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Long-term Clinical Course of Post-infectious Irritable Bowel Syndrome After Shigellosis: A 10-year Follow-up Study

Young Hoon Youn,[1] Hyeon Chang Kim,[2] Hyun Chul Lim,[1] Jae Jun Park,[1] Jie-Hyun Kim,[1] and Hyojin Park[1]*

[1]Division of Gastroenterology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; and [2]Department of Preventive Medicine and Public Health, Yonsei University College of Medicine, Seoul, Korea

Background/Aims

A limited number of studies are available regarding the long-term natural history of post-infectious irritable bowel syndrome (PI-IBS). We aimed to investigate the long-term clinical course of PI-IBS.

Methods

A prospective cohort study was conducted from a 2001 shigellosis outbreak in a Korean hospital with about 2000 employees. A cohort of 124 hospital employees who were infected by *Shigella sonnei* due to contaminated food in the cafeteria, and 105 sex- and age-matched, non-infected, controls were serially followed for their bowel symptoms by questionnaire surveys for 10 years.

Results

The *Shigella*-infected cohort showed significantly higher odds ratio for irritable bowel syndrome (IBS) at 1-year (11.90; 95% CI, 1.49-95.58) and 3-year (3.93; 95% CI, 1.20-12.86) follow-up, compared to their controls. However, corresponding odds ratio for PI-IBS was not significantly increased at 5-year (1.88; 95% CI, 0.64-5.54) and 8-year (1.87; 95% CI, 0.62-5.19) follow-up. At 10-year follow-up survey, the prevalence of IBS was similar for the *Shigella*-infected cohort and their controls (23.3% versus 19.7%, P = 0.703). Risk factors which were independently associated with PI-IBS among the *Shigella*-infected cohort included younger age, previous history of functional bowel disorder, and longer duration of diarrhea at baseline.

Conclusions

Patients who were infected by *Shigella sonnei* experienced significantly increased risk of IBS until 3 years after shigellosis, and modestly increased risk until 8 years, but showed similar risk of IBS with uninfected controls at 10 years post-infection. PI-IBS is quite a chronic disorder, and follows a long-term natural course.
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Key Words

Cohort; Dysentery; Irritable bowel syndrome; Prognosis; *Shigella*

*Correspondence: Hyojin Park, MD, PhD
Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University Medical College, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea
Tel: +82-2-2019-3318, Fax: +82-2-3463-3882, E-mail: hjpark21@yuhs.ac

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Introduction

Irritable bowel syndrome (IBS) is one of most common chronic gastrointestinal disorders, and is characterized by abdominal pain or discomfort associated with disturbed and altered bowel habit in the absence of organic disease.[1] IBS is a common digestive disease, with a variable prevalence of 4-22% worldwide.[2] Although it is not a life-threatening disorder, IBS poses significant quality of life concerns and remains a substantial burden on the health care system.[3]

The pathophysiology of IBS is thought to be multifactorial, and possible mechanisms of IBS include altered bowel motility, visceral hypersensitivity, psychosocial distress, abnormal brain-gut interaction, enteric infection, gut-immune activation, low grade inflammation, intestinal permeability, and alterations in intestinal microflora.[4-9]

The role of enteric infection in the pathogenesis of IBS has been recognized since Chaudhary and Truelove[10] first reported the association between infectious gastroenteritis and persistent gastrointestinal symptoms. While many enteric infections cause self-limiting illness, 5-30% of people experience new gastrointestinal symptoms that persist after bacterial dysentery, despite clearance of the inciting pathogen.[11] Additionally, approximately 10% of IBS patients reported that their symptoms began following a bout of infectious dysentery.[12]

Post-infectious IBS (PI-IBS) is defined as the acute onset of new IBS symptoms in an individual who has not previously met the criteria for IBS immediately following an acute illness characterized by 2 or more of the following: fever, vomiting, diarrhea, or positive bacterial stool culture.[12]

Although there have been many reports regarding PI-IBS associated with pathogens such as *Shigella* spp., pathogenic *Escherichia coli*, *Salmonella*, *Campylobacter jejuni*, and *Giardia duodenalis* in the past 20 years,[13-19] most of these reports address the short-term clinical course of PI-IBS, and only few examined the long-term course (≥ 5 years) of PI-IBS.[20-23]

We previously reported on the clinical course of PI-IBS in a homogenous cohort comprised of patients recovered from shigellosis.[17,23,24] In the current study, we report on the collective results of a 10-year, long-term follow-up of our small, well-followed, homogenous cohort of patients that developed PI-IBS after shigellosis.

Materials and Methods

Subjects

In December 2001, a shigellosis outbreak took place at Gangnam Severance Hospital (formerly "Youngdong Severance Hospital") in Seoul, Korea, due to the consumption of contaminated food in the hospital employee cafeteria. The causative pathogen was *Shigella sonnei*, and a total of 181 patients were diagnosed and treated for shigellosis. All patients were medical personnel including physicians, nurses, paramedics, and medical students. After termination of the shigellosis outbreak, we established a cohort of *Shigella*-exposed patients who agreed to participate in serial follow-up surveys. Patients who were pregnant, those who had already symptoms of IBS before shigellosis, and who had a history of abdominal surgery or chronic organic gastrointestinal disorders were excluded. The initial *Shigella*-exposed cohort was comprised of 143 subjects.

To serve as a control population, we recruited healthy age- and sex-matched volunteers who were working for the hospital at the time of the shigellosis outbreak (they were not exposed to the contaminated food), and among them, subjects who already had symptoms of IBS before shigellosis was excluded from control cohort and followed separately as sporadic IBS subjects in subsequent analyses.

For the 10-year follow-up survey, we built a list of 124 subjects in the *Shigella*-exposed cohort who were still working for the hospital, or those who were retired but contactable by phone calls. Among the control group, we were able to contact 105 subjects in the same manner.

Methods

Both the *Shigella*-exposed cohort and the control cohort were asked to participate in follow-up questionnaires at 1, 3, 5, 8, and 10 years after recruitment. The initial 1-year and 3-year surveys addressed epidemiologic data, past medical and surgical history, information regarding the presence of vomiting, fever, and duration of diarrhea during the acute illness, and information regarding current bowel symptoms according to the Rome II criteria.[17,24] The follow-up questionnaires at 5, 8, and 10 years after outbreak mainly addressed current bowel symptoms according to the Rome II criteria, as well as recent medical history of other gastrointestinal disorders, including incidence of additional enteric infection and/or abdominal surgery, which was exclusion criteria for subsequent analyses.[23] The diagnosis of IBS and other functional bowel disorders (FBDs) was

made using the Rome II criteria, and other FBDs included functional abdominal bloating, functional constipation, functional diarrhea, and unspecified FBDs

For the 10-year follow-up survey, investigators performed the survey questionnaire preferentially by face-to-face interview, and by telephone interview, if necessary. A small financial reward ($10) was given in acknowledgement of subjects' participation in the study. Written informed consent was obtained from each subject before the survey, and the University of Yonsei Medical School Ethics Committee approved the study protocol (IRB approval number: 3-2011-0242).

Statistical Methods

Cohort members and their controls were compared by independent t test for continuous variables, and by Chi-square test or Fisher's exact test for categorical variables. Logistic regression analysis was performed to calculate OR and 95% CI for prevalent IBS at each time interval or newly-developed IBS during a given time-interval, after adjustment for sex and age. All statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS, 18.0 Inc, Chicago, IL, USA). A P-value of less than 0.05 was regarded as statistically significant.

Results

Response Rate and General Characteristics

A total of 229 subjects (124 in the *Shigella*-exposed group, 105 in the control group) were surveyed periodically for 10 years following the December 2001 shigellosis outbreak. Ten years post-outbreak, the overall response rate was 70.7% (162/229), while the response rate of the *Shigella*-exposed group was 69.4%, which was not significantly different from the response rate (72.4%) of the control group (Table 1). The mean age of study subjects 10 years post-outbreak was 41.8 years for the *Shigella*-exposed group and 39.6 years for the control group ($P = 0.071$). The female-to-male ratio was 2.8 for the *Shigella*-exposed group and 2.9 for the control group ($P = 0.943$).

Prevalence of Irritable Bowel Syndrome at Each Time Point

The prevalence of IBS after the shigellosis outbreak was analyzed at each time point after exclusion of subjects who had symptoms of IBS prior to the outbreak (Table 2).

The prevalence of IBS after 1 year was 13.1% in the *Shigella*-exposed group and 1.1% in the control group. Thus, the risk of IBS

Table 1. Survey Response Rate at Each Time Point

Survey time (yr)	*Shigella*-exposed group		Control group	
	Planned subjects	Responded subjects (response rate)	Planned subjects	Responded subjects (response rate)
1st	143	101 (70.6%)	113	102 (90.3%)
3rd	124	95 (76.6%)	120	105 (87.5%)
5th	75	59 (78.7%)	78	60 (76.9%)
8th	133	71 (53.4%)	105	65 (61.9%)
10th	124	86 (69.4%)	105	76 (72.4%)

Table 2. Prevalence of Newly-developed Irritable Bowel Syndrome After Shigellosis Outbreak at Each Time Point

Survey time (yr)	*Shigella*-exposed group		Control group		Adjusted OR (95% CI)
	Total No.	No. of IBS	Total No.	No. of IBS	
1st	87	12 (13.8%)	89	1 (1.1%)	11.9 (1.49-95.58)
3rd	87	13 (14.9%)	89	4 (4.5%)	3.93 (1.20-12.86)
5th	53	11 (20.8%)	49	6 (12.2%)	1.88 (0.64-5.54)
8th	71	11 (15.4%)	65	6 (9.2%)	1.87 (0.62-5.19)
10th	86	20 (23.3%)	76	15 (19.7%)	1.61 (0.70-3.69)

IBS, irritable bowel syndrome.

in the *Shigella*-exposed cohort was significantly higher than that of the control cohort at the 1-year follow-up survey (adjusted OR, 11.90). The prevalence of IBS at the 3-year follow-up survey was also significantly higher in the *Shigella*-exposed group than the control group (adjusted OR, 3.93). However, at the 5-year and 8-year follow-up surveys, the prevalence of IBS in the *Shigella*-exposed cohort was modestly increased but not statistically significant compared to the control cohort. The 10-year follow-up survey showed similar IBS prevalence in both groups (23.3% for *Shigella*-exposed group, 19.7% for control group; $P = 0.703$).

Incidence of Irritable Bowel Syndrome During Each Time Interval

The incident of IBS during each time interval was defined as newly-developed IBS among subjects who did not report IBS symptoms in the previous survey (Table 3). The incidence of newly-developed IBS was significantly higher in the *Shigella*-exposed

group than the control group during the first year post-outbreak. However, no significant differences were demonstrated between the 2 groups at subsequent follow-up intervals.

Irritable Bowel Syndrome Prognosis

We were able to follow-up 12 patients who developed PI-IBS among the *Shigella*-exposed cohort up to 10 years after the shigellosis outbreak. Also, we could follow up the natural history of 14 sporadic IBS (not "post-infectious") patients among the control cohort who were initially recruited at the time of outbreak,[23] and were excluded from the subsequent analysis of newly-developed IBS because they already had symptoms of IBS prior to the outbreak.

The figure represents the 10-year natural history of PI-IBS patients (Figure A) and sporadic IBS patients (Figure B). About half of the PI-IBS patients showed remission of IBS symptom after 5 years. However, approximately 25-30% of PI-IBS patients had persistent IBS symptoms even after 8 to 10 years. The natural his-

Table 3. Incidence of Newly-developed Irritable Bowel Syndrome During Each Time Interval

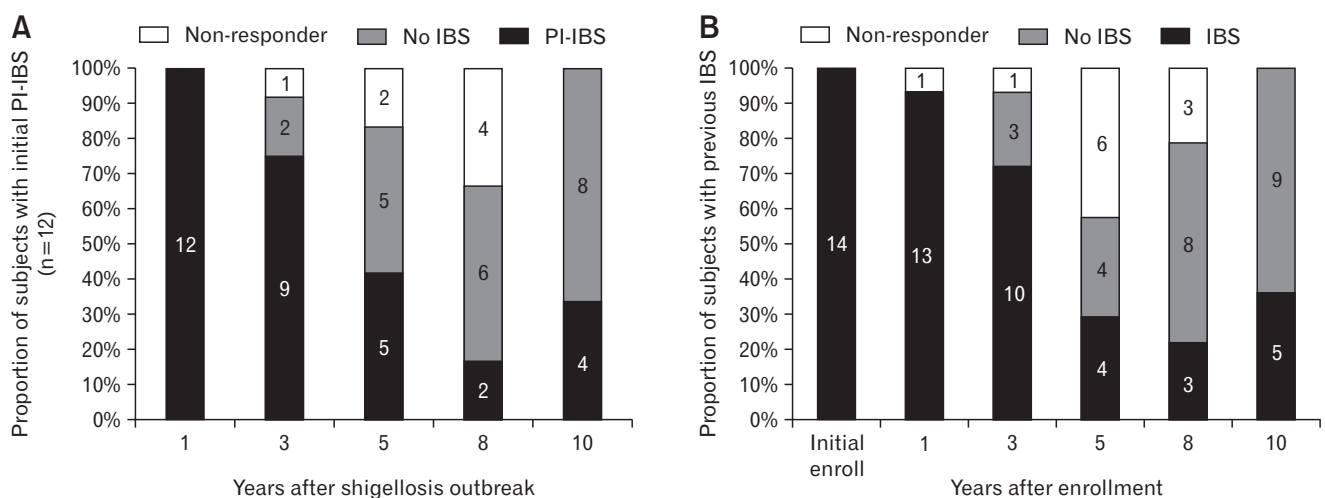| Time interval (yr)	*Shigella*-exposed group		Control group		Adjusted OR (95% CI)
	Total No.	No. of incident IBS	Total No.	No. of incident IBS	
0-1	87	12 (13.8%)	89	1 (1.1%)	11.9 (1.49-95.58)
1-3	71	4 (5.6%)	84	3 (3.6%)	1.61 (0.35-7.46)
3-5	46	6 (13.0%)	46	3 (6.5%)	2.15 (0.50-9.18)
5-8	71	4 (5.6%)	65	3 (4.6%)	1.23 (0.26-5.73)
8-10	71	11 (15.5%)	67	10 (14.9%)	1.04 (0.47-2.28)

IBS, irritable bowel syndrome.

Figure. Natural history of post-infectious irritable bowel syndrome (PI-IBS) after shigellosis (A), and sporadic IBS in control subjects (B) over 10 years. Twelve PI-IBS patients and 14 sporadic IBS patients were followed for 10 years. Approximately half the patients recovered from IBS after 5 years, but several patients had persistent IBS symptoms for the duration of the study. The natural history of PI-IBS and sporadic IBS seem to be quite similar.

Table 4. Analysis of Risk Factors Associated with Development of Post-infectious Irritable Bowel Syndrome in *Shigella*-exposed Group During 10-year Follow-up

Baseline characteristics	OR (95% CI)
Age (yr)	
< 40	1.00
≥ 40	0.94 (0.89-0.99)
Sex	
Male	1.00
Female	2.00 (0.75-5.54)
History of other FBD[a]	
No	1.00
Yes	5.10 (1.2-21.1)
Duration of diarrhea	
No	1.00
Yes	1.27 (1.01-1.60)
Vomiting	
No	1.00
Yes	0.58 (0.14-2.39)
Fever	
No	1.00
Yes	1.57 (0.68-3.64)

[a]Functional bowel disorders (FBDs) other than irritable bowel syndrome (IBS), including functional abdominal bloating, functional constipation, functional diarrhea, and unspecified FBDs by Rome II criteria.

tory of the 14 sporadic IBS (not-related to shigellosis) patients was quite similar to the prognosis of PI-IBS patients.

Risk Factors Associated with Post-infectious Irritable Bowel Syndrome Development

We analyzed the risk factors which were associated with the ever-developed PI-IBS in the *Shigella*-exposed subjects. Younger age, previous history of FBDs other than IBS at baseline, and duration of diarrhea in initial dysentery were significantly associated with PI-IBS development during the follow-up over 10 years (Table 4).

Discussion

Since Chaudhary and Truelove[10] first reported the concept of PI-IBS in 1962, there has been a substantial amount of epidemiologic data published regarding the association between PI-IBS and various pathogens, including bacterial, protozoal, and viral pathogens. Several studies have established the causative pathogens of PI-IBS, including *Shigella* spp.,[16,23] pathogenic *E. coli*,[22] *Salmonella* spp.,[13,18] *C. jejuni*,[15] *G. duodenali*,[19] *Trichinella britovi*,[25] norovirus,[26] or combinations of the preceding pathogens.[14,22]

The reported incidence of PI-IBS varies from about 5-30%,[11]

and PI-IBS is now a well-recognized consequence of acute infectious gastroenteritis. There is little doubt that bouts of infectious enteritis may cause some patients to suffer from chronic IBS symptoms, and this fact was also validated by the results of our study. However, little data is available for long-term natural history of PI-IBS.

As far as we know, there have been only 3 studies that have followed participants with PI-IBS for more than 5 years.[20-22] Among these relatively long-term reports, one is a 6-year follow-up study from a British cohort,[20] another is a 5-year follow-up study from a Swedish cohort,[21] and the other is an 8-year follow-up study from a Canadian cohort.[22] However, our study followed Korean patients for 10 years, and as such is the longest follow-up study concerning PI-IBS. Moreover, our cohort consisted of a homogenous group of patients who were infected with a single pathogenic strain (*S. sonnei*) from the same contamination source. The 8-year follow-up study with thousands of participants from Walkerton, Canada[22] could provide the most useful data due to the sample size and consequential statistical power, while our study is limited in its small sample size. However, in the Walkerton cohort, the infecting pathogens were variable combinations of *E. coli* 0157:H7, *C. jejuni*, and other pathogens, ultimately resulting in increased heterogeneity of the study population.

Our current study might improve our understanding of long-term prognosis of PI-IBS. Approximately half of the patients in our study recovered 5 years post-infection, whereas 25-33% still suffered from PI-IBS even 8-10 years post-infection. These results are generally consistent with those of previous long-term studies.[20-22] Additionally, we found that the long-term natural course of PI-IBS was similar to that of sporadic IBS in our cohort. Although we found a slightly higher incidence of IBS in the *Shigella*-exposed group than the control group at 5 and 8 years post-outbreak, the differences were not statistically significant. These findings are in contrast with those of the Walkerton study, where the difference in IBS prevalence was still significantly higher after 8 years in the infected group compared to the control group (OR, 3.12; 95% CI, 1.99-5.04).[22] This discrepancy might have resulted from the difference in sample size, infecting pathogens, or population characteristics. With this in mind, the non-significant difference in IBS prevalence between the infected and control groups in our study after 5 years does not indicate that acute infectious gastroenteritis did not affect the PI-IBS patients for longer than 5 years. The issue of how long the difference in the prevalence of IBS lasts between infected and control group cannot be clearly concluded yet, and we believe that this issue might be also influenced by regional socio-environmental factors of the each cohort.

The risk of newly-developing PI-IBS in the *Shigella*-exposed group is significantly higher only during the first year post-infection, whereupon the development of new sporadic IBS was the same in the 2 groups. Because PI-IBS is a chronic disorder, the difference in the prevalence of IBS between the 2 groups can persist for several years post-infection. After 10 years, however, IBS prevalence in the infected group decreased to nearly the same level as that of the control group. This is likely because the PI-IBS patients recovered gradually while patients in the control group developed new sporadic IBS.

The mechanisms that underlie PI-IBS remain largely unclear, but several mechanisms have been proposed including immune activation, chronic low grade inflammation, enterochromaffin cell hyperplasia, and alteration of epithelial permeability and neuromuscular function.[12,27] Additionally, functional gastrointestinal disorders following acute infectious gastroenteritis not only include PI-IBS, but also post-infectious dyspepsia.[18,28,29] The final symptom complex depends on the interaction between local mucosal injury and central factors including adverse life events, personality, and external stressors. Additionally, local injury is often more highly influenced by the nature of the infectious agent. Rotavirus and *Giardia* infection mainly involve the upper gastrointestinal tract, and thus may predominantly predispose patients to dyspepsia, whereas *Shigella* infection is confined to the left colon and exclusively predisposes patients to IBS. *Salmonella* or *Campylobacter* infections cause ileitis and colitis, equally predisposing patients to both dyspepsia and IBS. Because our cohort was comprised of patients exclusively infected by *S. sonnei*, the absence of post-infectious dyspepsia was expected. Conversely, post-infectious dyspepsia was common in the Walkerton cohort.[28]

Risk factors for PI-IBS in the results of our study are consistent with those from previously published studies, which suggest that duration and severity of initial illness, toxicity of infecting pathogens, female sex, younger age, previous history of functional gastrointestinal disorder, and psychosocial factors are risk factors for developing PI-IBS. In our study, younger age, previous history of FBD, and duration of diarrhea showed statistically significant associations with PI-IBS development, whereas female sex and fever showed increased but statistically nonsignificant odds ratios, possibly due to the small number of study subjects. Additionally, we found no association between vomiting and PI-IBS, which may be explained by the nature of *Shigella* (which primarily affects the left colon).

We followed our cohort with regular surveys on bowel symptoms 1, 3, 5, 8, and 10 years after outbreak. During the course of the surveys, the response rate and final number of participants were lowest at the 5-year survey, and gradually rose to about 70% at the 10-year survey. The small number of participants at the time of the 5-year survey might be due to the exclusion of all subjects who had been excluded from 1-year and 3-year analysis. The response rate of the 10-year survey was relatively higher than previous surveys, because we tried multiple contacts using both face-to-face interview and telephone interview.

The prevalence of IBS increased between 8-10 years post-outbreak in both the infected and control groups. The cumulative incidence of IBS between 8 to 10 years post-outbreak was 15.5% in the infected group and 14.9% in the control group, which are values quite high compared with other interval periods. We cannot definitively explain this increased IBS rates, but we posit that hospital workers may have been exposed to a stressful work environment during that period. Indeed, a series of hospital qualifying programs (Joint Commission International accreditation and Korean Institute for Healthcare accreditation) continued to proceed at the time of the 10th year survey, and the workload of many hospital workers was heavier than usual. We presume that stressful workload might be associated with increase of IBS at the 10th year survey.

The current study has also several limitations. Firstly, the relatively small size of cohorts may decrease the statistical reliability. Secondly, we tried to exclude new PI-IBS due to additional enteric infection after the initial bout of shigellosis, by surveying the history of additional enteric infection between the periods, however there might be some recall bias. Thirdly, the diagnosis of IBS was made by symptoms at only each time points of the surveys, and was not continuously monitored throughout the 10 years, and so, time dependent Cox regression analysis could not be applied to clarify the prognosis of PI-IBS.

In conclusion, the relative risk of PI-IBS was significantly higher in the infected group compared to the control group up to 3 years after shigellosis, but gradually decreased thereafter. The natural history of PI-IBS and sporadic IBS seem to be similar, and in our study approximately half of patients in each group recovered after 5 years, whereas symptoms persisted for 10 years in about one third of patients. The duration of diarrhea as an index of severity of initial illness, previous history of FBD, and younger age were risk factors for PI-IBS.

Conflicts of interest: None.

Author contributions: Young Hoon Youn analyzed data and wrote the manuscript; Hyeon Chang Kim contributed on data analysis, statistic, and revision of manuscript; Hyun Chul Lim, Jae Jun Park, and Jie-Hyun Kim contributed on patients interview and data acquisition; and Hyojin Park designed and supervised this study.

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