Journal of the Egyptian Society of Parasitology, Vol.43, No.3, December 2013
J. Egypt. Soc. Parasitol., 43(3), 2013: 755 – 766

SEROPREVALENCE OF HELICOBACTER PYLORI INFECTION AMONG FAMILY MEMBERS OF INFECTED AND NON-INFECTED SYMPTOMATIC CHILDREN

By

MOHAMMED E. HAMED[1*], HATEM M. HUSSEIN[1], HOSAM F. EL SADANY[1], ASHGAN A. ELGOBASHY[1] AND AMAL H. ATTA[2]

Departments of Pediatrics[1] and Microbiology[2], Faculty of Medicine, Zagazig University, Egypt (Correspondance[*]: E-mail:mhali.love580 @gmail.com Fax. 0552593096

Abstract

This study determined the prevalence of seropositivity of anti-*H. pylori* IgG antibodies, and evaluated some socio-epidemiologic characteristics among family members of infected and non-infected symptomatic children.

One hundred children with upper gastrointestinal symptoms without previous H. pylori eradication treatment were prospectively studied by both upper endoscopy with histopathological biopsies examination, and serum anti-*H. pylori* IgG test between July 2012 to June 2013. The patients were subdivided into: *H. pylori* infected children (GI), and *H. pylori* non-infected children (GII). Also, 320 of their family members were examined for serum anti-*H. pylori* IgG and stool antigen tests. Sheets were filled out included personal and medical history.

The results showed statistically significant difference between both groups as regard dyspepsia, anemia, and histopathological findings (chronic active gastritis, peptic ulcer, and duodenitis). Family members were subdivided into: those of *H. pylori* infected symptomatic children (165) and those of *H. pylori* non-infected symptomatic children (155). Anti-*H. pylori* IgG prevalence was significantly higher in relatives of GI than those of GII (69.1% vs. 29%; $p<0.05$). The seroprevalence of H.pylori infection in all family members was (49.7%). Mothers of GI showed the highest seroprevalence (39.5%) as compared to fathers and siblings (22.8%, & 37.7%, respectively). Relatives of GI with low socioeconomic status, and lived in rural area showed the highest seroprevalence (82.5%, &78.1 % respectively)

Keywords: *Helicobacter pylori*, IgG-positivity, Children, Parents, Socio-epidemiology

Introduction

Helicobacter pylori is a spiral gram-negative microorganism that is distributed worldwide. It is estimated that over 50% of the world population are infected with *H. pylori*. *H. pylori*–associated infection is either usually clinically silent or its signs and symptoms are non-specific. Gastro-esophageal reflux, esophagitis, delayed gastric emptying, and various motility disorders are the main signs or symp-

toms (Herbst, 2000; Go and Crowe, 2000).

The epidemiology of *H. pylori* is very complex as different factors influence the infection even within the same geographic area (Dore and Vaira, 2003). The infection is mainly acquired during childhood (Sykora *et al*, 2006). The prevalence is typically higher in developing countries (greater than 80%) and lower in the developed ones (typically less than 40%) with a declining pattern worldwide (Perez-Perez *et al,* 2004; Kusters *et al,* 2006).

The route of transmission of *H. pylori* is not completely understood. The only known reservoir of *H. pylori* is the human stomach (Megraud and Broutet, 2000). There is evidence supporting a gastro-oral, oral-oral and fecal-oral transmission, without conclusive fixed data of the main transmission route (Azevedo *et al*, 2009). Person-to-person transmission can be subdivided in two main categories: vertical and horizontal transmission. The vertical family transmission spreads from ascendants to descendants, while horizontal one involves contact with individuals out-doors but does not exclude environmental role (Schwarz *et al*, 2008). In Egypt, Abu-Zekry *et al*. (2013) stated that screening for *H. pylori* infection should be performed for school-aged children who have GI complaints, especially for those who complain of recurrent abdominal pain.

Many sero-tests are available; non-invasive and invasive tests, the last ones require gastric tissue for detecting the organism and include culture, rapid urease test, histopathology, PCR, and FISH test. Noninvasive tests include H. pylori Ag in stool, anti *H. pylori* IgG in serum, urine, and oral samples, and the ^{13}C-urea breath test (Guarner *et al*, 2010).

The present study aimed at determination of the prevalence of seropositivity of anti-*H. pylori* IgG antibodies, and evaluation of some socio-epidemiologic characters among family members of infected and non-infected symptomatic children.

Patients, Materials and Methods

This prospective study was carried out on one hundred children with upper gastrointestinal symptoms including the recurrent abdominal pain, repeated vomiting, dyspeptic symptoms, and hematemesis, admitted to the Pediatric Endoscopy and Gastroenterology Unit, Zagazig Department of Pediatrics, from July 2012 to June 2013 and their family members. All patients were subjected to full history taking, thorough clinical examination including anthropometric measurements i.e. weight, height relative to age, laboratory investigation as CBC, CRP, ESR, PT, PTT, liver function tests, routine stool, urine analysis, serum iron and ferritin by atomic absorption of Thermo 400 for those with hypochromic microcytic anemia, and serum *anti-H. pylori* IgG. Radiological investigations included abdominal ultrasound, and gastrographin swallow or meal when indicated. Upper GIT endoscopy was done. The patients were classified into: *H. pylori* infected GI, and non-infected GII. The presence of H. pylori infection was retained when histopathology examination of endoscopic biopsies and/ or anti-*H. pylori*

IgG were positive. A negative result was retained when both tests were concomitantly negative.

Regarding family members, we chose who were in close contact with the patients and sharing the same living conditions, they were mothers, fathers, and siblings. They were interviewed and the following data were recorded age, sex, presence or absence of dyspeptic symptoms, geographic distribution (rural or urban), and socioeconomic class based on the scoring system of Fahmy and El-Sherbini (1983). Family members were subjected to laboratory investigations in the form of measurement of *H. pylori* IgG antibodies in their sera and *H pylori* antigen in stools. The presence of *H. pylori* infection was retained when anti-*H. pylori* IgG and/or *H. pylori* stool antigen were positive. A negative result was retained when both tests were concomitantly negative

Exclusion criteria: Patients who were aged less than 4 years or aged over 15 years or who had any other chronic diseases or used medicines which affect the gastrointestinal system especially previous H. pylori eradication treatment were excluded.

Histology: During upper endoscopy down to the second part of the duodenum, multiple biopsies were taken from esophagus, pyloric antrum, corpus, and duo-denum by using the Fujinon endoscope. These biopsies were fixed in 10% formaldehyde solution, stained with hematoxylin, eosin, and modified Giemsa (Alam El-Din *et al*, 2013). All histological sections were evaluated by the same pathologist, who was blinded to the patients' clinical conditions. An expert pathologist characterized the presence of spiral bacteria in the mucosal layer or on the surface of epithelial cells as a positive test for *H. pylori*.

Detection of H. *pylori* IgG in sera: A venous blood sample was obtained from each patient and family member. Serum specimens were tested for the presence of IgG antibodies against *H. pylori* using a quantitative ELISA (HEL-pTEST II; AMRAD, Kew, Australia). Reference standards were used to produce a standard curve to quantitate *H. pylori* antibody levels in patients' and their family members' samples. The results were expressed in arbitrary units per milliliter. The antigen was an inactivated native antigen of *H. pylori*. Positive results can be expressed in units (U), interpolating the optical density values of the 5 calibrators and comparing the value of the sample with the following results: Positive results if > 16.0 U/ml, Negative results if <10.0 U/ml, Equivocal if it is 10.0- 16.0 U/ml.

Detection of *H. pylori* antigen in stool: Immunochromatographic or rapid or quick tests were used for all family members. This method based on an immune-chromography using monoclonal antibodies (Schwarzer *et al*, 2007).

The study was approved by the research and ethical committee, Faculty of Medicine, Zagazig University. The parents of patients signed written consents for the contribution of them and their children in the current study.

Statistical analysis: All data were analyzed using SPSS (version 15.0. SPSS Inc... Chicago, IL). Statistical analysis was performed using Students t-test or Mann-Whitney test, corrected X^2 test or Fisher's exact Test and Spearman correlation, when appropriate. The results are expressed as counts and percentages for qualitative variables and as medians and ranges for discrete variables. A p-value <0.05 was considered to be statistically significant. Data are presented as the mean ± SD in the tables.

Results

During the study period (100) patients were evaluated consecutively and classified into group I (50), and group II (50) according to histopathology, and serum anti-*H. Pylori* IgG test results, both positive and both negative respectively. H. pylori infected patients' ages ranged from 4 to 13 years (mean 10.24±2.16 years old). They were 28(56 %) males, and 22 (44%) females. H. pylori non-infected patients' ages ranged from 6 to 12 years (mean 9.5 ± 1.9 years old). They were 20(40%) males, and 30 (60%) females. There was no significant difference in rates of seroprevalence between boys and girls, nor for age between both groups (P > 0.05).

A statistically significant difference between group I, and group II patients was found (Tab. 1) in relation to dyspeptic symptoms, pallor, and epigastric tenderness (p<0.05), however, no statistically significant difference between both groups regarding other clinical profile (p>0.05). The Seroprevalence of H.pylori infection in all studied patients according to anti-*H.pylori* IgG was (44+8) /100 (52%).

The significant differences between GI, and GII patients were found in relation to Hb, serum iron, and ferritin with mean of 10.8±1.1 vs.11.8±0.8g/dl, 19.1 ±1.72 vs. 23.3±2.88µg/dl, and 7.37± 0.74 vs. 8.33±0.57ng/ml, respectively (p<0.05).

In the present study, showed a significant difference between GI & GII patients regarding histopathologic results as chronic active gastritis, peptic ulcer, and duodenitis (p<0.05) but, without significant difference between both groups regarding reflux oesophagitis (Tab. 2).

Validity of IgG antibodies in diagnosis of *H. pylori* infection in GI & GII was assessed. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 88%, 84%, 84.6%, 87.5 & 86%, respectively.

Family members were evaluated consecutively for infection and subdivided into 2 groups: family members of *H. pylori* infected symptomatic patients (GI relatives =165), and family members of H. pylori non-infected symptomatic patients (GII relatives=155). Family members of GI who lived in rural area showed the highest prevalence (72.7%), which was statistically highly significant (p<0.001). Low socioeconomic class in family members of GI showed the highest prevalence (72.7%), which was highly significant (p<0.001). No significant difference was among family members of GI & GII in relation to non-ulcer dyspepsia

including heart burn, postprandial fullness and vomiting (Tab. 3).

A highly statistically significant difference among family members of GI & GII was found in relation to serum IgG (mean 24.82±6.7 vs. 14.63±4.8U/ml), which were significantly higher prevalent in family members of GI than that of GII (69.1% vs. 29% as $p<0.05$). IgG antibodies showed highly significantly prevalent in mothers of GI than that of GII (90% vs. 18% as $p<0.001$). Mothers of GI showed the highest prevalence (39.5%) (45/114) of IgG antibodies among other family members, which included the fathers and siblings (22.8%, & 37.7%).

Also, the fathers, and siblings of GI showed higher prevalence of IgG antibodies than those of GII (52% vs. 28%, and 66.2% vs. 40%, respectively). The highest seroprevalence of IgG antibodies (78.1%) was found in Family members of GI who lived in rural area. Family members of GI with low socioeconomic status showed the highest seroprevalence (82.5%) of IgG antibodies (Tab. 4).

The prevalence of *H. pylori* IgG in all family members was (114+45) / (165+155) (49.7%). Concordant results between the two noninvasive methods were found in 117 of 165 (70.9%) relatives of GI, and 48 of 155(31%) relatives of GII (Tab. 5).

Validity of IgG antibodies in diagnosis of *H. pylori* infection in family members was assessed and the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 80.3%, 81.3%, 82.5%, 79.1%, & 80.8%, respectively.

Table 1: Clinical profile and seroprevalence of anti-H. pylori IgG among groups.

Clinical profile	GI (N=50)		G II (N=50)		χ^2	P-value
Symptoms	NO	%	NO	%		
Recurrent abdominal pain (RAP)	26	52.0	23	46.0	0.36	0.548
Repeated vomiting	20	40.0	22	44.0	0.16	0.685
Haematemesis	10	20.0	8	16.0	0.27	0.60
Dyspeptic symptoms	20	40.0	6	12.0	10.19	0.001**
Signs						
Pallor	18	36.0	6	12.0	7.89	0.004**
Epigastric Tenderness	16	32.0	4	8.0	9	0.003 **
Periumbilical Tenderness	26	52.0	24	48.0	0.16	0.689
weight for age < 5 th centile	10	20.0	8	16.0	0.27	0.603
Height for age < 5 h centile	10	20.0	8	16.0	0.27	0.603
Anti-H.Pylori IgG X±SD	22.3±6.7		10.0±3.3		t-test	
Range	9.0-34.0		7.0-17.0		8.1	0.0001**
Anti H.pylori IgG Pos	44	88	8	16	χ^2	
Anti H.pylori IgG Neg	6	12	42	84	51.92	<0.001**

** Boldface indicate $p<0.05$, Pos; positive, Neg; Negative

Table 2: Histopathological results among groups.

Socio-demographic characters	GI Relatives (N = 165)		GII Relatives (N=155)		t-test	P-value
Age (years)						
$\bar{X}$ ±SD	32.47±8.2		31.90±7.4		0.32	0.571
Range	6.07-48.4		7.1-46.7			
Gender	No	%	No	%	χ^2	
Male	75	45.5	70	45.2	0.00	0.958
Female	90	54.5	85	54.8		
Relatives					χ^2	
Father	50	30.3	50	32.3	0.14	0.706
Mother	50	30.3	50	32.3	0.14	0.706
Sibling	65	39.4	55	35.4	0.52	0.47
Geographic distribution						
Rural	120	72.7	85	54.8	11.11	<0.001**
Urban	45	27.3	70	45.2		
Socioeconomic Class					χ^2	
Low	120	72.7	70	45.2		
Middle	30	18.2	61	39.4	25.51	<0.001**
High	15	9.1	24	15.4		
Clinical profile	NO	%	NO	%	χ^2	P-value
No dyspeptic symptoms	72	43.7	80	51.6		
Heart burn	30	18.2	14	9		
Postprandial fullness	57	34.5	52	33.5	6.76	0.08
Vomiting	6	3.6	9	5.9		

** Boldface indicate p<0.05

Table 3: Sociodemographic characters and clinical profile among family members.

Socio-demographic	GI Relatives (N =		GII Relatives		t-test	P-value
Age (years)						
X SD	32.47 8.2		31.90 7.4		0.32	0.571
Range	6.07-48.4		7.1-46.7			
Gender	No	%	No	%	χ^2	
Male	75	45.5	70	45.2	0.00	0.958
Female	90	54.5	85	54.8		
Relatives					χ^2	
Father	50	30.3	50	32.3	0.14	0.706
Mother	50	30.3	50	32.3	0.14	0.706
Sibling	65	39.4	55	35.4	0.52	0.47
Geographic distribution						
Rural	120	72.7	85	54.8	11.11	<0.001*
Urban	45	27.3	70	45.2		
Socioeconomic Class						
Low	120	72.7	70	45.2		
Middle	30	18.2	61	39.4	25.51	<0.001*
High	15	9.1	24	15.4		
Clinical profile	NO	%	NO	%	χ^2	P-value
No dyspeptic symptoms	72	43.7	80	51.6		
Heart burn	30	18.2	14	9		
Postprandial	57	34.5	52	33.5	6.76	0.08
fullness Vomiting	6	3.6	9	5.9		

** Boldface indicate p<0.05

Table 4: Seroprevalence of *H. pylori* among family members regards anti-IgG.

Virulent	GI Relatives (N = 165)	GII Relatives (N=155)	t-test	P-value
Anti-H.pylori IgG (U/ml)				
X ±SD	24.82±6.7	14.63±4.8		
Range	2.0 – 38.22	3.0 - 24.23	174.98	<0.001**
IgG^{Pos} > 16 U/mL	No %	No %	χ^2	
IgG^{Neg}	114 69.1	45 29		
< 10 U/mL	51 30.9	110 71	51.3	<0.001**
Mothers	No (50) %	No (50) %		
IgG^{Pos}	45 90	9 18		
IgG^{Neg}	5 10	41 82	52.17	<0.001**
Fathers	No (50) %	No (50) %		
IgG^{Pos}	26 52	14 28		
IgG^{Neg}	24 48	36 72	6	0.014*
Siblings	No (65) %	No (55) %		
IgG^{Pos}	43 66.2	22 40		
IgG^{Neg}	22 33.8	33 60	8.21	0.004*
Geographic distribution	No (114) %	No (45) %		
Rural	89 78.1	27 60		0.02*
Urban	25 21.9	18 40	5.34	
Socioeconomic Class	No (114) %	No (45) %		
Low	94 82.5	28 62.2		
Middle	15 13.2	11 24.4	7.97	0.019*
High	5 4.3	6 13.4		

** Boldface indicate p<0.05, Pos ; Positive, Neg ; Negative

Table 5: *H. pylori* in family members of both non-invasive tests (anti-IgG & stool antigen).

both non-invasive tests	GI Relatives (N = 165)	GII Relatives (N=155)	χ^2	P-value
	No %	No %		
Pos	117 70.9	48 31.0	49.5	<0.001**
Neg	48 29.1	107 69.0		
Mothers	No (50) %	No (50) %		
Pos	46 92	10 20	51.05	<0.001**
Neg	4 8	40 80		
Fathers	No (50) %	No (50) %		
Pos	26 52	14 28	6	0.014*
Neg	24 48	36 72		
Siblings	No (65) %	No (55) %		
Pos	45 69.2	24 43.6	7.99	0.005*
Neg	20 30.8	31 56.4		
Geographic distribution	No (117) %	No (48) %		
Rural	92 78.6	30 62.5	4.6	0.032*
Urban	25 21.4	18 37.5		
Socioeconomic Class	No (117) %	No (48) %		
Low	93 79.5	29 60.4	6.43	0.04*
Middle	15 12.8	12 25.0		
High	9 7.7	7 14.6		

Discussion

Helicobacter pylori infection is usually acquired in early childhood. Non-invasive methods for detection of H. pylori infection are required to study its incidence, and transmission (Konstantopoulos *et al*, 2001). Serology is the noninvasive technique to detect infection because it is simple, widely available, and inexpensive. The reported sensitivity, and specificity of IgG serology is highly variable, ranging from

30% to 100% (Taha *et al,* 1993; Schembri *et al,* 1993), in agreement with those of our study which were 80.3%, and 81.3%, respectively. The present study showed seroprevalence of *H. pylori* infection of 52% among 100 children, aged 4-13 years, in similarity with investigators from Turkey reported the seropositivity of *H. pylori* in 43.9% of 346 children aged 6 months-16 years and in 64.4% of 466 children aged 6-17 years (Yilmaz *et al,* 2002; Selimoğlu *et al,* 2002).

In the present study, no significant association of H. pylori infection and recurrent abdominal pain (RAP), which agreed with Spee ***et al.*** (2010) however, Mukherjee *et al.* (2005) reported that there is a significant association of H. pylori infection and RAP. No significant association of H. pylori infection and hematemsis was found, in contrast to Lianes *et al*. (2012) who reported that haematemesis was significantly higher in *H. pylori* infected children. This may be attributed to few number of cases presented with hematemesis in our study .A significant association of *H. pylori* infection and dyspeptic symptoms was reported, in agreement with Babu *et al.* (2005) who reported that there was a statistically significant benefit of eradication of H. pylori inpatients with ulcer-like non ulcer dyspepsia. However, Ribeiro *et al.* (2010) reported that there was no statistical association between dyspepsia and positive serology for *H. pylori.* A significant association of *H. pylori* infection and epigastric tenderness was found, in agreement with Yang *et al.* (2005) who reported that the presentation of epigastric pain can be considered as a warning alarm to screen for *H. pylori* infection. No significant association of H. pylori infection and growth parameters affection was found, in agreement with Chi *et al*. (2009) who reported no evidence that infection with *H. pylori* is related to growth failure. But, Goodman *et al*. (2011) reported that chronic *H. pylori* infection is accompanied by slowed growth in school-age Indian children. There was a significant association of *H. pylori* infection and iron deficiency anemia, which agreed with Muhsen *et al*. (2010) who found that *H. pylori* was associated with higher prevalence of anemia in school-age children independently of socioeconomic variables. But, Zamani *et al*. (2011) did not find a significant relationship between *H. pylori* infection and low serum Ferritin or iron deficiency anemia.

In the present study, upper GIT endoscopy and histopathological examination showed that chronic active gastritis, peptic ulcer, and duodenitis were associated with H. pylori infection, which agreed with Bittencourt *et al*. (2006); Yakoob *et al*. (2010) and Genta *et al*. (2010). No significant relation was found between *H. pylori* and reflux oesophagitis, which agreed with Chung *et al*. (2011) who found that *H. pylori* positive patients were less likely to have GERD and the oesophagitis severity decreased compared to those who were *H. pylori* negative. Ali (2012) reported that *H. pylori* infection was associated with infantile colic and might be a main causative factor.

Some authors demonstrated intrafamilial clustering of *H. pylori*-associ-

ated infection strong evidence of intra-familial spread (Bujanover *et al*, 1993). The positivity of parents converted infection to their children (Zhou *et al*, 2000).

In the present study, *Helicobacter pylori* infection among family members of infected symptomatic children was significantly higher than that in non-infected symptomatic children. This finding agreed with Roma *et al*. (2009) who reported that the prevalence of *H. pylori* infection was significantly higher among families of infected children. The presence of at least one infected family member in all *H. pylori*-positive children suggested person to person *H. pylori* transmission.

In the present study, mothers of infected symptomatic children showed the highest sero-prevalence of infection among all family members that agreed Weyermann *et al.* (2009) who reported that control for *H. pylori* status of family members was crucial for estimating the role of mothers, fathers, and siblings in the transmission of childhood *H. pylori* infection. In populations with low *H. pylori* prevalence, the infected mother was likely to be the main source for childhood infection. Also, Fialho *et al.* (2010) reported that the transmission of *H. pylori* occurs from infected mothers to their offspring and among siblings, notably from younger siblings to the older ones. This can be explained that infected mother mouth secretions may be the source of transmission to the infant and child. Also by using common spoons, the licking of pacifiers or teats of feeding bottles, or even for chewing or tasting children's food must be taken into consideration.

In the present study, siblings of infected symptomatic children showed (66.2%) sero-positive. Drumm *et al*. (1990) found seropositivity up to 80% of siblings of children colonized with *H. pylori* compared to 13% of age-matched controls.

The fathers' of infected symptomatic children was positive in 52%, which was lower than 86 % reported by Escobar *et al*. (2004)**.**

As infected children and their family members were in close contact, and shared in the same environmental factors, our study showed the highest seroprevalence of *H. pylori* infection was in family members of infected children with low socioeconomic class, and those lived in rural areas. Páez Valery *et al*. (2006) reported high prevalent among socially and economically deprived children, and poor housing conditions. Also, Etukudo *et al.* (2012) reported that *H. pylori* infection in Nigerian children was high and associated with low social class, poor domestic water and poor sanitation. Improvement of water supply, human and domestic waste disposal systems and ultimately poverty alleviation would control this bacterial infection that has severe long term consequences.

The present overall higher rate of infection in family members of infected children lived in a rural area was 78.1% than in an urban area (21.9%). However, Ceylan *et al.* (2007) reported that infection in an urban population (25.8%) than in a rural population

(10.2%), which may be attributed to environmental and habitual conditions

Conclusion

The seroprevalence of *H. pylori* infection is significantly higher among family members of infected symptomatic children. Infected family members, especially mothers, have an important role of transmission of *H. pylori* within families. All children having any upper gastrointestinal complaints should be tested for infection and whether *H. pylori* was prevalent among their family members. Low socioeconomic status, and/or living in rural area are major risk factors for a higher prevalence of *H. pylori* infection.

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