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EFFECT OF H. PYLORI ERADICATION IN HEPERAMMONIEMIA AND HEPATIC ENCEPHALOPATHY IN YEMENI CIRRHOTIC PATIENTS

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Abstract

Background: H. pylori infection promotes the production of ammonia, which is an etiological factor involved in gastric mucosal disorders. This study aims to evaluate the benefit of H. pylori eradication in cirrhotic patients and its effect on H. encephalopathy.

Methods and Materials: This retrospective study included 79 patients that were included in this study including 43 (54.43 %) males & 36 (45.56%%) females conducted at Specialized Hepatobiliary and Gastroenterology Research Center in Sana'a, Yemen. The cohort was divided into 3 age groups: one patient (younger than 20 years old), 27 patients (20-40 years old) , and 51 patients (> 40 years old) . All cases are diagnosed as chronic liver disease on the basis of clinical features and laboratory investigations. Survival of liver disease patients was assessed using Child-Turcotte-Pugh score.

Results: There were 79 H. pylori-positive cirrhotic patients who received eradication therapy, among whom H. pylori-eradicated group of patients included 42 patients and the eradication rate was 53.61% (42/79) . H. encephalopathy rate is 100% in our case.

The results of our study showed that there was a statistically significant association between the group of cirrhotic patients with H. pylori eradication and mild elevation of serum ammonia only (P value 0.019). Furthermore, there was a statistically significant association between hepatic encephalopathy grade (0-1) and the group of patients with H. pylori eradication (P value 0.024).

Conclusion: H. pylori eradication may be helpful for the treatment and prevention of early grades of hepatic encephalopathy.

Keywords: H. pylori eradication, cirrhosis, ammonia, encephalopathy, Yemen.

INTRODUCTION

Hepatic encephalopathy (HE) or portosystemic encephalopathy (PSE) is a reversible syndrome of impaired brain function occurring in patients with advanced liver failure, however, HE is not a single clinical entity, it may reflect either a reversible metabolic encephalopathy, brain atrophy, brain edema, or any combination of these conditions. The mechanisms causing brain dysfunction in liver failure are still unknown. These factors are directly related to liver failure (e.g, decreased metabolism of ammonia). Unless the underlying liver disease is successfully treated, HE is associated with poor survival and a high risk of recurrence. (5)

Helicobacter pylori is a gastric Gram-negative spiral-shaped microaerophilic pathogen closely associated with gastric and extra-gastric diseases (chronic gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, gastric cancer, iron deficiency anemia, etc) (13). Recently, it has been suggested that H. pylori contributes to hyperammonema in cirrhosis, and bacteria eradication decreases blood ammonia concentration in these patients (1).

Patients & Methods

Methods and Materials

This study was conducted at Specialized Hepatobiliary and Gastroenterology Research Center in Sana'a (Yemen) with patients treated in our center over six years, from April 2008 to April 2014. Patients included in the present study were 79 patients with liver cirrhosis classified into three age groups: one patient (1.7%) (younger than 20 years old), 27 patients (34%) (20-40 years), and 51 patients (64.6%) (< 40 years

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old). They included 43 (54.4%) males and 36 (45.6%) females.

Serum ammonia level was expressed as Normal (Less than 60 micromol /L) including 10 patients (12.7%)– Mild elevation (60-100 micromol L) including 30 patients (37.9%) and Marked elevation (more than 100 micromol /L) including 39 patients (49.4%) According to the class of liver cirrhosis A, B, C all patients with established Chronic Liver Disease with HE were included. Chronic liver disease (CLD) was diagnosed on the basis of clinical features like finger clubbing, palmar erythema, spider naevi, splenomegaly, hepatomegaly or shrunken liver, or persistent elevation of liver enzymes for more than 6 months, namely, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT), plus a positive abdominal ultrasound for irregular liver margins, coarse liver appearance, and a dilated portal vein measuring 13–15 mm or more. Survival of liver disease patients was assessed using *the Child-Turcotte-Pugh classification. This score is based on the degree of encephalopathy, the presence of ascites, prothrombin time (PT) , and the serum levels of bilirubin and albumin.. Accordingly, the patients had either compensated liver disease (Class A, 5-6 points), moderate liver disease (Class B, 7-9 points), or severe liver disease (Class C, 10-15 points)*. Assessment of HE was clinically as well as a psychometric test and classified in the present study int mild HE (0-1), moderate HE (1-2), and severe HE (2-3).

Diagnosis of H. pylori was done by pathological examination of endoscopic gastric biopsied after staining by Gimsa stain ± stool examination for H. pylori.

After H. pylori eradication therapy, the method used to confirm eradication was H. pylori in stool.
H. pylori eradication therapy received by the included patients for 14 days and included Proton pump inhibitor standard dose twice daily + Metronidazole 500 mg thrice daily or Amoxicillin 1 g twice daily + Tetracycline 500 mg 4 times daily + Bismuth subsacitrate 120 mg 4 times daily.

Ammonia Measurement:
Fasting venous blood samples were obtained from each patient to measure ammonia concentration (micromole / L), according to the manufacturer's instructions.

Inclusion Criteria
All Yemeni Patients with chronic liver disease complained of manifestations suggestive of hepatic encephalopathy whatever the grade, these patients are infected by H. pylori and received eradication therapy.

Exclusion Criteria:
Patients with liver cirrhosis and advanced renal , cardiac, or neurological disease

Statistical Analysis

Data was stored and analyzed by the statistical program, SPSS Version 16. The quantitative variables (e.g, age, blood ammonia levels), were analyzed using mean ± standard duration . Frequencies and percentages were calculated for categorical variables (e.g., gender, Child-Pugh grade). Hyperammonemia was stratified amongst disease severity grade (CP grade) to see effect modification. Chi-square test (X2 test) was used to compare qualitative variables between two independent groups. Value of less than 0.05 was taken as a criterion standard (i.e. significant).

Aim of the study

The aim is to evaluate the benefit of H. pylori eradication and its effect on H. encephalopathy.

Results

There were 79 H. pylori positive cirrhotic patients who received eradication therapy, among them the H. pylori eradicated group included 42 (53.16%) patients and H. pylori non- eradicated group included 37 (46.83%) patients. As regards gender, the present study included 43 (54.4%) males and 36 (44.9%) females.

As regards the comparison between H. pylori eradicated and non- eradicated group of patients, there were a statistical significant association between Child-Pugh class A and H. pylori eradicated groups of patients (P 0.002). Furthermore, there were a statistical significant association between mild ascites and H. pylori eradicated groups of patients (P 0.012) . However, there were no statistical significant differences between H. pylori eradicated and non- eradicated groups of patients as regards age, sex, hematemesis, melena, and renal impairment. Table (2).

Risk factors for H. encephalopathy: Through Logestic multiple regression analysis, we found that constipation is a risk factor for hepatic encephalopathy (P 0.023 and OR value 1.203). However, age, sex, diet, gastrointestinal bleeding, H. pylori infection, diuretics, and renal impairment were not significantly associated with hepatic encephalopathy Table (1).

Table (1): Risk factors of hepatic encephalopathy analysed by logistic multiple regression:

	P. value	OR value [1}	95% CI
Age	0.954	-0.030	-1.042 to 0.983,
Sex	0.319	0.500	-0.483 to 1.482
Diet	0.054	-1.145	-2.308 to 0.017
GIT bleeding	0.803	-0.210	-1.855 to 1.436
Constipation	0.023	-1.203	-2.238 to -0.167
H. pylori Infection	0.449	0.504	-0.801 to 1.809

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Diuretics	0.051	-1.167	-2.337 to 0.004
Drug induced	0.294	-1.398	-4.873 to 1.218
Renal impairement	0.239	-1.828	-4.873 to 1.218

Table (2) : Characteristics of H. Pylori eradicated and non-eradicated groups:

		Eradication HP		
		Eradicated	Not Eradicated	P. value
Sex	Male n(%),	20 (25.3)	23 (29.1)	0.195
	Female n (%),	22 (27.8)	14 (17.1)	
Age	Less than 20 n(%)	1 (1.2)	0	0.637
	20- 40 n (%),	14 (17.7)	13 (16.5)	
	More than 40 n (%)	27 (34.1)	24 (30.4)	
Child – Pugh class	A n (%)	13 (16.4)	1 (1.3)	0.001
	B n (%)	22 (27.8))	19 (24.1)	
	C n(%)	7 (8.9)	17 (21.5)	
Hematemesis/ Melena	Absent	34	25	0.172
	Present	8	12	
Renal impairment	Absent	42	34	0.060
	Present	0	3	
Ascites	mild controlled	18	10	0.012
	mild – moderate	4	10	
	moderate – severe	2	9	

EFFECT OF H. PYLORI ERRADICATION:

The results of the present study showed that the eradicated group of patients included 4 (5.1%) patients with normal serum ammonia (less than 60 micromol / L) and 22 (27.8 %) patients with mild elevation of serum ammonia (60-100 micromol / L) and 16 (20.3%) patients with elevated serum ammonia and there were a statistical significant association between H. pylori eradicated group of patients and mild elevation of serum ammonia only (P value 0.019) Table (3) & Figure (1).

Table (3): Relation between H. pylori eradication and serum ammonia

		H. Pylori eradication		P.value
		Eradicated	Not Eradicated	
SERUM AMMONIA	LESS THAN 60 n (%),	4 (5.06))	6 (7.59))	0.019
	60-100 n (%),	22 (27.85)	8 (10.13)	
	MORE THAN 100 n (%)	16 (20.25)	23 (29.11)	

Figure (1) : Relation between serum ammonia and H. pylori eradication,

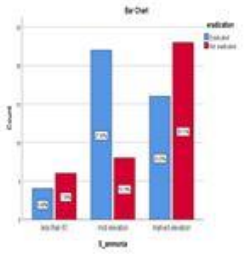
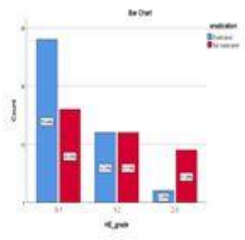


Figure (2): Relation between HE GEADE and H. pylori eradication.



Relation between Hepatic encephalopathy grade and H. pylori eradication: We found that the eradicated group of patients included 28 (35.4%) patients with mild hepatic encephalopathy grade (0 -1) and 12 (15.1%) patients with moderate hepatic encephalopathy grade (1-2) and 2 (2.5%) patients with severe hepatic encephalopathy grade (2—3) On the other hand the non eradicated group of patients included 16 (20.1%) patients with mild H. encephalopathy grade (0-1), 12 (15.1%) with moderate hepatic encephalopathy grate and 9 (11.4%) patients with severe H. encephalopathy grade (2-3). We found that a statistical significant association between the group of patients with H. pylori eradication and mild hepatic encephalopathy (grade 0=1) (P 0.024). Table (4) & figure (2).

Table (4) Relation between HE grade and H. pylori eradication, Child-Pugh and serum ammonia

		H.E grade			
		0-1	1-2	2-3	P. value
HP Eradication	Eradicated n (%)	)28 (	12 (15.19)	2 (2.53)	0.024

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	Not Eradicated (%) n	16 20.25) (	12 15.19) (	9 11.39) (	
Child-Pugh Class	A n (%)	11 13.9)(	2 2.5)(	1 1.3) (	0.003
	B n(%)	26 (32.9)	13 (16.5)	2 (2.5)	
	C n(%)	7 (8.9)	9 (11.4)	8 (10.1)	
Serum ammonia	Less than 60 n(%)	8 (10.1)	0 (13.9)	2 (2..5)	0.147
	60-100 n(%)	17 (21.5)	11 (16.4)	2 (2.5)	
	More than 100 n(%)	19 (24.1)	13 (16.5)	7 (8.8)	

Discussion

Recent studies have shown that H. pylori may interfere with many biological processes and determine or influence the occurrence of many diseases outside the stomach (14). Our study concluded that H. pylori eradication may be helpful for the treatment and prevention of early grades of hepatic encephalopathy.. **Agrawal A et al. (2011)** concluded that anti-H. Pylori therapy results in a reduction in blood ammonia levels and improvement in minimal hepatic encephalopathy (2). **Dsani BM (1998) and Miyaji H (1997**) concluded that H. pylori eradication may benefit the long-term management of hepatic encephalopathy (4) and (10), however **Miquel J (1997) , Scotiniotis IA (2001)** and have reported negative results (9) and (12).

Seham S. El-seid et al. (2014) found that treatment of H. pylori infection resulted in a reduction in blood ammonia levels and an improvement in MHE (11) . However, **Huber M et al. (2001) and Kini D et al. (2001)** showed that there were no associations between eradication of H pylori infection and improvement of HE **(6)** and **(8).**

The results of our study showed that there were a statistically significant association between H. pylori eradicated group of patients and mild elevation of serum ammonia only. Moreover there were a statistically significant association between H. pylori eradicated group of patients and mild (grade 0-1) hepatic encephalopathy.

Udayakumar N et al. (2007) reported that in view of the association of H pylori infection with hyperammonemia and HE, bacteria, eradication may theoretically reduce ammonia concentration in cirrhotic patients (15) **. Ito et al. (1995)** initially gave H. pylori eradication therapy to cirrhotic patients and found reduced ammonia concentration and recovery from HE after eradication, without relapse in the following 5 mo (7) . **Chen SI et al. (2008)** found that blood ammonia concentration in H pylori-positive cirrhotic patients was significantly reduced by bacteria eradication ($P < 0.01$) . And found that HE rate significantly dropped to 34.1% after H pylori eradication ($P < 0.01$) (3) . However, several investigators have questioned whether the effect of eradication therapy on hyperammonemia is due to the nonspecific effect of antibiotic therapy on the ammonia-producing gut flora. In **Miyaji et al. (1997) and Ito's et al. (1995)** , all patients were given lactulose, branched-chain enriched amino acid solution, low-protein diet, and kanamycin for 2 weeks before H pylori eradication therapy **to reduce the effect of the gut flora on hyperammonemia.**

The blood ammonia concentration in patients with diffuse distribution of H pylori in the stomach was significantly reduced after bacteria eradication compared with the concentration after conventional treatment to reduce the gut flora (10) and (7).

Miyaji H. et al (1997) reported that eradication of H pylori to reduce bacterial ammonia production in the stomach is effective in patients with hyperammonemia with diffuse H. pylori infection in the stomach, even after conventional therapy with a low protein diet, antibiotics, lactulose and branched-chain enriched amino acid solution (10).

Conclusion

H. pylori eradication may be helpful for the treatment and prevention of early grades of HE.

Recommendations

For better control of Hepatic encephalopathy, we recommend eradication of H. pylori in cirrhotic patients with mild hepatic encephalopathy grade

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