Gut, 1992, 33, 16–20

Intestinal metaplasia and *Helicobacter pylori*: an endoscopic bioptic study of the gastric antrum

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Abstract

To study the relationship between intestinal metaplasia and *Helicobacter pylori* infection, 2274 gastroscopic antral biopsies taken from 533 patients were examined. Overall, intestinal metaplasia was found in 135 patients (25·3%) and *H pylori* in 289 patients (54·2%). The prevalence of intestinal metaplasia and *H pylori* was age related, being more common in patients ≥50 years compared with patients <50 years (intestinal metaplasia, $p<0·001$ and *H pylori*, $p<0·05$). Intestinal metaplasia was found more often in *H pylori* positive patients compared with *H pylori* negative patients (33·9% *v* 15·2%, $p<0·001$). The mean age of intestinal metaplasia positive patients who were also *H pylori* positive was 64 (13·3) years, whereas the mean age of intestinal metaplasia positive patients who were *H pylori* negative was 72 (14·7) years ($p<0·005$). The extent of intestinal metaplasia was not statistically different in the latter two groups. Although our data do not prove a causal relationship between *H pylori* infection and the histogenesis of intestinal metaplasia it is suggested that *H pylori* infection is an important factor in the development of intestinal metaplasia, which is generally recognised as a precursor lesion of intestinal type gastric carcinoma.

In 1983 Warren and Marshall reported unidentified curved bacilli in gastric antral biopsies from patients with chronic active gastritis and peptic ulcer disease.[1] This bacterium, first called *Campylobacter pylori*, has recently been renamed *Helicobacter pylori*. Since their report many studies have confirmed a close association between the presence of *H pylori* in the gastric mucosa, chronic active gastritis and gastric and duodenal ulcers.[2–8]

Detailed studies of the gastric mucosa in populations with a high risk of developing gastric carcinoma have described a series of lesions which may represent a continuum of change from normal to carcinoma,[9] starting with chronic active gastritis which may progress to chronic atrophic gastritis with intestinal metaplasia and finally to dysplasia and gastric carcinoma.[10]

Based on these data, we speculated that there might be a relationship between *H pylori* and intestinal metaplasia in the gastric mucosa, thereby assuming that Helicobacter gastritis might evolve into intestinal metaplasia. Because both show a predilection for the gastric antrum[2 11 12] which in case of *H pylori* may be related to a specific glycerolipid receptor,[13] we undertook this endoscopic bioptic study of the gastric antrum to assess whether intestinal metaplasia can be more often found in positive patients as compared with *H pylori* negative patients.

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Accepted for publication
2 April 1991

Methods

PATIENTS

All patients reported in this study were referred to the endoscopy department of St Elisabeth's of Groote Gasthuis for upper gastro-intestinal endoscopy on clinical grounds between December 1988 and June 1990. Patients requiring emergency endoscopy or having undergone previous gastric surgery were excluded.

Endoscopy was carried out after an overnight fast. The endoscopes (Olympus GIF Q10, Q20) were cleaned with detergent, disinfected with 70% ethanol, and rinsed with sterile water after each examination. Only patients with macroscopically suspected antral gastritis or any other antral lesion were included, resulting in a total of 533 patients. The number of antral biopsies taken depended on the gross macroscopic diagnosis made by the endoscopists and were taken from the lesions and adjacent mucosa along the lesser and/or greater curvature within 4 cm of the pylorus. All biopsies were fixed in 10% formalin, embedded in paraffin and cut at 5 μ. Routine staining with haematoxylin and eosin (H&E) was done for histopathologic diagnosis and detection of *H pylori*. In case of doubt as to whether *H pylori* was present, additional Giemsa staining was carried out. *H pylori* was judged to be absent if both staining methods were negative for *H pylori*. The extent of intestinal metaplasia in the gastric biopsies was cumulatively graded as follows: (0) none; (1) mild degree, consisting of a few tubules to one third of the total area biopsied; (2) moderate degree, consisting of one third to two thirds of the total area biopsied; (3) severe degree, consisting of two thirds or more of the total area biopsied.

The χ^2 and two-tailed Student's *t* test were used for statistical analysis of the data collected.

Results

HISTOPATHOLOGIC DIAGNOSIS

Two thousand two hundred and seventy four antral biopsies obtained from 533 patients were examined. Both gastritis and gastric ulcer were significantly associated with *H pylori* as compared with normal gastric mucosa ($p<0·001$) (Table I).

RELATIONSHIP BETWEEN AGE INTESTINAL METAPLASIA AND HELICOBACTER PYLORI

The prevalence of intestinal metaplasia in gastric antral biopsies increased from 0% in the age

TABLE I *Characteristics of patients according to diagnosis (533)*

Histological diagnosis	*Patients (n)*	*Biopsies (total)*	*Biopsy (range)*	*Mean no. biopsy (SD)*	*Age (range)*	*Mean age (SD)*	H pylori *positive (%n)*	*Intestinal metaplasia positive (%n)*
Normal	126	359	1–9	2·9 (1·8)	18–88	51·6 (17·7)	2 (1·6%)	0 (0%)
Erosion	26	82	1–10	3·2 (2·2)	27–64	60·0 (15·7)	12 (46·1%)	1 (3·9%)
Gastritis	298	1082	1–14	3·6 (2·8)	20–93	58·4 (16·3)	228 (76·5%)	88 (29·5%)
Gastric ulcer	67	581	3–30	8·7 (3·8)	23–90	63·8 (15·8)	47 (70·2%)	37 (55·2%)
Gastric cancer								
Intestinal type	8	71	5–13	8·9 (2·5)	67–87	77·5 (6·5)	0 (0%)	8 (100%)
Diffuse type	8	99	5–19	12·4 (4·1)	49–80	57·9 (11)	0 (0%)	1 (12·5%)
	533	2274					289 (54·2%)	135 (25·3%)

group <20 years to 46·6% in the age group ≥80 years (Table II). When all patients were divided into two age groups – namely, (i) <50 years (163 and (ii) ≥50 years (370), intestinal metaplasia was found significantly more often in patients ≥50 years ((i) 10·4%, (ii) 31·9%, p<0·001) (Table III).

The prevalence of *H pylori* in gastric antral biopsies increased from 0% in the age group <20 years to 65·1% in the age group 50 to 59 years, after which a decrease to 44·8% in the age group ≥80 years was observed (Table II). When all patients were divided into the same two age groups – namely (i) <50 years and (ii) ≥50 years, *H pylori* was found significantly more often in patients ≥50 years ((i) 46·6%, (ii) 57·6%, p<0·05) (Table IV).

RELATIONSHIP BETWEEN INTESTINAL METAPLASIA AND HELICOBACTER PYLORI

Overall, *H pylori* was found in 289 patients (54·2%), whereas intestinal metaplasia was found in 135 patients (25·3%). When all 533 patients were divided into two groups – namely, (i) *H pylori* positive (289) and (ii) *H pylori* negative (244), intestinal metaplasia was significantly found more often in the *H pylori* positive group ((i) 33·9%, (ii) 15·2%, p<0·001) (Table V). When all 135 intestinal metaplasia positive patients were divided into two groups according to *H pylori* status, we found that the mean age of the intestinal metaplasia positive *H pylori* positive group (98) was significantly lower than that of the intestinal metaplasia positive *H pylori* negative group (37), (64 (13·3) years *v* 72 (14·7) years, p<0·005) (Table VI).

The mean age of intestinal metaplasia positive patients with intestinal type carcinoma (eight) was significantly higher than that of all other intestinal metaplasia positive patients (127) – namely, 77·5 (6·5) years *v* 65·8 (14·2) years (p<0·025). As these eight were all *H pylori* negative, this could possibly explain the mean age difference found between the intestinal metaplasia positive *H pylori* positive and intestinal metaplasia positive *H pylori* negative group. Even after having excluded all patients with intestinal-type gastric carcinoma, however, (eight) yielding a total of 127 intestinal metaplasia positive patients, the mean age of *H pylori* positive patients was still significantly lower than that of the *H pylori* negative patients ((i) 64 (13·3) years, (ii) 71·1 (15·6) years, 0·005<p<0·01).

The extent of intestinal metaplasia in the intestinal metaplasia positive *H pylori* positive and intestinal metaplasia positive *H pylori* negative group did not differ in a statistically significant way. When moderate and severe intestinal metaplasia were grouped together, 20·4% of

TABLE II *Prevalence of intestinal metaplasia (IM) and* Helicobacter pylori *(HP) according to age group (533)*

Age group (yr)	*Patients (n)*	*Intestinal metaplasia positive patients (%n)*	H pylori *positive patients (%n)*
<20	2	0 (0%)	0 (0%)
20–29	34	1 (2·9%)	12 (35·3%)
30–39	41	3 (7·3%)	21 (51·2%)
40–49	86	13 (15·1%)	43 (50%)
50–59	106	25 (23·6%)	69 (65·1%)
60–69	114	28 (24·6%)	66 (57·9%)
70–79	92	38 (41·3%)	52 (56·5%)
≥80	58	27 (46·6%)	26 (44·8%)
	533	135 (25·3%)	289 (54·2%)

% in parenthesis is related to number of patients per age group.

TABLE III *Relationship between age and prevalence of intestinal metaplasia in the gastric antrum (533)*

Age group (yr)	*Total*	*Intestinal metaplasia positive patients (n)*	*Intestinal negative patients (n)*
<50	163	17	146
≥50	370	118	252
	533	135	398

χ^2 test; p<0·001.

TABLE IV *Relationship between age and prevalence of* Helicobacter pylori *in the gastric antrum (533)*

Age group (yr)	*Total*	H pylori *positive patients (n)*	H pylori *negative patients (n)*
<50	163	76	87
≥50	370	213	157
	533	289	244

χ^2 test; p<0·05.

TABLE V *Relationship between intestinal metaplasia and* Helicobacter pylori *in the gastric antral mucosa (533)*

	Patients (total)	H pylori *positive patients (n)*	H pylori *negative patients (n)*
Intestinal metaplasia positive	135	98	37
Intestinal metaplasia negative	398	191	207
	533	289	244

χ^2 test; p<0·001.

TABLE VI *Mean age of intestinal metaplasia positive patients according to* Helicobacter pylori *status (135)*

	Patients (total)	H pylori *positive patients (n)*	H pylori *negative patients (n)*
Patients (n)	135	98	37
Age range (yr)	23–93	33–88	23–93
Mean age (SD)	66·6 (14)	64 (13·3)*	72 (14·7)

*Student's *t* test; p<0·005.

TABLE VII *Extent of intestinal metaplasia according to* Helicobacter pylori *status in intestinal metaplasia positive patients (135)*

Extent intestinal metaplasia	H pylori *positive*	H pylori *negative*
Mild	78 (79·6%)	25 (67·6%)
Moderate	16 (16·3%)	11 (29·7%)
Severe	4 (4·1%)	1 (2·7%)
	98 (100%)	37 (100%)

χ^2 $0{\cdot}2<p<0{\cdot}3$.

intestinal metaplasia positive *H pylori* patients and 32·4% of intestinal metaplasia positive *H pylori* negative patients showed this extent of intestinal metaplasia ($0{\cdot}2<p\leq0{\cdot}3$) (Table VII).

Discussion

This study again confirms the strong association of *H pylori* with gastritis and gastric ulcer and our results compare favourably with the results reported by others.[1 14–17] Our data also substantiate those of others[18 19] showing that the prevalence of *H pylori* increases with age which suggests age related acquisition of *H pylori* infection. In view of this, it is of interest that intestinal metaplasia and gastritis are also well known to be age related, both being more common in the older age groups.[20 21]

In 1965 Lauren divided advanced gastric carcinoma into two main types – namely, 'intestinal' and 'diffuse' type carcinoma, which differ not only morphologically but also in their clinical and epidemiological characteristics.[22] Moreover, a different histogenetic process has been postulated by many authors since Morson pointed out that intestinal type gastric carcinomas might arise from areas with intestinal metaplasia.[23] Although the exact relationship between intestinal metaplasia and gastric carcinoma has still not been elucidated, it is suggested that intestinal type gastric carcinoma originates from intestinal metaplasia and that diffuse type gastric carcinoma originates in normal gastric mucosa, with no precursor lesion being identified yet.[24–26] Our finding that all patients with intestinal type carcinoma were found to be intestinal metaplasia positive in contrast with one of eight patients with diffuse type carcinoma lends further support to this theory.

From detailed histological studies it is known that the process leading from chronic active gastritis through the stages of chronic atrophic gastritis, intestinal metaplasia and dysplasia to carcinoma takes a long time – that is, 16–24 years.[27] Our finding that intestinal metaplasia was found significantly more often in the gastric antrum of *H pylori* positive patients as compared with *H pylori* negative patients may turn out to be an important observation because it suggests that *H pylori* related gastritis may evolve into intestinal metaplasia. Since the time of colonisation with *H pylori* appears to be the crucial factor, the occurrence of *H pylori* related gastritis at a young age, eventually evolving into intestinal metaplasia at a younger age, might render such individuals at greater risk for developing gastric cancer of the intestinal type over a longer period of life span. Within this realm, the case report by Scott *et al* is of great importance. Their study of a gastric cancer family showed that of the eight children, five (63%) had *H pylori* related chronic atrophic gastritis (age at diagnosis 10·26 years) and in three of those five 60%) intestinal metaplasia developed, at 21, 23, and 34 years. In all three intestinal metaplasia was confined to the gastric antrum. They postulate that *H pylori* acts as a promoter in the progression from normal to metaplastic epithelium, possibly by inducing a hyperproliferative state in the inflamed gastric mucosa.[28] In view of their report, the treatment of *H pylori* related gastritis, leading to eradication of the microorganism, might be of help in removing a potential risk factor in gastric cancer prone patients. At present the concept that *H pylori* and intestinal metaplasia are related is still a subject of much debate. This is highlighted by the controversy in the major classifications of chronic gastritis, concerning the aetiology of intestinal metaplasia. In the classification by Whitehead, based on morphologic criteria, the major categories of gastritis are thought to reflect increasingly severe changes in a progressive process starting with superficial gastritis gradually evolving into chronic atrophic gastritis with intestinal metaplasia. A separate entity, socalled gastric atrophy, was introduced to describe biopsies showing marked glandular atrophy, widespread intestinal metaplasia and near absence of inflammation.[29] The classification by Cheli and Giacosa regarded the latter entity merely as an end stage in the spectrum of chronic atrophic gastritis.[30] Although these classifications brought a more uniform histologic reporting, they did not add anything to the understanding of the pathogenetic mechanisms involved. The first attempt in addressing this important topic was the classification by Strickland and Mackay, which was further expanded by Glass and Pitchumoni.[31 32] Both stressed the importance of the topographical distribution of chronic atrophic gastritis in relation to the underlying aetiopathogenetic mechanisms involved. One should note, however, that these classifications were proposed in the 'pre *H pylori* era'. The discovery of *H pylori* led Wyatt and Dixon to propose another aetiopathogenetic classification taking into account the pivotal role of *H pylori* in the process of gastric inflammation.[33] In the classifications briefly discussed so far, intestinal metaplasia is considered to be more or less a sequel to inflammation and part of a progressive process. This leaves room for the concept that intestinal metaplasia might be a result of *H pylori* related gastritis as our data suggest.

In the classification by Correa,[34] recently revised,[35] and in the classification by Yardley,[36 37] however, the presence of intestinal metaplasia in gastric biopsies indicate an aetiology for gastritis distinct from *H pylori*. In their classifications *H pylori* is related to diffuse antral gastritis and chronic non-specific gastritis respectively. Both have in common that intestinal metaplasia is typically absent or minimal. In contrast, it is the multifocal atrophic gastritis in Correa's classification corresponding to the meta plastic atrophic gastritis type B in Yardley's classification, which is often accompanied by intestinal metaplasia. It is thought that this type of chronic gastritis is the result of environmental agents and/or dietary

factors like excessive intake of salty foods and nitrates, deficiency in fresh fruits and leafy vegetables.[35-39] Adopting their classification implies that gastritis, in which the concomitant presence of *H pylori* and intestinal metaplasia is demonstrated, must have a dual aetiology.

This controversy, whether or not intestinal metaplasia is a result of *H pylori* related gastritis, can only be solved in long term follow up studies. Interestingly, the longitudinal study by Kekki *et al* showed that non-atrophic and non-metaplastic chronic gastritis can evolve into chronic atrophic gastritis with intestinal metaplasia.[40]

The interpretation of our finding that the mean age of intestinal metaplasia positive patients was significantly lower when they were also *H pylori* positive as compared with *H pylori* negative patients is rather complex. Of course, it is tempting to speculate that *H pylori* accelerates the process leading to intestinal metaplasia, but there are certain other aspects to be considered. First, because *H pylori* is only found on foveolar gastric epithelium, a difference in the extent of intestinal metaplasia – an inhospitable site for *H pylori* – in the intestinal metaplasia positive *H pylori* negative group as compared with the intestinal metaplasia positive *H pylori* positive group might explain the age difference. Our data show, however, that the extent of intestinal metaplasia in both groups does not significantly differ. This suggests that the age difference found cannot be explained on the basis of a difference in extent of intestinal metaplasia. Second, our study is not a follow up cohort study, so we are neither informed about whether the intestinal metaplasia positive *H pylori* negative group has never been colonised with *H pylori* nor are we informed about the time of colonisation with *H pylori* in the intestinal metaplasia positive *H pylori* positive group. Third, the greater frequency of antibiotics use among older age groups might be a confounding factor as this may have led to the eradication of *H pylori*. Finally, we must stress an inherent flaw of any endoscopic bioptic study, as these studies create the possibility of sampling error. Therefore, although there is a significant age difference between intestinal metaplasia positive *H pylori* positive and intestinal metaplasia positive *H pylori* negative patients, its meaning remains unsolved in our study and other studies are necessary for its correct interpretation. The possibility remains, however, that early acquisition of *H pylori* not only leads to early development of intestinal metaplasia but may even accelerate the development of intestinal metaplasia.

In conclusion, although our data do not prove a causal relationship between *H pylori* infection and the histogenesis of intestinal metaplasia, we suggest that *H pylori* plays an important role in the development of intestinal metaplasia in the gastric mucosa. Whether *H pylori* has to be present at all times during this process or is only necessary as a 'trigger', needs further research.

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