

A comparison of symptoms between non-ulcer dyspepsia patients positive and negative for *Helicobacter pylori*

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SUMMARY

The role of Helicobacter pylori infection in the symptom complex associated with non-ulcer dyspepsia is uncertain, despite the presence of the organism in a high proportion of these patients. In order to exclude physician bias in history taking, 18 patients (9 female) diagnosed as non-ulcer dyspepsia, after endoscopy and gallbladder ultrasonography, underwent computer interrogation using the Glasgow Diagnostic System for Dyspepsia (GLADYS). Five antral and 3 fundal endoscopic biopsies from these patients were also histologically examined for the presence of Helicobacter pylori and quantitatively analysed for polymorph and chronic inflammatory cell densities per mm² of lamina propria using computer-linked image analysis. In the group of 9/18 patients who were positive for Helicobacter pylori, there were significantly higher antral and fundal inflammatory cell counts than in negative patients. However, analysis of the GLADYS interrogation data showed no significant positive relationships between Helicobacter pylori positivity and any gastrointestinal symptoms. These results confirm a significant association between Helicobacter pylori and superficial gastritis but suggest that non-ulcer dyspepsia in patients with Helicobacter pylori colonisation is probably not a clinically identifiable and distinct syndrome.

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INTRODUCTION

In 1983, Warren and Marshall reported a *Campylobacter*-like organism present on the superficial gastric epithelium.¹ Subsequently, the presence of this organism, now named *Helicobacter pylori*, has been closely associated with superficial active gastritis and duodenal ulcer disease.²⁻⁵ However, the association between the presence of this organism and dyspeptic symptoms, particularly in the absence of peptic ulceration, is more controversial. While two human volunteer studies have suggested that ingestion of *Helicobacter pylori* leads to an acute dyspeptic illness,⁶⁻⁷ few studies have attempted to relate the presence of chronic dyspeptic symptoms to colonisation by this organism in the gastro-duodenal mucosa using an unbiased or blinded study design. In this study, we have examined both antral and fundal endoscopic biopsies from a defined group of patients with non-ulcer dyspepsia and obtained a medical history using an independent, single-bias computer questionnaire or interrogation — the Glasgow Diagnostic System for Dyspepsia (GLADYS) — in an attempt to show significant differences in symptomatology between *Helicobacter pylori* positive and negative subjects.

METHODS

Patients were recruited following presentation to a gastroenterology clinic, with a broad definition of dyspepsia as “episodic, recurrent or persistent abdominal pain or discomfort or any other symptom referable to the alimentary tract, excepting rectal bleeding or jaundice”.⁸ Exclusion criteria were the ingestion of non-steroidal anti-inflammatory drugs, aspirin, H-2 receptor antagonists, bismuth salts or sucralfate within the previous three months. Patients with a recent history of upper gastrointestinal bleeding within the previous three months and those with a previous history of gastric or duodenal surgery were also excluded. Local ethical committee approval of the protocol was obtained, and written, informed consent was obtained from each patient prior to study participation.

Computer interrogation

Following routine history-taking and clinical examination, patients were asked to complete a computer-based questionnaire using the Glasgow Diagnostic System for Dyspepsia (GLADYS). This system requires the patient to answer a series of questions relating to a series of diagnostic indicants. An individual patient's response can then be compared with those of a previously investigated group of patients with various dyspeptic diagnoses from whom diagnostic weights or scores were derived.^{9, 10} In this way, the symptoms can be recorded in a single-bias manner without direct assessment by the attending physician or any other observers. The system comprises an Apple II microcomputer with double disk drives linked to a video display unit. A specially built keyboard is used with keys limited in number and clearly labelled for a variety of responses from the patient. Numerical keys permit responses which are selected from a simple list of options. For questions requiring a yes/no response, the keyboard permits three levels of response by having keys labelled “certainly yes/no”, “probably yes/no” or “possibly yes/no”. The answer to each question is followed by the next relevant question appearing on the screen (obtained from a fixed flow chart relating all questions to prior responses). Each patient was given a brief explanation of the

operation of the keyboard and then completed the interrogation in 20–30 minutes without supervision. Question responses were stored on floppy disk for transfer to a main frame computer for statistical analysis using the Statistical Package for the Social Sciences, SPSSX.

Endoscopy / biopsy

Sixty patients (40 males) underwent computer interrogation and proceeded to upper gastrointestinal endoscopy. Those patients who had normal findings were considered to have non-ulcer dyspepsia. Biopsies were taken from five sites in the gastric antrum 5 cm proximal to the pyloric channel, and three sites in the gastric fundus at a distance of 50 cm from the incisor teeth, as measured on the endoscope shaft. Biopsies were orientated with the mucosal-side downwards on small pieces of dental wax using a needle and hand lens before fixation in 1% formalin solution. Following routine processing, 4 micron sections were stained using the Giemsa technique and independently examined for the presence of *Helicobacter pylori* on the mucosal surface. Both endoscopist and histopathologist were unaware of the results of the computer interrogation. After endoscopy, all patients proceeded to gallbladder ultrasonography to exclude cholelithiasis as a cause of their dyspeptic symptom complex.

Quantitative analysis of biopsies

Using a MOP Kontron Videoplan semi-automatic image analyser, three contiguous microscopic fields were analysed at $\times 400$ magnification in each antral and fundal section for mean polymorph and mononuclear cell number per mm^2 of superficial lamina propria (P/mm^2 ; MNC/mm^2), by counting individual acute and chronic inflammatory cells within a defined area. A mean value for observations at each site was obtained for antral and fundal gastric biopsies. The mean values for acute and chronic inflammatory cell counts were compared between *Helicobacter pylori* positive and negative subjects with non-ulcer dyspepsia using the Mann-Whitney U-test.

The GLADYS symptom collection was assessed for association of *Helicobacter pylori* infection with symptoms using the Chi-squared test with Yates' correction. A level of $p < 0.05$ for significant associations was set.

RESULTS

Of 20 patients diagnosed as non-ulcer dyspepsia following normal endoscopy and negative ultrasonography of the gallbladder, all completed the GLADYS questionnaire, and 18 biopsies suitable for both *Helicobacter pylori* and quantitative inflammatory cell assessment were obtained. Of these 18 patients, nine were positive for *Helicobacter pylori* in the antrum and 10 in the fundus. Mean values for polymorph and mononuclear cell counts at both sites are shown in Table I. The concentrations of both lamina propria polymorphs and mononuclear cells were significantly higher in *Helicobacter pylori* positive subjects ($p < 0.01$ Mann-Whitney U-test).

Analysis of results from data collected using the GLADYS computer interrogation in the 18 subjects showed only one association, between the absence of *Helicobacter pylori* on biopsy and gastrointestinal symptoms or demographic

TABLE I

Mean values of lamina propria polymorphs (P/mm^2) and mononuclear cells in *Helicobacter pylori* positive and negative antral and fundal biopsies in non-ulcer dyspepsia patients using Mann-Whitney U-test

	<i>Helicobacter pylori</i> status	P/mm^2	MNC/mm^2
Antrum (n = 18)	+ve 9	4.5**	4224**
	-ve 9	2.1	1532
Fundus (n = 18)	+ve 10	4.4**	4126***
	-ve 8	1.9	1318

** $p < 0.01$ *** $p < 0.001$

indicants; in the negative patients, there was a significantly higher affirmative response (75%) to a question designated "Are you highly strung or a worrier?" Two or three significant results would have been expected by chance out of the total of 58 symptoms analysed (Table II). There were no significant differences in the frequency of responses between positive and negative patients.

TABLE II

Number of computer-collected indicants analysed between patients positive and negative for *Helicobacter pylori* infection

Symptom / indicant	Number of indicants in category	Frequency comparison between positive and negative <i>Helicobacter pylori</i> patients for antrum and fundus
Demography	6	NS
Pain/discomfort	18	NS
Pain attacks	4	NS
Vomiting	4	NS
Acid reflux	6	NS
Nervous stress	6	$p < 0.05^*$
Bowel habit	6	NS
Miscellaneous	8	NS

* $p < 0.05$ for antrum and fundus.

DISCUSSION

The presence of *Helicobacter pylori* in association with gastritis with or without dyspepsia and peptic ulcer has been well documented but the relationship of the organism to symptoms has not been established. Two volunteer studies have suggested that infection with this organism produces an acute polymorph-dominant gastritis which progresses to a chronic form with time,^{6, 7} and an outbreak of gastritis in healthy volunteers undergoing nasogastric intubation for acid secretion studies, using inadequately sterilised equipment, may have resulted from such an infection.^{11, 12}

Helicobacter pylori infection appears to be a common finding in patients with non-ulcer dyspepsia. One study has reported 70% incidence, compared to 20% in asymptomatic volunteers, and found histological improvement in the gastritis score after therapy.¹³ Follow-up of individuals with untreated *Helicobacter pylori*-associated gastritis and non-ulcer dyspepsia has shown persistent infection over 12–28 months, but non-infected dyspeptic patients remained negative but with persisting symptoms over the same period.¹⁴ However, dyspeptic symptoms were not clearly correlated with the presence of the organism in either of these studies. It is surprising that few studies have previously compared dyspeptic symptoms in subjects positive and negative for *Helicobacter pylori*.

Non-ulcer dyspepsia is a commonly encountered gastroenterological disorder in outpatient care but still lacks a clear definition. The relationship of the syndrome to stress-related gastric secretion, functional motility disorders or histologically demonstrated gastroduodenitis has been extensively investigated with inconclusive results.^{15–17} The theory that some cases of non-ulcer dyspepsia could be attributed to an infective agent is attractive. Patients defined as non-ulcer dyspepsia usually present with an array of symptoms referable to the gastrointestinal tract and it may be difficult to grade or assess each symptom individually. In this study, we have recorded symptoms in a well-defined group of such patients, all of whom had normal endoscopy and negative gallbladder ultrasonography. The GLADYS system, which has been developed as a screening system for dyspepsia,^{9, 10, 18} provides a method of eliciting symptoms without the bias of direct physician contact with the individual subject. Within the study group, subjects were evenly distributed into positive (50%) and negative (50%) on histological assessment for *Helicobacter pylori*. Despite objective grading of biopsies confirming the presence of a significantly higher inflammation in the presence of the organism as noted in previous studies,^{2, 3, 13} analysis of dyspeptic symptom frequency between the positive and negative patients produced only one significant negative result, which was identical for gastric antral and fundal biopsies.

There are few similar studies of this type for comparison. Rokkas and colleagues prospectively studied 55 consecutive patients with non-ulcer dyspepsia using direct history-taking and found an association with gastritis, male sex and post-prandial bloating in 45% of their group who were positive for *Helicobacter pylori* compared to 15 controls.¹⁹ They postulated that urease activity from the organism could lead to increased intragastric CO₂ production as a cause of gastric gaseous distension. Using a standardised questionnaire, Loffeld and colleagues showed no positive symptomatic associations which could identify 60 non-ulcer dyspepsia patients with *Helicobacter pylori*-associated gastritis and 49 negative subjects, although a marked quantitative association between the presence of the organism and inflammation was again confirmed.²⁰ The theory that disturbed gastric motility is a possible cause of non-ulcer dyspepsia in association with bacterial colonisation was recently investigated by Wegener and colleagues.²¹ They were unable to show a significant delay in gastric emptying between *Helicobacter pylori* positive and negative patients, although both groups had emptying significantly delayed compared to asymptomatic controls. The largest survey to date used a standard symptom questionnaire to collect symptom data in 251 dyspeptic patients, of whom 65 had peptic ulceration and 186 non-ulcer dyspepsia,²² and did not find a clinically distinct syndrome in the patients positive for the organism.

We have used a single-bias computer questionnaire combined with quantitative histology to survey patients with non-ulcer dyspepsia. Our results support a close association between chronic active gastritis and the presence of *Helicobacter pylori* in the gastric mucosa but there are no significant symptom relationships which point to a distinct non-ulcer diathesis related to this organism. Despite continued interest in this association, there is no report to date showing any clinical pointer of value. Serological tests show promise as a non-invasive method of detection of *Helicobacter pylori*,²³ and the therapeutic effect of eradication of this organism in these patients is awaited.²⁴ Single bias symptom assessment techniques as described are important in the analysis of symptoms in this difficult area.

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