Original Article

ASSOCIATION BETWEEN HELICOBACTER PYLORI SEROPOSITIVITY AND HEPATIC ENCEPHALOPATHY

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ABSTRACT

Objective: The knowledge on Helicobacter pylori (H. pylori) contribution in the pathology of the liver and biliary tract diseases in human is very limited. The aim of this study was to assess the probable association between H. pylori seropositivity and hepatic encephalopathy.

Methodology: This is a case control study conducted through three groups, cirrhotics with hepatic encephalopathy (HE), cirrhotics without HE and healthy controls. All subjects were examined serologically for determination of IgG class antibodies to H. pylori based on ELISA technique.

Results: H. pylori seropositivity was present in 88% cirrhotic patients with hepatic encephalopathy, 86% cirrhotics without hepatic encephalopathy and 66% healthy controls.

Conclusion: According to our results, H. pylori seropositivity rate in cirrhotic patients with or without hepatic encephalopathy was higher than healthy controls. But H. pylori seropositivity rate was not significantly different among cirrhotics with hepatic encephalopathy and those without it.

KEY WORDS: Hepatic Encephalopathy, Cirrhosis, Helicobacter pylori infection.

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INTRODUCTION

In the recent years, attention has been drawn to the possible association of Helicobacter pylori (H. pylori) infection not only with upper gastrointestinal tract diseases but also with several extra gastrointestinal diseases e.g. chronic cardiovascular, liver and biliary diseases or colorectal cancers.[1] Hepatic encephalopathy is a common and serious complication affecting patients with liver disease.[2]

The knowledge on H. pylori contribution in the pathology of the liver and biliary tract diseases in human is very fragmented. Helicobacter pylori infection has been implicated in the development of encephalopathy, This is possibly due to increased production of ammonia by the action of bacterial urease on urea in the gastric lumen. The role of H.pylori as a cause of hyperammonaemia in patients with liver cirrhosis has still not been fully clarified. The intial study implicating H. pylori as a risk factor for hepatic encephalopathy was published in 1993.[3]

The clinical observations have demonstrated conflicting opinions. Some authors have

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pointed out to the advantageous influence of the eradication therapy on the course of hepatic encephalopathy; hence, this opinion has not been supported by others.[1] The aim of this study was to investigate the association between H. pylori seropositivity and hepatic encephalopathy.

METHODOLOGY

Our study was conducted at the Department of Gastroenterology Medicine of the Urmia University of Medical Sciences between January 2006 and September 2007 on three groups; cirrhotic patients with hepatic encephalopathy (HE), cirrhotic patients without hepatic encephalopathy and healthy controls without any disease.

Fifty consecutive patients with hepatic encephalopathy and liver cirrhosis, 50 patients with liver cirrhosis without hepatic encephalopathy and 50 controls were included in this prospective study.

Exclusion criteria for cases in this study were: prior H. pylori eradication therapy, consumption of acid suppressive drugs, H2 receptor blocker, proton pump inhibitors (PPIs), antibiotics and bismuth compounds in the preceding of six months, history of vagotomy or operations on the upper gastrointestinal tract, peptic ulcer disease (PUD) in upper endoscopy and other causes of coma in patients group. Group one and two were matched with group three in age and gender.

All patients in group one and two underwent upper endoscopy and the evaluation for PUD was negative and rapid ureas test for H.pylori infection. Controls were normal volunteers of out-of-hospital persons who did not have any of the exclusion criteria in addition to hepatic cirrhosis.

In cirrhotic patients, cirrhosis had confirmed with liver biopsy or based on the clinical manifestations of cirrhosis such as ascites, esophageal varices and abnormal Prothrombin time (PT). Presence of encephalopathy was determined by clinical assessments including mental status (alertness, mood, worry, and orientation), and complaints of sleep pattern disturbance i.e. day-night reversal (insomnia, day time naps). All patients were subjected to clinical evaluation including fever, jaundice, anemia, spider naevi, edema, palmar erythema, abdominal collateral veins, ascites, hepatomegaly, splenomegaly, gastrointestinal hemorrhage, and improved response to lactulose. Patients in coma due to other causes were excluded from the study (i.e. diabetic, uremic, cerebrovascular accident). All subjects were evaluated in a serological survey for determination of IgG class anti-H. pylori antibodies based on ELISA technique (Biological laboratories Gmbh Hamburg, Germany). According to brochure that is linked to such kit, sensitivity and specificity of test is reported more than 98%. The seropositive results were cofirmed by rapid ureas test.

This research was started after having approval from the University ethical committee and was performed upon receiving letters of consent from the patients.

Statistical analysis: Statistical data analysis was performed with SPSS 10 software in Windows platform. The relationship between Hepatic encephalopathy and H. pylori infection was assessed by fisher exact test. Then case and control groups were compared with one another by frequency of H. pylori infection.

All results were compared among three groups by percentage. In addition odds ratio (OR) and 95% confidence interval were estimated for percentage of Hepatic encephalopathy and H. pylori infection relationship.

RESULTS

Gender distribution of the studied cases was (81.8%) male positive and (78.1%) female positive for anti-H. pylori ($p = 0.56$). Mean age in cirrhotic patients with hepatic encephalopathy was 48.92 (SD = 16.95) and in cirrhotic patients without hepatic encephalopathy was 48.86 (SD = 18.45) along with mean age of 45.96 (SD=11.33) in controls ($p = 0.56$).

Mean age in seropositive and seronegative subjects was 47.81 (SD = 16.20) and 48.33 (SD = 14.49), respectively ($p = 0.44$). H. pylori antibody was positive in 44 of 50 (88%) patients of liver disease with hepatic encephalopathy, in 43 of

50 (86%) patients of liver disease without hepatic encephalopathy and in 33 of 50 (66%) healthy controls (p = 0.01). The most common etiology of cirrhosis was hepatitis B (43%) with 88.37% seropositivity for H. pylori.

Of 50 cirrhotics with HE, 44 were positive for anti-H. pylori and of 50 cirrhotics without HE, 43 were positive for anti-H. pylori. (p = 0.766) [OR 1.19 (95% CI: 0.33- 4.43)]. The odds ratio for the presence of anti-H. pylori IgG in cirrhotics without HE in comparison to controls was 3.16. (95% CI: 1.07 – 9.62) (p = 0.019) (Table-I).

The odds ratio for the presence of anti-H.pylori IgG in cirrhotics with HE compared with healthy individuals was 3.78. (95% CI: 1.22- 12.16) (p = 0.01). Also, H. pylori seropositivity rate was more in higher grades of hepatic encephalopathy (data not shown).

DISCUSSION

The contribution of the H. pylori infection of upper gastrointestinal tract in the hepatic encephalopathy results from its synthesizing capability of ammonia because this pathogen expresses highly active urease on its surface and in the periplasma.

The evidence for a pathogenic role of H. pylori infection in hepatic encephalopathy was reported by Suto et al. [4] They demonstrated a significant increase in portal and peripheral ammonia levels in H. pylori-infected gerbils with cirrhosis.[4]

Table-I: Association between Helicobacter pylori infection in cirrhotics with and without hepatic encephalopathy in comparison with control group

Group	*Positive*		*Negative*	
	N	*%*	*N*	*%*
Cirrhosis with hepatic encephalopathy	44	88	6	12
Cirrhosis without hepatic en cephalopathy	43	86	7	14
Control	33	66	17	34
Total	120	80	30	20

(P = 0.766) [OR 1.19 (95% CI: 0.33 - 4.43)]

According to our results H. pylori seropositivity rate in cirrhotic patients with or without hepatic encephalopathy was higher than healthy controls. In our study we did not consider the genomic structure of H. pylori, neither did previous studies.

One of the important inclusion criteria in our study was absence of PUD in endoscopy of cirrhotic patients, because the relationship between H. pylori and PUD could have had influence on the results. According to what was reported by Shirmali et al., H. pylori seropositivity increases with the severity of hepatic encephalopathy.[2] These findings do not correlate with our findings. In our study H. pylori seropositivity in higher grades of hepatic encephalopathy was more that correlated with the findings of Gubbins et al study. In their study, they found H. pylori seropositivity in hepatic encephalopathy- G I (77.63%), G II (78.13%), G III (100.00%), G IV (75.00%).[5] The main reason may possibly be the inadequacy of study population included in subgroups. Shavakhi et al. compared the seroprevalence of anti-H. pylori antibodies in cirrhotic patients with that in controls in Iran. According to their results, IgG antibody to H. pylori was present in 73% of cirrhotic patients and 52% of control group (P < 0.003). They found that the relative frequency of IgG antibody to H. pylori was higher in cirrhotic patients than in controls.[6]

Sethar et al. studied this hypothesis; seventy six patients of porto-systemic encephalopathy due to liver diseases were selected. In this study frequency of H. pylori antibodies was significantly high in patients with porto-systemic encephalopathy.[3]

Wang et al. found that H. pylori prevalence significantly differed among cirrhotic with hepatic encephalopathy (74.4%), and those with subclinical HE (69.1%) or without HE (53.3%). They stated that H. pylori infection was an important factor of inducing high blood ammonia concentration and hepatic encephalopathy in cirrhotic patients.[7] In these studies, patients with PUD were not excluded from the study.

A number of previous studies did not investigate the association between H. pylori

seropositivity and hepatic encephalopathy. Nam et al.[8] assessed this subject. The pH and NH_3 concentration were measured in gastric juice obtained by endoscopy. H. pylori infection was diagnosed by using the rapid urease test. The prevalence of H. pylori in liver cirrhotic patients was similar to that in controls and no correlation was found between gastric and blood NH_3 level.[8]

Chakrabarti et al. evaluated the relationship among H. pylori infection gastric juice ammonia concentration and arterial ammonia levels in patients with cirrhosis, overt hepatic encephalopathy, subclinical hepatic encephalopathy and those without encephalopathy and found no significant difference.[9] Zullo et al. studied this subject and failed to find a relationship between H. pylori, plasma ammonia levels and psychometric testing scores in cirrhotic patients with latent or mild hepatic encephalopathy.[10] Studies have not shown significant effect of H. pylori infection on the fasting ammonia level or on other parameters used for the assessment of hepatic encephalopathy.[11]

The fact that some people develop overt disease whereas others do not is probably due to a combination of bacterial strain differences, host susceptibility to disease, and environmental factors.[12] The cag status of a H. pylori strain is relevant to the risk of a number of clinical outcomes. The cag A protein is highly immunogenic.[13]

Limitations of the study: The main limitations of present study were small sample size, absence of psychometric tests for diagnosis of probable subclinical encephalopathy and using only antibody test for H. Pylori infection detection. However, as our aim was assessment of seroprevalence of H. Pylori this limitation is not very important.

It seems that understanding the role of H. pylori infection in cirrhosis and its complications, for instance hepatic encephalopathy warrants further studies. Until further information is obtained, it would be advisable to follow the same H. pylori eradication strategies in cirrhotic patients as in non-cirrhotic patients. Also, we suggest that in future studies H. pylori genomic structure and influence of this organism strains (for example, cag A^+ and cag A^-) on hepatic encephalopathy to be assessed.

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