Diagnostic yield of esophagogastroduodenoscopy in children with chronic abdominal pain

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Abstract

Introduction: Chronic abdominal pain (CAP) is one of the most common indications of esophagogastroduodenoscopy (EGD) in the pediatric population. However, there is not enough information about the diagnostic yield of EGD in children with CAP. We aimed to evaluate the diagnostic yield of EGD in children with CAP in the Eastern Black Sea region of Turkey.
Material and methods: The study included children (n = 372) who underwent EGD for the primary indication of chronic abdominal pain during an 18-month period. We collected data on demographic features (age, sex), clinical characteristics (alarm symptoms), and EGD results for each patient.
Results: Patients' mean age was 13 years (range: 4–17 years; mean ± SD: 12.65 ±3.39 years), and the majority were female (n = 234, 62.9%). Endoscopy was diagnostic in 209 patients (56.2%; 95% CI: 30.35–40.05%). The most common diagnosis was *Helicobacter pylori* gastritis (35.2%) followed by reflux esophagitis. Significantly greater diagnostic yield of EGD was determined in patients with alarm symptoms (65.1%) compared to those without (45.2%) (OR = 2.26, 95% CI: 1.49–3.44, p = 0.001).
Conclusions: We determined a high diagnostic yield of EGD in children with CAP. Although the diagnostic yield of EGD in the assessment of CAP was found to be higher in the presence of alarm symptoms, a significant number of children without alarm symptoms were also found to have gastrointestinal system pathology diagnosed by EGD.

Key words: children, abdominal pain, endoscopy.

Introduction

Chronic abdominal pain (CAP) is one of the most common indications of esophagogastroduodenoscopy (EGD) in the pediatric population. The CAP has a negative impact on the daily life of children and causes anxiety in parents. It is demonstrated by three or more bouts in at least a three-month period [1]. This symptom can also be an indicator of severe diseases that needs to be clarified [2]. Since most of the pediatric CAP was functional, EGD was not recommended in children with this type of pain [3, 4]. Particularly, in pediatric cases with normal abdominal examination and without alarm symptoms, the diagnosis of functional abdominal pain is likely without the need for further investigation [4, 5]. Moreover,

previous studies have shown that EGD has a low diagnostic yield in children with CAP (4%) [6]. However, the small sample size and disregard of specific histopathological findings such as reflux esophagitis or eosinophilic esophagitis as pathological in most of these studies might have undermined their power and reliability. In contrast to earlier research, wider-ranging studies conducted in recent years have shown that EGD has a rather high diagnostic yield of 35–38% in children with CAP [7–9].

In this study, we aimed to evaluate the diagnostic yield of EGD in children with CAP of unknown etiology in the Eastern Black Sea region of Turkey.

Material and methods

This prospective study was performed at the Kanuni Training and Research Hospital Pediatric Gastroenterology Department with 398 children with CAP who were 4–17 years old and undergoing EGD over a 16-month period. The hospital is a tertiary health centre in the Eastern Black Sea region of Turkey, which has a population of approximately 2.7 million (the population of those aged 4–17 is approximately 800,000). Following approval by the local ethics committee and with the explicit consent of patients and/or parents, the study was performed in accordance with the Declaration of Helsinki.

Subjects with previous known organic diseases (such as inflammatory bowel disease, celiac disease, or peptic ulcer), with a history of corticosteroid or nonsteroidal anti-inflammatory drug use, with psychiatric disorders and/or neurological diseases (such as cerebral palsy), or who had previously undergone gastrointestinal endoscopy were excluded from the study.

All patients enrolled were evaluated individually (UEA). Age, sex, height for age, duration of abdominal pain, presence of alarm symptoms, previous proton-pump inhibitor (PPI) use, presence of *Helicobacter pylori* and/or peptic ulcers in the family (in parents or siblings), and laboratory data (hemoglobin, platelet number, sedimentation, amylase, albumin and antitissue transglutaminase IgA (tTG-IgA)) were recorded for all subjects. Dysphagia, weight loss, chronic diarrhea (for more than 2 weeks), abdominal pain awaking the child from sleep (at least 25% of pain attacks awaking the child), persistent right upper quadrant pain, unexplained fever, persistent vomiting, retardation of growth (height < –2 SD for age), family history of inflammatory bowel disease (in parents or siblings), gastrointestinal bleeding (history, physical examination, or occult blood in stool), anemia (hemoglobin < 11 mg/dl), and elevation of erythrocyte sedimentation rate (ESR) (ESR > 20/h) were regarded as alarm symptoms [4, 10, 11].

Esophagogastroduodenoscopy was performed in all patients with alarm symptoms. However, it was also performed in children with CAP severe enough to significantly affect routine daily activities, who did not respond to the treatment administered (PPI), who had constipation that improved with treatment but without any remission in persistent pain in the epigastric region, and/or whose parents experienced serious anxiety even in the absence of alarm symptoms (social indication). However, patients undergoing EGD for the evaluation of elevated tTG-IgA (> 200 RU/ml) were not included.

Esophagogastroduodenoscopy procedures were performed by a pediatric endoscopist (UEA) in the endoscopy unit using an Olympus GIF-H180 device. Gross endoscopic findings such as peptic ulcer and erosion in the distal esophagus and stomach were regarded as pathological. Nonspecific findings such as hyperemia or increased or decreased vascularity were not considered pathological [12, 13].

At least two biopsies, from the esophagus, stomach (antrum) and the second part of the duodenum, were taken for all patients. Biopsy specimens were evaluated by two pathologists blinded to patients' clinical status and endoscopic findings (FGK, AL). Findings such as papillary elongation in the esophagus, basal cell hyperplasia, and an increase in intraepithelial neutrophils were evaluated in favor of reflux esophagitis [14]. These patients received PPI therapy (lansoprazole 1 mg/kg per dose twice daily) for 8 weeks, and their dietary habits were modified. Their symptoms resolved at the end of treatment; reflux esophagitis was regarded as the cause of CAP, and EGD was considered diagnostic. The presence of nonspecific histopathological changes such as reactive changes, edema, and mild inflammation was not regarded as pathological. Eosinophilia in the esophagus was defined as ≥ 30 eosinophils in one high-power field and/or observation of eosinophilic microabscesses [15]. In these cases, EGD was repeated subsequent to the administration of high-dose PPI (lansoprazole 1 mg/kg per dose twice daily) for 8 weeks. Persisting eosinophilia in the esophagus was regarded as eosinophilic esophagitis (EoE) [15]. Histopathological findings for gastric mucosa were assessed using the Sidney scoring system [16]. Inflammation was classified as mild, moderate, or severe depending on the density of lymphocyte and plasma cells in the lamina propria. Mild inflammation was not regarded as pathological. These patients received PPI therapy (lansoprazole 1 mg/kg per dose twice daily) for 8 weeks, and their dietary habits were modified. Their symptoms resolved at the end of treatment; gastritis was regarded as the cause of

CAP, and EGD was considered diagnostic. The presence of *H. pylori* infection was defined as the presence of *H. pylori* at antral biopsy and of positive rapid urease test [12, 13, 17]. When symptoms of the patient resolved and *H. pylori* stool antigen test became negative after the treatment of clarithromycin 15 mg/kg/day for 2 weeks, amoxicillin 50 mg/kg/day for 2 weeks and lansoprazole 1 mg/kg per dose twice daily for 4 weeks, then CAP was linked to *H. pylori* infection, and EGD was considered diagnostic. The detection of ≥ 30 eosinophils in the stomach and ≥ 25 eosinophils in the duodenum in at least five high-power fields subsequent to the exclusion of parasitic infections, *H. pylori* infection, celiac disease, inflammatory bowel disease, hypereosinophilic syndrome, malignity, and connective tissue diseases (Churg-Strauss syndrome etc.) was regarded as eosinophilic gastroenteritis (EG) [18].

Table I. Demographic characteristics of patients

Parameter	Value
Total patients, *n*	372
Gender, *n* (%):	
Female	234 (62.9)
Male	138 (37.1)
Age, mean ± SD (range) [years]	12.65 ±3.39 (4–17)
Duration of abdominal pain, mean ± SD (range) [months]	15.11 ±16.20 (3–120)
Patients using PPI, *n* (%)	32 (8.6)
Patients with constipation, *n* (%)	57 (15.3)
History of *H. pylori* infection and/or ulcer disease in family, *n* (%)	123 (33.0)
Patients with alarm symptoms, *n* (%):	
Elevated ESR	19 (5.1)
Anemia	25 (6.7)
Dysphagia	58 (15.5)
Persistent vomiting	21 (5.6)
Weight loss	32 (8.6)
Awakens from sleep	113 (30.3)
Growth failure	30 (8.0)
Chronic diarrhea	6 (1.6)
Rectal bleeding	9 (2.4)
Unexplained fever	2 (0.5)
Endoscopic-histopathological findings, *n* (%):	
H. pylori gastritis	131 (35.2)
Erosive gastritis	11 (2.9)
Gastric ulcer	7 (1.9)
Duodenal ulcer	23 (6.1)
Reflux esophagitis	32 (8.6)
Eosinophilic esophagitis	2 (0.5)
Eosinophilic gastroenteritis	2 (0.5)
Crohn's disease	1 (0.3)

Statistical analysis

Data were analyzed on SPSS 13.0 software (SPSS Inc., Chicago, IL). Descriptive statistics were presented as mean ± standard deviation (SD). Student's *t* test was used for normally distributed variables in two-group comparisons and the Mann-Whitney *U* test for non-normally distributed variables. The χ^2 test was used to compare categorical variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated between groups. Significance was set at $p < 0.05$.

Results

Esophagogastroduodenoscopy was performed on 398 children with CAP. Twenty-two patients from whom sufficient biopsy material could not be taken or with missing data were excluded from the study. Four patients exhibited tTG-IgA positivity (> 200 RU/ml). A total of 372 patients were thus finally enrolled. Patients' mean age was 13 years (range: 4–17 years; mean ± SD: 12.65 ±3.39 years), and the majority were female (*n* = 234, 62.9%). Mean duration of abdominal pain was 18 months (range: 3–120 months; mean ± SD: 15.11 ±16.20 months). Thirty-two (8.6%) patients had a history of PPI use for at least 1 week before presenting to our clinic. Mean length of PPI use was 4 weeks. Constipation was present in 57 (15.3%) patients. A history of *H. pylori* and/or peptic ulcers was present in the families of 123 (33.0%) patients (Table I). Thrombocytosis (> 4×10^5 K/µl) was detected in 32 (8.6%), whereas no amylase elevation (> 120 U/l) or hypoalbuminemia (< 3.5 g/dl) was detected in any patient. Alarm symptoms were present in 204 (54.8%) patients, of whom 90 (24.1%) exhibited two or more alarm symptoms. Alarm symptoms of patients are detailed in Table I.

Resolution of symptoms and negativity in the *H. pylori* stool antigen test occurred in 131 (87.3%) of the 150 patients in whom *H. pylori* gastritis was determined. Abdominal pain symptoms resolved after treatment in 11 (78.5%) of the 14 patients with erosive gastritis and 32 (82.0%) of the 39 patients with reflux esophagitis, and EGD was considered diagnostic in these patients. Symptoms resolved after treatment in all patients with peptic ulcer, and absence of ulcer was determined at control EGD. Eosinophilia was detected in the esophagus of 2 patients. These patients were treated with PPI for 8 weeks and then reevaluated by control EGD. Eosinophilia was found to be persisting in both patients after 8 weeks of PPI treatment. Thus these 2 patients received the diagnosis of eosinophilic esophagitis. Two other

patients were diagnosed with eosinophilic gastroenteritis. Symptoms of patients with eosinophilic esophagitis and gastroenteritis resolved after an elimination diet.

Endoscopy was diagnostic in 209 patients (56.2%; 95% CI: 30.35–40.05%). The most common diagnosis was *H. pylori* gastritis (35.2%) followed by reflux esophagitis. Abdominal pain, weight loss, and elevated ESR persisting over the previous 6 months were present in a 16-year-old girl diagnosed with Crohn's disease (Table I).

No correlation was determined between patients' age and sex and the diagnostic yield of the EGD procedure. In terms of the diagnostic yield of EGD, no difference was determined between subjects using or not using PPI, with or without constipation, with or without *H. pylori* infection and/or peptic ulcers in the family, or with or without thrombocytosis (Table II).

No significant difference in diagnostic yield of EGD was found when patients with alarm symptoms including elevated ESR, persistent vomiting, rectal bleeding, dysphagia and growth retardation were compared with patients without these symptoms. However, the diagnostic yield of EGD was greater in children with weight loss (p = 0.004, OR = 3.71, 95% CI: 1.49–9.26), anemia (p = 0.018, OR = 3.34, 95% CI: 1.22–9.11) or abdominal pain awaking the child from sleep compared to those without (p < 0.001, OR = 2.74, 95% CI: 1.70–4.44) (Table II).

No difference was observed between patients with or without alarm symptoms in terms of sex, age, duration of abdominal pain, PPI use or presence of *H. pylori* and/or peptic ulcer in the family (p > 0.05), whereas a higher rate of constipation constipation was determined in patients with alarm symptoms (p = 0.032). The diagnostic yield of EGD was 65.1% in patients with alarm symptoms and 45.2% in patients without alarm symptoms. Significantly greater diagnostic yield of EGD was determined in patients with alarm symptoms compared to those without (p = 0.001, OR = 2.26, 95% CI: 1.49–3.44) (Table III).

Discussion

In contrast to earlier research, recent studies have shown that EGD has a high diagnostic yield in children with CAP. Thakkar *et al.* determined a diagnostic yield for EGD in children with CAP of 38% [9]. Sheiko *et al.* determined endoscopic abnormality in 28.9% of children with CAP undergoing endoscopy and histopathological abnormality in 35.2% [8]. The diagnostic yield of EGD in children with CAP in our study was high with a rate of 56.2%. *Helicobacter pylori* (+) gastritis (35.2%) was the most common diagnosis, followed by reflux esophagitis (8.6%).

Table II. Comparison of EGD with diagnostic yield with EGD without diagnostic yield

Parameter	Diagnostic, *n* (%)	Nondiagnostic, *n* (%)	*P*-value
Gender:			
Male	74 (35.4)	64 (39.2)	0.329
Female	135 (64.6)	99 (60.8)	
Age [years]	12.87 ±3.39	12.25 ±3.37	0.741
Thrombocytosis:			
Present	19 (9.1)	13 (7.9)	0.463
Absent	190 (90.9)	150 (92.1)	
Constipation:			
Present	32 (14.8)	25 (15.3)	0.909
Absent	177 (85.2)	138 (84.7)	
PPI use:			
Present	17 (8.1)	15 (9.2)	0.586
Absent	192 (91.9)	148 (90.8)	
Alarm symptom:			
Present	133 (63.6)	71 (43.5)	0.015
Absent	76 (34.4)	92 (56.5)	
≥ 2 Alarm symptoms:			
Present	67 (32.0)	23 (14.1)	0.017
Absent	142 (68.0)	140 (85.9)	
Elevated ESR:			
Present	11 (5.2)	8 (4.9)	0.950
Absent	198 (94.8)	155 (95.1)	
Anemia:			
Present	20 (9.5)	5 (3.0)	0.018
Absent	189 (91.5)	158 (97.0)	
Dysphagia:			
Present	38 (18.1)	20 (12.2)	0.121
Absent	171 (81.9)	143 (87.8)	
Persistent vomiting:			
Present	12 (5.7)	9 (5.5)	0.882
Absent	197 (94.3)	154 (94.5)	
Weight loss:			
Present	26 (12.4)	6 (3.6)	0.004
Absent	183 (87.6)	157 (96.4)	
Awaking from sleep:			
Present	82 (39.2)	31 (19.0)	< 0.001
Absent	127 (60.8)	132 (81.0)	
Growth failure:			
Present	20 (9.5)	10 (6.1)	0.231
Absent	189 (91.5)	153 (93.9)	

ESR – erythrocyte sedimentation rate, PPI – proton pump inhibitor.

Table III. Comparison of patient characteristics, diagnostic yield and endoscopic abnormalities with respect to the presence of alarm symptoms

Parameter	Alarm symptoms (+) (*n* = 204)	Alarm symptoms (–) (*n* = 168)	*P*-value
Female, *n* (%)	133 (65.1)	101 (60.1)	0.268
Age, mean ± SD (range) [years]	12.70 ±3.40	12.60 ±3.38	0.748
Duration of abdominal pain, mean ± SD (range) [months]	13.94 ±16.25	16.01 ±15.60	0.368
Patients using PPI, *n* (%)	21 (10.3)	11 (6.5)	0.200
Patients with constipation, *n* (%)	39 (19.1)	18 (10.7)	0.032
History of *H. pylori* infection and/or ulcer disease in family, *n* (%)	71 (34.8)	52 (31)	0.513
Diagnostic yield, *n* (%)	133 (65.1)	76 (45.2)	0.001

PPI – proton pump inhibitor.

Some studies have reported that children manifesting CAP with alarm symptoms often have the functional type of CAP [10, 19]. Gijsbers *et al.* found that alarm symptoms were present in 59% of children with functional CAP [10]. Moreover, they indicated that alarm symptoms were useful in the diagnosis of significant diseases such as Crohn's disease but useless in the diagnostic process of functional CAP. In another study, Thakkar *et al.* diagnosed gastrointestinal system (GIS) pathologies by EGD with a high rate (39%) in children having CAP with alarm symptoms. However, in contrast to Gijsbers *et al.*, they diagnosed GIS pathologies by EGD in a considerable proportion (34%) of children with CAP and without alarm symptoms [9]. Furthermore, they reported diagnostic yields for EGD in the presence of two or more alarm symptoms but not with one [9]. In our study, we found that EGD has a high diagnostic yield in children having CAP with alarm symptom(s) compared to those without. Of note, we also detected GIS pathologies in 45.2% of children with CAP even in the absence of alarm symptoms.

Thakkar *et al.* diagnosed *H. pylori* gastritis by EGD in 8 (2.8%) of 290 children with CAP. However, in our study, *H. pylori* (+) gastritis was the most common pathology in children with CAP (35.2%). The prevalence of *H. pylori* infection in Europe is 6.5–31.0% [20–22], whereas it is reported at 53.0–66.3% in Turkey [23–26]. The most important risk factors for the spread of *H. pylori* infection are a low socioeconomic level, poor living and hygiene conditions, crowded conditions and intra-familial contact. The infection spreads from person to person through fecal-oral or oral-oral transmission [27]. The relation between *H. pylori* infection and CAP in children is still the subject of debate. Apart from peptic ulcer development, no proven association has been found between CAP and *H. pylori* infection [28–31]. In addition, some studies have reported that there is no improvement in abdominal pain or gastric inflammation following *H. pylori* eradication in children [32]. In contrast, the eradication of *H. pylori* infection has been recommended by certain reports in children with CAP living in endemic areas [27, 33, 34]. In Turkey, Ozen *et al.* identified *H. pylori* infection in 60.3% of children presenting with CAP [35]. Moreover, they observed resolution of CAP in a significant majority of children (87%) with the eradication of *H. pylori* infection. These findings suggest that *H. pylori* infection may be an important cause of CAP in children living in areas where this infection is endemic.

The second most common pathological finding in our study was reflux esophagitis (8.6%). The diagnosis of esophagitis has increased in recent years due to the increase in the prevalence of gastroesophageal reflux as well as to the improvements in diagnostic methods. Thakkar *et al.* reported that the rate of reflux esophagitis was 21% in their series of 290 children with CAP [9]. In that study, the symptom of CAP was resolved in 62% of the children with reflux esophagitis after anti-reflux treatment (PPI or H2 blockers). The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and the European Society of Gastrointestinal Endoscopy (ESGE) do not recommend EGD in cases of uncomplicated gastroesophageal reflux, whereas they suggest performing EGD in cases of chronic GERD to exclude other diseases or for surveillance of Barrett esophagus in pediatric patients [36]. In our study and, in similar previous studies, the frequency of reflux esophagitis was found to be considerably high in children presenting with CAP. Therefore endoscopy may be performed to exclude reflux esophagitis in selected pediatric patients with CAP.

Esophagogastroduodenoscopy is generally considered to be safe for all ages [37]. In a pediatric cohort study with a series of 345 endoscopic procedures (231 EGD alone, 26 colonoscopy alone,

44 combined EGD and colonoscopy), adverse events were reported in only 20 (5.8%) of the interventions (14 procedure-related, 6 anesthesia/sedation related) and none of the adverse events reported were fatal [38]. Despite the given low rate of adverse events during endoscopy, to minimize the complication rate, EGD should only be performed with appropriate indications. In the recent guidelines by the ESPGHAN and ESGE, EGD was recommended in the presence of alarm symptoms such as weight loss, persistent vomiting, retardation of growth, unexplained anemia, chronic diarrhea, dysphagia or gastrointestinal bleeding in pediatric patients [36].

In our study, even though findings such as histopathological reactive changes, edema and mild inflammation were not regarded as pathological, we determined a high diagnostic yield of EGD in children with CAP. Although the diagnostic yield of EGD in the assessment of CAP was found to be higher in the presence of alarm symptoms, a significant number of children without alarm symptoms were also found to have GIS disorders diagnosed by EGD. Additionally, in contrast to the studies from Europe and the US, the rate of *H. pylori* infection was found to be high among children with CAP in our study. However, our study was limited to children referred to the gastroenterology centre due to CAP. Our sample therefore represents only a small percentage of all children with CAP. Additionally, the need for biopsy to determine CAP-related GIS diseases including reflux esophagitis and *H. pylori* infection is controversial.

In conclusion, we suggest that EGD can be performed even in the absence of alarm symptoms in children having persisting CAP despite comprehensive clinical evaluation, laboratory investigation and appropriate empiric drug use. Because EGD is an invasive procedure, further wider-ranging studies are needed to establish when and under what conditions EGD should be used in children with CAP.

Conflict of interest

The authors declare no conflict of interest.

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