Helicobacter pylori infection in Turkish children with gastrointestinal symptoms and evaluation of serology

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Helicobacter pylori infection is a common etiopathogenetic factor in children with gastrointestinal symptoms in the developing world. Although serology offers an easy noninvasive method of diagnosis, its sensitivity and specificity are reported to be low among children. In this prospective study, we investigated the frequency and endoscopical and morphological findings of H. pylori infection in 180 Turkish children who underwent upper gastrointestinal endoscopy either for peptic symptoms or on a routine basis and in asymptomatic pediatric patients who underwent endoscopy for other reasons, and then evaluated the diagnostic accuracy of serology in our population. Overall H. pylori infection was diagnosed in 77 of the 180 patients (42.7%) by histology and urease test. The sensitivity of H. pylori specific IgG antibody assay by ELISA was determined to be 100%, while the specificity was 98%, the positive predictive value 97.4%, the negative predictive value 100%. Frequency of H. pylori infection is high in Turkish pediatric patients without gastrointestinal symptoms as well as in children with gastrointestinal complaints. H. pylori specific antibody assay is a noninvasive and sensitive method for the diagnosis of H. pylori infection in the Turkish pediatric population.

Key words: Helicobacter pylori, children, symptoms, endoscopical findings, diagnosis, serology.

Marshall and Warren[1] reported an association between the presence of Helicobacter pylori (H. pylori) in the gastric mucosa and antral gastritis in adults for the first time in 1983. This association was also noted in children[2]. H. pylori infection is considered to be one of the most common chronic infections in humans and usually persists during a lifetime if left untreated[2-3]. Although the infection commonly remains asymptomatic, chronic inflammation can predispose to the development of gastric or duodenal ulcers and even gastric cancer[4]. H. pylori infection can be detected in children with chronic abdominal pain, dyspepsia, malnutrition, growth retardation, and chronic diarrhea[5-8]. H. pylori associated with peptic ulcer disease is less frequently seen in children compared to adults. In the pediatric patients, the histological response to H. pylori infection is also different from that seen in adult patients. In infancy and early childhood, lymphocytic infiltration is more common in gastric mucosa, whereas in adults neutrophils are also frequently observed.

In the diagnosis of H. pylori infection, serology is one of the most well known, inexpensive, noninvasive and simple techniques. For that reason, ELISA is being widely used particularly in epidemiological studies. Especially in developing countries, it is preferable to another noninvasive assay, the breath test, since it is cheaper, readily available and more practically applicable in children.

In this study, our goal was to evaluate the reliability of serology by ELISA test in the diagnosis of H. pylori infection in our pediatric population, by comparing it with the rapid urease test and histological examination. Furthermore, we aimed to determine the frequency of the

H. pylori infection and the relation between the symptoms and both the endoscopical and histopathological findings in Turkish children.

Material and Methods

This study was carried out at the İstanbul Faculty of Medicine Pediatric Gastroenterology Department during a three-year period between May 1996 and June 1999. We investigated prospectively 180 consecutive children (108 boys and 72 girls; mean age 10.8±3.7 years, range 1-18 years) who underwent upper gastrointestinal endoscopy for symptoms related to upper gastrointestinal tract (139 patients) or for intestinal biopsy in growth retarded children (11 patients) or on a routine basis in patients with chronic renal failure before renal transplantation (30 patients). Upper gastrointestinal symptoms leading to endoscopic investigation in our study group were recurrent abdominal pain, vomiting, melena/hematemesis and dyspepsia. Symptoms such as nausea without vomiting, and bloating and belching without definite abdominal pain were defined as dyspepsia. The patients having more than one symptom were grouped according to the predominant symptom which was most disturbing for the patient. Patients who had received antibiotics, anti-inflammatory drugs or drug therapy for peptic ulcer disease during the preceding month and patients with portal hypertension and/or coagulation disorders were excluded from the study.

Fiberoptic endoscopes (GIF-P20, Olympus, Tokyo, Japan and FG-100PE Fujinon) were used in all endoscopic procedures. During endoscopy, at least four mucosal biopsy specimens were obtained from the gastric antrum, gastric corpus and from all areas with a pathological appearance, for rapid urease test and histopathological examination. In every patient, one of the antral biopsy samples was placed into the rapid urease test plate (CLO test, Delta, West Beutley, Western Australia) at 25°C; other biopsy specimens were stained with hematoxylin-eosin and Giemsa for histological examination to determine the presence of H. pylori infection and the morphological changes.Each biopsy sample was examined under light microscope by the same pathologist who was unaware of the results.

During endoscopic examination, the presence of eosophagitis defined by hyperemia or erosions in the distal esophagus, gastritis defined by edematous and hyperemic gastric mucosa with or without superficial erosions, gastric ulcer, antral nodularity, duodenal ulcer and duodenitis defined by mucosal congestion with exudates were investigated in every patient. In histological examinations, chronic gastritis was defined by the infiltration of the lymphocytes, monocytes and/or plasma cells whereas chronic active gastritis was defined as the inflammation characterized by neutrophil infiltration. Additionally, the peresence of intestinal metaplasia and lymphoid follicles was recorded.

Children were considered to be H. pylori positive if urease test and histological examination were both positive and H. pylori negative if both tests were negative. If one of the two test results was negative, the patients were excluded from the study. Two of the 182 children studied were excluded since they had positive histological examination but negative urease test for H. pylori.

Venous blood samples were obtained from each child at the time of endoscopy. The serum was separated, divided into aliquots, and stored at –20°C before testing. Sera were assayed for H. pylori specific IgG antibodies (HP-IgG) using a commercial system, which is a qualitative enzyme-linked immunoassay kit (Biomerica Newport Beach). The assays were performed in the laboratory blinded to the children's H. pylori status. The concentrations of IgG antibody in the serum samples were determined by interpolation form a standard curve constructed by dilution of the positive control and by plotting absorbance values obtained for each standard against the corresponding anti-H. pylori concentrations in units per milliliter. A cut off value of 20 U/ml was accepted according to the manufacturer's instructions. Values above 20 U/ml were considered positive, and values below 12 U/ml were considered negative. Equivocal values between 12-20 U/ml necessitated repeat testing. One patient with an equivocal result at the initial assay had a H. pylori specific IgG level below 12 U/ml on the repeat testing and was considered negative for H. pylori serology. Sera that showed discrepant ELISA results with the histology and CLO test were also retested.

The performance of the test was evaluated by determination of the sensitivity, specificity and positive and negative predictive values.

Student's t test, χ^2 test and Fisher's exact test were performed for statistical analysis where appropriate. A value of $p \leq 0.05$ was considered as statistically significant.

Results

Among the 180 children participating in the study, 77 (42.7%) were H. pylori positive determined by the positive results of the histopathological investigation and the rapid urease test. The mean age of H. pylori positive children was significantly higher than that of the H. pylori negative group (11.3±3.1 years vs 9.2±4.0 years, $p<0.01$). H. pylori infection was more common in males (50.9% vs 30.6%, $p<0.01$). Incidence of H. pylori infection was significantly higher in children over 10 years (28.8% vs 54%, $p<0.01$) (Table I).

Table I. Frequency of Helicobacter pylori infection in different age groups

Age (years)	Number of patients	H. pylori positivity (%)
1-4	21	4 (19)
5-9	59	19 (32.2)
10-14	86	46 (53.4)
15-18	14	8 (57.1)

No significant difference existed between H. pylori positive and H. pylori negative groups with regard to family history of acid peptic disease or abdominal cancer (15.5% vs 12.6% and 2.5% vs 1.9%, respectively; $p>0.05$).

Abdominal pain was the main indication for endoscopic examination in our study group. Sixty-three patients had recurrent abdominal pain. Epigastric pain was the predominant type of abdominal pain (84.6% of the patients with abdominal pain). Frequency of H. pylori infection was highest (65.4%) in 26 patients with dyspepsia as the main symptom. Among 41 patients without gastrointestinal symptoms (11 with chronic diarrhea and growth retardation, 30 with chronic renal failure) who underwent upper gastrointestinal endoscopy either for intestinal biopsy or on a routine basis before renal transplantation, H. pylori was positive in 24.4% in total (18.2% and 27.6%, respectively), which was the lowest rate. Overall H. pylori positivity was significantly higher in children with gastrointestinal symptoms (48.2%, $p<0.05$). Distributon of different symptoms in H. pylori positive and negative groups are shown in Table II. Incidence of dyspepsia was significantly higher in the H. pylori positive patients compared to the H. pylori negative group (22% vs 8.7%, $p<0.05$).

Endoscopical findings were normal in 17 of 77 H. pylori positive children (22%). Incidence of endoscopical gastritis, antral nodularity, and duodenal ulcer were 33.8%, 27.3% and 13%, respectively, in the H. pylori positive group. Among these patients, only two had esophagitis (2.6%), and another one had gastric ulcer. Table III shows the incidence of different endoscopical findings in the H. pylori positive group compared to the H. pylori negative children. Incidence of gastritis, duodenal ulcer and antral nodularity was significantly higher in the H. pylori positive group ($p<0.01$).

In the context of endoscopical findings, H. pylori positivity was 91.3% in patients with antral nodularity, 71.4% in patients with duodenal ulcer, 61.9% in those with gastritis, 25% in

Table II. Helicobacter pylori infection rate according to clinical symptoms and frequency of clinical symptoms in Helicobacter pylori positive versus negative children

		H. pylori positive		H. pylori negative		
Symptoms	Percentage of H. pylori infected cases	Number of cases	%	Number of cases	%	P value
Recurrent abdominal pain	46%	29	37.7	34	33	NS
Melena/hematemesis	42%	14	18.2	19	18.4	NS
Dyspepsia	65.4%	17	22	9	8.7	0.017
Nausea/vomiting	41.2%	7	9.1	10	9.7	NS
Gastrointestinal	48.2%	67	87	72	69.8	
Growth retardation	18.2%	2	2.6	9	8.7	NS
Chronic renal failure	26.7%	8	10.4	22	21.4	NS
Extraintestinal	24.4%	10	13	31	30.2	

NS: not significant.

those with gastric ulcer and 16.6% in patients with esophagitis (Table III). Frequency of H. pylori infection among children with apparently normal mucosa on endoscopy was 20%.

Distribution of histopathological findings was also evaluated in the children participating in the study. Overall, in 122 (67.8%) of 180 patients, histological gastritis was observed (106 chronic gastritis and 16 chronic active gastritis). Intestinal metaplasia was seen in one patient and lymphoid follicles in four patients. Histopathological examination was normal in 58 patients who also did not have macroscopic abnormality on endoscopy. H. pylori frequency was 62.2% in the histological gastritis group, whereas it was 1.7% in patients with normal histology ($p<0.001$). H. pylori infection did not differ significantly in patients with chronic gastritis and chronic active gastritis (75% vs 65.5% $p>0.05$). Among 122 patients with histological gastritis, 42 (34.4%) had gastritis on endoscopy while 23 (18.8%) had antral nodularity.

Table III. Helicobacter pylori infection rate according to endoscopic findings and frequency of endoscopical findings in Helicobacter pylori positive and negative children

		H. pylori positive		H. pylori negative		
Endoscopical findings	Percentage of H. pylori infected cases	Number of cases	%	Number of cases	%	P value
Normal	20%	17	22	68	66	<0.01
Gastritis	61.9%	26	33.8	16	15.5	<0.01
Antral nodularity	91.3%	21	27.3	2	1.9	<0.01
Esophagitis	16.7%	2	2.6	10	9.7	NS
Duodenal ulcer	71.4%	10	13	4	3.9	<0.05
Gastric ulcer	25%	1	1.3	3	2.9	NS
Total	42.8%	77		103		

NS: not significant.

H. pylori specific IgG antibodies by ELISA method were positive in 79 of 180 patients. IgG antibodies were positive in all of 77 H. pylori infected patients as determined by CLO test and histopathological examination, whereas two of 103 noninfected patients were H. pylori IgG positive, which is considered to be false positivity. False negativity was not seen. By means of ELISA method, the sensitivity of H. pylori specific IgG antibody determination was found to be 100%, while the specificity was 98%, positive predictive value 97.4%, and negative predictive value 100%.

Discussion

In developing countries, H. pylori infection is generally acquired early in childhood, and frequency increases in line with low socioeconomic conditions, family lifestyle and low educational level of the family members[9-11]. Our findings indicate that Turkish children are more likely to be infected around the age of 10 years.

In our study population of 180 pediatric cases, frequency of H. pylori infection was 42.7%. H. pylori infection rate was determined to be 48.2% among 139 cases with gastrointestinal symptoms, whereas 24.4% of the 41 asymptomatic patients (those without gastrointestinal symptom) were infected. In two studies from Italy, H. pylori incidence in symptomatic children was reported as 52.3% and 56%, similar to our results[12,14]. Mitchell et al.[15] determined this ratio to be 14.1% in their study population in Australia. Our results are in accord with two other studies from our country in which H. pylori positivity was reported to be 41.3% and 53.1% in symptomatic patients[16,17].

Frequency of H. pylori infection was highest (65.4%) in 26 patients with dyspepsia as the main symptom. Association of nonulcer dyspepsia with H. pylori positivity has been shown previously[18]. Nevertheless, some authors have failed to demonstrate a relationship between dyspepsia and H. pylori status[19]. We believe that our sample size and characteristics are adequate to suggest a significant association. No significant difference existed between the groups with different gastrointestinal symptoms other than dyspepsia with regard to H. pylori infection rate.

Several previous studies indicate that the percentage of antral nodularity in children infected with H. pylori may vary between 30-100%[15,20,23]. In our study group this ratio was even lower (27.3%), suggesting a decreased sensitivity. In their prospective study, Ganga-Zandzou et al.[24] clearly demonstrated that the frequency of nodular gastritis increased significantly, from 11% at the baseline to 64%

at the end of one year and to 80% at the end of the second year, in parallel to the duration of H. pylori infection. Though not very sensitive, especially in the early periods of infection, antral nodularity was also a specific finding for H. pylori infection in our pediatric patients. Nevertheless, it may rarely be seen in the absence of H. pylori infection[23]. In our study, only two of the 23 patients with antral nodularity (8.7%) were H. pylori negative. It may be suggested that these patients had experienced H. pylori infection previously and that after antral nodularity developed, the infection spontaneously cleared, as has been reported by several investigators[24,25]. Reversal of antral nodularity might take some time after the microorganism is cleared.

When H. pylori infection rate was determined in children with different endoscopical findings, antral nodularity was the endoscopical finding most suggestive of H. pylori positivity; 91.4% of patients with antral nodularity were infected (Table III). The finding of such a high rate of infection among our pediatric patients with endoscopical gastritis suggests that H. pylori might be responsible for most cases of gastritis in Turkish children. Frequency of H. pylori infection among children with gastritis has been reported to vary between 41-82.4% in different populations[26,27]. H. pylori incidence in children with duodenal ulcer ranges between 33-100% in different studies[15,28]. H. pylori seems to contribute highly to the development of duodenal ulcer, evidenced by a high ratio of H. pylori infected children among those with duodenal ulcer in our pediatric population. Our finding of a significantly higher frequency of duodenal ulcer among H. pylori positive children compared to the H. pylori negative group is also supportive of this association (Table III). In our study group, 16.6% of children with esophagitis were infected whereas 20% of those with endoscopically apparently normal mucosa were found to be H. pylori positive.

Although the difference between these two groups is not significant, the low rate of infection among the children with esophagitis is suggestive of the negative correlation between H. pylori and esophageal inflammation reported in adults[29,30]. Our inability to demonstrate a significant difference between H. pylori positive and negative groups in terms of the incidence of esophagitis and gastric ulcer might be due to the limited number of children with these findings in our study group.

Distribution of histopathological findings and their association with H. pylori positivity were also evaluated in our pediatric population. Overall, histological gastritis was observed in 122 of 180 patients: 106 had chronic gastritis (86.8%), while 16 had chronic active gastritis (132.2%). In compliance with our findings, it has been previously shown that chronic active gastritis is more frequently encountered in adults and histological activity is minimal in children[15,22]. In our study group, frequency of H. pylori infection did not differ significantly in patients with chronic gastritis and chronic active gastritis, implying that histological activity of the gastritis was not suggestive of the presence of H. pylori infection (75% vs 65.5%, $p>0.05$). However, H. pylori infection rate was 62.2% in children with histological gastritis, whereas only 1.7% of children with normal histology were found to be H. pylori positive ($p<0.01$). Though rare, H. pylori positivity associated with normal gastric mucosa may be explained in two ways: infection can be at a very early phase during the endoscopic examination, or the bacteriological type of the H. pylori variant may affect the degree of mucosal damage[27,31]. Nevertheless, many investigators claim that H. pylori infection inevitably causes chronic inflammation and that the absence of antral inflammation should exclude H. pylori infection[32-34].

We found that determining the presence of H. pylori IgG antibodies in the sera had a high diagnostic yield in our pediatric population. H. pylori IgG were positive in all of the 77 infected patients as well as in all of the 10 H. pylori infected children with duodenal ulcer and in two of the 103 noninfected children, providing a sensitivity of 100%, specificity of 98%, positive predictive value of 97.4% and negative predictive value of 100%. Only two of the noninfected children who had not received antibiotics at least in the preceding four weeks had H. pylori IgG positivity (1.1%). This may be explained by false positivity due to cross-reaction with other IgG antibodies or failure to normalize of the high antibody levels after the infection was cleared.

Marked differences in both sensitivity and specificity of ELISA in children have been reported[35-37]. Oliveria et al.[12] found H. pylori IgG antibodies to be positive in all 20 infected children with duodenal ulcer while 54 of the

68 infected (79.4%) and five of the 62 noninfected children (8.1%) were determined to be antibody positive, suggesting lower sensitivity, specificity, and positive and negative predictive values (79.4%, 91.9%, 91.5% and 80.3%, respectively) in children without duodenal ulcer than those we observed. These findings have led us to conclude that though ELISA provides high sensivity and specificity in children with dueodenal ulcer in the diagnosis of H. pylori infection, it is not a reliable method in 2-11 year-old pediatric patients without duodenal ulcer. Because immune responses against H. pylori infection can take a few months, antibody test results might be false negative during the early periods of infection. Furthermore, the cutoff value of the antibody tests must be determined individually for each population. In our study, 20 U/ml was accepted as the cutoff value in accordance with the manufacturer's recommendations. Values higher than 20 U/ml were considered positive and values lower than 12.5 U/ml were considered negative. Our finding of H. pylori antibody positivity in all infected children in our study group can be associated with the long duration of the infection as a consequence of acquiring the H. pylori infection at an early age or with a high bacterial load. In light of the low rate of nodular gastritis in our patients, suggesting a shorter duration of infection, another possibility is that a more immunogenic strain, such as Cag-A protein, might have influenced the outcome. Unfortunately, we were not able to study H. pylori strains in our population. However, Mitchell et al.[38] indicated that particular ethnic or socioeconomic groups may be more susceptible to infection with Cag-A positive strains of H. pylori[38]. In this context, contribution of Cag-A and other specific H. pylori antigens to the pathogenesis of infection in Turkish children remains to be determined.

In conclusion, we found that ELISA assay provides a sensitivity of 100% and a specificity of 98% in the diagnosis of H. pylori infection in our pediatric population, independent of the age and the presence of duodenal ulcer, contradicting the results of Oliveria et al.[12] in 63 Brazilian children (79.4% and 91.9% respectively) and the results of Ni YH et al.[37] in 53 Taiwanese children (88.9% and 80.9%, respectively). We strongly suggest that every population must determine its own infection characteristics and accuracy of diagnostic tests. ELISA test for IgG antibodies against H. pylori proves to be an inexpensive and reliable method in the primary diagnosis of H. pylori infection in Turkish society regardless of the age. However, since serological investigation cannot predict the underlying gastrointestinal pathology, upper gastrointestinal endoscopy should be performed for final diagnosis in children with positive H. pylori IgG antibodies. In addition to revealing the mucosal lesions, the positivity of at least two of the CLO test, or histological or microbiological investigations in gastric biopsy samples obtained from antrum and corpus mucosa will be confirmatory in the diagnosis.

REFERENCES

1. Warren JR, Marshall BJ. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983; 1: 1273-1275.
2. Drumm B, Sharman P, Cutz, Karmali M. Association of Campylobacter pylori on the mucosa with antral gastritis in children. N Engl J Med 1987; 316: 1557-1561.
3. Veldhuyzen van Zanten SJ, Pollak PT, Best LM, Bezanson GS, Marrie T. Increasing prevalence of Helicobacter pylori infection with age: continuous risk of infection in adults rather than cohort effect. J Infect Dis 1994; 169: 434-437.
4. Personnet J, Hansen S, Rodriguez L, et al. Helicobacter pylori infection in gastric lymphoma. N Engl J Med 1994; 330: 1267-1271.
5. Radhakrishnan S, Al Nakib B, Kalaoui M, Patric J. Helicobacter pylori associated gastritis in Kuwait: endoscopy based study in symptomatic and asymptomatic children. J Pediatr Gastroenterol Nutr 1993; 16: 126-129.
6. Raymond J, Bergret M, Benhamou PH, Mensah K, Dupont C. A 2 years study of Helicobacter pylori in children. J Clin Microbiol 1994; 32: 461-463.
7. Kehrt R, Becker M, Brosicke H, Krüger N, Helge H. Prevalence of Helicobacter pylori pylori infection in Nicaraguan children with persistent diarrhea, diagnosed by the ^{13}C-urea breath test. J Pediatr Gastroenterol Nutr 1997; 25: 84-88.
8. Perri F, Pastor M, Leonardo G, et al. Helicobacter pylori infection and growth delay in older children. Arch Dis Child 1997; 77: 46-49.
9. Mitchell HM, Li YY, Hu PJ, et al. Epidemiology of Helicobacter pylori in southern China: identification of early childhood as the critical period for acquisition. J Infect Dis 1992; 166. 149-153.
10. Malaty HM, Evans DG, Evans DJ Jr, Graham DY. Helicobacter pylori in Hispanics: comparison with blacks and whites of similar age and socioeconomic class. Gastroenterology 1992; 103: 813-816.
11. Webb PM, Knight T, Greaves S, Wilson A, Newell DG, Forman D. Relation between infection with Helicobacter pylori and living conditions in childhood: evidence for person to person transmission in early life. Br Med J 1994; 308: 750-753.

12. Oliveria AM, Rocha GA, Queriroz DM, et al. Evaluation of enzyme-linked immunosorbent assay for the diagnosis of Helicobacter pylori infection in children from different age groups with and without duodenal ulcer. J Pediatr Gastroenterol Nutr 1999; 28: 157-161.

13. Logan RP, Polson RJ, Misiewicz JJ, et al. Simplified single sample ^{13}C-urea breath test for Helicobacter pylori: comparison with histology, culture and ELISA serology. Gut 1991; 32: 1461-1464.

14. Bonamico M, Luzzi I, Annibale B, et al. High incidence of Helicobacter infections in an endoscopic pediatric patient series. Minerva Pediatr 1994; 46: 429-436.

15. Mitchell HM, Bohare TD, Tobias V, et al. Helicobacter pylori infection in children: potential clues to pathogenesis. J Pediatr Gastroenterol Nutr 1993; 16: 120-125.

16. Gürakan F, Koçak N. Yüce A. Helicobacter pylori serology in childhood. Turk J Pediatr 1996; 38: 329-334.

17. Öztürk H, Şenocak ME, Uzunalimoğlu B, Hasçelik G, Büyükpamukçu N, Hiçsönmez A. Helicobacter pylori infection in symptomatic and asymptomatic children: a prospective clinical study. Eur J Pediatr Surg 1996; 6: 265-269.

18. Kemmor TP, Dominguez E, Kingel H, Zemmler T, Kuhn K, Malfertheiner P. The association between non-ulcer dyspepsia and Helicobacter pylori infection. Eur J Gastroenterol Hepatol 1994; 6: 571-577.

19. Patel P, Mandall MA, Khulusi S, et al. Salivary antibodies to Helicobacter pylori: screening dyspeptic patients before endoscopy. Lancet 1994; 344: 511-512.

20. Chong SK, Lou Q, Asnicar MA, et al. Helicobacter pylori infection in recurrent abdominal pain in childhood: comparison of diagnostic tests and therapy. Pediatrics 1995; 96: 211-215.

21. Queiroz DM, Rocha GA, Mendes EN, et al. Differences in distribution and severity of Helicobacter pylori gastritis in children and adults with duodenal ulcer disease. J Pediatr Gastroenterol Nutr 1991; 12: 178-181.

22. Ashorn M, Ruuska T, Karikoski R, Valipakka J, Maki M. Gastric mucosal cell densities in Helicobacter pylori-positive and negative dyspeptic children and healthy controls. J Pediatr Gastroenterol Nutr 1994; 18: 146-151.

23. Maherzi A, Fendri C, Ben Jilani S, Bousnina S. Symptomatic Helicobacter pylori infection: prospective study of epidemiological, diagnostic and therapeutic aspects in children in Tunisia. Arch Pediatr 1996; 3: 329-334.

24. Ganga-Zandzou PS, Michaud L, Vincent P, et al. Natural outcome of Helicobacter pylori infection in asymptomatic children: a two-year follow-up study. Pediatrics 1999; 104: 216-221.

25. Perri F, Pastore M, Clemente R, et al. Helicobacter pylori infection may undergo spontaneous eradication in children: a 2 year follow-up study. J Pediatr Gastroenterol Nutr 1998; 27: 181-183.

26. Lopez DM, Elitsur Y. A study of Helicobacter pylori in 100 pediatric patients from the Tri-State area. WV Med J 1994; 90: 367-369.

27. Gottrand F, Cullu F, Turck D, et al. Normal gastric histology in Helicobacter pylori infected children. J Pediatr Gastroenterol Nutr 1997; 25: 77-78.

28. Macarthur C, Saunders N, Feldman W. Helicobacter pylori gastroduodenal disease and recurrent abdominal pain in children. JAMA 1995; 273: 729-734.

29. Vanasi RV, Fantry GT, Wilson KT. Protective role of Helicobacter pylori infection in gastroesophageal reflux disease. Gastroenterology 1998; 114: A322.

30. Werdmuller BF, Loffeld RJL. Helicobacter pylori infection has no role in the pathogenesis of reflux esophagitis. Dig Dis Sci 1997; 42: 103-105.

31. Tytgat GN. Does the stomach adapt to Helicobacter pylori? Scand J Gastroenterol 1992; 27 (Suppl): 28-32.

32. Dooley CP, Cohen H, Fitzgibbons PL, et al. Prevalence of Helicobacter pylori infection and histologic gastritis in asymptomatic persons. N Engl J Med 1989; 321: 1562-1566.

33. Gormally S, Drumm B. Helicobacter pylori and gastrointestinal symptoms. Arch Dis Child 1994; 70: 165-166.

34. Faigel DO, Furth EE, Childs M, Goin J, Metz DC. Histological predictors of active Helicobacter pylori infection. Dig Dis Sci 1996; 41: 937-943.

35. Van den Barre C, Cadranel S, Butzler JP, Glupezynski Y. Serum reactivity to Helicobacter pylori antigens assessed by Helico Blot 2.0 in H. pylori positive children from different ethnic groups (Abstract). Gut 1995; 37: A315.

36. Personnet J, Replogle M, Yang SF, Hiatt R. Seroprevalence of cag A-positive strains among Helicobacter pylori-infected, healthy young adults. J Infect Dis 1997; 175: 1240-1242.

37. Ni YH, Lin JT, Huang SF, Lang JC, Chang MH. Accurate diagnosis of Helicobacter pylori infection by stool antigen test and 6 other currently available tests in children. J Pediatr 2000; 136. 823-827.

38. Mitchell HM, Hazell SL, Bohane TD, Hu P, Chen M, Li YY. The prevalence of antibody to CagA in children is not a marker for specific disease. J Pediatr Gastroenterol Nutr 1999; 28: 71-75.