Dyspepsia and Irritable Bowel Syndrome After a Salmonella Gastroenteritis Outbreak: One-Year Follow-up Cohort Study

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Background & Aims: It has been reported that some patients develop functional digestive disorders, particularly irritable bowel syndrome (IBS), after acute gastroenteritis (AGE). However, the presence of dyspepsia has not been specifically addressed. We prospectively evaluated development of dyspepsia and IBS during a 1-year follow-up in a cohort of adult patients affected by a Salmonella enteritidis AGE outbreak.

Methods: Questionnaires were sent to 1878 potential participants at baseline and 3, 6, and 12 months; 677 had experienced a Salmonella enteritidis AGE on June 23, 2002, and 1201 had not (randomly selected controls, matched for village of residence, age, and sex). At 12 months, 271 patients and 335 controls returned the questionnaires. Data permitted the establishment of dyspepsia and IBS diagnosis by Rome II criteria.

Results: Before the AGE outbreak, the prevalence of dyspepsia was similar in cases and controls (2.5% vs 3.8%); the prevalence of IBS was also similar (2.9% vs 2.3%). At 3, 6, and 12 months, the prevalence of both dyspepsia and IBS had increased significantly in exposed compared with unexposed subjects. Overlap between dyspepsia and IBS was frequent. At 1 year, the relative risk for development of dyspepsia was 5.2 (95% confidence interval, 2.7–9.8) and for IBS was 7.8 (95% confidence interval, 3.1–19.7). Prolonged abdominal pain and vomiting during AGE were positive predictors of dyspepsia. No predictive factors for IBS were found.

Conclusions: Salmonella gastroenteritis is a significant risk factor not only for IBS but also for dyspepsia; at 1 year of follow-up, 1 in 7 and 1 in 10 subjects developed dyspepsia or IBS, respectively.

Functional gastrointestinal disorders (FGIDs), including functional dyspepsia and irritable bowel syndrome (IBS), are very frequent and imply significant personal, social, and economic consequences. The etiology and pathophysiology of FGIDs are not completely clear, and no single physiologic abnormality can be implicated as the cause of symptoms in every patient. Diverse pathophysiologic mechanisms appear to contribute to FGIDs, including altered motility, visceral hyperalgesia, brain-gut disturbances, genetic and environmental factors, and psychosocial upsets, among others. Some patients with IBS report the onset of symptoms as following an episode of acute gastroenteritis (AGE); thus, theories of infectious and inflammatory etiologies for IBS have been proposed. A similar situation has been described in some cases of functional dyspepsia, although predisposition to persistence of dyspepsia after an episode of AGE is more controversial.

A retrospective survey found that approximately 1 in 6 individuals reported acute onset of IBS following an episode of AGE. Thus, patients attending either hospital specialists in the United States or general practice in the United Kingdom attributed their IBS to an attack of gastroenteritis in 6% and 17%, respectively.

Some prospective studies also found a relationship between AGE and subsequent IBS. After an outbreak of salmonellosis, 31% of patients developed new IBS symptoms that were still present 1 year after infection. Another study examined 75 individuals with AGE admitted to an infectious disease unit, of whom 25% had developed new IBS when assessed 6 months after infection, an outcome confirmed by a more detailed study of mechanisms 3 years later. A community-based study of 357 individuals with culture-positive bacterial AGE found that 7% met Rome I criteria for IBS at 6 months, although 25% reported a persistent change in bowel habit. A further community survey evaluating only patients with Campylobacter gastroenteritis confirmed this percentage, with 9% new IBS cases.

More recently, a published case-control study using Rome II criteria for IBS showed an incidence of new postinfectious IBS of 16.7% over 6 months compared with just 1.9% of controls (odds ratio, 10; 95% confidence interval [CI], 3–31).
However, postinfectious dyspepsia has not been extensively examined and, to our knowledge, the only published data failed to show a statistically significant difference in the incidence of dyspepsia between cases and controls at either 3 or 6 months postinfection.  

In June 2002, an outbreak of *Salmonella enteritidis* AGE occurred in a Spanish village affecting 1243 people, which provided a unique opportunity to evaluate the evolution of gastroenteritis in a large cohort of subjects after a single outbreak of AGE by the same microorganism and of simultaneous onset and compare the results with those of matched controls from the same village followed up under the same conditions. Thus, our aim was to prospectively evaluate the development of dyspepsia and IBS during a 1-year follow-up in patients with *S. enteritidis* AGE.

**Materials and Methods**

**Study Design**

On June 23, 2002, an outbreak of AGE occurred in a Spanish village of 9004 inhabitants (Torroella de Mongri) located in the Baix Empordà county (Catalonia) with 106,828 inhabitants. The cause was *S. enteritidis* colonization of traditional cream cakes, all made in the same baker's shop to celebrate Saint John’s Eve. A total of 1243 persons were affected; about 40% were Torroella residents, 40% from other villages of the same county, and 20% visitors. Information with demographic (name, age, sex, and address) and clinical data related to the outbreak of AGE (symptoms and treatment) were available from the primary health center database of the county. Thus, we decided to conduct a prospective cohort study only in Baix Empordà inhabitants, attended to in the same county, because this was a unique opportunity to evaluate the evolution of gastroenteritis in a large sample of subjects after a single outbreak of AGE of a single origin by the same microorganism and of simultaneous onset and similar follow-up circumstances. A prospective cohort study was planned; unexposed participants (ratio of approximately 2 controls per 1 case) were randomly selected from the primary health center database and matched for village of residence, age, and sex.

A subject was considered to have AGE if diarrhea, fever, and abdominal pain appeared on June 24, 25, 26, or 27, 2002; in some, but not all, patients, *S. enteritidis* AGE was confirmed by a positive stool culture. However, given the epidemiologic context, stool culture was not required to diagnose salmonellosis. Controls did not experience any of the previously mentioned symptoms during the outbreak of salmonellosis, whether or not they had been in contact with the cream cake that originated the outbreak.

Initially, 677 adults with AGE and 1201 unexposed individuals were detected; thus, 1878 questionnaires were sent to potential participants. A total of 1208 (481 AGE-exposed persons and 547 unexposed persons) returned the questionnaires. Responses were reviewed and matched with the clinical charts in the database; 467 were confirmed as AGE-exposed persons and 561 as having been unexposed. A flow chart of recruitment is shown in Figure 1.

Follow-up was made at 3, 6, and 12 months to examine the frequency of FGIDs, mainly dyspepsia and IBS. All subjects were requested to complete a self-administered questionnaire and return it by mail. Each questionnaire was mailed twice; if no reply was obtained, subjects were contacted by telephone to encourage participation. No personal interviews were held, either with patients or controls, to avoid interference with responses and potential clinician assessment bias.

**Outcome Measure**

All potential participants were requested to complete a self-administered questionnaire at study entry and at 3, 6, and 12 months. The questionnaire was based on the modular Rome II questionnaire, which incorporates basic questions for clinical diagnosis of functional dyspepsia and IBS.  

It contained 5 questions (a total of 8 items) related to dyspepsia and 4 questions on intestinal symptoms (a total of 9 items). The questionnaires referred to symptoms in the previous 3 months.

On entry into the study, subjects were requested to specifically exclude symptoms related to their recent infection. This first questionnaire included a separate sheet with 9 questions regarding ingestion of the bakery product implicated in the outbreak of salmonellosis, gastrointestinal symptoms during their AGE bout, and treatment received, if any.

Diagnosis of dyspepsia and IBS was based on the questionnaire responses according to Rome II clinical criteria, accepting 25% (3 weeks) of the previous 3 months (12 weeks) as the minimum duration of symptoms. Thus, dyspepsia was diagnosed when persistent or recurrent pain or discomfort centered in the upper abdomen were present and not exclusively relieved by defecation or were not associated with onset of
change in stool frequency or form. When patients had dyspepsia and met criteria for IBS, they were considered to present an overlap between dyspepsia and IBS.

The study was approved by the ethics committee of the Centro Médico Teknon and the research committee of Serveis de Salut Integrats Baix Empordà.

**Data Management and Statistical Analysis**

Two Microsoft Access (Microsoft Corp, Redmond, WA) databases were created: one with the administrative data for registry and control of ensuing mailings, and the other to collect and validate the responses of each participant. Validated data were transferred to the software package SPSS for Windows 10.0 (SPSS Inc, Chicago, IL) for statistical analysis.

Bivariate analysis was performed with respect to age, sex, and prevalence of previous dyspepsia and IBS at each point of the study to assess the comparability of exposed and unexposed groups. The prevalence of each functional disorder was calculated at each point of the study with the observed frequencies in exposed and unexposed groups to evaluate the association between the AGE and dyspepsia or IBS. The following association measures were calculated at 12 months: relative risk, attributable risk, and number of persons needed to be exposed to AGE for one case of dyspepsia or IBS to appear. For the latter analysis, participants with dyspepsia or IBS before AGE were excluded and numbers of new cases of dyspepsia or IBS at 12 months of follow-up (cumulative incidence) were used. Significance was assessed by calculating the 95% CI.

In a separate analysis, possible factors that might have influenced the development of dyspepsia or IBS after the outbreak of salmonellosis were evaluated in the group of exposed subjects. Participants with FGID symptoms before the AGE were excluded from this analysis. Demographic and clinical data were compared between subjects with postinfectious dyspepsia or postinfectious IBS at the end of follow-up and those without gastrointestinal symptoms at that time. The comparison was performed using Student t test for independent data and \( \chi^2 \) test (using Fisher exact test when necessary). Differences were considered significant when the \( P \) value was <.05.

**Results**

Demographic and clinical data at study entry are shown in Table 1. Almost all (96.1%) of the patients with AGE had eaten the infected cake; the origin of the infection in the remainder could have been interpersonal or another product from the same bakery also containing *Salmonella*. In the control group, 6.8% of subjects reported having eaten some type of cake bought at the same bakery where the infected cake was made.

The prevalence of dyspepsia before AGE was similar in patients and controls (2.5% vs 3.8%), as was the prevalence of IBS (2.9% vs 2.3%). At month 3, the prevalence of dyspepsia and IBS had not changed significantly in the unexposed group; however, a significant increase was observed in patients who had had AGE (Figure 2). At 6 and 12 months of follow-up, the prevalence of dyspepsia had slightly decreased compared with that at 3 months, whereas the prevalence of IBS had slightly increased. Nevertheless, at all evaluated points, the prevalence of dyspepsia and IBS had increased more than 3-fold that of the initial prevalence. A significant number of patients met clinical criteria for both dyspepsia and IBS (between 23% and 36% at each point of follow-up; Figure 3). In

![Figure 2. Changes in the prevalence of dyspepsia and IBS during the 1-year follow-up.](image-url)
patients with dyspepsia, the overlap with IBS was 35%, 33%, and 46% at 3, 6, and 12 months, respectively. In patients with IBS, the overlap with dyspepsia was 70%, 54%, and 62% at 3, 6, and 12 months, respectively. Two participants in the exposed group and one in the control group presented a chronic organic illness (ulcerative colitis and a history of colon cancer in the exposed group and ulcerative colitis in the control group). None of the 3 participants presented with dyspepsia or IBS at the end of follow-up.

Excluding participants with previous FGID symptoms, at 1 year, dyspepsia had appeared in 46 of 267 exposed participants and 11 of 330 controls; this cumulative incidence is shown in Figure 4. According to these data, the relative risk of developing dyspepsia at 1 year of follow-up was 5.2 (95% CI, 2.7–9.8) and the number of subjects needed to have S enteritidis AGE for one case of dyspepsia to appear was 7.2 (95% CI, 6.9–11.3). The attributable risk of developing dyspepsia to S enteritidis AGE was 13.9 (95% CI, 8.9–18.8). Similarly, at 1 year, IBS had appeared in 31 of 266 exposed participants and in 5 of 333 controls; therefore, the relative risk of developing IBS at 1 year of follow-up was 7.8 (95% CI, 3.1–19.7), the number of subjects needed to have S enteritidis for one case of IBS to appear was 9.9 (95% CI, 8.6–12.1), and the attributable risk was 10.1 (95% CI, 6.1–14.2). As expected in FGIDs, symptoms were not present during the entire study period. Thus, 47% of patients with dyspepsia at the end of the 1-year follow-up had had this diagnosis at least at one other previous point of follow-up. In the same way, for patients with IBS at 12 months, the rate of concordance with previous diagnosis was very similar (48%).

At 12 months, 33 exposed participants had symptoms of dyspepsia; in 54% of cases, the predominant symptom was pain. The remainder of patients with dyspepsia presented with epigastric discomfort consisting of epigastric bloating (73%), postprandial fullness (55%), and, less frequently, nausea (18%); weight loss was not evaluated. Twenty-four exposed participants had symptoms of IBS; diarrhea-predominant IBS was the most frequent IBS subtype in 17 cases (70.8%), whereas constipation-predominant IBS was present in only 7 cases (29.2%).

Some risk factors for development of postinfectious dyspepsia were detected. The following variables were significantly higher in the postinfectious dyspepsia group: vomiting during AGE (71% vs 41%; \( P = .003 \)) and days with abdominal pain during AGE (9.3 days vs 5.1 days; \( P = .001 \)). No statistically significant differences were found between patients with and without postinfectious dyspepsia with respect to age (46 vs 48 years), emergency department attendance during AGE (16% vs 9%), or hospitalization (10% vs 3%). Female sex predominated in the postinfectious dyspepsia group (74% vs 55%; \( P = .051 \)).

No risk factors for development of IBS were found, and there were no statistically significant differences
between patients with and without postinfectious IBS with respect to age (45 vs 49 years), sex (63% men vs 54% women), vomiting during AGE (61% vs 42%), emergency department attendance during AGE (13% vs 9%), or hospitalization beyond 3 days (8% vs 3%).

Antibiotic treatment was administered in only 8% of AGE cases. The prevalence of dyspepsia and IBS was higher in this small subgroup (20% vs 12% and 17.6 vs 9.3%, respectively; \( P = NS \)).

**Discussion**

Several previous studies related AGE to development of IBS. Between 6% and 17% of patients attributed their IBS to an attack of gastroenteritis. Prospective investigations also found an increase in the prevalence of IBS after AGE, but data vary depending on the severity of the infection (ambulatory or hospitalized patients) and infectious agent (with *Campylobacter* and *Shigella* carrying more risk than *S. enteritidis*). Moreover, in prospective studies, no control group was included to ascertain the spontaneous appearance of IBS, with the exception of those reported by Parry et al\(^5\) and Wang et al.\(^13\) We had an exceptional opportunity to evaluate the evolution of gastroenteritis of a single AGE origin caused by the same microorganism and of simultaneous onset in a large cohort of subjects and compare it with matched controls from the same small village followed up under the same circumstances.

In our study, the cumulative incidence of IBS at 1 year of follow-up was 11.6% in postinfectious patients and 1.5% in controls, yielding a significant relative risk of 7.8. McKendrick et al\(^13\) found that 31% of patients developed new symptoms of IBS after an outbreak of salmonellosis that were still present 1 year after infection. This higher frequency possibly reflects a more severe illness because all patients were hospitalized. However, data similar to ours were obtained in a community survey restricted to *Campylobacter* AGE, with 9% new cases of IBS in a cohort of 189 infected individuals.\(^11\) Therefore, it is not completely clear whether type of infectious agent or degree of severity mainly predispose to development of IBS.

In a large study of 584,308 patients whose records form part of a large general practice research database in the United Kingdom, Rodriguez and Ruigomez\(^14\) found 318 patients with documented bacterial enteritis (54% *Campylobacter*, 57% *Salmonella*), 12 of whom had a new diagnosis of IBS over the following 12 months, an incidence of 40/1000 patient-years yielding a relative risk of 11.9 compared with uninfected controls; postinfectious IBS in those infected by *Campylobacter* or *Salmonella* was not compared.

Wang et al\(^15\) recently reported that the incidence of other functional bowel disorders, and not only IBS, was increased after bacillary dysentery; thus, the incidence of functional bowel disorders after a follow-up period of 1–2 years was 22.4% (8.1% IBS). Functional bowel disorders included functional diarrhea, functional abdominal bloating, functional constipation, and unspecified functional bowel disorders. However, the incidence of dyspepsia was not reported. Parry et al\(^5\) found the incidence of FGIDs to be increased at 3 and 6 months of follow-up in AGE cases compared with controls; this was mainly due to a higher incidence of IBS, but a significant difference was also observed in the incidence of functional diarrhea. In this study, no statistical difference was found in the incidence of dyspepsia between cases and controls at either 3 or 6 months of follow-up (odds ratios of 1.89 and 2.91, respectively). However, we found a clear risk of developing dyspepsia after AGE; thus, at 1 year, the risk for dyspepsia was increased 5-fold. Different results might be due to bacterial factors because in the study by Parry et al,\(^5\) the majority of cases were due to *Campylobacter* infection and <20% to *Salmonella*.

In fact, according to our data, the risk of developing dyspepsia or IBS attributable to *S. enteritidis* AGE is similar, to the extent that within 1 year approximately 14% of affected persons will develop postinfectious dyspepsia and 10% will develop postinfectious IBS attributable to the previous AGE. In approximately one third of patients, upper abdominal symptoms and IBS symptoms will be associated.

The phenomenon of upper abdominal and IBS symptoms overlapping is being increasingly acknowledged. In fact, the rate of overlap in our study was not higher than the 40% described in previous epidemiologic studies.\(^15\) We would like to emphasize that the rate of IBS in patients with a previous diagnosis of functional dyspepsia, investigated by a Rome II modular questionnaire, was as high as 50%.\(^16\) Also, as previously reported,\(^15\) there is a significant symptom fluctuation in individual patients with FGIDs; however, it has also been pointed out that when these symptoms are evaluated in a population over time, the prevalence of dyspepsia and IBS does not change significantly.\(^15\)

As in previous studies,\(^17\) most of our cases of postinfectious IBS met Rome II criteria for diarrhea-predominant IBS. It has been described that clinical manifestations of postinfectious IBS are similar to those of spontaneous IBS in pain, urgency, and bloating but with significantly more days with loose stools.\(^17\)\(^18\) Whether this has pathophysiologic significance is not fully estab-
lished. Some patients with IBS have an increased number of inflammatory cells in the colonic and ileal mucosa, and human and animal studies support the concept that inflammation may perturb gastrointestinal reflexes and activate the visceral sensory system even when the inflammatory response is minimal and confined to the mucosa. Moreover, in patients with postinfectious IBS, rectal biopsy specimens continued to show increased chronic inflammatory cells (enteroendocrine cells; CD3, CD4, and CD8 intraepithelial lymphocytes) 3 months after the episode of gastroenteritis. Also, inflammatory mediators such as interleukin 1β were more expressed in biopsy specimens taken from patients with postinfectious IBS than in postinfectious non-IBS controls. The appearance of postinfectious IBS might depend on the genetic capacity of the anti-inflammatory synthesis; some patients with IBS may be genetically predisposed to produce lower amounts of the anti-inflammatory cytokine interleukin 10. The notion that postinfectious IBS results from an enhanced inflammatory response is also supported by the observation that expression of interleukin 1 in the intestinal mucosa is significantly increased in these patients. These results confirm data reported by Barbara et al showing close proximity of tryptase-positive mast cells and nerves along with correlation of these intimate nerve-to-mast cell interactions with severity of abdominal pain in patients with IBS. The increased number and activation of mast cells in the intestinal mucosa, and release of its mediators, probably reflect enhancement of the immune response to previous inflammation in patients with postinfectious IBS.

Regarding postinfectious dyspepsia, much less information is available and no specific pathogenetic studies have been conducted. Nevertheless, it is plausible to consider that mechanisms similar to that of postinfectious IBS might exist. It has been shown, mainly in children, that acute viral infection may induce delayed gastric emptying, but in most cases this rapidly resolves. Seven adult patients who had gastroparesis after a presumed viral illness and who were identified in a retrospective review of 103 consecutive cases of gastroparesis have also been reported. Persistent nausea, vomiting, and epigastric pain developed in these patients; during a mean follow-up of 32 months, 5 of the 7 patients had complete resolution of gastroparetic symptoms, and the remaining 2 patients had improvement in their condition. Moreover, Tack et al reported that presumed postinfectious dyspepsia was present in 68 (17%) of 400 consecutive dyspeptic patients. Postinfectious dyspepsia was associated with more prevalent early satiety, weight loss, nausea, and vomiting compared with nonpostinfectious functional dyspepsia; impaired gastric accommodation was significantly more frequent, and this was attributable to a gastric nitrenergic neuron dysfunction. Almost no histologic and immunohistologic studies exist in patients with dyspepsia, and there are very few on gastroparesis. The case of a patient who presented with chronic intractable vomiting and weight loss associated with idiopathic myenteric ganglionitis of the stomach has been reported, as well as Cajal cell degeneration in another.

In cases of postinfectious dyspepsia, we were able to detect predictive factors such as duration of abdominal pain during the AGE episode and gender, although in the latter a P value of only .051 was obtained; vomiting during AGE, a factor described as protective for postinfectious IBS, also appeared to predispose to postinfectious dyspepsia. Some risk factors for developing IBS after AGE have been reported. The strongest predictor seemed to be duration of the initial illness, possibly a marker of severity. The relative risk steadily increased in proportion to duration. This was not found in our study where no illness duration, hospitalization need, or presence of fever or vomiting were predictive factors of postinfectious IBS. Sex has also been implicated in postinfectious IBS, with women being 3 times more likely to develop IBS than men; however, we found only a slight trend toward this. It is possible that a type II error precluded the identification of significant risk factors for developing postinfectious IBS, because it would have been necessary to analyze 55 patients with postinfectious IBS to detect a 20% difference in the proportion of women developing postinfectious IBS or not with 90% power at the 5% significance level. A further limitation of the present study that possibly precluded the determination of all risk factors for the development of postinfective FGIDs was the lack of information on psychological status and stressful events, which were not evaluated.

Antibiotic treatment appeared to be associated with a higher rate of postinfectious dyspepsia and postinfectious IBS, although the difference did not reach statistical significance owing to the low number of patients with AGE who received antibiotic treatment. Nevertheless, we believe the reason for this difference to be that antibiotics were used in the more severe cases of AGE.

In summary, Salmonella AGE is a risk factor for developing dyspepsia and not only IBS. The relative risk of developing dyspepsia at 1 year of follow-up was 5.2 (95% CI, 2.7–9.8), and the number of infected subjects needed for one case of dyspepsia to develop was 7.2 (95% CI, 6.9–11.3); the relative risk of developing IBS was 7.8 (95% CI, 3.1–19.7), and the number of infected subjects
needed for one case of IBS to develop was 9.9 (95% CI, 8.6–12.1). Prolonged abdominal pain and vomiting during AGE were positive predictors of dyspepsia.

References


