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Childhood Infections and the Risk of Inflammatory Bowel Disease

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Adults with inflammatory bowel disease from North Carolina were questioned during 1986 and 1987 to assess risk due to a variety of childhood infections and treatments with antibiotics. Responses were compared with those of neighbor controls. Persons with Crohn's disease were more likely to report an increased frequency of childhood infections in general (odds ratio 4.67, 95% CI 2.65–8.23) and pharyngitis specifically (odds ratio 2.14, 95% CI 1.30–3.51). This was validated by an increased frequency of tonsillectomy (odds ratio 1.53, 95% CI 1.07–2.20). Crohn's cases were more likely to report frequent treatment with antibiotics for both otitis (odds ratio 2.07, 95% CI 1.03–4.14) and pharyngitis (odds ratio 2.14, 95% CI 1.20–3.84). Although Crohn's cases were more likely to report frequent exposure to penicillin (odds ratio 1.81, 95% CI 0.98–3.31), there did not appear to be excess risk conferred by penicillin after controlling for frequency of infections. Persons with ulcerative colitis also reported an excess of infections generally (odds ratio 2.37, 95% CI 1.19–4.71), but not an excess of specific infections or treatments with antibiotics. Persons who reported an increased frequency of infections tended to have an earlier onset of Crohn's disease ($P < 0.0001$) *and ulcerative colitis* ($P = 0.04$). *Finally, it was noted that urban living in childhood increased the risk for Crohn's disease. We conclude that childhood infections may be a risk factor for Crohn's disease and may presage the early onset of disease.*

KEY WORDS: Crohn's disease; epidemiology; inflammatory bowel disease; ulcerative colitis; antibiotics; penicillin.

Environmental factors appear to have an important influence on the expression of inflammatory bowel disease (IBD). Studies in monozygotic twins show that concordance within pairs is less than 100% for both Crohn's disease (CD) and ulcerative colitis (UC) (1, 2). Environmental factors are further implicated by significant geographic variation in disease incidence (3) and an increased incidence of disease in urban areas as compared with rural areas (4–8).

As these diseases occur in young persons and appear to be immune-mediated, it is reasonable to suspect that childhood events that modulate immune function may be significant in the pathogenesis of disease. Infections may represent such events. It has been postulated that infections may precipitate IBD by unmasking antigens that are present in the gut or by generating an immune response directed against cross-reacting proteins in the mucosa. These proteins theoretically become

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targets because of their resemblance to antigens of pathogens. Alternatively, it may be that childhood infections lead to IBD by altering gut immune regulatory function or by leading to exposures, such as to antibiotics or nonsteroidal antiinflammatory drugs (9), which in turn precipitate disease.

We investigated the above hypotheses in a case–control study of adults with IBD. Cases and controls were asked to report the frequency of a variety of childhood infections and treatments. We also investigated frequency of hospitalization, appendectomy, and tonsillectomy. Breast feeding has been reported as protective in IBD (10–13), so we examined the frequency of this exposure in cases and controls. Locale of childhood environment was also considered as a possible risk factor.

MATERIALS AND METHODS

Names of potential cases were obtained from the membership rolls of North Carolina chapters of the Crohn's & Colitis Foundation of America (formerly The National Foundation for Ileitis & Colitis). Since not all members have IBD, a screening questionnaire was mailed to determine case status and basic demographic characteristics. Screening questionnaires were mailed to 1131 persons. Nonrespondents received an additional mailing and a phone call. Ultimately, 989 (87%) completed questionnaires were returned. Of these respondents, 686 were determined to have IBD and were mailed a comprehensive questionnaire. After two mailings and a phone call, surveys were completed by 503 persons (73%) of identified IBD cases.

In order to find suitable controls, cases were asked to provide the name of their closest neighbor of the same sex, race, and age (within five years). If no such neighbor could be found, a colleague or friend could be substituted. We were able to contact 445 potential controls, of whom 353 agreed to participate. For the 92 controls who declined participation, 55 additional nominees were contacted and 50 of this group agreed to participate, bringing the total number of controls recruited to 403.

Participating subjects were asked to report the relative frequency of a variety of exposures including pharyngitis, otitis, tonsillitis, colds, and treatment with antibiotics during childhood. Childhood was considered to be that period when individuals lived in their parents' home and attended primary and secondary school. They were also asked to report on whether or not they had undergone tonsillectomy, appendectomy, or had been otherwise hospitalized. History of breast-feeding and of sharing a bedroom with other children was also elicited. The location of the subjects' upbringing was determined at ages 0–5, 6–11, and 12–15.

Odds ratios were calculated using 2 × 2 contingency tables. Exposures that were described categorically were collapsed into trichotomous variables reflecting the degree of exposure. For example, subjects were asked, "Do you think you had more or fewer infections than other children?" Available responses were: 1, many more; 2, somewhat more; 3, about the same; 4, less; and 5, many less. Frequency of responses 1 and 2 were combined to create the category, "more infections," while those responding "about the same" were put in the category "some infections." Responses 4 and 5 were combined to create the category "fewer infections." Odds ratios were calculated relative to the referent exposure of "fewer infections." Viral infections, with the exception of colds, were dichotomized as yes–no (or "ever vs never") variables. Missing values were not included in the analysis. Confidence intervals were calculated using the method of Cornfeld (14). Summary relative risk estimates were calculated using the Mantel-Haenszel method (15). Trends were tested using the Mantel extension test (16). Crude odds ratios were adjusted for age and gender differences.

To determine if excess risk attributable to penicillin was independent of infections, likelihood of penicillin exposure was stratified by infection frequency, eg, cases reporting fewer infections were compared with controls reporting fewer infections. To evaluate the possibility that excess pediatric infections were due to an increased number of siblings among cases, numbers of siblings were compared by chi-square analysis. Subjects with five or more siblings were collapsed into one category, so that expected counts for large sibships would not be too small to preclude chi-square analysis. Odds of having shared a bedroom with other children were calculated using 2 × 2 contingency tables. Finally, a multivariate logistic regression was undertaken in order to confirm results from stratified analyses. Models were run separately for Crohn's disease and ulcerative colitis. Variables put into the model included known and potential risk factors for IBD. Parsimonious models were derived by a stepwise backwards elimination procedure.

We hypothesized that cases reporting frequent childhood infections would, on the average, have an earlier index age than cases reporting fewer infections. Index age was considered to be the age of symptom onset, or age at diagnosis if age of symptom onset was unknown. The distribution of index ages of cases reporting more infections was compared with that of cases reporting fewer infections using the Wilcoxon rank sum test. As childhood infections are frequently seasonal, chi-square analyses of month of birth and season of birth were done in hopes of isolating a period of increased risk. Winter was defined as occurring in December, January, and February, and other seasons were defined in three-month intervals before and after winter. Finally, places of childhood upbringing (city, suburb, small town, rural area) were compared to upbringing on a farm using 2 × 2 contingency tables. All analyses were done using the Statistical Analysis System (SAS Institute, Cary, North Carolina).

RESULTS

Cases and controls were demographically similar. Results are summarized in Table 1. There was a slight preponderance of women in all groups. The group was generally white, married, and well educated.

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF CASES DRAWN FROM CCFA ROSTERS AND NEIGHBOR CONTROLS

	Crohn's disease	*Controls*
Total number	322	262
Male/female ratio	0.64	0.67
Age at diagnosis	29.0 (SD 13.0)	Not applicable
Age at interview	41.3 (SD 13.1)	41.6 (SD 12.5)
Married (%)	73	80.1
White (%)	95	96.2
College education (%)	36.6	40.9
	Ulcerative colitis	
Total number	181	141
Male/female ratio	0.68	0.62
Age at diagnosis	32.2 (SD 16.6)	Not applicable
Age at interview	45.3 (SD 14.4)	43.7 (SD 14.0)
Married (%)	75.6	80.1
White (%)	98.9	99.3
College education (%)	42.8	34.3

Frequent childhood infections increased the risk of Crohn's disease 4.7-fold (95% CI 2.6–8.2). The risk of UC was increased 2.4-fold (95% CI 1.2–4.7). Risk for a variety of common bacterial infections is shown in Table 2. Pharyngitis increased risk for CD 2.1-fold (95% CI 1.3–3.5) and tonsillitis increased risk similarly [odds ratio (OR) = 1.6, 95% CI 1.0–2.6]. Risk appeared to be increased for otitis, but the confidence interval included 1.0. Bacterial infections did not affect the risk for UC.

Among viral infections (Table 3), colds occurred with greater frequency among Crohn's cases (OR = 2.4, 95% CI 1.4–4.2). Among UC cases, there was an increased risk attributable to measles (OR = 2.1, 95% CI 0.97–4.74). No other infections were associated with increased risk.

History of treatment with antibiotics paralleled the histories of infections among Crohn's cases (Table 4). CD cases were more likely to be treated frequency for pharyngitis (OR = 2.1, 95% CI 1.3–3.5), otitis (OR = 2.1, 95% CI 1.0–2.6), tonsillitis (OR = 1.8, 95% CI 0.99–3.4), and colds (OR = 1.9, 95% CI 1.0–3.7). Risk was not increased for UC. History of exposure to penicillin increased the risk of CD (OR = 1.8, 95% CI 1.0–3.3). This effect disappeared after adjusting for frequency of infections. In UC, treatment with antibiotics appeared to have a protective effect, although this was not statistically significant (Table 4).

TABLE 3. RISK OF IBD DUE TO VIRAL INFECTIONS

	*Crohn's disease**	*Ulcerative colitis**
Mumps	1.01 (0.67–1.52)	1.31 (0.76–2.27)
Rubella	1.09 (0.72–1.66)	1.03 (0.57–1.81)
Measles	1.32 (0.77–2.26)	2.14 (0.97–4.75)
Varicella	1.13 (0.64–2.00)	1.89 (0.89–4.00)
Colds	2.42 (1.38–4.24)	1.31 (0.60–2.86)

*Odds ratio adjusted for age and gender (95% confidence interval).

CD cases who reported frequent childhood infections were significantly more likely to have an early disease onset than their counterparts who reported fewer infections ($P < 0.0001$, Figure 1). The same was true for UC cases reporting more childhood infections ($P = 0.042$).

We examined history of childhood hospitalizations and surgeries. Incidence of tonsillectomy was higher for CD (OR = 1.5, 95% CI 1.1–2.2). There was no increased risk of appendectomy for CD, but risk appeared to be somewhat decreased for UC (OR = 0.3, 95% CI 0.1–1.1), as only three cases had appendectomies. UC patients were less likely to have had childhood hospitalizations than controls (OR = 0.5, 95% CI 0.2–0.9). CD cases did not differ from controls in this regard.

The number of siblings per subject did not differ between cases and controls. Month of birth and season of birth were not risk factors. An excess of

TABLE 2. RISK OF IBD DUE TO BACTERIAL INFECTIONS

	Crohn's disease		*Ulcerative colitis*	
	*Some vs fewer**	*Frequent vs fewer**	*Some vs fewer**	*Frequent vs fewer**
Infections in general	2.20 (1.52–3.19)	4.67 (2.65–8.23)	2.04 (1.25–3.35)	2.37 (1.19–4.71)
Otitis	1.22 (0.78–1.92)	1.59 (0.91–2.78)	1.43 (0.78–2.61)	0.60 (0.27–1.34)
Pharyngitis	1.36 (0.94–1.98)	2.14 (1.30–3.51)	1.51 (0.88–2.57)	1.37 (0.78–2.54)
Tonsillitis	1.25 (0.82–1.90)	1.64 (1.02–2.63)	1.33 (0.77–2.30)	0.90 (0.48–1.70)
Scarlet fever†		1.20 (0.65–2.21)		1.84 (0.84–4.03)

*Odds ratio adjusted for age and gender (95% confidence interval).
†Ever vs never.

TABLE 4. RISK OF IBD DUE TO ANTIBIOTIC TREATMENT BY ILLNESS

	Crohn's disease		*Ulcerative colitis*	
	*Some vs fewer**	*Frequent vs fewer**	*Some vs fewer**	*Frequent vs fewer**
Otitis	0.98 (0.59–1.62)	2.07 (1.03–4.14)	0.88 (0.43–1.82)	0.46 (0.19–1.10)
Pharyngitis	1.16 (0.76–1.78)	2.14 (1.20–3.84)	1.58 (0.87–2.89)	0.60 (0.27–1.33)
Tonsillitis	1.05 (0.67–1.64)	1.83 (0.99–3.38)	1.03 (0.55–1.90)	0.85 (0.41–1.75)
Colds	0.90 (0.59–1.38)	1.92 (1.00–3.66)	1.08 (0.59–1.98)	0.89 (0.36–2.23)

*Odds ratio adjusted for age and gender (95% confidence interval).

springtime births was noted among UC cases, but this did not reach statistical significance ($P = 0.14$). There was no difference between cases and controls with respect to breast or bottle feeding. Cases and controls did not differ with respect to frequency of sharing a bedroom with other children.

The effect of location of upbringing is demonstrated in Table 5. Risk for Crohn's disease increased with increasingly urban environs. The effect was statistically significant for city dwellers in the 0–5 age group (OR 1.8, 95% CI 1.1–3.0) and 12–15 age group (OR 1.7, 95% CI 1.0–3.0). Suburbanites were most significantly effected in the 6–11 age group (OR 2.0, 95% CI 1.1–3.8). Trend tests were statistically significant for each group. No consistent effect was seen for ulcerative colitis, although increased risk was seen for small-town living (OR 2.3, 95% CI 1.1–4.6) in the 12–15 age group.

The results of multivariate logistic regression were consistent with those attained through stratified analysis. For Crohn's disease, only family history of IBD (OR 3.1 95% CI 1.6–6.1), positive smoking history (OR 1.7, 95% CI 1.1–2.5), and history of frequent childhood infections were significant risk factors for disease. Persons reporting "more infections" (OR 2.57, 95% CI 1.3–12.5) or "many more infections" (OR 3.2, 95% CI 1.3–23.5) were compared with persons reporting "fewer," "many fewer," or "about the same" number of infections as childhood friends. For ulcerative colitis, only family history of IBD (OR 2.6, 95% CI 1.1–6.3) was a significant risk factor for disease. Exposure to penicillin was not a risk factor for either disease.

DISCUSSION

This study demonstrates an increased frequency of childhood infections among persons with Crohn's disease. Crohn's cases who reported more infections were also more likely to report frequent treatment with antibiotics and an early onset of

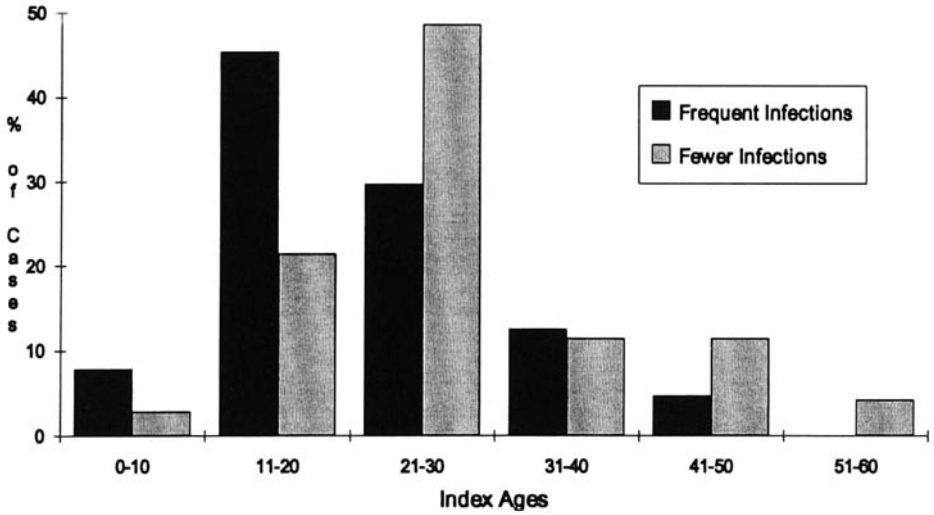

Fig 1. Distribution of index ages, Crohn's cases reporting frequent childhood infections, compared with Crohn's cases reporting fewer infections. $P < 0.0001$ by the Wilcoxon rank sum test. Survey of North Carolina cases, 1986–1987.

TABLE 5. RISK OF CROHN'S DISEASE WITH INCREASINGLY URBAN LIVING RELATIVE TO FARM LIVING

	*Ages 0–5**	*Ages 6–11*†	*Ages 12–15*‡
Rural	1.32 (0.76–2.29)	1.34 (0.77–2.35)	1.38 (0.78–2.44)
Small town	1.34 (0.82–2.18)	1.04 (0.62–1.73)	1.11 (0.66–1.87)
Suburb	1.43 (0.77–2.67)	2.05 (1.12–3.77)	1.57 (0.86–2.87)
City	1.81 (1.07–3.03)	1.57 (0.92–2.67)	1.73 (1.01–2.97)

*Trend test $P = 0.031$.
†Trend test $P = 0.048$.
‡Trend test $P = 0.047$.

disease. These results are in keeping with previous studies.

In a multicenter trial involving 302 cases with CD, Gilat et al (17) reported that childhood respiratory infections were more common in cases than in controls and that CD cases were more likely to have taken antibiotics. Ekbom et al (18) analyzed birth records of 257 IBD cases and compared them with normal controls. Persons who subsequently developed CD or UC were more likely to have suffered infectious as well as noninfectious perinatal health events. Risks were higher for Crohn's disease than ulcerative colitis. Whorwell et al (13) noted an increased incidence of gastroenteritis in the first six months of life among Crohn's cases, while Koletzko et al (19) found an increased incidence of diarrheal illness in infants among UC cases.

We found that CD cases were more likely to suffer infections of the upper airway and oropharynx. This finding was validated by the finding of more frequent tonsillectomies among CD cases. The finding of increased colds in CD cases suggests a generalized increased susceptibility to both bacterial and viral infections. Other viral infections (varicella, rubella, mumps) were not associated with increased risk; however, these infections are ubiquitous and tend to occur once only. The fact that they were equally represented in cases and controls speaks against systematic overreporting by IBD cases.

Sartor et al (20) have hypothesized that the inflammatory response in Crohn's disease is directed against bacterial antigens that have gained access to the lamina propria of the gut. This is in keeping with the typical localization of CD to segments of the bowel where bacterial counts are high. Antibiotics, especially penicillin, may be precipitants of disease in that they increase the availability of cell wall products to the lamina propria by decreasing their molecular weight and thereby increasing their solubility (21).

In crude analysis it appeared that CD patients were more likely to have been exposed to penicillin; however, this effect disappeared when analysis was stratified by frequency of infections. In UC, antibiotics appeared to have a protective effect, although this was not statistically significant. This would be in keeping with a bacterial etiology for UC. The protective effect seen for antibiotic treatment of pharyngitis recalls protection from rheumatic fever by antibiotics, another chronic relapsing inflammatory condition. Of note, Kirschner and Newcomb (22) have reported an increased incidence of rheumatic fever in families of IBD patients. The finding of significantly decreased childhood hospitalizations among UC cases is consistent with a diminished likelihood of antibiotic exposure.

The observation of a diminished incidence of appendectomy in UC patients was not convincing because of the small numbers available for analysis. It is noteworthy, however, that Gilat et al (17) made the same observation in 1987. An excess of appendectomies was expected among Crohn's cases because of the classic presentation of Crohn's disease as pseudoappendicitis and the frequent occurrence of incidental appendectomy in CD patients undergoing laparotomy. It is likely, however, that appendectomies were underrepresented in our population as the questionnaire only sought information on appendectomies occurring before age 10.

This study was subject to recall bias in that exposures predated participation in the study. To argue that CD patients, as sickly persons, would be more likely to recall childhood infections, does not explain why UC patients do not recall infections with a similar frequency. While UC patients did report more infections generally, they did not report an excess of specific infections. Moreover, the effect of infections in general was quite strong in CD cases (OR = 4.7) and was twice as strong as that seen in UC cases. The observed excess of tonsillectomies in Crohn's cases, a relatively hard end point, weighs against an overreporting of upper respiratory infections. We argue that the magnitude and consistency of risk estimates for childhood infections in CD patients supports the existence of a real association between infections and disease.

Our findings do not support an etiologic role for penicillin or antibiotics in IBD. Crohn's patients do appear to suffer a surfeit of childhood infections. Whether additional infections represent an insult with etiologic significance or rather the expression of an underlying immune defect remains to be seen.

If we postulate that Crohn's disease is caused by an inability to down-regulate inflammation, one can imagine that the observed excess of upper respiratory infections reflects an increased propensity for clinical expression. Persons with Crohn's disease may suffer symptomatic ear and throat infections, while normal individuals would not note these infections as clinical events. It can be argued that the increased frequency of tonsillitis is just an early harbinger of more generalized dysfunction in gut lymphoid tissue. Past reports of early gastroenteritis in IBD patients may be of similar significance.

The above findings are consistent with previous reports in the literature. Studies of incident cases of IBD may offer more precise estimates of risk conferred by childhood exposures. Because of the relative rarity of these conditions, multicenter collaborative efforts would be most appropriate for further studies and should be pursued.

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