Treatment failure in intestinal strongyloidiasis: an indicator of HTLV-I infection

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Background: The association of severe strongyloidiasis with HTLV-I is well known; however, the seroprevalence of HTLV-I in other groups with strongyloidiasis is still unknown. We conducted a prospective study in patients with intestinal strongyloidiasis without known immunodepression who failed to respond to standard therapy with ivermectin or thiabendazole (failure was defined as one positive stool examination at the post-therapy follow up). All these patients were tested for HTLV-I by ELISA and Western Blot.

Results: Forty seven patients were evaluated: 74.5% (35 out of 47) were HTLV-I positive, without significant difference between males (76%) and females (72.7%).

Conclusions: We recommend that all patients with uncomplicated intestinal strongyloidiasis, who fail standard therapy, be studied for HTLV-I infection.


Strongyloides stercoralis (S. stercoralis) is a soil-transmitted intestinal nematode with a worldwide distribution but with a higher prevalence in tropical regions. Global prevalence is estimated at 60 million people and infection is usually acquired by penetration of the skin by filariform larvae.1

Low-grade, most often clinically asymptomatic, internal autoinfective cycles may develop in a proportion of untreated immunocompetent individuals; an intact immune system apparently is able to prevent widespread dissemination. Occasionally, more severe cases of strongyloidiasis autoinfection are detected, with pulmonary involvement and strongyloides larvae in sputum. In those that are severely immunosuppressed, massive dissemination of invasive filariform larvae from the intestine to the lung, liver, central nervous system, or kidney, frequently results in a fatal outcome.2 The results of several studies have documented an association between strongyloides infection and malignancy, severe malnutrition, corticosteroid therapy and renal transplantation.3 We and others have recently described the strong association between disseminated strongyloidiasis and HTLV-I infection in otherwise healthy patients.4-6

A three-day course of thiabendazole has been shown to have an efficacy of 88% or greater in uncomplicated intestinal infection. However, the high incidence of severe nausea and dizziness often limit the ability of patients to complete the full-course.7 Recently, ivermectin in one or two consecutive single daily doses has given a cure rate of 88% with few side effects and excellent tolerance.8 The experience at our institution with uncomplicated infection has been similar. The objective of the present study was to evaluate for concomitant HTLV-I infection this group of patients who fail to respond to standard therapy.

MATERIAL AND METHODS

Patients who met the following criteria were included:

(a) Patients with gastrointestinal discomfort such as abdominal pain, diarrhea, and weight loss without other systemic or pulmonary signs, and in whom S. stercoralis is detected in stools but not in sputum (with 1–2 negative tests); Patients with two or more organs involved with S. stercoralis, and who in addition had positive sputum test for S. stercoralis defined in our institution as having hyperinfestation;

(b) Patients who received standard treatment against intestinal strongyloidiasis: thiabendazole 25 mg/kg/day for three days (maximum dose 2 gm) (Merck Sharp & Dohme) or ivermectin (Merck Sharp & Dohme, France) 200 mcg/kg/day as a single dose, which was provided free of charge to the patients.

(c) Patients who underwent post-treatment stool examinations at 1 week, 1 month, or at least three times within 6 months after treatment (minimum three post-treatment examinations), with the use of the Baermann method modified by Lumbreras.9

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Prolonged or repeated treatment. This is because only with clearly disseminated hyperinfection require ivermectin. In the authors' institution, since 1970, for lung and other organs are killed by thiabendazole or standard regimen was used of thiabendazole 25 mg/kg/day for 3 days and then 1g daily for 15–30 days with excellent results. Recently, with ivermectin the 2-day cycle was repeated two or three times at 15–30 days intervals and there is a cure rate of >90% in these severe chronic cases with positive sputum examination (Terashima A. Unpublished data.)

In the present study, the authors did not examine HTLV-I seroprevalence rates in a matched control group with uncomplicated intestinal strongyloidiasis that was completely responsive to therapy; such patients respond to three days of thiabendazole or a single dose of ivermectin with a cure rate of >90%. The rate of HTLV-I in such uncomplicated patients in a previously published study from the same patient population was 10% and for the healthy control group 3.9%. Patients non-responsive to the therapy have a 74.5% rate of HTLV-I seropositivity (if the children are excluded, the rate of HTLV-I infection is 80%). One Japanese study has recognized a low therapeutic efficacy of standard treatment against strongyloides in patients with HTLV-I, however, no details of the clinical manifestations of infection was provided for those patients.

Because of the lack of larvae in the sputum, the 47 patients described here are not recognized as severe strongyloidiasis but would be classified as uncomplicated intestinal strongyloidiasis. Some more advanced degree of autoinfection or dissemination has likely occurred, but without detectable larvae in the sputum. Most authorities, using current paradigms, would not allow these individuals to be considered as disseminated hyperinfection. This type of patient has been seen as early as 1973 and they have been described by Alvarez. At that time, however, HTLV-I was not yet described; these patients are 'intermediate' between uncomplicated intestinal strongyloidiasis and disseminated hyperinfection. This 'intermediate' clinical group described as failure to respond to standard treatment, here likely represents an earlier phase in the progression of the immunosuppression against strongyloidiasis due to HTLV-I. None of the patients in this study had HAM/TSP or lymphoma/leukemia (ATLL).

HTLV-I does not seem to predispose to the S. stercoralis infection, but appears to alter the clinical patterns. Recently, Neva et al. published that the PBMC in HTLV-I-infected individuals spontaneously produce a high level of interferon IFN-\(\gamma\) and produce little IL-4 in response to mitogenic stimulation. This would relate to a poor ability to make IgE immunoglobulin isotype, thought to play the major role in host defense against strongyloides.

**RESULTS**

Between 1990 and 1998, 47 patients (25 males:22 females) were enrolled who met the inclusion criteria for strongyloides treatment failure; 41/47 had some positive stools cultures during the first month, 6/47 over one to six months. The majority of cases had two to three positive stools cultures and needed a second cycle of our standard therapy. As shown in Table I, overall HTLV-I seropositivity was high at 74.5% (35/47). HTLV-I seropositivity did not differ by gender. Children under 10 years of age were uniformly suffering from clinical malnutrition and only 2/6 (33%) were HTLV-I positive.

In the authors' institution, 50–60 patients a year with S. stercoralis are seen; only those patients were entered who could be appropriately followed. No bias was found in patient selection.

**DISCUSSION**

The association between HTLV-I and strongyloides was initially recognized in Kagoshima, an HTLV I endemic tropical region in Japan. In Jamaica, 58% of the patients with strongyloides in stools were also HTLV-I seropositive compared with a seropositivity of 15% in those with negative stools. However, neither of the above studies provided any data on the clinical manifestations of the strongyloides infection in their patients.

In the authors' recently published study, we described patients in Peru with clinical manifestations of disseminated hyperinfection with S. stercoralis. Using the parasitologic criteria of a positive sputum examination for S. stercoralis larvae, the authors found that 86% of these individuals were HTLV-I positive. Such patients with clearly disseminated hyperinfection require prolonged or repeated treatment. This is because only adult worms, and not immature migrating larvae in the lung and other organs are killed by thiabendazole or ivermectin. In the authors' institution, since 1970, for patients with sputum positive and hyperinfection a standard regimen was used of thiabendazole 25 mg/kg/day for 3 days and then 1g daily for 15–30 days with excellent results. Recently, with ivermectin the 2-day cycle was repeated two or three times at 15–30 days.

**Table 1.** HTLV-I seropositivity in patients with intestinal strongyloidiasis and parasitologic failure to standard therapy

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 years</td>
<td>2/5</td>
<td>0/1</td>
<td>2/6</td>
</tr>
<tr>
<td>10–29 years</td>
<td>6/7</td>
<td>3/6</td>
<td>9/13</td>
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<tr>
<td>30–49 years</td>
<td>8/8</td>
<td>5/7</td>
<td>13/15</td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>3/5</td>
<td>8/8</td>
<td>11/13</td>
</tr>
<tr>
<td>Total</td>
<td>19/25 (76%)</td>
<td>16/22 (72.7%)</td>
<td>35/47 (74.5%)</td>
</tr>
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</table>
In the Amazon Region of Peru, the prevalence of strongyloides infection is estimated to be 30-70%.\textsuperscript{14} Severe clinical manifestations are mostly observed in malnourished children but not in adults, since HTLV-I is not endemic in the jungle. The Andean Valleys are endemic for HTLV-I but not for strongyloides. Fifty to sixty percent of patients were born in the Andean region but they had in common a history of temporary residence in the Amazon Region to find temporary work; they then acquired strongyloidiasis and, because of their HTLV-I status, developed the more severe clinical manifestations of infection. This internal migration of the Andean population to the Amazon region has permitted the association of these two infections and created a new health problem in Peru. In the cases of HAM/TSP (HTLV-I myelopathy or tropical spastic paraparesis), 50% were born in the Andean cities.\textsuperscript{15}

In conclusion, all patients with uncomplicated intestinal strongyloidiasis, who fail standard therapy and who do not have any other obvious immunosuppression, should be studied for HTLV-I infection.

REFERENCES