ORIGINAL ARTICLE

FREQUENCY OF HELICOBACTER PYLORI ANTIBODIES IN PORTO-SYSTEMIC ENCEPHALOPATHY

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ABSTRACT

Objective: To study the frequency of *Helicobacter pylori* antibodies in patients presenting with porto-systemic encephalopathy due to liver disease.

Study Design: An observational, cross-sectional study.

Place and Duration of Study: Different medical units at Civil Hospital, Karachi between May 2001 and April 2002.

Patients and Methods: During the study period, seventy-six patients of porto-systemic encephalopathy due to liver diseases were selected. These subjects were evaluated for hepatic encephalopathy grade, modified Child-Pugh classification and were managed according to the standard practices. These patients were evaluated for *Helicobacter (H. pylori)* antibody status by ELISA(Abbott Laboratories) method.

Results: Out of 76 patients studied and tested for *H. pylori* antibodies, 48(63.2%) were males and 28(36.8%) were females with age ranging between 17 and 85 years. Out of 76 patients who presented with porto-systemic encephalopathy, 59(77.6%) had a positive *H. pylori* antibody test. Thirty five of these were males and 24 were females. A significant number of patients who presented with higher grade of encephalopathy were *H. pylori* antibody positive ($p<0.001$).

Conclusion: In this study, frequency of *H. pylori* antibodies was significantly high in patients of porto-systemic encephalopathy.

KEY WORDS: *Porto-systemic encephalopathy. Helicobacter pylori. Cirrhosis.*

INTRODUCTION

Porto-systemic encephalopathy (PSE) is a reversible, complex neuropsychiatric syndrome characterized by disturbances in consciousness and behaviour, personality changes, fluctuating neurological signs and distinctive electro-encephalographic changes, which occur secondary to chronic liver disease.[1] It may be present in 50 to 70% of all patients with cirrhosis including those in whom abnormalities are demonstrable only by psychometric testing.[2]

There are many precipitating factors, which may lead to development of PSE such as accumulation of ammonia, production of false neurotransmitters,[3] decreased activity of urea-cycle enzymes due to zinc deficiency,[4] and deposition of manganese in the basal ganglia.[5] 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.[6] Colonic bacteria are considered the main source of ammonia and stomach is believed to be an alternative site in *H. pylori* infected subjects.[6] *H. pylori* infection is common through out the world and approximately half of the world's population is infected.[7] An estimated prevalence of *H. pylori* infection is 30% to 40% in United States and Western Europe and about 80% in many developing countries.[8]

The relationship between *H. pylori* and PSE has been reported in many studies[9-11] in which hyperammonemia was significantly reduced after eradication of *H. pylori* with remission of PSE. The ammonia produced in the stomach by *H. pylori* is not absorbed normally except in cases of severe atrophic gastritis, renal failure and liver dysfunction.[12]

Chronic liver disease is common in local population and so is the prevalence of *H. pylori.*[13,14] This study was conducted to see the frequency of *H. pylori* infection and to evaluate its possible role in the pathogenesis of porto-systemic encephalopathy.

PATIENTS AND METHODS

This was an observational and cross-sectional study, conducted in the medical units of Civil Hospital, Karachi from May 2001 to April 2002. Subjects presenting with porto-systemic encephalopathy (PSE) were evaluated for enrolment in the study. Seventy-six subjects were included who were more than 12 years of age with chronic liver disease and PSE. Exclusion criteria included acid peptic disease, patients who had received specific *H. pylori* eradication therapy in the past, those with secondary peritonitis and the patients who had

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received antibiotics with anti-*H. pylori* spectrum in the past two weeks.

Informed consent was obtained and clinical assessment for hepatic encephalopathy grading and Child-Pugh classification was done on admission and recorded in the pre-designed performa. Standard protocol for the management of PSE was initiated and the patients were followed-up in the intensive care units. Blood sample was drawn for the investigations like blood count, urea, creatinine, electrolytes, liver function tests, serum protein, prothrombin time, viral profile (HbsAg and anti-HCV). In addition to these chest X-ray, ultrasound of abdomen and upper gastrointestinal endoscopy was conducted in selected cases.

The status of *Helicobacter pylori* was checked using ELISA (Abbott Laboratories) kit and the presence or absence of *Helicobacter pylori* IgG antibodies was documented. The testing kits were provided by Abbott Laboratories (Pakistan) Ltd. at discounted price for which the investigators paid.

Frequency of *H. pylori* antibodies in patients with porto-systemic encephalopathy was calculated and statistical analysis was done on SPSS version 10.01. Continuous variables were analysed by student's 't' test for difference in means. Fischer's exact test was also used where applicable. Discrete non-continuous variable were analysed by using Chi-square test. p-value < 0.05 was taken as significant.

Results

Among the eligible patients with porto-systemic encephalopathy, 48 (63.2%) were males and 28 (36.6%) were females. Age of the patients ranged between 17 and 85 years. Severity of the encephalopathy was graded as shown in (Table I).

Hepatic decompensation was also evaluated based on Childs-Pugh classification (Table II). All the patients had porto-systemic encephalopathy due to liver disease; the etiological factors are shown in (Table III).

The results showed that most of the patients who were in Child's class 'C' presented with higher grade of encephalopathy (p<0.001). There were only three patients in class 'A' and all presented with grade 2 encephalopathy. In Child's 'B' there were 6,18 and 5 patients who presented with hepatic encephalopathy grade 1,2 and 3 respectively, while in Child's 'C' there were 3,5,17 and 19 patients with hepatic encephalopathy grade of 1,2,3 and 4 respectively (Table IV).

Table I: Classification of hepatic encephalopathy.

Encephalopathy grade	Male	Female	Total
1	05	04	09
2	18	08	26
3	13	09	22
4	12	07	19

Table II: Patients with Childs-Pugh classes.

Child-Pugh class	Number of patients
A	03
B	29
C	44

Table III: Viral serology in patients with porto-systemic encephalopathy.

Serological test	Number of patients
HbsAg	20
Anti HCV	37
HbsAg + Anti HCV	12
Undetermined	07

Table IV: Child's classification and hepatic encephalopathy grading.

Child's class	Hepatic encephalopathy grade			
	Grade 1	Grade 2	Grade 3	Grade 4
A	--	03	—	—
B	06	18	05	—
C	03	05	17	19

Majority [59 (77.6%)] patients had the test positive for *H. pylori* antibodies. Of these 35 were males and 24 were females.

The relationship of *Helicobacter pylori* antibodies and the age of the patients is shown in Figure 1. There was a strong relationship (p<0.001) between the presence of *H. pylori* antibodies and the patients presenting with higher grade of encephalopathy.

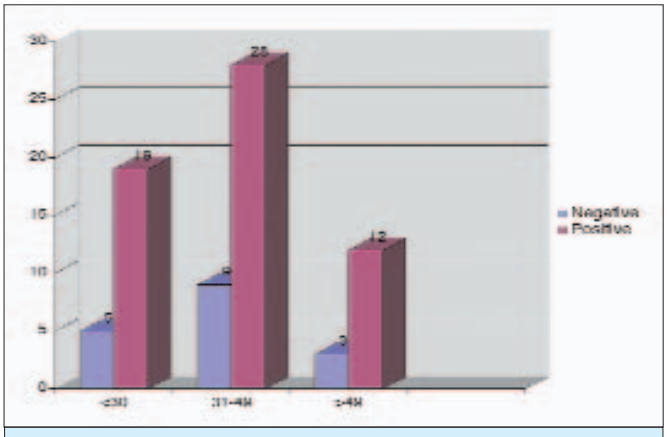

Figure 1: Relationship of *H. pylori* and age of the patients.

Discussion

Porto-systemic encephalopathy (PSE) is a neuropsychiatric syndrome associated with advanced liver disease. Porto-systemic shunting is a requisite for the development of PSE. Porto-systemic shunting of ill-defined substances is suspected to result in neurotoxicity. This has led to many investigative and therapeutic efforts aimed at identifying and eliminating the putative poisons that originate from the gut lumen. There are various mechanisms for pathogenesis of hepatic encephalopathy. Ammonia is the substance most often incriminated in the pathogenesis of encephalopathy. Most of the precipitating factors of PSE produce hyperammonemia, such as gastrointestinal bleeding, excess dietary protein, constipation and hypokalemia- induced renal production of ammonia.

Ammonia levels increase as liver function declines and decrease with the treatment. Although disturbances in urea cycle metabolism may result in hyperammonemia, similar encephalopathy does not exist in patients with isolated hyperammonemia in the absence of other evidence of hepatic dysfunction.

Colonic bacteria are considered the main source of ammonia and its clearance is impaired in patients with cirrhosis due to decreased urea-cycle function, increased porto-systemic shunting and decreased uptake by muscle cells peripherally. It is responsible for the neurotoxic manifestations of PSE.[15] *H. pylori* mainly infects the stomach and is known to produce copious amount of ammonia due to its strong urease activity many times greater than that of urease positive enterobacter.[16] The role of *H. pylori* in the pathogenesis of PSE has been a subject of ongoing debate.

Previous studies have reported that ammonia levels of gastric juice and serum ammonia levels in cirrhotic patients were significantly higher in *H. pylori* positive patients as compared to those with negative status.[17] This study on patients with PSE was conducted to explore the significance of *H. pylori* infection in hepatic encephalopathy.

The results of the study have shown that the prevalence of *Helicobacter pylori* infection was high (77.6%) in patients presenting with porto-systemic encephalopathy. The results of this study (76.5%) are comparable to study conducted in Italy, by Siringo *et al.*[18] and 76% as reported by Tsai *et al.*[19] in Taiwanese population with cirrhosis. In Pakistan, the frequency of *H. pylori* antibodies has been reported to be 74% in cirrhotic patients.[11]

Xu reported the frequency of *H. pylori* antibodies to be 71.4% in Chinese patients with PSE[20] and 67% in American population with PSE as reported by Dasani *et al.*[6] There are other studies which have reported a lower frequency (20.3% to 60%) of *H. pylori* associated with PSE in patients with cirrhosis.[15,21-29] Several extra-intestinal diseases have been associated with *Helicobacter pylori* infection. Hepatic encephalopathy has been linked to *H. pylori* infection because of the ammonia produced by the organism in the stomach. *H. pylori* infection is commoner in cirrhotic patients with hepatic encephalopathy than in those without. Increased ammonia levels have been observed in the gastric juice and blood more commonly in cirrhotics with *H. pylori* infection than in those without. Though the amount of ammonia produced by *H. pylori* may be too small to contribute to hepatic encephalopathy, eradication of *H. pylori* has been shown to improve the blood ammonia levels and hepatic encephalopathy.[30,31]

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. The test for stool antigen was not widely available when the study was conducted. However, the *H. pylori* titre was observed to be rising with the severity of hepatic encephalopathy. This suggests that *Helicobacter pylori* may have a role in the pathogenesis of hepatic encephalopathy. However, a large number of cases should be studied for further confirmation.

Conclusion

In this study, frequency of *H. pylori* antibodies was significantly high in patients of porto-systemic encephalopathy. This may suggest that presence of *Helicobacter pylori* may have some role or may add to the pathogenesis of encephalopathy in patients with liver disease. However, larger studies are needed to establish *H. pylori* as a cause of porto-systemic encephalopathy in patients with liver disease with porto-systemic shunting.

References

1. Chung RT, Podosky DK. Cirrhosis and its complications. In: Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, *et al.* Harrison's principles of internal medicine. Vol. 2. 15th ed. New York: *Mc Graw Hill;* 2001: 1754-67.
2. Riordan SM, Williams SR. Treatment of hepatic encephalopathy. *N Engl J Med* 1997; **337**: 473-9.
3. Basile AS, Jones EA. Ammona and GABA nergic neurotransmitters: inter-related factors in the pathogenesis of hepatic encephalopathy. *Hepatology* 1997; **2**:1303-5.
4. Marchesini G, Fabri A, Bianchi G, Brizi M, Zoli M. Zinc supplementation and amino-acid nitrogen metabolism in patients with advanced cirrhosis. *Hepatology* 1996; **23**: 1084-92.
5. Krieger D, Krieger S, Jansen O, Grass P, Theilmann L, Lichtnecker H. Manganese and chronic hepatic encephalopathy. *Lancet* 1995; **346**: 270-4.
6. Dasani BM, Sigal SH, Lieber CS. Analysis of risk factors for chronic hepatic encephalopathy: the role of *Helicobacter pylori* infection. *Am J Gastroenterol* 1998; **93**: 726-31.
7. Hunt RH. Eradication of *Helicobacter pylori*. *Am J Med* 1996; **100**: 425-50.
8. Peterson WL, Fendrich AM, David AP, Garabedian R, Loren L. *Helicobacter pylori* related diseases. *Arch Intern Med* 2000; **160**: 1285-91.
9. Ito S, Miyagi H, Azuma T, Li Y, Ito Y, Kato T, *et al*. Hyperammonemia and *Helicobacter pylori*. *Lancet* 1995; **346**: 124-5.
10. Suto H, Azuma T, Ohtani M, Dojo M, Ito Y. *Helicobacter pylori* infection induces hyperammonemia in Mongolian gerbils with liver cirrhosis. *Gut* 2001; **48**:605-8.
11. Qureshi H, Ahmed W, Qazi J, Zuberi SJ. *Helicobacter pylori* in portal hypertension. *J Pak Med Assoc* 1993; **43**: 249.
12. Cho YD, Bong HK, Lee YH, Kim JO, Cho JY, Kim YS, *et al*. The role of *Helicobacter pylori* infection on the blood level of ammonia in patients with liver cirrhosis. *Gastroenterology* 1997; **112**: A89.
13. Shaikh WM, Shaikh SM, Shah SR, Jatoi NN. Prevalence of *Helicobacter pylori* infection in acid peptic disorders in Northern Sindh, Pakistan. *Pak J Gastroenterol* 1996; **10**: 3-6.
14. Mehdi I, Qureshi H, Ahmed W, Ghazala M, Ahmed E. CLO antibody assay: can it be an alternate to endoscopy and biopsy. *J Pak Med Assoc* 1998; **48**: 203-4.
15. Scotiniotis IA, Lucey MR, Metz DC. *Helicobacter pylori* infection is not associated with sub- clinical hepatic encephalopathy in stable cirrhotic patients. *Dig Dis Sci* 2001; **46**:2744-51.
16. Zullo A, Rinaldi V, Folino S, Diana F, Attili A. *Helicobacter pylori* urease inhibition and ammonia levels in cirrhotic patients. *Am J Gastroenterol* 1998; **93**: 851-2.
17. Plevris J, Morgen R, Hayes P, Bouchier I. Hyperammonemia in cirrhosis and *Helicobacter pylori* infection. *Lancet* 1995; **346**:1104-7.
18. Sirinigo S, Vaira D, Menegatti M, Piscaglia F, Sofia S, Gaetani M, *et al*. High prevalence of *Helicobacter pylori* in liver cirrhosis: relationship with clinical and endoscopic feature and the risk of peptic ulcer. *Dig Dis Sci* 1997; **42**: 2024-30.

19. Tsai CJ. *Helicobacter pylori* infection and peptic ulcer disease in cirrhosis. *Dig Dis Sci* 1998; **43**: 1219-25.

20. Xu C, Jiang X. Relationship between *Helicobacter pylori* and cirrhosis of liver. *Hunan Yi Ke Da Xue Xue Bao* 1998; **23**: 382-4.

21. Vasconez C, Elizalde J, Llach J, Gines A, Delarosa C, Fernandez R, *et al. Helicobacter pylori*, hyperammonemia and sub-clinical porto- systemic encephalopathy: effects of eradication. *Hepatology* 1999; **30**: 260-4.

22. Nilsson I, Lindgren S, Eriksson S, Wadstrom T. Serum antibodies to *Helicobacter pylori* in the patients with chronic liver disease. *Gut* 2000; **46**: 410-4.

23. Huber M, Rossle M, Siegerstetter V, Ochs A, Haag K, Kist M. *Helicobacter pylori* infection does not correlate with plasma ammonia concentration and hepatic encephalopathy in patients with cirrhosis. *Hepatogastroenterology* 2001; **48**: 541-4.

24. Chang C, Kao C, Yeh H, Lien H, Chen G, Wang S. *Helicobacter pylori* infection and gastric emptying in cirrhotic patients with symptoms of dyspepsia. *Hepatogastroenterology* 1999; **46**: 3166-71.

25. Shimamoto C, Hirata I, Katsu K. Breath and blood ammonia in liver cirrhosis. *Hepatogastroenterology* 2000; **47**: 443-5.

26. Zullo A, Rinaldi V, Meddi P, Folino S, Lauria V, Diana F, *et al. Helicobacter pylori* infection in dyspeptic cirrhotic patients. *Hepatogastroenterology* 1999; **46**: 395-400.

27. Calvet X, Navarro M, Gil M, Mas P, Rivero E, Sanfeliu I, *et al.* Sero- prevalence and epidemiology of *Helicobacter pylori* infection in patients with cirrhosis. *J Hepatology* 1997; **26**: 1249-54.

28. Zullo A, Rinaldi V, Meddi P, Hassan C, Win S, Attili A. *Helicobacter pylori* infection, plasma ammonia levels and psychometric testing in cirrhotic patients. *Am J Gastroenterol* 1999; **94**: 2214-8.

29. Dong L, Zhang Z, Fang P, Ma S. Portal hypertensive gastropathy and its interrelated factors. *Hepatobiliary Pancreat Dis Int* 2003; **2**: 226-9.

30. Duseja A, Sachdev A, Dhiman R, Chawla A. *Helicobacter pylori* and hepatic encephalopathy. *Indian J Gastroenterol* 2003; **2** (suppl 2): S31-2.

31. Zullo A, Hassan C, Morini S. Hepatic encephalopathy and *Helicobacter pylori* : a critical reappraisal. *J Clin Gastroenterol* 2003; **37**: 164-8.