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Association of Helicobacter pylori Infection with Portal Hypertensive Gastropathy in Patients with Liver Cirrhosis

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Abstract

Portal hypertensive gastropathy(PHG) is a complication of portal hypertension and considered one of the causes of upper gasterointestinal bleeding. Helicobacter pylori as one of the most common pathogenic organism worldwide because it infects 50% of the population all over the world. The role of H. Pylori infection in the development of PHG and its severity is controversal. The aim of this study is to determine the frequency of H. pylori infection in cirrhotic patients with PHG and to find out the possible association of H. pylori infection with PHG severity. This study was carried out on 90 patient with cirrhotic liver, divided into two groups according to prescence or absence of PHG diagnosed by upper endoscopy. H.Pylori infection was significantly more frequent in patients with PHG than patients without PHG. H.Pylori infection was significantly more frequent in patients with sever PHG than patients with mild PHG .Splenomegaly, presence of esophageal varices, gastric varices and H.Pylori infection are independent predictors for PHG presence.

Keywords: Portal hypertensive gastropathy, Helicobacter pylori.

1. Introduction

Cirrhosis is a major health problem with high incidence and prevalence worldwide, it is associated with alterations in the gastrointestinal mucosa, portal hypertensive gastropathy (PHG) is one of the clinically important gastric mucosal lesion because it may cause acute or chronic gastrointestinal blood loss leading to anemia, it is characterized by endoscopic appearance of the gastric mucosa that is classically described as a mosaic-like pattern that resembles snake skin, with or without red spots [1]. The prevalence of PHG varies widely frequencies from 4% to 98% have been recorded in studies of patients with portal hypertension [1] . Several pathophysiological mechanisms have been postulated for PHG, they include increased serum gastrin leading to increased acid secretion, alteration in blood flow, decreased secretion of prostaglandin in the gastric mucosa and the presence of Helicobacter pylori (H. pylori) infection [2]. Infection by H. pylori is highly prevalent,especially in low socioeconomic strata of developing countries,being responsible for lesions like gastroduodenal erosion and ulcers [3].The prevalence of H. pylori infection and endoscopic lesions associated with cirrhosis, concluded that infection by H. pylori was present in 60.7% of the patients with increased risk of developing peptic ulcer [4]. If H. pylori infection is found to contribute to the pathogenesis of PHG, then eradication of H. pylori should be beneficial in the management of PHG bleeding which usually results in anemia [5]. There is a significant association between H. pylori infection and PHG in cirrhotic patients which is also related to severity of PHG [5].

2. Subjects and methods

2.1 Subjects

The current study was carried out on 90 patients with liver cirrhosis, divided into two groups according to prescence or absence of PHG diagnosed by upper endoscopy ,these patients attended or admitted to Hepatology, Gastroenterology Department , Nasser Institute of Health Hospital and Department of Hepatology, Gastroentrology and Infectious diseases of Benha University Hospital, within the period between November 2018 and April 2019 , after approval by the scientific committee of Faculty of Medicine .

Patients with cirrhosis diagnosed by clinical manifestations , laboratory investigations and ultasonography, which may reveal (nodularity, increase echogenicity of the liver, rarified hepatic central vein, enlarged caudate lobe, splenomegaly and collateralls [5].

2.2 Methods

Full history taking with stress on

Age , sex , smoking , occupation and residence, Abdominal pain, abdominal enlargement, Jaundice, hepatic encephalopathy and blood transfusion and history of previous attacks of bleeding.

Thorough clinical examination with stress on

General examination: Blood pressure, pulse, temperature, Jaundice , ecchymosis, clubbing, palmer erythema, flabby tremors and lower limb edema and abdominal examination: Organomegaly(hepatomegaly and spleenomegaly) and ascites.

Laboratory investigations including

Complete blood count (CBC),Fasting blood sugar,markers of Liver injury :ALT (Alanine aminotransferase), AST (aspartate aminotransferase), ALP (alkaline phosphatase), Liver function tests :Serum bilirubin (total, direct), Serum albumin, P.T. (Prothrombin time), INR (INR, international

normalized ratio),Serum creatinine.

Modified Child's Pugh score [6].
MELD score (Model for End Stage Liver Disease) [7].
UMELD score (Updated Model for End Stage Liver Disease) [8].
Pelvi-abdominal Ultrasonography

This was done using (LOGIC LG) with a convex probe (3.75 MHZ}.

- Evaluation of liver (size,echopattern and portal vein, presence of focal lesion).
- Evaluation of spleen (size and echopattern).
- The presence of ascites .

Esophagogastroduodendoscopy (EGD)

This was done using disinfected upper gastrointestinal video scope(OLYMPUS model) after good preparation of the patient.

Esophageal varices were classified as

Small esophageal varices were defined as

- varices that flatten with insufflation or minimally protrude into the esophageal lumen.
- while large esophageal varices were defined as:
- varices that protrude into the esophageal lumen and touch each other (presence of confluence), or that fill at least 50% of the esophageal lumen [9].

The grading (I-IV) classification

Grades I and II were reclassified as small and grades III and IV were reclassified as large for this study[9].

portal hypertensive gastropathy (PHG): were reported according to Modified grading system proposed by the Baveno III meeting

PHG is mild when a pink mosaic-like mucosal pattern with no red signs or black–brown spots is present.

PHG is severe when the mosaic-like mucosal pattern is red and superimposed by any red sign (red point lesions and/or cherry-red spots) or black–brown spots [10].

Gastric varices

varices are present in about 20% of patients with cirrhosis, gastro-oesophageal varices type 1, which are the most common (75% of gastric varices), are oesophageal varices extending below the cardia into the lesser curvature [11].

Signs suggesting H.pylori infection e.g inflammation, erosions and ulcers.

Histopathological examination of H. pylori

Routinely processed, Formalin-fixed, paraffin-embedded gastric antral tissues were used in this study and cut into three to four micronsthick serial sections then mounted on grease-free slides and subjected to:

H&E (Haematoxylin-Eosin) stain

Examined for the presence of H. pylori (Gram negative spiral to comma-shaped organisms, sometimes cocci), degree of gastritis, presence of atrophy, complete intestinal metaplasia, dysplasia or lymphoid follicles according to Updated Sydney Classification [12].

2.3 Statistical methods

IBM SPSS statistics (V. 25.0, IBM Corp., USA, 2017-2018) was used for data analysis. Date were expressed as Mean±SD for quantitative parametric measures in addition to both number and percentage for categorized data.

The following tests were done

Comparison between two independent mean groups for parametric data using Student t test.

Chi-square test to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data.

The probability of error at 0.05 was considered significant., while at 0.01 and 0.001 are highly significant.

Logistic Multi-Regression analysis was used to search for a panel (independent parameters) that can predict the target parameter (dependent variable). By using logistic stepwise multi-regression analysis, we can get the most sensitive ones that predict the dependent variable. They can be sorted according to their sensitivity to discriminate according to their p values.

3. Results

A total (90) patients with liver cirrhosis diagnosed clinically, laboratory and radiologically and referred to the endoscopy unit at Nasser Institute of Health and Researh and Department of Hepatology, Gastroentrology and Infectious diseases of Benha University Hospital were enrolled in the study.

They were 47males (52.5%) and 43 females (47.5%); with their age ranged from 38 to 66 years. The patients were divided into two groups according to presence or absenc Group I with PHG and group II without PHG.

Portal hypertensive gastropathy (PHG) tends to be more common in males, however of no statistical significance and the mean age is higher in patients with PHG with statistical significance.

There was no statistically significant difference between the two groups as regards residence and occupation, however PHG tends to be more common in rural areas .

Most of patients with PHG were Child B and Child C ,in contrast to the patients without PHG which were mostly of Child A.

A statistically higher MELD and UMELD scores were detected in patients with PHG.

Regarding to ultrasound examination, prescence of ascites, splenomegaly and increased portal vein

diameter were significantly higher in patients with PHG than patients without PHG.

Esophageal varices and gastric varices were significantly present more in patients with PHG than patients without PHG.

H.Pylori infection was significantly igher in patients with PHG than patients without PHG. H.Pylori infection was significantly higher in patients with sever PHG than patients with mild PHG.

By multi-variant analysis, splenomegaly, presence of esophageal varices , gastric varices and H.Pylori infection were independent predictors for PHG presence.

Table (1) Demographic features of the studied patients.

	WithoutPHG (n = 45)		WithPHG (n = 45)		Total (n = 90)		P-value
	No.	%	No.	%	No.	%	
Gender							
Male	19	42.2	28	62.2	47	52.2	0.058
Female	26	57.8	17	37.8	43	47.8	
Age (years)							
Range	38.0 – 66.0		39.0 – 66.0		38.0 – 66.0		0.048
Mean ± SD.	52.42± 7.753		55.51± 6.814		51.96 ± 7.02		
Urban	16		35.6	12	26.7		0.362
Rural	29		64.4	33	73.3		
Occupation							
Farmer	4		8.89	8	17.8		0.215
Non farmer	41		91.1	37	82.2		

Table (2) The severity of liver disease assessed by Child – Pugh Classification among the studied patients.

	Group I Without PHG		Group II With PHG		P-value
Child grade	**N**	**%**	**N**	**%**	
Child A	43	95.7	8	17.8	
Child B	2	4.3	28	62.2	0.000
Child C	0	0	9	20	

Table (3) The severity of liver disease in patients assessed by MELD and uMELD scores.

Parameter	Group I Without PHG		Group II With PHG		P-value
	Range	**Mean±SD**	**Range**	**Mean±SD**	
MELD	8.0 – 16.0	12.64± 2.28	7.0 – 23.0	16.56± 4.36	0.000
UMELD	2.5 – 4.3	3.15 ± 0.27	2.7–4.5	3.66± 0.49	0.000

Table (4) Abdominal ultrasonographic features of the studied patients.

Parameter	Group I Non PHG no=45		Group II PHG no=45		P-value
	Range	**Mean± SD**	**Range**	**Mean ± SD**	
Spleen size (normal: 12-14cm)	11 - 14.06	12.56±0.92	12 – 21.5	15.77± 2.39	0.000
PV (cm) (normal: 1-1.3)	1.06 – 1.5	1.37±0.108	1.2 – 1.8	1.46± 0.282	0.048
	no	**%**	**no**	**%**	**P-value**
Ascites	6	13.3	34	75.5	0.000
Liver					
Enlarged	2	4.4	0	0	
Shrunken	43	95.5	45	100	0.153

Table (5) Endoscopic features of the studied patients.

Parameter	Group I non PHG no=45		Group II PHG no=45		P-value
	No	%	No	%	
Esophageal varices	6	13.33	43	95.5	0.000
Small varices					
Large varices	4	8.88	14	32.5	0.000
Gastric varices	2	4.4	29	67.4	
PHG grade	1	2.22	9	16.1	0.007
Mild					
Severe	0	0	25	55.6	
	0	0	20	44.4	0.000

Table (6) Association between H. pylori and PHG .

	Without PHG (n = 45)		With PHG (n = 45)		P
	No.	%	No.	%	
H. Pylori					
Negative	31	68.9	15	33.3	0.001
Positive	14	31.1	30	66.7	

Table (7) Association between the severity of PHG and H. pylori.

	With PHG				P
	Mild (n = 25)		Sever (n = 20)		
	No.	%	No.	%	
H. pylori					
Negative	12	48	3	15	0.012
Positive	13	52	17	85	

Table (8) Multi-variant analysis for prediction of PHG presence.

Multi-Regression analysis: Dependent Variable: PHG				
Item	Reg. Coef.	T	P	Sig.
(Constant)	-0.602	-0.809	0.422	NS
Age	0.004	0.928	0.357	NS
Jaundice	-0.062	-0.584	0.561	NS
Abdominal enlargement	0.018	0.128	0.898	NS
Splenomegaly	0.068	4.52	0.000	HS
ascites	0.104	0.78	0.439	NS
Hemoglobin	-0.013	-0.719	0.475	NS
ALT	3.626E-06	0.004	0.997	NS
AST	0.001	1.327	0.190	NS
Creatinine	0.097	0.387	0.701	NS
Child classification	0.109	0.822	0.415	NS
MELD	-0.015	-0.483	0.631	NS
u.MELD	0.019	0.053	0.958	NS
Portal vein diameter	-0.411	-1.575	0.121	NS
Esophageal varices	0.218	4.413	0.000	HS
Gastric Varices	-0.141	-2.141	0.037	S
Positivity of H.Pylori infection	-0.227	-3.175	0.002	HS

4. Discussion

Portal hypertensive gastropathy defines the characteristic appearance which is a mosaic-like pattern or a diffuse, erythematous and reticular cobblestone pattern of gastric mucosa consisting of small polygonal areas, with or without superimposed red punctate lesions, >2 mm in diameter and a depressed white border , Portal hypertensive gastropathy (PHG) is diagnosed based on esophagogastroduodenoscopy (EGD) findings [13].

PHG develop as a consequence of portal hypertension which resulted in increase gastric blood flow and congestion of mucosal and submucosal blood vessels causing decrease of the mucous secretion and the local mucosal defense and the mucosa become susceptible to injurious agents such as non steroidal anti inflammatory drugs and H. Pylori infection [14,15].

This study aimed to determine the frequency of H. pylori infection in cirrhotic patients with PHG and to find out the possible association of H. pylori infection with the severity of PHG.

In the present study 90 patients with liver cirrhosis were enrolled and divided into two groups according to the prescence of PHG.

In this study,PHG tends to be more common in males, and this come in agreement with [5],who mentioned that PHG appeared to be more common in males , and [16] who mentioned that male predominance was observed in the collected data for 78.7 % of the PHG patients.

Regarding to the age , the mean age was higher in patients with PHG with statistical significance which goes with agreement with [17], who mentioned that the PHG patients were significantly older than the non PHG patients.

Ascites was more predominant in patients with PHG than patients without PHG which goes in agreement with [18], in their study showed, a significant relation between PHG and presence of ascites where ascites was more in cirrhotic patients with PHG, and also this goes in agreement with [19], who showed that there was a significant association of PHG with presence of ascites.

Regarding to the severity of liver disease assessed by Child –Pugh score , most of patients with PHG were Child B and Child C ,in contrast to the patients without PHG which were mostly of Child A, this agreed with [20], who reported a significantly higher prevalence of PHG in Child-Pugh stages B or C, as compared to stage A , also agreed with [13], who reported that there was significant association between Child-Pugh class and PHG presence.

As regard severity of liver disease assessed by MELD and uMELD scores , there was a statistically higher MELD and uMELD scores in patients with PHG which come in agreement with [21], who showed that there was a significant relation between PHG and MELD scores . but that was in contrary with [22], who showed that no statistically significant association between PHG and MELD scores, with mean score for PHG patients being 17.4±3.22 and for non PHG patients being 16.7±1.94 (P=0.396)., it is also disagreed with [13] who reported that there was a non-significant association between MELD score and PHG. This could be due to limitations of the MELD scoring system itself.

Regarding to abdominal ultrasonographic features , the present study showed that the prescence of ascites, was significantly higher in patients with PHG than patients without PHG which agreed with [19] who found that there is significant association of PHG and presence of ascites (P = 0.01).

Regarding to examination of spleen by ultrasound, the present study showed that the splenic size was significantly higher in patients with PHG which agreed with [21], who reported that the mean of spleen size was higher in cirrhotic patients with PHG , but disagreed with [23] who documented that there was no statistically significant correlation could be detected between PHG and splenic diameter.

As regaed the Portal vein diameter by ultrasonography in the present study , the portal vein diameter was significantly higher in PHG patients compared to those without PHG which agreed with [24] who stated that the Portal vein was more dilated in cirrhotic patients with PHG which reflect increasing of the portal venous pressure with subsequent formation of the gastric mucosal spots(gastropathy).

Regarding endoscopic features of the studied patients in the present study, esophageal varices and gastric varices were significantly more predominant in patients with PHG than patients without PHG that agreed with [25] who reported that the presence of oesophageal varices had significant relation with PHG which suggesting presence of common pathophysiology of both entities , but disagreed with [13] who reported that their study cannot find a significant association between the presence and esophageal varices and the presence of PHG. (p =0.364), the variations in the results of the studies could be due to several factors. First, PHG is an objective diagnosis made during EGD, and so there is interobserver variation, moreover, several classifications exist for stratifying the severity of PHG, and different researchers have used different classification system, and similar reason holds of EV as well. Most of the studies have included heterogeneous groups of population of CLD, and others have included patients of non-cirrhotic portal hypertension as well.

The present study showed that the large varices were more detected than small varices in patients with PHG which agreed with [25] who reported that the prevalence of PHG was higher in patients with large esophageal varices than in those with small-sized varices and this might be due to sharing of a common mechanism.

Concerning the relation of H. pylori to PHG, the present study showed that H.Pylori infection was significantly more frequent in patients with PHG

(66.7%) than patients without PHG(31.1%) and this come in agreement with[26] who detected that the prevalence of H.Pylori infection was higher in patients with PHG in comparison to patients without PHG(69.2% vs. 42.9%; p=0.022) , also , [5] detected that the presence of H. pylori infection was observed in 31(44.3%) cirrhotic patients with PHG (cases) in comparison to 19(27.1%) cirrhotic patients without PHG (controls), so that they concluded that there is significant association between H. pylori infection and PHG in cirrhotic patients, also [22] showed a significant difference between PHG and non PHG patients in the prevalence of H. pylori infection (34 vs. 10%) (P=0.036), this realation between H.Pylori and PHG originated as the gastric mucosa in cirrhosis might provide a hospitable environment for the colonization of *H. pylori*, especially when there is severe hemorrhagic congestion and edema of the mucosa, factors like increased inducible nitric oxid synthase (iNOS) expression resulting in high reactive oxygen species, impairment of gastric mucosal defence due to PHG.

According to a.Ji-Ke Hu [27],the association between H.Pylori and PHG comes from the fact that the gastric mucosa in PHG has thinner mucus and higher pH because of the decreased acid secretion , prostaglandin, a protector of stomach, which increases the gastric blood flow and stimulates mucus release, is also decreased and the decrease of prostaglandin may weaken the gastric barrier, additionally, PHG has a lower resting gastric trans-mucosal potential difference, which is associated with increased H + back diffusion to the mucosa that results in a decrease in intracellular pH among mucosal cells and the reduction of mucus and the weakness of the gastric mucosal barrier facilitates mucosal lesions and these changes in stomach are suitable for *H. pylori* infection .

Regarding to the relation between PHG severity and H.pylori infection, H.Pylori infection was significantly more frequent in patients with severe PHG than patients with mild PHG , and this goes in agreement with [28] who showed a significant relation between H. pylori infection and severity of PHG (P= 0.002) as colonization of the gastric mucosa by H.pylori might have an indirect role in PHG as colonization is at least theoretically, associated with inflammation, H. pylori virulence factors induce the production of proinflammatory cytokines such as tumor necrosis factor-α, which enhance mucosal inflammation which predispose to severity of PHG.

By multi-variant analysis for prediction of PHG presence , splenomegaly, presence of esophageal varices , gastric varices and H.Pylori infection were significantly independent predictors for presence of PHG and this goes in agreement with [22]who documented that there is a significant association between H. pylori infection and PHG , also, there is significant correlation between splenic size in patients with cirrhosis and presence of PHG, also agreed with [29] who mentioned that a complex relationship between PHG and presence of oesophageal variceal (EV) has been observed in various studies, on one hand, new onset of PHG has been found to be associated with new onset or higher grade of EV, on the other hand and endoscopic obliteration of large grade varices and thus reduction in their size has been studied as a risk factor to endoscopic and pathologic deterioration of PHG.

5. Conclusion

H.Pylori infection was significantly associated with the presence of PHG .

H.Pylori infection was significantly associated with sever PHG.

Presence of splenomegaly , esophageal varices(EV), gastric varices and H.pylori infection can independantly predict presence of PHG.

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