



## Does Helicobacter Pylori Co-Infection Contribute to Hepatitis C Virus-Associated Thrombocytopenia in Egyptian Patients?

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### ABSTRACT

**Background:** Despite the strong association between HCV and *H. pylori* co infection and the well-known relation between *H. pylori* and immune thrombocytopenia, there is no available literature concerning the relation between HCV-associated thrombocytopenia and *H. pylori*.

**Objectives:** The aim of the present study was to investigate the frequency of *H. pylori* infection in Egyptian patients with chronic HCV infection with and without thrombocytopenia and whether anti-*H. pylori* therapy would improve thrombocytopenia in those patients.

**Methods:** 160 patients with chronic HCV infection including 80 patients with thrombocytopenia and 80 patients with normal platelet counts were enrolled in the study. Patients with hypersplenism, advanced liver disease or receiving antiviral therapy were excluded. *H. pylori* antigen was detected in the stools by rapid test. Triple therapy was administered to 30 *H. pylori*-positive thrombocytopenic patients for two weeks.

**Results:** *H. pylori* was detected in 123 out of 160 (76.90%) HCV patients. Moreover, a significantly greater number of thrombocytopenic patients (67/80) had positive stool test for *H. pylori* compared to HCV patients with normal platelet counts (56/80); { $p=0.039$ }. 19 out of 30 patients responded significantly to anti-helicobacter therapy with increase or normalization of platelet counts ( $p=0.001$ ). *H. pylori* was eradicated in all of those 19 subjects.

**Conclusion:** To our knowledge, this is the first study to suggest a strong association between HCV-associated thrombocytopenia and *H. pylori*. The significant platelet response to eradication of the bacterium may open the door for anti-*Helicobacter* therapy as an adjuvant in the management of this difficult disease. Therefore, screening for *H. pylori* infection and an attempt to eradicate the bacterium in positive cases seems appropriate in all patients with HCV-associated thrombocytopenia at diagnosis. Randomized placebo-controlled clinical trials are warranted.

**Key Words:** HCV, *H. pylori*, thrombocytopenia, Anti-helicobacter therapy, Egypt.

## INTRODUCTION

Helicobacter pylori (*H. pylori*) and hepatitis C virus (HCV) are the leading bacterial and viral human disease etiologies worldwide.<sup>(1)</sup> Egypt has the highest prevalence of HCV in the world, estimated nationally at 14.7%.<sup>(2-4)</sup> The overall prevalence of *H. pylori* is high in developing countries and lower in developed ones. The overall reasons for these variations involve socio-economic differences between populations. In Egypt, the prevalence is around 90% in adults.<sup>(5)</sup>

Thrombocytopenia is one of the most frequent hematological manifestations of HCV infection. A variety of pathogenic mechanisms have been postulated to explain this hematological abnormality. The binding to and possible infection of platelets and mega karyocytes by HCV has been reported. High affinity binding of HCV to platelet membrane with subsequent binding of anti-HCV antibody might lead to phagocytosis of platelets through an "innocent bystander" mechanism. Nonimmune mechanisms include sequestration of platelets in the enlarged spleen secondary to portal hypertension (hypersplenism), inadequate production of thrombopoietin by the diseased liver and direct infection of the platelets by the virus<sup>(6-11)</sup>.

*H. pylori*, a gram negative bacterium is the causative agent of chronic gastritis and the predominant cause of peptic ulceration.<sup>(12)</sup> It is a cofactor in the development of adenocarcinoma and mucosa-associated lymphoid tissue lymphoma (MALT). Eradication of *H. pylori* infection can result in platelet responses in patients with chronic ITP, which has led to speculation on a causal role of the bacterium in the development of thrombocytopenia.<sup>(13)</sup>

The role of *H. pylori* in the pathogenesis of ITP is still controversial. Several mechanisms have been proposed to explain the association. The first is molecular mimicry, i.e. the presence of cross reaction between antibodies against the cytotoxin associated gene A (CagA) of *H. pylori*, and platelet antigens causing accelerated

platelet clearance<sup>(14)</sup>. Another proposed mechanism is modulation of host immunity following colonization by *H. pylori* to favor the emergence of auto reactive B-1 cells and the enhancement of phagocytic capacity of monocytes together with low levels of the inhibitory Fcγ receptor IIB.<sup>(15)</sup>

Previous studies found that *H. pylori* could damage hepatocytes by cytopathic effect and induce hepatitis. Vacuolating cytotoxin of *H. pylori* could reach and damage the hepatocytes of patients with *H. pylori* infection without signs of known causes of liver disease. Chronic hepatitis is an inflammatory disease and is characterized by increased levels of the pro-inflammatory cytokines such as interleukins 1 and 6 (IL-1, IL-6), tumor necrosis factor and also by the presence of lympho-monocellular infiltrate and lymphoid follicle formation. Viruses, such as HCV, are only capable of inducing limited inflammation. On the other hand, Helicobacters are strong inducers of the inflammation cascade; infection with them could lead to the accumulation of extraordinary number of lymphocytes and polymorph nuclear cells in the infected tissue. IL1 gene cluster polymorphisms, thought to enhance IL-1b production, confer an increased risk of inflammation, accelerated hepatic damage and cancer.<sup>(16)</sup>

Despite the strong association between HCV and *H. pylori* co infection and the well-known relation between immune thrombocytopenia and *H. pylori* infection, literature survey concerning the relation between HCV-associated thrombocytopenia and *H. pylori* disclosed no available information. The aim of the present study was to investigate the frequency of *H.pylori* coinfection in Egyptian patients with chronic HCV infection with and without thrombocytopenia and whether anti-*H. pylori* therapy would improve thrombocytopenia in those patients.

## SUBJECTS AND METHODS

The study was conducted on 160 patients with chronic HCV infection.

### Inclusion criteria:

1. Age > 18 and < 60 years.

2. Gender: both.
3. HCV RNA detected by PCR.
4. ALT & AST < triple the upper limit of normal.
5. Total serum bilirubin < 1.5 mg/dl.
6. Serum albumin  $\geq 3$  g/dl.
7. Prothrombin concentration  $\geq 50$  %.
8. Hb conc.  $\geq 11$  g/dl in males and  $\geq 10$  g/dl in females.
9. TLC  $\geq 3 \times 10^9/L$ .
10. ANC  $\geq 1.5 \times 10^9/L$ .

#### Exclusion criteria:

1. Age < 18 or > 60 years.
2. Concomitant HBV coinfection.
3. ALT, AST > triple upper limit of normal.
4. Intra or extrahepatic cholestasis.
5. Ascites or encephalopathy (Child C).
6. Hepatocellular carcinoma or other malignancies.
7. Other causes of thrombocytopenia eg, aplastic anemia, collagen vascular disorders.
8. Other causes of chronic liver disease e.g., Schistosomal hepatic fibrosis, autoimmune hepatitis.
9. Prior or ongoing anti-HCV therapy.
10. Pregnant or lactating women.
11. Hypersplenism.
12. Other treatment for thrombocytopenia e.g., PLT transfusions, danazol, thrombopoietin receptor agonists, vitamins (except folic acid).

Eligible patients were divided into two groups according to their platelet counts:

1. Group I: 80 patients with normal platelet counts ( $\geq 150 \times 10^9/L$ ), including 38 males and 42 females. Their ages ranged between 24 and 70 years with a mean of  $41.8 \pm 13.65$  years.
2. Group II: 80 patients with low platelet counts ( $< 150 \times 10^9/L$ ), including 41 males and 39 females. Their ages ranged between 25 and 68 years with a mean of  $40.11 \pm 12.65$  years.

No statistically significant difference was found between the two groups regarding age and sex.

After approval of the research ethics committee of Alexandria Faculty of Medicine & obtaining a written informed consent from all subjects, the enrolled patients were subjected to full history taking, thorough clinical examination, complete blood picture, liver and renal function tests, HCV-RNA quantitation by RT-PCR and detection of *H. pylori* antigen in stools by rapid test.<sup>(17)</sup>

Thirty patients positive for *H. pylori* in group II were randomly selected to receive triple anti-*Helicobacter pylori* therapy (Amoxicillin, clarithromycin, proton pump inhibitor) for two weeks. Those patients presented with a platelet count ranging from  $10-100 \times 10^9/L$  with a mean of  $89.30 \pm 25.56 \times 10^9/L$ .

#### RESULTS

Table(I) illustrates the values of platelet count, alanine aminotransferase (ALT) and viral load in the two studied groups and their statistical comparison, while table (II) illustrates comparison between the results of *H. pylori* antigen testing in the stools in both groups.

Group I patients had a significantly higher mean platelet count compared to group II ( $p=0.001$ ), while the mean ALT level was significantly lower in group I compared to group II ( $p=0.011$ ). No significant difference was found between the two groups regarding the viral load as detected by RT-PCR ( $p=0.136$ ).

Overall, 123 out of 160 studied HCV patients showed positive test for *H. pylori* antigen in the stools (76.9%), reaching a significant level ( $p=0.039$ ). Moreover, a significantly higher number of thrombocytopenic patients had positive test (67 out of 80) compared to HCV patients with normal platelet count (56 out of 80).  $p=0.039$ .

Tables (III & IV) show the response of 30 *H. pylori* positive thrombocytopenic patients to two weeks course of triple therapy regarding the platelet count. 19 out of 30 (63.3%) responded with increase or normalization of platelet count ( $p=0.01$ ). On comparing the pre- and post-therapy

platelet counts in those patients, the difference was statistically significant (p=0.035). *H. pylori* was eradicated in all of those 19 subjects.

**Table (I):** Comparison between the two studied groups regarding platelet count, ALT and viral load.

	Group I (n=80)	Group II (n=80)	P
<b>Platelet count (X10<sup>9</sup>/L)</b>			
Range	150-244.3	10-100	0.001*
Mean±SD	226.44±42.12	89.30±25.56	
<b>ALT (U/L)</b>			
Range	22-49	42-122	0.011*
Mean±SD	32.6±10.9	75.6±15.9	
<b>Viral load (X10<sup>3</sup>)</b>			
Range	3.000-1.5X10 <sup>6</sup>	8.000-2X10 <sup>6</sup>	0.136
Mean±SD	1.1X10 <sup>5</sup> ±4.500	1.3X10 <sup>5</sup> ±6.200	

p was calculated using student t-test

**Table (II):** Comparison between the results of *H. pylori* antigen testing in the stools in the two studied groups.

<i>H.pylori</i> in stools	Ag	Group I		Group II		Total	
		No.	%	No.	%	No.	%
Negative		24	30.0	13	16.3	37	23.1
Positive		56	70.0	67	83.8	123	76.9
Total		80	100.0	80	100.0	160	100.0
X <sup>2</sup>		4.25					
P		0.039*					

p was calculated using Chi square test

**Table (III):** Platelet response of 30 *H. pylori* positive thrombocytopenic patients after two weeks course of triple therapy.

	Platelet Response to Triple Therapy	
	No.	%
Response	19	63.3
No response	11	36.7
Total	30	
Z-test	4.88	
P	0.01*	

P was calculated using Z-test

**Table (IV):** Comparison between mean platelet counts before and after two weeks course of triple therapy.

	Platelet count ((X10 <sup>9</sup> /L)	
	Before treatment	After treatment
Range	10-125	60-200
Mean±SD	89.30±35.56	116.95±50.43
t-test	2.65	
p	0.035*	

p was calculated using student t-test

## DISCUSSION

*Helicobacter pylori* has been considered for years as the only etiological agent of gastritis, peptic ulcer, gastric cancer and MALT lymphomas. More recently, it has been found to be associated with a number of autoimmune disorders including ITP.<sup>(18)</sup>

Hepatitis C virus is the principal cause of end stage liver disease worldwide. Progression of the disease is governed by multiple factors. Bacterial co-infection with *H.pylori* is an important factor in the development of cirrhosis and its decompensation.<sup>(19)</sup>

In the present study, we demonstrated a significant association between HCV infection and *H. pylori* as 123 out of 160 HCV patients (76.9%) had positive stool test for *H. pylori* antigen (p=0.039). This is consistent with findings of others who reported that *H. pylori* is common in Egypt and acquisition of infection occurs at a very young age.<sup>(20)</sup> Abdel-atti et al (2011) also found that out of 93 examined chronic HCV patients, 51 patients (55%) had *H. pylori* infection.<sup>(21)</sup>

An Italian case-control study (2000) demonstrated very high (89%) seroprevalence of *H.pylori* infection in cirrhotic HCV positive patients compared to controls (59%) which may explain the frequent occurrence of gastroduodenal ulcer in cirrhotic patients (< 0.001).<sup>(22)</sup>

An Egyptian study conducted by El-Masry et al (2010) investigated *H. pyloric* infection among patients with HCV with chronic active hepatitis and cirrhosis with different staging. They found *H. pylori* infection in 50 (55.6%) out of 90 HCV patients versus 26 (39.4%) out of 66 healthy controls. Moreover, the prevalence of *H. pylori* infection increased significantly from chronic active hepatitis to cirrhosis (p=0.04). These results reflect high prevalence of *H. pylori* infection in chronic HCV patients.<sup>(19)</sup>

However, previous studies<sup>(23, 24)</sup> have reported a lower prevalence of *H. pylori* infection in patients with liver cirrhosis. Kim et al (2008)<sup>(23)</sup> showed that the prevalence of *H. pylori* infection in patients with hepatitis virus-related liver cirrhosis



was 42.5%. The prevalence of *H. pylori* infection did not differ depending on whether there was peptic ulcer (35.6%) or not (34.9%) in patients with liver cirrhosis.

Auroux et al (2003)<sup>(24)</sup> detected *H. pylori* infection in 37 out of 64 consecutive patients with cirrhosis referred for gastroscopy. However, in the majority of their patients, cirrhosis was related to alcohol, while hepatitis B or C virus was the cause of cirrhosis in 14 patients only. They concluded that in patients with cirrhosis, the presence of gastroduodenal ulcer was significantly related to hypertensive gastropathy but not to *H. pylori* infection.

It is well-known that HCV-associated thrombocytopenia typically worsens with progression of liver disease mostly due to inadequate production of thrombopoietin by the diseased liver or sequestration of platelets in the enlarged spleen secondary to portal hypertension (hypersplenism).<sup>(10)</sup> Therefore, we adopted strict inclusion and exclusion criteria in the selection of our subjects in order to minimize the contribution of those factors to the etiology of thrombocytopenia. We also excluded cases who received or were receiving anti-HCV therapy because those drugs may result in a drop in the platelet count as an adverse event.<sup>(25)</sup>

The present study detected *H. pylori* coinfection in 67 out of 80 thrombocytopenic HCV patients compared to 56 out of 80 HCV patients with normal platelet count and the difference was statistically significant ( $p=0.039$ ). The relationship between *H. pylori* infection and chronic ITP has been confirmed;<sup>(14,26-28)</sup> however, no clear evidence exists so far for such an association in patients with HCV-associated thrombocytopenia. Scandellari et al (2009)<sup>(14)</sup> showed a cross-reaction of an *H. pylori* urease B monoclonal antibody with platelet glycoprotein IIIa and suggested that the immune response to Urease B may be involved in the pathogenesis of ITP.

An Iranian study conducted by Faranoush et al (2013)<sup>(26)</sup> found that *H. pylori*-DNA was positive in bone marrow aspiration of 5.9% of cases of

chronic ITP, 70% of cases had positive serum *H. pylori*-Ig A while positive serum *H. pylori*-IgG was observed in 51% of cases. They concluded that in chronic ITP, *H. pylori* infection can be considered as an additional disorder which aggravates the main disease.

The possible role of *H. pylori* infection in the development of ITP had been studied in some systemic reviews.<sup>(13,15)</sup> Franchini et al (2007)<sup>(13)</sup> conducted a systematic review and meta-analysis of the available literature. They concluded that there is a strict correlation between *H. pylori* eradication and increase in platelet count in patients with ITP.

In the present study, triple anti-*Helicobacter* therapy administered for two weeks resulted in an increase or normalization of platelet counts in 19 out of 30 (63.3%) treated patients who were thrombocytopenic and positive for *H. pylori*. This response to treatment was statistically significant ( $p=0.001$ ). *H. pylori* was eradicated in all of the 19 patients who responded by increase in platelet count compared to 6 out of the 11 who did not show platelet response. Similar results were reported by others in chronic ITP,<sup>(13, 15)</sup> but none for HCV-associated thrombocytopenia.

Arnold et al (2009)<sup>(15)</sup> showed an overall platelet response in more than 50% of ITP patients successfully treated for the infection and increased response rates in countries with a high prevalence of *H. pylori* infection in background populations, in patients with mild-to-moderate thrombocytopenia and in those with shorter disease duration. These findings strengthen the causal association between *H. pylori* infection and immune thrombocytopenia in some patients.

Our findings suggest a possible contribution of *H. pylori* coinfection to the pathogenetic background of HCV-associated thrombocytopenia. No previous studies have addressed such an association although Umemora et al (2007)<sup>(29)</sup> reported a possible connection between *H. pylori* coinfection and thrombocytopenia during interferon/ ribavirin treatment course, suggesting that preemptive eradication of *H. pylori* may

facilitate completion of treatment and increased sustained virological response.

To our knowledge, the present study is the first of its kind that found an association between HCV-associated thrombocytopenia and *H. pylori* infection. This could open new doors for a group of patients with a chronic disease that is difficult to manage. Further investigations on a larger number of patients might allow a better definition of the true prevalence of *H. pylori* infection in patients with HCV-associated thrombocytopenia. These positive results also justify placebo-controlled trials for the assessment of effect of eradication of *H. pylori* in those patients. Until the results of such trials are available, the screening for *H. pylori* infection and an attempt to eradicate the bacterium in positive cases seems appropriate in all patients with HCV-associated thrombocytopenia.

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