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CLINICAL—ALIMENTARY TRACT

Salmonella Gastroenteritis During Childhood Is a Risk Factor for Irritable Bowel Syndrome in Adulthood

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See editorial on page 18.

BACKGROUND & AIMS: Acute infectious gastroenteritis increases the risk for irritable bowel syndrome (IBS) and functional dyspepsia (FD). Children are particularly vulnerable to gastroenteritis because of the immaturity of their intestinal barrier, enteric nervous system, and immune response to pathogens. We investigated whether acute gastroenteritis in early life increases the risk of IBS and FD throughout adulthood. **METHODS:** In 1994, we identified and monitored a single culture-proven foodborne *Salmonella enteritidis* outbreak that involved 1811 patients (mostly pediatric) in Bologna, Italy. Clinical data were collected and a prospective, controlled, cohort study was designed. Long-term effects were assessed by mailing a questionnaire to 757 subjects 16 years after the outbreak (when all of the children were adults). We randomly selected a cohort of 250 adults exposed to *Salmonella* as children, all 127 individuals exposed as adults, and a cohort of nonexposed participants matched for number, age, sex, and area of residence (controls). **RESULTS:** Among 198 exposed participants, 64 reported FD (32.3%), compared with 51 of 188 controls (27.1%; $P = .268$). Among 204 exposed participants, 75 reported having IBS (36.8%) compared with 44 of 189 controls (23.3%; $P = .004$). The odds ratio for IBS among people exposed to the *Salmonella* was 1.92 (95% confidence interval: 1.23–2.98). The prevalence of IBS was higher in individuals exposed *Salmonella* as children than in controls (35.3% vs 20.5%; $P = .008$), but not in individuals exposed as adults, compared with controls. After multivariate logistic regression, post-infectious IBS was independently associated with anxiety and FD. **CONCLUSIONS:** Based on data collected from a single culture-proven foodborne *Salmonella enteritidis* outbreak in 1994, *Salmonella*-induced gastroenteritis during childhood (but not adulthood) is a risk factor for IBS.

Keywords: Bacteria; Epidemiology; Food Poisoning; Outcome.

The term *functional gastrointestinal disorders* encompasses a group of digestive disorders in which symptoms cannot be explained by the presence of structural or tissue abnormalities.[1] Among these disorders, functional dyspepsia (FD) and irritable bowel syndrome (IBS) affect 20%–30% of the population and are associated with reduced quality of life and high social costs.[1,2] The etiology of functional gastrointestinal disorders is not completely understood, resulting in unsatisfactory management.[1,2]

The mean number of annual episodes of infectious gastroenteritis per person worldwide is approximately 3, with children being most affected.[3] More than 70 years ago, Sir Arthur F. Hurst described the occurrence of long-term colonic irritability after acute bacillary dysentery for the first time, and termed this condition *post-dysenteric colonic irritability*.[4] Acute infectious gastroenteritis (eg, infections caused by *Salmonella*, *Shighella*, *Campylobacter*, or *Norovirus*)[5,6] represents the strongest known risk factor for the development of IBS, which occurs in 3.7%–36.2% of exposed individuals[5,7] and accounts for 6%–17% of all IBS cases.[8] FD after gastroenteritis has also been reported but remains a poorly defined condition.[9,10] Limited information is available on the long-term outcomes of post-infectious IBS and post-infectious FD.[11–14] The Walkerton Health Study, the largest available follow-up investigation of post-infectious functional gastrointestinal disorders, reported a high prevalence of FD and IBS 8 years after acute infectious gastroenteritis.[13,14] Multiple mechanisms contribute to the persistence of abnormal bowel physiology and symptoms after infection, including genetic factors (eg, genes involved in epithelial barrier function and the innate immune response to enteric bacteria),[15] psychological factors (eg, adverse life events, depression, and hypochondriasis), mucosal low-grade inflammation, increased epithelial permeability, the severity of the initial illness, and bacterial toxicity.[5]

We hypothesize that the risk of functional gastrointestinal disorders during adulthood is partly determined by early life experiences. Intestinal development during infancy is a critical stage that represents a window of

Abbreviations used in this paper: **CI, confidence interval; FD, functional dyspepsia; HADS, Hospital Anxiety and Depression Scale; HADS-A, Hospital Anxiety and Depression Scale for Anxiety; HADS-D, Hospital Anxiety and Depression Scale For Depression; HRQOL, health-related quality of life; IBS, irritable bowel syndrome; MCS, mental component summary; OR, odds ratio; PCS, physical component summary; SF-12, short-form 12 items health survey; SF-36, short-form 36 items health survey.**

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vulnerability.[16] Previous data indicate that younger age is a risk factor for development of post-infectious IBS,[13,17] but the role of acute gastroenteritis occurring early in life in the persistence of IBS and FD in adulthood is unknown.

An outbreak of *Salmonella enteritidis* group D involving 1811 patients, predominantly children,[18] gave us the opportunity to prospectively evaluate the prevalence of IBS and FD, the effect of early-life vs adult-life infection, and the risk factors associated with these functional gastrointestinal disorders 16 years after the outbreak, when all of the patients were adults.

Methods

Study Design

This is a prospective, controlled, cohort study on the long-term outcomes of a single culture-proven *Salmonella* outbreak on digestive functional symptoms, quality of life, psychological impairment, and related risk factors.

On October 19, 1994, a tuna sauce contaminated with *Salmonella* was delivered by a local catering service to 36 schools in the city of Bologna for lunch.[18] Acute symptoms of gastroenteritis (eg, vomiting, diarrhea, fever) appeared in 1811 patients, among which 1684 (93.0%) were children aged 3 to 10 years and 127 (7.0%) were adults (ie, teachers and other school employees, including janitors, kitchen personnel, cleaning staff, and administrative employees) aged 19 to 59 years. Of the 1811 affected individuals, 1543 (85.2%) completed symptom questionnaires and underwent repeated stool cultures (at least at onset and 3 months post infection).[18] In all investigated cases, microbiological culture of the patient's stools identified *Salmonella enteritidis* group D as the etiological agent of the outbreak.

We obtained 2 computer-generated lists of random subjects, 1 included a representative sample of the 1543 patients who had positive stool cultures and participated in our earlier study[18] and the second included the same number of nonexposed controls. The list of exposed individuals consisted of 377 patients, including 250 who were children at the time of exposure (current age 18–25 years), representing about one sixth of the original list of exposed children. One third of the participants were 3–5 years old and the other two thirds were 6–10 years old at the time of the outbreak. The other 127 exposed individuals were adults at the time of the outbreak (current age 34–74 years), representing the entire population of infected adults. The list of controls was obtained from the census of the city of Bologna and matched for area of residence, age, and sex. A flow chart of recruitment is provided in Figure 1. Participants who fulfilled the following criteria were eligible for inclusion: at least 18 years of age at the time of mailing the questionnaire; no diagnosis of dyspepsia, celiac disease, IBS, or inflammatory bowel disease before the outbreak (based on self report and review of medical records); and permanent residency in Bologna, as identified by the postal code, at the time of the outbreak. All invited participants received a postal questionnaire and were asked to complete it and return it by mail. The questionnaire was mailed up to 3 times to nonresponders. When no reply was obtained, the individuals were contacted by telephone to encourage participation in the study. No personal interviews were performed in order to avoid interference with responses and potential clinician assessment bias.

Information concerning acute illness experienced during the outbreak, including hospitalization, days of acute disease, diarrhea, abdominal pain, vomiting, fever, headache, and antibiotic exposure around the outbreak were collected in 1994 and available in our database.

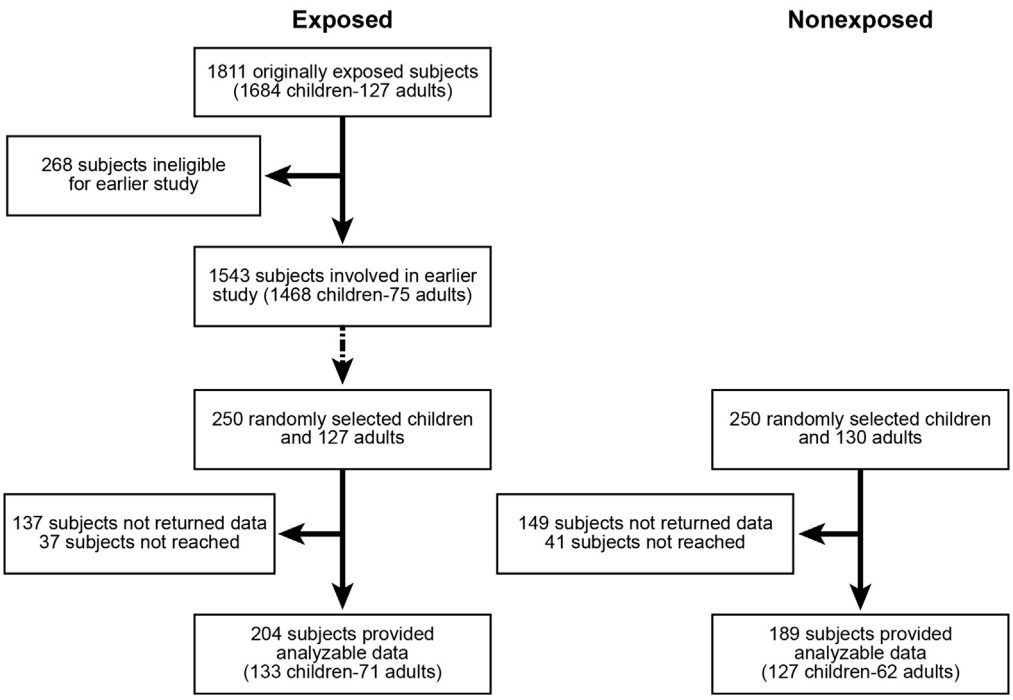

Figure 1. Flow of study participants.