IMPAIRMENT OF HOST IMMUNE RESPONSE AGAINST STRONGYLOIDES STERCORALIS BY HUMAN T CELL LYMPHOTROPIC VIRUS TYPE 1 INFECTION

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Abstract. A large-scale study was undertaken to clarify the prevalence rate of strongyloidiasis in Okinawa, Japan and to evaluate the relationship between strongyloidiasis and infection with human T cell lymphotropic virus type 1 (HTLV-1). The prevalence rate of Strongyloides stercoralis and HTLV-1 infection were 6.3% and 14.0%, respectively. Among 2,185 patients more than 50 years of age, the rate of S. stercoralis infection was significantly higher in patients with HTLV-1 infection compared with patients without HTLV-1 infection. In 252 patients treated with ivermectin, serum IgE levels and peripheral eosinophil counts were significantly lower in HTLV-1 co-infected patients compared with patients without HTLV-1 infection. In addition, the anthelmintic effect was significantly lower in patients with HTLV-1 infection compared with patients without HTLV-1 infection. Our prospective study demonstrated a prevalence rate for strongyloidiasis and HTLV-1 infections, and clearly demonstrated that co-infection with HTLV-1 impaired the immune response against S. stercoralis.

INTRODUCTION

Strongyloidiasis is widely distributed in tropical and subtropical areas. In Japan, Okinawa Prefecture, which is in the subtropics, has an endemic for Strongyloides stercoralis infection. In addition, Okinawa Prefecture has a high infection rate of human T cell lymphotropic virus type 1 (HTLV-1).

A close relationship between strongyloidiasis and HTLV-1 has been reported in disease-endemic areas.1–3 In addition, a high prevalence rate of infection with S. stercoralis and a high rate of therapeutic failure have been noted in HTLV-1 carriers.4–6 Furthermore, severe forms of strongyloidiasis have been documented in patients with HTLV-1 infection.7,8 These reports have indicated that HTLV-1 has strong immunologic implications in patients with S. stercoralis infection. It has also been reported that Th2 type of immune response is predominant in S. stercoralis infection and that serum IgE levels are low in patients coinfected with S. stercoralis and HTLV-1.9–10

However, there have been few prospective studies evaluating the relationship between strongyloidiasis and HTLV-1 infections. With this background, we have conducted a prospective inpatient survey to examine the prevalence rate of strongyloidiasis and HTLV-1 infection, and to evaluate the relationship between these infections. In addition, we also analyzed serum IgE levels and peripheral eosinophil counts to evaluate immune response in patients with strongyloidiasis who were treated with ivermectin.

SUBJECTS, MATERIALS, AND METHODS

Patients for evaluation of prevalence of S. stercoralis infection and HTLV-1 infection. The present study included 3,360 patients who were admitted to the First Department of Internal Medicine, Ryukyu University Hospital, Okinawa, Japan, between 1991 and 2004.

Patients for assessment of the therapeutic effect of ivermectin. These patients had mild-to-moderate strongyloidiasis for a period 11 years from 1990 to 2001. Before entry to this study, each patient was informed of the orphan-drug study, its purpose, and potential side effects. The study included 252 patients with strongyloidiasis who were treated with ivermectin (administered orally at a dose of 100 μg/kg, and the same dose was repeated two weeks later).

Assays to detect HTLV-1 infection and S. stercoralis infection. Serum antibody to HTLV-1 was prospectively measured in all patients by the gelatin particle agglutination method,11 and infection of S. stercoralis was prospectively diagnosed using the agar plate culture method.12 Written informed consent for examination was obtained from all patients. In patients where the therapeutic effect of ivermectin was assessed, total serum IgE levels were determined by latex nephelometry and peripheral eosinophils were counted by May-Giemsa staining.

Definition of the effect of anthelmintic treatment. The effect of anthelmintic treatment was assessed once 1–4 weeks after the administration of ivermectin and a second time 12 months after the initial treatment. In the assessment of the anthelmintic effect, as tested by the agar plate culture method, patients whose stool was negative for S. stercoralis at 12 months after the initial treatment were considered cured.

Statistical analysis. The chi-square test was used to assess differences between sex and between HTLV-1 positive and negative patients. The Mann-Whitney U test was used to compare serum IgE levels and peripheral eosinophil counts between HTLV-1-positive patients and HTLV-1-negative patients.

RESULTS

Prevalence of S. stercoralis infection and HTLV-1 infection. The study population was composed of 2,000 males and 1,360 females with a mean ± SD age of 54.9 ± 17.5 years. More than 95% of infected patients with S. stercoralis were more than 50 years of age. The total prevalence rate of S. stercoralis infection was 6.3% (213 of 3,360). The prevalence rate of S. stercoralis infection in males and females was 7.8% (155 of
Prevalence of *Strongyloides stercoralis* infection

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
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<tbody>
<tr>
<td>0–19</td>
<td>0/46 (0.0)</td>
<td>0/37 (0.0)</td>
<td>0/83 (0.0)</td>
</tr>
<tr>
<td>20–29</td>
<td>0/172 (0.0)</td>
<td>0/128 (0.0)</td>
<td>0/300 (0.0)</td>
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<tr>
<td>30–39</td>
<td>1/202 (0.5)</td>
<td>0/123 (0.0)</td>
<td>1/325 (0.3)</td>
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<tr>
<td>40–49</td>
<td>11/277 (4.0)</td>
<td>1/190 (0.5)</td>
<td>12/467 (2.6)</td>
</tr>
<tr>
<td>50–59</td>
<td>22/554 (4.2)</td>
<td>14/273 (5.1)</td>
<td>36/827 (5.7)</td>
</tr>
<tr>
<td>60–69</td>
<td>69/500 (13.8)</td>
<td>15/325 (4.6)</td>
<td>84/825 (10.2)</td>
</tr>
<tr>
<td>70–79</td>
<td>42/338 (12.4)</td>
<td>21/218 (9.6)</td>
<td>63/556 (11.3)</td>
</tr>
<tr>
<td>≥ 80</td>
<td>10/111 (9.0)</td>
<td>7/66 (10.6)</td>
<td>17/177 (9.6)</td>
</tr>
<tr>
<td>Total</td>
<td>155/2000 (7.8)*</td>
<td>58/1360 (4.3)</td>
<td>213/3360 (6.3)</td>
</tr>
</tbody>
</table>

*P < 0.001 for HTLV-1-positive vs. negative patients by chi-square analysis.

Serum IgE levels were significantly lower in patients with HTLV-1 infection (mean ± SD = 587.5 ± 442.6 IU/mL) compared with patients without HTLV-1 infection (1,116.2 ± 836.5 IU/mL) (P < 0.0001). In addition, peripheral eosinophil counts were also significantly lower in patients with HTLV-1 infection (381.6 ± 222.7/mm³) compared with patients without HTLV-1 infection (593.3 ± 891.0/mm³) (P = 0.0035) (Table 6).

### DISCUSSION

*Strongyloides stercoralis* lives in warm and wet soil. Filariform larvae infect humans through the skin of bare feet. After infection, larvae migrate to the duodenum and grow into mature females. Rhabditiform larvae hatched from eggs are ejected from the host. However, some develop into filariform larvae and reinfect through the colon or anal skin (autoinfection). Therefore, once infected, the carrier state of *S. stercoralis* lasts for a long time.

In the present study, the infection rate of *S. stercoralis* was 6.3% and most patients were more than 50 years of age. The increased rate of strongyloidiasis in patients more than 50 years of age was probably due to the cumulative risk of infection over time. The prevalence of *S. stercoralis* infection was significantly higher in males compared with females. This result was similar to those of previous reports.13,14 Hayashi and others reported that in the Yaeyama District in Okinawa, Japan, residents worked barefoot in rice paddies and used human excreta as fertilizer until 1965.13 In addition, since male farmers were primarily responsible for distributing human feces in fields, it was assumed that males were more readily exposed to *S. stercoralis*.13

Human T cell lymphotropic virus type 1 is transmitted by three routes: the first is vertical (in the breast milk or transplacental), the second is horizontal (sexual), and the third is
The development of strongyloidiasis in HTLV-1-infected individuals is due to two factors: impairment of the immune mechanism against *S. stercoralis* and decreased efficacy of anti-helminth drugs in patients co-infected with HTLV-1 and helminthes. The reasons for the decreased efficacy of anti-helminth drugs in patients infected with both *S. stercoralis* and HTLV-1 are not clear, but because the immune mechanisms against *S. stercoralis* are decreased in patients infected with HTLV-1, it is likely that the efficacy of the drugs also depends on intact immune responses.3

In *S. stercoralis* infection, a Th2 type immune response is predominant. However, patients infected with HTLV-1 have spontaneous T lymphocyte proliferation and infected T lymphocytes produce high levels of interferon-γ, which are associated with the Th1 type of immune response. In contrast, HTLV-1-infected T lymphocytes produce low levels of interleukin-4, as well as interleukin-5, which play an important role in the Th2 type immune response.10,17 However, as demonstrated in the present study, patients co-infected with HTLV-1 had significantly lower levels of serum IgE and peripheral eosinophil counts compared with patients without HTLV-1 infection. In accordance with this evidence, in the present study, the prevalence rate of *S. stercoralis* infection and the rate of therapeutic failure were high in patients with HTLV-1 infection compared with patients without HTLV-1 infection. Since the Th2 type immune response is necessary for defense against helminthes, and eosinophils and IgE have important roles against helminthes,9,10 these results suggest that co-infection with HTLV-1 may impair the Th2 type of immune response in patients infected with *S. stercoralis*. In conclusion, our prospective study clearly demonstrates the relationship between *S. stercoralis* infection and HTLV-1 infection. Since impairment of the immune response to *S. stercoralis* was evident in patients co-infected with HTLV-1, new strategies to eradicate *S. stercoralis* should be established in future studies.

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**REFERENCES**


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**Table 5**

<table>
<thead>
<tr>
<th>HTLV-1</th>
<th>No. cured/no. of subjects (%)</th>
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<tbody>
<tr>
<td>Positive</td>
<td>28/56 (50.0)*</td>
</tr>
<tr>
<td>Negative</td>
<td>80/96 (83.3)</td>
</tr>
<tr>
<td>Total</td>
<td>117/152 (77.0)</td>
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*P < 0.0001 for HTLV-1 negative patients vs. positive patients by chi-square analysis.

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**Table 6**

<table>
<thead>
<tr>
<th>HTLV-1</th>
<th>Serum IgE (IU/mL)</th>
<th>Eosinophils (mm³)</th>
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</thead>
<tbody>
<tr>
<td>Positive</td>
<td>587.5 ± 442.5</td>
<td>381.6 ± 222.7</td>
</tr>
<tr>
<td>Negative</td>
<td>1,116.2 ± 836.5</td>
<td>593.3 ± 891.0</td>
</tr>
</tbody>
</table>

*Values are the mean ± SD.

† P < 0.0001 for HTLV-1-positive vs. negative by the Mann-Whitney U test.

‡ P = 0.0035 for HTLV-1-positive vs. negative by the Mann-Whitney U test.


