLV-1 infection, activation of Th1 cells, characterized by high production of IFN-γ and TFN-α, is predominant in infected individuals (27). The magnitude of T cell activation, IFN-γ and TNF-α secretion, and of lymphocyte proliferation, is higher in patients who have HAM/TSP compared to those who are HTLV-1

Table 1 Main characteristics of the immune response in HTLV-1 and in helminthic infections

HTLV-1	Helminthic infections
Spontaneous and intense lymphocyte proliferation	Mild lymphocyte proliferation even in antigen-stimulated cultures
Increased frequency of lymphocyte-expressing activation markers	Small number of cells expressing lymphocyte activation markers
High spontaneous IFN-γ production	Absence or low production of IFN-γ even in antigen-stimulated cultures
Low levels of type 2 cytokines	High levels of IL-4, IL-5, IL-10 and IL-13

carriers (28). High levels of type 1 cytokine production are also observed in HTLV-1 carriers, and in some of these individuals the production of IFN-γ and TNF-α may be as high as that observed in patients with HAM/TSP (28).

In contrast to individuals infected with HTLV-1, patients with helminthic infections have a predominant type 2 immune response, high IgE levels, and increased numbers of eosinophils in peripheral blood (29,30). The main immunological findings in HTLV-1 infected subjects and in patients with helminthic infections are given in Table 1. Patients infected with *Strongyloides stercoralis* produce more IL-4 and IL-5 than IFN-γ when stimulated with parasite antigens, and high serum IgE levels against *Strongyloides stercoralis* antigen are found in these patients (31). IL-4 is an important cytokine for proliferation of precursor cells in bone marrow, to differentiate precursor cells into basophils, and in the activation of both mast cells and basophils. IL-4 and IL-13 are cytokines that cooperate in the differentiation of B cells to IgE-producing cells. IL-5 induces proliferation and differentiation of precursor cells into eosinophils, and induces proliferation and activation of these cells. All of these molecules (IL-4, IL-13, IL-5, IgE) and cells (basophils, mast cells and eosinophils) participate in the host defence mechanism against helminths. Although the host defence against helminths is a complex process that may involve both type 1 and type 2 immune responses, evidence has accumulated in experimental models that IL-4, IL-13, IgE mast cells and eosinophils have an important role in the elimination of these parasites and in parasite killing (32–34). In addition to the role of IL-4 and IL-13 in inducing IgE synthesis and in collaborating in the differentiation of basophils and activation of mast cells, these cytokines can increase amounts of digestive tract fluids by acting directly on intestinal mucosa. This augmentation of fluids is due to an increase in intestinal permeability, as well as to a decrease in fluid absorption (32,35). Through these mechanisms, these cytokines play an important role in the elimination of enteroparasitic eggs and larvae. As parasites penetrate tissues, mast cells and eosinophils play important roles in defence. Interaction of the parasite with IgE–mast cell complexes, leads to mast cell degranulation and parasite killing (36). Moreover, eosinophils can also kill helminths through antibody-dependent cellular cytoxicity (37).

The documentation that CD4 T cells are composed of Th1 and Th2 subpopulations based on the type of cytokine secretion has helped in the understanding of the pathogenesis of infectious diseases. Through the production of cytokines, these subpopulations of cells can down-regulate each other, allowing an effective but modulated immune response. In this way, IFN-γ, a typical type 1 cytokine, can down-regulate Th2 cells. On the other hand, IL-4 and IL-10 produced by Th2 cells have the ability to down-regulate Th1 cells (38,39). A comparative analysis of the cytokine profile of individuals co-infected with HTLV-1 and *Strongyloides stercoralis*, and patients who have only strongyloidiasis, has shown that dually infected individuals have significantly more IFN-γ, less IL-4 and IL-5, and less total IgE as well as *Strongyloides stercoralis*-specific IgE (40,41). The inverse correlation between IFN-γ levels and IL-5, IL-4 and IgE levels demonstrates the role of IFN-γ in down-modulating the type 2 immune response in patients with strongyloidiasis. Co-infection with HTLV-1 did not decrease IgG antibodies against *Strongyloides stercoralis* antigen, thereby allowing the use of a serological test for the diagnosis of strongyloidiasis in patients co-infected with HLTV-1. However, there is a marked decrease in parasite-specific IgE, which is highly associated with severity of helminthic infection. Whereas IgE antibodies against *Strongyloides stercoralis* were observed in 89% of patients who had mild strongyloidiasis, IgE antibodies were not detected in patients with the severe form of *Strongyloides stercoralis* infection (13). In the same study, it was found that whereas only 1% of the individuals with mild strongyloidiasis had a positive serological test for HTLV-1, 75% of the patients with severe strongyloidiasis had positive serology for HTLV-1 (13).

EPIDEMIOLOGY OF HTLV-1 AND *STRONGYLOIDES STERCORALIS* INFECTION

Concurrent infection with parasites, specifically *Strongyloides stercoralis*, in persons also infected with HTLV-1, was originally suggested as a cofactor in development of HTLV-1 disease (42). Some support for this hypothesis is provided by the high prevalence of *Strongyloides stercoralis* infection in some population groups within areas in which HTLV-1 is endemic, such as in Okinawa, Japan (42) and Jamaica (43).

However, the initial studies on the coincidence of *Strongyloides stercoralis* and HTLV-1 infections were contradictory. A positive association between *Strongyloides stercoralis* carriers and HTLV-1 antibody was initially reported in Japan (42), but further studies in the Japanese village of Tamaguskin concluded that these infections occurred independently (43). Whereas Nakada *et al*. (42) reported that in age groups over 50, the positive rate of HTLV-1 antibody was 60% in *Strongyloides stercoralis* carriers and 21% in non-carriers, Arakaki *et al*. (44) found no significant difference in the positive rate of anti-HTLV-1 antibodies between *Strongyloides stercoralis* carriers and non-carriers, suggesting that these two infections occur independently. Jamaica is another endemic area for both infections. Here one study showed no difference in the frequency of antibodies against *Strongyloides stercoralis* between HTLV-1 seropositive and HTLV-1 seronegative individuals (45). Another study showed an association between these two conditions (43).

The controversial results regarding the influence of HTLV-1 infection on the prevalence of strongyloidiasis, were due to the type of technique used to determine *Strongyloides stercoralis* infection, i.e. stool examination or serological test. Stool examination is still the gold standard for diagnosis of enteroparasitosis, due to the fact that serological tests may have a high rate of cross reactivity with several other helminthic infections. Generally, in areas where *Strongyloides stercoralis* is endemic, other enteroparasitoses also have a high prevalence. The study performed by Neva *et al*. (45) in Jamaica that did not find an association between these two infections was based on serological tests for *Strongyloides stercoralis* and HTLV-1. In the same region, a study performed with stool examination found a higher prevalence of strongyloidiasis in HTLV-1 carriers than in HTLV-1 negative individuals (43). This study also compared the prevalence of HTLV-1 in individuals with positive serologies for *Strongyloides stercoralis*, who had positive or negative stool examinations. It was found that the prevalence of HTLV-1 was higher in the group with positive stool examination than the group that had a positive serological test with a negative stool examination (43). In São Paulo, Brazil, the frequency of *Strongyloides stercoralis* in HTLV-1 carriers (12%) was higher than that observed in seronegative individuals (1·6%) (46). Recently we analysed the prevalence of intestinal parasites determined by stool examination in HTLV-1 positive and HTLV-1 negative blood bank donors (Table 2). The study was performed in Salvador, the capital of the state of Bahia, located in north-eastern Brazil. Salvador has the highest (1·35%) prevalence of HTLV-1 infection in Brazil (47). There was a significantly higher prevalence of *Strongyloides stercoralis* and *Schistosoma mansoni* among HTLV-1 carriers (15·7% and 10·5%, respectively), compared to seronegative controls (3·5% and 2·6%, respectively). There was no difference in the prevalence of other helminths such as *Ascaris lumbricoides* and *Ancylostoma duodenale*, or intestinal protozoa (*Entamoeba histolytica* and *Giardia lamblia*).

Table 2 Frequency of intestinal parasites in HTLV-1 infected individuals

Intestinal parasites	HTLV-1+ $N = 150$	HTLV-1– $N = 300$	P value
Helminths			
Strongyloides stercoralis	24 (15·7%)	10 (3·5%)	< 0·0001
Schistosoma mansoni	16 (10·5%)	8 (2·6%)	< 0·0002
Ascaris lumbricoides	18 (12%)	21 (7%)	0·1
Ancylostoma duodenale	10 (6·6%)	14 (4·6%)	0·4
Protozoa			
Entamoeba histolytica	9 (6%)	9 (3%)	0·2
Giardia lamblia	2 (1·3%)	6 (2%)	0·8

CLINICAL FEATURES OF STRONGYLOIDIASIS AND HTLV-1 INFECTION

The majority of individuals infected with *Strongyloides stercoralis* are asymptomatic or have few symptoms. Clinical evidence of disease is dependent on both the stage and severity of the infestation (48). Acute infection is usually asymptomatic. Cutaneous manifestations are due to a form of larvae migrans, called larvae currens because of the rapid migration of the lesions (49). It is characterized by short linear erythematous papules, usually in the anal margin and buttocks. The chronic phase of strongyloidiasis is usually asymptomatic or mild. Patients may have digestive manifestations such as abdominal pain and episodes of diarrhoea. The inflammatory process in the gut results in mild diarrhoea, with bulky liquid stools which do not contain mucus, blood or pus. The white blood cell count is slightly increased and shows an increase in eosinophils to several times the normal value (50).

A small number of patients with *Strongyloides stercoralis* infection develop a severe form of illness. Although rare, the severe form of strongyloidiasis is of great importance because it carries a high mortality rate even when properly diagnosed. The main clinical manifestation is diarrhoea. The inflammatory process in the small intestine hastens intestinal transit, and as the colon may also be involved, a large number of stools containing mucus and sometimes blood are observed. Abdominal pain and vomiting are usually present. The inflammatory changes result in an oedematous duodenitis. The hypotonia seen in the small intestine, as well as the parasite involvement of the stomach, are probably important factors in the aetiology of frequent vomiting. In a more advanced stage of disease, paralytic ileus appears

with consequent abdominal distension. The inflammatory process in the small intestine also leads to malabsortion, which results in hypoalbuminaemia and subsequently oedema.

In the majority of severe strongyloidiasis cases, peripheral eosinophils are typically infrequent or even absent. Depending on the intensity of vomiting and diarrhoea, alterations in water and electrolytic balance may be observed. Death in patients with severe strongyloidiasis can result from hypovolemic shock, but in the majority of the cases, is associated with larval dissemination (48). Massive alveolar haemorrhage, with documentation of larvae in the lungs or in the sputum, can cause respiratory failure. The presence of intestinal ulcers and the penetration of larvae into the circulation facilitates bacterial dissemination (51). Bacteraemia, respiratory tract infections, meningitis, and septicaemia are all complications of severe strongyloidiasis, and are associated with high mortality rates.

The majority of individuals infected with HTLV-1 are considered HTLV-1 carriers. This low morbidity is based on the low frequency (less than 5%) of patients who develop the more severe diseases associated with HTLV-1, including ATLL and HAM/TSP. However, other diseases and syndromes have been associated with HTLV-1, such as uveitis, alveolitis, poliarthritis and Sjögren syndrome.

ATLL is an aggressive lymphoproliferative disease that develops in approximately 1–2% of seropositive individuals (52). The leukaemic cells in ATLL are almost exclusively CD4+ T cells, reflecting the fact that HTLV-1 displays an *in vivo* cellular tropism for this cell population within the peripheral blood. The mechanism by which leukaemia is initiated by HTLV-1 infection remains under intense scrutiny. Of particular interest in the process of carcinogenesis is the viral protein Tax, which is strongly linked to the genesis of ATLL (53,54).

ATLL may present in 4 different clinical forms: smouldering, chronic, lymphomatous and acute. In ATLL, IL-2 production and the expression of IL-2 receptor is enhanced (55). Whereas in healthy individuals serum levels of the β chain of the IL-2 receptor are 65 ± 132 U/mL, they are highly elevated in the acute and lymphomatous forms of ATLL (mean of 9704 U/mL). The mean serum levels of the soluble IL-2 receptor in the chronic and smouldering phase were 1961 U/mL and 788 U/mL, respectively. In contrast, in HTLV-1 carriers the level was 475 U/mL (56). Patients with the smouldering form are usually asymptomatic, and the diagnosis is based on the presence of 5% or more atypical lymphocytes with the total lymphocyte count lower than 4000 cells/mm^3. These patients differ from HTLV-1 carriers because they have monoclonal integration of proviral DNA in T lymphocytes.

The chronic phase is characterized by mild hepatosplenomegaly. In this form of ATLL, the number of lymphocytes in peripheral blood is higher than 4000/mm^3 and there is a five-fold increase in the level of lactate dehydrogenase (LDH). The lymphomatous form is characterized by lymphadenopathy with or without extra-nodal involvement. The number of lymphocytes is normal, and there are no atypical lymphocytes. Patients with the lymphomatous form have a worse prognosis than those with the smouldering and chronic forms, and progression to leukaemia may occur. Death often occurs within 12 months due to opportunistic infections and septicaemia.

Acute T cell leukaemia is a very aggressive disease, with a high mortality rate in a period of weeks or months. Leukocytosis with atypical lymphocytes ('flower cells') and hypercalcaemia are common features. Hypercalcaemia is due to an increased production of osteoclast-stimulating factors, such as parathormone receptor (PTHr), leading to increased parathormone levels, increased bone reabsortion, and the appearance of bone lytic lesions (57). Infiltration of the central nervous system, bone or bone marrow may occur in this phase. Skin lesions are common and characterized by erythematous papules and nodules.

The other important clinical manifestation associated with HTLV-1 is HAM/TSP, a chronic progressive myelopathy with some similarities to multiple sclerosis. The main clinical manifestation of HAM/TSP is spastic paraparesis, characterized by a slowly progressive course of prominent upper motor neurone degeneration and mild sensory deficits with sphincter dysfunction. The onset of spastic paraparesis is insidious, and is associated with numbness, weakness, brisk deep tendon reflexus and a Babinsky sign. Difficulty in walking progresses to wheelchair dependence over the course of this disease. Onset typically occurs during the fourth decade of life, with a female to male rate of 2 : 1. Urinary manifestations such as nocturia, urgency, and incontinence are common in patients with HAM/TSP, and may be the first sign of neurological involvement in HTLV-1 (58). Host genetic and immunological factors may participate in the pathogenesis of HAM/TSP. For instance, individuals who have the MHC class I allele *HLA-A*02* have a lower frequency of HAM/TSP. It has been shown that *A*02*-restricted CD8 T cells are particularly efficient at recognizing Tax. Healthy carriers possessing the allele *A*02* have lower provirus loads than *A*02*-negative carriers (59). Although the pathogenesis of HAM/TSP is not completely understood, T cell activation and production of proinflammatory cytokines have an important role in the tissue damage. Proviral load is higher in HAM/TSP patients than in HTLV-1 carriers (60,61), as is the frequency of Tax-specific cytotoxic CD8 T cells (62,63). The main hypothesis to explain the pathogenesis of HAM/TSP involves: (a) an increased number of virus-infected CD4 T cells; (b) migration of these activated T cells to the central nervous system (64); (c) infiltration of HTLV-1-specific cytotoxic CD8+ T lymphocytes (60); and (d) secretion of high levels of

Table 3 Alterations of the immune response observed in patients co-infected with HTLV-1 and *Strongyloides stercoralis* that may predispose to the development of disseminated strongyloidiasis

Immunological abnormalities	Consequences
Decrease in IL-4 and IL-13	Reduces fluid in the intestine, decreases elimination of larvae in the stool, and increases autoinfection
Absence of IgE anti-*Strongyloides stercoralis*	Prevents mast cell degranulation
Decrease in IL-5	Decreases number of eosinophils and impairs eosinophil function

pro-inflammatory cytokines, such as IFN-γ, TNF-α and IL-6 (28,65) by CD4 and CD8 T cells and macrophages.

THE IMPACT OF HTLV-1 INFECTION ON THE CLINICAL COURSE OF STRONGYLOIDIASIS

Strongyloides stercoralis produces a chronic but usually asymptomatic infection in humans. The chronicity of the strongyloidiasis is due to the phenomenon of autoinfection. In autoinfection, the rhabditiform larvae transform into filariform larvae in the colon, and penetration through the intestinal mucosa occurs. In immunosuppressed individuals, autoinfection is also responsible for the increase in the parasite load, and for the development of disseminated strongyloidiasis (66). Due to the fact that most physicians are aware of dissemination by *Strongyloides stercoralis*, early treatment of strongyloidiasis has decreased the occurrence of disseminated *Strongyloides stercoralis* infection in immunosuppressed patients. In areas where HTLV-1 and *Strongyloides stercoralis* are endemic, recurrence of strongyloidiasis and severe strongyloidiasis has been observed in HTLV-1 carriers (7–10,67). In case reports, attention has been called to the occurrence of severe strongyloidiasis complicated by meningitis and hydrocephalus (68), duodenal obstruction caused by *Strongyloides stercoralis* enteritis (69) and fatal strongyloidiasis due to pyogenic abscess and severe pleuritis (70). However, the best evidence that HTLV-1 infection predisposes one to the development of severe strongyloidiasis, comes from two independent studies comparing the frequency of HTLV-1 infection in patients with disseminated vs. asymptomatic *Strongyloides stercoralis* infection. In Lima, Peru, 18 of 21 (85·7%) individuals with hyperinfection strongyloidiasis had positive serology for HTLV-1, whereasthe HTLV-1 infection rate in patients with intestinal strongyloidiasis was 10% (6/62). Co-infection was observed more often in adults than in children (8). In another study in Salvador, Brazil, seven of eught patients with severe strongyloidiasis were HTLV-1 positive, whereas only 1 of 50 individuals with asymptomatic strongyloidiasis had positive serology for HTLV-1 (13). These studies documented that HTLV-1 infection is the most important risk factor for the development of disseminated strongyloidiasis.

The development of severe strongyloidiasis in HTLV-1 infected individuals is due to two factors: (a) impairment of the defence mechanism against *Strongyloides stercoralis*; and (b) decreased efficacy of anti-helminth drugs in patients co-infected with HTLV-1 and helminths.

In the section on immunological responses in patients co-infected with HTLV-1 and strongyloidiasis we previously described how HTLV-1 modifies the immune response in patients infected with *Strongyloides stercoralis*. Now we will describe how changes in the immune response of patients co-infected with HTLV-1 allow increased autoinfection and predispose to the development of disseminated strongyloidiasis. Table 3 shows the abnormalities in the immune responses of patients dually infected and the consequences. Figure 1 shows how these immunological abnormalities alter the life cycle of the parasite, allowing hyperinfection.

The decrease in IL-4 and IL-13 observed in co-infected patients reduces the elimination of rhabditiform larvae in the faeces, allowing for transformation into the infective L3 filariform larvae. Two mechanisms have been proposed for killing of the penetrating infective larvae: mast cell degranulation, and direct killing of the parasite by eosinophils. Mast cells degranulation depends on the presence of IgE against parasite antigens and also activation of mast cells by IL-4. Expansion and activation of eosinophils for parasite killing depends on IL-5. In patients co-infected with HTLV-1 and *Strongyloides stercoralis*, the decrease in IL-4 and IgE prevents killing of the parasite by mast cell degranulation, and the decrease in IL-5 impairs eosinophil function, preventing these cells from killing larvae . As a result of the increase in autoinfection and decrease in parasite killing, hyperinfection occurs, leading to the disseminated or severe form of strongyloidiasis.

A decrease in the efficacy of treatment of *Strongyloides stercoralis* has been observed in patients dually infected with HTLV-1 and *Strongyloides stercoralis*. The reduced efficacy was initially documented with ivermectin (71) and thiabendazole (72), and more recently with albendazole (73). Evaluating 32 patients dually infected, and 47 patients infected only with *Strongyloides stercoralis*, Satoh *et al*. (73) found that the cure rate with albendazole was 40·6% in the HTLV-1 group and 66% ($P < 0·05$) in the HTLV-1 negative group.

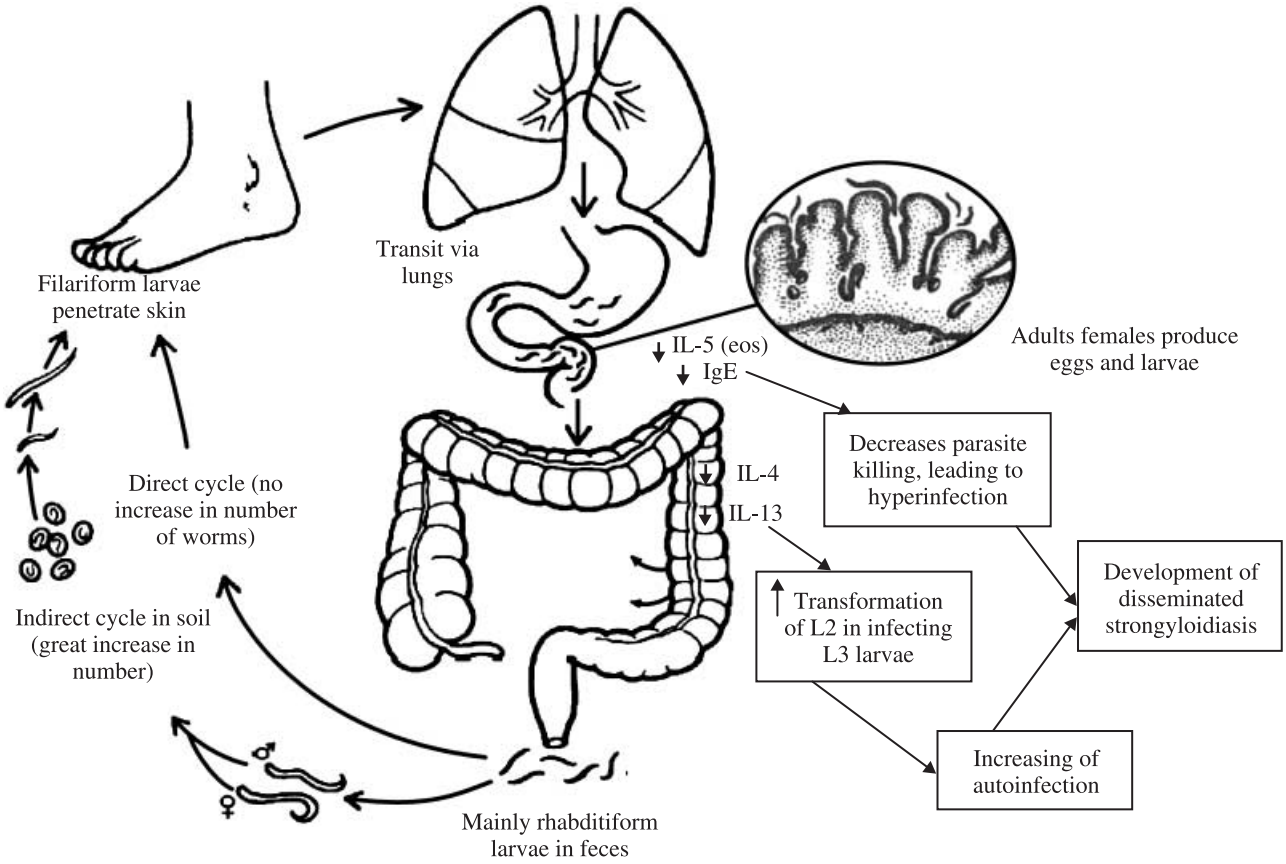

Figure 1 Life cycle of *Strongyloides stercoralis* and mechanism of disseminated strongyloidiasis in HTLV-1 infected patients. The decrease in IL-4 and IL-13 caused by HTLV-1 infection favours the transformation of rhabditiform (L2) in filariform (L3 larvae) and consequently auto-infection. The reduction in IL-5 and IgE levels observed in patients co-infected with HTLV-1 and *S. stercoralis* impair mast cell and eosinophil function, decreasing parasite killing. These alterations cause hyperinfection leading to disseminated strongyloidiasis.

With respect to thiabendazole, whereas the cure rate in patients infected only with *Strongyloides stercoralis* was 94%, in co-infected patients the cure rate was 70% ($P < 0{\cdot}05$) (72). We have also observed a decrease in the efficacy of cambendazole in dually infected patients. Whereas 38 of 40 (95%) of patients with strongyloidiasis were cured with cambendazole, in individuals co-infected with HTLV-1, cure occurred in 20 (29%) of 78 patients ($P < 0{\cdot}005$) (data not published).

The reasons for the decreased efficacy of anti-helminth drugs in patients infected with both *Strongyloides stercoralis* and HTLV-1 are not clear, but since the defence mechanisms against *Strongyloides stercoralis* are decreased in patients with HTLV-1, it is likely that the efficacy of the drugs is also dependent on an intact immune response. Satoh *et al*. (73) showed that patients who had strong expression of RNA messengers for IFN-γ and TGF-β and who were treated with albendazole, had a lower cure rate than those who were negative for both cytokines. Moreover, failure was also associated with low IgE anti *Strongyloides stercoralis* (73). The inverse correlation between IFN-γ and IL-4 and IL-5 levels in co-infected patients (40,41) supports the hypothesis that an impairment in the type 2 immune response, modulated by the high IFN-γ levels observed in HTLV-1 infected individuals, is associated with a decrease in the efficacy of anti-helminthic drugs against *Strongyloides stercoralis*.

To search for useful predictive markers for the risk of developing heavy *Strongyloides stercoralis* infection in patients infected with HTLV-1, stool and peripheral blood samples of individuals infected with both *Strongyloides stercoralis* and HTLV-1 were evaluated. Specifically, HTLV-1 proviral load and HTLV-1 IgG antibody levels were examined in relation to the *Strongyloides stercoralis* load as measured by the direct faecal smear method. Proviral load and IgG anti-HTLV-1 antibody titres were higher in patients who had heavy *Strongyloides stercoralis* infection than those with light infections (74).

THE INFLUENCE OF HELMINTHIC INFECTION ON DISEASE EXPRESSION IN HTLV-1

Although it is clear that HTLV-1 infection decreases the immune response against *Strongyloides stercoralis*, decreases the cure rate of anti-parasitic drugs, and is associated with dissemination of *Strongyloides stercoralis* infection, contradictory data have been published about the consequences of *Strongyloides stercoralis* and other helminthic infections, specifically schistosomiasis, on the clinical outcome of HTLV-1 infection.

Evaluating 36 patients with different grades of *Strongyloides stercoralis* infection and co-infected with HTLV-1, Nakada *et al*. (75) showed a high frequency (35%) of patients presenting a monoclonal integration of HTLV-1 proviral DNA in their blood lymphocytes, a condition designated as smouldering ATLL. The author also found a correlation between monoclonal integration of proviral DNA and abnormal lymphocytes in peripheral blood, with a trend for greater severity of the parasitic infection, measured by symptoms and by the number of eggs in the stools. The major criticism of this study is the absence of a control population of HTLV-1 patients not infected with *Strongyloides stercoralis*, matched for age and sex with the dually infected population. Moreover, a few demographic and clinical characteristics of the sample studied could have been confounding factors. For instance, the majority of the patients were older than 60 years (mean age of the group 61 ± 12·7 years) and many had associated chronic diseases such as chronic renal failure, diabetes mellitus, pulmonary tuberculosis, laryngeal cancer and lung cancer. Moreover, considering that the major form of HTLV-1 transmission is breast feeding, and that infection with *Strongyloides stercoralis* occurs predominantly in childhood, it is likely that these individuals had both diseases for a long period of time. Therefore, it would be incorrect to assume that *Strongyloides stercoralis* is a cofactor for development of leukaemia. In addition, these individuals had the less aggressive form of ATLL.

A separate study has also shown an association between *Strongyloides stercoralis* and ATLL, but an explanation for the association has not been given. Based on the fact that *Strongyloides stercoralis* antigen is able to induce IL-2 and to maintain IL-2-dependent T cell lines, Satoh *et al*. (76) suggested that *Strongyloides stercoralis* induces polyclonal expansion of HTLV-1 infected cells by activating the IL-2/IL-2 receptor system. They argue that this phenomenon could also explain the increased number of cells expressing CD4+ and CD25+ in patients co-infected with HTLV-1 and strongyloidiasis. One major concern is that this study relied on the ability of a crude parasite antigen to induce IL-2. This finding is not a surprise, considering that these crude antigens contain many different proteins, and that when used in high concentrations they are able to induce lymphocyte proliferation in non-infected individuals.

It is also important to point out that among HTLV-1 patients, those with ATLL have the highest unstimulated lymphocyte proliferation and secrete high levels of type 1 cytokines. Since this type of response decreases the efficacy of drugs and the defence mechanism against *Strongyloides stercoralis*, one could argue that the high frequency of strongyloidiasis in patients with ATLL, could be due to the alteration of the immune response observed in patients with ATLL, rather than the ability of *Strongyloides stercoralis* to induce malignant transformation of T lymphocytes.

Although several studies have claimed that HTLV-1 and *Strongyloides stercoralis* may be cofactors in the development of ATLL, Agape *et al*. (77) found that co-infection with *Strongyloides stercoralis* was associated with a better prognosis in ATLL. Comparing ATLL patients with and without strongyloidiasis, they found that remission rates after therapy, and overall survival rates were higher in ATLL patients with strongyloidiasis than those without *Strongyloides stercoralis* infection. The conclusion of the authors did not take into account the fact that the group with *Strongyloides stercoralis* and ATLL was much more younger than the group that had only ATLL, a confounding factor for the observed results.

More recently, we evaluated the ability of *Strongyloides stercoralis* and/or *S. mansoni* to down-modulate the immune response in HTLV-1 patients (78). Evaluating asymptomatic HTLV-1 carriers with and without co-infection with *Strongyloides stercoralis* or *S. mansoni*, it was found that co-infection with helminths decreased the production of IFN-γ, decreased the frequency of IFN-γ-secreting CD4+ and CD8+ T cells, and increased the frequency of cells secreting IL-10. Moreover, the decrease in the type 1 immune response in HTLV-1 carriers co-infected with helminths did not increase the proviral load. In fact, the proviral load in HTLV-1 carriers co-infected with helminths was lower than that observed in patients who only had HTLV-1. It was also found that helminthic infection was inversely associated with HAM/TSP. Whereas the frequency of helminthic infection was 23% in HTLV-1 carriers, it was only 3% in patients with HAM/TSP.

CONCLUSION

HTLV-1 increases the prevalence of strongyloidiasis, determined by stool examination, by interfering with the immune response to *Strongyloides stercoralis*. The high levels of IFN-γ observed in HTLV-1 infected subjects decreases IL-4, IL-5, IL-13 and IgE in response to parasite antigen. These molecules participate in defence mechanisms against *Strongyloides stercoralis*, and a decrease in this response allows not only an increasing

in autoinfection but also decreased parasite killing. As a consequence, hyperinfection occurs, with dissemination of *Strongyloides stercoralis* and development of the severe form of strongyloidiasis. HTLV-1 is recognized as the main risk factor for development of severe strongyloidiasis. Therefore, stool examinations should be performed with special attention to detect *Strongyloides stercoralis* larvae in all patients infected by HTLV-1. Early diagnosis of strongyloidiasis, before the development of hyperinfection, is highly desirable for initiation of specific therapy. Due to the decrease in efficacy of anti-helminthic drugs in patients co-infected with HTLV-1, a close follow-up of these patients is important, and other anti-parasitic drugs should be used in the event of therapeutic failure. Moreover, serological testing for HTLV-1 is recommended in all patients who have strongyloidiasis hyperinfection.

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