Is Helicobacter pylori infections in immunocompromised children a risk factor for cancer?

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ABSTRACT

The frequency of Helicobacter pylori in children with malignancy was evaluate in the present study.

Among 51 children included in the study, 29 children were in malignancy group (79.3% of them having positive one step diagnostic test),while 22 children were control group (54.5% of them having positive one step diagnostic test).h.pylori infection was significantly higher in the malignancy group comparedto the control group (P<0.05); 44.8% having positive culture for H.pylori ,while only 18.2% of control having positive culture for H.pylori. the results showing that there is no significant association between H.pylori and the type of cancer with P > 0.05. And there is a significant association between H.pylori and age more than 5 years with p< 0.05 which is statistically significant among patient groups. The results also showed that there is no significant association between H.pylori and sex among both patient and control groups with P> 0.05.

Key words: H. pylori, malignancy, children.

INTRODUCTION

Helicobacter pylori (H. pylori) has been classified as a carcinogenicpathogen (1). Its prevalence is high in developing countries. A part from the gastro-intestinal pathological changes caused by this organism, reports on the association between *H. pylori* infection and extra gastro-intestinal diseases have been increasing (2). Although impaired host immunity should be associated with a high prevalence of this infection, a definitive relationship has not been established. In this study a cross-sectional study had been conducted to determine the prevalence of *H. pylori* infection in immunocompromised Thailand children (3). From 2003 to 2004, a total of 60 children <18 years of age, who received corticosteroids, immunosuppressive drugs, or both, were enrolled consecutively into this study. Patients who had taken proton pump inhibitors and antimicrobial drugs 2 weeks before the study began were excluded. Stool specimens were collected and immediately stored at 20°C before analysis with the *H. pylori* stool antigen test (4). Although no study has validated this test in Thai children, most studies report its high sensitivity and specificity (>90%).The study reported a significant relation of *H. pylori* and childhood cancer with 16.6% among children with cancer and only 3.3% among those without cancer (2,5). Helicobacter pylori infection seems to be associated with an increased risk of developing gastric cancer. However, only a small number of infected individuals will develop gastric cancer (6), including mucosa-associated lymphoid tissue lymphoma and adenocarcinoma. The infection is contracted primarily in childhood and infection from childhood appears to enhance the risk for carcinogenesis (7). In 1994 Helicobacter pylori was classified as a group 1 carcinogen for gastric cancer by the International Agency for Research on Cancer (1). The colonization with *H. pylori* determine the development of gastric atrophy, also called multifocal atrophic gastritis. This involves loss of gastric

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mucosal glands and hence altered gastric secretion. The evolution of gastric atrophy may be the first step towards the development of gastric cancer. This lesion might then lead to further changes, among them intestinal metaplasia and dysplasia, conditions that typically precede cancer (3,6,8). Cancer affecting the mucosa-associated lymphoid tissue (MALT) in the stomach, or gastric MALT lymphoma, is a rare type of non-Hodgkin lymphoma characterized by B lymphocytes, a type of immune cell, that slowly multiply in the stomach lining (9). The lining of the stomach normally lacks lymphoid (immune system) tissue, but this tissue nearly always appears in response to colonization of the lining by *H. pylori* bacteria. MALT lymphomas account for approximately four percent of all cases of lymphoma (10). Nearly all patients with gastric MALT lymphoma are infected with *H. pylori*, and the risk of developing this tumor is over six times higher in infected people than in uninfected people (11). Furthermore, up to 80 percent of patients with gastric MALT lymphoma achieve complete remission of their tumors after treatment with *H. pylori*-eradicating antibiotic therapy (12).To colonize the stomach *H. pylori* must survive the acidic pH of the lumen and burrow into the mucus to reach its niche, close to the stomachs epithelial cell layer. The bacterium has flagella and moves through the stomach lumen and drills into the mucoid lining of the stomach (13). Many bacteria can be found deep in the mucus, which is continuously secreted by mucous cells and removed on the luminal side. To avoid being carried into the lumen, *H. pylori* senses the pH gradient within the mucus layer by chemotaxis and swims away from the acidic contents of the lumen towards the more neutral pH environment of the epithelial cell surface (5,14). *H. pylori* is also found on the inner surface of the stomach epithelial cells and occasionally inside epithelial cells (15). It produces adhesins which bind to membrane-associated lipids and carbohydrates and help it adhere to epithelial cells. *H. pylori* produces large amounts of the enzyme urease, molecules of which are localized inside and outside of the bacterium (16). Urease breaks down urea (which is normally secreted into the stomach) to carbon dioxide and ammonia (ammonia is converted into the ammonium ion by taking hydrogen from water upon its breakdown into hydrogen and hydroxyl ions, Hydroxyl ions then react with carbon dioxide, producing bicarbonate which neutralizes gastric acid) (11,17). The survival of *H. pylori* in the acidic stomach is dependent on urease, and it would eventually die without the enzyme (18,19). The ammonia that is produced is toxic to the epithelial cells, and, along with the other products of *H. pylori* including protease, vacuolating cytotoxin A (VacA), and certain phospholipases damages those cells (4,20,21).

The present study aimed to find the relationship between occurrence of H.pylori and children cancer by study the biopsy cultures of H.pylori from immunocompromised children.

MATERIALS AND METHODS

Patient group

A prospective comparative case-control study was carried out between March to September 2009 ,the study included 29 children (20 male and 9 female) with different types of malignancies who were admitted to pediatric oncology unit for treatment at Basrah Maternity and Children Hospital were included in the study ,and their age ranged between 18 month to 11 years, and regarded as patient group. Demographical and clinical data were prospectively recorded for all studied population as follows

- type of cancer (ALL, AML, solid tumor), risk group of patient with leukemia.

- clinical features including symptoms and signs: epigastric pain, dyspepsia, abdominal pain and Vomiting.

- history of peptic ulcer or endoscopy or recurrent abdominal pain.-consanguinity.

Control group

A total of 22 children (12 male and 10 female) with similar gender and age-were matched as control group.

Laboratory data

Investigations were done in form of gastric aspirate culture for H.pylori and one step diagnostic test (which detect the antigenin patient sera for H.pylori).

H.pylori gastric aspirate culture

Gastric aspirate culture was taken from the patients who are included in the study (by using nasogastric tube) and special culture media which is called (Columbia agar), three antibiotics (vancomycine, trimethoprim, polymyxin-B) had been used to inhibit all Gram positive and negative bacteria, the cultivation was done for five days and then examined to detect H.pylori.

Table 1: Distribution of patients and control according to age and gender.

Age/Gender		Patient group No.	%	Control group No.	%	P value
Age	>5years	15	51.7	12	54.5	>0.05
	<5years	14	48.3	10	45.5	
	Total	29	100	22	100	
Sex	Male	20	69	12	54.5	>0.05
	Female	9	31	10	45.5	
	Total	29	100	22	100	

One step diagnostic test for immunological study

One milliliter of serum was taken from the patient for the one step diagnostic test. One step diagnostic test (designed by human company, Belgium) detect the antibodies to H.pylori with 95.9% sensitivity and 89.6% specificity, but it can be positive in other campylobacters. The limitations of this test attributed to that the test is used as qualitative rather than quantitative and does not indicate the titer of the antibody in the specimen.

Statistical analysis

Statistical analysis was done using spss (standard program for social sciences) program ver. 17, data where expressed and comparison of proportions was performed using chi-square test. P value of less than 0.05 was considered as statistically significant, P value of less than 0.01 as highly significant and P value of less than 0.001 as extremely significant.

RESULTS

51.7% of patient were >5 years in comparison to 54.5%of control were >5 years so there was no significant difference regarding age group between patient and control.

29 children were patient group the majority of them were male with male: female ratio equal to 2.2, while 22 children were control group with male: female ratio equal to 1.2, with a p value >0.05, so there was no significant difference between the two groups regarding sex (Table 1).

Among 51 children included in the study, 29 children were patients (of them 79.3% having positive one step diagnostic test), while 22 children were control (of them 54.5 having positive one step diagnostic test). There is statistically significant higher percentage of patient group having H.pylori comparing to control group with a p value < 0.05 (Table 2).

Out of 29 patients; 44.8% having positive culture for *H. pylori*, while only 18.2% of control having positive culture for H.pylori. There is statistically significant higher percentage of patient group having H.pylori comparing to control group with a p value < 0.05 (Table 3).

The Table 4 showing that there is no significant association between H.pylori and the type of cancer with a p value > 0.05.

The Table 5 showing a highly significant association of H.pylori with symptom p < 0.01.

The Table 6 showed that there is a significant association between H.pylori and age more than 5 years with a p value more than 0.05 which is statistically significant among patient group.This table also showed that there is no significant association between H.pylori and sex among both patient and control groups with a p value less than 0.05 which is statistically not significant.

DISCUSSION

Helicobacter pylori represents one of the most common and medically prominent infection worldwide many researches done regarding H.pylori but only small number

Table 2: One step diagnostic test for H.pylori among patient and control.

One step diagnostic test	Patient	Control	Total	P value
ve+ H.pylori	23	12	35	< 0.05
	79.3%	54.5%	68.6%	
ve- H.pylori	6	12	18	
	20.7%	54.5%	31.4%	
Total	29	22	51	
	100%	100%	100%	

Table 3: H.pylori culture of the gastric aspirate among patient and control.

Gastric aspirate culture	Patient	Control	Total	OR	P value
ve+ H.pylori	13	4	17	0.274	< 0.05
	44.8%	18.2%	33.3%		
ve- H.pylori	16	18	34		
	55.2%	81.8%	66.7%		
Total	29	22	51		
	100%	100%	100%		

Table 4: Relation btween H.pylori gastric aspirate culture to types of malignancy.

	Acute lymphocytic leukemia	Solid tumor	Total	P value
ve+ H.pylori	10	3	13	>0.05
	76.9%	31.8%	100%	
ve- H.pylori	13	3	16	
	81.3%	18.7%	100%	

of researches done about the relation of H.pylori and childhood cancer including acute lymphocytic leukemia and solid tumor (22). This study reported that there was about 44.8% of patients with cancer had positive culture for H.pylori while 18.2% of control group. And these results was statistically significant (P > 0.05), similar results was observed by Nutpho P, Ukarapol N. et al in Thailand which also reported that there was statistically significant association between H.pylori and the type of cancer(specially acute lymphocytic leukemia) in contrast to our study which revealed no significant association between type of cancer and H.pylori (23). This study showed that patients with positive culture for H.pylori had high antibodies for H.pylori ,the same results was in the control group of our study this may be due to cross association between H.pylori and other campylobacters ,no study was done including the same results. Regarding the symptoms most of patients with H.pylori were symptomatic similar study were done by Luigi satacroce in Italy that reported 65% of patients with H.pylori were symptomatic while only 35%of them were asymptomatic (24). About the age group and sex the study reported that there was a significant association between H.pylori among patient group more than 5 years. Similar result was also reported in a study done in Australia by W. Hardikar *et al.* (25), but there was no significant association between H.pylori and sex of patients, this was similar to other study done by Mahmoud A Mohammad *et al.* in Egypt (26). In contrast with other study done by Mehmet Kanbay *et al.* in Turkey (27) which reported significant association between H.pylori and female gender. While in other study done by Marilyn L. *et al.* in California which reported a significant association between H.pylori and male gender (28). Once *H. pylori* colonize the stomach of an individual, it probably remains present for many years. However, many colonized people remain asymptomatic suggesting that the host factors are important for progression to *H. pylori* mediated diseases (29). Serology with IgG (as a non invasive test to detect H.pylori infection) is widely used in Europe. Unfortunately, serology does not provide any data as to whether there is an active or past infection (30). In this study, the Seroprevalence

Table 5: Symptoms and H.pylori among patient group.

	Symptomatic	Asymptomatic	Total	P value
ve+ H.pylori	9	4	13	<0.01
	69.2%	30.8%	100%	
ve- H.pylori	2	14	16	
	12.5%	87.5%	100%	

TABLE 6: Distribution of patient of both age and sex groups according to H.pylori gastric aspirate culture.

	Results of Gasrtric aspirate	Age		Total	P value	Sex		Total	P value
		<5years	>5year			male	female		
Patient	Gasrtric aspirate +ve	3	10	13	<0.05	8	5	13	>0.05
		23.1 %	76.9 %	100 %		61.5%	38.5%	100%	
	Gasrtric aspirate – ve	12	4	16		12	4	16	
		75 %	25 %	100 %		75 %	25 %	100 %	
Control	Gasrtric aspirate +ve	0	4	4	<0.05	3	1	4	>0.05
		0 %	100 %	100 %		75 %	25 %	100 %	
	Gasrtric aspirate – ve	10	8	18		9	9	18	
		55.6 %	44.4 %	100 %		50 %	50 %	100 %	

of anti-*H. pylori* antibodies was significantly higher in immunocompromised children than that in control subjects. Similar results were obtained by other studies in immunocompromised children, with chronic diarrhea, malnutrition, acute and chronic leukemia (31-35). The study reported a significant relation of H.pylori and children cancerwith 16.6% amongchildren with cancer and only 3.3% among those without cancer.

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