Helicobacter Pylori Infection in Patients with Hematological Diseases

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ABSTRACT:

BACKGROUND:

Helicobacter pylori (H. pylori) is a well known bacterial pathogen implicated in gastric diseases. Some studies refer to it's possible role in some hematological diseases.

OBJECTIVE:

The aim of this study is to determine the association between Helicobacter pylori infection and some hematological diseases.

MATERIALS AND METHODS:

This is a case-control study of 337 patients with a hematological disease (including acute and chronic leukaemias, Hodgkin's and non Hodgkin's lymphomas, hairy cell leukaemia, multiple myeloma, immune thrombocytopenic purpura and aplastic anemia) who were admitted to or attended hematology center at Marjan Teaching Hospital – Babylon – Iraq during the period from 1/7/2006 to 1/1/2009.

Age and sex matched control group of 337 patients who have no hematological disease. They were taken during the same period and from the same geographical area (Babylon governorate).Tests for H. pylori were done for both groups using One Step H. pylori Test Device with 93.7% total accuracy rate.

RESULTS:

H. pylori test was positive in 33.5% (113/337) and 37.3% (126/337) of control and patient groups respectively, while dyspeptic symptoms were found in 18.1% (61/337) and 39.4% (133/337) of control and patient groups respectively.

CONCLUSION:

There was no significant association between H. pylori infection and hematological diseases tested in this study in Iraqi patients from Babylon, however dyspeptic symptoms were more common in patients on steroids or chemotherapy.

KEY WORDS: helicobacter pylori (h. pylori), hematological diseases and peptic ulcer diseases.

INTRODUCTION:

Helicobacter pylori is a small, spiral-shaped bacterium that lives in the surface of the stomach and duodenum. It is the first formally recognized bacterial carcinogen and is one of the most successful human pathogens as over half of the world's population is colonized with this gram negative bacterium. Unless treated, This colonization usually persists lifelong, however; only a small proportion of infected patients experience H. pylori-associated illnesses[1].

The diagnosis of gastric infection with H. pylori usually involves upper endoscopy, However; serological methods have reached sufficient accuracy to be used as screening tests before endoscopy, or for sero-epidemiological surveys as individuals infected with H. pylori develop antibodies which correlate strongly with histologically confirmed H. pylori infection[2,3,4,5,6].

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H. pylori infection represents key factor in the etiology of various gastrointestinal diseases ranging from chronic active gastritis without clinical symptoms to non-ulcer dyspepsia, peptic ulceration, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma[1,7,8,9,10,11,12,13].

The disease outcome is the result of the complex interplay between the host and the bacterium:

- Host immune gene polymorphisms and gastric acid secretion largely determine the bacterium's ability to colonize a specific gastric niche[7,8].
- Despite the intensive proinflammatory response, the immune system isn't able to clear the organism. These immune escape mechanisms aren't well understood and it is definitely not through inhibition of dendritic cell (DCs) as H. pylori induces strong activation and maturation of human immature DCs[14]; again all these effects were found independent of the cagA and vacA status of H. pylori[15].

- Others have found role for H. pylori in the induction of apoptosis of macrophages to bypass host immune responses[8].
- H. pylori lipopolysaccharide (LPS) O-chain causes direct induction of the host immune response leading to gastritis[16].
- Bacterial virulence factors such as cagA and vacA aid in H. pylori colonization of the gastric mucosa and subsequently seem to modulate the host's immune system[7].
- cagA is translocated from H. pylori into gastric epithelial cells and undergoes tyrosine phosphorylation by Src family Kinases (SFKs). The distinctly different structures of cagA proteins in Western and East Asian H. pylori isolates may underlie the strikingly different incidence of gastric carcinoma in the two geographical areas[10]. The phosphorylated cagA may inhibit Focal Adhesion Kinase (FAK) leading to impaired cell adhesion forming elongated cell shape (hummingbird phenotype) involved in development of gastric lesions[17].
- On the other hand; cagA stimulates nuclear factor of activated T-cells (NFAT) in a manner independent of cagA phosphorylation; while vacA inhibits NFAT activity in T-lymphocytes[18].
- Many H. pylori strains have been described with different virulence genes named cagA, cage, cagT, vacA, iceA, oipA, babB and others[19,20,21]. cagA is an important virulence factor, However; it should not be used for diagnosis of H. pylori as high percentage of cagA seropositivity in H. pylori seronegative patients represents a false positive reaction[10,19].
- JHP947 is another carcinoma associated gene found in plasticity region in H. pylori[22].

  Some studies have posed the possibility that H. pylori infection may be beneficial in some humans based on increased incidence of gastro-esophageal reflux disease (GERD), barrett's esophagus and esophageal adenocarcinoma following eradication of H. pylori in some countries[1].

This may be explained by hypothesis suggesting that H. pylori induced extracellular signal regulated kinase 1 and 2 (ERK 1/2) activation may play a protective role against gastro-esophageal epithelial cell apoptosis through maintenance of bcl-2 gene expression[23].

From all these data; the role of H. pylori infection in gastrointestinal diseases is clear and by similar or other mechanisms it can induce hematological diseases. On the other hand; some infections were proved as causative or provocative factors for variable hematological diseases[24,25].

To this date; little data are available for the association between H. pylori and hematological diseases. This study is designed to look for the this possible link as H. pylori may play a causative or provocative effect in these diseases and it's eradication will have a role in treatment or the reverse may occur as these diseases may increase gastric colonization with H. pylori.

In this study; The one Step H. pylori Test Device was used which is a rapid chromatographic immunoassay for the qualitative detection of antibodies to H. pylori in serum or plasma. It is a simple test that utilizes a combination of H. pylori antigen coated particles and anti-human IgG to qualitatively and selectively detect H. pylori antibodies in serum or plasma.

Anti-human IgG is immobilized in the test line region. The sample is added to a specific area on the test device, it reacts with H. pylori antigen coated particles in the test. This mixture migrates chromatographically along the length of the test and interacts with the immobilized anti-human IgG. If the sample contains H. pylori antibodies, A colored line will appear in the test line region indicating a positive result; otherwise, it is negative[26].

This test is qualitative; so neither the quantitative value nor the rate of increase in H. pylori antibody titer can be determined[26].

This test has sensitivity > 99% and specificity about 86.7% with overall accuracy of 93.2% as compared with culture/histology of endoscopic specimens for H. pylori[6,26]. This device is produced by ACON Laboratories, San Diego, Cal, USA.

Materials and Methods

337 patients were taken representing most patients admitted to or attended hematology center at Marjan Teaching Hospital and have diagnosed with a hematological disease including malignancies (acute or chronic leukaemias, hodgkin's or non Hodgkin's lymphomas, hairy cell leukemia or multiple myeloma), aplastic anemia or immune thrombocytopenic purpura. For all of them; direct inquiry about dyspeptic symptoms was done.

The duration of the study was 30 months from 1st July 2006 to 1st January 2009.

The control group included 337 patients who were randomly selected from patients with normal blood film and negative medical history for hematological diseases (most of them were attending Al-Hilla Teaching Hospital for routine check up or for simple complaint).This control

group was chosen to be sex and age matched with patients group.

For all control cases; full medical history (including direct inquiry about dyspeptic symptoms), physical exam, Complete blood picture and blood film were done.

For both patients and control groups; a venous blood samples were taken, left to clot then centrifuged to obtain serum that tested for H. pylori using the one step H. pylori Test Device.

Statistical analysis was done using descriptive statistics, Chi-square test and Fisher's exact test (used for statistical analysis when sample size was small).

RESULTS:

A total of 337 patients were studied with age range 8-76 years and male:female ratio of 0.96:1. Age and sex matched control group of 337 patients were also taken. Tables 1 and 2

Table 1: Age distribution in control and patient groups

The group	The age group (years)			Total
	≤ 20	20 – 40	≥ 40	
Control	78	128	131	337
Patient	78	128	131	337
AL	41	64	23	128
CML	1	4	30	35
CLL	0	2	29	31
NHL	4	12	12	28
HL	5	6	10	21
MM	0	1	14	15
HCL	0	1	3	4
ITP	18	29	5	52
AA	9	9	5	23

AL: Acute leukaemia, CML: Chronic myeloid leukaemia, CLL: Chronic lymphocytic leukaemia, NHL: Non Hodgkin's lymphoma, HL: Hodgkin's lymphoma, MM: Multiple myeloma, HCL: Hairy cell leukaemia, ITP: Immune thrombocytopenic purpura, AA: Aplastic anaemia.

H. pylori test was positive in 33.5%(113/337) of control group and in 37.3%(126/337) of patient group distributed as 38.3%(49/128) in acute leukaemia(AL), 37.5%(9/35) in chronic myeloid leukaemia(CML), 35.4%(11/31) in chronic lymphocytic leukaemia(CLL), 39.3%(11/28) in non-Hodgkin's lymphoma(NHL), 38.1%(8/21) in Hodgkin's lymphoma(HL), 40.0%(6/15) in multiple myeloma(MM), 50.0%(2/4) in hairy cell leukaemia(HCL), 40.4%(21/52) in immune thrombocytopenic purpura(ITP), 39.1%(9/23) in aplastic anaemia(AA). Table 3

Dyspeptic symptoms were found in 18.1% (61/337) of control group and in 39.4% (133/337) in patient group.

Table 2: Sex distribution in control and patient groups

The group	The sex				
	Male no.	%	Female no.	%	Male:Female
Control	165	48.9	172	51.1	0.96:1
Patient	165	48.9	172	51.1	0.96:1
AL	61	47.6	67	52.3	0.91:1
CML	14	40.0	21	60.0	0.67:1
CLL	19	61.2	12	38.8	1.58:1
NHL	18	64.2	10	35.8	1.8:1
HL	10	47.6	11	52.4	0.9:1
MM	10	66.7	5	33.3	2:1
HCL	3	75.0	1	25.0	3:1
ITP	20	38.5	32	61.5	0.62:1
AA	10	43.5	13	56.5	0.77:1

AL: Acute leukaemia, CML: Chronic myeloid leukaemia, CLL: Chronic lymphocytic leukaemia, NHL: Non Hodgkin's lymphoma, HL: Hodgkin's lymphoma, MM: Multiple myeloma, HCL: Hairy cell leukaemia, ITP: Immune thrombocytopenic purpura, AA: Aplastic anaemia.

Table 3: Seropositivity of H. pylori in control and patient groups

The group	Positive H. pylori	Negative H. pylori	%	p-value
Control	113	224	33.5	-----
Patient	126	211	37.3	0.311
AL	49	79	38.3	0.539
CML	9	26	37.5	0.637
CLL	11	20	35.4	0.581
NHL	11	17	39.3	0.606
HL	8	13	38.1	0.922
MM	6	9	40.0	0.627
HCL	2	2	50.0	0.0001
ITP	21	31	40.4	0.447
AA	9	14	39.1	0.768

AL: Acute leukaemia, CML: Chronic myeloid leukaemia, CLL: Chronic lymphocytic leukaemia, NHL: Non Hodgkin's lymphoma, HL: Hodgkin's lymphoma, MM: Multiple myeloma, HCL: Hairy cell leukaemia, ITP: Immune thrombocytopenic purpura, AA: Aplastic anaemia. p-value was considered significant if < 0.001 (calculated between the specific group and the control group).

Table 4: Dyspeptic symptoms in control and patient groups

The group	Dyspepsia	No dyspepsia	%	P-value
Control	61	276	18.1	-----
Patient	133	204	39.4	0.0001
AL	60	68	46.9	0.0001
CML	8	27	22.8	0.656
CLL	5	26	16.1	0.784
NHL	11	17	39.3	0.0006
HL	8	13	38.1	0.0009
MM	5	10	33.3	0.0005
HCL	1	3	25.0	0.722
ITP	25	27	48.1	0.0001
AA	10	13	43.5	0.0001

AL: Acute leukaemia, CML: Chronic myeloid leukaemia, CLL: Chronic lymphocytic leukaemia, NHL: Non Hodgkin's lymphoma, HL: Hodgkin's lymphoma, MM: Multiple myeloma, HCL: Hairy cell leukaemia, ITP: Immune thrombocytopenic purpura, AA: Aplastic anaemia. p-value was considered significant if < 0.001 (calculated between the specific group and the control group).

DISCUSSION:

In this case – control study; there was no significant association found between H. pylori infection and a number of hematological diseases.

The only significant association was with HCL which is because of the small number of patients in HCL group as it wasn't significant when statistical analysis was done with Fisher's exact test.

The effect of age and sex was excluded by choosing age and sex matched control group, While the effect of geographical factors was excluded as 90% of patient group were from Babylon governorate and 95% of control group were from same governorate.

Despite that no similar studies were found, Some studies found no significant association between H. pylori infection and ITP[27,28,29,30]. On the other side, An important improvement in platelets count was found after a successful eradication of H. pylori[31,32].

Matti et al found that children born to mothers who tested positive for H. pylori were 2.8 times more likely to contract leukaemia during their 1st 15 years of life in Iceland group of patients, however; no similar association was found in Finland group of patients (the study included 550,000 mothers and their children from Iceland and Finland)[33].

Some studies found a significant association between H. pylori infection and both iron deficiency anemia(IDA) and megaloblastic anemia(MA) even in the absence of peptic ulcer disease[34,35,36,37,38,39,40,41,42], except one study performed by Sarker et al who found that H. pylori infection is neither a cause of IDA nor a reason for treatment failure of iron supplementation in young Bangladeshi children[43]. Some of these studies

insisted on eradication of H. pylori for successful treatment as elemental supplement alone may not be sufficient[34,41].

Another single study done by Diamantidis et al found a protective role for H. pylori eradication from the leukaemic transformation in myelodysplastic syndrome[44 c].

The dyspeptic symptoms were significantly different between patient and control groups as it is higher in patient group which is independent of H. pylori infection.

In this study; the dyspeptic symptoms were significantly more in patients with acute leukaemia, Non Hodgkin's lymphoma, Hodgkin's lymphoma, Multiple myeloma, Immune thrombocytopenic purpura and aplastic anemia. No similar studies were found. This association can be explained by chemotherapy in AL, NHL and HL as 79.2% (61/77) of those dyspeptic patients were on chemotherapy, while only 35% (35/100) of non-dyspeptic patients were on chemotherapy (they added to this study either at time of diagnosis or during follow up after remission or cessation of therapy). In cases of ITP and AA; steroids treatment may be the cause as 88.6% (31/35) of dyspeptic patients were on steroids therapy and just 47.5% (19/40) of non-dyspeptic patients were on steroids therapy. In multiple myeloma; gastric symptoms represent a well known feature of the disease itself.

CONCLUSION:

There was no significant association between H. pylori infection and hematological diseases tested in this study in patients from Babylon, However; dyspeptic symptoms were more common in patients on steroids or chemotherapy.

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