What is the association between *Helicobacter pylori* and hyperammonemia in liver disease?

Ammonia plays a key role in the multifactorial pathogenesis of hepatic encephalopathy in patients with cirrhosis of liver. Even though the kidneys and muscles also liberate ammonia, the major source is the gastrointestinal tract, where ammonia is produced by the action of colonic bacterial flora on dietary proteins, epithelial and bacterial debris, and mucosal secretions containing urea, peptides and amino acids.

Peptic ulcer disease has long been recognized to be more common in patients with cirrhosis of liver. After the recognition of the association of peptic ulcer disease with *Helicobacter pylori*, this infection has also been reported more commonly in patients with cirrhosis liver. Since *H. pylori* has the ability to produce ammonia by splitting gastric urea by the enzyme urease, it has also been implicated in the hyperammonemia and hepatic encephalopathy in patients with cirrhosis liver, thus adding another disease manifestation to the list of extraintestinal associations of *H. pylori*.

The data on the role of *H. pylori* in increasing blood ammonia levels and in causing encephalopathy is controversial. Ordinarily the amount of ammonia produced by gastric *H. pylori* is too small to contribute towards hyperammonemia and hepatic encephalopathy. The amount of ammonia in the gastric juice (4.58 [0.55] mmol/L) was found to be equivalent to 64 mg/L of nitrogen or 128 mg of nitrogen per day. This amount is the same as that derived from the deamination of 0.89 g of alimentary protein, which is too low to be a contributing factor for hepatic encephalopathy. The urea cycle converts ammonia produced by colonic bacteria and *H. pylori* in normal individuals to urea in the liver.

In cirrhosis, there is significant reduction of maximal rate of urea synthesis (MRUS), and cirrhotic patients with MRUS less than 20% are usually hyperammonemic. Presence of precipitating factors like GI bleeding, constipation or increased catabolism increases the ammonia load to the diseased liver, thus increasing the blood ammonia levels further, due to poor urea synthesis in the liver. Thus severity of underlying liver disease and the load of bacteria (*H. pylori*) are factors that determine its role in increasing blood ammonia levels and in causing encephalopathy.

In a study of 132 patients who had undergone TIPS, Huber et al. did not find any relationship of *H. pylori* either with blood ammonia levels or with the occurrence of encephalopathy. Some authors have also studied gastric juice ammonia levels in addition to arterial blood ammonia levels in cirrhotics with *H. pylori* infection, but did not find any correlation between the two. Demirturk et al. studied the effect of *H. pylori* eradication on gastric juice and arterial ammonia levels and visual evoked potentials (VEP). Even though ammonia levels improved at both sites after eradication of *H. pylori*, there was no significant improvement in the VEP. Similar observations have also failed to show any relationship between *H. pylori* and the psychometric tests used for minimal hepatic encephalopathy. On the other hand, Dasani et al. while analyzing the factors responsible for chronic hepatic encephalopathy, found *H. pylori* to be an important determinant especially in young patients with decompensated liver disease.

In this issue of the Journal, Nandakumar et al. have reported the effect of *H. pylori* eradication on serum ammonia levels in patients with chronic liver disease (CLD) without overt encephalopathy. *H. pylori* was documented in 21 of 46 (45.7%) patients of CLD. Arterial blood ammonia levels were found to be higher in patients with CLD as compared with 36 control patients with acid peptic disease (APD). Among patients with CLD, patients with severe liver disease (Child C) had higher arterial ammonia as compared to those with Child A and B severity. Ammonia levels, however, in patients with CLD were similar in *H. pylori*-positive and *H. pylori*-negative patients. Twenty patients (Child C 19, B 1) had history of encephalopathy in the past. Their ammonia levels were higher than in 26 patients without history of encephalopathy. Only 4 of the 20 (20%) patients with history of previous encephalopathy had *H. pylori* positive, in contrast to 17 of 26 (65%) patients who did not have history of encephalopathy. After *H. pylori* eradication there was a decrease in arterial ammonia levels in both CLD and APD patients. Thus this study shows higher ammonia levels in patients with CLD especially in those with severe disease and in those with past history of encephalopathy, without any relation to the presence of *H. pylori*. After *H. pylori* eradication there was decrease in arterial ammonia levels in both group of patients with CLD and APD.

The question that needs to be answered in this study is whether this decrease in arterial ammonia levels is a result of *H. pylori* eradication.

Colonic bacterial flora are the main source of ammonia, and antibiotics used for *H. pylori* treatment may have an effect on them; the improvement in ammonia levels in these patients could thus be because of sup-
pression of colonic bacteria. The authors could have sorted this out in two ways – taking care of colonic flora first or selective inhibition of H. pylori urease. In one study, 50 patients with cirrhosis of liver and hyperammonemia were first treated with a low-protein diet, kanamycin, lactulose and branched chain amino acids. Eighteen patients in whom hyperammonemia persisted despite this treatment were then divided into three groups depending on the distribution of H. pylori in the stomach and were given H. pylori treatment for two weeks. Ammonia concentration in blood and gastric juice decreased after treatment in those with diffuse distribution of H. pylori but did not improve in those with regional distribution or no H. pylori. This study showed that hyperammonemia may persist in some patients in spite of treatment of colonic bacteria and H. pylori may have a role in increasing ammonia levels in them. In addition they showed that the number of H. pylori are important in determining the amount of ammonia produced and thus their contribution to the total hyperammonemia seen in patients with cirrhosis of liver, otherwise the amount of ammonia produced by gastric H. pylori may be too small to have any clinical significance.

Nandakumar et al treated their patients directly with anti-H. pylori drugs, which could have inhibited the colonic flora as well. So it is difficult to draw conclusions from their study about the effect of H. pylori eradication on blood ammonia levels. In addition they did not find any difference in ammonia levels in CLD patients with or without the presence of H. pylori and there was no relation between the history of encephalopathy, severity of liver disease and H. pylori; they should have looked at the H. pylori density and distribution in their gastric biopsies to determine the bacterial load. It may be that the number of bacteria was too small to produce significant amount of ammonia!

Another way to prove a role of H. pylori in causing hyperammonemia is to selectively inhibit the enzyme urease produced by H. pylori. Acetohydroxamic acid (AHA) is a powerful non-antibiotic inhibitor of bacterial urease; it is absorbed in the upper intestine without reaching the colon. In one study, blood ammonia levels were determined in 20 cirrhosis before and at 15-minute intervals for 90 minutes after 750 mg of AHA. Blood ammonia levels were significantly reduced in those with severe liver disease and in those with high-density H. pylori infection in the stomach, proving that inhibition of urease enzyme decreases blood ammonia levels.

There is no doubt that H. pylori produces ammonia and contributes towards blood and gastric juice ammonia, but the amount produced depends on the number of bacteria; this determines its clinical importance in a patient with significant underlying liver disease. More data on this subject will probably clarify the contribution of H. pylori in causing hyperammonemia and hepatic encephalopathy.

Yogesh Chawla, Ajay Duseja
Department of Hepatology, Post Graduate Institute of Medical Education and Research, Chandigarh 160 012

References

Correspondence to: Dr Chawla, Professor and Head. Fax: (172) 274 4401. E-mail: pghepat@glide.net.in

208 Indian Journal of Gastroenterology 2003 Vol 22 November - December