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The prevalence of *Helicobacter pylori* infection in malignant and premalignant conditions of the head and neck

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Abstract

Helicobacter pylori is an accepted cause of chronic active gastritis and has a major causative role in peptic ulceration. It is a gastric carcinogen. Its role in non-ulcer dyspepsia (NUD) is less clear; yet 50 per cent of patients with NUD are infected with *H pylori*. *H pylori* has been investigated in several other organ systems, but has not been investigated extensively in squamous cell carcinoma of the upper aerodigestive tract, a region which could be directly exposed to the bacterium by gastro-oesophageal reflux (GOR).

In this study 61 patients with severe laryngeal dysplasia or frank carcinoma of the head and neck are striated by age, investigated for the presence of antibodies to *H pylori* and compared to age and sex matched controls.

In the age group of 46–61 years, the presence of *H pylori* antibodies was marginally greater in the experimental (63.0 per cent) than the control group (40.7 per cent) (Pearson Chi square $p = 0.055$, Fisher 2-sided exact test $p = 0.066$). When combining this age group with the younger age group and thereby creating two roughly equal groups (n = 31 and n = 30) there was also a statistical trend towards increased positivity in the experimental group. These findings are discussed in the light of other studies with gastro-oesophageal reflux disease (GORD).

Key words: Helicobacter Pylori; Gastro-oesophageal Reflux; Voice Disorders; Larynx; Head and Neck Neoplasms; Dysplasia

Introduction

Helicobacter pylori causes chronic persistent gastritis in virtually all infected individuals.[1] It is the accepted cause of chronic active gastritis and has a major causative role in duodenal ulcers (where the prevalence is 90–100 per cent) and gastric ulcers (where the prevalence is 60–100 per cent).[2–4] An individual with *H pylori* infection (HP+) has an estimated lifetime risk of 10–20 per cent for development of peptic ulcer disease, three to four times that of a non-infected individual.[2] HP is a gastric carcinogen.[1]

Approximately 50 per cent of patients with non-ulcer dyspepsia (NUD) are infected with *H pylori*, and HP+ is more common in patients with NUD than in asymptomatic controls.[5] Several attempts have been made to establish a link between these two processes, but the results have been conflicting.[6] Reasons given for these difficulties include the following: dyspepsia has not been adequately defined, it is a symptom complex, the mechanisms for dyspepsia are unknown.[7]

Other organ systems have been identified that are potentially at risk from *H pylori*. Patients with myocardial infarct (MI) or stroke had a higher incidence of HP+ (70 per cent and 68 per cent respectively *vs.* matched controls (57 per cent)).[8] *H pylori* has been implicated in certain dermatological ailments, particularly rosacea.[9] *H pylori* has been identified in dental plaque. Some feel that dental plaque may be a source of *H pylori* spread.[12] Others have reviewed the presence of *H pylori* in the mouth, found it to be intermittent and concluded that it is most likely associated with extra-oesophageal (pharyngeal) reflux.[13]

H pylori does not appear to play a major role in Barrett's oesophagitis, nor does its presence appear to alter the natural history of Barrett's.[14,15] Gastro-oesophageal reflux, however, has been associated with Barrett's oesophagus as well as with oesophageal and laryngeal carcinoma, the latter perhaps as a co-carcinogen.[16,17] Common sense, therefore, suggests that pharyngeal reflux, in the presence of *H pylori* infection of the stomach would expose the pharynx to the *H pylori* bacterium, and could conceivably act thereby as a co-factor for the development of inflammatory or malignant conditions.

Yet to the best knowledge of the authors little has been published on the possible role of *H pylori* in squamous cell carcinoma of the head and neck; and

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what has appeared, to date, has not supported such a thesis. This report presents the *H pylori* status of a group of patients with severe dysplasia of the larynx or squamous cell carcinoma of the upper aerodigestive tract (excluding oesophagus).

Materials and methods

Sixty-one subjects with severe dysplasia of the larynx or with invasive squamous cell carcinoma of the upper aerodigestive tract (excluding the oesophagus) are included in this report. The series represents a consecutive group of patients seen by the senior author (JR) with such pathology, as well as a consecutive group of patients from a series of combined head and neck clinics at the Royal National Throat Nose and Ear Hospital (all willing to give their consent). All patients with severe dysplasia and the majority of the patients with frankly malignant disease suffered from laryngeal pathology (Table I).

All patients and controls came from the greater London area, a region of great ethnic and social diversity. Fifty-one were males and 10 were females. The age range varied from 26 to 83. The mean was 61.5 years.

This report represents one arm of a larger study, totalling 162 patients and 187 controls. This larger study was designed to investigate the prevalence of *H pylori* positivity in patients presenting with chronic laryngitis and non-malignant hoarseness.

The control group consists of 187 subjects who were age and sex matched to the overall experimental groups, including the experimental group described here and the chronic laryngitis group described elsewhere.[19] The mean age was 51.3 years. Age matching was attempted by five-year quantiles. Age and sex matching was necessary, because the malignant/premalignant arm was statistically older ($p = 0.018$) than the chronic laryngitis arm mean age. It also had a marked male predominance, whereas the chronic laryngeal group had a female preponderance.

Ethical approval has been obtained for the study, prior to its inception through the Royal Free Hospital.

ELISA technique

The serum assay used for the large majority of patients included in this study was a validated commercially available specific IgG ELISA test, (Meridien Diagnostics, Cincinnati, USA). A positive cut off optical density of >0.10, measured at 450 nm, was used. Blood samples were obtained from each participant by standard venopuncture techniques. Each blood sample was labelled, spun down to collect serum and stored in −70°C until frozen. Each was transported to the serology laboratory for subsequent analysis.

Statistical analysis was performed by the Clinical Information Centre of the Royal Free Hospital. A stratified cross tabulation approach was utilized. Three age groups were identified, less than 45 years, 46–61 years, and greater than 62 years. This was done so on the basis that the experimental group in the combined study (chronic laryngitis (described elsewhere[19]) as well as the head and neck group reported on in this paper) divided equally into these three age groups, as did the age and sex matched controls.

That said, the head and neck cancer group was older than the chronic laryngitis group, and only four patients fell into the less than 45 years group. Thus the less than 45 years group was co-assigned with the 45–61 group thereby creating two equal groups: <62 (n = 31), >62 (n = 30).

Results

Reviewing the histology, site and *H pylori* positivity, of the 61 patients in this study, 42 patients had severe dysplasia or squamous cell carcinoma of the larynx. Twenty-five of these (59.5 per cent) tested positive for antibodies to *H pylori*. A further 19 patients had squamous cell carcinoma involving other areas of the head and neck (oesophagus excluded). Thirteen of these (68.4 per cent) tested positive for antibodies to *H pylori* (Table I).

Reviewing age breakdown and *H pylori* positivity, 38 (62.3 per cent) tested positive for *H pylori* overall. Under 62 years (n = 31), 19 (61.3 per cent) tested positive for *H pylori* (under 45 years (n = 4), 50 per cent were *H pylori* positive, and between 46–61 years, 63.0 per cent were *H pylori* positive). Over 62 years (n= 30), 65.5 per cent were *H pylori* positive).

Of the 187 control subjects, 47.1 per cent tested positive for *H pylori*. Under 62 years (n = 125), 41.6 per cent were *H pylori* positive (under 45 (n = 66), 42.4 per cent were *H pylori* positive and between 46–61 (n = 59) 40.7 per cent were *H pylori* positive). Over 62 years (n = 62) 57.8 per cent tested positive for *H pylori* (Table II).

TABLE I
BREAKDOWN OF LOCATION, HISTOLOGY AND H PYLORI POSITIVITY

Location	Histology	Total number	Number positive
Larynx	Severe dysplasia	6	3
Larynx	Sq cell CA	36	22
Hypopharynx		4	2
F.O.M./oral tongue		4	2
Tonsil		5	5
Nasopharynx		2	2
Tongue base/vallecula		2	1
Other		2	1
Total		61	38

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TABLE II
BREAKDOWN OF AGE VERSUS H PYLORI POSITIVITY

	<45	46–61	0–61	>62	Total
Experimental Total	n = 4	n = 27	n = 31	n = 30	n = 61
H pylori$^+$	50%	63.0%	61.3%	65.5%	62.3%
Control Total	n = 66	n = 59	n = 125	n = 62	n = 187
H pylori$^+$	42.4%	40.7%	41.6%	57.8%	47.1%

Pearson Chi Square, and Fisher's Exact Test (two-sided) were performed. Statistical significance was felt to be obtained only if the Fisher's Exact Test (two-sided) was <0.05.

The age of the patients with chronic laryngitis was found to be statistically lower than that of the head and neck cancer arm ($p<0.000$). Gender was found to have no statistical significance for the presence or absence of antibodies to *H pylori*.

The presence (or absence thereof) of antibodies to *H pylori* was examined in the experimental subjects and the control population between individual age groups and by combining age groups less than 45 years with the 46–61 group and age groups 45–61 with more than 62.

When comparing each of the three age groups separately, the experimental age group under 45 had too few patients to be compare with matched controls. The experimental age group 46–61 years demonstrated a trend toward statistical significance for *H pylori* positivity over matched controls (Pearson chi-square 0.055, two-sided Fisher's exact test 0.066). When the age groups of less than 45 years and 46–61 were combined, a similar trend was seen, (Pearson chi square 0.049, two-sided Fisher's exact test 0.069). The experimental age group more than 62 was not significantly more likely to be *H pylori* positive than matched controls (Pearson chi-square 0.653, two-sided Fisher's exact test 0.528).

Discussion

Several European studies have emphasized the increased *H pylori* positivity as a factor of age.[2,8,9,14,15,17,20] This finding was corroborated by our study.

Recent epidemiological findings in developed countries can be summarized as the following: *H pylori* is acquired in children and adolescence in over 50 per cent of cases. The risk and rate of acquisition is higher in early childhood and then falls exponentially. New infections do occur in adulthood but the annual incidence is low in the order of 0.4 to 0.5 per cent per year. *H pylori* gastritis is a birth cohort related phenomenon, i.e. different cohorts show a rate and prevalence that varies between cohorts. This rate and risk is higher in those cohorts born in the beginning of the 20th century but is much lower in those born later.[21,22]

In this study a trend was found for an increased likelihood of *H pylori* in the experimental subjects as compared to age-striated controls, in the younger age groups. It was unclear at the outset that this would be so. A similar but smaller study assayed for the presence of IgG antibodies to *H pylori* in the serum of 21 patients with head and neck squamous cell carcinoma and compared them with 21 matched controls. They found no significant differences in acquisition.[18] They postulate that the small sample size may have been an issue. This has been addressed to some degree by assaying almost three times as many patients.

The difference between the experimental and control groups was most apparent in the 46–61 year group. It is postulated that this may be so on the basis that the youngest group would presumably not have had long enough exposure to other known co-carcinogens (e.g. tobacco and alcohol) for the further exposure to *H pylori* to have made any significant difference in the development of cancer or precancerous conditions. (That stated, our study size in the youngest (<45 years) group is so small (n = 4), that little could be made of those results). Also the older group would perhaps have had long enough exposure to these other known co-carcinogens for further exposure to *H pylori* to have little clinical significance.

While the majority of patients in this study had laryngeal pathology, the study was not limited to the larynx on the basis that 1) *H pylori* was as (or perhaps more) likely to infect the pharynx as the larynx, and 2) this being a pilot study looking for possible correlations between *H pylori* and head and neck squamous cell carcinoma, it was felt that it was better to examine a broad group of head and neck pathology, and then, depending on the results, focus in on smaller groups in subsequent studies.

While not statistically significant, it is interesting that a larger percentage of non-laryngeal than laryngeal carcinomas tested positive for *H pylori*. It could be argued that *H pylori* has greater access to, and thus is more likely to infect, the pharynx than the larynx.

For the results to be meaningful, reflux of *H pylori* into the laryngopharynx needs to be postulated. Gastro-oesophageal reflux (GOR) has been associated with several non-gastric conditions. In children it has been associated with laryngeal abnormalities and pulmonary abnormalities,[23] and *H pylori* is acquired in children and adolescents in over 50 per cent of cases of *H pylori* positive pathology.[21,22] In adults, pharyngeal reflux has been associated with carcinoma of the larynx and with laryngotracheal stenosis.[24,25]

Borkowski *et al.*[26] have found a positive urease test in six out of 35 benign laryngeal biopsy specimens, or 17.1 per cent. They postulate that *H pylori* could have had a role in the aetiology of chronic laryngitis in certain patients.

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The jury is still out regarding any correlation between *H pylori* positivity and squamous cell carcinoma or premalignant disease of the head and neck. Nonetheless the World Health Organization (WHO) has classified *H pylori* as a definitive carcinogen for gastric carcinoma. Heatley[27] identifies the following theories associated with this malignant propensity: 1) N-nitroso compounds may be abundant in *H pylori* infection. 2) The presence of reactive oxygen species, ammonia, and cytotoxic-producing strains of *H pylori* have all been described. 3) *H pylori* has been associated with mucosal associated lymphoid tissue tumours (maltomas). And the possibility that *H pylori* could infect the pharynx and larynx through laryngopharyngeal reflux is intriguing.

We believe, therefore, that our findings are of interest and that they warrant further investigations, particularly those focusing on the identification of *H pylori* in head and neck cancer specimens. Identification of *H pylori* in gastric cancer specimens has proved difficult due to the associated mucosal atrophy.[27] However, it could well be argued that our findings may only be acting as a marker for gastro-esophageal reflux, another questionable co-factor in the development of head and neck cancer.

Summary

Sixty-one subjects with severe laryngeal dysplasia, or frankly invasive squamous cell carcinoma of the head and neck were studied by serology for the presence of antibodies to *H pylori* and were compared to age-matched controls. A higher level of *H pylori* positivity was identified in the experimental group than in the controls, particularly in the age-striated range of 46–61 years, and this trend almost reached statistical significance. The next stage of investigation should be a systematic search for evidence of *H pylori* in a series of head and neck squamous cell specimens to determine if this finding has any clinical relevance.

Reference

1 Kuipers EJ, Meuwissen SG. *Helicobacter pylori* and gastric carcinogenesis. *Scand J Gastroenterol* 1996;**218** (suppl):103–5
2 Kuipers EJ, Thijs JC, Festen HP. The prevalence of *Helicobacter pylori* in peptic ulcer disease. *Aliment Pharmacol Ther* 1995;**9**(suppl 2):59–69
3 Genta RM, Gurer IE, Graham DY. Geographical pathology of *Helicobacter pylori* infection: is there more than one gastritis? *Ann Med* 1995;**27**:595–9
4 Hunt RH. Eradication of *Helicobacter pylori* infection. *Am J Med* 1996;**20**:42S–50S
5 Buckley M, O'Morain C. Prevalence of *Helicobacter pylori* in non-ulcer dyspepsia. *Aliment Pharmacol Ther* 1995;**9**(suppl 2):53–8
6 O'Morain C, Buckley M. *Helicobacter pylori* and dyspepsia. *Scand J Gastroenterol* (suppl) **214**: 28–30
7 Armstrong D. *Helicobacter pylori* and dyspepsia. *Scand J Gastroenterol* (suppl) 1996;**215**:38–47
8 Whincup PH, Mendall MA, Perry IJ, Strachan DP, Walker M. Prospective relations between *Helicobacter pylori* infection, coronary heart disease, and stroke in middle aged men. *Heart* 1996;**75**:568–72
9 Rebora A, Drago F, Parodi A. May *Helicobacter pylori* be important for dermatologists? *Dermatology* 1995;**191**:6–8
10 Oshowo A, Gillam D, Botha A, Tunio M, Holton J, Boulos P, Hobsley M. *Helicobacter pylori*: the mouth, stomach and gut axis. *Ann Periodontol* 1998;**3**:276–80
11 Oshowo A, Tunio M, Gillam D, Botha AJ, Holton J, Boulos P, *et al*. Oral colonization is unlikely to play an important role in *Helicobacter pylori* infection. *Br J Surg* 1998;**85**:850–2
12 Nguyen AM, el-Zaatari FA, Graham DY. *Helicobacter pylori* in the oral cavity. A critical review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodont* 1995;**79**:705–9
13 Madinier IM, Fosse TM, Monteil RA. Oral carriage of *Helicobacter pylori*: a review. *J Periodontol* 1997;**68**:2–6
14 Ricaurte O, Flejou JF, Vissuzaine C, Goldfain D, Rotenberg A, Cadiot G, *et al*. *Helicobacter pylori* infection in patients with Barrett's oesophagus: a prospective immunohistochemical study. *J Clin Pathol* 1996;**49**:176–7
15 Abbas Z, Hussainy AS, Ibrahim F, Jafri SM, Shaikh H, Khan AH. Barrett's oesophagus and *Helicobacter pylori*. *J Gastroenterol Hepatol* 1995;**10**:331–3
16 Koufman J, Sataloff RT, Toohill R. Laryngopharyngeal reflux: consensus conference report. *J Voice* 1996;**10**:215–6
17 Freije JE, Beatty TW, Campbell BH, Woodson BT, Schultz CJ, Toohill RJ. Carcinoma of the larynx in patients with gastroesophageal reflux. *Am J Otolaryngol* 1996;**17**:386–90
18 Grandis JR, Perez-Perez GI, Yu VL, Johnson JT, Blaser MJ. Lack of serologic evidence for *Helicobacter pylori* in head and neck cancer. *Head Neck* 1997;**19**:216–8
19 Rubin JS, Prior A, Upile T, Lavy J, Ratcliffe P, Benjamin E. The prevalence of *Helicobacter pylori* infection in benign laryngeal disorders, in press. *J Voice*
20 Harris AW, Douds A, Meurisse EV, Dennis M, Chambers S, Gould SR. Seroprevalence of *Helicobacter pylori* in residents of a hospital for people with severe learning difficulties. *Eur J Gastroenterol Hepatol* 1995;**7**:21–3
21 Parsonnet J. The incidence of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 1995;**9**(suppl 2):45–51
22 Sipponen P. *Helicobacter pylori* gastritis – epidemiology. *J Gastroenterol* 1997;**32**:273–7
23 Little JP, Matthews BL, Glock MS, Koufman JA, Reboussin DM, Louglin CJ, *et al*. Extraesophageal pediatric reflux: 24-hour double-probe pH monitoring of 222 children. *Ann Otol Rhinol Laryngol Suppl* 1997;**169**:1–16
24 Jindal JR, Milbrath MM, Shaker R, Hogan WJ, Toohill RJ. Gastroesophageal reflux disease as a likely cause of 'idiopathic' subglottic stenosis. *Ann Otol Rhinol Laryngol* 1994;**103**:186–91
25 Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope* 1991;**101** (suppl 53):1–78
26 Borkowski G, Sudhoff H, Koslowski F, Hackstedt G, Radu HJ, Luckhaupt H. A possible role of *Helicobacter pylori* infection in the aetiology of chronic laryngitis. *Eur Arch Otorhinolaryngol* 1977;**254**:481–2
27 Heatley RV, ed. *The* Helicobacter pylori *Handbook*. Oxford: Blackwell Science Publication, 1995

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