Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Apr 13; 10(B):1029-1032.
https://doi.org/10.3889/oamjms.2022.9577
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Gastroenterohepatology*

The Difference in Serum Pepsinogen I, Pepsinogen II, Carcinoembryonic Antigen, and Carcinoma Antigen 72-4 Levels between Children with and without *Helicobacter Pylori* Infection

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Edited by: Ksenija Bogoeva-Kostovska
Citation: Nasution IPA, Ruslie RH. The Difference in Serum Pepsinogen I, Pepsinogen II, Carcinoembryonic Antigen, and Carcinoma Antigen 72-4 Levels between Children with and without *Helicobacter Pylori* Infection. Open Access Maced J Med Sci. 2022 Apr 13; 10(B):1029-1032. https://doi.org/10.3889/oamjms.2022.9577
Keywords: CA 72-4; Carcinoembryonic antigen; Children; *Helicobacter pylori*; Pepsinogen
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Received: 28-Mar-2022
Revised: 02-Apr-2022
Accepted: 03-Apr-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: *Helicobacter pylori* is a common infection in human. The infection is mainly acquired in childhood with global prevalence of 32.3%. Several markers such as pepsinogen I, pepsinogen II, carcinoembryonic antigen (CEA), and carcinoma antigen (CA) 72-4 are associated with *H. pylori* infection and its complications.

AIM: The aim of the study was to determine the difference in serum pepsinogen I, pepsinogen II, CEA, and CA 72-4 levels in children with and without *H. pylori* infection.

METHODS: A cross-sectional study was conducted in Samosir Island, Indonesia. Inclusion criteria were children aged 2−18 years who did not take antibiotics, bismuth-containing drugs, histamine-2 receptor antagonists, proton pump inhibitors, and immunomodulators for the past 4 weeks before the study. All subjects were divided into two groups: *H. pylori* positive and negative. Demographic and anthropometric data were gathered. Serum pepsinogen I, pepsinogen II, CEA, and CA 72-4 levels were evaluated. The differences were determined using Mann–Whitney U-test.

RESULTS: A total of 74 subjects were enrolled in this study. *H. pylori* positive and negative subjects were 38 and 36, respectively. Females were dominant in both groups. No difference was observed in gender, age, anthropometric characteristics, serum CEA level, and CA 72-4 level between both groups. Serum pepsinogen I and pepsinogen II levels were higher in *H. pylori* positive group compared to their counterparts ($p = 0.013$ and $p = 0.001$, respectively).

CONCLUSION: There are significant differences in serum pepsinogen I and II levels between children with and without *H. pylori* infection.

Introduction

Helicobacter pylori infection is one of the most common infections in human [1]. *H. pylori* infection is mainly acquired during childhood and persisted for a long period even for life [2], [3]. The global prevalence of *H. pylori* infection in children is estimated at 32.3% [4]. In Germany, the prevalence rate is reported at 13.4% [1]. A study in Turkey reported a prevalence of 23.6% [5]. In Indonesia, the prevalence of *H. pylori* infection in a population aged younger than 29 years is 20.5% [6]. In the age group of 12−18 years, the prevalence reported is 30.9% [7]. The prevalence is significantly higher in low- and middle-income countries compared to high-income ones. *H. pylori* infection is associated with low socioeconomic status [3], [4], more siblings or children, room sharing [4], poor sewage system quality [4], [8], [9] mother or siblings with *H. pylori* infection [4], utilization of non-treated water [3], [4], [6], [8], [9], and older age [4], [5]. Other factors such as nationality and migration have also influenced the infection. In Germany, the rate is higher in migrant children, particularly if they migrate after the 1st year of their life [1]. Ethnicity is also a contributing factor as reported by Syam *et al*. [6].

The majority *H. pylori* infections in children are asymptomatic. Association between *H. pylori* infection with abdominal pain [2], [3], failure to thrive, Type I diabetes mellitus, celiac disease [2], inflammatory bowel disease, and allergic disease is elusive. The most common symptoms associated with *H. pylori* infection are vomiting, digestive bleeding, iron deficiency anemia, and malnutrition, but still require further investigation [3]. The diagnosis of *H. pylori* infection is based on the upper-digestive endoscopy and biopsy of the stomach [2], [3]. Follow-up may be done using non-invasive methods such as urea breath test, stool antigen test, and serology [3]. Pepsinogens, other markers of gastritis, are proposed to be related to *H. pylori* infection and abdominal pain in children [10]. Carcinoembryonic antigen (CEA) is associated with gastric cancer as a complication of *H. pylori* infection [11]. Carcinoma antigen 72-4 (CA 72-4) is a cell surface glycoprotein produced by gastric carcinoma cells. It is reported that *H. pylori* infection induces elevation of CA 72-4 in

adults even without gastric carcinoma [12]. However, those markers have not been investigated deeply in the pediatric population [11], [12]. In this study, we would like to determine the difference in CEA, CA 72-4, pepsinogen I, and pepsinogen II levels between children with and without *H. pylori* infection.

Methods

This was a cross-sectional study conducted in Samosir Island, North Sumatera, Indonesia between August and December 2021. Subjects were obtained by consecutive sampling method. Inclusion criteria were children aged 2−18 years who did not take antibiotics, bismuth-containing drugs, histamine-2 receptor antagonists, proton pump inhibitors, and immunomodulators for the past 4 weeks before the study. Exclusion criteria were children with malignancies, immunosuppressed, metabolic diseases, upper gastrointestinal tract bleeding, and history of gastrointestinal procedures. This study was approved by the Health Research Ethical Committee of Universitas Sumatera Utara.

Written informed consent was obtained from each subject's parent or proxy after providing sufficient information about the study before enrolment. All subjects were divided into two groups: *H. pylori* positive and negative groups based on *H. pylori* diagnosis using 40C-urea breath tests (Headway, China) and stool antigen tests (CTK Biotech, USA). The positive result from one or both diagnostic tools was considered a confirmed *H. pylori* infection. Each subject underwent an interview to gather demographic characteristics and physical examination to obtain anthropometric data. Sample for laboratory evaluation was obtained from peripheral blood. CA 72-4 and CEA were determined using ECLIA assay kits (Cobas, Roche Diagnostics, Germany). Pepsinogen I and pepsinogen II were determined using Abbott ARCHITECT Pepsinogen I and II (Abbott Laboratories Inc., Chicago, IL, USA), respectively.

Qualitative data were presented in frequency and percentage while quantitative data undergo normality test. Normally-distributed data were presented in mean and standard deviation but non-normally-distributed one was presented in median and minimum-maximum values. To determine the difference in serum CEA, CA 72-4, pepsinogen I, and pepsinogen II between *H. pylori* positive and negative groups, Mann–Whitney U-test was utilized. All statistical analyses were done with 95% confidence interval and $p < 0.05$ was considered significant. Statistical Package for the Social Sciences software was utilized to support the analysis.

Results

A total of 74 subjects were enrolled in this study. Thirty-eight subjects had positive *H. pylori* result while the rest 36 subjects had negative result. Females were dominant in both groups. Mean age of subjects in both groups was not different. The anthropometric characteristics were also not different in both groups (Table 1).

Table 1: Demographic and anthropometric characteristics of study subjects

Characteristics	*H. pylori* positive	*H. pylori* negative	p
Gender, n (%)			
Male	15 (39.4)	13 (36.1)	0.801
Female	23 (60.6)	23 (63.9)	
Age, mean (SD), years	11.96 (3.18)	11.84 (3.26)	0.884
Weight, mean (SD), kg	36.1 (9.98)	36.9 (10.41)	0.736
Height, median (min-max), cm	140.4 (104 – 166)	140 (104 – 163)	0.815
BMI-for-age, mean (SD), Z score	0.36 (1.6)	0.48 (1.4)	0.658

BMI: body mass index; SD: standard deviation.

Statistical analysis using Mann–Whitney U-test showed no difference in serum CEA and CA 72-4 levels between *H. pylori* positive and negative groups. In contrast with serum pepsinogen I and pepsinogen II levels, there was statistically significant difference in both groups ($p = 0.013$ and $p = 0.001$, respectively. Subjects with *H. pylori* infection had higher serum pepsinogen I and pepsinogen II levels compared to those without *H. pylori* infection (Table 2).

Table 2: Difference in serum CEA, CA 72-4, pepsinogen I, and pepsinogen II between both study groups

Laboratory parameters	*H. pylori* infection		p
	Positive	Negative	
CEA, median (min-max), U/mL	0.9 (0.26–9.51)	0.85 (0.24−2.98)	0.284
CA 72-4, median (min-max), ng/mL	4 (2.6–9.8)	3.2 (2.5–5.8)	0.101
Pepsinogen I, median (min-max), ng/mL	41.3 (23.5–110)	31.3 (20.2–104.3)	0.013*
Pepsinogen II, median (min-max), ng/mL	13 (4.2–25.7)	6 (3.4–22.8)	0.001*

*$p < 0.05$.

Discussion

H. pylori is a Gram-negative microaerophilic bacteria. It has been isolated from mummies but started to gain the spotlights in 1983 since Barry Marshall and Robin Warren found its relationship with chronic gastritis and peptic ulcer. The disease progression is associated with virulence of the strain, genetic predisposition, host's immune response, time of exposure, and environmental factors [3]. The infection is usually acquired during childhood [2], [3]. Aitila *et al*. in their study found that most children contracting *H. pylori* infection are aged 6−10 years. Females were dominant in *H. pylori* positive group in their study [8]. A study from Sub-Saharan Africa reinforced the previous results. *H. pylori* was predominant in children aged 8–10 years. Female preponderance was also observed in their study [9]. In

Bangladesh, most children infected with *H. pylori* were also from the age group of 5−8 years [13]. In accordance with the previous studies, most subjects in the *H. pylori*-infected group in this study were females. Mean age of subjects with *H. pylori* infection in our study was slightly higher (11.96 years) but the standard deviation was still within age range like in the previous studies.

From the perspective of nutritional status, *H. pylori* infection may impair children's growth but the association is weak [14]. The statement is in concordance with another study by Janjetic *et al*. They reported that nutritional status along with height-for-age and BMI-for-age Z scores is not statistically significant even though the parameters are lower in children infected with *H. pylori* [15]. Our study is in line with the previous literatures. There were no significant differences in weight, height, and BMI-for-age Z score between both groups in our study.

Kassem *et al*. conducted a study to determine the level of serum pepsinogens in children with *H. pylori* infection. They detected the pepsinogens using enzyme-linked immunosorbent assay (ELISA). Higher pepsinogen I and pepsinogen II levels were observed in children infected with *H. pylori* along with higher pepsinogen I/II ratio. Children with serum pepsinogen II levels higher than 7.5 μg/L tend to suffer from abdominal pain with prevalence ratio of 1.73 compared to their counterparts [10]. A study from Korea also supported the previous results. Serum pepsinogen I and II levels were higher in children with *H. pylori* infection. In addition, serum pepsinogen II was also higher in children with nodular gastritis compared to children without gastritis [16]. Serum pepsinogen II level in children infected with *H. pylori* in Bangladesh is significantly higher compared to non-infected children. This raises awareness of the presence of gastritis even in asymptomatic *H. pylori* infection [13].

Roma *et al*. found that serum pepsinogen I level was higher in children with *H. pylori* infection and gastritis compared to children with non-*H. pylori* gastritis and *H. pylori* infection without gastritis. There was no significant association between serum pepsinogen I level and severity of gastritis [17]. Serum pepsinogen I level was correlated with inflammatory scores in children with *H. pylori* infection. Eradication of *H. pylori* is significantly lowering serum pepsinogen I level along with inflammatory scores [18]. Furthermore, children infected with *H. pylori* carrying cytotoxin-associated gene product (CagA) also had higher serum pepsinogen I and II levels compared to children infected with *H. pylori* with negative CagA. This was due to higher virulence of CagA-positive- compared to CagA-negative-*H. pylori* [19]. In this study, serum pepsinogen I and II were statistically significant higher in children in *H. pylori* positive compared to *H. pylori* negative group. Our results were similar with previously published studies.

Wu *et al*. investigated CEA levels in subjects with gastric cancer, benign gastric lesions, and healthy control. They found that CEA level is higher in subjects with gastric cancer compared to the benign lesion and healthy control groups [11]. Serum CEA is significantly associated with anti-*H. pylori* antibody. Subjects with positive *H. pylori* antibody tend to have higher serum CEA level. In addition, serum CEA level is positively associated with the severity of gastric cancer [20]. Xu *et al*. in their study in adults reported that serum CEA level has significant positive correlation with *H. pylori* infection. This enlightened the role of *H. pylori* infection in the incidence of gastric, pancreatic, and lung cancers [19]. Unfortunately, the study in pediatric population has not been published yet.

CA 74-2 is related to *H. pylori* infection in adult. Buzas *et al*. reported a case of elevated CA 74-2 level in a patient with *H. pylori* infection. The marker's level returned to normal after two courses of eradication therapy [12]. The previous study is confirmed by a study in China. Serum CA 74-2 was also found to be elevated in *H. pylori*-infected subjects compared to their counterparts [19]. A study by Gong *et al*. also reported that serum CA 72-4 is associated with the presence of *H. pylori* infection. It also had positive correlation with tumor stage, tumor size, and lymph node metastasis in gastric cancer [20]. However, again, published study regarding association between serum CA 74-2 level and *H. pylori* infection in children is scarce. The results of our study were in contrast with the previous studies, particularly regarding serum CEA and serum CA 74-2 levels. There were no significant differences in serum CEA and CA 74-2 levels between *H. pylori* positive and negative groups. This may be caused by different samples' age ranges and relatively shorter exposure to microorganisms compared to adults.

Our study has several strengths. It is the first study determining the difference in serum CEA and CA 74-2 between children with and without *H. pylori* infection. It is also the first study determining the difference in serum pepsinogen I, pepsinogen II, CEA, and CA 74-2 in Indonesia, particularly North Sumatera province. The utilization of serum pepsinogen I and pepsinogen II may be applied to diagnose *H. pylori* infection in asymptomatic children and may aid in decision-making to start eradication therapy and prevent further complications. However, further study regarding this topic in larger scale is mandatory to confirm our results.

Conclusion

Mean age of children with *H. pylori* infection is 11.96 (SD 3.18) years. Females are dominating in infected children. There are statistically significant differences in serum pepsinogen I and pepsinogen II levels between children with and without *H. pylori*

infection. Both parameters are higher in children with *H. pylori* infection. There is no significant difference in serum CEA and CA 72-4 between both study groups.

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