

# HELICOBACTER PYLORI & HEPATIC ENCEPHALOPATHY; DO THEY REPRESENT TWO SIDES OF THE SAME COIN?

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## DR. JAHANGIR LIAQUAT

MD (Internal Medicine),  
Deptt: of Medicine, LUMHS

## MR. IFTIKHAR KAZI

PG Student  
Department of Medicine, LUMHS

## MR. MUKHTIAR AHMED

PG Student  
Department of Medicine, LUMHS

## Dr. Akber Hussain Yousfani

MCPS (Family Med.), MD (Internal Med.)  
Assistant Professor,  
Deptt: of Medicine, LUMHS

## Dr. Raj Kumar, FCPS

Deptt: of Medicine, LUMHS

**ABSTRACT... Introduction:** Hepatic encephalopathy is a common and serious complication affecting patients with liver disease. Helicobacter pylori bacterium is postulated to be involved in worsening of this condition via its potential to create ammonia within the gastrointestinal tract. **Objective:** The objective of this study was to determine the frequency of H pylori infection in cirrhotic patients who were suffering from hepatic encephalopathy. **Design:** Case series study. **Setting:** Medical Unit-IV of Liaquat University Hospital, Hyderabad. **Period:** January to July 2010. **Methodology:** Every confirmed case of cirrhosis of liver who presented with acute confusional state, and loss of consciousness to the emergency department of hospital was considered for enrollment in the study. The presence of hepatic encephalopathy was confirmed and its severity grading was done clinically. Subsequently H pylori serological tests were done on every patient and a cut off value of 200:1 antibody titer was considered as positive. Primary outcome variable was presence or absence of H pylori antibody titer. **Results:** A total of 115 patients were selected, 69 (60%) were males and 46 (40%) were females. The mean age of patients was 49.36 years with a SD of 7.8. Antibody to H pylori was present in 83 (72.17%) patients, whereas it was absent in 32 (27.83%). Two out of ten patients (20%) who were in Grade I hepatic encephalopathy showed a positive test for H pylori antibody. In Grade II hepatic encephalopathy 17 out of 19 patients (89.47%) were having positive H pylori antibody, in grade III 29 out of 34 (85.29%) and grade IV 35 out of 52 patients (67.3%) were having the antibody to H pylori. **Conclusions:** Further studies are warranted to evaluate the arguments for and against the role of H pylori in the pathogenesis of hepatic encephalopathy.

**Key words:** Cirrhosis of liver – hepatic encephalopathy – H pylori antibody- ammonia.

## INTRODUCTION

Hepatic encephalopathy (HE) is a frequent complication of liver cirrhosis<sup>1</sup>. There are many precipitating factors, which may lead to development of portosystemic encephalopathy (PSE) such as accumulation of ammonia, production of false neurotransmitters, decreased activity of urea-cycle enzymes due to zinc deficiency, deposition of manganese in the basal ganglia and increased endogenous activity of benzodiazepines<sup>2</sup>. Among these factors, ammonia has a key importance in the pathogenesis of PSE. Most of the precipitating factors produce hyperammonemia such as gastrointestinal bleeding; excess dietary protein, constipation and hypokalemia induced renal production<sup>3</sup>.

The other predisposing factor other than described above, increased ammonia production due to Helicobacter pylori (H.Pylori) contributed one of the main

risk factor for hepatic encephalopathy in patients with cirrhosis of liver<sup>4</sup>. H pylori is known to produce copious amounts of ammonia due to its strong urease activity. The production of ammonia by H. pylori participated in the pathogenesis of hyperammonemia when this organism is widely distributed and present in significant numbers in the stomach, particularly in the presence of liver cirrhosis<sup>5</sup>. In this regard two theories have been postulated regarding relationship between H.pylori infection and hepatic encephalopathy which showed that ammonia has still essential role in pathogenesis of hepatic encephalopathy<sup>6</sup>.

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 person. 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<sup>7</sup>.

ii) Decrease in zinc level: cirrhotic patients were seen having decreased level of zinc which results in severity of encephalopathy. 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. 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<sup>8</sup>.

It has been postulated that ammonia level in stomach acid in *H. pylori* infected cirrhotic patients is higher than non infected patients. As a result, it can be postulated that *H. pylori* infection may potentially contribute to the development of HE<sup>9</sup>. However, conflicting data are available in the literature. Several studies have shown that ammonia levels do not significantly differ between cirrhotic patients with and without *H. pylori* infection, which suggests that although *H. pylori* infection is able to generate ammonia in the stomach, the amount appears to be not enough to affect arterial ammonia levels in patients with cirrhosis<sup>10</sup>. In view of the association of *H. pylori* infection with hyperammonemia and HE, bacterium eradication may theoretically reduce ammonia concentration in cirrhotic patients. The quantity of ammonia produced by *H. pylori* to HE may depend on the number of bacteria and their distribution in the stomach, gastric membrane permeability to ammonia, gastric pH liver impairment, and portal vein branch circulation. It has been supposed that *H. pylori* may increase blood ammonia concentration and induce HE when the bacterium is widely distributed in the stomach, and in the presence of severe liver impairment (Child-Pugh class B or C) with abundant portal vein branch circulation.

Various studies have been done which showed that after *H. pylori* eradication, grade of encephalopathy and blood level of ammonia has decreased<sup>11</sup>. 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. A study done by Chen et al<sup>12</sup>. Showed that the patient with hepatitis B who do not clear the virus in the presence of *H. pylori*, the prognosis of chronic liver disease may benefit from early eradication<sup>12</sup>.

## METHODOLOGY

This descriptive case series study was conducted in Medical Unit I, Lquat University Hospital Hyderabad from January to July 2010. A total of 115 patients were selected based on 95% confidence interval, 60% frequency, 13 and 9% margin of error. All patients above 18 years of age either male or female with clinical and radiological evidence of cirrhosis of liver with presence of hepatic encephalopathy at the time of admission were included. Patients with encephalopathy of other causes such as; encephalitis, meningitis, hyperglycemia or hypoglycemia, history of diuretic therapy and acute fulminant hepatic failure (all of these causes would create false positive hepatic encephalopathy causes) were excluded. Non-probability consecutive sampling was utilized for this study.

Every confirmed case of cirrhosis of liver who presented with acute confusional state, (inability to answer any one of the following: the name of person already known, time of the day and the place where he or she is present) somnolence (excessive daytime sleep) and loss of consciousness (a state of sleep from which a person can only be partially aroused by application of painful stimuli) to the emergency department of hospital was considered for enrollment in the study. The presence of hepatic encephalopathy was confirmed and its severity grading done clinically. Subsequently *H. pylori* serological tests were done on every patient and a cut off value of 200:1 antibody titer was considered as positive. Primary outcome variable was labeled as presence or absence of *H. pylori* antibody titer.

## DATA ANALYSIS

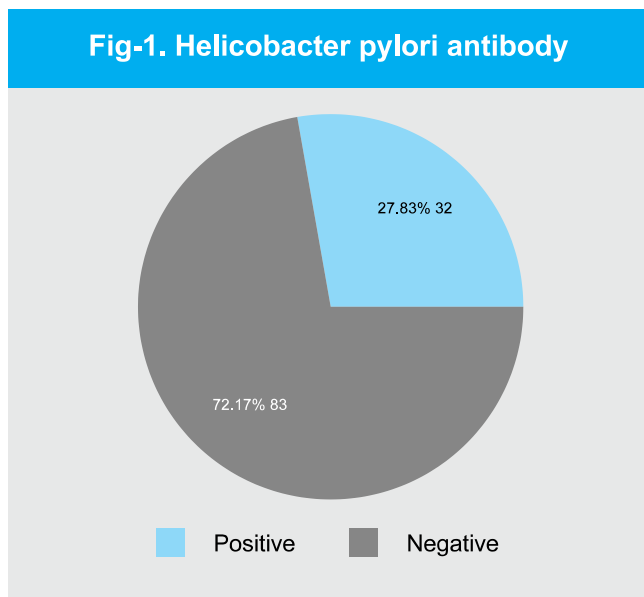
It was done by Statistical Package for Social Sciences (SPSS)™ software version 16. Continuous variables such as age are expressed as mean  $\pm$  SD. Categorical variables such as grade of encephalopathy, gender and anti *H. pylori* antibody status is presented as frequency

and percentage. Frequency of H pylori antibody was also be computed with respect to age, gender and hepatic encephalopathy grade to see the impact of these on the outcome.

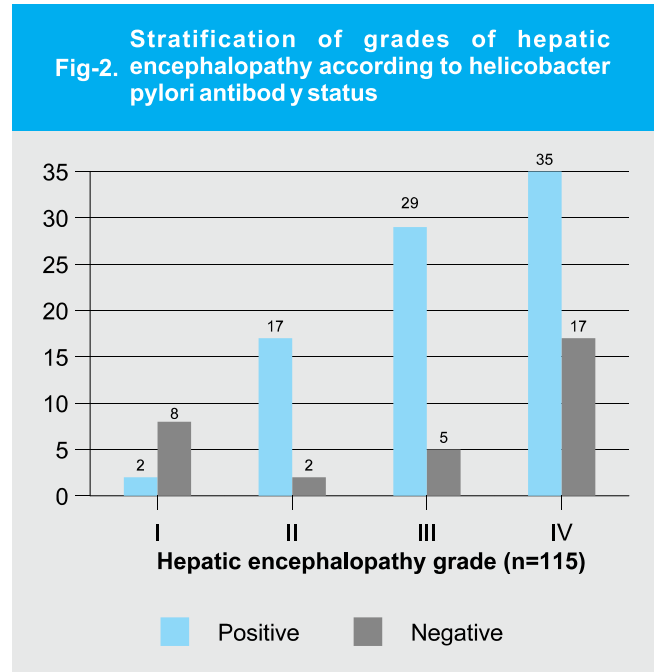
**RESULTS**

A total of 115 patients were selected, 69 (60%) were males and 46 (40%) were females. The mean age of patients was 49.36 years with a SD of 7.8. The patients were further grouped in different Age Ranges (18-30 years, 31-50 years and 51-70 years) and the grade of Hepatic Encephalopathy (Grade I to IV, West Haven Grading System). Antibody to H pylori was present in 83 (72.17%) patients, whereas it was absent in 32 (27.83%) (see Figure No: 1). Two out of ten patients (20%) who were in Grade I hepatic encephalopathy showed a positive test for H pylori antibody. In Grade II hepatic encephalopathy 17 out of 19 patients (89.47%) were having positive H pylori antibody, in grade III 29 out of 34 (85.29%) and grade IV 35 out of 52 patients (67.3%) were having the antibody to H pylori (see Figure No: 2).

**DISCUSSION**



Most currently available therapies for prevention of HE focus on reducing blood ammonia concentration<sup>14</sup>. H pylori is known to produce copious amounts of ammonia due to its strong urease activity. Ammonia produced by H pylori has a role in the pathogenesis of hyperammonemia when this organism is widely



distributed and present in large numbers in the stomach, particularly in the presence of liver cirrhosis.

Ammonia has still essential role in pathogenesis of encephalopathy. Two theories have been prepared for relationship between H pylori infection and level of ammonia in blood:

- 1). 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<sup>15</sup>.

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.

- 2). Decrease in zinc level: cirrhotic patients were seen having decreased level of zinc which results in severity of encephalopathy. 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<sup>16</sup>.

This suggested that H pylori infection was associated with increased production of ammonia in cirrhotic patients. It has previously been shown ammonia concentration in portal and venous blood significantly increased after the instillation of 1010 CFU/L H pylori in the stomach of cirrhotic rats<sup>17</sup>.

This landmark study has shown that ammonia levels do not significantly differ between cirrhotic patients with and without H pylori infection, which suggests that although H pylori infection is able to generate ammonia in the stomach, the amount appears to be too small to affect arterial ammonia levels in patients with cirrhosis<sup>18</sup>.

The contribution of ammonia produced by H pylori to HE may depend on the number of bacteria and their distribution in the stomach, gastric pH, gastric membrane permeability to ammonia, liver impairment, and portal vein branch circulation. It is supposed that H pylori may increase blood ammonia concentration and induce HE when the bacterium is widely distributed in the stomach, and in the presence of severe liver impairment (Child-Pugh class B or C) with abundant portal vein branch circulation.

In view of the association of H pylori infection with hyperammonemia and HE, bacterium eradication may theoretically reduce ammonia concentration in cirrhotic patients

In this study the H. pylori titre was observed to be rising with the severity of hepatic encephalopathy (please see

result), which is in accordance with Shrimali L et al in India<sup>19</sup>.

The Table No-I shows some selected studies which were conducted on the relationship of H pylori infection with the presence of hepatic encephalopathy. The result of this study is comparable with all the studies mentioned in this table.

The study had a limitation in determination of the status of H. pylori on the basis of IgG antibodies, which does not differentiate between an active infection and previous exposure.

**CONCLUSIONS**

Further studies are warranted to evaluate the arguments for and against the role of H pylori in the pathogenesis of hepatic encephalopathy.

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**REFERENCES**

1. Harris MK, Elliott D, Schwendimann RN, Minagar A, Jaffe SL. **Neurologic presentations of hepatic disease.** *Neurol Clin* 2010;28(1):89-105.
2. Ardizzone G, Arrigo A, Schellino MM, Stratta C, Valzan S, Skurzak S, et al. **Neurological complications of liver cirrhosis and orthotopic liver transplant.** *Transplant Proc* 2006;38(3):789-92.
3. Olde Damink SW, Jalan R, Deutz NE, Redhead DN, Dejong CH, Hynd P, et al. **The kidney plays a major role in the hyperammonemia seen after simulated or actual GI bleeding in patients with cirrhosis.** *Hepatology* 2003;37(6):1277-85.
4. Yang CS, Cao SY, He XJ, Wang YX, Zhang YL. **Study of**

**Table-I. Some selected studies about relationship of helicobacter pylori with hepatic encephalopathy**

Author (s)	Country	Year	No. of Pts	%age of H pylori antibody	Other variables
Chen SJ et al	China	2003-05	457	60.6	Ammonia levels, H pylori eradication
Shavakhi A et al	Iran	2007	42	71.42	H pylori eradication
Shrimali L et al	India	2001	100	78	-
Sethar GH	Pakistan	2001-02	76	77.6	-
Liaquat J et al	Pakistan	2010	115	72.17	-

- correlation between helicobacter pylori infection and hyperammonemia and hepatic encephalopathy in cirrhotic patients.** Zhongguo Weizhongbing Jijiu Yixue 2007; 19: 422-424.
5. Cylwik B, Dlugosz JW, Kemona A, Szmitkowski M. **The effect of intragastric ammonia production on titratable gastric acid output in Helicobacter pylori-infected patients with chronic gastritis.** Dig Dis Sci 2005; 50: 2094-9.
  6. Abdel-Hady H, Zaki A, Badra G, Lotfy M, Selmi C, Giorgini A, et al. **Helicobacter pylori infection in hepatic encephalopathy: Relationship to plasma endotoxins and blood ammonia.** Hepatol Res 2007; 37: 1026-1033.
  7. Lee OJ, Lee EJ, Kim HJ. **Correlations among gastric juice pH and ammonia, Helicobacter pylori infection and gastric mucosal histology.** Korean J Intern Med 2004; 19: 205-12.
  8. Umusig-Quitain P, Gregorio GV. **High incidence of zinc deficiency among Filipino children with compensated and decompensated liver disease.** J Gastroenterol Hepatol 2010;25(2):387-90.
  9. Zullo A, Hassan C, Morini S. **Hepatic encephalopathy and Helicobacter pylori: a critical reappraisal.** J Clin Gastroenterol 2003; 37: 164-8.
  10. Huber M, Rossle M, Siegerstetter V, Ochs A, Haag K, Kist M, Blum HE. **Helicobacter pylori infection does not correlate with plasma ammonia concentration and hepatic encephalopathy in patients with cirrhosis.** Hepatogastroenterology 2001; 48: 541-4.
  11. Nandakumar R, Naik AS, Pandit B, Kamat R, Bhatia SJ. **Effect of Helicobacter pylori eradication on serum ammonia levels in patients with chronic liver disease.** Indian J Gastroenterol 2003;22: 221-3.
  12. Chen NL, Bai L, Deng T, Zhang C, Kong QY et al. **Expression of hepatitis B virus antigen and Helicobacter pylori infection in gastric mucosa of patients with chronic liver disease.** Hepatobiliary Pancreat Dis Int 2004;3:223-5.
  13. Chen SJ, Wang LJ, Zhu Q, Cai JT, Chen T, Si JM. **Effect of H pylori infection and its eradication on hyperammonemia and hepatic encephalopathy in cirrhotic patients.** World J Gastroenterol 2008;14(12):1914-8.
  14. Romero-Gomez M, Grande L, Camacho I, Benitez S, Irlés JA, Castro M, et al. **Altered response to oral glutamine challenge as prognostic factor for overt episodes in patients with minimal hepatic encephalopathy.** J Hepatol 2002; 37: 781-7.
  15. Chakrabarti P, Zullo A, Hassan C, Pandit A, Chowdhury A, Santra A, et al. **Helicobacter pylori, gastric juice, and arterial ammonia levels in patients with cirrhosis.** J Clin Gastroenterol 2002; 34: 578-81.
  16. Miquel J, Barcena R, Boixeda D, Fernandez J, SanRoman AL, Martin-de-Argila C, et al. **Role of Helicobacter pylori infection and its eradication in patients with subclinical hepatic encephalopathy.** Eur J Gastroenterol Hepatol 2001; 13: 1067-72.
  17. Suto H, Azuma T, Ito S, Ohtani M, Dojo M, Ito Y, Kohli Y, Kuriyama M. **Helicobacter pylori infection induces hyperammonaemia in Mongolian gerbils with liver cirrhosis.** Gut 2001; 48: 605-8.
  18. Scotiniotis IA, Lucey MR, Metz DC. **Helicobacter pylori infection is not associated with subclinical hepatic encephalopathy in stable cirrhotic patients.** Dig Dis Sci 2001; 46: 2744-51.
  19. Shrimali L, Chadda VS, Singh VB, Soni PK, Nayak KX, Gupta BK. **Study of prevalence of H. pylori in hepatic encephalopathy due to various liver diseases.** Journ Ind Acad Clin Med 2001;2(3):195-7.

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**Correspondence Address:**  
Dr. Jahangir Liaquat.  
House # 305/E, Unit No. 9,  
Latifabad, Hyderabad.  
drjahangirliaquat@gmail.com

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