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Original Article

Insights into the Epidemiology and Determinants of Helicobacter Pylori Negative Gastritis: A Retrospective Study

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ABSTRACT

Introduction: The prevalence of Helicobacter pylori (HP)-negative gastritis is rising in the United States, yet its origins and risk factors remain largely unexplored. This study aims to assess the prevalence of HP-negative gastritis and explore the demographic, clinical, and risk factor profiles that differentiate HP-negative from HP-positive subjects with histological evidence of gastritis.
Methods: We conducted a retrospective analysis of 241 patients who underwent Esophagogastroduodenoscopy (EGD) for upper gastrointestinal symptoms at a tertiary care center between July 2020 and July 2021. Symptoms prompting referral included dysphagia, abdominal pain, nausea, and others. Gastric biopsies were collected from the antrum and body, and clinical, demographic, and laboratory data were analyzed to compare HP-negative and HP-positive gastritis cases.
Results: Of the patients biopsied, 38.2% (n=92) showed histological evidence of gastritis, with 78% of these being HP-negative and 22% HP-positive. HP-negative cases were predominantly chronic chemical gastritis (61.5%), while all HP-positive cases were active chronic gastritis. Significant ethnic disparities were noted; 61.5% of HP-negative patients were Caucasian, and 72.7% of HP-positive patients were African American. Medical comorbidities, particularly gastroesophageal reflux disease (GERD), were more associated with HP-negative gastritis. The antrum was more frequently affected in HP-negative cases compared to HP-positive cases.
Conclusion: HP-negative gastritis is significantly linked with Caucasian ethnicity and existing medical comorbidities but shows no strong associations with the analyzed lifestyle or medication factors. These findings highlight the need for further large-scale prospective studies to better understand the etiology, risk factors, and clinical implications of HP-negative gastritis.

1. Introduction

1. Introduction: Gastritis is an inflammatory condition of the stomach lining with diverse clinical presentations. Histologically, acute gastritis is identified by the presence of neutrophils whereas chronic gastritis is identified by the presence of lymphocytes and plasma cells. No universally accepted classification of gastritis exists. The Sydney system classifies gastritis based on etiology, topographical distribution of inflammation, and morphological features observed on histologic examination [1]. Helicobacter pylori (H. pylori) has long been identified as the leading cause of gastritis and peptic ulcer disease[2]. The Kyoto classification uses a scoring system based on the endoscopic findings to assess the presence or absence of H. pylori infection and the risk of gastric cancer [3]. Recent studies suggest a decline in the incidence of gastritis which can be attributed to the decreasing prevalence of H. pylori in much of the developed world [4, 5, 6]. In this evolving epidemiological landscape, a unique entity named Helicobacter pylori-negative (HP-negative) gastritis has come to light [7]. This entity was previously assumed to be merely cases of missed H. pylori infection. It has been argued that previous use of PPIs [8, 9], and antibiotics[10] may contribute to the eradication or migration of H. pylori from the biopsied antrum where they normally colonize, to the corpus, while gastric inflammation persists. Sampling errors have also been implicated in false negative errors in identifying H. pylori[11]. Studies using tests with higher sensitivity have been successful in identifying H. pylori signals in a small proportion of previously negative samples but a significant portion of these HP-negative cases remain unexplained [12]. The association between H. pylori infection and non-cardia gastric cancer is well known [13, 12]. It is unclear as to whether HP-negative gastritis confers a similar increased risk for histologic progression to intestinal metaplasia and

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Table 1: Prevalence and histological classification of gastritis cases

	Gastritis Cases (n=92)	HP-Negative Gastritis (n=71)	HP-Positive Gastritis (n=20)
Prevalence	38.2%	78%	22%
Histological Types	–	Chronic Chemical: 61.5%	Active Chronic: 100%
	–	Chronic Non-active: 33.2%	–
	–	Active Chronic: 5.1%	–

HP: Helicobacter pylori; n: number of patients

carcinoma. Furthermore, the etiology and clinical presentations of HP-negative gastritis remain poorly defined. This study aimed to assess the prevalence of HP-negative gastritis and characterize its demographic, clinical, and risk factor profile.

2. Methods

A retrospective study was conducted on 241 consecutive patients referred for Esophagogastroduodenoscopy (EGD) at a single tertiary care center from July 2020 to July 2021. Patients were referred for EGD due to various upper gastrointestinal symptoms, including dysphagia, abdominal pain, nausea, vomiting, weight loss, iron deficiency anemia, bloating, belching, and Barrett's esophagus surveillance. Biopsy samples were taken from the gastric antrum and body during the EGD procedure. The study focused on evaluating the prevalence of Helicobacter pylori (HP)-negative gastritis and characterizing demographic, clinical, and risk factor profiles distinguishing HP-negative from H. pylori positive subjects with histologic gastritis.

Clinical, demographic, and laboratory data were collected and compared between HP-negative and HP-positive gastritis cases. The presence of medical co-morbidities, including specific conditions such as gastroesophageal reflux disease (GERD), was analyzed. Ethnicity, anatomic location of gastritis, and other relevant factors were also assessed.

3. Results

3.1. Prevalence:

Among all patients (n=241), 38.2% (n=92) exhibited gastritis on biopsy. HP-negative gastritis accounted for 78% (n=71) of cases, while HP-positive gastritis accounted for 22% (n=20) **(Table 1)**.

3.2. Histological Characteristics:

In the HP-negative group, 61.5% had chronic chemical gastritis, 33.2% had chronic non-active gastritis, and 5.1% had active chronic gastritis. In the HP-positive group, all patients exhibited active chronic gastritis **(Table 1)**.

3.3. Anatomic Distribution

HP-negative gastritis predominantly affected antral biopsies (76.9%), differing significantly from HP-positive cases (antrum only: 36%, body: 36%, antrum and body: 27%, p=0.0162) **(Table 2)**).

Table 2: Anatomic distribution and ethnic variation

	Anatomic Distribution	Ethnic Variation
HP-Negative Group	Antrum: 76.9% Body: 10.3% Antrum & Body: 12.8%	Caucasian: 61.5% African American: 20.5% Asian: 5.1%
HP-Positive Group	Antrum: 36% Body: 36% Antrum & Body: 27%	Middle Eastern: 2.6% Other: 10.3%
Ethnic Variation	p=0.0162*	p=0.0004* & p=0.0013*

HP: Helicobacter pylori; * Significant

Table 3: Association between medical co-morbidities and HP

Medical Co-morbidities	HP-Negative Gastritis (%)	HP-Positive Gastritis (%)
Medical Co-morbidities	82.1%	18.2%
GERD	66.7%	9.1%
Other Conditions	NA	NA
P-value	0.0002*	0.0012*

HP: Helicobacter pylori; GERD: Gastroesophageal Reflux Disease; NA: Not Applicable; *: Significant.

3.4. Ethnic Variation

Significant ethnic variation was observed, with HP-negative patients more likely to be Caucasian (61.5% vs. 0%) and HP-positive patients more likely to be African American (20.5% vs. 72.7%, p=0.0004 and p=0.0013, respectively) **(Table 2)**.

3.5. Association with Medical Co-morbidities

HP-negative gastritis was notably associated with medical co-morbidities compared to HP-positive gastritis (82.1% vs. 18.2%, p=0.0002). GERD was the most common co-morbidity associated with HP-negative gastritis (66.7% vs. 9.1%, p=0.0012) **(Table 3)**.

No significant differences were observed in predominant symptoms, primary referral indication, age, gender, prior HP infection, tobacco use, alcohol use, proton pump inhibitor (PPI) use, non-steroidal anti-inflammatory drug (NSAID) use, or antibiotic use.

4. Discussion

Since the discovery and treatment of H. pylori, the prevalence of H. Pylori infection has been declining whereas HP-negative gastritis is becoming an increasingly recognized distinct entity. In one study by Nordenstedt et al., the prevalence of HP-negative gastritis was 21% in the study population, with a slight increase in prevalence in black males[13]. In another retrospective study, HP-negative chronic active gastritis was diagnosed in 12.7% of studied gastric biopsies with chronic active gastritis, and in 1.5% of the overall study population. There with a reported decline in prevalence from 2008 to 2014, and a slightly higher occurrence in females versus males [7]. Furthermore, Shiota et al. found that HP-negative gastritis was present in approximately 18% of patients with gastritis and 9.9% in all study subjects with a higher prevalence amongst non-Hispanic whites [14]. In our study population, HP-negative gastritis was more prevalent among patients of Caucasian ethnicity whereas H. pylori-positive gastritis demonstrated increased prevalence amongst African American ethnicity.

Endoscopically, Chatrangsun et al. described gross findings of HP-negative gastritis mostly as a regular arrangement of collecting venules as well as fundic gland polyps, using white light imaging endoscopy, compared to diffuse redness and antral nodularity seen in patients with H. pylori positive gastritis via the same endoscopic modality [15]. Furthermore, with HP-negative gastritis, mucosal involvement was found to be more likely in isolated portions of the stomach, either body or antrum and, to a lesser extent, in both body and antrum. By comparison, 70% of patients with H. pylori positive gastritis had both body and antral distribution [13]. In patients with HP-negative gastritis, our findings demonstrated an overwhelming predominance of isolated antral involvement (76.9%). In patients with H. pylori positive gastritis, we did not find a predominance of concurrent antral and corpus involvement, nor did we find a predilection for isolated sites in this group.

Histologically, in those with HP-negative gastritis, the majority of cases demonstrated chronic chemical gastritis and chronic inactive gastritis (94.7%) whereas all cases of H. pylori gastritis demonstrated chronic active gastritis. These findings are similar to other published studies that demonstrate HP-negative gastritis to be chronic on histology [13, 14]. Importantly, histologic examination alone is insufficient to define HP-negative gastritis [14].

Data are lacking regarding common risk factors for HP-negative gastritis. Factors including smoking history, ETOH use, NSAID use, and recent PPI or H2 blocker use have been the focus of multiple studies. However, to the best of our knowledge, no studies have demonstrated a clinically significant correlation between these risk factors and HP-negative gastritis. In our study, medical co-morbidities were notably associated with HP-negative gastritis compared to H. pylori positive gastritis (82.1% vs. 18.2%, p=0.0002), with GERD being the most prevalent co-morbidity (66.7% vs. 9.1%, p=0.0012). However, this may be confounded by the fact that H. pylori infection exerts a protective effect against reflux [16].

HP-negative gastritis may be attributed to multiple causes. Some authors attribute HP-negative gastritis to an undetectable H. pylori organism [17], recently treated H. pylori infection, false negative H. pylori test, infectious gastritis due to organisms other than H. pylori such as cytomegalovirus, herpes simplex virus and Epstein-Barr virus or simply due to other non-infectious causes such as chemical gastritis, gastritis associated with inflammatory bowel disease or autoimmune gastritis [18]. The discrepancies in classifications and nomenclature in the literature can lead to confusion in identifying and studying HP-negative gastritis as a unique clinical entity. It is imperative to acknowledge that HP-negative gastritis may constitute a broad classification encompassing various sub-diagnoses, including idiopathic chronic HP-negative gastritis (in other words, “HP-negative gastritis” proper). El-Zimaty et al. detail a four-step diagnostic approach to cases of gastritis in which H. pylori is not identified[18]. Although this categorization was not adopted in our study, we believe this distinction should be made in future research.

This study has several limitations, including generalizability to the general population, given that all biopsy samples were obtained from a cohort in the United States. H. pylori false negative results are possible in the presence of PPI use, low bacterial load, and variations in gastric biopsy sampling methods.

5. Conclusions

In this retrospective study, the prevalence of HP-negative gastritis was 78% of those identified to have gastritis. HP-negative gastritis was significantly associated with medical co-morbidity and Caucasian ethnicity, with a preference for the antrum anatomically when compared with the H. pylori positive group. No statistically significant associations were identified with referral symptoms, PPI use, or other risk factors. Large-scale prospective studies are warranted to further elucidate the etiology, risk factors, pathogenesis, and clinical significance of this increasingly common entity.

Conflicts of Interest

None

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Institutional Review Board (IRB)

This study was conducted with approval from the Institutional Review Board of the Faculty of Medicine, Cairo University, Cairo, Egypt. The approval was granted on September 15, 2021, with the IRB Approval Number: 34-5019824.

Large-Language Model

None

Authors’ Contribution

All authors have contributed equally to the conception, drafting, review, and final approval of this manuscript. Each author has read and agreed to the final version for publication.

Data Availability

Data from this study are not publicly available due to privacy concerns but can be obtained from the corresponding author upon request.

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