Med. J. Cairo Univ., Vol. 86, No. 3, June: 1281-1286, 2018
www.medicaljournalofcairouniversity.net

Association of Helicobacter Pylori Infection with Portal Hypertensive Gastropathy in Liver Cirrhosis

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Abstract

Background: Portal hypertensive gastropathy (PHG) is an important cause of morbidity in patients with Liver cirrhosis (LC). Helicobacter pylori (HP) infection is a common cause of gastritis and is an endemic disease in Egypt.

Aim of the Work: To study the presence of H. pylori infection in cases of LC with and without PHG.

Material and Methods: Fifty patients with LC including 25 cases with PHG and 25 cases without PHG who attended Sohag Faculty Hospital during the period 9/2016-3/2017 were examined for the presence of H pylori infection histologically using Hematoxyline and Eosin and Geimsa stains. The correlation between H pylori infection and the severity of PHG was studied statistically.

Results: H. pylori were detected in 76% of cases of LC (72% in LC with PHG and 80% of cases LC without PHG). Although there was an association between H pylori infection and the severity of PHG (5/7 cases), there was no statistically significant difference between H pylori infection and PHG.

Conclusion: H. pylori infection can be seen in cases of LC irrespective of the presence or absence of PHG more than in general population.

Key Words: *H. pylori – PHG – Liver cirrhosis – Geimsa stain.*

Introduction

PORTAL hypertensive gastropathy (PHG) is the term used to describe the endoscopic appearance of gastric mucosa, with a characteristic mosaic-like pattern with or without red spots, seen in patients with cirrhotic or non-cirrhotic portal hypertension. The mosaic pattern appears as white reticular network separating areas of raised red or pink mucosa resembling the skin of a snake. PHG is seen mainly in the body and the fundus of the stomach. When PHG is severe, it can include discrete cherry red spots, fine pink speckling, collectively called red marks. In fact, Portal hypertensive gastropathy (PHG) is an important cause of bleeding in patients with cirrhosis associated with portal hypertension. The characteristic histological finding of PHG is dilated capillaries and venules in the mucosa and submucosa without erosion, inflammation, or fibrinous [1].

The reported prevalence of PHG varies greatly. In a study of 373 cirrhotic patients, 299 (80.2%) had PHG [2]. In the HALT-C trial (Hepatitis C Antiviral Long Term Treatment against hepatitis C), 374 (37%) of 1011 patients with biopsy-proven cirrhosis or bridging fibrosis from hepatitis C had PHG [3].

The overall prevalence of PHG varies from 51% to 98%. The wide variation in the reported prevalence is perhaps related to patient selection, absence of uniform criteria and classification, and more importantly, the differences in inter- and intraobserver variation [4].

Hemodynamic changes in patients with portal hypertension lead to hyperdynamic congestion with a change in gastric mucosal blood flow that leads to activation of cytokines, growth factors, and hormones [5]. This hyperdynamic circulation impairs gastric mucosal defense mechanisms, causes release of proinflammatory mediators, and inhibits growth factors which render gastric mucosa more susceptible to injury and impair mucosal healing [6]. This vulnerable mucosa becomes predisposed to bleeding and the decreased gastric mucosal perfusion may explain the increased rate of erosions, ulcers, and bleeding in PHG [7]. Abnormal regulation of the gastric microcirculation

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in PHG may render gastric mucosa more vulnerable to hypoxia, and more susceptible to noxious factors. Tumor necrosis factor alpha (TNF-α) may directly contribute to the hyperdynamic circulation in PHG. Patients and animal models with portal hypertension had an elevated TNF-α level which stimulated release of nitric oxide (NO) and prostacyclin, important mediators of a hyperdynamic circulation [8].

Numerous molecular and cellular mechanisms have been investigated regarding the pathogenesis of PHG; P53-upregulated modulator of apoptosis (PUMA) was markedly induced in gastric mucosa in patients or mouse models of PHG [9].

H pylori infection continues to be a major public health issue worldwide. In 2015, approximately 4.4 billion individuals worldwide were estimated to be positive for H pylori [10].

H. pylori infection is closely related to peptic ulcer, chronic gastritis, and gastric cancer; but the relationship between H. pylori infection and PHG is not clear.

Aim of the work:

To determine the presence of H. pylori infection in cirrhotic patients with/without PHG and to find out an association between H. pylori infection and the severity of PHG.

Patients and Methods

This is a case control observational study. It included 50 patients with liver cirrhosis (LC) divided into 25 cases of LC with PHG and 25 cases of LC without PHG. Those patients attended Sohag University General Medicine department during the period from 9/2016 to 3/2017. The age range of the patients was 28-68 y and all patients agreed to share in this study with a written consent and the study was given an approval of the Scientific and Ethical Committee of Sohag, Faculty of Medicine. Exclusion criteria from the study were as followed: Patients with primary or metastatic hepatic malignancy, patients with gastric surgery or peptic ulcer, recent acute gastric or variceal bleeding, and patients with prior antibiotic medical therapy.

Investigations for the patients in the study: 1- liver function tests including serum bilirubin, serum albumen and prothrombin time. 2- Abdominal Sonography. 3- Upper endoscopy with gastric punch biopsy for histopathological detection of H. pylori using H&E and Geimsa staining. The severity of liver cirrhosis was assessed using Child-Pugh classification [11]. The severity of PHG was assessed using McCormack classification [1].

Table (1): Child-Pugh scoring system of severity of liver cirrhosis.

	1	2	3
Encephalopathy	None	Grade 1-2	Grade 3-4
Ascitis	None	Mild/moderate	Sever
Bilirubin (mg/dl)	<2	2-3	>3
Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time	>4	4-6	<6

A=5-6 points. B=7-9 points. C=10-15 points.

Table (2): McCormack classification of the severity of PHG.

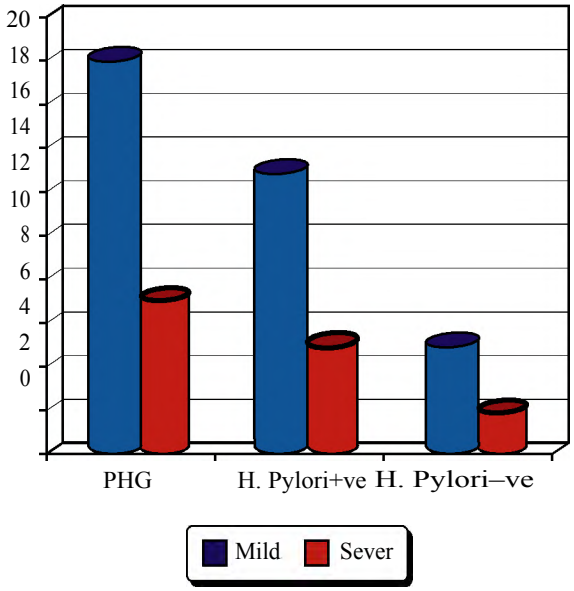
Mild	Fine pink speckling
	Superficial reddening
	Mosaic pattern
Sever	Discrete red spots
	Diffuse hemorrhagic lesion

Results

In the present study 50 cases of LC divided into 25 cases of LC with PHG (2 cases of HBV, 18 cases HCV, 1 case of HCV+HBV, and 4 cases free from viruses) and 25 cases of LC without PHG (2 cases HBV, 19 cases HCV, 1 case HBV+HCV and 3 cases free from viruses) (Table 3). Those cases included 24 females (14 cases LC+PHG and 10 cases LC without PHG) and 26 males (11 cases LC+PHG and 15 cases LC without PHG). The age range of the involved cases was 28-72 years with median 55 and mean ± SD 54.84± 11.06. H pylori infection was detected in 18 cases of LC+PHG with 5/7 sever PHG and in 20 cases of LC without PHG (Table 3, graph 1 and Fig. 1). There was no statistically significant difference between the presence of H. pylori infection in PHG patients and control group (p=0.51). The H. pylori infection was statistically similar in patients with severe PHG (5/7 cases) and mild PHG (13/18 cases (p=0.7). There was no statistically significant correlation between H pylori infection and the clinical variants as age of the patients, duration of the cirrhosis, type of viral hepatitis and the severity of cirrhosis.

Table (3): Main clinical and histopathological findings of the studied cases.

	Liver cirrhosis with PHG(25)	Liver cirrhosis without PHG(25)	Total
Male	11	15	26
Female	14	10	24
Child-Pugh:			
A	4	6	10
B	14	9	23
C	7	10	17
HBV	2	2	4
HCV	18 (72%)	19 (76%)	37
HCV+HBV	1	1	2
Free viruses	4	3	7
Ascitis	16	1	17
PHG:			
Mild	18	–	
Sever	7	–	
H. Pylori:			
+ve	13 5 18/25 (72%)	20 20/25 (80%)	38 (76%)
–ve	5 2 7/25 (28%)	5	12 (24%)



Graph (1): Relation between H pylori infection and severity of PHG

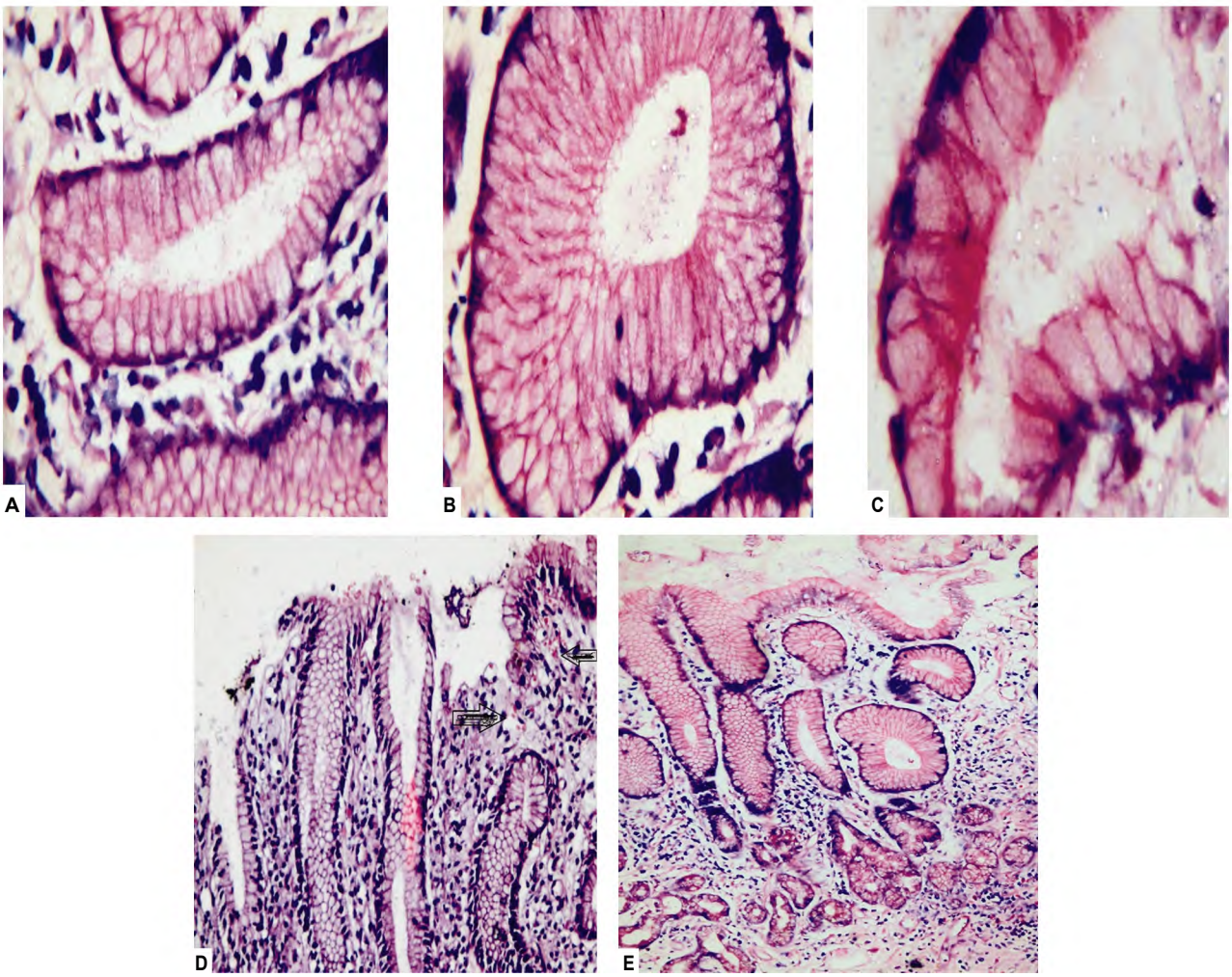


Fig. (1): H. pylori stained by Geimsa stain (A&B&C: X 300). D: Ectatic blood vessels at the gastric mucosa (black arrows) with H. pylori in the mucosa (red arrow) (X 100). E: Intestinal metaplasia and chronic inflammatory cell infiltration of the gastric mucosa in H. pylori infected cases (X 100).

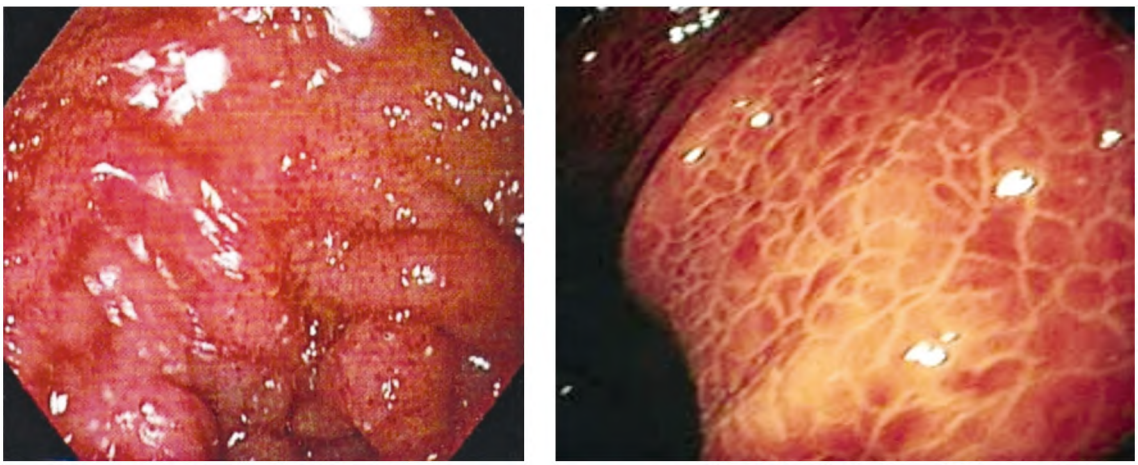


Fig. (2): Portal hypertensive gastropathy by endoscopy.

Discussion

The pathogenesis of PHG is not completely understood, however, evidence suggested that portal hypertension is a key factor, where elevated portal pressure can induce changes of local hemodynamics, thus causing congestion in the stomach. These changes may then activate cytokines and growth factors, such as tumor necrosis factor- a (TNF- a), which activate endothelial nitric oxide synthase and endothelin- 1. Nitric oxide induces hyperdynamic circulation and peroxynitrite overproduction which, together with endothelin-1 overproduction, may cause damage to gastric mucosa. When combined with the characteristics of impaired mucosal defense and healing, these factors may together produce PHG in patients with portal hypertension **[12]**.

Colonization of the gastric mucosa by H. Pylori might have an indirect role in PHG as colonization is associated with inflammation. H. pylori virulence factors induce the production of pro-inflammatory cytokines such as TNF- a which affect mucosal inflammation **[13]**.

Several investigators have evaluated the effect of H. pylori on liver cirrhosis and PHG with controversial results. Some studies have shown a higher prevalence and a synergistic effect of H. pylori on liver cirrhosis and PHG. However, most studies had not found any correlation between H. pylori and PHG **[14]**.

It found in a similar study that each of H. pylori and PHG independently increased inducible nitric oxide synthase (iNOS) in gastric mucosa of cirrhotic patients. However, its role in the development of PHG is still conflicting **[15]**.

A meta-analysis included seven studies that assessed 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 **[16]**.

In the present study, we found that H pylori were detected histopathologically in 76% of the studied cases. Two recent studies found a prevalence of 62.1% **[17]** and 60% **[18]** respectively, while a lower H. pylori prevalence (35.7%) was reported by Sathar et al **[19]**. This discrepancy could be attributed to the different tools of H. pylori diagnosis.

We found that H. Pylori infection in cirrhotic patients did not correlate with the presence or absence of PHG. A similar finding was documented by other researchers, after studying 60 cases of liver cirrhosis for H. Pylori infection and its correlation with PHG **[20]**.

Although we detected H pylori in 5 out of 7 cases of sever PHG, while H pylori was found in 13/18 cases in mild PHG, there was no statistically significant correlation between H pylori infection and severity of PHG (p>0.51).

Al Mofleh **[14]** found that there is no correlation between H. pylori and etiology, stage of cirrhosis, presence and severity of PHG.

Batmanabane et al., **[21]** study found that 16/37 patients were positive for H. pylori. H. pylori status was 52%, 22%, and 0% in patients with mild, moderate, and severe gastropathy respectively, indicating an inverse relationship of severity of PHG with H. pylori colonization.

A retrospective study compared H. pylori seroprevalence between 70 cirrhotic with PHG (cases) and 70 matched cirrhotic without PHG (controls). The main results were that the prevalence of infection was higher in cases than controls (44.3% vs. 27.1 %, p=0.034), and the prevalence of severe PHG was higher in the 31 H. pylori infected compared to the 39 uninfected patients (61.3% vs. 12.8%, p<0.001) **[22]**.

A more recent study concluded that H. pylori was detected in 33/60 (55%) patients with liver cirrhosis and in 26 cases of liver cirrhosis with PHG compared to 7 cases of cirrhosis without PHG with statistically-significant differences, p>0.0133 **[23]**. Another recent study concluded that there is significant association between H. pylori infection and PHG, but there is no significant correlation between H. pylori infection and the severity of PHG or the severity of liver cirrhosis **[24]**.

Conclusions:

Helicobacter pylori is highly prevalent in patients with liver cirrhosis with/without portal hypertensive gastropathy than in general population. Although there is no statistically significant relation between H. pylori and the severity of PHG, routine eradication therapy using appropriate antibacterial drugs is beneficial in patients with portal hypertension with/without PHG. large prospective studies are recommended to investigate the relation between H. pylori infection and gastropathy of hepatic etiology.

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ارتباط عدو ى الجرثومة الحلزونية بإعتلال الغشاء المخاطى المعدى الناتج عن ارتفاع ضغط الوريد البابى الكبدى فى مرضى التليف الكبدى

المقدمة: يعتبر تليف الكبد مشكلة صحية كبيرة ويرتبط معه بعض التغيرات فى الغشاء المخاطى المعدى ويزداد ايضاً معه نسبة حدوث ألتهابات المعدة يتسبب إعتلال الغشاء المخاطى المعدىالناتج عن ارتفاع ضغط الدم فى الوريد البابى الكبدى فى نزيف معدى حاد تهدد حياة نسبة كبيرة من مرضى تليف الكبد. تعتبر الإصابة بالجرثومة الحلزونية من الأمراض المتوطنة فى مصر وتزداد نسبة العدوى بها بين مرضى التليف الكبدى بشكل كبير .

الهدف من البحث: يهدف البحث الى تحديد و دراسة مدى إرتباط العدوى الجرثومة الحلزونية بين مرضى تليف الكبدى الذين يعانون من إعتلال الغشاء المخاطى المعدى بالإضافة الى ارتفاع ضغط الدم فى الوريدى البابى الكبدى

طرق البحث: تم إجراء الدراسة فى مستشفى سوهاج الجامعى قسم الباطنة العامة فى الفترة من سبتمبر ٢٠١٦ الى مارس ٢٠١٧ على إعتلال الغشاء المخاطى المعدى وتلف الكبد نتيجة ارتفاع ضغط الدم فى الوريدى البابى الكبدى . تم تقسيم المرضى الى مجموعتين واحدة تعانى من تلف الكبد (٢٥ حالة) والأخرى تعانى من تلف الكبد والإعتلال المعدى المخاطى (٢٥ حالة) وأخذ عينات بالمنظار من الغشاء المخاطى المعدى و فحصها تحت الميكروسكوب للكشف عن الإصابة بالجرثومة الحلزونية .

الأستنتاج: تبين من الدراسة عدم وجود علا قة احصائية بين الإصابة بالجرثومة الحلزونية وإعتلال الغشاء المعدى المخاطى المصاحب لإ رتفاع ضغط الدم فى الوريدى البابى الكبدى الناتج عن تليف الكبدى إلا أن الدراسات الأخرى المتعلقة بنفس الموضوع قد تأتى بنتائج أكثر تحريداً فى المستقبل.