MICROSPORIDIOSIS IN TRAVEL-ASSOCIATED CHRONIC DIARRHEA IN IMMUNE-COMPETENT PATIENTS

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Abstract. We analyzed retrospectively 21 immune-competent travelers with chronic traveler’s diarrhea (3–6 weeks) after returning from recreational travel to the tropics with stool samples positive for microsporidia. Nine patients had been treated with albendazole and 12 patients had been treated symptomatically. Diarrhea resolved in 8 of 9 and 12 of 12 patients, respectively. In the albendazole group, Encephalitozoon intestinalis was cleared in 4 of 4 patients and Enterocytozoon bieneusi persisted in 7 of 7 patients (2 patients were lost to follow-up). In the symptomatic treated group microsporidia persisted in stool samples of all patients. We conclude that there is only a transient correlation between detection of microsporidia in stool and gastrointestinal symptoms, and suggest that microsporidia infection may cause clinical symptoms during the early stages of infection that resolve even though the microsporidia may persist.

INTRODUCTION

Microsporidia, the intracellular spore-forming protozoa, have been recognized in various hosts1 and in humans.2–4 Among the more than 1,000 species of microsporidia, Enterocytozoon bieneusi and Encephalitozoon intestinalis have been associated with diarrhea in immune-incompetent patients, in particular in the context of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and organ transplantation.5 Albendazole is the recommended treatment for intestinal microsporidiosis in immune-suppressed patients, especially for E. intestinalis.6–8 However, only little data are available on their role in causing diarrhea in travelers9 and the efficacy of albendazole in microsporidia-associated diarrhea in immune-competent persons.10,11

We performed a retrospective chart review of 21 patients with chronic diarrhea after returning from recreational travel to the tropics with positive stool samples for microsporidia. Therapy was left to the discretion of the treating physician; 12 patients were treated only symptomatically, and 9 received albendazole in addition to symptomatic treatment. The Ethics Committee of our institution waived the need for informed consent.

SUBJECTS AND METHODS

We investigated 21 immune-competent travelers between 18 and 49 years of age (median = 26 years, 9 men and 12 women) who attended our infectious diseases outpatient clinic for chronic diarrhea lasting for more than 3 weeks (3–6 weeks, median = 4 weeks) after return from traveling to the tropics from January 2003 to January 2004 in whom stool samples were positive for microsporidia (E. bieneusi and/or E. intestinalis). Stool samples were obtained after return from travel and not prior to travel. A calcofluor white immunofluorescence stain was done as described and read at 360 nm.12,13 Speciation was done by size: E. bieneusi spores measure approximately 0.9 × 1.5 mm and E. intestinalis measure approximately 1.5 × 3.0 mm. After the exclusion of other causes for diarrhea, all patients with chronic diarrhea attending our clinic during this time had stool samples tested for microsporidia. Their medical history and results of physical examinations were otherwise unremarkable in all cases, the patients did not have any underlying diseases (had no risk factors) and none was taking medication. The patients returned from recreational travel to Thailand (n = 2), Zaire (n = 2), India (n = 11), Indonesia (n = 2), and Nigeria (n = 2). There was no occupational exposure. The duration of travel was between 2 and 16 weeks (median = 4 weeks). Two of the patients had a history of previous travel (both visited Thailand for the second time). All patients had a history of prior evaluation by a primary care physician, which resulted in no diagnosis with respect to diarrhea and the transfer of the patients to our clinic. Routine blood samples showed no electrolyte disturbance, a normal blood count and differential count, and normal liver and renal function test results in all patients. All patients were HIV negative. Four patients had a history of Entamoeba histolytica– or Giardia lamblia– associated diarrhea, which was treated effectively with standard courses of metronidazole prior to enrollment in this series. The control stool samples, which were obtained 3 and 4 weeks after the metronidazole standard treatment course, were negative for Entamoeba histolytica or Giardia lamblia, but diarrhea persisted for an additional 4–5 weeks in all cases. Thereafter, stool samples (chronic diarrhea ≥ 4 weeks) were tested for microsporidia. Two of these patients were treated with albendazole and two with symptomatic therapy.

RESULTS

The symptoms of the patients included watery, bloody surface, or unspecific diarrhea, abdominal discomfort, cramps, flatulence, fatigue, weight loss, loss of appetite, and subfebrile temperatures (Table 1). There was no difference in the duration of symptoms between the groups (Table 1). Twelve patients were treated symptomatically, and 9 of 21 received albendazole (400 mg twice a day for 4 weeks). Control stool samples were tested for microsporidia after four weeks. The laboratory was not biased by prior diagnosis, since no information regarding diagnosis or treatment was provided. Two of the albendazole-treated patients received a second treatment course with albendazole (for three and four weeks, re-
Symptoms and duration of symptoms of 21 immune competent patients with intestinal microsporidiosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of patients with symptom (duration in weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea (watery)</td>
<td>10 (4–6)*</td>
</tr>
<tr>
<td>Diarrhea (bloody)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Diarrhea (non-specific)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>12 (4–6)*</td>
</tr>
<tr>
<td>Flatulence</td>
<td>6 (4–5)*</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (4–6)*</td>
</tr>
<tr>
<td>Temperature (≤ 37.4°C)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>12 (4–6)*</td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td>3 (3–4)</td>
</tr>
<tr>
<td>Weight loss (3–5 kg)</td>
<td>12 (4–6)*</td>
</tr>
</tbody>
</table>

* Duration of symptom in days (median [range]).

In our study, spores persisted in all travelers despite the treatments were interrupted due to adverse drug reactions.

In the 12 symptomatically treated patients, all gastrointestinal symptoms were self-limiting and resolved completely within 1–2 weeks. However, control stool samples taken four weeks after the initial stool sample continued to be positive for microsporidia in all patients (Table 2). In seven of nine albendazole-treated patients, gastrointestinal symptoms also resolved completely within 2–4 weeks. In one patient, several gastrointestinal symptoms (abdominal discomfort and cramps, loss of appetite, flatulence, fatigue, subfebrile temperature, and weight loss [5 kg]) resolved, but an increased stool frequency (up to five times per day) persisted for months. This patient had slightly elevated levels of alanine aminotransferase (44 U/L) and aspartate aminotransferase (53 U/L). In another patient, all gastrointestinal symptoms (increased stool frequency [five times per day], flatulence, abdominal discomfort, and diffuse abdominal pain [only in situations with exceptional work load]) persisted despite a second treatment course with albendazole. This patient was lost to follow-up and a second patient was not willing to give a control stool sample. In four patients with *E. intestinalis* infection, control stool samples were negative for *E. intestinalis* after albendazole therapy. In the remaining seven patients, stool samples continued to be positive (Table 2).

Microsporidia were present in stool samples of all 21 patients regardless of albendazole treatment, and clinical symptoms of gastrointestinal infection, for which microsporidia were thought to have contributed, were self-limited in 19 (90.5%) of 21. In a previous report of microsporidiosis in four travelers, diarrhea was self-limited, and the spores were cleared from the stools in all travelers not infected with HIV (n = 3), but showed a chronic course in one HIV-infected patient. In our study, spores persisted in all travelers despite clinical cure. This could be due to a different method of detection, or the small sample size of the previous study. In another report of two patients with travel-associated chronic diarrhea and positive stool assay results for microsporidiosis, therapy based on albendazole had no influence on the intestinal disorder but cleared microsporidian spores in stool. The persistence of microsporidia and disappearance of the intestinal disorder in our series suggests only a transient pathogenic role of microsporidia in immunocompetent patients with traveler’s diarrhea. Microsporidia infection may cause clinical symptoms during the early stages of infection (e.g., diarrhea) that resolve even though the microsporidia may persist. This is not unusual for parasites, in which acute infections cause clinical symptoms that resolve in immunocompetent individuals, but where the parasites persist (e.g., toxoplasmosis) and is supported by data from animal studies. Most of what is known about microsporidiosis is based on studies in immunocompetent laboratory animals, including rabbits, rodents, and non-human primates. In these hosts, microsporidiosis commonly causes clinical symptoms during the acute stage of infection (e.g., ascites in mice) that resolve after a few weeks, yet the microsporidia persist for the life of the animal if left untreated.

Albendazole is the currently recommended treatment for microsporidiosis, especially for *E. intestinalis*, in immunosuppressed patients. In *E. bieneusi* infections, however, albendazole was reported to improve only the clinical status, while it failed to eliminate the organism from the stool. Our data are consistent with this finding since microbiologic efficacy of albendazole was seen only in *E. intestinalis* infection but not in *E. bieneusi* infection. However, since the microsporidia are so small, and size discrimination between *Encephalitozoon* and *Enterocytozoon* is inaccurate and often not possible (Table 2), a polymerase chain reaction (PCR) should be conducted to more reliably identify these species, and ultimately the efficacy of albendazole. Unfortunately, this was not possible in this study since stool samples were not available for PCR testing.

In immunocompetent individuals, microsporidia infections may persist even after clinical symptoms resolve, as this has been observed in other mammals. Thus, only a transient pathogenic role of microsporidia in immunocompetent patients with traveler’s diarrhea is likely: Microsporidia infection may cause clinical symptoms during the early stages of infection (e.g., diarrhea) that resolve even though the microsporidia may persist. Since other microorganisms that might contribute to diarrhea were not identified, since albendazole is ineffective against *E. bieneusi*, and since immunocompetent laboratory animals remain persistently infected with microsporidia after resolution of clinical symptoms, our
study supports the likelihood that microsporidiosis does contribute to chronic travelers' diarrhea.9,11,14-17

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