

## **HELICOBACTER PYLORI INFECTION IN RECURRENT ABDOMINAL PAIN**

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**Objective:** To study the relationship between *Helicobacter pylori* (Hp) infection and recurrent abdominal pain (RAP) and to evaluate various modalities to diagnose Hp infection. **Design:** Prospective case control study. **Setting:** Teaching hospital. **Methods:** Children between 3-12 years of age with RAP in whom upper gastrointestinal endoscopic examination was indicated were studied. Endoscopic biopsy specimen were collected from duodenum, antrum and esophagus. Apart from histopathological examination of biopsy material, rapid urease test (RUT) of the antral biopsy specimen and blood examination to estimate specific JgG antibodies to Hp by Indirect Solid Phase Enzyme Immunoassay was performed. The results of Hp IgG antibodies was compared with age matched controls. **Results:** Thirty one children with RAP were subjected to endoscopic examination and their anti Hp IgG antibodies status compared with 26 controls. Hp colonization was detected in 7 children (23%) with RAP; by RUT in 23% and antral biopsy in 16% of cases. Anti Hp IgG antibodies were also positive in almost equal proportion (19%) of controls ( $p = 0.757$ ). Endoscopic examination revealed esophagitis in 16% of cases and none had evidence of gastric or duodenal erosion, ulcer or cobblestone appearance of antrum. A significant correlation of Hp was noticed with chronic antral gastritis ( $p=0.002$ ), chronic duodenitis ( $p=0.02$ ) and age  $>W$  years ( $p=0.02$ ). No significant correlation was noticed between Hp colonization and various socioeconomic risk factors. **Conclusion:** Hp does not seem to be commonly associated with RAP in our patient population as Hp colonization was detected in only 23% of cases which was not significantly higher than the seroprevalence of anti Hp IgG antibodies in the controls. However, a small sample size of our study limits drawing any firm conclusions. Antral gastritis and chronic duodenitis had a significant correlation with Hp colonization. RUT was found to be a reliable diagnostic test to detect Hp.

**Key words:** *Indirect solid phase enzyme immunoassay, Helicobacter pylori, Rapid urease test, Recurrent abdominal pain.*

**R**ECURRENT abdominal pain (RAP) has been widely reported to affect at least 10% of children over the age of 5 years. Apley reported that an organic cause could be identified in fewer than 10% of such children(1). *Helicobacter pylori* (Hp),

discovered by Warren and Marshall 1983(2), has opened a new era of discovery and understanding of gastroduodenal pathology. Hp related gastritis has been suggested as a cause of recurrent abdominal pain but not consistently proven(3).

In an attempt to search for an organic cause of RAP in our population, this study was undertaken to investigate the relationship of RAP and Hp infection, and evaluate various modalities to diagnose Hp infection.

### Subjects and Methods

Children of either sex, below 12 years of age who fulfilled Apley's criteria of RAP (at least three discrete episodes of abdominal pain of sufficient severity, to interrupt normal daily activities or performance, occurring over a period of three or more months) were enrolled from General Pediatric OPD and investigated in the Division of Pediatric Gastroenterology and Nutrition, Kalawati Saran Children's Hospital, New Delhi. Prior to inclusion in the study, all the children were investigated for stool microscopy (to rule out intestinal parasites especially *G. lamblia*) and urine examination (to rule out urinary tract infection). Children who continued to have RAP and in whom other investigations and psychological evaluation were normal were hospitalized for further investigations. A detailed history was recorded on a proforma, with particular attention to socioeconomic status, housing conditions, source of water supply, storage of water, excreta disposal, sharing of bed and history of upper gastrointestinal complaints in other family members.

Upper gastrointestinal endoscopy was performed with a fiberoptic pediatric size endoscope (GIF Type PQ 20), after informed consent was obtained from the parents. Endoscopic changes were noted in the esophagus, stomach and duodenum. Multiple biopsy samples were taken endoscopically from duodenum and antrum, and evaluated by: (i) Hematoxyline and eosin staining to study morphological changes in mucosa, if any, and the severity

and type of inflammation; (ii) Giemsa staining of antral biopsy to demonstrate presence or absence of Hp; and (iii) One fresh biopsy from antrum was placed in Christensen's liquid urea medium to demonstrate rapid urease test (RUT). The presence and degree of gastritis and duodenitis was judged by the quantity- of the cellular infiltrate in the mucosa using standard classifications(4,5). Diagnostic criteria for Hp colonization was a positive RUT and/or positive histology for Hp.

Solid phase enzyme immunoassay was performed by collecting 1.5 ml of blood by venepuncture to estimate specific IgG antibodies to Hp (Immunocomb II, *Helicobacter pylori* IgG kit). For rapid and objective measurement of the color intensity of the spots on the immunocomb, test results were read as relative absorbance using program 92 of the Combscan reflectometer. The relative absorbance units were converted into titer values for anti Hp IgG. Titer values equal to or greater than 20 U/ml (relative color absorbance of 800 or more) indicated a positive test result. Blood samples for serology were also collected from 26 age and sex matched children with complaints other than those related to gastrointestinal tract, who served as controls.

Fisher exact test was performed on Epi Info Software.

### Results

Seventy two children with RAP were initially taken up and of these 41 children were diagnosed to have giardiasis (19.4%), urinary tract infection (11.1%), amebiasis (8.3%), worm infestation (8.3%) and overtly psychogenic cause (9.7%), and excluded from the final analysis. The remaining 31 children in whom no cause for RAP was detected by other investigations were subjected to upper GI endoscopic examination. Of these 31 children, most of the cases

(87%) were more than 5 years of age (Table I), with 17 males (55%) and 14 females (45%). Fifteen children (48%) presented with history of pain for 3-6 months, 3 (10%) between 6-12 months, 3 (10%) between 12-24 months and in 10 children (32%) duration of pain was 24 months or more. Pain around periumbilical region was the commonest (80.6%) followed by epigastric pain (19.4%). Majority (65%) of children belonged to lower socioeconomic status, practised open defecation (13%), used unsuitable drinking water (13%) and lived in overcrowded surroundings (84%). Family history of upper gastrointestinal complaints was elicited in 9 cases (23%). Vomiting was an additional symptom in 7 cases (23%).

Endoscopic examination revealed esophagitis in 5 cases (16%). None of the cases had any evidence of duodenal/gastric ulcer, erosion or cobblestone appearance of antrum. Antral biopsy was normal in 16 cases (52%) and the rest had evidence of chronic antral gastritis. Histological evidence of esophagitis was observed in only 3 out of 5 cases with endoscopically detected esophagitis. Duodenal biopsy was unremarkable in 17 cases (55%) and rest had non-specific chronic inflammation

(Table II). Significant titres of anti Hp IgG were present in 7 cases (23%). RUT was also positive in the same 7 cases. Antral biopsy revealed Hp on Giemsa stain in five (16%) of these cases. In the control population, serology for Hp was positive in 5 children (19%). There was no statistically significant difference in the seroprevalence of Hp in the cases and controls ( $p = 0.757$ ). No significant correlation with any of the risk factors was noticed with serology positive RAP cases as well as controls.

Chronic antral gastritis, duodenitis and age > 10 years, were the only significant findings associated with Hp. Other variables did not have any significant association (Table III).

No specific therapy was administered to the Hp positive cases, as present recommendations for treatment are limited to infected children with peptic ulcer disease(6). Suitable treatment for esophagitis was given as and when indicated.

### Discussion

The clinical manifestations of Hp infection are not very clearly defined in children. The infection is supposed to be acquired in early childhood, but complex

TABLE I -Age Distribution of Cases and Controls.

Age (years)	Total cass (n=31)		Hp positive cases* (n=7)		Total controls (n=26)		Hp positive controls** (n=5)	
	No.	%	No.	%	No.	%	No.	%
< 5	4	13	0	—	4	15	0	—
5 - 8	13	42	2	29	11	42	0	
8 - 10	4	13	0	—	4	15	2	40
10 - 12	10	32	5	71	7	27	3	60

\* Hp positive cases (Positive RUT and/or positive histology with or without positive serology)

\*\* Hp positive controls (Positive serology)

**TABLE II**—Distribution of Cases by Histopathological Findings.

Findings	Total cases (n=31)		Hp positive cases (n=7)	
	No.	%	No.	%
<i>Antral Gastritis</i>	<b>15</b>	<b>48</b>	7	100
• Mild	(9)	(29)	(3)	(43)
• Moderate	(6)	(19)	(4)	(57)
• Severe	(0)	(—)	(0)	(—)
<i>Duodenitis</i>	<b>14</b>	<b>45</b>	6	86
• Mild	(7)	(23)	(2)	(29)
• Moderate	(5)	(16)	(2)	(29)
• Severe	(2)	(6)	(2)	(29)
<i>Villus stunting</i>	<b>4</b>	<b>13</b>	2	29

host bacterium relationship determines the clinical manifestations of the disease(7). A diagnosis of Hp colonization could be made in 7 of our children (23%) based on histopathological changes on antral biopsy and RUT.

There is a proposed link between Hp infection and RAP reported to range from 5-34%(8,9). Estimation of prevalence of Hp in RAP in comparison to asymptomatic pediatric population by using endoscopy guided biopsies in the latter is obviously unethical. Therefore prevalence of Hp in asymptomatic children of developing and developed populations have been estimated using serology alone. This varies widely, from 4-75%, higher rates being generally from developing countries(10). Macarthur *et al.*(3) made a MEDLINE search from January 1983 through July 1994 and found inconsistent prevalence rates of infection in children with recurrent abdominal pain (range, 0-81%; median, 22%). The rates were still lower in children meeting Apley's criteria (range 0-9%; median 6%). Our results also do not support any significant association of Hp in the etiology of

RAP since as many as 19% controls also had significant titers of anti Hp IgG antibodies. However, a small sample size of the present study limits drawing any firm conclusions from these results.

Colonization of gastroduodenal mucosa by Hp appears to be the primary event in the pathogenesis of the infection. However, simply identifying the organism on histology or culture would not explain its association with RAP(7). The inconsistent link of Hp and RAP has not gained sufficient support to draw any casual inference, since it does not fulfill the Koch's postulates(11). In the absence of any gastric/duodenal ulcer in Hp colonized children in our study and the current understanding that DNA sequences in Hp genome are different in patients with peptic ulcer as compared to simple gastritis(12), no definite etiological role can be ascribed to Hp in causing RAP in these children. However, significant correlation of Hp with chronic antral gastritis is consistent with the large body of evidence for the same(13,14). Antral gastritis detected in our study primarily had chronic inflammatory cell infiltrate

**TABLE III**—Association of Hp With Risk Factors and Clinical/Histopathological Profile.

Histopathological changes/Risk factors	Cases (n=31)			Controls (n=26)		
	Total No.	Hp positive cases No.	(%)	Total No.	Hp positive cases No.	(%)
Chronic antral gastritis*	15	7	(47)	—	—	—
Chronic duodenitis**	14	6	(43)	—	—	—
Villus stunting	4	2	(50)	—	—	—
Esophagitis	5	2	(40)	—	—	—
Age > 10 yrs***	10	5	(50)	7	3	(43)
Associated vomiting	7	1	(14)	—	—	—
Overcrowding	26	5	(19)	19	4	(21)
Low socio-economic status	11	1	(9)	8	—	—
Family h/o upper GI complaints	7	3	(43)	1	—	—
Stored water used for drinking	25	6	(24)	20	5	(25)
Unsanitary disposal of excreta	4	—	—	—	—	—
Hand pump water	4	—	—	1	—	—
Unbricked house	2	—	—	—	—	—
Sharing of bed	29	7	(24)	22	5	(23)

\* Significant in cases ( $p = 0.002$ )

\*\* Significant in cases ( $p = 0.02$ )

\*\*\* Significant in cases ( $p = 0.02$ ) and controls ( $p = 0.04$ )

with evidence of lymphoid follicles in two positive cases. Lymphonodular hyperplasia of this type is unique to pediatric Hp infection. Cobblestone appearance of the antrum has also been described in children with Hp infection(15), but was not observed in our patients.

There is a strong correlation between duodenal ulceration and Hp gastritis in children(15). Duodenal ulcer was not observed in any child in our study. However, a statistically significant association ( $p=0.02$ ) was observed between histo-

pathological evidence of duodenitis and Hp colonization. Relatively few workers have identified Hp associated duodenitis. Madsen *et al.* in a study of 45 adult patients found increased frequency of chronic active duodenitis in patients with Hp compared with those lacking it ( $p=0.015$ )(16). Our study has also strengthened the association of Hp and duodenitis. This raises the question whether Hp induced duodenitis is harbinger of duodenal ulcer?

Detection of anti Hp IgG antibodies is not only a good screening test but its use in

monitoring the effectiveness of therapy has also been suggested. However, serology may be false negative in recently acquired infection and if the causative strain of Hp is genetically different from the one which the serology kit is expected to test (serology kits are procured from abroad at present). Serology has very little diagnostic value since a positive result does not always suggest acute infection and even though a significant drop in IgG antibodies is expected after eradication of Hp infection the decline in these levels is slow (takes months to reach these levels) which limits its use to evaluate efficacy of eradication therapy soon after it is completed.

Diagnosis with the help of serology as well as RUT are known to be highly sensitive and specific(17). Histology scores even better. However, sampling error is thought to be a minor difficulty in the histological diagnosis of Hp due to its patchy distribution(17). This could be the cause of false negative result of histology in two cases in this study. On the other hand, these two cases, who had both RUT and serology positive, could be false positive, which is less likely. If histology is regarded as the gold standard then the sensitivity and specificity of RUT/serology in the present study is 100% and 93%, respectively. These observations are similar to those reported by earlier workers(17).

Increasing age has consistently been shown to be a major risk factor for Hp infection and this is evident in this study group also. Recent data has shown that overcrowding(18), sharing a bed(19), low socio-economic group with low parental education, low family income and general living conditions(12,20), and consumption of contaminated water(20) are major risk factors for Hp infection. However, no such correlation is reflected by this study; overall low socio-economic status of most of the

children in the study group being the limiting factor.

In conclusion, Hp infection was not commonly associated with RAP in our patient population; however, a small size limits firm conclusions. Antral gastritis and chronic duodenitis had a significant correlation with Hp colonization. RUT was found to be a reliable diagnostic test to detect Hp.

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