

ORIGINAL
ARTICLEEffect of *Helicobacter Pylori* Eradication on Hepatic Encephalopathy

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Background and Aims: Ammonia has still essential role in pathogenesis of encephalopathy. It is probable that *helicobacter pylori* (*H. pylori*) infection leads to hyperammonemia and aggravates the hepatic encephalopathy via urease activity or its effect on zinc level. This study was aimed to assess the effect of *H pylori* eradication on hepatic encephalopathy.

Methods: In a cross-sectional study, 42 cirrhotic patients with encephalopathy were enrolled the study. For evaluation the encephalopathy, flapping tremor, number connection test (NCT) and grade of encephalopathy was determined for all of the patients. The prevalence of *H pylori* infection was evaluated based on positive serology by ELAISA method (Genesis Kit, UK), and/or rapid urease test (RUT) during endoscopic evaluation. One month later, after treatment, grading of encephalopathy, NCT and flapping tremor was evaluated again and data were analyzed by software SPSS.

Results: Serologic evaluation or RUT showed that 30 patients of 42 (71.42%) were positive for *H pylori*. In comparison between pre and post treatment, grade of encephalopathy and NCT were reduced significantly but alteration in flapping tremor was not statistically significant.

Conclusions: Our results indicate that eradication of *H pylori* may lead to improve the grade of hepatic encephalopathy and NCT.

Keywords: Hepatic Encephalopathy, *Helicobacter Pylori*, Cirrhosis

Introduction

Hepatic encephalopathy (HE) is defined as an alteration of mental state in the absence of other causes of encephalopathy ⁽¹⁾. Although the exact pathogenesis is unknown, accumulation of ammonia from poor hepatic function and portosystemic shunting has been implicated as a primary factor ⁽²⁾. The primary source of ammonia is the gut, especially the colon where ammonia is produced by the action of bacterial flora on dietary protein, on epithelial and bacterial debris and mucosal secretions ^(3, 4). *H pylori* is known to possess a constitutively-present urease activity, and therefore, might be an important source for ammonia production ⁽⁵⁾. Various studies have contain conflicting data, with several studies showing ammonia level in stomach acid in *H pylori*

infected cirrhotic patients is higher than non infected patients ^(6, 7).

Elevated levels of ammonia could deteriorate HE. As a result, it can be postulated that *H pylori* infection may potentially contribute to the development of HE. In one study Dasani *et al.* found that *H pylori* infection was significantly more frequent in patients with encephalopathy than

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without (8, 9). Despite above studies, in some studies on patients with cirrhosis and encephalopathy, there was no relation between *H pylori* infection and encephalopathy or it was not an independent risk factor for HE (10, 11). Since the importance of *H pylori* infection as an independent risk factor for the development of HE is not yet clear, we tried to determine the role of *H pylori* eradication in improvement of HE in cirrhotic patients.

Materials and Methods

In a cross-sectional study, subjects were evaluated for the presence of cirrhosis (based on clinical finding or liver histology) and encephalopathy (according to clinical signs and laboratory findings). Forty-two cirrhotic patients with encephalopathy (38.09% male and 61.90% female, mean age 48 ± 11 years) were enrolled into the study. For evaluation the encephalopathy, flapping tremor, number connection test (NCT), and grade of encephalopathy was determined for all the patients. Encephalopathy was graded with parsons-smith criteria corrected by Conn *et al.* (12). Diagnosis of *H pylori* infection was based on positive serology by ELAISA method (Genesis Kit, UK), and/or rapid urease test (RUT) during endoscopic evaluation. Patient was considered as infected if any of these tests were positive.

Patients with GI bleeding, active infection, antibiotic therapy during last month, hepatocellular carcinoma (HCC), electrolyte imbalance, renal failure ($\text{Cr} > 2 \text{ mg/dl}$), benzodiazepines, opium and/or alcohol consumption in last two weeks, diuretic, laxative and antacids in previous days were excluded from the study. In next step, all subjects gave written informed consent prior to inclusion in the study. All patients treated with lactulose, metronidazole and low protein diet and patients with *H pylori* infection treated with omeprazole (20 mg/bid), amoxicillin (1g/bid), azithromycin (250 mg/bid), bismuth (250 mg/bid) for a period of 10 days.

One month later, grading of encephalopathy (the highest grade in last month after treatment), NCT and flapping tremor was preformed again and eradication of *H pylori* was confirmed by UBT in infected patients. For statistical analysis SPSS version 13.0 was used. The mean differences of quantitative variables before and after treatment were evaluated using by paired-samples *t* test. The results were considered significant at the level of $P < 0.05$.

Results

Among 42 cirrhotic patients with encephalopathy, 21 patients were infected with HBV and 21 were HCV infected. The mean Child-Pugh score was 9.6 ± 1.5 . Serologic evaluation or RUT showed that 30 patients of 42 (71.42%) were positive for *H pylori*. With respect of grade of encephalopathy 2 patients (6.7%) were with grade II, 12 patients (40%) with grade III and 16 patients (53.3%) with grade IV. Treatment was started for all patients but we failed to follow one patient through the study and 2 patients were excluded from the study because of severe gastrointestinal discomfort, nausea or vomiting. Complete recovery from *H pylori* has been confirmed in 23 patients (85.18%).

Grading of encephalopathy was done after eradication in *H pylori* positive patients; one patient (4.3%) was recovered and classified as grade I, 8 patients (34.8%) were grade II, 9 patients (39.1%) grade III and 5 patients (21.7%) were grade IV. Grade 1-4 of NCT in our patients before treatment was 8 (26.7%), 15 (50%), 4 (13.3%) and 3 (10%) respectively. After treatment these numbers decreased to 12 (52.2%), 10 (43.5%) and 1 (4.3%) patients in grade 1-3, respectively. Flapping tremor were found in 4 patients (13.3%) in grade 0, 9 patients (30%) grade I, 11 patients (36.7%) grade II and 6 patients (20%) grade III before treatment. After treatment these numbers has decreased from 0-III grade in following order as 4 (17.4%), 11 (47.8%), 5 (21.7%), and 3 (13%), respectively. Grade of encephalopathy, NCT and Flapping tremor before and after treatment has been compared in Table 1.

Table 1. Comparison of encephalopathy grading, NCT and flapping tremor before and after eradication of *H pylori* infection.

Variable	Before treatment	After treatment	P value
NCT	2.06 ± 0.9	0.52 ± 0.59	0.038
Flapping tremor	0.63 ± 0.96	0.3 ± 0.92	0.248
Grade of encephalopathy	3.46 ± 0.62	2.78 ± 0.85	0.023

NCT: number connection test

Data are presented as mean $\pm$ standard deviation.

Discussion

Ammonia has still essential role in pathogenesis of encephalopathy (13). Two theories have been prepared for relationship between *H pylori* infection

and level of ammonia in blood: i) Presence of urease: ammonia production is essentially in intestine, according to urease activity, persons with *H pylori* infection have higher level of ammonia in the stomach compared with non-infectious persons ^(3, 6). Although ammonia production in stomach does not increase blood level of ammonia in normal persons, but it can elevate the ammonia level in blood of cirrhotic patients because of reduction in metabolism of ammonia in liver ⁽⁸⁾. ii) Decrease in zinc level: cirrhotic patients were seen having decreased level of zinc which results in severity of encephalopathy ⁽¹⁴⁾. This diminished level of zinc theoretically may be due to side effects of infection with *H pylori*, because there is a protein in cytosol and membrane of organism which is binding with zinc and does not allow zinc to get absorbed ⁽¹⁵⁾. It has been proved that ammonia level increase with decrement in absorption of zinc and also proved that long term usage of zinc has resulted in stimulation of enzyme urease and improvement in metabolism of urease ⁽¹⁶⁾.

Dasani *et al.* showed that the prevalence of *H pylori* infection in encephalopathic patients was 67% ⁽⁸⁾. In a study by Gubbins *et al.* the prevalence of *H pylori* infection in encephalopathic patients was 87.6% ⁽⁵⁾. In many studies, after HP eradication, grade of encephalopathy and blood level of ammonia has decreased ^(8, 17). In one study, after eradication of *H pylori*, blood level of ammonia has decreased but changes in visual evoke potential (VEP) findings were not significant ⁽³⁾. This decrease in level of ammonia was not due to effect of antibiotics on gut flora, in one study, in spite of the same treatment of two groups of patients (infected group with *H pylori* and non-infected group), grade of encephalopathy and NCT has shown to be decreased only in infected group ⁽⁸⁾.

In our study, after treatment grade of encephalopathy and NCT had a significant change as described above. Despite the results achieved in our study after treatment with infection, in some studies, grade of encephalopathy has not changed ^(18, 19). Theoretically these differences may be due to the effect of child score or microbe density that generally has not been evaluated. In one study, on cirrhotic patients by Zullo *et al.*, inhibitory effect of urease activity on decrease of blood ammonia was seen only in patients with child-Pugh B/C and high density microbe ⁽²⁰⁾.

Some specific species of *H pylori* was also found to be effective in formation of specific disease such as stomach cancer ⁽²¹⁾. Whether type of *H pylori* species has been effective in formation or exacerbation of encephalopathy or not, should be

evaluated in further study. In our study in contrast with grade of encephalopathy and NCT, no difference was found in grade of flapping tremor before and after treatment. This may be due to less number of patients in group under research and or may be due to difference in specificity and sensitivity in above two tests for diagnosis of encephalopathy.

Conclusions

Patients with advanced liver failure and encephalopathy may benefit minor changes in agents provoking encephalopathy. By accepting that *H pylori* infection may increase blood ammonia and deteriorate the encephalopathy, we confirmed that the eradication of *H pylori* may leads to improve the grade of HE and NCT.

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