Effect of *Helicobacter pylori* eradication on serum ammonia levels in patients with chronic liver disease

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**Background:** *Helicobacter pylori* infection has been implicated in the development of encephalopathy in chronic liver disease (CLD); this is possibly due to increased production of ammonia by the action of bacterial urease on urea in the gastric lumen. Aim: To evaluate whether *H. pylori* eradication in patients with CLD affects arterial ammonia levels. **Methods:** Forty-six patients with CLD (40 alcoholic, 6 post hepatitis B; Child's class A 7, B 17, C 22) and 36 patients with symptoms of acid-peptic disease (APD) underwent gastrointestinal endoscopy and biopsy; gastric biopsies were evaluated for *H. pylori* status using rapid urease test and histology. *H. pylori*-positive subjects received quadruple-drug eradication therapy for 2 weeks. Fasting arterial plasma ammonia levels were estimated before and after eradication of *H. pylori.* **Results:** *H. pylori* infection was present in 21 of 46 (45.7%) patients with CLD and 23 of 36 (63.9%) with APD. At baseline, mean (SD) ammonia levels were higher in the CLD group (97.4 [10.9] versus 81.3 [7.7] mcg/dL in the APD group; p=0.0001), irrespective of *H. pylori* status. Amongst patients with liver disease, arterial ammonia levels were similar in the *H. pylori*-positive and -negative patients (94.1 [9.7] and 100.2 [11.3] mcg/dL, respectively); however, ammonia levels were higher in patients in Child's class C (102.7 [11.4] mcg/dL) than in those in class A (88.4 [1.6] mcg/dL; p<0.002) or B (94.1 [9.7] mcg/dL; p<0.002). In patients with APD, ammonia levels were higher in *H. pylori*-positive patients (85.3 [6.4] versus 74.1 [3.3] mcg/dL; p<0.001). After eradication of *H. pylori* infection, ammonia levels decreased to 88.4 (10.0) mcg/dL in CLD and 76.7 (4.8) mcg/dL in APD (p=0.001 as compared to baseline). There was no difference in post-eradication ammonia levels between Child's classes. **Conclusion:** Levels of arterial blood ammonia are higher in CLD than in APD, and correlate with severity of liver disease. *H. pylori* eradication was associated with reduction in arterial ammonia levels in patients with CLD. [Indian J Gastroenterol 2003:22:221-223]

**Key words:** Hepatic encephalopathy

Elevated blood ammonia levels are believed to play a role in causation of hepatic encephalopathy in patients with chronic liver disease (CLD). Hepatic dysfunction can lead to increased ammonia levels because of disordered urea metabolism; these levels increase with the severity of CLD.¹,²

Although colonic bacteria are the main source of ammonia, the stomach infected with *Helicobacter pylori* may act as an additional source.¹ The proposed mechanism is an increase in production of ammonia by the action of *H. pylori* urease on urea that has diffused into the gastric lumen. Though the amount of ammonia contributed by this source is very small,³ it could contribute to the development and severity of encephalopathy. We conducted this study to evaluate whether arterial plasma ammonia levels are affected by *H. pylori* eradication in patients with CLD.

**Methods**

Forty-six consecutive patients (mean age 47.5 [8.7] years; 44 men) with CLD who did not have current clinical hepatic encephalopathy were enrolled. The etiology of CLD was alcohol abuse in 40 patients and hepatitis B in 6 patients. Seven patients were in Child-Pugh class A, 17 in B and 22 in C. Patients with constipation, gastrointestinal bleed, renal insufficiency (serum creatinine >2 mg/dL), spontaneous bacterial peritonitis, intake of an antibiotic or a proton pump inhibitor in the previous 2 weeks were excluded. Thirty-six patients (mean age 32.9 [10.2] years; 23 men) with symptoms of acid-peptic disease (APD) and no evidence of liver disease on biochemical and imaging modalities served as controls. In the latter group, those with antibiotic or intake of proton pump inhibitor in the previous 2 weeks were excluded. The protocol was approved by the institution ethics committee. All patients gave informed consent for the study.

In all patients, arterial blood was collected in the fasting state for estimation of plasma ammonia levels.⁴ All patients underwent upper gastrointestinal endoscopy and antral biopsy after an overnight fast. Two pieces from the antrum were obtained, one each for rapid urease test (RUT) and histology. Patients with evidence of *H. pylori* infection on either of these tests were admin-
istered quadruple-drug anti-*H. pylori* therapy for 2 weeks (amoxicillin 750 mg bid, tindazole 500 mg bid, omeprazole 20 mg bid and bismuth 240 mg bid), and endoscopy and measurement of arterial plasma ammonia levels were repeated 4 weeks after completion of therapy. During repeat endoscopy, two biopsies each were obtained from the gastric antrum, body and fundus for RUT and histology. Eradication of infection was defined as negative RUT and absence of *H. pylori* on histology in biopsies from all three sites.

ANOVA was used for comparison of ammonia levels in patients in the two groups and patients with different Child classes. Comparison of pre- and post-treatment plasma ammonia levels was done using the Student's *t* test for paired data.

**Results**

Mean (SD) arterial ammonia levels at baseline were higher (97.4 [10.9] mcg/dL) in the 46 patients with CLD than in the 36 patients with APD (81.3 [7.7] mcg/dL; *p=0.001*).

At endoscopy, 5 patients in the CLD group and 6 in the APD group had duodenal ulcer. *H. pylori* infection was present in 21 patients with CLD and 23 with APD. In the APD group ammonia was higher in *H. pylori*-positive patients (85.3 [6.4] mcg/dL) than in the infected group (74.1 [3.3] mcg/dL; *p<0.001*). In the CLD patients, arterial ammonia levels were similar in *H. pylori*-positive and -negative patients (Table 1); ammonia level was higher in Child C patients (102.7 [11.4] mcg/dL) than in those in Child's classes A or B (*p=0.002*). Twenty patients (Child class C 19, B 1) had history of previous encephalopathy. Their mean ammonia levels at baseline were higher (104.7 [9.5] mcg/dL) than in the 26 patients who did not have previous encephalopathy (91.9 [8.4] mcg/dL; *p=0.02*). Four of 20 patients who had previously had encephalopathy were *H. pylori*-positive versus 17 of 26 patients who had not (*p=0.02*).

All *H. pylori*-positive patients received eradication therapy. The treatment was successful in 21 patients with APD and 20 patients with CLD; of the latter, 3 were in Child A, 11 in B, and 6 in C. After eradication of *H. pylori*, there was decrease in ammonia to 76.7 (4.8) mcg/dL (*p<0.001*) and 88.4 (10) mcg/dL in the APD and CLD patients, respectively (Table 2). There was no difference in post-eradication ammonia levels in patients in each Child class.

**Discussion**

Patients with CLD without overt hepatic encephalopathy had high blood levels of ammonia. Levels were higher in those with Child C cirrhosis. Arterial ammonia levels were similar in CLD patients with or without *H. pylori* infection, but *H. pylori* eradication therapy decreased the ammonia levels.

Increased blood ammonia is believed to play an important role in the pathogenesis of hepatic encephalopathy. Some studies have shown that patients with CLD and *H. pylori* infection have higher blood ammonia levels than those with CLD but no *H. pylori* infection. It has therefore been proposed that *H. pylori* infection may contribute to development of clinical or subclinical hepatic encephalopathy through increased gastric luminal ammonia synthesis by breakdown of urea by bacterial urease enzyme. However, the amount of urea produced in the stomach by *H. pylori* is equal to that produced from 0.89 g of ingested protein, a quantity insufficient to produce encephalopathy except possibly in those with very advanced liver disease. Also, CLD may by itself lead to an increase in blood ammonia levels. Thus, the role of *H. pylori* in causation of neuropsychiatric alterations in patients with CLD remains unclear. If *H. pylori* infection contributes to hyperammonemia, treatment of this infection may be expected to lower blood ammonia levels, as we found in the present study.

Levels were higher in patients with more severe CLD, irrespective of the *H. pylori* status. This suggests that increase in blood ammonia levels in patients with CLD is related to the underlying liver dysfunction but not to the presence of *H. pylori* infection. Chakrabarti et al found that patients with encephalopathy had higher

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**Table 1: Baseline arterial ammonia levels in various groups**

<table>
<thead>
<tr>
<th>Acid peptic disease</th>
<th>All patients with chronic liver disease</th>
<th>Child's class</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Ammonia levels</td>
<td>No.</td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
<td>------</td>
</tr>
<tr>
<td>Baseline</td>
<td>36</td>
<td>81.3 (7.7)</td>
</tr>
<tr>
<td><em>H. pylori</em> negative</td>
<td>13</td>
<td>74.1 (5.3)</td>
</tr>
<tr>
<td><em>H. pylori</em> positive</td>
<td>23</td>
<td>85.3 (6.4)*</td>
</tr>
</tbody>
</table>

All values as mean (SD). *p=0.001* as compared to acid peptic disease; **p=0.05 as compared to Child's class A and B; *p=0.001 as compared to *H. pylori*-negative subjects.

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arterial ammonia and more severe liver disease, irrespective of *H. pylori* infection; however, gastric juice ammonia levels were higher in those with *H. pylori* infection.

In patients with decompensated cirrhosis of liver, Dasani et al\(^1\) found evidence of *H. pylori* infection in 67% of patients with encephalopathy as compared to 53% of those without. Even after adjustment for severity of cirrhosis and age, *H. pylori* infection had a significant association with presence of hepatic encephalopathy. Several studies failed to show an association between *H. pylori* infection and encephalopathy. In a multivariate analysis, Calvet et al\(^10\) did not find *H. pylori* infection as a risk factor for the development of encephalopathy. In patients with cirrhosis who had undergone transjugular intrahepatic portosystemic shunt, plasma ammonia concentration and incidence of hepatic encephalopathy were similar in patients with or without *H. pylori* antibodies. In two studies, ammonia levels and the incidence of abnormal psychometric tests were similar in patients with or without *H. pylori* infection.\(^12\)\(^-\)\(^13\)

*H. pylori* eradication in hyperammonemic patients with liver cirrhosis has been shown to produce a short-lasting decrease in blood ammonia levels. However, many studies have shown no decrease after *H. pylori* eradication.\(^13\)\(^-\)\(^15\) The improvement in encephalopathy or decrease in blood ammonia levels in response to *H. pylori* eradication therapy in patients with CLD may not be due to *H. pylori* eradication, but instead to concomitant suppression of colonic flora by the antibiotics included in anti-*H. pylori* treatment regimens. In one study, improvement after antibiotic therapy was observed only in patients with *H. pylori* infection; the authors thus suggested that the cause of improvement was *H. pylori* eradication rather than suppression of colonic flora.

Our study has certain limitations. We studied only one parameter, viz., arterial ammonia levels pre- and post-*H. pylori* eradication. Also, though patients with overt encephalopathy were excluded, we did not assess for the presence of subclinical hepatic encephalopathy.

In conclusion, ammonia levels are higher in patients with chronic liver disease; those with Child C cirrhosis have the highest values. Since eradication of *H. pylori* causes a decrease in the ammonia levels, the infection may have a role to play in the increased ammonia levels in cirrhosis. Whether this contributes to generation of encephalopathy is as yet speculative.

References


