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Helicobacter pylori sero-prevalence in different liver diseases

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This study was carried out to investigate the seroprevalence of *Helicobacter pylori* infection in patients with different liver diseases and determine the association and correlation between the seroprevalence of *H. pylori* infection and the liver diseases. The presence of a *H. pylori* antigen was investigated in serum samples from 274 individuals with liver diseases as well as 120 healthy individuals. *H. pylori* antigen was detected using enzyme-linked immunosorbent assay (ELISA) and Western blot based on specific anti-*H. pylori* antibody. The result was analyzed using the chi-square test. *H. pylori* was detected in sera samples of 31.7% (20/63) (X^2 = 3.7) of non-cirrhotic, 50% (11/22) (X^2 = 3.9) of cirrhotic and 56.1% (106/189) (X^2 = 5.2) of hepatocellular carcinoma (HCC) individuals, compared to 8.4% (10/120) of healthy individuals. The levels of *H. pylori* antigen were significantly higher ($p < 0.05$) in sera of different stages of liver diseases compared by healthy individuals. We found a good correlation between *H. pylori* antigen levels and the severity of the liver diseases (Pathology) ($r = 0.368$, $p < 0.001$). Also, there is a correlation between age and *H. pylori* antigen levels ($r = 0.25$, $p < 0.001$). *H. pylori* infection is correlated with occurrence and development of different stages of liver diseases.

Key words: Liver diseases, *Helicobacter pylori.*

INTRODUCTION

In African countries, there is a high prevalence of *Helicobacter pylori* infection (Lindkvist et al., 1996). *H. pylori* is a Gram-negative spiral organism which colonizes the gastric mucosa causing chronic gastritis (Yang et al., 2003; Dawsey et al., 2002; Peterson et al., 1991). Genetic research has identified polymorphisms of *H. pylori* virulence factors and the host which could play a role in the clinical outcome of the infection (peptic ulcer or gastric cancer) (Buzás, 2012). *H. pylori* are successful colonizers of the human gastric mucosa. Colonization increases the risk of peptic ulcer disease and adenocarcinoma. However, potential benefits of *H. pylori* colonization include protection against early-onset asthma and against gastrointestinal infections (Kienesberger et al., 2012). *H. pylori* was classified as a group 1 carcinogen for gastric cancer by the International Agency for Research on Cancer (1994).

It was found that between two to 20 percent of people infected with *H. pylori* will develop ulcers (Kusters et al., 2006). Some evidence also links *H. pylori* infection to gastric cancer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and perhaps pancreatic cancer and cardiovascular disease (Kusters et al., 2006). Also, smoking is identified as a modifiable risk factor for *H.*

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pylori infection (Bastos et al., 2013)

Histology investigation of endoscopic biopsies showed the golden standard in the diagnosis of *H. pylori* related gastritis (El-Zimaity et al., 1996). However, endoscopy is an invasive procedure that requires general anesthesia (Bourke et al., 2005). Attallah (2004) developed a sensitive and specific noninvasive immunoassay based on the detection of an *H. pylori* circulating antigen (HpCA) in sera *of H. pylori*-infected individuals (Abdel fattah et al., 2004). Concerning hepatic fibrosis (non-cirrhotic) is a common sequel to diverse liver injuries (Lun-Gen et al., 2003), fibrosis could be a cause of functional hepatic failure (Ahn et al., 2002). Progression of non-cirrhotic liver with the development of cirrhosis is a feature of almost all chronic liver diseases (De Ledinghen et al., 2004). This progression may continually cause hepatocellular carcinoma (HCC) (Giannell et al., 2003). HCC is the fourth cause of death due to cancer worldwide (Poon and Borys, 2011).

A striking finding indicated by Ward et al. (1994) was that a bacterial infection of the liver in healthy A/JCr male mice was capable of inducing a strong inflammatory change in the parenchyma (that is, hepatitis) leading to hepatocellular carcinoma. This bacterial pathogen was demonstrated to belong to *Helicobacter* genus. *H. pylori* infection is also very common in subjects suffering from liver cirrhosis (Goo et al., 2009; Ponzetto et al., 2000), but its prevalence has never been reported in HCC patients.

In this study, we show *H. pylori* sero-prevalence in different liver diseases compared with control subjects. Also, we want to find a correlation between levels of *H. pylori* antigen and the severity of the liver diseases (Pathology).

MATERIALS AND METHODS

A total 274 patients suffered from different liver diseases were recruited in this study (mean age = 50.9±10.8 years), beside 120 healthy individuals (mean age = 32.4 ± 6 years). All patients were taken from Gastroenterology Department, Mansoura University. Patients were classified according to histology into three groups.

1. First group: Non-cirrhotic group included 63 patients (mean age = 45.7±9.5).
2. Second group : Cirrhotic group included 22 patients (mean age = 49.5±9.6).
3. Third group : HCC group included 189 patients (mean age = 52.8±10.9).

ELISA for *H. pylori* circulating antigen (HpCA) in serum

Each well of polystyrene microtiter plates was coated with 50 µl of a tested human serum sample diluted in carbonate-bicarbonate buffer (pH 9.6). The plates were incubated overnight at room temperature and washed three times with 0.05% (vol/vol) PBS-T20 (pH 7.2), and then free active sites were blocked with 0.2% (wt/vol) nonfat milk in carbonate-bicarbonate buffer. After washing of the plates, 50 µl of the specific antisera/well was added to the 58-kDa antigen diluted 1:100 in PBS-T20, and the mixture was incubated at 37°C for 2 h. After the plates were washed, 50 µl of anti-rabbit IgG alkaline phosphatase conjugate (Sigma)/well diluted in 0.2% (wt/vol) nonfat milk in PBS-T20 was added, and the mixture was incubated at 37°C for 1 h. The amount of coupled conjugate was determined by incubation with 50 µl of p-nitrophenyl phosphate substrate (Sigma)/well for 30 min at 37°C. The reaction was stopped by using 3 M NaOH, and absorbance was read at 405 nm. The cutoff level of the ELISA, above or below which the tested sample is considered positive or negative, was calculated as the mean ELISA optical densities (range, 0.135 to 0.377) of a group of 24 serum samples from noninfected healthy individuals ± 3 standard deviations [i.e., 0.257 ± (3 × 0.047) = 0.398]. The mean absorbance value of a group of 32 H. pylori-positive individuals was 0.751 (range, 0.411 to 1.250).

Statistical methods

Results were expressed as mean ± SD and were analyzed by using the Student's t test, and ANOVA tests, as appropriate. Correlation between different parameters was performed using Pearson's correlation test. $P \leq 0.05$ was considered to be significant. All statistical procedures were performed using SPSS software, version 11 for Windows.

RESULTS

A total of 274 hepatic patients and 120 control subjects were recruited into this study. The demographic and clinical details of these subjects are shown in Table 1. The group of patients is classified into, a non-cirrhotic patients (n = 63), cirrhotic patients (n = 22) and hepatocellular carcinoma (n = 189). Detection of *H. pylori* circulating antigen (HpCA) in human serum by a novel ELISA was developed by Attallah (2004) for the diagnosis of *H. pylori* infection. Investigation of the seroprevalence of *H. pylori* showed that (Table 1):

1. There were significant differences in the *H. pylori* Antigen levels between the control and study groups of different stages of liver diseases (< 0.05).
2. The levels of *H. pylori* antigen were significantly higher in sera of non-cirrhotic group (p = 0.008), cirrhotic group (p = 0.003) and HCC group (p = 0.001) compared to healthy individuals, where, *H. pylori* antigen levels in control group was 0.23 ± 0.07, compared to non-cirrhotic group (0.29 ± 0.16), cirrhotic group (0.34 ± 0.18) and HCC group (0.35 ± 0.15).

However, there was a good correlation between *H. pylori* antigen levels and the severity of the liver diseases (Pathology) (r = 0.368, p < 0.001). Also, there was a

Table 1. Clinical and *Helicobacter pylori* serological parameters in patients and control subjects.

Parameter	Controls (n=120)	Patients							
		Non-cirrhotic		Cirrhotic		HCC		All patients	
		(n=63)	*p*-value	(n=22)	*p*-value	(n=189)	*p*-value	(n=274)	*p*-value
Age (years)	32.4±6	45.7±9.5	0.001	49.5±9.6	0.001	52.8±10.9	0.001	50.9±10.8	0.001
H. pylori Ag level	0.23±0.07	0.29±0.16	0.008	0.34±0.18	0.003	0.35±0.15	0.001	0.34±0.16	0.001

Data shown are mean ± SD. p-values are for comparing data between controls and different patient groups.

Table 2. Positivity of *H. pylori* antigen in different liver diseses.

H. pylori Ag	Patholgy			
	Normal	Non-Cirrhotic	Cirrhotic	HCC
+ve	10	20	11	106
-ve	110	43	11	83
Total number	120	63	22	189
Positivity (%)	8.4	31.7	50	56
Association	-	3.7	3.9	5.2

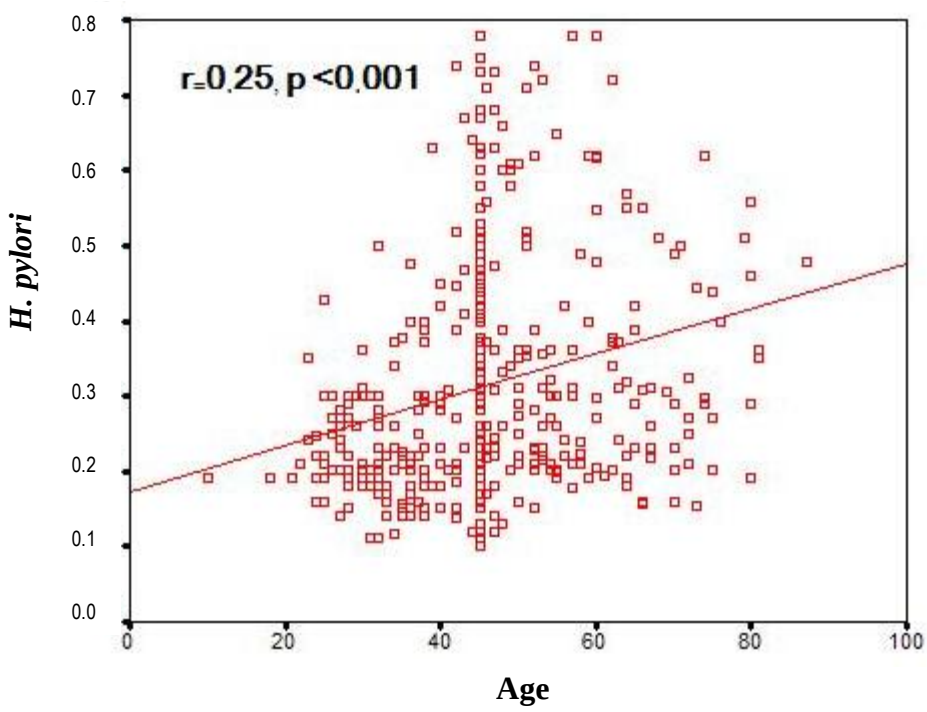

Figure 1. Correlation between age and *H. pylori* antigen levels.

correlation between age and *H. pylori* antigen levels (r = 0.25, p < 0.001) as shown as in Figures 1 and 2. *H. pylori* seropositivity was more prevalent among patients with HCC (106/189, 56.1%) than in controls (10/120, 8.4%) (p < 0.05) (X^2 = 5.2). While *H. pylori* seropositivity among patients with cirrhosis (11/22, 50%) than in controls (p <

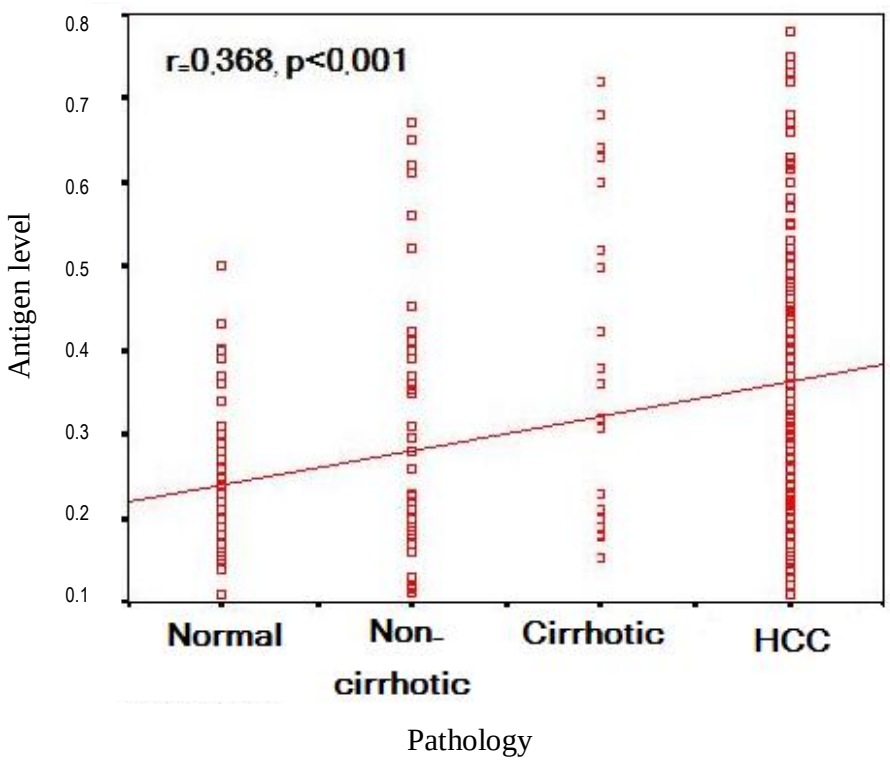

Figure 2. Correlation between Pathology and *H. pylori* antigen levels.

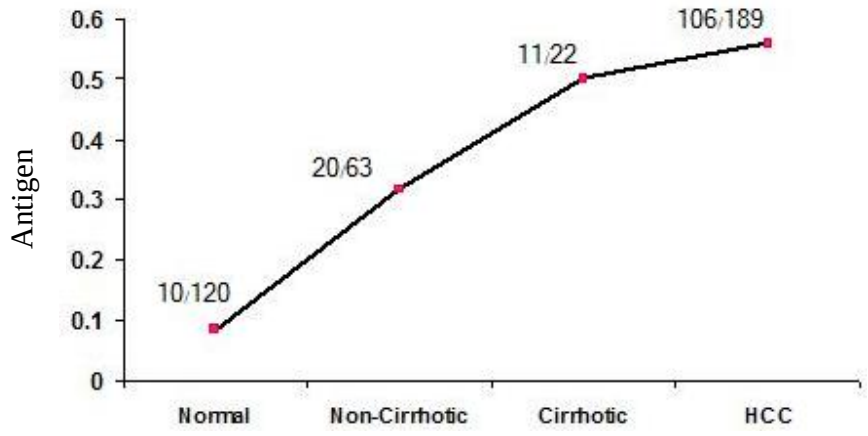

Figure 3. Prevalence of *H. pylori* antigen.

0.05) (X^2 = 3.9). Also, seropositivity was (20/63, 31.7%) among non-cirrhotic patients compared by controls ($p < 0.05$) (X^2 = 3.7) (Table 2 and Figure 3).

DISCUSION

H. pylori infection is a chronic infection (Nicola et al., 2003). In most instances, it is acquired during childhood, and is often associated with low socio-economic class (Mendall et al., 1992; Queiroz et al., 2012). The presence of this bacterium has been strongly established as the main cause of several gastroduodenal diseases, including peptic ulcer disease (Hopkins et al., 1996), gastric carcinoma, and gastric MALT lymphoma

(Wotherspoon et al., 1993). A very high prevalence of *H. pylori* infection in patients with cirrhosis of the liver has been mentioned in several reports: a higher prevalence of *H. pylori* infection was noted by Siringo et al. (1997) and Spinzi et al. (2001), in cirrhotics as compared with blood donors ($p < 0.0005$), in two North Italian towns.

The prevalence of *H. pylori* infection in patients with liver disease needed to be studied on the basis of clinical and experimental considerations (Marilena et al., 2004). From a clinical point of view, the medical history of cirrhotic patients was punctuated by frequent and recurrent hospitalisations due to high rate of complications. Among the most relevant of them, peptic ulcer and upper GI hemorrhage were of peculiar relevance, being life-threatening for the patient and of high cost for Health Care Services, requiring both emergency care and subsequent long hospital stay (Rosina et al., 1996). An important association was observed between recurrent abdominal pain and *H. pylori* infection in some populations (Abolfazl et al., 2013).

From an experimental point of view, infection of healthy A/JCr male mice with *H. hepaticus* could result in chronic hepatitis and liver cancer in a short time (Ward et al., 1994). Since this report, several other *Helicobacter* species have been subsequently found in the liver and biliary tract of cats and dogs suffering from hepatitis and hepatocellular carcinoma (Andersen, 2001). Kirk et al. (1980) demonstrated a frequency 33% of peptic ulcer in patients with chronic liver disease. In an Italian multicentre study, between 12 and 20% of cirrhotic patients were demonstrated to bear gastric or duodenal ulcer with a high prevalence in the gastric site (Gottardello et al., 1991).

Since peptic ulcer is related to the presence of *H. pylori* infection in non-cirrhotic patients, it is logical to suppose a role for the same bacterium also in subjects with cirrhosis. To search for the presence of the bacterium and to be cured of it, stems from the rationale is used to prevent the development of peptic ulcer and its complications in cirrhotics, too, as we usually do in non-cirrhotic patients. From an epidemiological point of view, several data indicated that only a proportion of patients infected by hepatitis C virus (HCV) develops liver cirrhosis (Guadagnino et al., 1997), and among these only a minority ultimately succumbed to liver cancer, and also that “classical” prognostic features do not explain all the variations of the disease (Wiese et al., 2000). These observations suggested that other factors besides the viral pathogen could concur in generating HCC.

The experimental demonstrated by Ward et al. (1994) showed that *H. hepaticus* causes hepatitis and HCC in male A/JCr mice. A number of *Helicobacter* sp. have been isolated from the liver of cats and dogs with hepatitis (Fox et al., 1996) and from the human biliary tract and gallbladder. In western countries, HCC arises almost invariably on the background of cirrhosis representing a long-term complication of the disease, after decades of continuing inflammation (Tomiyama et al., 2013; Fox et al., 1998).

One “new” possible mechanism capable of inducing pro-inflammatory cytokines and lymphoid proliferation might indeed be liver or biliary tract infection by bacteria belonging to *Helicobacter* genus. A few papers in the last years reported the finding of genomic sequences belonging to *Helicobacter* spp. in the liver of patients with HCC. We have shown sequences of *Helicobacter* spp. in 23 of 25 human livers with cirrhosis and HCC (Ponzetto et al., 2000).

Avenaud et al. (2000) confirmed these data by demonstrating genomic sequences of *Helicobacter* spp. In eight of liver specimens from patients with HCC and the sequenced polymerase chain reaction (PCR) products confirmed *H. pylori* and *Helicobacter felis* (Nicola et al., 2003). Moreover, Agha-Amiri et al. (1998) found that seven out of 20 patients with HCC, genomic sequences of a bacterium belong to the RNA superfamily VI (Campylobacter, Helicobacter, Arcobacter) with highest homology to *Arcobacter* spp. The role of *Helicobacter* spp. in the evolution of cirrhosis and HCC in humans is unknown, but a potential mechanism has been reported by Taylor et al. (1995), who described a new liver-specific toxin produced by several *Helicobacter* spp.

Conclusion

We found that infection is correlated and associated with occurance and development of different stages of liver diseases, where the seroprevalence of *H. pylori* in subjects with cirrhosis of the liver and HCC is much more frequent than in controls.

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