

Helicobacter pylori: Findings in a Native American Population

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INTRODUCTION:

Two decades after the association between *Helicobacter pylori* infection and peptic ulcer disease was shown in 1983 (1) it can still be regarded as one of the most important advances in gastroenterology. The introduction of the fiberoptic endoscope at around the same time (2--6) underscored the dramatic change of the state-of the art in the diagnosis and treatment of dyspepsia, peptic ulcer and other upper gastrointestinal pathologies. Most recently, the description of the *H. pylori* genome in 1997 (1.67 million base pairs coding for approximately 1500 proteins) has offered an important insight into this gram negative microaerophilic organism (7). Analysis of the genetic data confirmed epidemiological evidence (8) that *H. pylori* lives mostly in the human stomach with direct person to person transmission and little or none zoonotic transmission and that iron scavenging is crucial in the survival of *H. pylori* in the stomach mucosa. Given the variable clinical course of the *H. pylori* infection, which can be followed by gastritis, duodenal or gastric ulcers, gastric cancer or lymphoma, identification of and treatment for this pathogen are important issues for any clinician (4). Among the multiple diagnostic tests available for *H. pylori* detection in a symptomatic patient (9--14), esophagogastroduodenoscopy (EGD) has the distinction of being the only one that allows direct examination of the upper GI tract and is recommended for patients presenting associated anemia, gastrointestinal bleeding, weight loss, especially for patients older than 50 years (2).

Navajo Native Americans form a unique ethnic group among the approximately 500 tribes and 310 reservations recorded in the United States in the most recent census. Navajo Nation is the home for about 300,000 Navajo members, forming the largest Native American tribe, on the largest such reservation in US that covers 25,000 square miles in Arizona, New Mexico and Utah (15). The patients considered by us belong to a Native American community of about 15,000 spread over an area of 1,500 square miles in Northeast Arizona (16).

We have conducted a retrospective study involving patients that received care at the community hospital during a 38 month timeframe for symptoms suggesting upper gastrointestinal pathology and who were assessed for H. pylori infection by three methods: serologic testing, EGD with biopsy followed by a rapid urease test (RUT) and/or histological examination.

The study has been approved by the Navajo Nation Human Research Review Board (NNHRRB).

MATERIALS AND METHODS:

All patients were referred for EGD by a primary care physician and had the procedure performed at the community hospital by a single physician (S.H.A.); all upper endoscopies successfully performed at this location by this operator were included in this study. To ensure that all endoscopies were considered, the Operating Room Procedure Log Book was searched for all EGD's performed by this operator. After the patients were tabulated using MS Excel, an electronic search was performed using Meditech (which incorporates all patient files in electronic format) for patients who had EGD's performed by the same operator in that timeframe; no other patients were found. Patient records both in paper form (medical charts) and electronic format were then searched for all the information pertinent to the patients' care.

All patients had a signed informed consent form in the chart for EGD with biopsy and the physician doing the endoscopy evaluated them with a history and physical examination. Special attention during history taking was paid to the abdominal symptoms, use of NSAIDS, H2 blockers, proton pump inhibitors, antacids, and water supply. If not already done blood was drawn to detect H. pylori antibody.

Patients were NPO for at least 8 hrs prior to the procedure and standard preparations were given to each. Conscious sedation was attained with 1-3 mg of Midazolam and the oropharynx was anesthetized with Lidocaine spray.

During endoscopy biopsies were taken from the gastric mucosa in 118 EGD's; some were tested bedside and the rest were sent for histological examination. Suspicious lesions had multiple biopsies. Biopsy specimen were tested with a Rapid Urease Test (Pyloritek, BARD, Billerica, MA) and the results were checked at one hour. Histological exam of specimens was performed by sending the harvested tissue to the Pathology Lab of Tricore from Albuquerque, NM. The specimen was stained with Giemsa's stain to detect H. pylori and the result was a qualitative determination (positive vs. negative) by a certified Pathologist. Although the histological grading proposed by the Sydney system offers a more elaborate evaluation of the H pylori infection, a recent study that compared this grading system with the number of H pylori genomes obtained by PCR (14) concluded that a positive/negative histopathology result is as useful as the 4 grades of infection proposed by the Sydney system. The serology testing was also expressed as a qualitative result (positive vs. negative) after a quantitative determination of plasma antibodies to H. pylori. If any of the above three tests came positive, the patient was considered positive for H. pylori.

The resulting data was then analyzed using MS Excel for descriptive statistics and SPSS for inferential statistics.

RESULTS:

A total of 154 consecutive EGD's were successfully performed during a 38-month timeframe (08/2000 - 10/2003) by a single physician (SHA). The total number of patients examined was 145.

Demographics: 92 patients were female (63.44%), and 53 pts. (36.55%) male; age range between 15 and 95 yrs; average age for the females: 50.14 +/- 17.62 yrs and for males: 54.4 +/- 14.96 yrs.

Table 1: Patients' history and physical exam summarizes the number and frequency of symptoms in patients undergoing the procedure. Epigastric pain is the most common complaint, followed by heartburn. More than half of patients reported using NSAIDS regularly. Patients' intake of medication relevant to the diagnosis was recorded based on the patient history taken by the physician prior to the endoscopy and previous medical chart data and it was considered positive if the patient was on that medication daily for at least 2 weeks and within 6 months prior to the endoscopy.

Testing for H. pylori by using one or more of the three tests described above was performed in 131 of the 145 pts (90.34%). Of these, 95 (72.51%) were positive, with the rest of 36 (29.92%) testing negative for H. pylori. Three more patients had positive serology results for H. pylori and another four had negative serologic tests but these blood tests were performed more than 6 months after the EGD's (for the positive ones) or more than 6 months prior to the EGD (the negative results) and were excluded from the analysis. We have found that 67 of 90 serology tests were positive for H pylori (74.44%); also 23 of 45 RUT's (51.11%) and 42 of 109 histology tests

(38.53%). Of the 30 pts who had all three tests: IgG, RUT and histology; 13 were concordant (43.33%).

EGD notes: of the 154 endoscopies, in 137 (88.96%) there were abnormal (positive) findings as documented in the procedure note by the physician. There was one histologically confirmed Barrett's esophagus, one case with esophageal acanthosis, one patient had an ulcerated polypoid mass in esophagus, 4 pts had esophageal varices of which one was bleeding, and there was one esophageal pseudodiverticulum (lower esophagus). The gastric pathology included two pts with fundic polyps of which was one ulcerated but benign, 4 pts with gastric mucosal atrophy and one pt with hemochromatosis. One patient was diagnosed with in situ gastric neoplasm on histopathology; another had previously diagnosed gastric adenocarcinoma for which he had partial resection more than 10 years prior to EGD. *Table 2:* Findings on EGD summarizes the endoscopic findings.

Histology: of the 109 pathology examinations, a total of 83 (76.14%) showed active inflammation of the gastric mucosa (corpus or antrum): 26 mild, 35 moderate and 22 severe. Additionally, 16 reports (14.67%) diagnosed chronic, inactive inflammation. Intestinal metaplasia was detected in 13 of the 109 histologic examinations performed (11.92%); 9 of the 13 patients (69.23%) with intestinal metaplasia tested positive for presence of *H. pylori* using one or more of the three tests used above. Another 3 pts had lymphoid hyperplasia without intestinal metaplasia on the histology exam.

Laboratory findings: the mean hematocrit (Hct) for females was 38.25 +/- 6.98 %; for males: 41.46 +/- 6.81 %; both in normal range. Anemia, defined as Hct below 37% in females and below 40% in males was found in 44/145 patients (30.34%). Blood groups of the patients were also documented. *Table 3:* Patients with anemia:

In the same patient subset there was not a statistically significant higher number of H pylori positive patients (23/44 or 52.27%) than H pylori negative patients (12/44 or 27.27%); $\chi^2 = 3.45$; $p = 0.063$.

An interesting fact was that most patients tested (as part of the chemistry profile ordered in some patients before the EGD for various reasons) had elevated globulins and low albumins, with a subsequent low albumin/globulin ratio – *Table 4* -. 120 patients were tested for plasma albumins and globulins and the average was 3.52 +/- 0.46 for albumins, 95% CI = 0.003; min 2.0, max 4.40. For globulins: average 3.99 +/- 0.47, 95% CI = 0.003; min 2.90, max 5.70. Of the 120 patients tested for albumin, 77 (64.2%) were below normal (<3.8 g/dL). For globulins, 111 pts (92.50%) were above the normal limit (>3.3 g/dL); 104 were at 3.5 g/dL or above (86.6%). Albumin / globulin ratio was < 1 in 90 pts and only 8 pts (6.7%) were in normal range (>1.1)

DISCUSSION:

H. pylori infection has been rarely studied in ethnic groups in North America. Parkinson et al (17) showed that H. pylori infection is associated with low ferritin levels in an Alaska Native population. Bernstein et al (18) published results from testing a Canadian Indian population and found that the H pylori seroprevalence was 95%. In another ethnic study, Fennerty et al (19) observed that H. pylori was significantly associated with intestinal metaplasia in Hispanics in Southwestern United States; while Perez-Perez showed that more than 80% of Whiteriver Apache mothers were H pylori seropositive and 20% of the childhood infections were transient (20).

With the prevalence of H pylori infection being strongly correlated with the socioeconomic environment (3) and the local conditions being compared to those of a third-world country (15),

H pylori is expected to be found in 80% or more of the community members. The 72% rate found in this study may reflect the fact that some patients undergoing endoscopy have had treatment with histamine receptor blockers and proton pump inhibitors and in some cases antibiotics unrelated to dyspepsia in the weeks and months prior to endoscopy.

Also regarding epidemiology, we have found no correlation between the presence of H pylori and the patient having current running water at home (from the patients' history, where there was a separate question on the quality of water supply). One possibility may be the contamination of some water distribution systems themselves, which may harbor H pylori in the biofilms covering the pipes, especially those made of cast iron, as it was shown in Scotland and Peru (21,22). Another study has shown that H pylori is more resistant than E Coli to commonly used water disinfectants (chlorine, ozone); only monochloramine was found to be efficient against H pylori (23).

The lack of association between H pylori positivity and blood group O or H pylori and anemia is in concordance with previous studies (24, 25), although a recent study in Brazil found an association between blood group O and H pylori positivity (26). We have found that patients with anemia are more likely to have blood group O but overall the mean hematocrit of patients with blood group O (34.17%) stopped short of being statistically different than that of patients of blood group A (mean Hct = 40.10%), $p = 0.063$. Considering that H pylori was shown to be associated with low levels of ferritin in various populations (27, 28) and with iron deficiency anemia refractory to iron therapy (29), it may be of interest to explore the association between patients with both anemia and blood group O and active H pylori infection (as given by histology, RUT or urea breath test) in an epidemiological study of adequate power, for it is

possible that virulence factors harbored by H pylori may predispose patients with blood group O to anemia.

The World Health Organization and International Agency for Research on Cancer officially confirmed the role of H. pylori infection in gastric cancers in 1994 and classified H. pylori as a definite carcinogen for its association with gastric adenocarcinoma and mucosa associated lymphoid tissue lymphoma of the stomach (MALT lymphoma) (30). Recent studies showed that H pylori was present in 98% by immunohistology in specimens taken from gastric cancers (31); gastric cancer develops only in patients infected with H. pylori but not in uninfected person (30); gastric cancer did not develop in any of the patients who received eradication therapy early in follow up (30) and eradication of H. pylori alone induces regression of gastric MALT lymphoma in 70 to 80 percent of cases (32,33).

For the patients included in our study, about 12 % were found to have intestinal metaplasia and 1 patient was diagnosed with in situ adenocarcinoma. These findings re-emphasize that endoscopy with histology cannot be replaced by other tests (serology, immunoblotting, urea breath test, rapid urease test) in detecting the most serious pathology related to H pylori: neoplastic and pre-neoplastic lesions, which are found most frequently in patients older than 50.

Finally, the finding of elevated globulins and low albumins in a majority of patients with upper GI symptoms (who subsequently had endoscopy) is probably not specific to this pathology, but rather a characteristic of the whole community and a reflection of poor nutritional status and inadequate hygiene conditions. Further studies will be undertaken to try to define the extent and direction of this problem.

Conclusion:

In the United States, there has been a decline in *H. pylori* infections as improvements in hygiene and economic conditions have interfered with the transmission cycle of the organism (4). But as the data from the literature and this study shows, in certain ethnic groups with high poverty rate, *Helicobacter pylori* infection is a pervasive problem that needs to be considered in a variety of gastrointestinal, hematological and oncological pathologies. From a practical standpoint, *Helicobacter pylori* infection should be considered by the primary care provider practicing in an underserved area whenever symptoms of dyspepsia, anemia refractory to iron therapy or weight loss in a patient over 50 are present.