Commentary

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Helicobacter pylori, ammonia and the brain

Across the world, the human upper gastrointestinal tract is commonly infected with *Helicobacter pylori*. This urea splitting bacterium is now considered to be a causal agent in a spectrum of human disease, ranging from a limited antral gastritis to frank duodenal ulceration, in addition to an association with gastric carcinoma and MALT (mucosa associated lymphoid tissue) lymphoma. However, it is the presence of the bacterial urease which has stimulated recent interest into whether *H pylori* contributes to the hyperammonaemia frequently observed in patients with chronic liver disease. If infection with this organism that produces ammonia was significantly to effect the circulating blood ammonia concentrations, then it was hypothesised that eradication treatment would improve hepatic encephalopathy.[1]

Chronic hepatic encephalopathy is a neuropsychiatric disorder with protean manifestations, the pathogenesis of which is poorly understood.[2] It is generally underdiagnosed because, in most patients, the condition is subclinical.[3] Psychometry and electroencephalography (EEG) have been the mainstay of objective diagnosis, but new techniques with diagnostic potential, such as magnetic resonance spectroscopy, are now becoming available.[3 4]

Raised systemic ammonia concentrations as a consequence of impaired hepatic ureagenesis or because of shunting of ammonia rich portal blood away from the liver have long been causally implicated in the development of hepatic encephalopathy.[5] However, in each patient, the disorder probably has many contributing factors with increases in circulating gut derived toxins, including ammonia, and disturbances in cerebral neurotransmitters considered to be important.[2] Nevertheless, blood ammonia concentrations are not always raised in patients with hepatic encephalopathy and ammonia concentrations do not necessarily correlate with patient symptoms or with the underlying neuropsychiatric status.[6]

The initial study implicating *H pylori* as a risk factor for hepatic encephalopathy was published in 1993.[7] In a multicentre study of 273 patients with alcoholic hepatitis, 79% of those with hepatic encephalopathy had positive serology for *H pylori*, compared with 62% of those without overt encephalopathy. However, this study did not involve any endoscopic or breath test confirmation and can be criticised, because the use of serology alone did not distinguish between patients with an active infection or those with a previously eradicated infection. Most of the study patients who were not considered to be encephalopathic also had a high prevalence of *H pylori* seropositivity in common with the population at large. It is, therefore, difficult to concur with the authors' ascertation that *H pylori* was a significant risk factor for the development of hepatic encephalopathy.

The initial letter to the *Lancet* by Ito and colleagues on two patients with chronic liver disease who had received *H pylori* eradication treatment reported a subsequent reduction in circulating ammonia concentrations.[8] However, further correspondence cast doubt on the suggestion that infection with the organism might contribute to encephalopathy. A Dutch group also reported a reduction in blood ammonia concentrations after treating *H pylori* in 10 patients with chronic liver disease, but hyperammonaemia returned after a couple of months.[9] A study from Edinburgh found that the presence of *H pylori* made no difference to blood ammonia concentrations measured up to two hours after a urea load was given orally to 20 such patients.[10] Both the latter two research groups concluded that any effect that eradication of *H pylori* had on hyperammonaemia was probably as a result of antibiotic treatment on gut bacterial flora.

The issue is complicated because ammonia absorption is often unpredictable in liver disease, whereas that which might be attributed to *H pylori* could be influenced by such factors as the nature of any gastric pathology present, the distribution and extent of bacterial colonisation in the stomach, and the presence of a collateral circulation. Careful studies looking at the relation between *H pylori* as an ammonia producing organism and its possible effects on patients with chronic liver disease are required. The report by Miyaji and colleagues in this issue is therefore timely (see page 726). These investigators have tried to tackle some of the criticisms of the other groups in their study design. They looked at 50 patients with chronic liver disease of varying functional severity, but of undisclosed aetiology; not all patients underwent liver biopsy to confirm cirrhosis. It is not documented whether patients were abstinent from alcohol, as this may be a confounding factor when assessing hepatic encephalopathy. However, none had received *H pylori* eradication treatment previously. In order to minimise any effects that triple therapy for *H pylori* infection might have on other gut flora, all subjects received a regimen designed to reduce the colonic bacterial load for the two weeks prior to investigation. It should be noted that 32 patients subsequently had normal blood ammonia concentrations. This group contained 12 subjects who were *H pylori* positive in two or more of the tests for the presence of the organism, including the instillation of phenol red dye into the stomach at endoscopy. This latter test allowed the subdivision of patients who were judged to have a limited or more generalised infection from the staining pattern produced. However, only those 18 patients who remained hyperammonaemic were selected for further study. Two thirds were infected with the organism, but all received triple therapy, which was found to be effective at repeat endoscopy four weeks later. Only the six patients with a generalised staining pattern had a significantly reduced blood ammonia concentration after eradication, which was maintained at three months. The authors therefore

conclude that the extent of *H pylori* colonisation affects blood ammonia concentrations in these patients.

Several criticisms can be made of this study. Reduction in gastric ammonia concentrations after triple therapy simply reflects eradication of *H pylori* and no extrapolation can be made from this to blood ammonia concentrations. Furthermore, it would have been interesting to have documented the natural history of the 32 patients who developed normal circulating ammonia concentrations after the anti-encephalopathy regimen. We were not told whether blood ammonia returned to pretreatment concentrations. Did the subset of 12 patients who were *H pylori* positive behave any differently to the others? It is therefore still not clear whether eradication therapy for *H pylori* really does have an effect on hyperammonaemia, distinct from the effects of altering colonic bacterial flora by administration of antibiotics. Another major criticism is that no attempt was made to correlate ammonia concentrations either with the presence of a collateral circulation or with neuropsychiatric status.

Although hyperammonaemia is probably one of the most important causal factors in the development of hepatic encephalopathy, not all patients have high blood concentrations, whereas others may do so without any demonstrable ill effect. Future studies relating *H pylori* infection to the hyperammonaemia of chronic liver disease should also document the clinical, neuropsychometric and EEG response of patients with hepatic encephalopathy to therapeutic interventions to clear the organism.

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