Gastrointestinal Symptoms After Infectious Diarrhea: A Five-Year Follow-Up in a Swedish Cohort of Adults

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Background & Aims: **Gastrointestinal infection is a well-recognized trigger for functional bowel disorder. This study evaluated gastrointestinal symptoms and risk factors for their development after diarrheal disease of proven or strongly suspected infectious etiology in adults.** ***Methods:*** **The cohort of patients was derived from a previous study that determined the rate at which enteropathogens could be isolated at the time of diarrheal disease in adults. After 5 years, 717 of 851 patients were accessible for a questionnaire asking for persistence of gastrointestinal symptoms.** ***Results:*** **Of 508 returned questionnaires, 333 were from patients with no previous gastrointestinal complaints. Forty-one (12%) of them had gastrointestinal symptoms for 3 months or more after the infectious diarrhea, and 31 (9%) still had symptoms at the end of the follow-up period. Irritable bowel syndrome was most common (68%), but other functional bowel disorder diagnoses were found in all but one of the others. Female gender (odds ratio, 2.65, 95% confidence interval, 1.28–5.50) and use of antibiotic treatment (odds ratio, 2.37; 95% confidence interval, 1.07–5.25) were risk factors for development of postinfectious functional bowel disorder. No increase in risk was associated with the type of enteropathogen causing diarrhea.** ***Conclusions:*** **Infectious diarrhea in previously healthy adults carried a substantial risk of triggering postinfectious functional bowel disorder. Irritable bowel syndrome was the most common, but other functional bowel disorders were also found. We did not find any new clinical tools that would facilitate the prediction of long-standing symptoms.**

Postinfectious irritable bowel syndrome (PI-IBS) is now a well-recognized condition. The illness that initiates a change in bowel habits should fulfil at least 2 of the following criteria: fever, diarrhea, or vomiting. A positive stool culture is not a necessary criterion but adds to the evidence for the diagnosis.[1] The predominance of diarrhea is most common in PI-IBS, which otherwise seems to behave much like "spontaneous" IBS, including the prognosis.[2] It is not only IBS that might occur as a sequel to acute gastroenteritis. Other functional bowel disorders (FBDs), such as functional dyspepsia (FD),[3] have been reported to follow from an enteric infection.

Characterization of a disease's normal history is important, particularly if one intends to conduct a trial to modulate its course. In the case of PI-IBS, this is soon likely to become a growing field of interest. If the microbe is most important, efforts to prevent the development of PI-IBS might be needed in the acute phase of the infection. If host factors such as genetic differences in the inflammatory response, as suggested in recent research,[4–6] are more important, other efforts would probably be required, such as identifying persons at risk, either in advance or early in the event of symptoms compatible with PI-IBS. In the latter instance, perhaps the growing insight into mechanisms that dampen abnormal inflammatory responses will be of assistance in the future.[7]

In a previous study at our hospital, all adult patients admitted for diarrheal disease to the Department of Infectious Diseases between October 1, 1996–September 30, 1997 were included in a study of the rates at which potential enteropathogens could be isolated from stool specimens. An extensive microbiologic investigation (bacteriology, including detection of virulence factor genes for diarrheogenic *Escherichia coli* by polymerase chain reaction, virology, and parasitology) resulted in detection of a potential enteropathogen in 56% of these patients.[8]

This group of patients, with well-defined clinical baseline data and a gastrointestinal illness of proven or strongly suspected infectious etiology, constitutes an excellent cohort to follow up. We did this retrospectively with the primary aim of describing the natural history of an infection-initiated change in bowel habits compatible with a postinfectious functional bowel disorder (PI-FBD) but also to identify risk factors for this to happen.

Materials and Methods

All the 851 patients from the original study[8] were included in the present study of sufferers from a diarrheal disease of proven or strongly suspected infectious etiology (infectious diarrhea). Of these, 134 persons could not be reached for the following reasons: 107 had died, 14 had a non-traceable social security number, and 13 had no known address or a protected identity. At the end of 2002, the remaining 717 persons were sent a questionnaire to fill in and return by mail. The questionnaire was designed to be as simple as possible, with only 5 questions:

1. Have you had persistent stomach trouble after the acute intestinal infection? Yes or no to mark in boxes.
2. If you answered yes to question 1, put a cross under each year in which you had stomach trouble. The years 1997–2002 were presented with boxes to mark.
3. Did you use to have stomach trouble before you had the acute intestinal infection? Yes or no to mark in boxes.
4. Have you been told by a doctor that you have a gastrointestinal disease? Yes or no to mark in boxes. If yes, which gastrointestinal disease?

Abbreviations used in this paper: FBD, functional bowel disorder; FD, functional dyspepsia; GI, gastrointestinal; IBS, irritable bowel syndrome; PI-FBD, postinfectious functional bowel disorder; PI-IBS, postinfectious irritable bowel syndrome.

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1542-3565/07/$32.00
doi:10.1016/j.cgh.2007.01.007

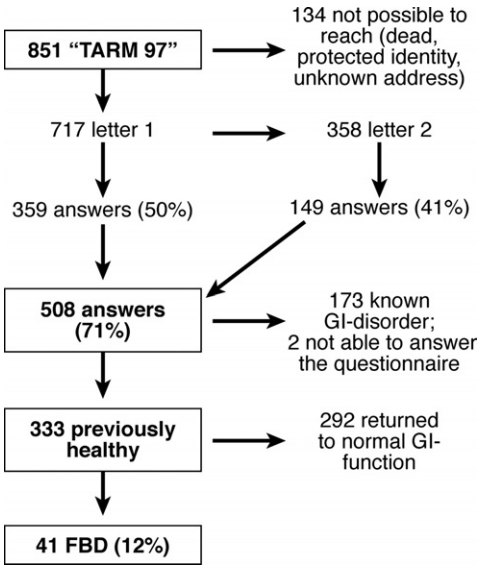

Figure 1. Flow chart of recruitment of patients from the study population.

5. Have you been told by a doctor that you have some other disease? Yes or no to mark in boxes. If yes, which disease?

A definition of stomach trouble was given in the introduction of the questionnaire: By "stomach trouble" we mean one or several of the following symptoms, either continuous or periodical (altogether at least 3 months in a year): stomach pain, gases/flatulence, nausea/vomiting, disturbed bowel function (diarrhea, constipation or alternating bowel habits).

After 2 months, a reminder was sent to those who had not responded.

Each person who gave a combination of answers compatible with new gastrointestinal (GI) symptoms persisting after the infectious diarrhea (Q1 = Yes, Q2 = Marked 1997 or more, Q3 = No) was sought for a telephone interview. If the patient was not already diagnosed as having an organic disease, a symptom-based diagnosis was made, following the Rome-II criteria for FBD.[9] Recall bias was checked by referring to the questionnaires from the original study regarding previous GI disease mentioned by the patient at that time. The county diagnosis register and available medical records were used as additional checkups for organic diseases interfering with the diagnosis of FBD. One age- and gender-matched control (Q1 = No) was selected for each patient. They were all interviewed by telephone to check the validity of symptom reporting by the questionnaire.

The study was approved by the Ethics Committee of Karolinska University Hospital Huddinge.

Statistics

Nominal data were compared by using the χ^2 test or Fisher's exact test. Parametric data were compared by Student's *t* test. Multiple regression analysis was performed to test for independent significance. *P* values $<.05$ were considered statistically significant. Statistical analysis was carried out with the software package StatView for Windows (SAS Institute Inc, Cary, NC).

Results

A total of 508 patients (71%) returned the study questionnaire. Of these, 173 were excluded because of pre-existing symptoms compatible with FBD or other GI diseases, and 2 were in a physical condition that prevented them from answering the questionnaire. This meant that 333 previously healthy patients, denying any GI problems before the infectious diarrhea, formed the study population. Forty-one (12%) patients had developed persistent (3 months or longer) GI symptoms, and 31 (9%) patients still had their symptoms 5 years after the initiating infectious diarrhea. Thus, 24% of initially affected individuals recovered during the follow-up period (Figures 1 and 2).

Forty of 41 patients could be classified as having FBD. IBS was the most common diagnosis, 28 of 41 patients (68%). In decreasing order of frequency, 5 of 41 (12%) had FD, 4 of 41 (10%) had functional diarrhea, and 1 patient each had loose stools, functional abdominal pain, and levator ani syndrome. One patient could not be reached for an interview and had no available diagnosis in the diagnosis register or other available medical records. Women had a higher risk than men of developing persistent GI symptoms, with an odds ratio of 2.65 (95% confidence interval, 1.28–5.50; $P = .008$, Fisher's exact test). All controls denied persisting GI symptoms after the infectious diarrhea.

Enteric pathogens were identified in stool specimens from 176 of 333 patients (53%). No specific enteropathogen was found to be a risk factor for persisting GI symptoms (Figure 3). The viral infections that led to persistent GI symptoms were 1 each of rotavirus and adenovirus and 2 of calicivirus. Two cases had an association with parasite infection, one with *Giardia lamblia* and the other with a co-infection from *Blastocystis hominis* and *Campylobacter jejuni*. Of those patients without a known enteropathogen, 20 of 157 (13%) developed FBD, compared with 21 of 176 (12%) of those in whom an enteropathogen was found. Having 2 or more enteropathogens in the stools was not associated with an increased risk of persistent GI symptoms. Use of antibiotics during the infectious diarrhea was significantly more common in the group developing FBD (odds ratio, 2.37; 95% confidence interval, 1.07–5.25; $P = .05$, Fisher's exact test) compared with those who did not. The wide range in the interval before seeking medical care originated from a small cohort of patients who contracted diarrhea abroad in areas in which health care availability was low. There was no correlation between this "pre-health care" duration of symptoms and risk of PI-FBD. In all other respects, no significant risk factors or protective factors could be identified from the available baseline data (Table 1).

Analysis of those not responding to the questionnaire showed them to be slightly younger than the responders (39 vs

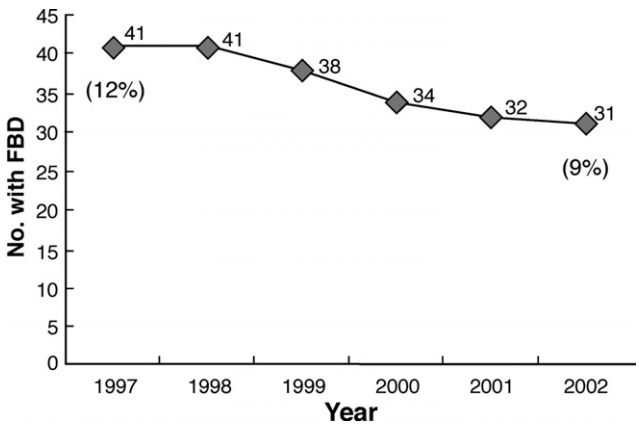

Figure 2. Spontaneous recovery in patients suffering from persistence of GI symptoms during the study period.

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