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ORIGINAL ARTICLE

Role of *Helicobacter pylori* infection in the pathogenesis of minimal hepatic encephalopathy and effect of its eradication

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Abstract
Background and Aim *Helicobacter pylori* (*H. pylori*) bacteria convert urea to ammonia, which has been implicated in causation of hepatic encephalopathy in patients with liver cirrhosis. The role of *H. pylori* infection in causation of minimal hepatic encephalopathy (MHE) has not been well studied. We looked at the relationship of *H. pylori* infection with MHE and hyperammonemia in patients with liver cirrhosis and the effects of anti-*H. pylori* treatment in patients with MHE and *H. pylori* infection.
Methods Patients with liver cirrhosis underwent psychometric tests for detection of MHE, rapid urease test to look for evidence of *H. pylori* infection and measurement of fasting blood ammonia levels. Patients with MHE were treated with triple-drug anti-*H. pylori* treatment for one week. Rapid urease test, blood ammonia levels, and psychometric tests were repeated four weeks after treatment.
Results *H. pylori* infection was found more often in patients with MHE (63%) than in those without MHE (37%). Blood ammonia levels were significantly higher in patients with MHE than those without. After *H. pylori* treatment in patients with MHE, blood ammonia levels showed a significant decline and psychometric test results returned towards normal.
Conclusion In patients with liver cirrhosis, there is a significant association between *H. pylori* infection and MHE. Anti-*H. pylori* therapy results in reduction in blood ammonia levels and improvement in MHE.

Keywords Ammonia · Liver cirrhosis · Minimal hepatic encephalopathy

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Introduction

Patients with cirrhosis are prone to hepatic encephalopathy. In addition, some patients have minimal hepatic encephalopathy (MHE), which is not discernible at clinical examination but can be detected using sensitive tests of coordination, such as number connection tests (NCT), figure connection test (FCT) and line tracing test, electroencephalography and visual, auditory, and somatosensory evoked potentials [1]. NCT and FCT have been shown to be sensitive tests for detection of MHE [2]. The most common biochemical abnormality in patients with chronic hepatic encephalopathy is hyperammonemia [3, 4]. Elevated blood ammonia levels have also been implicated in the causation of MHE [1].

Helicobacter pylori bacteria are rich in urease enzyme and are known to produce ammonia from urea that is rapidly absorbed from gastric lumen into circulation. Infection with these bacteria has been shown to be associated with elevated blood ammonia levels and recurrent attacks of overt hepatic encephalopathy [5]. Eradication of *H. pylori* infection has been shown to be associated with reduction in blood ammonia levels [6–9] and improvement in hepatic encephalopathy [5, 6]. However, the role of *H. pylori* in causation of MHE has not been studied in detail.

The current study was undertaken to find the prevalence of MHE in patients of cirrhosis and to establish the correlation between the presence of *H. pylori* infection and hyperammonemia in these cases and to study the effects of anti-*H. pylori* treatment in patients of MHE.

Methods

Subjects

Patients of suspected cirrhosis of liver were subjected to ultrasound and endoscopic examination. Those with ultrasonographic findings of chronic liver disease and esophageal varices on endoscopic examination were included in the study after obtaining a written informed consent in accordance with the recommendations of the institutional ethics committee. Those with history of recent upper gastrointestinal bleeding, overt hepatic encephalopathy (based on clinical examination), neurological illness, poor vision, and with history of *H. pylori* eradication treatment within the previous three months were excluded. Of the 210 patients with liver cirrhosis screened, 145 had one or more exclusion criterion; the study thus included 65 patients. Biochemical tests and psychometric tests were performed initially on all patients included in the study. Patients with abnormal results on two or more psychometric tests were taken as having MHE.

Laboratory investigations

All study patients underwent routine hematological and biochemical investigations (as guided by clinical condition), HBsAg, anti-HCV, and ultrasonography. Ascitic fluid, if present, was examined. In addition, a fasting venous blood specimen was collected in EDTA and ammonia level in the plasma was measured using the Menagent Ammonia Test Kit II (Menarini Diagnostic, Firenze, Italy). In this technique, ammonia combines with alpha-oxoglutarate and NADH in the presence of glutamate dehydrogenase to yield glutamate and NAD^+; a decrease in absorbance at 340 nm is measured and is proportional to plasma ammonia concentration. All patients also underwent an upper gastrointestinal endoscopy and a rapid urease test (Delta West, Bentley, Australia) on an antral biopsy; a color change from yellow to red at one hour was taken as evidence of *H. pylori* infection.

Psychometric tests

All patients underwent NCT, FCT and line tracing test. Before the actual tests, the procedure was explained and demonstrated, and a dummy run was done, which was not taken into account. Time taken for completion of each test and the number of errors were recorded. Normative values for psychometric test results were obtained from 200 normal control subjects.

Treatment and follow up

Patients with MHE (irrespective of *H. pylori* status) received a triple anti-*H. pylori* therapy (clarithromycin 250 mg, lansoprazole 30 mg, and tinidazole 500 mg, each twice daily) for one week along with lactulose. Fasting blood ammonia level and psychometric tests were repeated four weeks after completion of anti-*H. pylori* treatment. Patients with *H. pylori* infection also underwent a repeat endoscopic examination at this time to ascertain their *H. pylori* status.

Statistical analysis

Data were analyzed using mean (standard deviation), Chi-square test, and student's 't' test.

Results

Baseline data

Cut-off values for psychometric tests based on 200 healthy control subjects are shown in Table 1. Based on results of the psychometric tests, 35 (54%) of the 65 patients with liver cirrhosis had MHE. Clinical and demographic characteristics of the study patients are shown in Table 2. Hepatitis B virus infection was the most common (37%) cause of cirrhosis. In the study group, most patients were in Child-Pugh class A (26%) or B (57%); most patients in Child-Pugh class C who were screened fulfilled one or more exclusion criteria. Presence of MHE had no significant relationship with age, sex, Child-Pugh grade, and cause of cirrhosis (Table 2).

H. pylori infection was found in 22 (63%) of 35 patients with MHE and 11 (37%) of 30 patients without MHE ($p< 0.001$). Fasting blood ammonia level were significantly higher in patients with MHE (1.66 [0.35] μg/mL) than in those without (1.07 [0.24] μg/mL; $p<0.001$). Among patients with MHE, fasting blood ammonia levels were significantly higher in patients who tested positive for *H.*

Table 1 Psychometric test results in 200 healthy subjects and cut-offs based on these

Test	Time taken for test completion (sec)	Upper cut-off value (sec)
Number connection test	39–65	65
Figure connection test	65–99	100
Line tracing test	19–39	35

Table 2 Clinical and demographic characteristics of study patients

Characteristic	Patients screened (n=210)	Patients enrolled (n=65)	MHE (n=35)	NMHE (n=30)
Male: Female	152:58	50:15	25:10	25:5
Mean age (years)	37.4	35.5	35.7	34.6
Child-Pugh class				
A	36	17	8	9
B	111	37	19	18
C	63	11	8	3
Varices				
Yes	164	35	20	15
No	46	30	15	15
Etiology				
Alcohol	42	12	7	5
Hepatitis B virus	86	24	13	11
Hepatitis C virus	18	10	4	6
Alcohol + hepatitis B	5	2	1	1
Others	59	17	10	7

MHE Minimal hepatic encephalopathy (abnormal results in at least two abnormal psychometric tests), *NMHE* No minimal hepatic encephalopathy

pylori (1.80 [0.34] μg/mL) than in those who tested negative (1.39 [0.14] μg/mL; $p<0.001$).

Effect of anti-*H. pylori* treatment on blood ammonia and psychometric tests

Patients of MHE received a one-week triple anti-*H. pylori* treatment. Blood ammonia levels in patients with MHE, with and without *H. pylori* infection, before and after treatment are shown in Table 3. Patients with MHE and *H. pylori* infection showed a significant reduction in blood ammonia levels after anti-*H. pylori* treatment ($p<0.001$).

Table 4 shows the changes in psychometric tests in patients with MHE after treatment. There was a significant reduction in the time taken to complete the psychometric tests after anti-*H. pylori* treatment. Of 35 patients with MHE before treatment, 15 (43%) did not have MHE after anti-*H. pylori* treatment.

Of the 22 patients with MHE and *H. pylori* infection before treatment, repeat endoscopy was done in 15 cases who consented; of these 15 patients, 14 tested negative for *H. pylori*.

Discussion

In the current study, we found that *H. pylori* infection was more common in patients with liver cirrhosis and MHE than in those with liver cirrhosis but no MHE. Patients with evidence of MHE on psychometric tests had significantly higher ammonia levels than those without MHE. Moreover, the blood ammonia levels in patients with MHE and *H. pylori* infection were significantly higher than in those with MHE but no *H. pylori* infection. These finding support a possible role for infection with these bacteria in the causation of MHE.

Ammonia has been one of the most widely studied etiological factors in the pathogenesis of hepatic encephalopathy [10]. About half of the ammonia produced in the intestine is synthesized by luminal bacteria, with the remainder coming from dietary protein and glutamine. *H. pylori* are rich in urease and can produce ammonia from urea. Previous studies have shown that ammonia levels in gastric juice were higher in patients with liver cirrhosis who had *H. pylori* infection than in those who did not have such infection [11]. Infection with these bacteria has also been shown to be associated with

Table 3 Pre-treatment and post-treatment fasting blood ammonia level in *H. pylori*-positive and *H. pylori*-negative patients with minimal hepatic encephalopathy

H. pylori status	Blood ammonia levels (μg/mL)		p-value
	Pre-treatment	Post-treatment	
Positive (n=22)	1.80 (0.34)	1.18 (0.27)	<0.001
Negative (n=12)	1.39 (0.14)	1.16 (0.16)	<0.001

Data are as mean (SD)

Table 4 Results of psychometric tests before and after treatment for *H. pylori* infection in patients with minimal hepatic encephalopathy

Psychometric test	Pre-treatment	Post-treatment	p-value
Number connection test (sec)	86 (15)	75 (15)	<0.001
Figure connection test (sec)	127 (19)	110 (21)	<0.001
Line tracing test (sec)	48 (13)	39 (12)	<0.001

Data are as mean (SD)

elevation of blood ammonia levels and recurrent attacks of overt encephalopathy [5]. However, some other studies have failed to find a significant difference between fasting venous blood ammonia concentrations in patients with *H. pylori* infection and those without [12].

Furthermore, we found a significant reduction in blood ammonia levels in both *H. pylori*-positive and *H. pylori*-negative patients with MHE after triple-drug anti-*H. pylori* treatment for one week. This reduction was more marked in patients with *H. pylori* infection. This finding indicates that *H. pylori* may contribute to the development of hyperammonemia in patients with liver disease and MHE. The role of *H. pylori* in the pathogenesis of hyperammonemia has been shown in previous studies which showed a reduction in blood ammonia levels after eradication of *H. pylori* infection [6, 13]. However, some other studies have failed to show an association between *H. pylori* infection and hepatic encephalopathy [14–16].

We found a reduction in blood ammonia levels following anti-*H. pylori* treatment not only in patients with MHE who had *H. pylori* infection, but also in those who did not have the infection. The reduction in blood ammonia in the latter group may be explained by inhibition of the intestinal flora with anti-*H. pylori* drugs. This effect of anti-*H. pylori* drugs on intestinal flora would have been expected to be similar in patients with and without *H. pylori* infection. Thus, our finding of a greater improvement in blood ammonia levels in patients with *H. pylori* infection than in those without this infection appears to indicate that *H. pylori* infection contributed at least partially to high blood ammonia production in these patients.

The reduction in blood ammonia levels following treatment with anti-*H. pylori* drugs was associated with resolution of MHE in 15 of our 35 patients with MHE. Normalization of psychometric tests with reduction in blood ammonia levels has been reported previously, and suggests a role of hyperammonemia in the pathogenesis of MHE [17].

In conclusion, data from our study suggest that *H. pylori* infection plays a role in the causation of MHE in patients with liver cirrhosis, and that eradication of this infection may help ameliorate the manifestations of this complication.

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