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RAPID COMMUNICATION

Effect of *H pylori* infection and its eradication on hyperammo-nemia and hepatic encephalopathy in cirrhotic patients

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Abstract

AIM: To investigate the relationship between *H pylori* infection, blood ammonia concentration and hepatic encephalopathy (HE), and the effect of *H pylori* eradication in cirrhotic patients.

METHODS: From July 2003 to January 2005, 457 cirrhotic patients in five regions of Zhejiang Province were enrolled. Patients were evaluated for demographics, number connection test, *H pylori* infection, liver impairment, blood ammonia concentration and HE. Patients with *H pylori* infection were given 1 wk therapy with omeprazole plus clarithromycin and tinidazole. ^{14}C urea breath test was performed and mental symptoms and blood ammonia level were reassessed after bacterium eradication.

RESULTS: Overall *H pylori* infection rate was 60.6%, and HE occurred in 47.5% of cirrhotic patients. Subclinical HE (SHE) was detected in 55 of 117 cirrhotic patients. Blood ammonia concentration in *H pylori* negative (n = 180) and positive (n = 277) cirrhotic patients was 53.8 ± 51.4 and 78.4 ± 63.6 μmol/L, respectively (P < 0.01), which was significantly reduced to 53.5 ± 37.7 μmol/L after bacterium eradication (n = 126) (P < 0.01). Blood ammonia was 97.5 ± 81.0 μmol/L in *H pylori*-positive cirrhotic patients, and this did not significantly change in those with persistent infection after *H pylori* eradication (n = 11). HE was more frequently observed in patients with *H pylori* infection than in those without (58.5% *vs* 30.6%, P < 0.01). HE rate significantly dropped to 34.1% after *H pylori* eradiation (P < 0.01). *H pylori* prevalence significantly differed among cirrhotic patients with HE (74.4%), SHE (69.1%), and those without HE (53.2%) (P < 0.05). Blood ammonia level was significantly different among cirrhotic patients with HE (94.5 ± 75.6 μmol/L), SHE (59.9 ± 49.2 μmol/L), and without HE (47.3 ± 33.5 μmol/L) (P < 0.05). Logistic regression analysis showed that blood ammonia concentration, Child-Pugh stage, upper gastrointestinal bleeding, electrolyte disturbance, and urea nitrogen were risk factors for HE.

CONCLUSION: *H pylori* infection is an important factor for inducing high blood ammonia concentration and HE in cirrhotic patients. *H pylori* eradication may be helpful for treatment and prevention of HE.

Key words: Cirrhosis; *Helicobacter Pylori*; Hepatic encephalopathy; Hyperammonemia

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INTRODUCTION

Hepatic encephalopathy (HE) is a frequent complication of liver cirrhosis. Although the pathogenesis is unclear, ammonia is one of the key factors involved. Recently, it has been suggested *H pylori* contributes to hyperammonemia in cirrhosis, and bacterium eradication decreases blood ammonia concentration in these patients[1-8]. However, the literature contains conflicting data, with several other studies showing ammonia levels do not significantly differ between cirrhotic patients with and without *H pylori* infection. Ammonia production in the stomach by *H pylori* urease appears to be inadequate to clinically affect ammonia disposal in the majority of cirrhotic patients[2,9-13]. The possible role of *H pylori* in the pathogenesis of HE deserves further investigation.

MATERIALS AND METHODS

Subjects

From July 2003 to January 2005, 457 cirrhotic patients in 18 hospitals from five regions of Zhejiang Province in China were enrolled in this prospective study. Diagnosis of liver cirrhosis was carried out by history, clinical examination, laboratory findings, and radiological findings according to the principles established by Chinese Hepatology Association in 2002. The main exclusion criteria included: (1) Severe cardiac, pulmonary, cerebral and renal disorders; (2) severe HE of grades Ⅲ and Ⅳ; (3) currently receiving *H pylori* eradication therapy; (4) currently undergoing surgery, (5) active gastrointestinal bleeding where non-surgical therapy is ineffective; (6) psychological disorders other than HE; and (7) current alcohol or sedative-drug abuse.

Patients were evaluated for demographic checklists, number connection test (NCT), *H pylori* infection, liver impairment (according to Child-Pugh classification, including the total score of HE, ascites, prothrombin time, albumin concentration and bilirubin level, which ranked as Child-Pugh class A, B and C), blood ammonia concentration, and HE status. All patients received a low-salt, low-protein diet, and lactulose was given to all patients to induce two to four bowel movements a day. Protein intake was restricted to about 20-40 g daily. One hundred and thirty-seven patients with *H pylori* infection were given 1 wk eradication therapy. Mental symptoms and blood ammonia levels were reassessed 1 mo after eradication therapy.

Detection of H pylori infection

Gastric specimens were taken from the antrum when performing endoscopic biopsies, which were assessed by rapid urease test, histology (Giemsa staining) or *H pylori* culture. The presence of *H pylori* was detected by ^{14}C urea breath test in those who did not undergo biopsy. Subjects who had *H pylori* were identified by at least one of the above tests showing a positive result.

Ammonia measurement

Fasting venous blood samples were obtained from each patient to measure ammonia concentration (μmol/L), according to the manufacturer's instructions.

NCT

The NCT (part A) was performed to detect subclinical HE. Subjects were required to connect numbers printed on paper consecutively from 1 to 25, as quickly as possible. NCT abnormality was defined as taking > 66 s to fulfill this task.

HE stage

HE stage was established by clinical characteristics, electroencephalography (EEG) and NCT results. Patients were classified as cirrhotic without HE, with subclinical HE (SHE), and with HE. SHE was characterized by normal traditional clinical evaluation with definite and quantifiable neuropsychological defects (NCT abnormality).

Table 1 Clinical characteristics of *H pylori*-positive and -negative patients

	H pylori (+)	*H pylori* (-)	*P* value
Sex (male/female)	196/81	141/39	0.045
Age (yr)	57.6 ± 12.7	56.9 ± 13.4	0.604
Child-Pugh class A/B/C	67/124/86	55/77/48	0.309
Upper gastrointestinal hemorrhage	155	95	0.263
Hepatorenal syndrome	19	11	0.448
Ascites	197	136	0.208

H pylori eradication therapy

The 137 cirrhotic patients with *H pylori* infection received 7 d dual eradication therapy (omeparazole 20 mg b.i.d plus clarythromicin 500 mg b.i.d plus tinidazole 500 mg b.i.d). One month after completion of treatment, a ^{14}C-urea breath test was performed to reassess *H pylori* status.

Statistical analysis

Statistics were calculated using SPSS ver. 11.0. Qualitative variables were expressed by means of frequency and percentiles, and were analyzed using the χ^2 test. Quantitative results are expressed as means ± SD. Groups were compared by using Student's *t* test or ANOVA. Risk factors for HE were analyzed using logistic multiple regression. Odds ratio (OR) values were calculated from 95% CI, and OR > 1.00 was considered a significant risk factor. Statistical significance was established at $P < 0.05$.

RESULTS

Effect of H pylori infection on blood ammonia and HE

Overall *H pylori* infection rate was 60.6% (277/457). There were 137 *H pylori*-positive patients who received eradication therapy, among whom the eradication rate was 91.4% (126/137). HE occurred in 47.5% of cirrhotic patients (217/457), and SHE was detected in 47.0% (55/117) of those without HE. There was no significant difference in liver impairment (Child-Pugh class), and complications (upper gastrointestinal bleeding, hepatorenal syndrome, and ascites) between *H pylori* positive and negative groups (Table 1). Blood ammonia concentration in *H pylori* negative and positive cirrhotic patients was 53.8 ± 51.4 and 78.4 ± 63.6 μmol/L, respectively ($P < 0.01$). Blood ammonia was 78.4 ± 63.6 μmol/L in *H pylori*-positive cirrhotic patients before treatment ($n = 137$), and 97.5 ± 81.0 μmol/L in those with persistent infection after treatment ($n = 11$). Blood ammonia was significantly reduced to 53.5 ± 37.7 μmol/L ($P < 0.01$) in the *H pylori* eradication group ($n = 126$). HE was more frequently observed in patients with *H pylori* infection than in those without (58.5% *vs* 30.6%, $P < 0.01$). HE rate significantly dropped to 34.1% after *H pylori* eradiation ($P < 0.01$). Data are shown in Table 2.

Relationship between HE and H pylori infection and blood ammonia

H pylori prevalence differed significantly between cirrhotic patients with HE (74.4%), those with SHE (69.1%), or

Table 2 Effect of *H pylori* infection on blood ammonia concentration and HE

H pylori infection	*n*	Ammonia concentration (μmol/L)	HE rate
H pylori (–)	180	53.8 ± 51.4[bd]	55 (30.6%)[bd]
H pylori (+)	277	78.4 ± 63.6	162 (58.5%)
Eradicated	126	53.5 ± 37.7[bd]	43 (34.1%)[bd]
Failed to eradicate	11	97.5 ± 81.0	6 (54.5%)

[b]$P < 0.01$, *vs* failed to eradicate (+) group; [d]$P < 0.01$, *vs H pylori* (+) group.

Table 3 Relationship between HE and *H pylori* infection and blood ammonia

	HE (*n* = 217)	SHE (*n* = 55)	Cirrhotic (*n* = 62)	*P* value	χ^2
H pylori infection	74.4%	69.1%	53.2%	< 0.01	9.999
Child–Pugh class				< 0.01	29.154
A/B/C	27/100/90	9/30/16	22/33/7		
Ammonia concentration (μmol/L)	94.5 ± 75.6[b]	59.9 ± 49.2	47.3 ± 33.5		

[b]$P < 0.01$, *vs* SHE group ($t = 4.117$); *vs* cirrhotic ($t = 1.601$).

without HE (53.2%) ($P < 0.05$). Blood ammonia level differed significantly between cirrhotic patients with HE (94.5 ± 75.6 μmol/L), those with SHE (59.9 ± 49.2 μmol/L), or without HE 47.3 ± 33.5 μmol/L) ($P < 0.05$). Liver impairment of Child-Pugh class B and C in patients with HE and SHE were 87.6% and 83.6%, respectively. Child-Pugh class A and B accounted for 88.7% of cirrhotic patients without HE (Table 3).

Risk factors for HE

Through logistic multiple regression analysis, we found blood ammonia concentration ($P = 0.000$, OR = 4.701), Child-Pugh class ($P = 0.000$, OR = 3.416), *H pylori* infection ($P = 0.007$, OR = 2.113), gastrointestinal hemorrhage ($P = 0.048$, OR = 1.798), electrolyte disturbance ($P = 0.045$, OR = 1.875), and blood urea nitrogen ($P = 0.041$, OR = 1.854) were risk factors for HE. Sex, age, ascites, spontaneous bacteria peritonitis infection, hemoglobin, white blood count, platelet count and creatinine were not significantly associated with HE (Table 4).

Table 4 Risk factors for HE analyzed by logistic multiple regression

	P value	OR value	95% CI
Sex	0.341	0.751	0.416-1.354
Age	0.881	0.959	0.555-1.657
Etiology	0.125	1.564	0.883-2.769
H pylori infection	0.007	2.113	1.222-3.654
Blood ammonia level	0.000	4.701	2.773-7.970
Child-Pugh class	0.000	3.416	1.823-6.398
Ascites	0.277	1.395	0.765-2.541
Hemorrhage	0.048	1.798	1.004-3.218
Infections	0.934	1.027	0.546-1.932
Electrolyte disturbance	0.045	1.857	1.015-3.398
Leukocyte count	0.840	1.056	0.625-1.782
Hemoglobin	0.592	1.192	0.626-2.270
Platelet count	0.430	1.279	0.694-2.356
Creatinine	0.489	0.768	0.364-1.621
Blood urea nitrogen	0.041	1.854	1.025-3.353

DISCUSSION

Most currently available therapies for prevention of HE focus on reducing blood ammonia concentration[14,15]. *H pylori* is known to produce copious amounts of ammonia due to its strong urease activity. Ammonia produced by *H pylori* has a role in the pathogenesis of hyperammonemia when this organism is widely distributed and present in large numbers in the stomach, particularly in the presence of liver cirrhosis[16-19]. We did not find a significant difference in age, liver impairment and complication rate (upper gastrointestinal bleeding, hepatorenal syndrome and ascites) between *H pylori*-positive and -negative groups. However, blood ammonia concentration in *H pylori*-positive patients was significantly higher than that in *H pylori*-negative patients ($P < 0.01$). This suggested that *H pylori* infection was associated with hyperammonemia in cirrhotic patients. It has previously been shown ammonia concentration in portal and venous blood significantly increased after the instillation of 10^{10} CFU/L *H pylori* in the stomach of cirrhotic rats[20]. Oral administration of acetohydroxamic acid significantly reduced blood ammonia levels in cirrhotic patients with *H pylori* infection, compared with those without infection[21]. We have previously reported that ammonia level in portal vein blood of cirrhotic patients with *H pylori* infection is significantly higher than that in patients without infection[22].

In the present study, HE was more frequently observed in patients with *H pylori* infection than in those without (58.5% *vs* 30.6%, $P < 0.01$), which was consistent with that reported elsewhere[23-25].The hypothesis that *H pylori* infection plays a pathogenic role in HE was initially devised by Gubbins *et al*[26]. In their study, seroprevalence for *H pylori* was detected in 78.6% of 117 alcoholic liver disease patients with HE, and in 62% of 71 patients without ($P = 0.013$). *H pylori* was detected only by serology, which has been reported to be inaccurate in cirrhotic patients. Therefore, the results of that study should be interpreted with caution. In a study of 55 cirrhotic patients, Dasani *et al*[17] detected *H pylori* infection more frequently in those with HE compared with those without (67% *vs* 33%, $P = 0.004$). However, conflicting data are available in the literature. Several studies have shown that ammonia levels do not significantly differ between cirrhotic patients with and without *H pylori* infection, which suggests that although *H pylori* infection is able to generate ammonia in the stomach, the amount appears to be too small to affect arterial ammonia levels in patients with cirrhosis[2,9,14,31]. The contribution of ammonia produced by *H pylori* to HE may depend on the number of bacteria and their distribution in the stomach, gastric pH, gastric membrane permeability to ammonia, liver impairment, and portal vein branch circulation. We suppose *H pylori* may increase blood ammonia concentration and induce HE when the bacterium is widely distributed in the stomach, and in the presence of severe liver impairment (Child-Pugh class B or C) with abundant portal vein branch circulation.

Through logistic multiple regression analysis, we found blood ammonia, Child-Pugh class, upper gastrointestinal bleeding, electrolyte disturbance, and urea nitrogen were significantly associated with HE. Dasani *et al*[17] have documented that risk factors associated with HE include older age ($P = 0.001$), lower albumin ($P = 0.001$), *H pylori* infection ($P = 0.004$), greater ascites score ($P = 0.01$), and greater Child-Pugh class ($P = 0.001$).

In view of the association of *H pylori* infection with hyperammonemia and HE, bacterium eradication may theoretically reduce ammonia concentration in cirrhotic patients[27-29,32]. Ito *et al*[30] initially gave *H pylori* eradication therapy to cirrhotic patients, and found reduced ammonia concentration and recovery from HE after eradication, without relapse in the following 5 mo. In our study, blood ammonia concentration in *H pylori*-positive cirrhotic patients was significantly reduced by bacterium eradication ($P < 0.01$). HE rate significantly dropped to 34.1% after *H pylori* eradiation ($P < 0.01$). However, several investigators have questioned whether the effect of eradication therapy on hyperammonemia is due to the non-specific effect of antibiotic therapy on the ammonia-producing gut flora. In Miyaji and Ito's study[16], all patients were given lactulose, branched-chain enriched amino acid solution, low-protein diet, and kanamycin for 2 wk before *H pylori* eradication therapy, to reduce the effect of the gut flora on hyperammonemia. The blood ammonia concentration in patients with diffuse distribution of *H pylori* in the stomach was significantly reduced after bacterium eradication compared with the concentration after conventional treatment to reduce the gut flora. The ammonia concentration at 12 wk after eradication treatment was still significantly lower than that before. Therefore, eradication of *H pylori* to reduce bacterial ammonia production in the stomach is effective in patients with hyperammonemia with diffuse *H pylori* infection in the stomach, even after conventional therapy with a low-protein diet, antibiotics, lactulose and branched-chain enriched amino acid solution[1,16,17]. *H pylori* eradication may be helpful for the treatment and prevention of HE. However, further studies are warranted to evaluate the arguments for and against the role of *H pylori* in the pathogenesis of HE.

COMMENTS

Background

Hepatic encephalopathy (HE) is a frequent complication of liver cirrhosis. Although the pathogenesis is unclear, ammonia is one of the key factors involved. Recently, it has been suggested *H pylori* contributes to hyperammonemia in cirrhotic patients and bacterium eradication decreases blood ammonia concentration. However, several other studies have shown ammonia levels do not significantly differ between cirrhotic patients with and without *H pylori* infection. The possible role of *H pylori* in the pathogenesis of HE merits further investigation.

Research frontiers

Recent research has focused on determining the relationship between *H pylori* infection, blood ammonia concentration and HE status in prospective and multicenter studies, and on investigating the effect of *H pylori* eradication on blood ammonia level and HE in cirrhotic patients.

Innovations and breakthroughs

We designed this prospective study to evaluate the effects of *H pylori* infection and eradication on hyperammonemia and HE in 457 cirrhotic patients in five regions of Zhejiang Province, China. We observed blood ammonia concentration was significantly higher and HE was more frequent in patients with *H pylori* infection than in those without. Moreover, eradication of *H pylori* infection resulted in reduction in both blood ammonia concentration and frequency of HE.

Applications

H pylori infection is an important factor for inducing high blood ammonia concentration and HE in cirrhotic patients. *H pylori* eradication may be helpful for treatment and prevention of HE.

Terminology

SHE is characterized by normal, traditional clinical evaluation with definite and quantifiable neuropsychological defects.

Peer review

This study evaluated the relationship between *H pylori* infection, blood ammonia concentration and HE, and determined the effect of *H pylori* eradication on blood ammonia level and HE in cirrhotic patients. This study is of important clinical significance and should be of interest to readers of the journal.

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