Is Traveler’s Diarrhea a Significant Risk Factor for the Development of Irritable Bowel Syndrome? A Prospective Study

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A total of 564 travelers were enrolled in a study aimed at investigating the influence of traveler’s diarrhea in the development of irritable bowel syndrome. At 6–7 months after repatriation, we found that an episode of traveler’s diarrhea was associated with a quintuple risk of developing irritable bowel syndrome.

Functional gastrointestinal disorders—and irritable bowel syndrome (IBS), in particular—have a high prevalence among the general population [1]. The pathophysiology of this syndrome is multifactorial and includes alterations in gut motor function, psychological factors, and alterations in visceral perception [2].

Recent studies have suggested that patients who experience an episode of infectious diarrhea may develop new IBS at a relatively high rate [3–5]. Because infectious diarrhea commonly occurs among travelers, it has been postulated that traveler’s diarrhea may trigger development of IBS [6–8]. One study went further and established infection with *Shigella* species as the cause of postinfectious IBS in 8% of cases [6]. However, in some of these studies, the patient groups were rather small, and the studies consequently lacked power to detect a true difference [8]. We set out to examine, in a large group of travelers, the hypothesis that traveler’s diarrhea is associated with the development of IBS after travel. In addition, we attempted to determine parameters that would predict which travelers were at a higher risk for developing IBS.

**Travelers and methods.** The Travel Clinic at the Bnai Zion Medical Center (Haifa, Israel) provides counseling and vaccinations for >3000 travelers each year. For the purpose of this study, we addressed all sequential travelers who visited the travel clinic between June and November 2004. We included only travelers aged 18–65 years who planned a trip of at least 14 days and up to 180 days. Potential participants received a full explanation of the purpose of the study, and those who were willing to participate were included after signing the informed consent form. The study was approved by the ethics committee of Bnai Zion Medical Center.

To exclude travelers who might have developed IBS before the trip, participants were asked to fill out a questionnaire that asked for demographic data and a brief gastrointestinal history. Those travelers who were found to have IBS on the basis of the Rome 2 criteria for IBS [9] were excluded from the study. The Rome 2 criteria for IBS were at least 12 weeks (which need not be consecutive) in the preceding 12 months with abdominal discomfort or pain associated with 2 of the following 3 features: (1) looser stools with the onset of pain, relieved with defecation, (2) onset of abdominal discomfort associated with a change in the frequency of stool, and (3) onset of abdominal discomfort associated with a change in form (i.e., appearance) of stool. All eligible travelers were also asked about their itinerary and the length of their journey, and they received a second questionnaire (table 1) that they were asked to complete during the trip. Traveler’s diarrhea was defined as at least 3 loose stools within 24 h beginning at least 48 h after arrival at the destination country [10].

Travelers were instructed to adhere to this definition of traveler’s diarrhea and were requested to mail the completed questionnaire to us upon repatriation; those who failed to mail the

<table>
<thead>
<tr>
<th>Question</th>
<th>Table 1. Questionnaire to be completed by travelers during their trip.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you suffer from diarrhea during your trip (at least 3 loose stools within 8 h that started at least 48 h after arrival to the destination country)?</td>
<td>If yes, continue with the following questions:</td>
</tr>
<tr>
<td>Did you suffer from fever?</td>
<td>Did you suffer from fever?</td>
</tr>
<tr>
<td>Abdominal pain?</td>
<td>Abdominal pain?</td>
</tr>
<tr>
<td>In which country or countries?</td>
<td>In which country or countries?</td>
</tr>
<tr>
<td>How many stools per day did you have?</td>
<td>How many stools per day did you have?</td>
</tr>
<tr>
<td>For how long did you suffer from diarrhea?</td>
<td>For how long did you suffer from diarrhea?</td>
</tr>
<tr>
<td>Did you receive any treatment?</td>
<td>Did you receive any treatment?</td>
</tr>
<tr>
<td>Did you receive antibiotics?</td>
<td>Did you receive antibiotics?</td>
</tr>
<tr>
<td>Did you receive any other treatment?</td>
<td>Did you receive any other treatment?</td>
</tr>
</tbody>
</table>
questionnaire were contacted by telephone 2–4 weeks after the tentative date of return.

To elucidate the rate of posttravel IBS, each of the returning travelers was contacted by telephone by one of the investigators (A.L.) 6–7 months after repatriation and was asked to respond to the third questionnaire, which was intended to determine those travelers who had developed IBS. This questionnaire was similar to the initial questionnaire.

We used the statistical features of Microsoft Excel to calculate rates, means, and SDs. The Instat software (GraphPad) was used to compare means (with Student’s t test) or categorical variables (with Fisher’s exact test or the $\chi^2$ test) and to calculate relative risk.

**Results.** A total of 564 travelers were requested to participate in the study; 64 travelers were excluded for various reasons (figure 1). Because 17 of the individuals who were recruited for the study cancelled their trip, only 483 were potential candidates. Of these 483 potential candidates, only 412 were followed up after returning home, and 405 were contacted 6 months after repatriation to evaluate the occurrence of IBS.

The great majority of our subjects (84%) traveled to Asia, and 5% traveled to Africa and South America. The mean age of the entire study group was 30.8 years, and slightly more than one-half of the subjects (53.3%) were male. We tried to find distinctive features that would characterize those who developed IBS (table 2). Most remarkable was the finding that the rate of IBS was significantly higher among those who had diarrhea during the trip (13.6%) than it was among those without diarrhea (2.4%) ($P < .0001$; relative risk, 5.2; 95% CI, 2.2–12.3). The causes of the study subjects’ cases of diarrhea are unknown, because only 5 travelers sent stool samples for examination, and only 1 of these had positive results (for *Campylobacter* species).

In total, 15 travelers received an antibiotic for their diarrhea. In 5 cases, these antibiotics were quinolones; the other patients received roxithromycin, doxycycline, amoxicillin, or unknown antibiotics. Of interest, among those patients for whom the type of antibiotic could be ascertained, 4 of 23 travelers who eventually developed IBS received an antibiotic for their diarrhea, compared with 4 of 95 travelers who did not develop IBS ($P = .046$; relative risk, 4.13; 95% CI, 1.1–15.3). In an attempt to find specific characteristics associated with travelers who developed IBS, we compared various parameters. However, none of the following parameters demonstrated a statistical difference: mean age (28.4 vs. 30.8 years for the IBS and non-IBS groups, respectively), mean duration of trip (32.3 vs. 30.7 days), and rate of fever (31% vs. 27%). The rate of use of antidiarrheics (e.g., loperamide) was higher in the IBS group compared with the non-IBS group (37.5% vs. 21%), but the difference was not statistically significant ($P = .2$). Malaria prophylaxis was received by only 14% of the IBS group, compared with 24% of the entire study group ($P$ value was not significant). By contrast, abdominal pain was significantly more common among subjects who developed IBS than among subjects who did not (56.5% vs. 20.4%; $P = .0003$), and the duration of diarrhea was longer (mean duration, 8.1 vs. 5.5 days; $P = .08$). Female subjects were over-represented among those who developed IBS (60.9% of the IBS group was female, compared with 46.7% of the entire cohort). The destination country–specific data revealed that the destinations associated with the highest rates of IBS were Argentina, Cuba, and Bolivia, and that, in Asia, India was the destination associated with the highest rate of IBS.

**Discussion.** Traveler’s diarrhea (or Montezuma’s revenge, as it has been historically named) is a frequent condition among travelers to a large list of destinations, particularly among travelers to underdeveloped countries. The etiology of IBS is not well established and seems to be multifactorial. The first association of IBS with an episode of gastroenteritis dates to 1962 and is reported in the landmark article by Chaudhary and Truelove [11]. Recently, this entity has been termed postinfectious IBS [12]. In fact, epidemiological evidence suggests that this condition is a common sequel of acute gastroenteritis [3–5]. Bacterial pathogens, such as enterotoxigenic *Escherichia coli* and *Salmonella*, *Shigella*, and *Campylobacter* species seem to be
found that enterotoxigenic E. coli were the most prevalent pathogens among the travelers to Mexico described in their study. However, parasites have also been implicated in the etiology of this syndrome [14, 15]. Parasitic infections have symptoms that are similar to those of IBS and have a protracted course. It is well known that the probability of discovering a protozoan pathogen, relative to that of discovering a bacterial one, increases with a longer duration of symptoms. For example, among travelers to Nepal, protozoa were found in 10% of travelers whose symptoms lasted >2 weeks [16, 17]. Our results indicate that there was a >5-fold higher risk of developing new-onset IBS among travelers who experienced diarrhea during their journey, compared with travelers who did not experience diarrhea. Only 2 prospective studies (with divergent results) have addressed the question of IBS among travelers who experienced acute diarrhea during their journey. Ilnyckyj et al. [8] found no significant difference between travelers with and travelers without diarrhea with respect to the development of IBS; by contrast, Okhuysen et al. [13] found that 10% of their study group developed new-onset IBS after experiencing diarrhea. Both studies recommended performing further studies involving postinfectious IBS before drawing definitive conclusions.

The use of antibiotics during the acute phase of the infectious episode—albeit in a small number of individuals—showed a trend towards association with the development of IBS. The hypothesis that the use of antibiotics during acute bacterial gastroenteritis is associated with postinfectious IBS is not new [18]. Receipt of antibiotics during infectious gastroenteritis has also been implicated in the development of hemolytic-uremic syndrome following E. coli O157:H7 infection [19]. Although we found the rate of use of antidiarrheics to be higher in the IBS group than in the non-IBS group (37.5% vs. 21%), this difference did not reach statistical significance. We could find no other studies involving travelers that addressed this point. Of interest, DuPont et al. [20] have shown that preventive administration of rifaximin reduces the incidence of traveler’s diarrhea.

Allegedly, IBS has a worldwide distribution [21]. It seemed, therefore, intriguing to examine the destination country–specific rates of new IBS in this large group. The highest rate of IBS was found among travelers to Argentina. However, none of our travelers traveled solely to Argentina, but always visited Argentina as part of a South American tour; therefore, this finding may not be revealing.

This study has several limitations. First, we were unable to demonstrate an association between a specific agent and the subsequent development of IBS. In a group of long-term travelers, this seems an impossible undertaking. Second, we did not examine the influence of psychological factors, which are known to play a role in the etiology of IBS. Third, we used the standard follow-up period of 6 months, which may be too short for a study involving a disease like IBS, which can wax and wane over years.

We conclude that an episode of traveler’s diarrhea is associated with a quintuple risk of developing IBS. Abdominal pain, duration of diarrhea, and female sex seem to influence the rate of developing IBS.

Acknowledgments

E.S. and I.P. contributed equally to the article. This article fulfills part of the requirements for the MD thesis of A.L.

Potential conflicts of interest. All authors: no conflicts.

References


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Table 2. Demographic data, destinations, and symptoms for travelers who developed irritable bowel syndrome (IBS), compared with those who did not.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Travelers who developed IBS (n = 23)</th>
<th>Travelers who did not develop IBS (n = 382)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years ± SD</td>
<td>28.4 ± 8.4</td>
<td>30.8 ± 11.3</td>
<td>.3</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>9/14</td>
<td>207/175</td>
<td>.2</td>
</tr>
<tr>
<td>Duration of trip, mean days ± SD</td>
<td>32.3 ± 18.0</td>
<td>30.7 ± 16.1</td>
<td>.6</td>
</tr>
<tr>
<td>Country in which diarrhea started, no. of travelers&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Thailand, 7; India, 5; other, 5; unknown, 6</td>
<td>Thailand, 47; India, 34</td>
<td></td>
</tr>
<tr>
<td>Diarrhea during trip, no. of travelers</td>
<td>16</td>
<td>102</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Abdominal pain, no. of travelers</td>
<td>13</td>
<td>78</td>
<td>.0003</td>
</tr>
<tr>
<td>Vomiting, no. of travelers</td>
<td>1</td>
<td>20</td>
<td>1.0</td>
</tr>
<tr>
<td>Duration of diarrhea, mean days ± SD</td>
<td>8.1 ± 7.9</td>
<td>5.5 ± 6.9</td>
<td>.08</td>
</tr>
</tbody>
</table>

* Two-tailed P values.
<sup>b</sup> Some travelers visited >1 country.