Irritable Bowel Syndrome and Chronic Fatigue 6 Years After Giardia Infection: A Controlled Prospective Cohort Study

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Background. Functional gastrointestinal disorders and fatigue may follow acute infections. This study aimed to estimate the persistence, prevalence, and risk of irritable bowel syndrome and chronic fatigue 6 years after Giardia infection.

Methods. We performed a controlled prospective study of a cohort of 1252 individuals who had laboratory-confirmed Giardia infection during a waterborne outbreak in 2004. In total, 748 cohort cases (exposed) and 878 matched controls responded to a postal questionnaire 6 years later (in 2010). Responses were compared to data from the same cohort 3 years before (in 2007).

Results. The prevalences of irritable bowel syndrome (39.4%) by Rome III criteria and chronic fatigue (30.8%) in the exposed group 6 years after giardiasis were significantly elevated compared with controls, with adjusted relative risks (RRs) of 3.4 (95% confidence interval [CI], 2.9–3.9) and 2.9 (95% CI, 2.3–3.4), respectively. In the exposed group, the prevalence of irritable bowel syndrome decreased by 6.7% (RR, 0.85 [95% CI, 0.77–0.93]), whereas the prevalence of chronic fatigue decreased by 15.3% from 3 to 6 years after Giardia infection (RR, 0.69 [95% CI, 0.62–0.77]). Giardia exposure was a significant risk factor for persistence of both conditions, and increasing age was a risk factor for persisting chronic fatigue.

Conclusions. Giardia infection in a nonendemic setting is associated with an increased risk for irritable bowel syndrome and chronic fatigue 6 years later. The prevalences of both conditions decrease over time, indicating that this intestinal protozoan parasite may elicit very long-term, but slowly self-limiting, complications.

Keywords. Giardia; irritable bowel syndrome; chronic fatigue; postinfectious.

Fatigue and gastrointestinal symptoms are common manifestations of several infections and other diseases [1, 2]. In some cases, these symptoms may persist after the infection has resolved [3–5]. Irritable bowel syndrome (IBS) is characterized by prolonged abdominal pain or discomfort combined with diarrhea and/or constipation of variable intensity, and may occur after gastroenteritis, including travelers’ diarrhea [3, 4]. Between 6% and 17% of IBS cases have been reported to be preceded by gastroenteritis [6]. Some longitudinal follow-up studies have been performed and support gradual recovery of abdominal complaints after infectious gastroenteritis. However, after 6 years of follow-up, postinfectious IBS (PI-IBS) may persist in >50% of cases [7, 8]. Similarly, fatigue has also been reported to persist after acute infection, but long-term studies are scarce [5, 9–11]. Long-term follow-up data of chronic fatigue (CF) following enteric infections and its association with PI-IBS has not been reported.

The ubiquitous protozoan intestinal parasite Giardia lamblia is a frequent cause of waterborne gastroenteritis.
outbreaks in many countries, and it is commonly seen in returning travelers with diarrheal disease [12]. During a waterborne outbreak of *G. lamblia* gastroenteritis in Bergen, Norway, in autumn 2004, approximately 2500 individuals were treated for giardiasis [13]. Patients with persistent, metronidazole-refractory giardiasis were successfully treated during the initial follow-up [14]. Since the outbreak, all individuals with laboratory-confirmed giardiasis during the outbreak (n = 1252) have been followed up, with special attention to prolonged postinfectious abdominal symptoms and fatigue [15–19]. The main objective was to evaluate the prevalences and relative risks of IBS and CF 6 years after *Giardia* infection; secondary objectives were to evaluate changes in prevalence from 3 to 6 years after infection and to evaluate risk factors for persistence of these conditions.

**METHODS**

**Participants**

This study presents data from a prospective follow-up in 2010 of a cohort of 1252 individuals 6 years after verified *Giardia* infection during a waterborne outbreak (exposed group). A randomly sampled 2:1 age- and sex-matched control group of 2504 individuals was established with the aid of Statistics Norway during 2007, and made it possible to compare developments over time in both groups. Table 1 shows details of the exposed and control groups approached in October 2007 and October 2010. The study was approved by the Regional Committee for Ethics in Medical Research (2010/721).

### Table 1. Description of the Cohorts Available for Analyses of Irritable Bowel Syndrome and Chronic Fatigue 3 and 6 Years After the 2004 *Giardia* Outbreak in Norway

| Cohort                              | Exposed⁺ | Controls⁻ | Total No. |
|-------------------------------------|----------|-----------|-----------|
| Target population 2007 [19]         | 1252 (100.0) | 2504 (100.0) | 3756      |
| Study population 2007               | 817 (65.3)   | 859 (34.3)   | 1676      |
| Lost to follow-up                    | 13 (1.0)     | 60 (2.4)     | 73        |
| Target population 2010              | 1239 (100.0) | 2444 (100.0) | 3683      |
| Questionnaires returned              | 748 (60.4)   | 888 (36.3)   | 1636      |
| *Giardia* during outbreak            | 7 (0.3)      |            |           |
| Incomplete/ambiguous response        | 3 (0.1)      |            |           |
| Study population in 2010             | 748 (60.4)   | 878 (35.9)   | 1626      |

Data are presented as No. (%).

⁺ *Giardia* exposed.

⁻ Age- and sex-matched individuals from the general population in Bergen, Norway.

⁻ Emigrated or died between 2007 and 2010, or address not found in 2010.

**Variables**

The primary outcome of this study was the presence of CF and IBS 6 years after giardiasis in the *Giardia*-exposed and control groups. Secondary outcomes were the changes in the prevalence of CF and IBS and mean fatigue scores [20] in the exposed group and the control group between 3 and 6 years after *Giardia* infection, where those who had a condition at both time-points were defined as having a persistent condition. We also evaluated factors potentially influencing persistence of CF and IBS from 2007 to 2010.

IBS was defined using the Rome III criteria [21]. IBS limiting or restricting daily activities at least “often” was termed “severe IBS.”

Fatigue was measured using the validated 11-item Fatigue Questionnaire [20]. To each of the 11 questions, there are 4 possible answers (“less than normal,” “as normal,” “more than normal,” “much more than normal”). These are scored (0, 1, 2, 3) and added, giving a score range from 0 to 33. Responses are also dichotomized (0 and 1 into 0, 2 and 3 into 1), and a total dichotomized score of ≥4 defined CF, if symptoms lasted >6 months.

The combination of CF and a total fatigue score of ≥23 was defined as severe fatigue. The Fatigue Questionnaire was accepted if ≥8 of the 11 questions were answered. Unanswered questions were assigned the same value as the mean of all responses to that particular question. To describe the substantial overlap of IBS and CF, we also analyzed prevalences of having only 1 of the conditions or a combination of both.

Questions on the demographic variables sex, age (categorized in 20-year groups), marital status, education level (3 categories), and main occupation (4 categories) were also included in the questionnaire. These variables were considered potential confounders. Sex was also considered a potential effect modifier.

**Analyses and Statistical Methods**

Descriptive statistics are given as percentage, mean, and standard deviation (SD). Nonresponders were only included in nonresponder analyses and compared with responders. Participants with missing data were excluded from analyses pertaining to that specific variable. For associations in 2 × k tables, we used Pearson exact $\chi^2$ test. Continuous variable means were compared between groups using Gosset paired and unpaired $t$ test [22].

Prevalences at 6 years are compared using relative risks (RRs) with 95% confidence intervals (CIs). IBS and CF were analyzed separately with respect to the risk factors and possible interactions using multiple logistic regression, producing adjusted odds ratios (ORs) with 95% CIs. In this model, backward stepwise selection was applied removing variables with a $P$ value >.05; thus, variables that did not influence the results were excluded. Also, it was checked that removing a variable did not change the estimated effects of the remaining variables in a
substantial way. Because ORs and RRs correspond poorly when outcome prevalence is high, we converted adjusted ORs from logistic regression analyses to RRs and corresponding CIs by the method of Zhang and Yu [23]. The ratio of RRs was calculated using the formula of Altman and Bland [24], using the RR from 3 to 6 years in the exposed group as a reference.

The attributable fraction among the exposed (AFE)—that is, the proportion of the outcome conditions in the exposed group that can be attributed to the *Giardia* infection—was calculated as a percentage given by the formula AFE% = (1 – 1/RR) × 100 [25].

A binary logistic regression analysis using generalized estimating equations (GEEs) was used to evaluate changes in IBS and CF prevalence from 3 to 6 years, making it possible to include data from all respondents at both time-points and accounting for correlation between repeated measures and the matched design.

Comparisons of new and recovered cases from 2007 to 2010 were done using McNemar test for symmetry. Evaluation of risk factors for persistence of CF or IBS from 2007 to 2010 was done among individuals who had responded at both time points using multiple logistic regression analysis with respect to age, sex, and exposure.

The level of statistical significance was set at .05, and all tests were 2-sided. All analyses were done using IBM SPSS Statistics version 19.

**RESULTS**

In total, 748 (60.4%) exposed individuals and 878 (35.9%) controls responded to the 6-year questionnaire (Table 1). More nonresponders to the 6-year questionnaire were male (43.1%) compared with responders (33.7%; *P* < .001) and they were younger (mean age, 36.9 years) than responders (mean age, 38.2 years; *P* < .001). Table 2 shows the characteristics of responders in the exposed and control groups.

Six years after the outbreak, the prevalence of CF was 30.8% (226/733) in the exposed group and 11.0% (96/874) in controls, giving an adjusted RR of 2.9 after *Giardia* exposure. The fraction of CF (AFE) attributable to previous giardiasis was 65% (95% CI, 57.3%–70.8%) in the exposed group. The prevalence of IBS was 39.4% (291/739) in the exposed group and 11.6% (101/870) in controls. This gave an adjusted RR of 3.4 in the *Giardia*-exposed group (Table 3). For IBS,

| Characteristics | All Responders in 2010 (n = 1626) | Responders in 2007 and 2010 (n = 1160) |
|-----------------|-----------------------------------|--------------------------------------|
|                 | Exposed, No. (%) | Controls, No. (%) | *P* Valuea | Exposed, No. (%) | Controls, No. (%) | *P* Valuea |
| Female sex      | 502 (67.1) | 578 (65.8) | .599 | 410 (68.2) | 380 (68.0) | .950 |
| Age, y          | Mean (range) | 38.1 (7–97) | 38.9 (6–95) | .283 | 39.2 (8–97) | 40.0 (7–83) | .313 |
|                 | 0–19     | 29 (3.9) | 37 (4.2) | .288 | 18 (3.0) | 12 (2.1) | .187 |
|                 | 20–39    | 451 (60.3) | 516 (58.8) | 347 (57.7) | 325 (58.1) |
|                 | 40–59    | 207 (27.7) | 238 (27.1) | 180 (30.0) | 164 (29.3) |
|                 | 60–79    | 48 (6.4) | 78 (8.9) | 44 (7.3) | 54 (9.7) |
|                 | 80–99    | 13 (1.7) | 9 (1.0) | 12 (2.0) | 4 (0.7) |
| Marital status  | Single   | 202 (27.3) | 184 (21.1) | .017 | 157 (26.3) | 98 (17.7) | .002 |
|                 | Married  | 499 (67.5) | 631 (72.3) | 405 (67.7) | 428 (77.3) |
|                 | Divorced | 28 (3.8) | 47 (5.4) | 27 (4.5) | 23 (4.2) |
|                 | Widowed  | 10 (1.4) | 11 (1.3) | 9 (1.5) | 5 (0.9) |
| Education       | Primary school | 35 (4.7) | 72 (8.3) | <.001 | 29 (4.9) | 32 (5.8) | .056 |
|                 | Secondary school | 136 (18.4) | 225 (26.0) | 112 (18.8) | 133 (24.1) |
|                 | University | 567 (76.8) | 567 (65.6) | 455 (76.3) | 387 (70.1) |
| Main occupation | Worker   | 561 (76.2) | 688 (78.8) | .121 | 450 (75.5) | 458 (82.2) | .005 |
|                 | Student  | 63 (8.6) | 78 (8.9) | 50 (8.4) | 37 (6.6) |
|                 | Unemployed/retired | 89 (12.1) | 94 (10.8) | 78 (13.3) | 58 (10.4) |
|                 | Other    | 23 (3.1) | 13 (1.5) | 18 (3.0) | 4 (0.7) |

*P* values derived from the exact *χ*² test from 2 × k table for categorical data, and from *t* test for independent samples for the mean age.
the AFE due to giardiasis was 70.5% (95% CI, 65.1%–74.6%). Relative risks for the subgroups of severe IBS and severe CF were also elevated in the exposed group (Table 3).

The mean total fatigue score was 14.8 (SD, 5.5) in the exposed group and 12.2 (SD, 4.2) in controls (P < .001). The mean total fatigue scores in 2007 and in 2010 showed a reduction from 16.0 to 12.2 in the exposed group and 12.0 to 11.9 (P < .001). A similar pattern was seen in the controls, with corresponding figures of 29.0% and 8.4% (P < .001).

Female sex was found to be a risk factor for IBS in the control group (females, 13.8% and males, 7.4%; P = .007), but not in the Giardia-exposed cohort (females, 41.0% and males, 36.1%; P = .228). There was no significant sex difference in CF prevalence in the 2 groups; CF in exposed females was 31.6%, and in males 29.3% (P = .55), whereas it was 11.8% in female controls and 9.4% in male controls (P = .31).

We found a significant decrease in prevalence of both IBS (46.1%–39.4%) and CF (46.1%–30.8%) from 3 to 6 years in the exposed group, but not among the controls (Table 4). When comparing the changes in prevalence between the exposed group and the controls with logistic regression analysis, we found that the decrease in CF and severe CF from 3 to 6 years was significantly different between the 2 groups, whereas the change in IBS was not (Table 4).

Some of the participants fulfilled criteria for a condition in 2007 but not in 2010, indicating that they had “recovers.” Likewise, there were also “incident” cases of both conditions that fulfilled the criteria in 2010 but not in 2007.

In the exposed group, recovery from IBS was significantly more common with 96 individuals (16.9%) no longer fulfilling the criteria, whereas there were 53 (9.3%) incident cases (P = .001). In the control group, 39 (7.1%) had recovered, whereas 31 (5.7%) individuals had incident IBS (P = .403).

In the exposed group, 105 (18.3%) individuals had recovered from CF, whereas 32 (5.6%) cases were incident (P < .001). In controls, 42 (7.6%) individuals had recovered from CF and there were 31 (5.6%) “incident” cases (P = .24).

Table 3. Prevalence of Irritable Bowel Syndrome and Chronic Fatigue 6 Years After the 2004 Giardia Outbreak in Norway

| Condition | All | Exposed, No. (%) | Controls, No. (%) | Unadjusted RR (95% CI) | Adjusted RR (95% CI) |
|-----------|-----|-----------------|------------------|------------------------|---------------------|
| IBS       | 1609 | 291 (39.4) | 101 (11.6) | 3.4 (2.8–4.2) | 3.4 (2.9–3.9) |
| Severe IBS| 1595 | 55 (7.2) | 18 (2.1) | 3.5 (2.0–5.9) | 3.1 (1.9–5.1) |
| CF        | 1607 | 226 (30.8) | 96 (11.0) | 2.8 (2.3–3.5) | 2.9 (2.3–3.4) |
| Severe CF | 1607 | 66 (9.0) | 23 (2.6) | 3.4 (2.1–5.4) | 3.1 (1.9–4.8) |
| Both IBS and CF | 1586 | 135 (18.6) | 29 (3.3) | 5.6 (3.8–8.2) | 5.5 (3.8–7.7) |
| Only IBS | 1586 | 150 (20.7) | 71 (8.2) | 2.5 (1.9–3.3) | 2.5 (2.0–3.2) |
| Only CF | 1586 | 87 (12.0) | 64 (7.4) | 1.6 (1.2–2.2) | 1.7 (1.2–2.3) |

Abbreviations: CF, chronic fatigue; CI, confidence interval; IBS, irritable bowel syndrome; RR, relative risk.

*a Adjusted for sex, age, level of education, marital status, and main occupation.

Table 4. Changes in Prevalences of Irritable Bowel Syndrome and Chronic Fatigue Including Subgroups and Combinations of These Conditions at 3 Years and 6 Years After the 2004 Giardia Outbreak in Norway

| Condition | Giardia Exposed | Controls | Between Groups Ratio of RRb (95% CI) |
|-----------|----------------|----------|-----------------------------------|
| IBS       | 3 y No. (%) | 6 y No. (%) | % Change | RRb (95% CI) | 3 y No. (%) | 6 y No. (%) | % Change | RRb (95% CI) |
| Severe IBS | 106 (13.8) | 57 (7.2) | −6.6 | 0.52 (0.40–0.60) | 30 (2.7) | 18 (2.1) | −0.6 | 0.77 (0.44–1.34) | 0.68 (0.37–1.32) |
| CF        | 366 (46.1) | 226 (30.8) | −15.3 | 0.69 (0.62–0.77) | 134 (12.0) | 96 (11.0) | −1.0 | 0.91 (0.72–1.13) | 0.76 (0.59–0.98) |
| Severe CF | 120 (15.1) | 66 (9.0) | −6.1 | 0.60 (0.47–0.75) | 24 (2.1) | 23 (2.6) | 0.5 | 1.21 (0.73–1.99) | 0.49 (0.28–0.86) |
| Both IBS and CF | 216 (28.6) | 135 (18.6) | −10.0 | 0.66 (0.57–0.77) | 49 (4.5) | 29 (3.3) | 0.8 | 0.75 (0.48–1.15) | 0.88 (0.56–1.41) |
| Only IBS | 129 (17.1) | 150 (20.7) | 3.7 | 1.19 (0.98–1.42) | 104 (9.5) | 71 (8.2) | 1.0 | 0.89 (0.69–1.15) | 1.34 (0.97–1.86) |
| Only CF | 125 (16.6) | 87 (12.0) | −4.7 | 0.73 (0.58–0.92) | 85 (7.7) | 64 (7.4) | −0.3 | 0.95 (0.72–1.26) | 0.77 (0.54–1.10) |

Abbreviations: CF, chronic fatigue; CI, confidence interval; IBS, irritable bowel syndrome; RR, relative risk.

a Data taken from Wensaas et al [19].

b RR with 95% CI for having the condition 6 years after Giardia infection compared to 3 years after. The RR was calculated from the odds ratio (OR) derived from binary logistic regression analysis using generalized estimating equations (GEE) for IBS and chronic fatigue with only time as factors, and separately for exposed and controls.

c Evaluation of the statistical significance of the difference between changes in exposed and controls by testing model effects in GEE for interaction between exposure and time. The OR returned in this model was used to calculate the RR using the method of Zhang and Yu [23], and the ratio of RR was calculated by the method of Altmann and Bland [24].
Prevalences of persisting IBS and CF were estimated among the individuals who fulfilled the criteria for IBS or CF in 2007, and who also responded in 2010 (Supplementary Table 1). Among 251 exposed individuals with CF in 2007, 146 (58.2%) still had CF in 2010, whereas the corresponding figures in controls were 16 of 58 (27.6%). In a logistic regression model including sex, age, and Giardia exposure, we found that Giardia exposure was significantly associated with persisting CF (RR, 2.13 [95% CI, 1.55–2.64]). Increasing age was associated with increased risk for CF, with an RR of 1.43 (95% CI, 1.14–1.69) in those 40–59 years of age, and an RR of 1.57 (95% CI, 1.12–1.91) in those 60–97 years of age, compared with the younger (20–39 years) age group.

Among the 262 exposed individuals with IBS in 2007, 164 (63.1%) still reported IBS in 2010. Among the 64 controls with IBS in 2007, 25 (39.1%) reported IBS again in 2010. Giardia exposure was significantly associated with persisting IBS in 2010 (RR, 1.64 [95% CI, 1.29–1.95]), whereas age and sex were not.

DISCUSSION

The main finding in this study was that there was a high prevalence of CF (30.8%) and IBS (39.4%) 6 years after laboratory-confirmed giardiasis and that these 2 conditions were strongly associated. We also show that during the period from 3 to 6 years after the infection, the prevalence of both conditions decreased, and that recovery from chronic fatigue (15.3%) was more pronounced than recovery from IBS (6.7%). In the exposed group, both conditions were more persistent over time than in controls. Persisting chronic fatigue was associated with higher age.

The strengths of this study are that it includes a high number of participants, who all had laboratory-confirmed infection with the same pathogen during a short time period, and that questionnaires with identical questions were mailed to the same groups of exposed and control individuals at the same time of the year with a 3-year interval.

We judged that questions regarding preoutbreak fatigue and IBS would be too prone to recall bias in the present study, but from a previous study of 124 patients referred with severe abdominal symptoms 2–18 months after the outbreak, we know that approximately 15% reported preoutbreak IBS-like symptoms [15]. Also, we found it questionable whether it would be correct to exclude persons with preoutbreak fatigue and/or IBS. Treating the whole Giardia-exposed cohort as a group has its merits, as the Giardia infection may have modulated preexisting fatigue or IBS.

The higher percentage of women among the exposed can partly be explained by women drinking more tap water [13]. There is a possibility that those in the exposed group had a stronger tendency to consult the health services, given that they were selected based on consultation and sampling during the outbreak, compared with the controls that were randomly chosen among the population. This might again influence the way they evaluated their health and how they answered the questionnaire, and to some extent account for the high prevalences of CF and IBS. However, from follow-up data, we know that the response rate of the initially hospital-referred individuals, presumably experiencing more severe symptoms, was similar to that of nonreferred individuals within the exposed group.

Sampling bias is possible, as the response rate differs between the 2 groups. Although the response rate ideally should be higher in the control group, the prevalences of CF and IBS at 3 and 6 years are comparable to previous Norwegian population-based studies [26, 27]. The response rate of 60.4% in the exposed group 6 years after the outbreak is acceptable, but there still could be a bias toward responders having and reporting more symptoms than nonresponders, and this relationship may be different in the control group. However, we do not find it plausible that this could account for the high RR among the exposed group.

Chronic giardiasis may give an IBS-like clinical picture. During the 2 years after the outbreak, patients with persisting symptoms in this cohort were thoroughly investigated in this respect at the hospital or by their general practitioners. All positive cases identified were successfully treated [14], and the carrier status in the exposed general population was very low [28]. Five years after the outbreak, chronic giardiasis was assessed in this cohort by polymerase chain reaction of stool samples from 53 exposed persons with long-term CF and/or IBS and 20 exposed persons without sequelae, and none were found to be positive [29, 30]. We therefore are convinced that the prevalence of chronic giardiasis in the exposed group is very low.

Interpretation

PI-IBS may follow bacterial [7, 31] and parasite-induced gastroenteritis [19, 32, 33], as well as viral disease [34]. Studies after an outbreak of bacterial gastroenteritis in Walkerton, Canada, showed the prevalence of PI-IBS to be 36% by Rome I criteria 2–3 years after infection [35]. Six years after the infection, the prevalence had decreased to 22% [7]. Our data show a somewhat higher prevalence at both 3 and 6 years even when correcting for the background IBS prevalence present in our data. The difference in PI-IBS prevalence may be influenced by different IBS criteria used (Rome I vs Rome III), selection bias in the examined populations, or real differences due to the eliciting pathogens or host responses.

Following an outbreak of Q fever in the United Kingdom in 1989, controlled studies showed a high and significantly elevated level of fatigue both 5 and 10 years after the outbreak [36]. No long term follow-up studies of CF elicited by gastroenteritis have so far been performed. In the present study, the prevalence of both CF and IBS in the exposed group decreased from 3 to 6 years postexposure. The decrease in prevalence of CF was also statistically significant when compared with the change in the
control group, whereas the corresponding decrease in IBS prevalence did not reach statistical significance (Table 4). PI-IBS thus seems to be more protracted than PI-CF after *Giardia* infection.

A large part of the *Giardia*-exposed individuals who reported IBS and/or CF in 2007 had persisting complaints also in 2010. This must be seen in conjunction with the large turnover found in both examined conditions over the 3-year period, especially in the control group. *Giardia*-exposed individuals were more likely to have had this complication for 3 years already in the 2007 questionnaire study and therefore to have a more established condition than controls. So whereas *Giardia* exposure is associated with persistence of IBS and CF, the risk may be overestimated due to initial differences in the exposed and control groups. Still, we conclude that the individuals with *Giardia*-associated IBS and/or CF reported a more persisting phenotype than controls.

The mechanisms by which a ubiquitous noninvasive intestinal parasite such as *G. lamblia* may elicit both CF and IBS remain elusive, but are probably multifactorial. Fatigue syndromes and IBS in general share some predisposing risk markers such as frequent physician consultations, sickness certificates, atopy, mood, and other symptom-based disorders [10]. Most of these predisposing factors are difficult to assess retrospectively. Atopy was assessed in a previous study in this cohort, and of these predisposing factors are difficult to assess retrospectively. Atopy was assessed in a previous study in this cohort [40]. Protracted *Giardia* infection and associated duodenal inflammation described by us previously [15] indicate a strong immune activation in a large proportion of the affected population that may precipitate long-term sequelae.

Our data are based on a waterborne *Giardia* outbreak, causing gastroenteritis in a large population of individuals presumed not to have been exposed to this parasite previously. This unfortunate event made it possible to study the natural course of IBS and CF after giardiasis, and shows a significantly increased risk for both IBS and CF even 6 years after the infection.

Based on our findings, *Giardia*-induced IBS and/or CF could be considered a differential diagnosis, especially in returning travelers who present with such symptoms and where infectious microorganisms are not detected.

**Supplementary Data**

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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**Potential conflicts of interest.** All authors: No potential conflicts of interest.

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**References**

1. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? Gastroenterology 2002; 122:1140–56.
2. Simren M, Svedlund J, Posserud I, Bjornsson ES, Abrahamsson H. Predictors of subjective fatigue in chronic gastrointestinal disease. Aliment Pharmacol Ther 2008; 28:638–47.
3. Nair P, Okhuysen PC, Jiang ZD, et al. Persistent abdominal symptoms in US adults after short-term stay in Mexico. J Travel Med 2014; 21:153–8.
4. Connor BA. Sequelae of traveler’s diarrhea: focus on postinfectious irritable bowel syndrome. Clin Infect Dis 2005; 41(suppl 8):S577–S86.
5. Hickie I, Davenport T, Wakefield D, et al. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. BMJ 2006; 333:575.
6. Longstreth GF, Hawkey CJ, Mayer EA, et al. Characteristics of patients with irritable bowel syndrome recruited from three sources: implications for clinical trials. Aliment Pharmacol Ther 2001; 15:595–64.
7. Marshall JK, Thabane M, Garg AX, Clark WF, Moayyedi P, Collins SM. Eight year prognosis of postinfectious irritable bowel syndrome following waterborne bacterial dysentery. Gut 2010; 59:605–11.
8. Neal KR, Barker L, Spiller RC. Prognosis in post-infective irritable bowel syndrome: a six year follow up study. Gut 2002; 51:410–3.
9. Morroy G, Peters JB, van Nieuwenhooi M, et al. The health status of Q-fever patients after long-term follow-up. BMC Infect Dis 2011; 11:97.
10. Hamilton WT, Gallagher AM, Thomas JM, White PD. Risk markers for both chronic fatigue and irritable bowel syndromes: a prospective case-control study in primary care. Psychol Med 2009; 39:1913–21.
11. Moss-Morris R, Spence M. To “lump” or to “split” the functional somatic syndromes: can infectious and emotional risk factors differentiate between the onset of chronic fatigue syndrome and irritable bowel syndrome? Psychosom Med 2006; 68:463–9.
12. Okhuysen PC. Traveler’s diarrhea due to intestinal protozoa. Clin Infect Dis 2001; 33:110–4.
13. Nygard K, Schimmer B, Sobstad O, et al. A large community outbreak of waterborne giardiasis—delayed detection in a non-endemic urban area. BMC Public Health 2006; 6:141.
14. Morch K, Hanevik K, Robertson LJ, Strand EA, Langeland N. Treatment-ladder and genetic characterisation of parasites in refractory giardiasis after an outbreak in Norway. J Infect 2008; 56:268–73.
15. Hanevik K, Hausken T, Morken MH, et al. Persisting symptoms and duodenal inflammation related to *Giardia duodenalis* infection. J Infect 2007; 55:524–30.
16. Hanevik K, Dizdar V, Langeland N, Hausken T. Development of functional gastrointestinal disorders after *Giardia lamblia* infection. BMC Gastroenterol 2009; 9:27.
17. Morch K, Hanevik K, Rortveit G, Wensaas KA, Langeland N. High rate of fatigue and abdominal symptoms 2 years after an outbreak of giardiasis. Trans R Soc Trop Med Hyg 2009; 103:530–2.

18. Wensaas KA, Langeland N, Rortveit G. Post-infectious gastrointestinal symptoms after acute giardiasis. A 1-year follow-up in general practice. Family Pract 2010; 27:255–9.

19. Wensaas KA, Langeland N, Hanevik K, Morch K, Eide GE, Rortveit G. Irritable bowel syndrome and chronic fatigue 3 years after acute giardiasis: historic cohort study. Gut 2012; 61:214–9.

20. Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. J Psychosom Res 1993; 37:147–53.

21. Rome Foundation. Rome III diagnostic questionnaire for the adult functional GI disorders. Available at: http://www.romecriteria.org/pdfs/AdultFunctGIQ.pdf. Accessed 22 February 2013.

22. Student. The probable error of a mean. Biometrika 1908; VI:1–25.

23. Zhang J, Yu KF. What’s the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998; 280:1690–1.

24. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003; 326:219.

25. Levin ML. The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum 1953; 9:531–41.

26. Vandvik PO, Lydersen S, Farup PG. Prevalence, comorbidity and impact of irritable bowel syndrome in Norway. Scand J Gastroenterol 2006; 41:650–6.

27. Loge JH, Ekeberg O, Kaasa S. Fatigue in the general Norwegian population: normative data and associations. J Psychosom Res 1998; 45(1 spec no): 53–65.

28. Mellingen KM, Midtun A, Hanevik K, Eide GE, Sobstad O, Langeland N. Post epidemic giardiasis and gastrointestinal symptoms among preschool children in Bergen, Norway. A cross-sectional study. BMC Public Health 2010; 10:163.

29. Hanevik K, Kristoffersen EK, Sornes S, et al. Immunophenotyping in post-giardiasis functional gastrointestinal disease and chronic fatigue syndrome. BMC Infect Dis 2012; 12:258.

30. Morch K, Hanevik K, Rivenes AC, et al. Chronic fatigue syndrome 5 years after giardiasis: differential diagnoses, characteristics and natural course. BMC Gastroenterol 2013; 13:28.

31. Mearin F, Perez-Oliveras M, Perello A, et al. Dyspepsia and irritable bowel syndrome after a Salmonella gastroenteritis outbreak: one-year follow-up cohort study. Gastroenterology 2005; 129:98–104.

32. Chaudhary NA, Truelove SC. The irritable colon syndrome. A study of the clinical features, predisposing causes, and prognosis in 130 cases. Q J Med 1962; 31:307–22.

33. Soyturk M, Akpinar H, Gurler O, et al. Irritable bowel syndrome in persons who acquired trichinellosis. Am J Gastroenterol 2007; 102:1064–9.

34. Zanini B, Ricci C, Bandera F, et al. Incidence of post-infectious irritable bowel syndrome and functional intestinal disorders following a waterborne viral gastroenteritis outbreak. Am J Gastroenterol 2012; 107: 891–9.

35. Marshall JK, Thabane M, Garg AX, Clark WF, Salvadori M, Collins SM. Incidence and epidemiology of irritable bowel syndrome after a large waterborne outbreak of bacterial dysentery. Gastroenterology 2006; 131:445–50.

36. Wildman MJ, Smith EG, Groves J, Beattie JM, Caul EO, Ayres JG. Chronic fatigue following infection by Coxiella burnetii (Q fever): ten-year follow-up of the 1989 UK outbreak cohort. QJM 2002; 95: 527–38.

37. Hunskar GS, Langeland N, Wensaas KA, et al. The impact of atopic disease on the risk of post-infectious fatigue and irritable bowel syndrome 3 years after Giardia infection. A historic cohort study. Scand J Gastroenterol 2012; 47:956–61.

38. Villani AC, Lemire M, Thabane M, et al. Genetic risk factors for post-infectious irritable bowel syndrome following a waterborne outbreak of gastroenteritis. Gastroenterology 2010; 138:1502–13.

39. Wang LH, Fang XC, Pan GZ. Bacillary dysentery as a causative factor of irritable bowel syndrome and its pathogenesis. Gut 2004; 53:1096–101.

40. Morch K, Hanevik K, Rortveit G, et al. Severity of Giardia infection associated with post-infectious fatigue and abdominal symptoms two years after. BMC Infect Dis 2009; 9:206.