

ORIGINAL ARTICLE

## 배양검사로 확진된 지역사회 세균성 장염 환자에서 과민성 장증후군의 발생률과 위험요인

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### Incidence and Risk Factors of Irritable Bowel Syndrome in Community Subjects with Culture-proven Bacterial Gastroenteritis

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**Background/Aims:** The aim of this study was to investigate the incidence and risk factors of irritable bowel syndrome (IBS) in community subjects with culture-proven bacterial gastroenteritis.

**Methods:** This was a prospective, community-based, cohort study, which followed patients with a recent history of culture-proven bacterial gastroenteritis. IBS was diagnosed with the use of the Rome II criteria at 3 and 6 months after bacterial dysentery.

**Results:** Sixty five cases were included and completed the 6 month follow-up. Thirty four cases (52.3%) were female. *Salmonella* was the pathogen most frequently identified and seen in 41 patients (63.1%). The cumulative incidence of IBS among patients with microbiologically proven bacterial gastroenteritis within a community was 9.2% and 12.3% at 3 and 6 months of follow-up, respectively. The duration of initial diarrhea ( $\geq 7$  days) was associated with an increased risk for the development of IBS (aOR, 14.50 [95% CI, 1.38-152.72];  $p=0.022$ ).

**Conclusions:** Our study suggests that the incidence of IBS among patients with culture-proven bacterial gastroenteritis within a community is similar to that reported among Western populations. A large, prospective study is encouraged to confirm our results and to evaluate the influence of the microbial species on the epidemiology of IBS in Asian populations. (Korean J Gastroenterol 2012;60:13-18)

**Key Words:** Irritable bowel syndrome; Bacterial gastroenteritis; Diarrhea

## INTRODUCTION

Irritable bowel syndrome (IBS) is a highly prevalent gastrointestinal disorder characterized by abdominal pain or discomfort and a change in bowel habits.<sup>1</sup> There is no single biochemical or structural marker to diagnose IBS. Therefore, a

diagnosis of IBS relies on consistent symptoms with the exclusion of other organic or functional diseases that may share in its symptoms through chemical tests or endoscopic examination.<sup>2</sup> Although it has been proposed that IBS is attributable to the interplay among altered motility, visceral hypersensitivity, brain-gut disturbances, and genetic and envi-

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ronmental factors, the pathogenesis of IBS still remains obscure.

Acute enteric infection has been proposed as a cause of IBS. It has been demonstrated that severe inflammation can impair the functions of the sympathetic nerve.<sup>3</sup> The infiltration of inflammatory cells such as enteroendocrine cells, CD4, and CD8 lymphocytes in the rectal mucosa was found despite the resolution of bacterial infection in stool cultures.<sup>4,5</sup> In addition, interleukin-1 $\beta$  mRNA expression in the rectal mucosa and terminal ileum significantly increased in patients with post-infectious IBS (PI-IBS) compared to those without IBS after bacterial infection.<sup>6,7</sup> These studies have provided a basis for understanding the role of enteric infection in developing IBS.

The epidemiological evidence for a relationship between acute bacterial gastroenteritis and the development of IBS has also been studied. A study estimated that the rate of PI-IBS among patients with culture-proven bacterial infections was 4.4%, which was significantly higher than that in the control subjects after a 12-month follow-up period.<sup>8</sup> In addition, it was demonstrated that IBS developed more frequently in patients with bacterial gastroenteritis compared to the controls in a well-designed prospective cohort study.<sup>9</sup> Furthermore, a recent meta-analysis showed that acute gastrointestinal infection significantly increased the risk of developing IBS.<sup>10</sup> Although these studies provide evidence for a relationship between acute bacterial gastroenteritis and developing IBS, marked differences in respect to the incidence of PI-IBS exist among studies.<sup>11</sup> Moreover, there have been few reports which analyzed determining the incidence and risk factors in patients with culture-proven bacterial gastroenteritis among Asian populations.

The Korean government has developed the sentinel surveillance system for communicable disease since 2000. Disweb, an internet-based reporting system established by the Korea Centers for Disease Control and Prevention (KCDC) provides information to the public and health care workers in regard to community patients with legal epidemics such as *Salmonella*, *Shigella*, *Escherichia coli* (*E.coli*) O157 and *Vibrio cholera*. Therefore, a prospective observational study for the community subjects with legal enteric infection is an exclusive way to provide the accurate incidence and risk factors of PI-IBS within a community following culture-proven bacterial gastroenteritis in Korea. This was a commun-

ity-based, prospective cohort study which aim was to elucidate the incidence and risk factors of IBS in patients with culture-proven bacterial gastroenteritis in Korea.

## SUBJECTS AND METHODS

### 1. Study design

This was a prospective, community-based, cohort study, which followed patients with a recent history of bacterial dysentery. The follow-up interview was at 3 and 6 months after acute enteric infection to identify the incidence and risk factors of PI-IBS.

### 2. Setting

This study was done in Gyeonggi-Do, the national capital region that includes urban, semirural, and rural inhabitants. This study was done between January 2008 and February 2010.

### 3. Participants

The data collected from Disweb has been used for the present study. The access to Disweb was permitted by an epidemic intelligence service officer in Gyeonggi-Do, a co-author of the study. Patients infected with *Salmonella*, *Shigella*, *E.coli* O157, and *Vibrio cholera* were identified from January 2008 to July 2009 in the Gyeonggi-Do area of Korea. All patients between the ages of 15 and 75 years with culture-proven bacterial gastroenteritis were eligible as cases. Potential patients were contacted by telephone. Interviewers explained the study protocol and obtained verbal informed consent from the patients who agreed to participate in this study. Patients with acute gastroenteritis were defined as showing a positive stool culture or acute onset illness characterized by 2 or more of the following along with a positive blood culture: fever, vomiting, and diarrhea. The exclusion criteria for the cases included the inability to give informed consent, pregnancy, severe psychiatric disease, chronic illnesses that might be predicted to contribute to gastrointestinal symptoms such as cancer, inflammatory bowel disease or hyperthyroidism, and previous abdominal surgery. In addition, patients who had been diagnosed with IBS by a physician before bacterial gastroenteritis were also excluded.

#### 4. Outcome measure

Patients who consented to participate were interviewed by telephone using the questionnaire based on the modular ROME II questionnaire, which incorporated the questions for diagnosis of IBS under clinical research. Follow up was made at 3 and 6 months after bacterial dysentery. To elucidate the risk factors of post-infectious IBS, the case reports of the patients were reviewed using the national communicable disease surveillance system, as investigated through a standardized questionnaire provided by the KCDC at the time of initial illness. Forty nine case reports including 8 PI-IBS patients were available at the time of the investigation. The case reports contained demographic data (age, sex, address, and occupation), symptoms of acute enteric illness (fever, nausea, vomiting, abdominal pain, tenesmus), and characteristics of the diarrhea (duration of diarrhea). The Ethics Committee of Seoul National University Bundang Hospital approved the study.

#### 5. Statistical analysis

Univariable analyses were done using the Mann-Whitney U for continuous variables and the chi-square test or Fisher's exact test for categorical variables. A p-value < 0.20 was required for entry into a binary logistic regression analysis model, which was used to identify the risk factors for the development of PI-IBS. Additionally, the variables evaluated as risk factors for the development of PI-IBS were selected from previous reports and the authors' experience. The variables included age, sex, and gastrointestinal manifestations (fever, vomiting, and nausea, duration of diarrhea). Statistical significance was determined using a p-value of less than 0.05.

**Table 1.** Characteristics of Study Participants Compared to All Culture-proven Bacterial Gastroenteritis

Variables	Potential cases from Gyeonggi-Do	Included cases
Number	119	65
Age, yr	35 (1-93)	40 (16-70)
Sex, male	57 (47.9)	31 (47.7)
<i>Salmonella</i>	64 (53.8)	41 (63.1)
<i>Shigella</i>	47 (39.5)	22 (33.8)
<i>E.coli</i> O157	7 (5.9)	1 (1.5)
<i>Vibrio Cholera</i>	1 (0.8)	1 (1.5)

Values are presented as number, median (range), or n (%).  
*E. coli* O157, *Escherichia coli* O157.

All analyses were carried out using the software package SPSS for Windows ver. 12.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### 1. General characteristics

A total of 119 individuals with culture-positive bacterial gastroenteritis were reported between January 1, 2008 and July 31, 2009 in the Gyeonggi-Do area. Among the 119 cases, 65 cases (54.6%) were eligible and agreed to be participants. Thirty-two cases whose age was less than 15 (n=27) or more than 75 (n=5) were ineligible for the study. Fifteen cases could not be contacted or refused to participate in the study. Seven individuals were excluded due to previous IBS (n=3), psychological illness (n=1), hyperthyroidism (n=1), abdominal surgery (n=1) and malignancy (n=1). Of the 65 cases who completed the 6-month follow-up, 34 cases (52.3%) were female and 31 (47.7%) were male. The median age was 40 (range 16 to 70). *Salmonella* was the pathogen most frequently identified and seen in 63.1% of the cohort. *Shigella* species were identified in 33.8% of the study population (Table 1).

The clinical characteristics of the 8 patients who had IBS symptoms during the 6-month of follow-up period were summarized in Table 2. Three patients were female and the median age was 45 (range 22 to 66). During the 6-month period, 5 patients (12.2%) with *Salmonella* infections and 3 patients (13.6%) with *Shigella* infections had IBS symptoms after the infection. Fever was the most common manifestation while vomiting was less frequent.

### 2. The incidence of IBS after culture-proven bacterial gastroenteritis

Among the 65 patients, 6 patients (9.2%) showed IBS symptoms during the first 3 months. Of the 6 patients, 2 did not have IBS symptoms for the next 3 months. However, 2 patients who had not shown IBS symptoms during the initial 3 months had IBS symptoms for the next 3 months. Therefore, 8 patients (12.3%) were identified as having IBS symptoms, as defined by the modular ROME II criteria during the 6-month follow-up period after bacterial dysentery (Fig. 1).

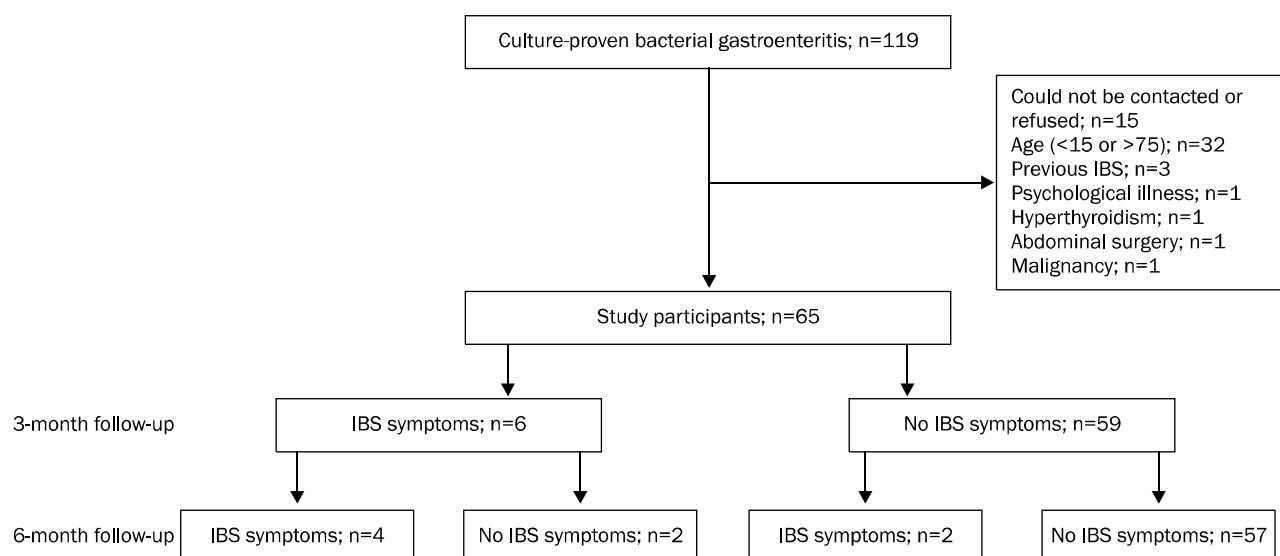


Fig. 1. The development of irritable bowel syndrome (IBS) after bacterial dysentery during the 6-month of follow-up.

Table 2. Univariate Analysis of Potential Risk Factors for Developing Irritable Bowel Syndrome after Bacterial Dysentery

Variables	PI-IBS	Non PI-IBS	p-value
Number	8	41	
Age, yr	45 (22-66)	37 (16-69)	0.700
Sex, male	5 (62.5)	19 (46.3)	0.463
Gastrointestinal manifestation			
Fever	6 (75)	29 (70.7)	1.000
Nausea	3 (37.5)	8 (19.5)	0.355
Vomiting	1 (12.5)	10 (24.4)	0.663
Abdominal pain	4 (50)	21 (51.2)	1.000
Tenesmus	2 (25)	7 (17.1)	0.457
Duration of diarrhea, day	8 (4-18)	3 (0-20)	0.016
Organism			
<i>Salmonella</i>	5 (62.5)	28 (68.3)	1.000
<i>Shigella</i>	3 (37.5)	11 (26.8)	0.672

Values are presented as number, median (range), or n (%).  
PI-IBS, post-infectious irritable bowel syndrome.

### 3. Risk factors for the development of IBS after bacterial dysentery

In the univariate analyses, the duration of diarrhea ( $p=0.016$ ) was significantly associated with the development of PI-IBS (Table 2). However, there was no association between the development of IBS and age, sex, other gastrointestinal manifestations or causative agents. In the multivariate logistic regression analysis, the duration of initial diarrhea ( $\geq 7$  days) (aOR, 14.50 [95% CI, 1.38-152.72];  $p=0.022$ ) significantly increased the risk of developing IBS (Table 3).

Table 3. Risk Factors for the Development of Post-Infectious Irritable Bowel Syndrome after Bacterial Dysentery (Multivariate Analysis)

Variables	p-value	OR (95% CI)
Age, yr	0.190	1.05 (0.97-1.14)
Sex, male	0.945	1.70 (0.17-6.77)
Gastrointestinal manifestation		
Fever	0.986	0.98 (0.12-8.03)
Nausea	0.053	14.82 (0.96-228.52)
Vomiting	0.263	0.22 (0.01-3.17)
Duration of diarrhea ( $\geq 7$ days)	0.022	14.50 (1.38-152.72)

## DISCUSSION

PI-IBS is generally defined as the new onset of IBS symptoms in an individual immediately following an acute enteric infection.<sup>11</sup> It was first proposed more than 5 decades ago.<sup>12</sup> After that, retrospective and prospective studies that included various ethnic groups were done to determine the incidence and risk factors of PI-IBS. These studies reported that the incidence of PI-IBS ranged from 3.7% to 36%.<sup>7,13-15</sup> Although it has been demonstrated that PI-IBS is a global phenomenon, wide discrepancies exist among different studies with regard to the incidence and risk factors of PI-IBS. In addition, there have been few epidemiological studies done in patients with culture-positive bacterial gastroenteritis within a community in Asian populations. Therefore, we performed an epidemiological study using a prospective, community-based design that included patients with culture-proven bacterial gastroenteritis. The results of the present study in 65

patients with culture-proven bacterial gastroenteritis showed that the cumulative incidence of PI-IBS was 9.2% and 12.3% at 3 and 6 months of follow up. The duration of the initial diarrhea was associated with an increased risk of IBS. To the best of our knowledge, this was the first prospective, community-based, cohort study, which included all cases of patients with microbiologically confirmed bacterial gastroenteritis in an Asian population.

Rodríguez and Ruigómez<sup>8</sup> reported a 4.4% incidence of PI-IBS in 318 patients with microbiologically confirmed gastroenteritis during a 1-year follow-up period. A prospective cohort study reported that the incidence of PI-IBS was 3.7% among a community of subjects with previous acute enteric infection confirmed by positive stool cultures.<sup>16</sup> In addition, a well-designed prospective cohort study showed that the incidence of PI-IBS was 16.7% during a 6-month follow-up period.<sup>17</sup> In the present study, the cumulative incidence of IBS in patients with culture-proven bacterial gastroenteritis was 9.2% and 12.3% at 3 and 6 months of follow-up, respectively. These observations are consistent with those of Western studies, suggesting that enteric infection is one of the important factors in the epidemiology and pathogenesis of IBS in Asian populations.

It has been demonstrated that risk factors for the development of PI-IBS are psychological factors such as adverse life events, depression, hypochondriasis, host factors including the female gender and young age (<60 years), and the duration of the initial illness.<sup>11</sup> A meta-analysis demonstrates that young age, anxiety, depression, and prolonged fever are risk factors for the development of IBS after acute enteric infection.<sup>10</sup> In the present study, multivariable analysis indicated that the duration of the initial diarrhea was an independent risk factor for the development of IBS after bacterial dysentery. This result is consistent with that of the previous studies performed in Asian populations.<sup>7,14</sup> However, this result should be interpreted with caution because our study could not exclude the existence of inflammatory mediators in the bowel mucosa after the resolution of gastroenteritis. In addition, several important risk factors such as psychological distress, past medical history, social factors, and other environmental factors were not investigated. Finally, it may be limited by its small number of PI-IBS cases, which may reduce statistical power of the multivariable analysis.

We believe that the present study provides valuable in-

formation for the following reasons. First, in the present study, patients were recruited from a community, which included urban, semirural and rural inhabitants and the enrolled patients had suffered from infectious colitis by various pathogens. Therefore, we were able to deliberately avoid selection bias that arises from the recruitment of hospital inpatients or outbreak patients. In addition, we enrolled only microbiologically confirmed gastroenteritis patients because some IBS patients were frequently assumed to have had enteric infections based on gastrointestinal symptoms. Finally, we carefully excluded patients with prior IBS and underlying causes that would be predicted to affect IBS symptoms. By strictly excluding such patients, we believe that our results have provided precise estimates of the incidence of IBS over a 6-month period after bacterial gastroenteritis.

The present study is limited because of small study population and short-term duration of follow-up. Previous studies reported a fairly high drop-out rate in the eligible cases,<sup>9,16,17</sup> which could increase the possibility of selection bias in evaluating the incidence of IBS because patients who completed the follow-up were more likely to have severe enteric illness. In the present study, we completed the follow-up interview in 65 patients who initially enrolled in the study. In addition, a significant proportion of potential cases were not included because of young age and underlying causes that would be predicted to affect gastrointestinal symptoms including prior IBS. Therefore, we think that this study has provided additional information on the epidemiology of PI-IBS despite the small sample size and short-term duration of follow-up.

In conclusion, the incidence of IBS among patients with microbiologically proven bacterial gastroenteritis within a community was 9.2% and 12.3% at 3 and 6 months of follow-up, respectively. These observations are similar to that reported among Western populations. A large, community-based and prospective epidemiological study is encouraged to confirm our results and to understand the influence of the microbial species on the epidemiology of IBS in Asian populations.

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