STRONGYLOIDES STERCORALIS HYPERINFECTION ASSOCIATED WITH HUMAN T CELL LYMPHOTROPIC VIRUS TYPE-1 INFECTION IN PERU

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Abstract. A study was conducted in Lima, Peru to determine if patients with Strongyloides hyperinfection had human T cell lymphotropic virus type-1 (HTLV-1) infection. The study included patients with Strongyloides hyperinfection and a control group consisted of sex- and age-matched asymptomatic healthy individuals whose stools were negative for Strongyloides. A third group included patients with intestinal strongyloidiasis. Sera from each study subject were tested for HTLV-1/2 by an ELISA and Western blot. The HTLV-1 infection rates (85.7%, 18 of 21) were significantly (P < 0.001) associated with Strongyloides hyperinfection compared with the control group (4.7%, 1 of 21). The HTLV-1 rate (10%, 6 of 62) for patients with intestinal strongyloidiasis was significantly (P < 0.001) lower than patients with Strongyloides hyperinfection, but did not differ significantly (P > 0.05) from the control group. The association of HTLV-1 infection was observed among 17 of 19 patients more than 20 years of age and one of two younger patients. None had HTLV-2 infection. In conclusion, Strongyloides hyperinfection among Peruvian patients was highly associated with HTLV-1 infection.

Strongyloides stercoralis is a soil-transmitted intestinal nematode that has been estimated to infect at least 60 million people, especially in tropical and subtropical regions. The parasite is unique among the parasitic nematodes because of its ability to multiply within the human host for many decades, with the potential to cause life-threatening disease in immunocompromised patients. The usual route of transmission is by penetration of the skin by filariform larvae (infectious form), following contact with contaminated soil. After migration through the lung, the larvae crawl over the glottis, and are then swallowed and develop to adults in the small bowel mucosa. The uncomplicated intestinal form of disease produces nonspecific abdominal symptoms with or without mild sporadic diarrhea. Many infected patients are completely asymptomatic. However, an autoinfective cycle may develop in a proportion of untreated cases. In these cases, infectious filariform larvae develop in the intestines from rhabditiform larvae. Penetration of the colon or the anal skin by filariform larvae, and migration through lung allow reinfection of the same host. The autoinfective cycle, which usually results in a low-grade, chronic infection in immunocompetent hosts, is poorly understood. A large number of cases of chronic, asymptomatic Strongyloides infections were reported among World War II in Southeast Asian prisoners of war and in refugees up to 40 years after leaving endemic regions.

In contrast to autoinfection, Strongyloides may produce a disseminated infection in immunocompromised hosts incapable of mounting an immune response against the parasite. Massive dissemination of invasive filariform larvae from the colon to the lung, liver, central nervous system, or kidney frequently results in a fatal outcome. Carriage by Strongyloides larvae of enterobacteria from the colon often produces sepsis or meningitis. The results of several studies have documented an association of disseminated Strongyloides infection with malignant tumors, severe malnutrition, corticosteroid therapy, and renal transplantation.

Some reports have described a significant association between human T cell lymphotropic virus type-1 (HTLV-1) infection and the carriage of S. stercoralis larvae in the stools of both Japanese and Jamaican patients. This virus is endemic in Peru and has been associated with high risk sexual behavior, Japanese origin, and Quechua ethnicity. As reported for other endemic areas, clinical sequelae, such as tropical spastic paraparesis and acute T cell lymphoma are associated with HTLV-1 infection in Peru.

The possible clinical sequelae associated with HTLV-1 and Strongyloides coinfection are unknown. The Japanese and Jamaican studies addressed only the high Strongyloides stool carriage rates or Strongyloides seropositivity rates among HTLV-1-positive individuals. Over the last 30 years, a substantial number of patients were diagnosed at the Cayetano Heredia Hospital in Lima, Peru with Strongyloides hyperinfection syndrome who were apparently normal hosts without any of the classical predisposing immunosuppressive conditions listed above. Because Strongyloides and HTLV-1 coexist in Peru, this study was conducted to determine if HTLV-1 is associated with Strongyloides infections.

MATERIALS AND METHODS

Study subjects. The study subjects were enrolled at the Cayetano Heredia Hospital and included a group of patients who presented with a Strongyloides hyperinfection. A hyperinfection case was defined by a systemic illness with chronic diarrhea, abdominal pain, loss of weight, cough, edema, hypoproteinemia, and anemia, and with two or more organs (usually lung, intestines, liver, and the central nervous system) involved, with stools positive for Strongyloides larvae, and at least one larvae in a sputum specimen. The study subjects included 21 patients who presented with Strongyloides hyperinfection (group I), 21 age- and sex-matched control healthy subjects with stools negative for Strongyloides (group II), and 62 patients with intestinal Strongyloides infections (group III) but without any systemic signs and negative sputum examination results.
**Human use statement.** The research protocol using human subjects in this study was reviewed and approved by the Naval Medical Research Institute Committee for the Protection of Human Subjects and by the Ethics Committee of the Universidad Peruana Cayetano Heredia. All patients provided written informed consent before entering the study.

**Assay techniques.** Stool samples were obtained from each study subject and tested for *Strongyloides stercoralis* larvae by the Baermann concentration technique as modified by Lumbreras. 

Serum samples from each subject were tested for HTLV-1/2 antibody by an ELISA (Cambridge Bioscience, Worcester, MA) and repeatedly reactive samples were tested by a Western Blot assay (Dupont, Wilmington, DE). Sera samples were considered positive for HTLV antibody by the presence of reactivity to the p24 and gp46 antigens and the differentiation of HTLV-1 and HTLV-2, as recommended by the manufacturer.

**Statistical analysis.** Differences in HTLV seropositivity among the three groups of study subjects were analyzed by the chi-square test with continuity correction when indicated.

**RESULTS**

The HTLV-1 seropositivity rates (18 of 21, 85.7%) among the patients with *Strongyloides* infections were significantly ($P < 0.001$) higher than the rates (1 of 21, 4.7%) for the matched control subjects (Table 1). Among the patients with uncomplicated intestinal strongyloidiasis, the HTLV-1 infection rate (6 of 62, 10%) was significantly less than rates observed for *Strongyloides* hyperinfection. Of the six HTLV-1-positive intestinal *Strongyloides* cases, two eventually developed hyperinfection with larvae in the sputum despite two previous courses each of two days of ivermectin therapy (200 µg/kg/day). None among the three groups was positive to HTLV-2.

**DISCUSSION**

Our results showed that *Strongyloides* hyperinfection was significantly associated with HTLV-1 infection. Twenty-one age- and sex-matched healthy individuals presenting to the hospital were used as controls to determine the prevalence of HTLV-1 infection in the general population. Patients with intestinal *Strongyloides* carriage only were used as indicators for exposure to the parasite in the environment. Clearly, infection by the parasite without concomitant HTLV-1 infection was insufficient to result in more severe strongyloidiasis with any significant frequency.

The results of previous studies carried out mostly in Japan and Jamaica showed a significant association between HTLV-1 infection and *Strongyloides* infection. The diagnostic criteria used in these studies for *Strongyloides* was either the presence of *S. stercoralis* larvae in stool or seroreactivity antigens. For example, in Southeast Japan, 60% of the individuals who had intestinal *Strongyloides* were seropositive for HTLV-1 compared with a 20% rate of HTLV-1 seropositivity in the parasite-free control group.

Similarly, in Jamaica, 67% the of patients with *Strongyloides*-positive stool cultures were also positive for HTLV-1 infection, while only 15% of the patients with negative stool cultures were positive for HTLV-1 infection. None of these earlier studies contain sufficient clinical data to determine whether the high rate of *Strongyloides* carriage had any influence on the clinical manifestations of HTLV-1-infected individuals. However, an association between disseminated *Strongyloides* infection syndrome and concomitant HTLV-1 infection has been suggested by several isolated case reports.

The mechanism(s) of the immune response that allows the human host to control *Strongyloides* infection, but not to eradicate the parasite, remain unclear. The cellular immune response may be of less importance since there is no increased incidence of disseminated strongyloidiasis in patients with acquired immunodeficiency syndrome with low CD4 counts. A role for parasite-specific antibody, in particular IgE, has been strongly implicated in *Strongyloides* infections.

### Table 1

<table>
<thead>
<tr>
<th>Study subjects</th>
<th>HTLV-1 seropositivity rate*</th>
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<tbody>
<tr>
<td>1) <em>Strongyloides</em> hyperinfection</td>
<td>18/21 (85.7%)</td>
</tr>
<tr>
<td>2) Control: asymptomatic healthy</td>
<td>1/21 (4.7%)</td>
</tr>
<tr>
<td>(matched by age and sex)</td>
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<tr>
<td>3) Intestinal <em>Strongyloides</em> infection</td>
<td>6/62 (9.7%)</td>
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</tbody>
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* $P < 0.001$, group 1 versus 2; $P < 0.001$, group 1 versus 3; $P > 0.05$ (not significant) group 2 versus 3.

### Table 2

<table>
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<tr>
<th>Age and gender stratification of <em>Strongyloides Stercoralis</em> hyperinfection patients*</th>
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<tbody>
<tr>
<td>Infection by HTLV-1</td>
</tr>
<tr>
<td>≤20 years of age</td>
</tr>
<tr>
<td>&gt;20 years of age</td>
</tr>
<tr>
<td>Hyperinfection syndrome (n = 21)</td>
</tr>
<tr>
<td>Male:</td>
</tr>
<tr>
<td>Female:</td>
</tr>
<tr>
<td>Intestinal strongyloidiasis (n = 62)</td>
</tr>
<tr>
<td>Male:</td>
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<tr>
<td>Female:</td>
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* HTLV-1 = human T cell lymphotropic virus type-1; NS = not significant.
immunity, 3 but definitive evidence is lacking. In disseminated strongyloidiasis, low serum IgE levels and few or no eosinophils in the peripheral blood have been described.26,27 In more than 92% of our cases with Strongyloides hyperinfection, no eosinophilia was noted and none had HIV infection.

The epidemiologic data indicated that almost 50% of the cases of Strongyloides hyperinfection were born in the Andes, while only 11% of the general Lima population, where our center is located, is native to the Andes.27,28 Similarly, in our patients with tropical spastic paraparesis and HTLV-1 infection, almost 50% were born in the Andes.19 Strongyloides is not endemic in the Andean region; however, Andean-born individuals frequently work in the Amazon Region where Strongyloides, but not HTLV-1, is endemic. These individuals acquire the parasite and when they return, they develop Strongyloides hyperinfection, which is very rare in those individuals native to the Amazon.

Data have been published that showed a reduced efficacy of chemotherapy with thiabendazole among Strongyloides patients in Okinawa with concomitant HTLV-1 infection.29 Clinical findings at our Institute (Terashima A, unpublished data) with Strongyloides hyperinfection showed that thiabendazole or ivermectin was associated with more failures in patients with HTLV-1 infection compared with HTLV-negative patients. A report of a case with severe strongyloidiasis and HTLV-1 infection who developed acute T cell leukemia has also been published.34 In our series, two patients with strongyloidiasis and HTLV-1 infection developed acute T cell lymphoma 15 and two years, respectively, after diagnosis of the strongyloidiasis.

On the basis of our findings, we recommend testing for HTLV-1 infection in any patient who presents with a Strongyloides hyperinfection without an obvious cause. In addition, we suggest HTLV-1 testing for any individual with intestinal strongyloidiasis who fails to clear parasites from their stools after two courses of standard treatment with either ivermectin or thiabendazole.

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