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Helicobacter pylori-associated chronic atrophic gastritis involving the gastric body and severe disease by *Vibrio cholerae*

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Summary

Evidence has associated chronic infection by *Helicobacter pylori* with chronic gastritis, low gastric acid production and an increased risk of life-threatening cholera. However, the relationship of specific patterns of histological damage in the gastric mucosa associated with *H. pylori* infection and the occurrence of cholera has not been described. The purpose of this study was to compare the gastric pH and histopathological findings in gastric biopsies taken from patients with severe diarrhoeal disease due to *Vibrio cholerae* with those taken from a control (cholera-negative) population. Thirty-five *H. pylori*-positive patients who had severe dehydration from culture-confirmed cholera (cases) and 40 patients with *H. pylori* but with no history of cholera (controls) were recruited. Gastric pH was measured and multiple biopsies were taken from the gastric antrum and body for histopathological examination. The results revealed that patients with severe cholera had a significantly higher prevalence of hypochlorhydria at endoscopy compared with controls. Furthermore, cases had significantly more chronic atrophic gastritis (45.7% vs. 12.5%; $P = 0.002$) and intestinal metaplasia (37.1% vs. 2.5%; $P < 0.01$) in the gastric body than controls. Our findings suggest that the nature and location of these gastric lesions may predispose a subset of *H. pylori*-infected individuals to severe disease by *V. cholerae*.

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Keywords

Helicobacter pylori; Vibrio cholerae; Atrophic gastritis; Diarrhoea; Pathology; Peru

1. Introduction

It is well known that (i) gastric acid secretion constitutes a protective barrier against ingested enteropathogens, (ii) *Vibrio cholerae* is acid sensitive and (iii) individuals with cholera are frequently hypochlorhydric (Sack et al., 1972). However, the histopathological changes present in the stomach of cholera patients have not been described.

In Peru, *Helicobacter pylori* infection occurs early and frequently, and histopathological descriptions are well documented (Recavarren-Arce et al., 1997). In 30 Peruvian children who underwent endoscopy, 40% had *H. pylori*-associated chronic gastritis; however, none had chronic atrophic gastritis (CAG) or intestinal metaplasia (IM). *Helicobacter pylori*-associated gastritis has been reported in 80% of 30 Peruvian adolescents, occurring as chronic superficial gastritis (CSG) in 37%, chronic deep gastritis (CDG) in 30% and CAG of moderate to severe degree in 13%; IM of the gastric mucosa was not found (Recavarren-Arce et al., 1995). Of 102 Peruvian adults undergoing endoscopy for abdominal complaints in a poor peri-urban area in Lima, 95% had *H. pylori*-associated chronic gastritis, 34% with CAG of moderate to severe degree and 21% with IM of the gastric mucosa (Recavarren-Arce et al., 1995). In another series of 54 Peruvian patients, 67% were reported to have CAG (The Gastrointestinal Physiology Working Group, 1986). In all series describing lesions found in *H. pylori*-infected Peruvian patients, the lesions were found to be more severe in the antrum than in the body of the stomach (Recavarren-Arce et al.,1995,2005; The Gastrointestinal Physiology Working Group, 1986).

The prevalence of *H. pylori* infection in the developing world is often very high, exceeding 50% by 5 years of age (Frenck and Clemens, 2003), and in the lower socioeconomic population of developing countries it is over 90% (Bardhan, 1997). It is therefore very difficult in a developing country like Peru to find *H. pylori*-uninfected low socio-economic controls. Negative *H. pylori* controls are not included in this study because: (1) *H. pylori* infection is present at such high rates that negative controls are rare in the study population; and (2) in Peru, the frequent use of over-the-counter antibiotics makes it difficult to distinguish patients never infected from those who have recently cleared their infection by antibiotic treatment (Ramirez-Ramos et al., 1997).

Evidence has been reported linking chronic infection by *H. pylori* with chronic gastritis (Annibale et al., 2001), low gastric acid production and an increased risk of life-threatening cholera (Clemens et al., 1995; Frenck and Clemens, 2003). The relationship of specific patterns of histological damage in the gastric mucosa associated with *H. pylori* infection and the occurrence of cholera has, however, not been described. The purpose of this study was to compare the gastric pH and histopathological findings in gastric biopsies taken from patients with severe diarrhoeal disease due to *V. cholerae* with those taken from a control population who had no prior history of cholera infection.

2. Materials and methods

2.1. Subjects

Individuals meeting the definition of cases and controls and giving informed consent to the study procedures were evaluated for endoscopy. Patients were excluded from participation if they had received H2 antagonists or antacids in the previous 48 h, or chemotherapeutic agents, antimicrobials or Bismuth compounds in the 2 weeks prior to the scheduled endoscopy.

Participants who were found on endoscopy to have active gastric or duodenal ulcers, a gastric neoplasm or prior gastric surgery were excluded from the analysis. The study was approved by the Institutional Review Board at the Universidad Peruana Cayetano Heredia, Lima, Peru.

2.1.1. Cholera group (cases)

The cholera group was composed of 38 adult patients (older than 18 years) coming from shantytowns located on the outskirts of Lima and who presented to the Universidad Peruana Cayetano Heredia in 1993—1994 with severe dehydrating diarrhoea and culture-confirmed *V. cholerae* O1 infection. The severity of dehydration was based on standard criteria recommended by the WHO (1991). Cholera patients who had recovered completely from their disease and were well nourished and hydrated were invited to participate in the study and scheduled for endoscopy 3—4 weeks following their acute illness. Only those patients who were *H. pylori*-positive on biopsy specimens (35 patients) were included in the analysis. Three *H. pylori*-negative patients were thus excluded from the analysis.

2.1.2. Control group

The control group was composed of 40 patients who presented with upper gastrointestinal symptoms to the Hospital Arzobispo Loayza or the Comas Clinic between 1989 and 1992 and had been found to have *H. pylori* on biopsy specimens. These two referral centres serve patients in the marginal neighbourhoods and shantytowns of Lima. None had a history of severe diarrhoea associated with cholera. This group of patients were all positive for *H. pylori* and had been enrolled in a treatment study of that organism (Ramirez-Ramos et al., 1997).

2.2. Methods

Fiberpanendoscopy was performed in all the patients from the cholera and control groups following an overnight fast. During endoscopy, four mucosal biopsies were taken from the lesser curvature of the stomach, two at the level of the antrum and two at the body. Sections were considered adequate for evaluation of CAG when they fulfilled two conditions: (1) the histological sections were oriented from the surface mucinous epithelium to the muscularis mucosae; and (2) a portion of the muscularis mucosae was present (Recavarren-Arce et al., 1997). Patients with shallow biopsy specimens were excluded from further analysis.

The biopsy specimens were fixed in buffered formalin, embedded in paraffin, sectioned at 4 μm and stained with haematoxylin/eosin, Periodic acid Schiff and Warthin—Starry silver stains. Sections were examined to evaluate gastric histological changes and the presence of *H. pylori*. The gastric histological changes evaluated included type and/or degree of mucinous surface epithelium damage, CSG, CDG and CAG, with or without IM of the gastric mucosa.

To study morphological changes, each evaluable histological section was assessed using a specially designed format, as previously described (Recavarren-Arce et al., 1995), which considered the following characteristics. All biopsy specimens were coded, and histopathological readings were performed by a pathologist blinded to the status of the participant as a case or control. Briefly, the descriptive categories are defined below.

2.2.1. Chronic superficial gastritis (CSG)

This lesion is nearly always coincident with damage to the mucinous surface epithelium. The inflammatory infiltrate is usually chronic—active in type, consisting of poly-morphonuclear cells and mononuclear cells. Occasionally, however, the infiltrate is chronic, consisting of mononuclear cells only. The inflammatory infiltrate involves the entire interfoveolar space but does not extend deeper than the neck region of the gastric glands. The combination of damage to the surface mucinous epithelium and superficial inflammatory infiltrate has been called CSG

and is patchy when caused by *H. pylori* infection (Recavarren-Arce et al., 1997). In Peru, CSG is nearly always associated with *H. pylori* infection (Recavarren-Arce et al., 1991; The Gastrointestinal Physiology Working Group, 1986). The alterations, i.e. degree of damage, to the mucinous epithelium, the severity of the inflammatory infiltrate and the type of inflammatory infiltrate present were graded and expressed as mild (<10%) or moderate—severe (>10%) with regard to the extent of the biopsy affected.

2.2.2. Chronic deep gastritis (CDG)

CDG is characterised by a chronic inflammatory infiltrate in the deep portion of the lamina propria, below the level of the gland necks and without antral gland loss. CDG was expressed as mild (<10%) or moderate—severe (>10%) with regard to the extent of the biopsy affected and the density of inflammation.

2.2.3. Intestinal metaplasia (IM)

The extent of IM was noted, but special stains were not performed for typing the metaplasia.

2.2.4. Chronic atrophic gastritis (CAG)

Loss of glandular tissue is considered the essential component of CAG along with inflammation. Atrophy is a common denominator in all pathological processes causing severe mucosal damage and may result from ulceration, erosion or prolonged inflammation where individual glands are destroyed in a piecemeal fashion (Dixon et al., 1996). Consequently, in advanced CAG there are small glands, remnants of glands and areas where lost glands are replaced by a fibrocellular substrate (Recavarren-Arce et al., 1997). Total deep gland loss (TDGL) was considered as loss of deep glands owing to CAG, IM or a combination of both (Recavarren-Arce et al., 2005). The severity of CAG and TDGL was graded and expressed as mild (<10%) or moderate—severe (>10%) with regard to the extent of the biopsy affected.

2.2.5. Gastric pH

The gastric pH of all participants was measured by fluid aspirated from the gastric body and fundus during endoscopy using a standard gastric pH paper (Universalindikator®; Merck, Darmstadt, Germany) with a range from 0 to 7. Hypochlorhydria at endoscopy was defined as a gastric pH ≥ 4.5 (Sobala et al., 1989).

2.3. Statistical analysis

Cholera cases who were *H. pylori*-positive were compared with unmatched controls using the Student's *t*-test, χ^2 test and Fisher's exact test when the expected frequencies were lower than 5. For each individual patient, it was also determined whether the percent of TDGL was greater in the antrum or the body and the frequencies were compared using the abovementioned tests. Gastric pH was analysed in two ways. Median values were compared using the Mann—Whitney *U*-test as well as categorical tests to determine differences in individuals with hypochlorhydria at endoscopy (pH ≥4.5). Means± SD and the median with their quartiles (25—75%) were expressed using the statistical program SPSS for Windows, 10.0.5 (SPSS Inc, Chicago, IL, USA).

3. Results

Both study groups had similar mean ages (37.5 (SD 8.5) years in controls vs. 39.3 (SD 11.4) years in cases; $P = 0.419$), however the controls had significantly more females compared with the case group (67.5% of controls vs. 25.7% of cases; $P < 0.01$).

3.1. Chronic superficial gastritis (CSG)

CSG of the lamina propria was equally prevalent both in controls and cholera patients. However, when only patients with moderate—severe inflammation were analysed, there were significant differences between controls and cholera patients. There was a significantly increased prevalence of moderate—severe superficial inflammation in the antrum of control versus cholera patients (97.5% (39/40) vs. 80% (28/35); $P = 0.022$). The opposite was true in the body of the stomach of cholera patients. Cholera patients had a significantly higher prevalence of moderate—severe superficial gastritis in the body than did controls (88.6% (31/35) vs. 55% (22/40); $P = 0.002$). Controls had a higher prevalence of mucin damage in the body of the stomach than the cholera group (95% (38/40) vs. 74.3% (26/35); $P = 0.019$). No difference was seen between either group in the type of inflammatory infiltrate (i.e. chronic versus chronic—active) found in the superficial mucosa.

3.2. Chronic deep gastritis (CDG)

CDG, a forerunner lesion to CAG, was significantly more prevalent in the gastric body of cholera patients compared with controls (74.3% vs. 37.5%; $P = 0.002$) (see Table 1).

3.3. Chronic atrophic gastritis (CAG), intestinal metaplasia (IM) and total deep gland loss (TDGL)

A similar pattern was observed for CAG and IM. Controls had a higher prevalence of CAG in the antrum than cases, whilst cholera patients had significantly more CAG, IM or a combination of these two lesions (i.e. TDGL) in the body of the stomach than control patients. Of note was the finding that only one patient in the control group (2.5%) had IM of the body compared with 13 (37.1%) in the cholera patient group (Table 1).

When differences in the pattern of the antrum versus the body were examined in the same individual, the cholera group had significantly more patients with more IM and TDGL in the body than occurred in the antrum (11.4% (4/35) vs. 0% (0/40); $P < 0.05$). In contrast, the opposite was true in the controls. In the controls, the antrum was the focus of IM and TDGL rather than the body (77.5% (31/40) vs. 28.6 (10/35); $P < 0.05$) (Table 2).

3.4. Gastric pH

There was significantly higher gastric pH at endoscopy in cholera patients than in controls (6.5 (range 3—7) vs. 3 (2—6); $P = 0.003$). Cholera patients also had a significantly higher prevalence of hypochlorhydria at endoscopy than controls (68.6% (24/35) vs. 32.5% (13/40); $P = 0.002$). In addition, individuals with cholera who had moderate— severe body TDGL had a significantly higher prevalence of hypochlorhydria at endoscopy than did control patients with the same pathology (100% (5/5) vs. 0% (0/2); $P = 0.047$). The prevalence of hypochlorhydria at endoscopy associated with other body lesions did not differ significantly between cholera and control groups.

There was no significant difference in the prevalence of hypochlorhydria at endoscopy when patients in the control group were compared with regard to the presence of gastric body lesions. On the other hand, cholera patients with TDGL of moderate—severe grade compared with those without that lesion tended to have an increase in the prevalence of hypochlorhydria at endoscopy (100% (5/5) vs. 63.3% (19/30); $P = 0.072$), respectively.

4. Discussion

This study demonstrates that patients with severely dehydrating cholera have a significantly higher prevalence of CAG and IM in the body, i.e. the acid-producing portion, of the stomach compared with non-cholera controls. Generally, an antral preponderance of TDGL is the

pattern seen in all our previous endoscopy studies of Peruvian patients presenting with *H. pylori* infection in the absence of acute ulcer disease. Cholera patients had a more severe superficial and deep inflammatory infiltrate in the lamina propria of the body of the stomach than controls. Patients with cholera also had significantly higher pH values than controls. To our knowledge, no other study of *H. pylori*-associated gastritis has demonstrated a pattern where the body has increased CAG or IM compared with the antrum (Correa et al., 1994). This pattern of distribution of lesions does occur with pernicious anaemia, a disease classically associated with atrophy and dysplasia of the fundus and body of the stomach with antral sparing (Toh et al., 1997) that is rare in Peru.

It remains unclear why individuals infected with *H. pylori* develop divergent distributions of histopathological lesions. However, our findings suggest that the nature and location of the gastric lesions may predispose a subset of *H. pylori*-infected individuals (specifically those with a greater amount of CAG and IM in the gastric body) to disease caused by acid labile enteric pathogens such as *V. cholerae*. It should be emphasised that non-cholera controls came from the same socio-economic status and that all patients in both groups had *H. pylori* infection. We have rarely seen patients that are not infected with *H. pylori* in this socio-economic group. When found, these patients nearly always have lesions in the stomach compatible with prior *H. pylori* infection (R.H. Gilman, personal observation). In general, CAG and gastric atrophy may be a result of agents other than *H. pylori* (most notably autoimmune in origin, as in pernicious anaemia), nevertheless *H. pylori* is now recognised as the principal cause of CAG (Cheli et al., 1995; Kapadia, 2003). Given the young age of the study population, the low incidence of pernicious anaemia and the frequency and severity of *H. pylori*-related gastritis in Peru, it is extremely unlikely that autoimmunity or other undescribed aetiologies were responsible for the observed pathological changes. Therefore, although it is not possible to conclude definitively that *H. pylori* infection resulted in the gastric pathology described here, since all the participants in this study were *H. pylori* positive, this is by far the most likely explanation.

The loss of deep glands in the gastric body of cholera patients suggests that these patients have a lowered capacity for producing gastric acid than controls and were therefore more susceptible to develop severe dehydrating cholera diarrhoea. We also observed that the median gastric pH and the prevalence of hypochlorhydria at endoscopy (3— 4 weeks following the acute disease) in the cholera group were higher than in the control group. These findings suggest that there are a proportion of cholera patients who have an increased susceptibility to bacterial gastrointestinal infection owing to loss of the gastric acid barrier. Presumably these individuals would also be more susceptible to other acid labile bacterial enteropathogens.

The control group consisted of patients with upper gastrointestinal symptoms rather than non-symptomatic individuals without cholera and this may limit interpretation of the results. However, what is clear is that the chronic gastric mucosal damage in convalescent cholera patients is greatest in the body of the stomach, whereas in low socio-economic controls with upper gastrointestinal symptoms it is predominantly antral in location. All previous studies investigating the gastric pathology associated with *H. pylori* both in Peru and other countries have shown that the histopathological changes associated with *H. pylori* are more severe in the gastric antrum than in the body of the stomach. Reversal of this pattern in the cholera patients studied strongly suggests that the hypochlorhydria, which occurs as a result of increased CAG in the gastric body, appears to predispose subjects to developing severely dehydrating diarrhoeal disease due to *V. cholerae*.

We doubt that any bias could explain these differences. No patient had either a gastric or a duodenal ulcer. All patients were of mixed native American and European ancestry and came from poor socio-economic strata. The control group in this study came from Comas, a poverty

zone of Lima severely affected by the cholera epidemic. Furthermore, symptomatic cholera is rare in upper or middle class individuals but common in the poor (Ackers et al., 1998). Previous studies have shown that the prevalence of *H. pylori* infection and severe gastric mucosa inflammation seen in the study groups, both of which are poor, is close to twice as common as that found in middle and upper class Peruvians (The Gastrointestinal Physiology Working Group of the Cayetano Heredia and the Johns Hopkins University, 1992).

5. Conclusions

In conclusion, we report that in comparison with controls from the same socio-economic status, a subset of patients who had recovered from severely dehydrating diarrhoea due to cholera had hypochlorhydria associated with an increase in deep gland loss due to CAG and IM in the body of the stomach. Lesions such as CAG and IM are considered non-reversible. These body lesions presumably pre-dated the episode of cholera. Loss of the gastric barrier due to hypochlorhydria in individuals with gastric body lesions appears to increase their susceptibility to severely dehydrating cholera diarrhoea.

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Table 1

Histological findings by group

	Control (*N* = 40)		Cholera (*N* = 35)		*P*-value
	n	%	n	%	
CDG					
Antrum	33	82.5	22	62.9	0.070
Body	15	37.5	26	74.3	0.002
Moderate—severe CDG					
Antrum	14	35	9	25.7	0.456
Body	6	15	13	37.1	0.035
CAG					
Antrum	36	90	24	68.6	0.040
Body	5	12.5	16	45.7	0.002
Moderate—severe CAG					
Antrum	30	75	19	54.3	0.088
Body	2	5	11	31.4	0.004
IM					
Antrum	8	20	9	25.7	0.591
Body	1	2.5	13	37.1	<0.01
TDGL					
Antrum	36	90	26	74.3	0.124
Body	5	12.5	20	57.1	<0.01

CDG: chronic deep gastritis; CAG: chronic atrophic gastritis; IM: intestinal metaplasia; TDGL: total deep gland loss (i.e. IM + CAG).

Table 2

Number of patients with gastric antral or body dominant total deep gland loss (TDGL = chronic atrophic gastritis and/or intestinal metaplasia)

Dominant TDGL[a]	Control		Cholera	
	n	%	n	%
Antrum < body*	0	0	4	11.4
Antrum > body**	31	77.5	10	28.6
Antrum = body**	9	22.5	21	60
Total	40	100	35	100

[a]Whether the percent of TDGL was higher in: the body than in the gastric antrum; the antrum than in the gastric body; or was similar in the antrum and gastric body.

*P <0.05.

**P <0.01.