Inverse correlation between *Helicobacter pylori* infection and inflammatory bowel disease

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Abstract

***Aims*—To determine the seroprevalence of *Helicobacter pylori* in patients with Crohn's disease or ulcerative colitis and in controls without inflammatory bowel disease (IBD).**

***Methods*—One hundred consecutive patients with Crohn's disease, 100 consecutive patients with ulcerative colitis, and 100 age and sex matched controls were studied. Serum *H pylori* IgG and IgA antibody titres were measured by enzyme immunoassay.**

***Results*—The seroprevalence of *H pylori* was 15% in patients with IBD (13% in patients with Crohn's disease and 18% in patients with ulcerative colitis), whereas the corresponding figure for the controls was 43%. When compared with controls, the seroprevalence of *H pylori* in patients with IBD was considerably lower in all age groups tested. There was no important difference in treatment with sulphasalazine or in any other medical therapy administered to *H pylori* positive and negative patients. At the time of blood sampling there was no difference in the level of education or in the employment status between the patients and the controls.**

***Conclusions*—Patients with IBD were less likely to be infected with *H pylori* than their age and sex matched controls. Neither medical treatment nor socioeconomic factors could explain the difference.**

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Keywords: *Helicobacter pylori*, Crohn's disease, ulcerative colitis, seroprevalence, IgG, IgA.

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The cause of inflammatory bowel disease (IBD) is still unknown, although several bacterial and viral agents have been strongly implicated in the aetiology of Crohn's disease.[1–4] It has also been suggested, however, that the absence of infectious agents ingested in childhood might lead to a functionally impaired mucosal immune system, as is found in patients with Crohn's disease.[5] El-Omar *et al*[6] hypothesised that patients with IBD might be predisposed to gastric mucosal *Helicobacter pylori* infection; however, they found a surprisingly low prevalence of *H pylori* in these patients and suggested that this was because of sulphasalazine treatment.

In our previous study we found that gastritis was present at high frequency in gastric mucosa of patients with Crohn's disease but the prevalence of *H pylori* was low.[7] In the present study, we wanted to investigate further the seroprevalence of *H pylori* in patients with Crohn's disease, in those with ulcerative colitis and in subjects without IBD whose serum samples were collected after an acute episode of diarrhoea.

Methods

Frozen serum samples for *H pylori* serology were available from 200 consecutive patients with previously diagnosed IBD (100 patients with Crohn's disease and 100 further patients with ulcerative colitis). The serum samples were taken between January 1989 and November 1994 and were kept at −20°C before use. To register all possible drug treatment regimens, the patients were interviewed and their medical records re-examined prior to sample collection.

Age and sex matched control serum samples were selected from samples collected in 1990 from patients with an acute episode of bacterial diarrhoea. Fifty six per cent of patients and controls were men. The mean age of the patients with IBD was $42{\cdot}9 \pm 14{\cdot}6$ years and that of controls was $42{\cdot}1 \pm 14{\cdot}7$ years. Serum samples were stored at −20°C before use. The 100 controls resided in the same southern part of Finland as the patients with IBD. As a part of the examination of the enteritis, the patients had completed a questionnaire regarding their personal data, symptoms and possible underlying disorders. None of these patients had a history of IBD.

H pylori IgG and IgA antibodies were measured separately by enzyme immunoassay.[8 9] The lower limit of raised titres (expressed as reciprocals) was 700 for IgG and 100 for IgA.

STATISTICAL METHODS

Pearson's χ^2 test, Fisher's exact test and the two tailed t test were used to analyse the results.

Results

PREVALENCE OF *H PYLORI*

Fifteen per cent of patients with IBD (13% of patients with Crohn's disease and 18% of those with ulcerative colitis) had raised IgG or IgA, or both, antibody titres against *H pylori*. The corresponding figure for the controls was 43% ($p<0{\cdot}005$). The seroprevalence of *H pylori* in the patients with IBD was significantly lower than in the controls in each age group tested (group 1, 18–25 years; group 2, 26–35 years; group 3, 36–45 years; group 4, 46–55 years;

Table 1 Elevated IgG and/or IgA antibody titres against H pylori *in 200 patients with IBD and in 100 controls*

Age (years)	No. of antibody positive patients with: Crohn's disease	No. of antibody positive patients with: Ulcerative colitis	No. of antibody positive controls	p*
18–25	0/10 (0%)	0/7 (0%)	3/11 (27%)	<0·05
26–35	1/34 (3%)	3/19 (15%)	9/30 (30%)	<0·03
36–45	5/27 (19%)	1/30 (3%)	9/26 (35%)	<0·03
46–55	4/13 (31%)	4/19 (21%)	9/16 (56%)	<0·005
56–65	3/8 (37%)	5/16 (31%)	6/8 (75%)	<0·05
>65	0/8 (0%)	5/9 (56%)	7/9 (78%)	<0·03
All	13/100	18/100	44/100	<0·005

* IBD *v* controls.

group 5, 56–65 years; and group 6, over 65 years; table 1). In age groups 2 and 6, the seroprevalence of *H pylori* was significantly lower in patients with Crohn's disease than in controls ($p<0·01$). In age groups 3 and 4, the seroprevalence of *H pylori* was significantly lower in patients with ulcerative colitis than in age and sex matched controls ($p<0·05$). Of the 31 patients with IBD with positive serology, 17 had raised IgG and IgA titres, 11 had raised IgG titres and three had raised IgA titres. The corresponding figures for the 43 seropositive controls were 29, 10 and 4, respectively.

The mean age of the 31 *H pylori* positive patients with IBD was $52·8 \pm 12·8$ years and that of *H pylori* negative patients was $41·0 \pm 13·6$ years ($p<0·003$). Mean duration of IBD was $12·0 \pm 7·0$ years in *H pylori* positive and $9·5 \pm 8·1$ years in *H pylori* negative patients (NS). Mean age of the seropositive controls was $48·0 \pm 16·0$ years and that of the seronegative controls was $37·7 \pm 11·8$ years ($p<0·003$).

PREVIOUS MEDICAL TREATMENT

None of the patients with IBD had undergone treatment for *H pylori* infection; none had received bismuth or acid suppressive agents combined with antimicrobial agents. Medical treatment for IBD is presented in table 2. For any of the medical treatment regimens shown, there was no significant difference between *H pylori* positive and negative groups. The duration of sulphasalazine treatment in relation to the prevalence of *H pylori* is shown in the figure. Before blood sampling, 13 (42%) *H pylori* positive and 68 (39%) *H pylori* negative patients had undergone gastrointestinal surgery on one or more occasions (NS).

SOCIAL STATUS

There was no difference in the level of education between the patients with IBD and the controls (table 3). At blood sampling, there was no significant difference between the patients and controls with respect to employment status (table 4).

Discussion

Our results show that the prevalence of serum IgG and IgA antibodies directed against *H pylori* was significantly lower in patients with

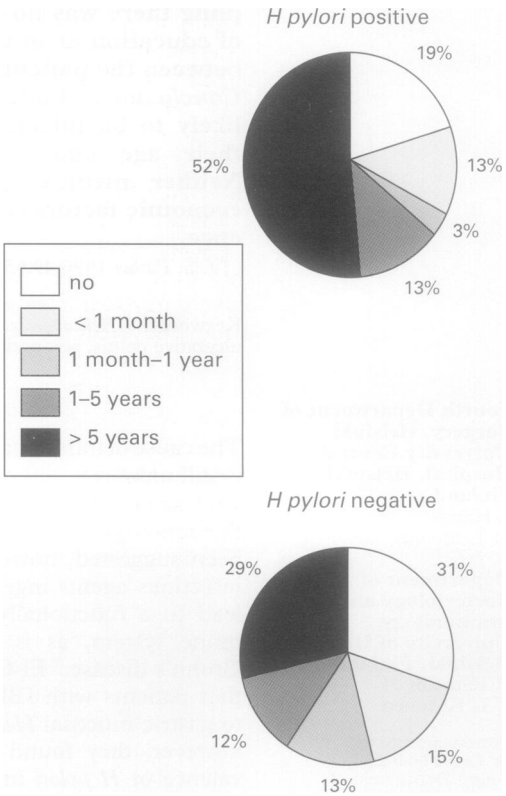
Table 2 Previous medical treatment for IBD in H pylori *positive and negative patients. Therapies longer than a month are included. There was no significant difference between the groups*

Medical therapy	No. of patients: H pylori *positive* (n=31)	No. of patients: H pylori *negative* (n=169)
Sulphasalazine	21 (68%)	88 (52%)
5-ASA	6 (19%)	39 (23%)
Steroids	10 (31%)	45 (27%)
Long term antibiotics*	3 (10%)	15 (9%)
Immunosuppressive drugs	0	4 (3%)

* Metronidazole, ciprofloxacin or ofloxacin.

Table 3 Education level of patients with IBD and controls. There was no significant difference between the groups

Education	Crohn's disease (n=100)	Ulcerative colitis (n=100)	Controls (n=100)
University degree	7	14	5
Other theoretical	48	41	40
Skilled worker	31	38	39
Unskilled worker	14	7	2
Unknown	0	0	5



Duration (less than one month, one to 12 months, one to five years, more than five years) of sulphasalazine treatment in H pylori *positive and negative patents. Only uninterrupted periods are included. Patients with adverse events are included in the group of one month or less.*

Table 4 Level of employment in patients with Crohn's disease and ulcerative colitis compared to controls. There was no significant difference between the groups

Employment	*Crohn's disease (n=100)*	*Ulcerative colitis (n=100)*	*Controls (n=100)*
Employed	72	77	79
Unemployed	0	0	0
Housewife	3	0	0
Student	8	5	8
Disabled*	9	3	1
Pensioner	8	15	12

* Patients who were out of work for more than six months were included.

IBD than in age and sex matched controls. Although an age dependent increase in seroprevalence was observed in both groups, patients with IBD had raised *H pylori* antibody titres significantly less often than controls. The present study confirms our previous findings in patients with Crohn's disease[7] and the earlier findings of other authors in patients with IBD.[6] In the present study serum samples from age and sex matched patients with acute bacterial diarrhoea were used as controls. Both the patients and the controls resided the same part of Finland.

In an earlier study, we demonstrated an age dependent increase in *H pylori* antibody titres in Finnish blood donors.[8] Although only blood donors with IgG titres of 900 or higher were regarded as positive, the seroprevalence of *H pylori* was higher in the blood donors than in patients with IBD in each age group tested.

El-Omar *et al*[6] suggested that the low prevalence of *H pylori* antibodies in patients with IBD was a result of long term treatment with sulphasalazine. However, in their study *H pylori* was resistant to sulphasalazine in vitro and *H pylori* infection could not be eradicated with sulphasalazine treatment alone. In the present study, most of the *H pylori* positive patients had been treated with sulphasalazine for one year at least. Furthermore, *H pylori* positive patients underwent treatment with sulphasalazine more regularly than *H pylori* negative patients, although the difference was not significant. Taha *et al*[10] were unable to demonstrate that the prevalence of *H pylori* was lower in patients with rheumatoid arthritis undergoing treatment with sulphasalazine. In our study none of the treatment regimens were associated with a low *H pylori* seroprevalence. Corticosteroids suppress epithelial proliferation, which is thought to render the mucosa susceptible to the effects of ulcerogens.[11] However, in our study there was no significant difference in *H pylori* status between patients taking and those not taking steroids.

In Denmark, patients with Crohn's disease were found to belong to higher socioeconomic groups than controls.[12] *H pylori*, on the contrary, has been found to be more frequent in lower socioeconomic groups.[13] The recent reports of decreasing seroprevalence of *H pylori* in developed countries (unpublished data)[14] could be because of improved standards of living. In our study, however, there was no difference either in education level or employment status for patients with IBD and controls; a similar classification was used as in the Danish study (tables 3 and 4). However, as childhood seems to be the critical period for the acquisition of *H pylori* infection,[14–16] living conditions in childhood rather than those in adult life could play a major role. Absence of a hot water supply in the childhood home was shown to be a risk factor for *H pylori* infection in England,[17] whereas Gent *et al*[5] found that patients with Crohn's disease had had very high level of domestic hygiene in their childhood, more often having hot running water and separate bathrooms than controls. Unfortunately, the childhood living conditions of the subjects in the present study could not be traced. It is tempting to speculate that some factors, environmental or pathogenetic, protect against *H pylori* infection but increase susceptibility to IBD.

In conclusion, patients with IBD were significantly less likely to be infected with *H pylori* than controls in all age groups studied, although they showed an age dependent increase in seroprevalence. Neither medical treatment nor socioeconomic factors could explain this difference.

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