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Helicobacter pylori and recurrent abdominal pain in children: Is there any relation?

Mansour MMHK,[1] Al Hadidi Kh M,[2] Omar MA[3]

Departments of Pediatrics,[1] Cairo University, Egypt
Clinical Pathology[2] and Hepatogastroentrology,[3] Jeddah Clinic Hospital, Jeddah, KSA

Correspondence:
Dr Maha Mahmoud Hamdi Khalil Mansour
Email: fractaledge3@yahoo.com

ABSTRACT

Background: The role of *Helicobacter pylori* (HP) as a cause of recurrent abdominal pain (RAP) and gastrointestinal symptoms is controversial and there still remains a big debate whether to test and treat or not.

Aim: To investigate the correlation between HP infection and RAP as well as other GI symptoms.

Methods: We conducted a case control study at the Jeddah Clinic Hospital from January 2009 to December 2010. It included 244 cases (group I) aged 2-16 years with RAP after exclusion of any organic disease. Cases receiving antibiotics, bismuth, H2 antagonists or proton pump inhibitors during last 45 days were excluded. 122 age and gender matched asymptomatic children (group II) were enrolled as controls. Both groups were tested for *Helicobacter pylori* infection using stool antigen and/ or urea breath test.

Results: The mean age of cases was 7.76 ± 3.38 years. 48% of cases were males. There was no significant statistical difference between both groups regarding age and sex distribution, nationality and body weight (BW). 42.6% cases were positive for *H. pylori* infection in group I and 45% in group II. Comparison between HP positive cases and HP negative cases in group I revealed a statistically significant difference in incidence of vomiting, epigastric pain, history of infected family member and iron deficiency anemia (p=0.001, 0.000, 0.000 and 0.025 respectively).

Conclusion: HP infection is documented in more than 40% of both symptomatic and asymptomatic children. There is no association between RAP and HP.

KEYWORDS: *Helicobacter pylori* infection, recurrent abdominal pain, children

Introduction

Helicobacter pylori (HP) infections and recurrent abdominal pain (RAP) are two major childhood challenges presenting a dilemma in diagnosis and treatment. Despite decades of clinical observations resulting in numerous articles, books, and monographs, the subject of recurrent abdominal pain in childhood remains one of ambiguity and concern for most pediatric health care professionals.[1]

According to Apley's criteria, recurrent abdominal pain is defined as at least 3 discrete episodes of abdominal pain of sufficient severity to interrupt normal daily activities or performance over a period of not less than 3 months.[2]

HP infection is one of the most common bacterial infections in humans affecting nearly 50% of the world's population.[3] It is usually acquired in childhood and is associated with socio-demographic factors such as low socio-economic status, poor hygiene, and overcrowding.[4] The prevalence of HP infection is markedly high in developing countries,[5] where up to one half of the children in 10-year-old age group are infected with HP.[6]

Acute infection is often silent, with symptoms and disease manifesting later in life, as does an increased risk of gastritis, peptic ulcer and HP related malignancy.[3] Controversial results have been found in assessing the role of HP infections as the etiology of specific symptoms in children like RAP.[7]

Guidelines on screening for HP in children are often contradictory. Recommendations vary from no need to routine screening of children with gastrointestinal symptoms[8] and from no need of screening children with RAP[9] to screening all children with upper GI symptoms.[10] These first recommendations were based on the lack of proof that infection with HP is a significant cause of GI symptoms.[11] Symptoms suggestive of acute HP infection are similar to several common childhood disorders, manifesting as recurrent abdominal pain, dyspepsia, epigastric pain, diarrhea and vomiting.[12]

For the diagnosis of HP infection, gastrointestinal endoscopy with tissue culture is considered to be the "gold standard". Several noninvasive methods for the detection of *H. pylori* infection are available.[13] The ^{14}C labeled urea breath test (UBT) gives an excellent performance, in both adults and children, but its specificity decreases in very young children and collection of exhaled air is difficult in this age group.[14] HP stool antigen detection based on monoclonal antibodies showed excellent results with very high sensitivity and specificity.[15] Owing to the presumptive link between HP infection and RAP, there is an increasing pressure on pediatricians to screen for HP infection in symptomatic children. This emphasizes the need for up-to-date guidelines with indications for investigating and treating children with HP infection.[11] The purpose of this work is to investigate whether there exists any correlation between HP infection and RAP as well as other GI symptoms in children and thereby to evaluate the clinical significance of HP infection.

Methods

This case control study was conducted at the Jeddah Clinic Hospital, KSA, from January 2009 to December 2010 after approval of the ethics committee. We enrolled 244 cases (group I) aged 2-16 years with RAP after exclusion of any organic disease by CBC, ESR, serum albumin, stool analysis, urine analysis and abdominal ultrasound. Iron deficiency anemia (IDA) was evaluated by serum iron and ferritin. Cases receiving antibiotics, bismuth, H2 antagonists or proton pump inhibitors during last 45 days were excluded. A total of 122 age and gender matched asymptomatic children (group II) were enrolled as controls after written consent from their parents. Both groups were tested for HP infection using stool antigen and/ or urea breath test based on their age and cooperation. Upper endoscopy was performed in selected cases.

Urea breath test

The urea breath test was carried out using the PYtest kit (TRI-MED, Subiaco, Australia). To detect *H. pylori*, ^{14}C labeled urea supplied in a capsule is swallowed by the patient. If gastric urease synthesized by *H. pylori* is present, urea is split to form CO_2 and NH_3. Ten minutes after the patient ingests the capsule, a breath sample is collected into a balloon. The breath sample is later transferred to collection fluid to trap the labeled CO_2. The liquid sample is then analyzed in a liquid scintillation counter. Results are reported as disintegrations per minute (DPM). Analysis for accuracy was done using the ten minute breath sample. A breath sample DPM <50 was defined as a negative result. A breath sample DPM >50 was defined as a positive result.

H. pylori stool antigen

H. pylori stool antigen testing was done using the CerTest *H. pylori* assay, which is a one step colored chromatographic immunoassay for the qualitative detection of *Helicobacter pylori* antigen in faeces.

Statistics

Data was tabulated and subjected to analysis using Microsoft Excel version 5.0 and the Statistical Package for Social Science (SPSS) version 11.0. The following methods were employed: frequency and percentage distributions; mean, standard deviation and range of numerical data; comparison of means using the Student t test; testing differences between means for statistical significance; and non-numerical data were compared using the chi-square test. In general, p values less than 0.05 were considered significant, less than 0.01 highly significant and those below 0.001 very highly significant.

Results

The mean age of the symptomatic group (group I) was 7.76 ± 3.38 years and the range was 2-16 years. 117 (48%) cases were males and 127 (52%) were females. 95 (38.93%) were Saudis, 85

(34.84%) were Yemenis and 26 (10.66%) were Egyptians. A total 38 (15.57%) children were below the 5th percentile for body weight (BW), 95 (38.93%) had history of HP infected family members and 32 (13.12%) had associated IDA. In the asymptomatic group (group II), the mean age was 7.38 ± 3.16 years. This group has 58 (47.54%) males and 64 (52.46%) females. 48 (39.34%) were Saudis, 44 (36.06%) were Yemenis and 11 (9.02%) were Egyptians. A total of 23 (18.8%) were below the 5th percentile for BW, 44 (36.06%) had history of HP infected family members and 15 (12.3%) had associated IDA. There was no significant statistical difference between both groups with regards to their age and sex distribution, nationality, incidence of IDA, BW or history of infected family members (p>0.05). In all 104 (42.6%) cases were positive for HP infection in the symptomatic group and 55 (45%) in the asymptomatic group (p>0.05) (**Table 1**).

In HP positive cases, 30 (28.85%) had persistent epigastric pain, 25 (24.04%) had recurrent vomiting and 20 (19.23%) had associated IDA. Comparison between HP positive cases and HP negative cases in group I revealed a statistically significant difference in the incidence of vomiting, epigastric pain, history of infected family members and IDA (p=0.001, p=0.000, p=0.000 and p= 0.025 respectively). However, there was no difference in age and sex distribution, nationality, BW, and symptoms of diarrhea and nausea (p>0.05) (**Table 2**).

Comparison between HP positive and HP negative asymptomatic children revealed no statistically significant differences. (p>0.05) Further, the statistical analysis of HP positive subgroups in both symptomatic and asymptomatic groups revealed no statistically significant differences in any of the parameters studied. (p>0.05) (**Table 3**).

Upper GI endoscopy and biopsy was carried out in 10 children with ages ranging from 8 to 16 years and presenting with persistent epigastric pain and vomiting. They represented 4% of symptomatic patients and 9.6% of HP positive

Table 1: A comparison of symptomatic cases and asymptomatic controls

	Group I Cases n=244	Group II Controls n=122
Age		
• Mean	7.7 (3.4)	7.3 (3.1)
• Male	117 (47.95%)	58 (47.54%)
Nationality		
• Saudi	95 (38.93%)	48 (39.34%)
• Yemeni	85 (34.84%)	44 (36.06%)
• Egyptian	26 (10.66%)	11 (9.02%)
• others	38 (11.57%)	19 (15.58%)
Body weight		
• <5th percentile	38 (15.57%)	23 (18.8%)
• >5th percentile	206 (84.435)	99 (81.2%)
Another infected family member	95 (38.93%)	44 (36.06%)
Anemia	32 (13.12%)	15 (12.3%)
H pylori infection	104 (42.62%)	55 (45.08%)

**There wasn't any significant statistical difference between both case and control groups (p>0.05)*

Table 2: A comparison of *H pylori* positive cases and pylori negative cases in symptomatic group

	H pylori positive cases n=104	*H pylori* negative cases n=140
Age		
Mean (SD)	7.9 (3.4)	7.6 (3.4)
Male	46 (44.23%)	71 (50.71%)
Nationality		
Saudi	40 (38.46%)	55 (39.3%)
Yemeni	36 (34.62%)	49 (35%)
Egyptian	14 (13.46%)	12 (11.54%)
others	14 (13.46%)	24 (14.16%)
Body weight		
<5th percentile	18 (17.3%)	20 (14.29%)
>5th percentile	86 (82.7%)	120 (85.71%)
Another infected family member	55* (52.9%)	40 (27.8%)
Symptoms		
Epigastric pain	30* (28.85%)	13 (9.3%)
Vomiting	25* (24.04%)	12 (8.6%)
Nausea	2 (1.92%)	1 (0.71%)
Diarrhea	8 (7.7%)	8 (5.71%)
Anemia	20* (19.23%)	12 (8.6%)

**p<0.05 is statistically significant*

Table 3: A comparison of *H. pylori* positive cases and H. pylori positive controls

	H pylori positive cases n=104	*H pylori* positive controls n=55
Age		
Mean (SD)	7.96 (3.47)	7.34 (3.19)
Male	46 (44.23%)	24 (43.67%)
Nationality		
Saudi	40 (38.46%)	22 (40%)
Yemeni	36 (34.62%)	18 (32.73%)
Egyptian	14 (13.46%)	7 (12.73%)
others	14 (13.46%)	8 (14.54%)
Body weight		
<5th percentile	18 (17.3%)	14 (24.45%)
>5th percentile	86 (82.7%)	41 (74.55%)
Another infected family member	55 (52.9%)	21 (38.2%)
Anemia	20 (19.23%)	11 (20%)

**There wasn't any significant statistical difference between both HP positive cases and control groups (p>0.05)*

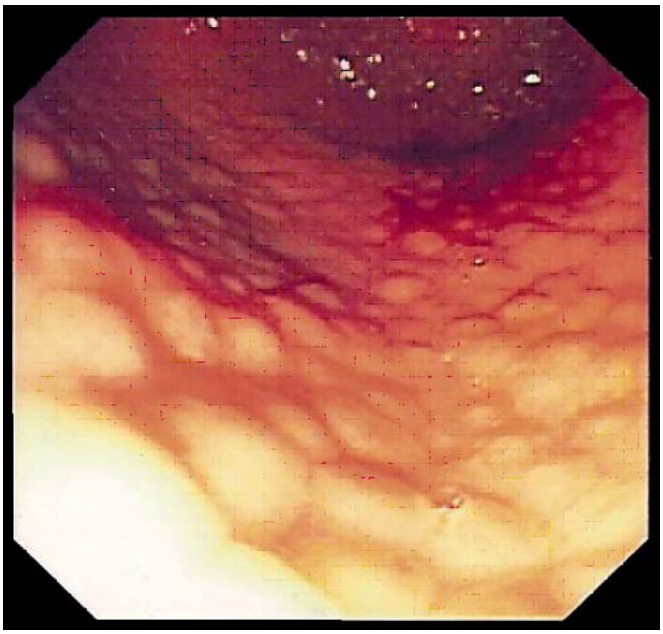

Figure 1: Upper endoscopy showing nodular gastritis in 14 years old female patient with HP infection

symptomatic patients. All of them revealed positive pathological changes including, antral gastritis in 1 (10%) patient (8 years old), antral and fundal gastritis in 2 (20%) patients (10 years old) and diffuse nodular gastritis in 7 (70%) patients (aged between 12 and 16 years) denoting a significantly higher incidence of nodular gastritis in *H. pylori* infected cases especially in older children ($p<0.05$) (**Figure 1**).

Discussion

In the present study, the prevalence of *H. pylori* infection was 42.6% in symptomatic children (group I) and 45% in the asymptomatic group (group II). In other studies, the prevalence rate was very variable ranging from 6% in Finland[16] to 95% in Perth, Australia.[5] This variability depends on inadequate living conditions, poor hygiene and overcrowding. In Saudi Arabia, this high prevalence could be attributed to the fact that most of the people take at least one meal at restaurant and fast food outlets. The cooks and other staff managing these joints come from developing Asian countries, where the prevalence of *H. pylori* is very high in addition to inadequate maintenance of proper hygiene.[6,17] Another factor related to *H. pylori* infection is transmission through contaminated water.[6,17-19]

The mean age of our symptomatic group was 7.76 ± 3.38 years and the age range was 2-16 years. There was no difference in age distribution between *H. pylori* positive and negative cases.[7,20] However, other studies found that children with *H. pylori* infection were significantly older.[5,18] Gender has not been identified as a relevant influencing characteristic for *H. pylori* infection.[18-20] However, females were reported with higher prevalence of *H. pylori* infection than males in a study conducted in Saudi Arabia.[6] On the contrary, in a study conducted in Uganda, Hestvik et al[21] found a significant gender difference in the prevalence of *H. pylori* colonization, boys being infected more often than girls.

We did not find any significant relation between the different nationalities and *H. pylori* infection in neither cases nor controls which could be explained by similar living conditions prevalent for both groups of children.[3,5] However, marked differences in *H. pylori* seroprevalence have been observed and reported among various ethnic and racial groups from other studies.[17] In this study it was confirmed that HP prevalence in children was significantly higher if family members were also HP infected regardless of other socioeconomic and environmental factors.[5,20] This finding supports the concept of person to person transmission through feco-oral route.

Comparison between HP positive and HP negative children in both groups (symptomatic and asymptomatic) revealed no significant difference in relation to body weight.[20,22] In contrast, studies from Italy, Germany and USA have shown that *H. pylori* infection is associated with growth delay especially in older children.[23,24] They explained their hypothesis by the coexistence of diarrhea and iron-deficiency anemia with HP infection.[25] It is not yet clear whether the difference in anthropometry between *H. pylori* infected and non-infected children in other studies is solely due to *H. pylori* infection or the socioeconomic and ethnic factors are contributory confounders.[26]

There was no statistical significant difference in the incidence of *H. pylori* infection between the symptomatic and asymptomatic group of children (42.65 and 45%, $p>0.05$) indicating existence of no relation between RAP and *H. pylori* infection.[11,26-28] However, the association of recurrent abdominal pain (RAP) and *H. pylori* is still debatable and other studies have reported an association between the two.[29,30] On the other hand, there is evidence against this association. First, if this association were true then *H. pylori* should have been seen more frequently in RAP cases than in controls.[26] Secondly, studies carried out to investigate the response in symptoms after *H. pylori* eradication in children with RAP, show that bacterial eradication and healing of gastric inflammation did not lead to symptomatic relief of recurrent abdominal pain in children.[31,32]

The European Pediatric Task Force[8] concluded that *H. pylori* infection is not related to GI symptoms in children. We

do partly agree with their report on RAP, which recommends that RAP is not an indication for test-and-treat strategy for *H. pylori* infection in children; however, children with upper GI symptoms should be tested after exclusion of other likely causes of these symptoms.[10] Pérez-Pérez et al,[33] stated that once fully established, the colonizing *H. pylori* population is robust, resisting the ongoing immune response and consistent with phenotypic plasticity due to genetic variation within the colonizing population. These patients are also at increased risk for developing long-term *H. pylori*–related morbidity such as peptic disease or neoplasia. The theoretical benefits involved in decreasing the lifetime risk have to be weighed against drawbacks of trying to eradicate the organism and consequent increasing resistance to antibiotic therapy.[34]

Further placebo-controlled studies with minimal loss to follow-up should be conducted to test the outcome of these symptoms after eradication therapy. We should also take self-limiting infections and cure into consideration as it ranges from 0.3% per year among black American children, age 7-21 years to 7% per month among Peruvian children (6-30 months old). High prevalence of HP found in neonates and infants tends to decrease in older babies and toddlers, suggesting cure of infection and that acquisition of *H. pylori* infection in children does not necessarily result in persistent infection in all cases.[21]

There was a significant statistical difference in the incidence of epigastric pain when compared between *H. pylori* positive and negative cases (28.85% versus 9.3%, p=0.00). Epigastric pain as a localizing symptom associated with *H. pylori* infection has been documented in other studies as well.[6,35-37] However, epigastric pain was less frequently encountered in the study by Kalach et al.[38]

Upper GI endoscopy and biopsy was carried out in 10 children with persistent epigastric pain and vomiting. It revealed a significantly higher incidence of nodular gastritis in *H. pylori* infected cases especially among older children ($p<0.05$), and indicates histopathological evolution of the lesions with chronicity of infection. In a 2 year follow-up study by Ganga-Zandzou et al,[39] it was found that in most cases, significant to moderate aggravation of histologic features occurs with the persistence or appearance of active gastritis and an attendant increase in the frequency of nodular gastritis, despite the stability of *H. pylori* density on gastric mucosa.[39] However a unique case report showed that untreated HP acquired during early childhood persists without major progression in gastritis. Not only is the duration of infection, but also the exposure to other gastric aggressors and /or carcinogens are responsible for gastric atrophy and metaplasia. Moreover, the lack of aggravation of histologic features supports recommendations not to screen and treat asymptomatic HP infected children.[22]

In the present study, vomiting was significantly higher in *H. pylori* infected children than in non-infected ones (24.04% versus 8.6%, p=0.001).[15,30,40] However, we did not find any significant difference in the incidence of nausea,[37] or diarrhea.[35] Other studies reported positive association between diarrhea and *H. pylori* infection in children.[16,30] Comparison between HP positive cases and HP negative cases revealed a statistically significant difference in the incidence of iron deficiency anemia (p=0.025).[41,42] The postulated mechanisms for IDA in *H. pylori* infection include, poor absorption of iron due to low gastric acid secretion, poor dietary intake and utilization of iron by the bacteria itself.[26] A meta-analysis of observational studies suggests an association between *H. pylori* and IDA.[43]

HP infection and RAP are two major childhood challenges presenting a dilemma in diagnosis and treatment. In our study, HP infection was documented in more than 40% of both symptomatic and asymptomatic children. There was no association between HP infection and RAP. There was a significant association between HP infection and epigastric pain, vomiting and IDA in symptomatic children and not in asymptomatic children suggesting that RAP is not an indication for a test-and-treat strategy for HP infection in children..

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