

Lymphoid follicles in children with *Helicobacter pylori*-negative gastritis

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Purpose: The prevalence of *Helicobacter pylori* gastritis has been declining, whereas *H. pylori*-negative gastritis has become more common. We evaluated chronic gastritis in children with regard to *H. pylori* status and celiac disease (CD).

Patients and methods: Demographic, clinical, endoscopic, and histologic features of children who underwent elective esophagogastroduodenoscopy were reviewed retrospectively. Gastric biopsies from the antrum and corpus of the stomach were graded using the Updated Sydney System. *H. pylori* presence was defined by hematoxylin and eosin, Giemsa, or immunohistochemical staining and urease testing.

Results: A total of 184 children (61.9% female) met the study criteria with a mean age of 10 years. A total of 122 (66.3%) patients had chronic gastritis; 74 (60.7%) were *H. pylori*-negative. Children with *H. pylori*-negative gastritis were younger ($p=0.003$), were less likely to present with abdominal pain ($p=0.02$), and were mostly of non-Arabic origin ($p=0.011$). Nodular gastritis was found to be less prevalent in *H. pylori*-negative gastritis (6.8%) compared with *H. pylori*-positive gastritis (35.4%, $p<0.001$). The grade of mononuclear infiltrates and neutrophil density was more severe in the *H. pylori*-positive group ($p<0.001$). Pan-gastritis and lymphoid follicles were associated most commonly with *H. pylori*. Although less typical, lymphoid follicles were demonstrated in 51.3% of *H. pylori*-negative patients. The presence or absence of CD was not associated with histologic findings in *H. pylori*-negative gastritis.

Conclusion: Our findings suggest that lymphoid follicles are a feature of *H. pylori*-negative gastritis in children independent of their CD status.

Keywords: child, gastritis, *Helicobacter pylori*, lymphoid follicles

Introduction

The presence of *Helicobacter pylori* entails a 10%–15% lifetime risk of complications. Early acquisition of *H. pylori* can lead to accelerated development of preneoplastic gastric lesions and to an increased risk of gastric carcinomas.¹⁻⁴

There are very little data regarding the risk factors as well as the clinical and histologic characteristics of non-*H. pylori*-induced chronic gastritis and intestinal metaplasia (IM) in the pediatric literature, as opposed to *H. pylori*-positive (Hp+) gastritis. *H. pylori*-negative (Hp-) chronic gastritis has multiple etiologies: non-*H. pylori* gastric microorganisms; autoimmune gastritis; allergic and eosinophilic gastritis; lymphocytic gastritis due to other diseases, such as Crohn's disease. Gastritis because of external causes, such as drugs and alcohol, does not have roles in pediatric populations.⁵

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In a prospective study, Nordenstedt et al reported gastritis in 200 (40.7%) adults, of whom 41 (20.5%) had Hp– gastritis and 73.2% had chronic gastritis.⁶ The prevalence of Hp– gastritis in children living in North America is 46%–63%.⁷ Recently, Kara et al reviewed the histology of cells obtained from upper-endoscopy procedures in children. From 358 procedures, 144 (40%) children had Hp– gastritis.⁸ Biopsies from the antrum of the stomach from 82 children with chronic gastritis (36 Hp+, 46 Hp–) living in Mexico revealed atrophy and follicular disease more frequently in Hp+ biopsies, whereas IM showed no significant correlation with *H. pylori* status.⁹ Elitsur et al reported a higher prevalence of Hp– gastritis in children (~50%) compared with adults (~20%).⁷

Here, we attempted to evaluate the prevalence, risk factors, and clinical correlations of chronic gastritis and IM in childhood in a large cohort. We also tried to determine the relationship between *H. pylori* infection and celiac disease (CD) to pathologic abnormalities.

Patients and methods

Ethical approval of the study protocol

The study protocol was approved by the ethics committee of the Assaf Harofeh Medical Center (Tzrifin, Israel). Written informed consent was waived for this study because of the retrospective nature of the study. Patient data confidentiality was never broken because all data were anonymously gathered.

Study design and study cohort

We evaluated (retrospectively) clinical data and biopsy specimens from all patients aged <18 years who had gastric biopsies at our medical center over a 12-month period. Inclusion criteria were: children aged between 2 and 18 years who had ≥5 biopsies obtained routinely during endoscopy (two from the antrum and two from the corpus of the stomach) for histologic study. Another biopsy from the antrum was evaluated for *H. pylori* using a rapid urease test (Pronto Dry; Gastrex, Paris, France). Exclusion criteria were: patients with chronic inflammatory bowel disease, 4 weeks prior treatment with antibiotics, or 2 weeks with proton pump inhibitors.

Esophagogastroduodenoscopy (EGD)

All endoscopies had been carried out by very experienced and highly qualified endoscopists using a FG-2490K or EG-29i10 video gastroscope (Pentax, Tokyo, Japan). Endoscopy was done under sedation. The endoscopic aspect of nodular gastritis was based on the military nodular appearance of the mucosa.¹⁰

Histology

Four biopsy specimens (two from the antrum and two from the corpus of the stomach) were fixed in 4% neutral formalin, embedded in paraffin, and stained with hematoxylin and eosin (H&E), Giemsa, and alcian blue at pH 2.5. The biopsies from these patients were reviewed and analyzed for gastritis, IM, and *H. pylori*. In the absence of *H. pylori* with chronic or chronic active gastritis upon H&E staining, immunohistochemical staining for *H. pylori* using polyclonal antibodies (DAKO, Glostrup, Denmark) was undertaken.

Definitions

“Chronic inflammation” was defined as >5 mononuclear cells per 100 epithelial nuclei in H&E-stained specimens.¹¹ The severity and activity of gastritis, the presence of *H. pylori*, *H. pylori* density, and IM were recorded using the criteria for visual analog scale set by the updated Sydney classification.¹¹ For statistical analyses, we condensed the gastritis scale into “chronic active” or “chronic inactive”, “antrum-predominant” or “corpus-predominant”, “Hp+ gastritis”, and “Hp– gastritis”. H&E-stained specimens were evaluated for epithelial damage, mucous depletion, and erosions; atrophy, intestinal, pseudopyloric, or pancreatic metaplasia; and lymphoid follicles. CD was diagnosed according to the latest criteria set by the European Society for Paediatric Gastroenterology Hepatology and Nutrition: positive serology and some evidence of villous atrophy.¹² Patients with potential CD (positive serology with Marsh 1/Marsh 2 lesions) were excluded. Gastritis was considered to be *H. pylori*– if no *H. pylori* organisms were seen in H&E and immunohistochemical staining and negative rapid urease test.

“Ethnicity” was defined as the country of origin of the child’s parents and grandparents. Participants were classified into Sepharadi (Asia/Africa/Middle East), Ashkenazi (Western Europe/America), formerly Soviet Union, Ethiopia, and Arabs.

Statistical analyses

Statistical analyses were carried out using SPSS v21 (IBM, Armonk, NY, USA). The Mann–Whitney *U*-test or Student’s *t*-test was used for analyses of ordinal or continuous variables. The χ^2 test was used to analyze categorical variables. The Fisher’s exact test was used if the conditions for using the χ^2 test were not met. $p < 0.05$ was considered significant.

Results

Two-hundred and sixty-one children underwent EGD from July 2014 to August 2015. Thirty patients who had undergone

urgent EGD (11 with inflammatory bowel disease and 5 with other gastrointestinal diseases) and 31 children with missing or incomplete biopsies were excluded. Thus, 184 patients remained for further evaluation. Biopsies with evident chronic gastritis were identified from 122 patients (66.3%). Histopathologic examination of the stomach was normal, without gastritis, in 62/184 (33.7%) patients. Only 48 (39.3%) of the 122 patients with chronic gastritis were associated with *H. pylori* infection, whereas the remaining 74 children had Hp– gastritis. According to the Marsh classification,¹² 16 (33.3%) of the 48 patients with Hp+ gastritis had evidence of CD compared with 41 children (55.5%) diagnosed with CD in the Hp– gastritis group ($p=0.016$) (Figure 1).

Demographic and clinical characteristics

Patient demographics and clinical characteristics at presentation are summarized in Table 1. There were more females in “gastritis” and “nongastritis” groups. Distribution of the mixed ethnic group was more common in the nongastritis group (33.3% vs 19.7%, $p=0.045$), whereas more children of Ethiopian origin were in the gastritis group (6.8% vs 0%, $p=0.038$). The only significant difference in clinical findings was a higher prevalence of iron-deficiency anemia ($p=0.013$) and short stature ($p=0.008$) among the gastritis group.

H. pylori infection was more common in children of Arab origin ($p=0.011$) and in older children (mean age of 11.6 ± 4.1 vs 9.1 ± 4.5 years compared with Hp– children). Abdominal

Table 1 Demographic and clinical characteristics of patients with and without gastritis

Characteristics	Without gastritis n=62, (%)	With gastritis n=122, (%)	p-value
Age, mean±SD	10±4.7	10.1±4.5	0.892
BMI, mean±SD	18.4±3.6	17.7±3.9	0.323
Female	35 (56.5)	79 (64.8)	0.273
Sefaradi	16 (26.7)	40 (34.2)	0.308
Ashkenazi	9 (15)	18 (15.4)	0.946
Mixed	20 (33.3)	23 (19.7)	0.045
Soviet Union	12 (20)	14 (12)	0.153
Arab	3 (5)	14 (12)	0.137
Ethiopian	0	8 (6.8)	0.038
Relatives with <i>H. pylori</i>	12 (19.7)		
Clinical characteristics			
Heartburn	1 (1.6)	6 (4.9)	0.268
IDA	5 (8.1)	28 (23)	0.013
Abdominal pain	42 (67.7)	68 (55.7)	0.116
FTT	6 (9.7)	10 (8.2)	0.736
Short stature	1 (1.6)	17 (13.9)	0.008
Vomiting	5 (8.1)	7 (5.7)	0.546
Diarrhea	0	7 (5.7)	0.054
PPI treatment	3 (4.8)	8 (6.6)	0.633

Abbreviations: BMI, body mass index; FTT, failure to thrive; IDA, iron deficiency anemia; PPI, proton pump inhibitor; SD, standard deviation.

pain was more prevalent among patients with Hp+ gastritis ($p=0.020$) with no differences in other symptoms.

Demographic and clinical characteristics did not differ with regard to the presence or absence of *H. pylori* among patients with CD. No significant difference was noted in the

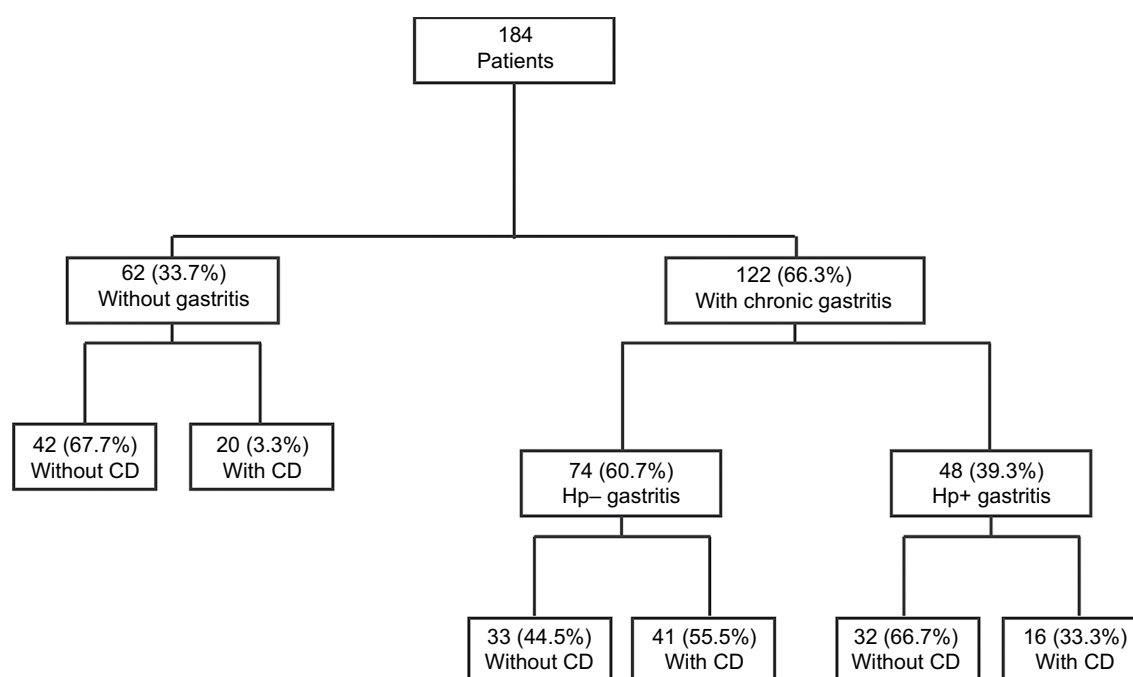


Figure 1 Study patients with gastritis according to their *H. pylori* and CD status.

Abbreviations: CD, celiac disease; Hp+, *H. pylori*-positive, Hp–, *H. pylori*-negative.

ethnic background symptoms or in the use of proton pump inhibitors. CD patients without *H. pylori* were younger than CD patients with *H. pylori* (6.7 ± 3.3 vs 9.6 ± 4 , $p=0.006$).

Gastritis and *H. pylori*

Nodular gastritis occurred in 35.4% of patients with Hp+ gastritis and in 6.8% of children with Hp- chronic gastritis ($p<0.001$). The presence of *H. pylori* was correlated positively with endoscopic nodular gastritis in patients with or without CD. None of the children with CD and Hp- gastritis had nodular gastritis upon endoscopy. Hp+ gastritis involved the entire stomach in 95.8% of children, whereas 50% of children without *H. pylori* had pan-gastritis. Eighty-three percent of patients with gastritis on account of *H. pylori* had chronic active gastritis, as opposed to 9.5% of patients without *H. pylori* ($p<0.001$) with a specificity of 90.5%, a sensitivity of 83.3%, a negative predictive value of 89.3% and a positive predictive value of 85.1%. Histopathologic-graded variables are presented in Figure 2. Patients with *H. pylori* had more severe gastritis, and this was the trend in the antrum and corpus.

The histopathologic nongraded variables evaluated in our patients, and their relationship with *H. pylori*, are presented in Figure 3. Atrophic gastritis, intestinal, pseudopyloric, or

pancreatic metaplasia, or hyperplasia of endocrine cells was not detected in any patient. Lymphoid follicles in the antrum and corpus were correlated positively with *H. pylori* regardless of the presence of CD. However, we found a high prevalence of lymphoid follicles in Hp- gastritis in CD (46.3%) or non-CD (57.5%) patients. Epithelial damage, mucous depletion, and erosions were much more common in Hp+ patients (Figure 3). The typical histologic characteristics of Hp+ gastritis and Hp- gastritis are demonstrated in Figure 4.

Hp- gastritis

Comparison between children with Hp- gastritis with no CD and children with Hp- gastritis with CD revealed several differences. As expected, patients with CD-associated Hp- gastritis had a lower body mass index (15.8 ± 2.44 vs 19.5 ± 4.83 kg/m², $p<0.001$) and presented more frequently with short stature (19.5% vs 3%, $p=0.031$). However, abdominal pain was less common in this group (31.7% vs 66.7%, $p=0.003$). More children of Ethiopian origin and fewer of mixed ethnic origin were in the non-CD Hp- gastritis group (Table 2). Endoscopic features such as nodular gastritis were more prominent in the non-CD Hp- gastritis group ($p=0.010$), but the histopathologic characteristics of gastritis between these groups were not significantly different (Figure 4).

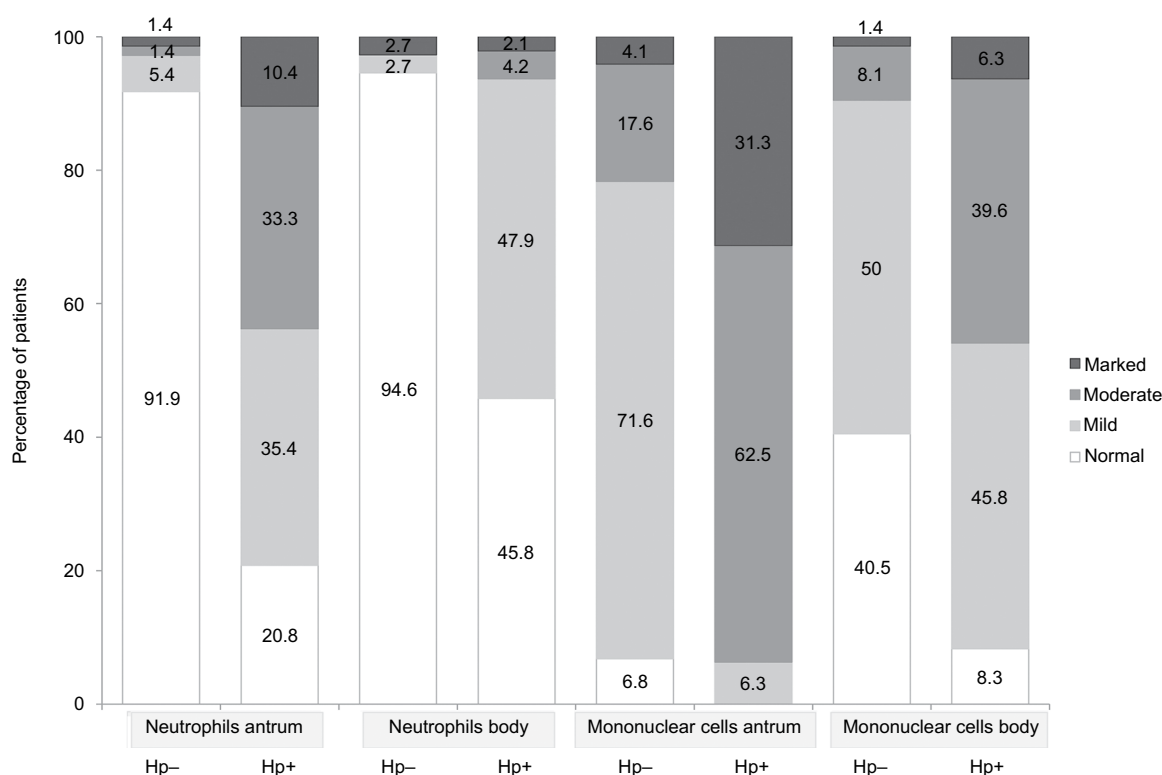


Figure 2 Histological characteristics of graded variables of patients according to their *H. pylori* status.

Abbreviations: Hp+, *H. pylori*-positive, Hp-, *H. pylori*-negative.

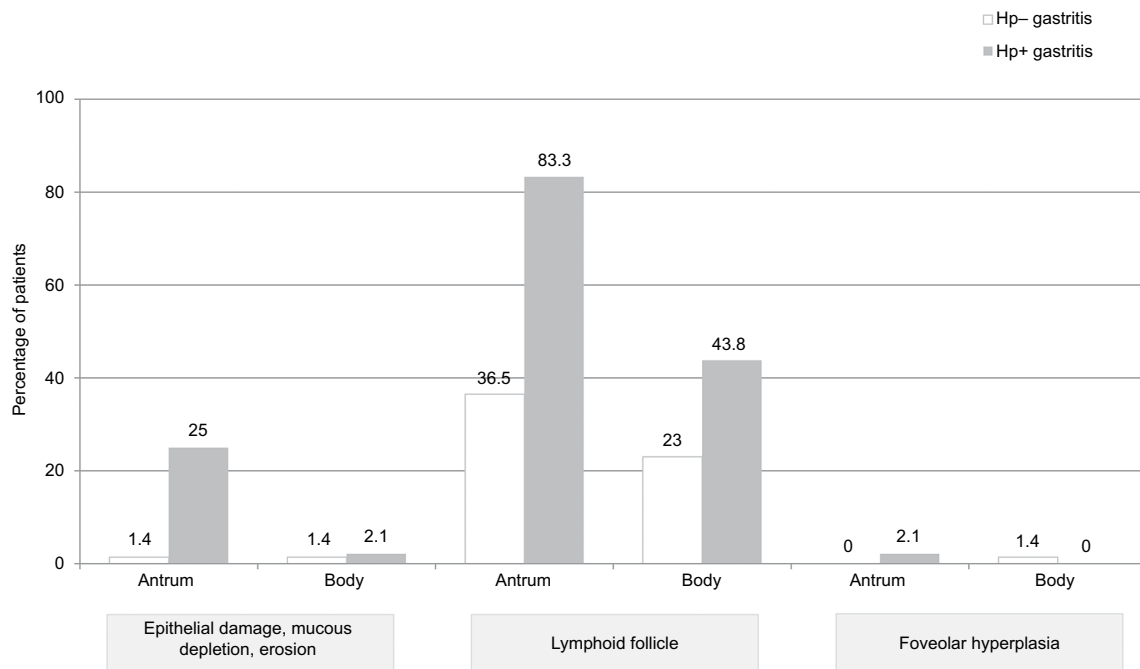


Figure 3 Histological characteristics of nongraded variables of patients according to their *H. pylori* status.
Abbreviations: Hp+, *H. pylori*-positive; Hp-, *H. pylori*-negative.

Table 2 Demographic and clinical characteristics of patients with nonceliac Hp- gastritis and patients with CD-associated Hp- gastritis

Characteristics	Nonceliac Hp- gastritis n=33, (%)	CD-associated Hp- gastritis n=41, (%)	P-value
Age, mean±SD	12.2±3.96	6.7±3.28	<0.001
BMI, mean±SD	19.5±4.83	15.8±2.44	<0.001
Female	18 (54.5)	27 (65.9)	0.322
Sefaradi	12 (40)	12 (30)	0.383
Ashkenazi	3 (10)	11 (27.5)	0.070
Mixed	3 (10)	14 (35)	0.016
Soviet Union	5 (16.7)	2 (5)	0.107
Arab	3 (10)	1 (2.5)	0.181
Ethiopian	4 (13.3)	0	0.017
Relatives with <i>H. pylori</i>	7 (21.2)	3 (7.3)	0.082
Clinical characteristics			
Heartburn	2 (6.1)	0	0.110
IDA	8 (24.2)	9 (22)	0.816
Abdominal pain	22 (66.7)	13 (31.7)	0.003
FTT	1 (3)	6 (14.6)	0.090
Short stature	1 (3)	8 (19.5)	0.031
Vomiting	4 (12.1)	2 (4.9)	0.257
Diarrhea	1 (3)	3 (7.3)	0.418
PPI treatment	5 (15.2)	0	0.010

Abbreviations: BMI, body mass index; CD, celiac disease; FTT, failure to thrive; Hp-, *H. pylori*-negative; IDA, iron deficiency anemia; PPI, proton pump inhibitor

Discussion

In our study, *H. pylori* was found in 26% of participants with gastritis who had undergone EGD. Our results correlate with recent data suggesting a prevalence of seropositivity

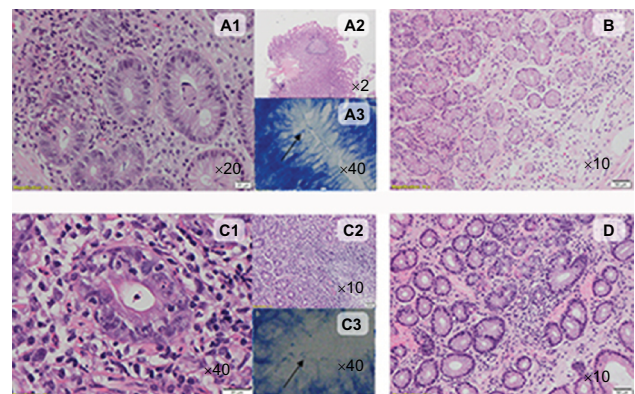


Figure 4 The typical histological characteristics of Hp+ gastritis and Hp- gastritis in celiac and nonceliac patients.

Notes: Typical Hp+ gastritis in nonceliac children with chronic active inflammation, H&E stain, and LPF (A1); lymphoid follicles, H&E, and LPF (A2); and organisms visible in Giemsa stain, and HPF (A3). (B) Hp- gastritis in nonceliac children with chronic inactive gastritis and no lymphoid follicles, H&E stain, and LPF. (C1–C3 and D) Similar pictures of typical Hp+ gastritis and Hp- gastritis, respectively, in children with celiac disease.

Abbreviations: H&E, hematoxylin and eosin; Hp+, *H. pylori* positive; Hp-, *H. pylori* negative; HPF, high-power field; LPF, low-power field.

of 30%–45.2% in children living in Israel.^{13,14} This is significantly higher than that reported in children in the USA (3%–7%).¹⁵ We also found a higher prevalence (60.7%) of gastritis without *H. pylori* than observed previously in children from Turkey (40%), Mexico (44%), and the USA (50%).^{7–9} Studies in adults have shown a much lower proportion of Hp- gastritis.^{6,7}

Though our study was retrospective, four biopsies (two from the antrum and two from the corpus) had been taken from each stomach and slides were evaluated by a lone expert pathologist, as recommended by Sydney guidelines.¹¹ Histologic comparison between the two types of gastritis revealed pan-gastritis, active gastritis, lymphoid follicles, mucous depletion, erosions, and surface epithelial damage to be significantly more common in the Hp+ group. There was no pathologic finding of IM in our patients, confirming studies in children with Hp+ gastritis that showed an absence of IM or low prevalence of IM in such cases.¹⁶

H. pylori infection promotes an immunologic response that leads to the development of lymphoid aggregates and lymphoid follicles with germinal centers.^{8,17} Genta et al stated that lymphoid follicles in a gastric biopsy specimen are associated with chronic active gastritis and provide a useful marker for *H. pylori* infection.¹⁸ Moreover, these follicles are thought to represent the pathophysiologic substrate for mucosa-associated lymphoid tissue-lymphomas.^{19,20} In our study, lymphoid follicles were associated most commonly with *H. pylori* infection, but lymphoid follicles were also present in 51.3% of patients with evidence of Hp– gastritis. Our results are in accordance with a study that also detected lymphoid follicles in almost half of cases with Hp– gastritis and idiopathic gastritis,²¹ but are not in accordance with two more recent studies which reported that lymphoid follicles are relatively rare (prevalence of 4.1% in Houston, USA²² or 14% in Tunis, Tunisia²³ in Hp– gastritis). Lymphoid follicles in gastric biopsies from children, while of potential pathophysiologic importance, are of uncertain clinical importance and raise important issues: 1) should we treat young patients with lymphoid aggregates differently; 2) should we carry out a different type of surveillance in these patients?

The increased prevalence of Hp– chronic gastritis may be related to several variables. It has been suggested that Hp– gastritis comprises mainly “missed” *H. pylori* infections.²⁴ However, recently Genta et al showed that Hp– gastritis may occur only in 1.1% of patients with chronic inactive gastritis, which is a distinct entity according to nosologic and epidemiologic criteria.²⁵ It has also been suggested that chronic gastritis can be caused by viruses such as the Epstein–Barr virus²⁶ or non-*H. pylori* strains. A substantial number of novel *Helicobacter* spp. have been described. A high incidence of gastric *H. pylori* infection has been described in China, and multiple case reports have detailed involvement of enterohepatic *Helicobacter* spp. (especially *Helicobacter cinaedi*)

in a wide range of diseases.²⁷ These strains are susceptible to sampling error with high rates of false-negative results which are probably due to the focal and decreased colonization of bacteria in the gastric mucosa.²⁸

Limitations

Our study had three main limitations. First, it was a retrospective cohort, so other infectious etiologies for gastritis (as well as autoimmune gastritis) were not excluded fully. Second, our sampling methods were inadequate to judge the area involved. Third, the high proportion of children with lymphoid follicles but no *H. pylori* may have reflected a selection bias because our center serves a tertiary center for CD diagnosis. Indeed, the high proportion of children who had CD (57 of 122 [46.7%] of gastritis cases) suggests that this may be the case. Nevertheless, CD was not associated with chronic gastritis, and there were no histopathologic differences between CD-associated Hp– gastritis and non-CD-associated Hp– gastritis. Moreover, the prevalence of CD was correlated inversely with *H. pylori*, which indicates that *H. pylori* may reduce CD risk, as reported previously.²⁹ Nevertheless, the predominant histologic features in patients with Hp+ gastritis and CD were related to *H. pylori*, as manifested by chronic active gastritis with polymorphonuclear neutrophils, lymphoid follicles, and curved, rod-shaped bacteria.

Conclusion

Taken together, our results suggest that Hp– gastritis is a common phenomenon in children, alone or with CD, with a high prevalence of lymphoid follicles in the antrum or corpus of the stomach. The clinical relevance and prognosis of this finding are not known: Is it self-limiting or is further investigation warranted? Additional long-term follow-up studies in young patients with lymphoid follicles should help elucidate the significance of this finding. Such studies may also facilitate the identification, surveillance, and optimal treatment strategy for these young patients with chronic gastritis.

Disclosure

The authors report no conflicts of interest in this work.

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