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# STUDY TO EVALUATE ROLE OF HELICOBACTER PYLORI INFECTION IN THE PATHOGENESIS OF MINIMAL HEPATIC ENCEPHALOPATHY AND EFFECT OF ITS ERADICATION AT MAYO HOSPITAL LAHORE

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**Abstract:**

***Background and Aim*** *Helicobacter pylori (H. pylori) bacteria's main activity is to convert urea to ammonia, but in patients with liver cirrhosis it has been implicated in causation of hepatic encephalopathy. There has not been enough research in studying the role of H. pylori infection in causation of minimal hepatic encephalopathy (MHE). We looked at the relationship of H. pylori infection with MHE and hyper- ammonemia 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 psycho- metric tests for detection of MHE, rapid urease test to look for evidence of H. pylori infection and fasting blood ammonia levels measurements. 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's occurrence is found more 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*** *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 in patients with liver cirrhosis.*

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## INTRODUCTION:

Patients with cirrhosis are prone to hepatic encephalopathy. In addition, some patients have minimal hepatic encepha- lopathy (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, electro- encephalography 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].

Urease enzyme in Helicobacter pylori bacteria are rich 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 recur- rent 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 in Medicine Department Of Mayo Hospital lahore to find the prevalence of MHE in patients of cirrhosis and to establish the correlation between H. pylori infection and hyperammonemia to study the effects of anti-H. pylori treatment.

## METHODS:

**Subjects:** Patients of suspected cirrhosis of liver were subjected to ultrasound and endoscopic examination. Those with ultrasonography 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. Of the 210 patients only 65 patients were included in the study. 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, blood sample was collected in EDTA and ammonia level in the plasma was measured. 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:** NCT, FCT and line tracing test was performed on all patients. 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.

## 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 | | |
|---|---|---|
| **Test** | **Time of 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 | | | | |
|---|---|---|---|---|
| **Characteristics** | **Patients screened (n=210)** | **Patients controlled (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 encepha- lopathy (abnormal results in at least two abnormal psychomet- ric tests), NMHE No minimal hepatic encephalopathy.

**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 negatives for H. pylori.

**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 |

**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 |

## 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 encephalop- athy [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 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 hyper- ammonemia 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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