Original paper

Association between *Helicobacter pylori* infection and cirrhosis in children

Związek między zakażeniem Helicobacter pylori a marskością wątroby u dzieci

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Słowa kluczowe: *Helicobacter pylori*, marskość, dzieci.

Abstract

Introduction: Liver cirrhosis is often accompanied by fibrosis, loss of liver function, and liver cancer. Identification of the factors associated with this disease has always been a goal because they can be effective in its treatment. Several reports showed that *Helicobacter pylori* (*H. pylori*) can cause multiple gastrointestinal complications.
Aim of the research: To investigate the association between *H. pylori* infection and liver cirrhosis in children.
Material and methods: In this case-control study, 60 children under the age of 18 years with liver cirrhosis participated as the cases, and 236 healthy children were included as controls. For evaluation of the *H. pylori* antigen (Ag) of the samples, fresh stool samples were prepared.
Results: Thirty-two (53.3%) samples in the cases, and 46 (19.5%) samples in controls had positive *H. pylori* Ag test. The results showed that the two groups had significant differences in terms of infection by *H. pylori* stool antigen; the presence of this Ag in the case samples was more than in the controls ($p < 0.001$).
Conclusions: That the rate of *H. pylori* infection in children with cirrhosis was significantly higher than among healthy children. This result can indicate the effect of this bacterium on the incidence and development of liver cirrhosis.

Streszczenie

Wprowadzenie: Zwłóknienie, utrata funkcji wątroby, a także rak wątroby często towarzyszą marskości wątroby. Zawsze określano czynniki związane z marskością, ponieważ może się to okazać skutecznym podejściem w leczeniu. Wyniki szeregu badań wykazały, że *Helicobacter pylori* (*H. pylori*) może być przyczyną licznych powikłań żołądkowo-jelitowych.
Cel pracy: Zbadanie związku między zakażeniem *H. pylori* i marskością wątroby u dzieci.
Materiał i metody: W badaniu kliniczno-kontrolnym wzięło udział 60 dzieci w wieku do 18 lat (grupa badana) oraz 236 zdrowych dzieci (grupa kontrolna). Wykonano badanie próbek kału na obecność antygenu (Ag) *H. pylori*.
Wyniki: Pozytywne wyniki na obecność antygenu *H. pylori* uzyskano w przypadku 32 (53,3%) próbek pochodzących od chorych dzieci i 46 (19,5%) próbek od grupy kontrolnej. Na podstawie wyników stwierdzono różnice między tymi grupami pod względem zakażenia *H. pylori*; wykazano większą częstość występowania antygenu w grupie badanej w porównaniu z grupą kontrolną ($p < 0,001$).
Wnioski: Częstość występowania zakażenia *H. pylori* u dzieci chorych na marskość była istotnie większa niż w grupie zdrowych dzieci. Wynik ten wskazuje na wpływ bakterii na występowanie i rozwój marskości wątroby.

Introduction

Cirrhosis is a chronic liver disease that is characterised by the destruction of the hepatocytes and replacing with fibrosis, the destruction of parenchymal cells, and cellular regeneration along with the formation of nodules. This disease is associated with loss of liver function as well as liver cancer [1–4]. Therefore, due to the principal role of liver as a detoxification, damage to this organ can be very important [5, 6]. There are many causes for cirrhosis of the liver, including long-term alcohol use, hepatitis B, C, and D viruses, followed by inherited diseases such as cystic fibrosis, α1-antitrypsin deficiency, galactosaemia, glycogen storage disease, Wilson syndrome, haemochromatosis, and biliary tract obstruction and biliary atresia in children [4, 7–10].

Helicobacter pylori (*H. pylori*) is a non-spore-forming gram-negative microaerophilic bacterium [9]. *Helicobacter pylori* is the most common chronic bacterial infection in humans and has infected half of the world's population. This organism has various species that affect the pathogenicity of this organism [1]. *Helicobacter pylori* is an important cause of gastric ulcer and is considered as a risk factor for gastric cancer [2].

This organism can be associated with peptic ulcer, gastric mucosal-associated lymphoid tissue lymphoma, and chronic gastritis [11–13].

Today, the role of *H. pylori* infection is reported in many diseases, including idiopathic thrombocytopenic purpura [14], iron deficiency anaemia [15], and hepatic and cardiovascular symptoms and biliary tract disease [16, 17]. Moreover, in some studies, the role of *H. pylori* in cirrhosis [18–21], hepatic encephalopathy [22, 23], primary biliary cirrhosis [24], and bleeding oesophageal varices [25] is emphasised.

Therefore, it can be concluded that this bacterium can contribute to the progression of some of these diseases [18]. Identification of the relationship between *H. pylori* infection and cirrhosis is critical to the decision to eradicate this bacterium before liver transplantation [18, 22, 23]. On the other hand, the eradication of *H. pylori* requires high-cost, multi-drug treatment, which is associated with drug-related side effects and some treatment failure rate, and requires robust evidence-based studies to decide on eradication of *H. pylori* in this group [26–28].

Considering the key role of the liver in maintaining health, cirrhosis can lead to high financial costs, disability, and death [3, 4, 7]. Therefore, identifying the factors involved in the incidence and severity of the disease can be highly useful and important [3, 6, 29]. Most studies have suggested the pathogenicity of this microbe in adults. However, the available evidence in children is very limited [30–32]. Understanding the prevalence, causes, treatment, and the factors influencing the cirrhosis prognosis is very important in the process of treatment.

Aim of the research

Therefore, the aim of this study was to investigate the association between *H. pylori* infection and liver cirrhosis in children.

Material and methods

This case-control study aimed to investigate the association of *H. pylori* infection and liver cirrhosis in children.

Informed consent was obtained from the parents of the participants before entering the study. Approval from the Ethics Committee of Shiraz University of Medical Sciences was obtained for this study.

The sample size of the case group was 60 children under the age of 18 years, referred to Namazi hospital in Shiraz, Iran in 2018. These children had cirrhosis, and their condition was confirmed by liver biopsy. The control group comprised 236 healthy children under the age of 18 years, who were randomly assigned to the study. The samples were examined in terms of lack of underlying disease and clinical symptoms.

Exclusion criteria were dissatisfaction of the patient's parents, the use of proton pump inhibitors for two weeks before the test, the use of antibiotics within four weeks before the test, suffering from diarrhoea during the collection of stool samples, coagulopathy, stomach ache, and abdominal pain within the four weeks prior to study.

Demographic characteristics and clinical symptoms of the samples were recorded at the beginning of the study. Then, fresh stool samples were collected for *H. pylori* antigen test. The stool specimens collected in each of the case and control groups were immediately transferred to the laboratory of the Gastroenterology Research Centre, Shiraz University of Medical Sciences, Shiraz, Iran, to be tested in terms of *H. pylori* antigen under appropriate conditions. The *H. pylori* antigen test was measured by ELISA (enzyme-linked immunosorbent assay) method using the *H. pylori* Stool antigen kit (ACON Company, United Kingdom) based on the manufacturer's protocol.

Statistical analysis

The results were analysed using SPSS (Statistical Package for the Social Sciences) software version 16. Descriptive data were collected from the frequency distribution table, central indexes, distribution, and percentages. Continuous quantitative and qualitative data were compared between the two groups using the independent *t*-test, and the χ^2 was used to compare the discrete data between the groups. $P < 0.05$ was considered as a significant level.

Results

This case-control study was conducted among 60 patients with cirrhosis as the case group and 233 healthy samples as the control group. The case group included 23 (38.3%) boys and 37 (61.7%) girls with a mean age of 78.20 ±57.61 months. The control group consisted of 122 (51.7%) boys and 114 (78.3%) girls with a mean age of 68.30 ±48.56 months. There were no significant differences between the two groups in terms of age and gender (Table 1).

The results of the *H. pylori* stool antigen test showed that 32 (53.3%) samples in the case group and 46 (19.5%) samples in control group had positive *H. pylori* antigen test (Figure 1). The results showed that the two groups had a statistically significant difference in terms of the prevalence of stool Ag for *H. pylori*. The presence of this Ag in the samples of

Table 1. The baseline characteristics of the children with liver cirrhosis in the current study

Variation		Cases	Controls	*P*-value
Sex	Male	23 (38.3%)	122 (51.3%)	0.065
	Female	37 (61.7%)	114 (48.3%)	
Age [months]		78.20 ±57.61	68.30 ±48.56	0.17

the case group was more than in the control group ($p < 0.001$) (Figure 1).

In this study we observed an association between positive stool *H. pylori* antigen and cirrhosis (OR = 4.72; 95% CI: 2.59–8.60; $p < 0.001$).

Discussion

The factors associated with cirrhosis have always been sought because they can be effective in the treatment process. Studies have shown that along with drug therapies to improve liver tissue, the elimination of progressive and causative agents of cirrhosis can delay the destruction of the liver cells and minimise cirrhosis and improve liver tissue [33, 34]. Therefore, identifying the factors associated with cirrhosis seems very important [35].

The results of this study showed that the prevalence of *H. pylori* infection was significantly higher in children with cirrhosis than in the control group; the *H. pylori* stool antigen test was positive in 53.3% of patients with cirrhosis. However, it declined to 19.5% in healthy subjects.

Casswall *et al.* reported the prevalence of *H. pylori* in liver and gastric tissue in children with chronic liver disease (CLD). The results of this study showed that *H. pylori* DNA can be detected in the livers of some children with liver diseases [36].

Feng *et al.* in a meta-analysis evaluated the association between cirrhosis and *H. pylori* infection. This meta-analysis showed a significant difference in *H. pylori* infection between patients with cirrhosis and controls [37].

According to a study by Săndulache *et al.* the seroprevalence of *H. pylori* infection in cirrhotic patients was significantly more than in healthy subjects. They stated that the role of urease in this bacterium could increase plasma ammonia. However, they concluded that *H. pylori* was not an independent risk factor in patients with cirrhosis [26]. Siringo *et al.* reported that anti-*H. pylori* IgG antibody seroprevalence rates in patients with cirrhosis were significantly higher than in controls [38].

Xu *et al.* identified the association between *H. pylori* and hepatic cirrhosis and hepatocellular carcinoma; it was concluded that *H. pylori* may be a risk factor for patients with cirrhosis and HCC [28].

Sathar *et al.* concluded that there is a significant association between *H. pylori* infection and portal hypertensive gastropathy (PHG) in patients with cirrhosis, which is associated with PHG severity, thereby necessitating *H. pylori* eradication [27].

Apart from PHG, hepatic encephalopathy (HE) is another complication of portal hypertension that remains a major cause of morbidity in patients with cirrhosis [2]. Hepatic encephalopathy encompasses a spectrum of neuropsychiatric disorders related to liver failure, and the mechanisms responsible for the neurological alterations in hepatic encephalopathy begin to emerge [22, 23].

Moreover, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are among the most common causes of liver cirrhosis worldwide; *H. pylori* infection is strongly associated with HBV- and HCV-related cirrhosis in Europe; *H. pylori* infection is more common in cirrhotic patients with hepatic encephalopathy than in those without this problem [18, 39].

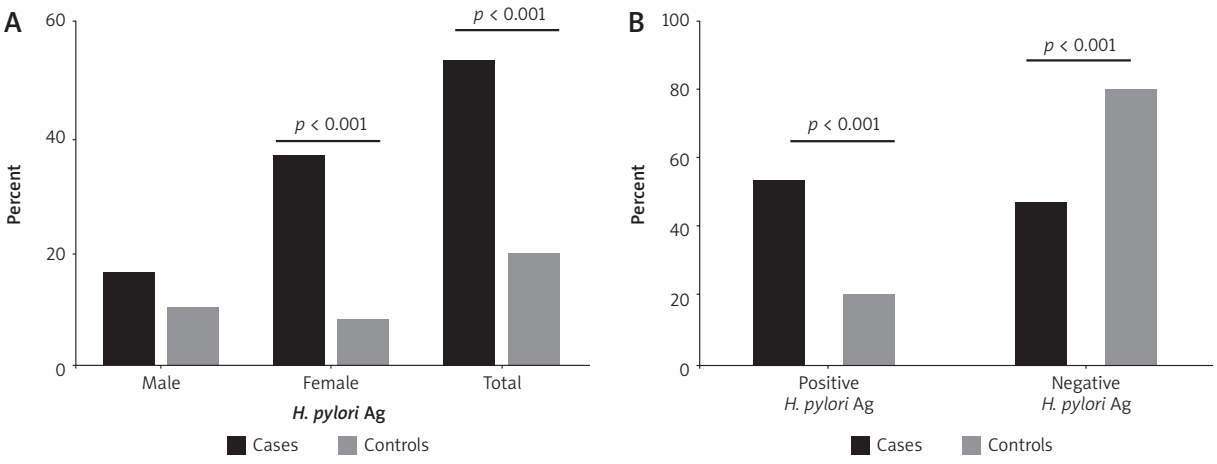

Figure 1. Comparison of frequency distribution of case and control groups based on the results of the *H. pylori* stool antigen test divided by groups (**B**) and gender (**A**)

These findings suggest that this bacterium can affect liver cirrhosis. This bacterium affects liver cells through the production of urease and increase in plasma ammonia [40–42]. In addition, considering the effects of *H. pylori* infection on peptic ulcer, liver and cardiovascular problems, and liver encephalopathy, *H. pylori* infection is likely to be effective in cirrhotic patients. Nevertheless, further studies are required to obtain reliable results. It is also suggested that the effectiveness of eradication of *H. pylori* before transplantation in patients with cirrhosis be investigated.

Several studies reported that *H. pylori* may cause symptoms of extra-gastrointestinal diseases such as peptic ulcer [11], idiopathic thrombocytopaenic purpura [14], iron deficiency anaemia [15], hepatic and cardiovascular symptoms [16, 17], and biliary duct diseases [24]. Therefore, it can be concluded that this bacterium can affect the development and progress of some diseases. Identification of the relationship between *H. pylori* infection and cirrhosis, in addition to the change in the therapeutic nature of the disease, is crucial to the decision to eradicate this microbe before liver transplantation [18, 39].

Conclusions

The results of this study showed that the rate of *H. pylori* infection in children with cirrhosis was significantly higher than in healthy subjects. This result can indicate the effect of this bacterium on the incidence and development of liver cirrhosis.

Conflict of interest

The authors declare no conflict of interest.

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