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Original Research Article

A Hospital Based Study to Assess the Role of Helicobacter Pylori Infection in the Pathogenesis of Minimal Hepatic Encephalopathy and Effect of its Eradication

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Abstract:

Aim: The aim of the study was to find the role of Helicobacter pylori infection in the pathogenesis of minimal hepatic encephalopathy and effect of its eradication.

Methods: A prospective study was conducted in the Department of Gastroenterology for the period of 2 years. 200 patients were included in the study. In patients of suspected cirrhosis of liver ultrasound and endoscopic examination were performed.

Results: Hepatitis B virus infection was the most common (35%) cause of cirrhosis. In the study group, most patients were in Child-Pugh class A (25%) or B (57.5%); most patients in Child-Pugh class C who were screened fulfilled one or more exclusion criteria. Presence of MHE had no significant relationship with age, sex, Child-Pugh grade, and cause of cirrhosis. H. Pylori infection was found in 90 of 140 patients with MHE ($p< 0.001$). Patients with MHE and H. Pylori infection showed a significant reduction in blood ammonia levels after anti-H. Pylori treatment ($p<0.001$).

Conclusion: This study concluded that H Pylori infection plays a role in the causation of MHE in patients with liver cirrhosis. H Pylori infection can induce an increase in serum ammonia in patients with liver dysfunction, and the peripheral serum ammonia measurement may replace the portal vein serum ammonia as a monitoring method. Eradication of H Pylori in cirrhotic patients may prevent hepatic encephalopathy (HE).

Keywords: H. Pylori, hepatic encephalopathy, cirrhosis

Introduction

Hepatic encephalopathy (HE) has a broad spectrum of neurological symptoms varying from minimal hepatic encephalopathy (MHE) to deep coma and death. [1] Patients with MHE appear clinically well and lack overt encephalopathy; subtle cognitive defects may be present. [2] The diagnosis of MHE is difficult and is made on the basis of neuropsychometric tests. [3] Helicobacter pylori bacteria are rich in urease enzyme producing ammonia from gastric leumen into circulation, causing HE have observed that eradication of H. pylori may reduce the concentration of ammonia in cirrhotic patients. [4-6]

Hepatic encephalopathy (HE) is a frequent complication of chronic liver disease (CLD). [7] HE can be precipitated by various factors like gastrointestinal bleeding, sepsis, azotemia, drugs (e.g. sedatives, diuretics), electrolyte imbalance and constipation. The most relevant substance considered in the pathogenesis of HE is ammonia, although the exact mechanisms of its neurotoxic effects are still under study. [8]

A substantial number of patients with advanced CLD have minimal hepatic encephalopathy (MHE), which is the earliest stage in the spectrum of HE. One study reported the occurrence of MHE to be as high as 50% in patients with CLD. [9] MHE, by definition, has no obvious clinical manifestations and is characterized by neurocognitive impairment in attention, vigilance and integrative function. [10] It develops in patients with significant liver function impairment or with porto-systemic shunting. MHE is associated not only with impaired daily functioning and quality of life, but is also considered as an occupational and public health hazard i.e. patient may be unfit to drive a car, operate a machinery, handle finances etc. [11]

Helicobacter pylori bacteria are rich in urease enzyme and are known to produce ammonia from urea that is rapidly absorbed from gastric lumen into circulation. Infection with these bacteria has been shown to be associated with elevated blood ammonia levels and recurrent attacks of overt hepatic encephalopathy. [12] Eradication of H.

pylori infection has been shown to be associated with reduction in blood ammonia levels [13,14] and improvement in hepatic encephalopathy. [12,13]

The aim of the study was to find the role of Helicobacter pylori infection in the pathogenesis of minimal hepatic encephalopathy and effect of its eradication.

Materials and Methods

A prospective study was conducted in the Department of Gastroenterology, PARAS, HMRI Hospital, Patna, Bihar, India for the period of 2 years. 200 patients were included in the study. In patients of suspected cirrhosis of liver ultrasound and endoscopic examination were performed. Those with ultrasonographic findings of chronic liver disease and esophageal varices on endoscopic examination were included in this study. The history of recent upper gastrointestinal bleeding, overt hepatic encephalopathy (based on clinical examination), neurological illness, poor vision, and with history of H. Pylori eradication treatment within the previous two to three months were excluded.

All study patients underwent routine hematological and biochemical investigations (as guided by clinical condition), HBsAg, anti-HCV, and ultrasonography. Ascitic fluid, if present, was examined. In addition, a fasting venous blood specimen was collected in EDTA and ammonia level in the plasma was measured. In this technique, ammonia combines with alpha-oxoglutarate and NADH in the presence of glutamate dehydrogenase to yield glutamate and NAD+; a decrease in absorbance at 340 nm is measured and is proportional to plasma ammonia concentration. All patients also underwent an upper gastrointestinal endoscopy and a rapid urease test on an antral biopsy; a color change from yellow to red at one hour was taken as evidence of H. Pylori infection.

Psychometric Tests

All patients underwent NCT, FCT and line tracing test. Before the actual tests, the procedure was explained and demonstrated, and a dummy run was done, which was not taken into account. Time taken for completion of each test and the number of errors were recorded. Normative values for psychometric test results were obtained from 100 normal control subjects. Patients with MHE (irrespective of H. Pylori status) received a triple anti-H. Pylori therapy (clarithromycin 250 mg, lansoprazole 30 mg, and tinidazole 500 mg, each twice daily) for one week along with lactulose. Fasting blood ammonia level and psychometric tests were repeated four weeks after completion of anti-H. Pylori treatment. Patients with H. Pylori infection also underwent a repeat endoscopic examination at this time to ascertain their H. Pylori status.

Statistical analysis

Data were analyzed using mean (standard deviation), Chi-square test, and paired ‘t’ test.

Results

Table 1: Psychometric test results in 200 healthy subjects and cut-offs

Test	Time taken for testcompletion (sec)	Upper cut-off value (sec)
Number connection test	38–64	30
Figure connection test	63–98	50
Line tracing test	18–38	20

Table 2: Clinical and demo-graphic characteristics of study patients

Characteristic Patients screened	Patients enrolled(n=200)	MHE (n=140)	NMHE(n=60)
Male: Female	140:60	90:50	45:15
Mean age (years)	35.5	33.7	32.8
Child-Pughclass			
A	50	30	20
B	115	70	45
C	35	30	5
Child-Pughclass			
Varices			
Yes	110	70	40
No	90	60	30
Etiology			
Alcohol	50	40	10
Hepatitis B virus	70	48	22
Hepatitis C virus	30	14	16
Alcohol +hepatitis B	6	3	3
Others	40	32	8

Hepatitis B virus infection was the most common (35%) cause of cirrhosis. In the study group, most patients were in Child-Pugh class A (25%) or B (57.5%); most patients in Child-Pugh class C who were screened fulfilled one or more exclusion criteria. Presence of MHE had no significant relationship with age, sex, Child-Pugh grade, and cause of cirrhosis.

Table 3: Pre-treatment and post-treatment fasting blood ammonia level in H. Pylori- positive and H. Pylori-negative patients with minimal hepatic encephalopathy

H. Pylori status	Blood ammonia levels(µg/mL)		p-value
	Pre-treatment	Post-treatment	
Positive (n=90)	1.82 (0.34)	1.18 (0.22)	<0.001
Negative (n=50)	1.36 (0.14)	1.16 (0.14)	<0.001

H. Pylori infection was found in 90 of 140 patients with MHE (p< 0.001). Patients with MHE and H. Pylori infection showed a significant reduction in blood ammonia levels after anti-H. Pylori treatment (p<0.001).

Discussion

Cirrhosis represents the final common histological pathway for a wide variety of chronic liver diseases. The blood ammonia levels of cirrhotic patients are usually higher than that of normal people. Patients with cirrhosis are prone to hepatic encephalopathy. In addition, some patients have minimal hepatic encephalopathy (MHE), which is not discernible at clinical examination but can be detected using sensitive tests of coordination, such as number connection tests (NCT), figure connection test (FCT) and line tracing test, electro-encephalography and visual, auditory, and somatosensory evoked potentials. [15] Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome characterized by disturbances in consciousness and behavior, personality changes, fluctuating neurologic signs, flapping tremor (asterixis) and distinctive electroencephalographic (EEG) changes, due to hepatocellular dysfunction and Porto systemic shunting. [16,17] Cirrhosis of liver accounts 50 – 70% cause of HE. [18]

The H. Pylori urease in the gastric juice breaks down urea into ammonia and carbon dioxide, and the ammonia is then rapidly absorbed into the blood. [19] Previous studies showed that ingestion of ammonia leads to a rise in arterial levels in half of normal subjects and in virtually all cirrhotic patients, the latter demonstrating a considerable increment with peak levels at 15 min. [20,21] Hepatitis B virus infection was the most common (35%) cause of cirrhosis. In the study group, most patients were in Child-Pugh class A (25%) or B (57.5%); most patients in Child-Pugh class C who were screened fulfilled one or more exclusion criteria. Presence of MHE had no significant relationship with age, sex, Child-Pugh grade, and cause of cirrhosis. H. Pylori infection was found in 90 of 140 patients with MHE (p< 0.001).

Patients with MHE and H. Pylori infection showed a significant reduction in blood ammonia levels after anti-H. Pylori treatment (p<0.001). we found a significant reduction in blood ammonia levels in both H. Pylori- positive and H. Pylori- negative patients with MHE after triple-drug anti-H Pylori treatment for one week. This reduction was more marked in patients with H. Pylori infection. This finding indicates that H. Pylori may contribute to the development of hyperammonemia in patients with liver disease and MHE. The role of H. Pylori in the pathogenesis of hyperammonemia has been shown in previous studies which showed a reduction in blood ammonia levels after eradication of H Pylori infection. [22] However, some other studies have failed to show an association between H Pylori infection and hepatic encephalopathy. [23-25] The reduction in blood ammonia in the latter group may be explained by inhibition of the intestinal flora with anti-H Pylori drugs. This effect of anti-H Pylori drugs on intestinal flora would have been expected to be similar in patients with and without H Pylori infection. Thus, our finding of a greater improvement in blood ammonia levels in patients with H Pylori infection than in those without this infection appears to indicate that H Pylori infection contributed at least partially to high blood ammonia production in these patients. The reduction in blood ammonia levels following treatment with anti-H Pylori drugs was associated with resolution of MHE in few patients with MHE. Normalization of psychometric tests with reduction in blood ammonia levels has been reported previously, and suggests a role of hyperammonemia in the pathogenesis of MHE. [26,27]

Cocnlusion

This study concluded that H Pylori infection plays a role in the causation of MHE in patients with liver cirrhosis. H Pylori infection can induce an increase in serum ammonia in patients with liver dysfunction, and the peripheral serum ammonia measurement may replace the portal vein serum ammonia as a monitoring method. Eradication of H Pylori in cirrhotic patients may prevent hepatic encephalopathy (HE).

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