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Peptic Ulcer Disease in Children with Chronic Abdominal Pain

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Abstract

Background: Data on the prevalence of ulcers in children are insufficient. We aimed to investigate the frequency of peptic ulcer and evaluate the effects of *H. pylori* infection, gender, age on peptic ulcer, and the value of endoscopy in children.

Methods: Eight hundred patients with chronic abdominal pain were enrolled. Upper endoscopy was performed if all the initial evaluations were normal. Clinical findings, laboratory results, endoscopic and pathologic findings were investigated retrospectively.

Results: Among all patients with chronic abdominal pain, ulcer disease was identified in 84 (10.5%) patients. Ulcer was observed 1.7 times more frequently in patients with *H. pylori* positivity. There is a significant relationship between *H. pylori* infection and the ulcer frequency (p=0.03). There was a non significant relationship between *H. pylori* infection and ulcer types as duodenal or gastric ulcer (p=0.08). There was no statistical relationship between ulcer and sex (p=0.45). We determined no statistical relationship between the ulcer types and sex (p=0.68). Age had an impact on ulceration, age was a good indicator for the discrimination of patients with or without ulcer (p=0.010). Each one-year increase of age caused a 1.1 fold increase in ulceration. The results revealed that age, sex and *H. pylori* positivity were not risk factors for gastric ulcer.

Conclusions: Ulcer disease is one of organic causes of chronic abdominal pain in children. Endoscopy is an important procedure for the diagnosis. However, more studies are needed to determine the causes and accurate prevalence of the ulcer.

Keywords: Chronic abdominal pain; Children; Endoscopy; Ulcer disease

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Introduction

Chronic abdominal pain is one of the most common clinical complaints for applying to the hospital in childhood, and defined as functional and organic [1,2]. The prevalence of organic causes was reported between 5% and 10% in the first epidemiological study performed by [3]. Making a diagnosis of functional abdominal pain can be a challenge, as it is unclear which further diagnostic tests are required to exclude an organic cause. The initial evaluation is still essential to rule out most organic causes and to make a true diagnosis. Diagnostic process should begin with a detailed history, physical examination and fundamental laboratory tests, and then, the Rome IV criteria is currently used for the diagnosis of functional abdominal pain disorders [4-6].

Ulcer disease diagnosis rate has increased especially by the common use of endoscopy while ulcer disease is considered as rare in children. However, the prevalence of ulcers differs among countries, and data on the prevalence of gastric or duodenal ulcers are also insufficient [7-10]. Particularly, more pediatric studies related to the prevalence of gastric and duodenal ulcer are needed. We need more studies to investigate the trend of ulcer and *Helicobacter pylori* (*H. pylori*) prevalence.

In this study, we aimed to investigate the frequency of peptic ulcer and the effects of *H. pylori* infection, gender, and age on peptic ulcer among patients with chronic abdominal pain. Besides, the value of endoscopy was investigated.

Materials and Methods

Between April 2007 and June 2015, a total of 800 patients with chronic abdominal pain who

Table 1: The relationship between age, gender, *H. pylori* infection and ulcer/ulce type.

Variable		Ulcer Positive n=84	Ulcer Negative n=716	p
Age (years)†		13.2 ± 3.9	12.0 ± 3.9	0.01
Gender††	Female	40 (47.6)	372 (52.0)	0.45
	Male	44 (52.4)	344 (48.0)	
H. Pylori††	Positive	57 (67.8)	394 (55.0)	0.03
	Negative	27 (32.1)	322 (44.9)	
Variable		**Duodenal ulcer (n=78)**	**Gastric ulcer (n=6)**	**p**
Age (years)†		13.5 ± 3.6	9.0 ± 5.4	0.01
Gender††	Female	38 (48.7)	2 (30.3)	0.68
	Male	40 (51.3)	4 (66.7)	
H. Pylori††	Positive	55 (70.5)	2 (33.3)	0.08
	Negative	23 (29.5)	4 (66.7)	

†Data is presented as mean ± standard deviation.
††Categorical variable is presented as frequency (percentage).

Table 2: Relationship between gender, *H. pylori* infection and ulcer/ulcer types in 10 years of age and older patients group.

Variable		Ulcer Positive n=68	Ulcer Negative n=511	P
Gender††	Female	35 (51.5)	284 (55.6)	0.5
	Male	33 (48.5)	227 (44.4)	
H. Pylori††	Positive	52 (76.5)	322 (63.0)	0
	Negative	16 (23.5)	189 (37.0)	
Variable		**Duodenal Ulcer n=66**	**Gastric Ulcer n=2**	**p**
Gender††	Female	34 (51.5)	1(50.0)	1
	Male	32 (48.5)	1(50.0)	
H. Pylori††	Positive	51 (77.3)	1(50.0)	0.4
	Negative	15 (22.7)	1(50.0)	

applied to pediatric gastroenterology, hepatology, and nutrition clinics were included in this study.

Initial evaluations were performed with a detailed history, physical examination and fundamental first step laboratory tests including complete blood count, peripheral blood smear, sedimentation rate, the level of AST, ALT and amylase, a urine analysis and culture, direct microscopic examination of stool, and abdominal ultrasound. Patients aged more than 18 years, with known chronic abdominal pain etiology as constipation, with complaints of diarrhea and dyspeptic symptoms after drinking milk, with a history of predisposing factors for peptic ulcer (eg, sepsis, aspirin, or non-steroidal anti-inflammatory ingestion), and other chronic diseases such as neurologic disorders were excluded.

Upper gastrointestinal endoscopy was performed in all patients if the initial evaluations were normal after informed consent was obtained, and endoscopic findings were noted; two esophageal, three antral and two duodenal biopsy specimens were obtained for histological examination, and one of the antral biopsies was used for the rapid urease test. Each specimen was stained with hematoxylin and eosin, and the histologic findings were described according to modified Sydney criteria [11].

Peptic ulcer was defined as the presence of active, healing, or scaring ulcer under endoscopy. *H. pylori* presence was screened for all patients. *H. pylori* infection was diagnosed when histology and at least one of 13C-urea breath test or urease test were positive.

Finally, the Rome III criteria had been used for the diagnosis abdominal pain related functional gastrointestinal disorders in the patients enrolled. "Abdominal pain related functional gastrointestinal disorders" has been changed to "functional abdominal pain disorders" by Rome IV committee [4]. This updating did not affect the results of our study.

Statistical analysis

The relationship between categorical variables was calculated by the Chi-square test. If expected frequencies were smaller than 5, Fisher-Exact test was used. Odds Ratio (OR) was calculated for significant relationships (95% Confidence Interval (CI)). Categorical variables were expressed as frequencies and percentages. Continuous variables were summarized as mean ± Standard Deviation (SD). For normally distributed data, Independent sample t test was used for group comparison. Cut off value for age was determined by Roc Curve Analysis. Logistic regression was analysed to determine risk factors for disease. Statistical analysis was performed with MedCalc version 10.3.0. The results were considered statistically significant if P values were less than 0.05. All reported p values were two-sided.

Results

The study included 800 patients. The mean (SD) age was 12.1 (3.9) years (range 3 to 18 years). The numbers of males and females were 388 (48.5%) and 412 (51.5%) with a mean (SD) age of 11.5 (4.0) and 12.6 (3.7) years, respectively.

All patients were admitted with the complaint of chronic abdominal pain. Of those, 347 had additional complaints: heartburn in 114 (32.8%), nausea and/or vomiting in 90 (25.9%), a bad taste in

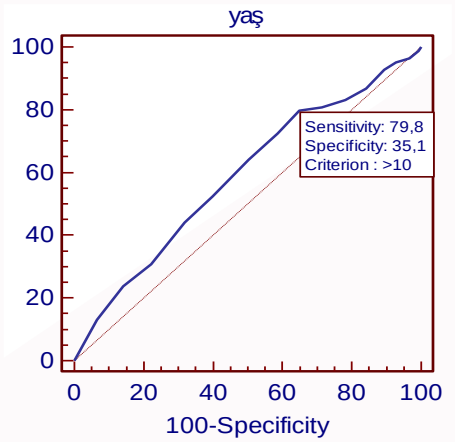

Figure 1: Cut off value for age. Age is a good indicator for the discrimination of patients with or without ulcer as a result of Roc Curve Analysis (Area under curve=0.588, 95% CI= 0.553-0.622, p=0.010).

mouth in 57 (16.4%), halitosis in 26 (7.5%), failure to thrive in 25 (7.2%), fatigue in 12 (3.4%), loss of appetite in 10 (2.9%), weight loss in 6 (1.7%), paleness in 4 (1.1%), and dysphagia in 3 (0.9%).

Among all patients, ulcer disease was identified in 84 (10.5%). Of those, 78 (9.7%) had duodenal ulcer and 6 (0.7%) had gastric ulcer. *H. pylori* were positive in 451 patients (56.3%) and negative in 349 (43.6%) patients. Of 451 patients with *H. pylori* positivity, 57 (12.6%) had ulcers. Of 349 patients with *H. pylori* negativity, 27 (7.7%) had ulcers. We assessed the relationship between the ulcer frequency and *H. pylori* infection, and this result indicated a potent relationship between *H. pylori* infection and the ulcer frequency (p=0.03). Ulcer was determined 1.7 times more frequently in patients with *H. pylori* positivity, compared to those with *H. pylori* negativity [Odds Ratio (OR)=1.7; 95% CI (1.07-2.79)]. We also analyzed the relationship between *H. pylori* infection and ulcer types. *H. pylori* was positive in 55 (70.5%) of 78 cases with duodenal ulcer. *H. pylori* was positive in 2 (33.3%) of 6 patients with gastric ulcer. There was a non-significant relationship between *H. pylori* infection and ulcer types (p=0.08).

In addition, we studied the relationship between sex and ulcer frequency. Of 84 patients with ulcer, 44 (52.4%) were males and 40 (47.6%) were females. Of 716 patients without ulcer, 344 (48%) were males and 372 (52%) were females, which indicated no relationship between ulcer frequency and sex (p=0.45). The relationship between ulcer types and sex was also evaluated. We found no relationship between the ulcer types and sex (p=0.68). There was a statistically significant difference between ulcer positive and negative groups in terms of age (p=0.01). At the same time, there was a statistically significant difference between ulcer types in terms age (p=0.006) (Table 1).

Logistic regression analysis was performed for ulcer and age. Age had a significant effect on ulceration (p=0.04). Each one-year increase of age caused a 1.1 fold increase in ulceration (OR=1.1; 95 % CI (1.01-1.14)). The cut-off point of age for ulcer was found to be over 10 years of age (area under the curve=0.588, 95% CI=0.553-0.622, p=0.010) (Figure 1).

When considering ulcer type, age affected duodenal ulceration significantly (p=0.009). Each one-year increase in age caused a 1.1 fold increase in the duodenal ulcer risk (OR=1.1, 95% CI (1.02-1.17)). For gastric ulceration age, sex and *H. pylori* positivity were not risk factors (p=0.15, p=0.52, p=0.59). There was a statistically significant relationship between *H. pylori* positivity and increased ulcer frequency at 10 years and older (p=0.03). In 10 years and older patients the relationship between ulcer types and *H. pylori* positivity was statistical insignificant (p=0.42) and we found no relationship between ulcer/ulcer types and sex (p=0.52, p=1.00) (Table 2). We observed no significant relationship between *H. pylori* positivity and increased ulcer frequency at younger than 10 years of age (p=0.74) and there was not a statistically significant relationship between sex and ulcer positivity, ulcer types (p=0.36, p=1.00) (Table 3).

Gross endoscopic findings of 800 cases were as follows: 375 (46.9%) normal, 322 (40.2%) with nodular gastritis, 14 (1.7%) with esophagitis, 5 (0.6%) with scalloped mucosa aspect of duodenum and 84 (10.5%) with ulcer disease.

Microscopic examination results were as follows: 192 (24%) normal, 451 (56.4%) with *H. pylori* positive chronic gastritis, 133 (16.6%) with chronic non-specific gastritis and/or duodenitis, 15 (1.87%) with esophagitis, 5 (0.62%) with celiac disease and 4 (0.5%) with giardiasis.

Among all patients, endoscopic and microscopic organic pathologies were identified in 608 (76%). Other 192 (24%) patients with completely normal findings were diagnosed with abdominal pain related functional gastrointestinal disorders, according to the Rome III diagnostic criterias.

Discussion

The pathophysiological mechanisms of chronic abdominal pain are clarifying and our knowledge is expanding. Although the importance of peptic ulcer disease among the organic causes of abdominal pain has been emphasized, the prevalence of ulcer

Table 3: Relationship between gender, *H. pylori* infection and ulcer/ulcer types in younger than 10 years of age patients group.

Variable		Ulcer Positive n=16	Ulcer Negative n=205	p
Gender††	Female	5 (31.3)	88 (42.9)	0.36
	Male	11 (68.7)	117 (57.1)	
H. Pylori††	Positive	5 (31.3)	72 (35.1)	0.74
	Negative	11 (68.7)	133 (64.9)	
Variable		**Duodenal Ulcer n=12**	**Gastric Ulcer n=4**	**p**
Gender††	Female	4 (33.3)	1(25.0)	1
	Male	8 (66.7)	3(75.0)	
H. Pylori††	Positive	4 (33.3)	1(25.0)	1
	Negative	8 (66.7)	3(75.0)	

shows variations between countries in the literature [9]. *H. pylori* is associated with antral gastritis and duodenal ulcer; however, there have been few data published in the literature to investigate the prevalence of peptic ulcer caused by *H. pylori* in children [9,12-14].

Our results have revealed that ulcer disease is an important organic cause in patients with chronic abdominal pain and *H. pylori* infection is an independent risk factor for ulcer disease. Probability of ulcer incidence is 1.7 times higher in patients with *H. pylori* positivity than those with *H. pylori* negativity. There are two European multicenter studies conducted on the incidence of ulcer disease in children [1,15]. Kalach et al. [15] reported ulceration in 10% and Oderda et al. [16] reported duodenal ulceration in 12.3% of cases with *H. pylori* infection. However, in the latest series from Russia ulcer reported in 35% versus 6.7% in European children. Uhlig et al. [17] determined ulcers in only 1% and suggested that peptic ulcer is a rare finding of *H. pylori*-positive children with abdominal pain. Tam et al. [14] found that peptic ulcer occurred in 6.9% cases with upper gastrointestinal symptoms. Thus, the prevalence of *H. pylori*-positive ulcers differed between countries and the difference was not completely explained by the prevalence of the infection in the studied population [9]. These results indicate that despite different *H. pylori* positivity frequencies, the rates of ulcers are reported to be similar. Peptic ulcus is not rare, and it should be investigated in children with chronic abdominal pain. Peptic ulcer disease should be kept in mind as an organic cause even if *H. pylori* are negative.

The studies from two different regions of Turkey reported the prevalence of peptic ulcer disease as 13.4% and 3.4% respectively [7,8]. We determined the prevalence as 10.5%. In the first study the number of subjects was fewer and the mean age was higher than that of our study, and the higher prevalence seems to be due to the inclusion of patients with a high probability of ulcer disease such as patients with gastrointestinal bleeding [7]. In the other study, although some clinical characteristics were similar with our study, the prevalence was much lower. Additionally, in that study ulcer symptoms were reported to be less prominent in children than in adults [8]. However, our results didn't confirm that. When a child with a chronic abdominal pain was evaluated carefully, and then underwent an endoscopy, the ulcer symptoms can not be mild nor can the rate be low. Different study populations and different study designs affect the results of the studies. That is why standard study designs should be developed to be used by all the researchers.

Macarthur et al. [18] suggested a mounting evidence for a relationship between *H. pylori* infection and antral gastritis and duodenal ulcer disease, conversely an inadequate evidence for gastric ulcer. Nonetheless, Kato et al. [19] suggested *H. pylori* were a definite risk factor for gastric ulceration. Bontems et al. [10] reported the prevalence of *H. pylori* in duodenal and gastric ulcer as 31.6%. Consequently, the effect of *H. pylori* infection on gastric and duodenal ulcer rates was reported differently. Our results revealed that *H. pylori* infection was an independent risk factor for duodenal ulcer, however, did not have a significant impact on gastric ulcer in all ages and genders. It is stated that gastric ulcer incidence is expected to be low in developed countries in which *H. pylori* prevalence is low [10]. In spite of highness of *H. pylori* prevalence in a region of a developing country in which this study performed, gastric ulcer incidence also determined to be low. These outcomes did not support the results of studies reporting an increase of gastric ulcer incidence. Additionally, age was a good indicator in determination of patients with or without ulcer. The increased rates of duodenal ulcer in 10 years and older patients with *H. pylori* colonization suggest that there is a need for a period before duodenal ulcer development. So it must be discussed whether the asymptomatic patients with *H. pylori* colonization should be treated or not. There is no consensus on the treatment of patients with chronic abdominal pain and *H. pylori* positiveness. In our previous study, we reported that the treatment significantly reduced the abdominal pain in patients with *H. pylori* infection [20]. Since this study demonstrates the role of *H. pylori* in duodenal ulcer development, the infection treatment modality seems to gain importance.

Our results revealed that the prevalence of idiopathic peptic ulcer in children is high. Bontems et al. [10] concluded a high proportion of children with idiopathic ulcers had no identified associated risk factor. It was suggested that further studies were needed to find a causal etiology in these patients such as another exogenous infectious agent, a gastric dysbiosis, mucosal defense mechanisms, and some intrinsic factors [21-24]. Whether there is a similar mechanism or not in children should be investigated. Male gender was also reported as a risk factor. The risk was explained with hormonal differences [25-27]. However, in our study gender had no effect on ulcer frequency and types. It may be possible that the declining prevalence of *H. pylori* unmasks patients with peptic ulcer disease unrelated to *H. pylori*, since it will help us to understand the etiology of ulcer disease [28,29]. Our knowledge in peptic ulcer may begin to resemble an iceberg. More studies on this issue are needed to determine other factors causing ulcer disease.

An inflammation of gastrointestinal mucosa may cause an increase in the intensity of the stimulus transmitted on brain-intestine axis or not should be investigated. This hypothesis is supported with recent physiological studies [30]. Faure et al. [30] have analysed the inflammatory cells in the colonic and gastric mucosa. They found that the patients with functional abdominal pain had variable degrees of inflammation; nevertheless, the location of inflammation was not specified, which is a drawback of this important study. However, the real clinical utility of such findings is not clear. Additionally, the Rome IV committee recommended being defined functional disorder subgroups and the role of upper gastrointestinal endoscopy [4]. Our results showed that the endoscopy is necessary for approach to chronic abdominal pain. However, more studies are needed if there is an importance of the microscopic findings in the differential diagnosis of organic and functional abdominal pain disorders.

Conclusion

Ulcer disease is an important organic cause of chronic abdominal pain. However, more studies are needed to show the causes and accurate prevalence of the ulcer disease. The other etiologic factors should be identified although *H. pylori* are still an important risk factor. Especially the intrinsic factors have not been explained satisfactorily. The importance of the microscopic findings in the differential diagnosis of chronic abdominal pain has not been defined yet. Endoscopic examination is an important procedure for the diagnosis of chronic abdominal pain in the selected patients.

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