

Campylobacter associated gastritis in patients with non-ulcer dyspepsia

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SUMMARY Gastric biopsy specimens from 109 patients with non-ulcer dyspepsia were retrospectively examined. Sixty one patients had gastritis and there was a strong correlation with the presence of *Campylobacter pyloridis*. Ninety eight per cent were positive in large numbers for *C pyloridis* by histological examination or by culture, or both. Of 48 patients with normal histological results, 21 had evidence of *C pyloridis* by histological examination or culture, or both, but in small numbers. It is concluded that there is a quantitative rather than a qualitative association between *C pyloridis* and gastritis.

Every year about 1% of the total population will seek medical advice about upper abdominal complaints.¹ In about two thirds of these patients peptic ulcer, oesophagitis, active duodenitis, or gastric and oesophageal cancer are diagnosed. In one third, however, upper gastrointestinal endoscopy or x-ray picture fail to show disease. These patients are therefore diagnosed as having so called non-ulcer dyspepsia. This group of patients is heterogenous, has disorders such as gallstones and motility disorders like the irritable bowel syndrome,² and is notoriously difficult to manage. Histological examination will often show the presence of gastritis.³⁻⁵

Marshall and Warren's report on Campylobacter-like organisms, subsequently designated *C pyloridis* and their association with gastritis,⁶ renewed interest in this condition.⁷⁻⁹ The nature of this association remains controversial,^{10,12} but it has been shown that drugs active against *C pyloridis* can cure gastritis.¹³ As yet no exact data are available on the prevalence of *C pyloridis* associated gastritis among patients with non-ulcer dyspepsia. We therefore studied prospectively the presence of *C pyloridis* in gastric mucosa of these patients by histological and microbiological examination, in the hope of identifying a subgroup of patients who would possibly benefit from antimicrobial treatment.

Patients and methods

We studied 109 consecutive patients referred to the

endoscopy department because of upper abdominal pain. Patients with gastric or duodenal ulcers, reflux oesophagitis, active duodenitis, gastrectomy and carcinoma were excluded. Also excluded were those who had taken corticosteroids, non-steroidal anti-inflammatory drugs, and antibiotics up to two weeks before endoscopy.

A standard history was taken from all patients using a questionnaire, which included current complaints, smoking habits, alcohol consumption, medication, and family history of upper abdominal complaints and peptic ulcer disease (table 1).

One hundred and nine patients were included, 50 men (mean age 43.3 years, range 18-75) and 59 women (mean age 56.5 years, range 16-82). All patients underwent upper gastrointestinal endoscopy with an Olympus GIF Q gastroscope. The macroscopic appearance of the upper gastrointestinal mucosa was recorded and biopsy specimens were taken from the gastric antrum for culture and histological examination.

HISTOLOGY

Two biopsy specimens were fixed in Bouin's fixative. Sections were stained with haematoxylin and eosin for histological grading of gastritis according to the modified Whitehead classification¹⁴ (table 2). Biopsy specimens showing features consistent with grades 2 and 3 were regarded as showing gastritis, whereas grades 0 and 1 were regarded as morphologically normal. Sections for histological detection of Campylobacter-like micro-organisms were stained according to the Warthin and Starry method¹⁵ and with a modified Giemsa stain.^{12,16,17}

Table 1 Symptoms of patients with non-ulcer dyspepsia expressed in per cent

	<i>C. pyloridis</i> and Gastritis (n = 50)	Normal histology <i>C. pyloridis</i>	
		Positive (n = 16)	Negative (n = 24)
Pain	88	94	100
Nausea	60	50	67
Vomiting	16	19	25
Duration of complaints:			
Years	50	25	42
Months	36	50	21
Weeks	14	25	37
Association with eating:			
Heartburn	50	25	33
Burping	64	44	71
Meteorism	64	69	79
Food intolerance	84	81	79
Weight loss > 1 kg	50	44	67
Appetite	40	44	37
Good	68	75	54
Bad	32	25	46
Alcohol consumption	32	56	54
Smoking	56	56	50
Family history of peptic ulcer disease	20	25	33

Table 2 Modified Whitehead classification of gastritis

Grade 0:	Normal histology
Grade 1:	Slight increase of mononuclear cells in the lamina propria of the gastric mucosa, but within normal limits
Grade 2:	Increase of mononuclear and polynuclear cells in the lamina propria of the gastric mucosa
Grade 3:	Increase of mononuclear and polynuclear cells in the lamina propria of the gastric mucosa, presence of intraepithelial polynuclear cells

All sections were investigated by two pathologists independently without prior knowledge of the patients complaints, gastroscopic findings, or culture results. At least 10–15 microscopic fields were examined for the presence of the typical rod-like Campylobacter-like organisms in the mucus overlying the mucosa; if Campylobacter-like organisms were not grade 2 or 3 the whole biopsy specimen was examined. For semi-quantitative grading, the following criteria were used: grade 0, no bacteria detectable; grade 1, sporadic bacteria observed; grade 2, clusters of bacteria seen in most microscopic fields at high power magnification

Table 3 Gastritis and presence of *C. pyloridis*

Patients with non-ulcer dyspepsia (n = 109)	Results of histological examination			Results of microbiological examination	
	Grade 0	Grade 1	Grades 2–3	Positive	Negative
Whitehead classification					
Grade 0 (n = 38)	20 (52)	16 (42)	2 (5)	0	38 (100)
Grade 1 (n = 10)	6 (60)	2 (20)	2 (20)	3 (30)	7 (70)
Grades 2–3 (n = 61)	1 (2)	20 (33)	40 (66)	36 (59)	23 (41)

($\times 400$); and grade 3, numerous micro-organisms found in the superficial mucus layer in all fields examined.

MICROBIOLOGY

One biopsy specimen was put in sterile saline 0.9% and then transported to the microbiology department for culture. The biopsy specimens were incubated on a blood agar medium of 6% sheep blood under micro-aerophilic conditions (carbon dioxide 10%, oxygen 5%) for five to seven days at 37°C. The culture was regarded as positive when typical colonies of *C. pyloridis* were seen. If the culture did not show growth after seven days it was regarded as negative.

Results

The patients were divided into two groups. Group A comprised all patients (n = 61) who had gastritis (Whitehead grades 2 and 3). In all but one the presence of *C. pyloridis* was shown histologically or by a positive culture, or both. Campylobacter-like organisms were classified as grade 2 and 3 in 40 (67%) and grade 1 in 20 (33%). Culture was positive in 36 (59%) (table 3). Group B comprised all patients (n = 48) with normal gastric histological results (Whitehead grades 0 and 1). This group was further divided into two subgroups, one with and one without the presence of *C. pyloridis* either by culture or histological examination. In 21 (43%) patients Campylobacter-like organisms were detected (grades 2 and 3 in 9 (19%) and grade 1 in 9 (43%)). Culture was positive in 3 (7%). In all sections, however, the morphology and sites of the bacteria were characteristic of *C. pyloridis*. In both groups one positive culture failed to show Campylobacter-like organisms. These two cases were regarded as sampling errors and were graded as 1 for further analysis.

We found no correlation between a positive culture and the semiquantitative presence of *C. pyloridis* as (56%) of positive cultures had *C. pyloridis* of grades 2 and 3 in the slides and (44%) grade 1.

Nineteen questionnaires were incomplete and had to be eliminated from further analysis. We received 50 questionnaires from group A and 40 from group B. No differences existed between the groups for either one of the complaints (table 1). There also was no difference

for smoking, alcohol consumption, and family history.

The macroscopic appearances of the gastric mucosa during upper gastrointestinal endoscopy were normal in (80%) of the patients, being almost equally divided among the two groups. In the remainder hyperaemia or erosions, or both, were seen.

To evaluate the most sensitive staining method for Campylobacter-like organisms we compared the Warthin Starry silver stain with a modified Giemsa stain (omitting the differentiation step with acetic acid). In 34 cases of *C. pyloridis* infection confirmed by culture, the Giemsa stain was positive in 33 (97%) of cases; the Warthin Starry stain was positive in 27 (79%). All the sections were studied blind without prior knowledge of the culture results.

Discussion

Our data show a prevalence of (55%) of gastritis in patients with non-ulcer dyspepsia. This seemed to be strongly associated with the presence of Campylobacter-like organisms, generally in high numbers. Only one patient with gastritis showed no evidence of Campylobacter-like organisms. On the other hand, we found evidence of Campylobacter-like organisms in (13%) of patients with normal gastric histological findings, which was of grade 1 in (81%). This finding contrasts with reported data which generally indicate that Campylobacter-like organisms in the normal gastric mucosa comprise less than 10%.^{5,7,8,18-20} In contrast to the findings of previous reports,⁹ we found a quantitative rather than a qualitative association between gastritis and the presence of Campylobacter-like organisms in gastric biopsy specimens. Moreover, our results show that neither symptoms nor macroscopic appearances of the gastric mucosa can positively identify Campylobacter associated gastritis. Therefore the diagnosis ultimately relies on the histological or microbiological results of gastric biopsy specimens.

Cultures were positive in 59% of group A and 7% of group B. The total number of positive cultures was less than the number of positive histological sections. The average percentage of positive cultures in published reports is 75%.^{6,9,18,21,25} Many authors, however, do not report their findings comprehensively.^{10,22,26} These poor culture results probably reflect technical difficulties in culturing *C. pyloridis* as well as sampling errors incurred as only one biopsy was cultured. The high prevalence of *C. pyloridis* in normal gastric mucosa in our cases may be explained by the use of the modified Giemsa stain. The silver staining method is the one most commonly used but it does have several drawbacks: it requires technical skill, is time consuming, and expensive. Moreover, in our experience silver precipitation in the mucus covering the gastric mucosa

may interfere with the interpretation of the findings, so false negative results are possible.⁶ The modified Giemsa stain, which is easy to perform, inexpensive, and lacks colour precipitations, was also more sensitive.

Our results provide no definite clues to whether *C. pyloridis* causes gastritis or is just an epiphenomenon. Our finding that Campylobacter-like organisms were present in the gastric biopsy specimens of 43% of patients without gastritis may at first sight support the latter contention. These patients, however, generally showed grade 1 Campylobacter-like organisms whereas higher grades were observed in patients with gastritis. It is conceivable, therefore, that in patients who do not have gastritis an equilibrium exists between Campylobacter-like organisms and immunological defence mechanisms, which, when distorted may lead to uncontrolled expansion of Campylobacter-like organisms and gastritis. The finding of antibodies directed against *C. pyloridis* may support this.^{24,27,29} If and to what extent the presence of Campylobacter-like organisms in gastric mucosa is associated with upper abdominal complaints is still not known. Further studies investigating the effect of drugs action against *C. pyloridis*, the morphology of the gastric mucosa, and the patients' complaints will be required. Such studies are currently in progress.

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