Acute Gastroenteritis Is Followed by an Increased Risk of Inflammatory Bowel Disease

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Background & Aims: **Bacterial intestinal infections have been implicated as a possible cause of exacerbation of inflammatory bowel disease (IBD). We explored the relationship between infectious gastroenteritis and the occurrence of IBD using data from the General Practice Research Database.** ***Methods:*** **A cohort of patients aged 20–74 years with an episode of acute infectious gastroenteritis (n = 43,013) was identified. From the same source population, an age-, sex-, and calendar time-matched control group free of gastroenteritis was sampled (n = 50,000). Both cohorts were followed up for a mean duration of 3.5 years.** ***Results:*** **The estimated incidence rate of IBD was 68.4 per 100,000 person-years after an episode of gastroenteritis and 29.7 per 100,000 person-years in the control cohort. The hazard ratio of IBD was 2.4 (95% confidence interval [CI], 1.7–3.3) in the gastroenteritis cohort compared with the control cohort, and the excess risk was greater during the first year after the infective episode (hazard ratio, 4.1; 95% CI, 2.2–7.4). The relative risk of developing Crohn's disease in the gastroenteritis cohort was greater than that of ulcerative colitis, especially during the first year after the infective episode (hazard ratio, 6.6; 95% CI, 1.9–22.4).** ***Conclusions:*** **Our results are compatible with the hypothesis that infectious agents causing an episode of infectious gastroenteritis could play a role in the initiation and/or exacerbation of IBD.**

The prevailing theory of the pathogenesis of inflammatory bowel disease (IBD) suggests that the intestinal immune system is inappropriately activated due to a confluence of genetic and environmental factors, leading to the generation of inflammatory tissue damage. While critical to the understanding and treatment of IBD, little is known about the proximal events that set the process in motion. In addition to the use of tobacco and nonsteroidal, anti-inflammatory drugs, infections by pathogens such as *Mycobacterium paratuberculosis*, *Listeria monocytogenes*, and paramyxoviruses have been suggested as etiologic agents in IBD. However, a recently published critical appraisal of the literature concluded that the current evidence does not support a causal role for these infectious agents in the etiology of IBD.[1] An alternative explanation compatible with the failure to find specific pathogenic agents in IBD is the hypothesis that enteric pathogens may trigger an initial overshooting response or a defect in down-regulating the mucosal immune response, leading to chronic inflammation.

Several clinical observations support this notion. It has been observed that following epidemics of *Salmonella*, *Shigella*, or *Yersinia*, a small percentage of patients develop typical IBD,[2,3] but these analyses lacked a general population comparison cohort. A study performing a thorough microbiologic study could detect concurrent enteral infections at the time of diagnosis of IBD in 21% of cases.[4] Bacterial intestinal infections have also been implicated as a possible cause of exacerbation of IBD.[5,6]

In the past, we reported that the risk of irritable bowel syndrome was greatly increased after an episode of infectious gastroenteritis (GE).[7] The questions of whether infectious GE represents a risk factor for the development of IBD, the magnitude of this risk, the time span of increased risk after the episode of bacterial infection, or if IBD following infectious GE has some specific characteristics remain unanswered. In the current study, we used a large population-based study to address these questions.

Materials and Methods

Study Population

We explored the relationship between infectious GE and the occurrence of IBD, including Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis, using data from the General Practice Research Database. The database is composed of computerized medical records of approximately 2000 general practitioners from the United Kingdom and is managed by the United Kingdom's Medicines and Healthcare Products Regulatory Agency.[8] The age and sex distribution of

Abbreviations used in this paper: CI, confidence interval; GE, gastroenteritis; HR, hazard ratio; OR, odds ratio.

0016-5085/06/$32.00
doi:10.1053/j.gastro.2006.02.004

the population served by physicians collaborating with the General Practice Research Database is similar to that of the general UK population.[9] Each medical practice must demonstrate competency at entering data into the electronic database before their data are considered "up to standard." Subsequently, each practice is subject to monthly audits to ensure that the quality of the data remains up to standard. These audits include examining the electronic data for weekly numbers of consultations, completeness of drug indication data, and completeness of data on births and cause of death. Data recorded in the electronic record include demographic information, prescription information, clinical events and diagnoses, preventive care, hospital admissions, cause of death, and free text. In addition, significant diagnoses occurring before the initiation of the electronic medical record are recorded retrospectively. Diagnoses are recorded using Oxford Medical Indexing System codes and more recently using Read codes. Prescribed medications are recorded using codes issued by the Prescription Pricing Authority of the National Health Service.[8,10] Several studies have shown that the clinical information in the electronic record is sufficiently accurate for use in most epidemiologic studies, including studies of IBD.[11–13] In addition, prior research has documented very high rates of recording diagnoses resulting from specialist consultations.[14]

Study Cohorts

We identified all registered patients aged 20–74 years during the study period (January 1, 1992, to December 31, 2001) with a code suggesting an episode of infectious GE during the study period. We applied the following eligibility criteria. First, patients had to be free of cancer, alcohol abuse, prior GE, IBD, related gastrointestinal infectious disease, or enteritis/colitis at any time before the episode of GE. In addition, patients with a code of diarrhea or rectal bleeding or with recorded use of specific IBD treatment in the year before the episode of GE entry date were also excluded. For all patients identified with a code suggesting GE, computerized patient profiles were produced and reviewed (n = 47,852). Information included demographic data and all clinical information. Patient profiles were free of any personal identifiers. Patients in whom an enteric pathogen was identified in a stool culture performed for reasons other than an episode of GE were excluded (n = 4820). Finally, 6414 patients were considered to have "documented" bacterial GE with a specific bacteria isolated (*Salmonella*, *Campylobacter*, *Shigella*, or other bacteria), and 36,599 patients were classified as having "bacteriologically undocumented" GE (clinical diagnosis of GE with negative stool culture or no mention of a stool culture recorded). These 2 subgroups formed our final cohort of acute infectious GE (N = 43,013).

A comparison cohort of 50,000 individuals frequency matched by age, sex, and calendar year to the GE cohort was randomly sampled from the same source population (where the cohort of GE was ascertained), applying the same eligibility criteria as used in the ascertainment of the cohort of GE with the additional criteria of not having a recorded diagnosis of GE.

Follow-up to Ascertain Incident Cases of IBD

We followed up all individuals in the 2 cohorts from the date of GE diagnosis or the random date in the comparison control cohort. Follow-up ended at the first occurrence of IBD diagnosis, cancer, death, date of last data collection, or December 31, 2001, whichever came first.

All patients with a coded diagnosis of UC (5631), CD (5630CR; including regional enteritis [5630ER]), or "IBD not otherwise specified" (92N) were potentially eligible for inclusion in the study. Because previous studies have shown a lower reliability of the diagnostic code for "IBD not otherwise specified" (92N),[11] these patients were only considered cases if specific medication for the treatment of IBD, mainly mesalamine-containing drugs and prednisone, had been prescribed after the diagnosis was established. In this group of patients, if a diagnosis of UC or CD appeared later in the record, the latter was considered the final diagnosis; otherwise, the patients were categorized as IBD type unclassified. The validity and completeness of the General Practice Research Database for the diagnoses of IBD have been specifically assessed, and 92% of diagnoses recorded were found to be accurate.[11]

For all patients identified with one of the aforementioned codes of IBD (n = 335), we reviewed computerized patient profiles and classified them into "definite" IBD, "possible" IBD, and noncases. Definite cases were those patients with a first-ever recorded diagnosis of IBD together with specific treatment and/or confirmation by consultant letter or hospital discharge (n = 152). Possible cases were those patients with a diagnosis of IBD without specialist confirmation (n = 15). All remaining individuals were considered noncases (n = 168).

We sent a questionnaire to the general practitioners asking for confirmation of diagnosis among all definite and possible cases registered with collaborating practices (n = 83). Patient confidentiality was always preserved. Based on all information received from the general practitioners, we confirmed all 76 definite cases as IBD and 6 of 7 possible cases. As a result, we decided to include as confirmed IBD cases all other definite cases of IBD (n = 76) but not the other 8 possible cases for which we could not get access to the general practitioner.

Analysis

Incidence rates of IBD in the 2 cohorts were calculated by dividing the number of incident cases by the total follow-up experience in each study cohort. Incidence rates of specific IBD diagnoses stratified by age and sex were also calculated. The risk of developing IBD in the GE cohort compared with the control cohort was estimated using Cox proportional hazards regression, adjusting by age, sex, and calendar year. Estimates of hazard ratios (HR) and their 95% confidence intervals (CIs) were computed for the first year of follow-up and for the whole period of follow-up.