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Sex, Psychosocial Factors, and Reported Symptoms Influence Referral for Esophagogastroduodenoscopy and Biopsy Results in Children With Chronic Abdominal Pain

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Abstract

Objectives—To identify symptoms and psychosocial factors that predicted referral for esophagogastroduodenoscopy (EGD) and discriminated between patients with positive versus negative biopsy findings.

Patients and Methods—Children age 8 to 16 years old and parents completed validated questionnaires assessing gastrointestinal symptoms and psychosocial characteristics. Biopsy results of esophagus, stomach, and duodenum were reviewed.

Results—From the total sample of 461 patients (mean age 11.87 years, 62% girls), 127 (28%) underwent EGD with biopsy (mean age 12.1 years, 57% girls). Upper abdominal gastrointestinal symptoms predicted EGD referral, and psychosocial characteristics did not. From the total of 127 patients who underwent EGD, complete biopsy results were available for 124 patients and were negative at all sites for 34.7% of patients ($n = 43$), equivocal for 20.2% ($n = 25$), and positive at 1 or more sites for 45.2% ($n = 56$). Boys were more likely than girls to have positive biopsy results (56.6% vs 36.6%, $P < 0.03$) because of the higher rate of positive esophageal biopsy results (47.2% vs 26.8%, $P < 0.04$). Among boys, vomiting ($P < 0.02$) and family stress ($P < 0.04$) predicted positive esophageal biopsy findings. Among girls, depressive symptoms predicted positive biopsy findings ($P = 0.015$).

Conclusions—Upper abdominal symptoms, sex, stress, and depressive symptoms predict positive EGD biopsy findings in patients with chronic abdominal pain. Research on mechanisms linking these factors to mucosal damage in the gut is warranted.

Keywords

Biopsy; Depression; Sex; Inflammation; Stress; Esophagogastroduodenoscopy; Chronic abdominal pain

Chronic abdominal pain (CAP) is a frequent childhood symptom, occurring in 9% to 16% (1) of children and constituting 35% to 45% of referrals to pediatric gastroenterologists. Patients with CAP may present with a variety of upper and lower gastrointestinal complaints (eg, dysphagia, vomiting, nausea, bloating) and with anxiety, depression, and other symptoms that may be associated with stress. To rule out organic disease, the evaluation of patients with CAP often includes esophagogastroduodenoscopy (EGD). The most prominent symptoms leading to EGD referral in this patient group have not been described, to our best knowledge, and the correlation between patients' individual symptoms and histopathological findings is unknown. We are unaware of any pediatric studies to date that have prospectively investigated the relation of specific symptoms and psychosocial characteristics to objective findings obtained at each EGD biopsy site (esophagus, stomach, duodenum) in patients with CAP. Thus, the diagnostic utility of these factors in the evaluation of CAP has not been documented. Moreover, despite the higher risk of significant pathological changes observed in men compared with women undergoing EGD (2–4), pediatric studies have not examined potential sex differences in symptom reporting and psychosocial characteristics influencing EGD referral, or histopathological findings in patients with CAP.

This study had the following aims:

1. Identify patient symptoms and psychosocial characteristics that significantly predicted physicians' decisions to conduct EGD testing in patients referred to a pediatric gastroenterology clinic for evaluation of CAP
2. Describe histopathological changes at each biopsy site
3. Identify symptoms and psychosocial characteristics that significantly discriminated patients with positive biopsy findings overall and at each site from those without positive findings
4. Investigate sex differences in symptom reporting and psychosocial characteristics influencing referral for EGD, and subsequent biopsy findings

PATIENTS AND METHODS

Sample

The study was performed in the Pediatric Gastroenterology Clinic at Vanderbilt Children's Hospital, which attracts patients from Tennessee and adjacent states. The clinic is staffed by 9 board-certified pediatric gastroenterologists. The study population consisted of consecutive new patients referred for evaluation of abdominal pain of at least 3 months' duration. Patients were eligible for participation if they met the following criteria: primary presenting symptom of abdominal pain of at least 3 months' duration; no chronic illness, defined as any disease that has a prolonged course, does not resolve spontaneously, and rarely is completely cured (eg, diabetes, epilepsy, asthma); no known significant gastrointestinal disease (eg, Crohn disease, pancreatitis) by parent report at the time of referral; child and parent able to communicate in English; and age between 8 and 17 years.

Procedure

Parents of eligible patients were contacted by telephone several days before the child's scheduled clinic appointment to describe the study and to request that, if they were interested in participating, they arrive earlier than the scheduled appointment to complete the research protocol. Informed consent procedures for the questionnaire protocol were conducted at the clinic. Authorization to use/disclose protected health information was obtained in a separate consent that permitted use of the medical record for research purposes.

Children completed the questionnaires on the day of the clinic visit, before the medical evaluation. The questionnaires were administered by an interviewer in a separate room while the parent waited in the clinic waiting room. Responses to questionnaire items were recorded by the interviewer on printed questionnaires. Attending physicians did not have access to participants' responses to the research protocol.

Several months after the medical evaluation, the physician investigators reviewed the medical records to obtain information about the results of the children's medical evaluations and EGD with biopsy. Pathology review was performed on original slides. Reviewers were blinded to the children's clinical diagnosis.

Data were coded and entered into an electronic database. The confidentiality of all data was ensured according to current Health Insurance Portability and Accountability Act practices at Vanderbilt Children's Hospital. The study was approved by the Vanderbilt University Medical Center Institutional Review Board.

Gastrointestinal Symptoms

Patients' gastrointestinal symptoms were assessed with 10 items from the Children's Somatization Inventory (5), a self-report measure of symptoms experienced in the previous 2 weeks. Symptoms included difficulty swallowing, lump in the throat, vomiting, chest pain, nausea, abdominal pain, constipation, diarrhea, bloating, and "food making you sick." Patients rated the extent to which they had experienced each symptom during the previous 2 weeks, using a 5-point scale, ranging from 0 (not at all) to 4 (a whole lot). Ratings of each symptom were dichotomized according to the scoring procedure used by Little et al (6) and others, that is, by coding the symptom as "present" if patients rated it as "some," "a lot," or "a whole lot" and coding the symptom as "absent" if patients rated it "not at all" or "a little."

Psychosocial Characteristics

Depressive Symptoms—The level of children's depressive symptoms was assessed with the Children's Depression Inventory (CDI) (7), which contains 27 self-report items representing depressive symptoms that are rated on a 3-point scale and summed to obtain a total score. Reliability and validity have been well documented (8).

Activity Limitations—Children's self-reported difficulty in physical and psychosocial functioning caused by physical health during the previous 2 weeks was assessed by the Functional Disability Inventory (FDI) (9,10), a standardized measure with excellent validity and reliability.

Family Stressors—Accumulation of family stressors was assessed by parent report on the Family Inventory of Life Events (FILE) (11), which assesses 9 categories of family stress (eg, intrafamily conflict, illness, finances) and yields a single score representing the level of stress in the family during the previous year.

Biopsies

Endoscopy was performed, and biopsy specimens were obtained from esophagus, stomach, and duodenum. Biopsy results from the first EGD performed after the patient's initial medical evaluation were used. On average, 2.2 biopsy specimens were taken from each site (esophagus = 2.6, stomach = 2.0, duodenum = 2.1). Additional biopsy specimens (as many as 6 from 1 site) were taken if the endoscopic findings raised suspicion.

A pathologist blinded to the child's condition reviewed the biopsy slides and graded them. Her findings were compared with those of the initial pathology report. The 2 reports agreed

in 89% of the biopsies reviewed. In cases of disagreement, the final decision was made by an independent pediatric gastroenterologist.

Biopsy results at each site were scored as negative, equivocal, or positive. Negative scores, defined as no histopathological changes, were based on the following findings: for the esophagus, squamous mucosa without basal cell hyperplasia and no intraepithelial eosinophiles; for gastric antrum and fundus, normal gastric fundic or antral type mucosa; for the duodenum, normal villous architecture. Equivocal scores, defined as mild histopathological changes, were based on the following findings: for the esophagus, minimal or mild basal layer hyperplasia, mild vascular ectasia, and rare intraepithelial lymphocytes or eosinophiles; for gastric antrum or fundus, rare lymphoid aggregates; for duodenum, patchy mild villous blunting in duodenum with rare inflammatory cells. Positive scores, defined as significant histopathological changes, were based on the following findings: for the esophagus, marked basal layer hyperplasia, vascular ectasia, and numerous intraepithelial eosinophiles or lymphocytes; for gastric antrum or fundus, lymphoid aggregates; for duodenum, crypt hyperplasia, moderate or marked villous atrophy, or increased intraepithelial lymphocytes. Thus, each of the 3 sites (esophagus, stomach, and duodenum) was scored as negative, equivocal, or positive. The criteria for eosinophilic esophagitis were met if 20 eosinophils per high power field were found on esophageal biopsy.

In addition, a “composite score” was created to evaluate the overall diagnostic yield of EGD with biopsy regardless of underlying pathological process. For the composite score, each child’s histopathological findings were scored as negative when all of the sites (esophagus, stomach and duodenum) yielded negative results, as positive when at least 1 site (esophagus, stomach or duodenum) in that child yielded positive results, and as equivocal when the results were equivocal at 1 or more sites and not positive at any site. This composite score was used for general description of the overall diagnostic yield of the EGD with biopsy and for initial comparisons with psychosocial characteristics.

Further analyses were done by use of the original histopathological scoring (negative, equivocal, positive) for each anatomic site (esophagus, duodenum, stomach) separately. The equivocal group constituted a separate entity and was not included in the positive or negative group. Review of pre-EGD treatment regimens was performed to assess possible influences on histology results. Data were available for 114 patients from the group who underwent endoscopy. Before endoscopy, 35 (31%) patients were using histamine receptor antagonists, 47 (41%) were using proton pump inhibitors, and the remaining 32 (28%) were receiving various other medications (eg, anticholinergics, antihistaminics) without substantial relief.

Data Analysis

Data were first inspected for normality and heteroscedasticity. Means and standard deviations on all variables were calculated for the total sample and by sex. Descriptive statistics for the total sample were calculated for the following variables: age, symptoms reported, FDI, CDI, and FILE. These variables were then evaluated by EGD status (performed/not performed), composite biopsy results (positive, equivocal, negative), and biopsy results by site. Sex differences were assessed in all of the analyses. Categorical variables (EGD performed/not performed, sex, and biopsy) were evaluated by the Pearson χ^2 test or the Fisher exact test, and logistic regression was used for comparisons by age, FILE, FDI, and CDI. Continuous variables (CDI, FILE, FDI) in more than 2 categories (ie, biopsy results) were evaluated by the Kruskal-Wallis test because of their nonparametric nature. Pairwise comparisons for the nonparametric data were performed by the Wilcoxon rank sum

test and by applying the Bonferroni correction. All of the analyses were performed with the STATA 9.0 software package.

RESULTS

Characteristics of Total Sample

Demographics—The sample consisted of 461 consecutive patients who met eligibility criteria. The mean age was 11.87 years (SD = 2.5 y) and the majority (62%) were girls and white (97%). Ages did not differ significantly between girls (mean 11.95 y, SD 2.6) and boys (mean 11.75, SD 2.3).

Gastrointestinal Symptoms—Table 1 shows, for the total sample and by sex, the percent of patients reporting each gastrointestinal symptom during the 2 weeks before the clinic visit. In comparison with boys, girls reported significantly higher rates of bloating and food intolerance.

Psychosocial Characteristics—Depressive symptoms on the CDI were significantly higher for girls than for boys (mean 10.0 vs mean 8.8, $P < 0.01$), and girls also had higher levels of disability than did boys on the FDI (mean 0.86 vs mean .61, $P < 0.002$). The level of family stress did not differ by the child's sex.

Factors Associated with EGD Referral

From the total sample of 461 children, 127 (28%) underwent EGD with biopsy. Patients who underwent EGD with biopsy had a mean age of 12.1 years (SD 2.45), and 57% were female. Girls and boys who underwent EGD did not differ significantly by age (for girls, mean age 12.4 y, SD 2.6; for boys, mean age 11.7 y, SD 2.1).

Gastrointestinal Symptoms—The severity of upper abdominal symptoms (expressed as a mean upper abdominal symptom severity score) was significantly higher in children who underwent EGD than in those who did not undergo EGD (12.39 vs 10.78, $P = 0.02$). To identify specific symptoms associated with EGD referral, we compared the frequency of each gastrointestinal symptom for patients with and without EGD as a group and then by sex (ie, girls with vs without EGD, boys with vs without EGD). For the total sample, EGD performance was significantly more likely for those who reported vomiting, nausea, and "food making you sick" ($P < 0.05$).

Among girls, EGD performance was more likely for those who reported vomiting (27% vs 15%, $P < 0.01$), nausea (84% vs 53%, $P < 0.01$), and "food making you sick" (53% vs 44%, $P < 0.02$). Among boys, EGD performance was more likely for those who reported lump in the throat (22% vs 11%; $P < 0.03$) and difficulty swallowing (22% vs 8%; $P < 0.01$).

Psychosocial Characteristics—There was no statistical difference between patients with and without EGD by age or by level of functional disability, depressive symptoms, or family stress.

Biopsy Results Overall and at Each Site

From the total of 127 patients who underwent EGD with biopsy, 3 patients were excluded for incomplete data, leaving 124 patients with biopsy results for evaluation. The mean time from the first visit in our clinic to the first EGD was 37.7 days (range, 2–217 days from the first visit).

The overall diagnostic yield regardless of site undergoing biopsy (using the “composite score”) was negative in 34.7% of children ($n = 43$) and positive in 45.2% ($n = 56$). In the remaining 20.2% ($n = 25$), biopsy results were equivocal at 1 or more sites and not positive at any site. Overall, boys were significantly more likely than girls to have a positive composite biopsy score (56.6% vs 36.6%; $P < 0.03$).

Table 2 shows biopsy findings by site and sex for all patients who underwent EGD. Analysis by χ^2 test indicated a significant interaction between sex and biopsy findings in the esophagus ($P = 0.043$), with boys having a higher rate of positive esophageal biopsy results (47.2%) in comparison with girls (26.8%; $P < 0.04$), as shown in Fig. 1.

Of those whose esophageal biopsy results were positive ($n = 44$), clinical diagnoses included reflux esophagitis in 37 cases, Crohn disease in 1 case, and no definite clinical diagnosis in the remaining 6 cases. Of the 37 children with clinical diagnoses of reflux esophagitis, 6 had biopsy findings consistent with eosinophilic esophagitis. Boys were twice as likely as girls to have eosinophilic esophagitis ($n = 4$ vs $n = 2$).

Gastrointestinal Symptoms Predictive of Biopsy Results Overall and at Each Site

Vomiting was the only symptom that significantly predicted a positive composite biopsy finding among boys ($P < 0.02$), but it was not a significant predictor of a positive composite biopsy finding among girls. This finding was due to a sex difference in the association of vomiting with esophageal biopsy results, as shown in Fig. 2. Among boys who reported vomiting, 73% had a positive esophageal biopsy finding. By contrast, among girls who reported vomiting, only 21% had a positive esophageal biopsy finding.

Psychosocial Characteristics Predictive of Biopsy Results Overall and at Each Site

Higher levels of depressive symptoms on the CDI predicted a higher probability of a positive composite biopsy score ($z = -2.805$; $P = 0.005$) and an equivocal composite biopsy score ($z = -1.92$; $P = 0.05$) in girls. The mean CDI scores for girls were 7.4, 11.4, and 11.7 for girls with negative, equivocal, and positive biopsy findings, respectively, as shown in Fig. 3. This finding was driven by the association of increased CDI scores with increased esophageal damage in girls ($\chi^2 = 10.853$; $P = 0.004$).

Higher levels of family stress on the FILE predicted a higher probability of a positive composite biopsy score in boys ($z = -2.144$; $P = 0.032$). The mean FILE scores were 3.8, 5.6, and 6.9 for boys with negative, equivocal, and positive biopsy findings, respectively, as shown in Fig. 4. This finding was driven by the association of increased family stress with positive esophageal biopsy findings ($z = -2.08$, $P = 0.03$). The level of perceived disability did not predict biopsy scores for boys or girls.

DISCUSSION

There is an ongoing discussion regarding the use of EGD in children with CAP, with some arguing that it should be limited. Guidelines published by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (12,13) identified alarm symptoms more likely to be found in children whose pain is associated with organic disease. However, many children without identifiable organic disease present with symptoms similar to those of peptic ulcer disease, and their conditions are evaluated further with EGD in the tertiary care setting. Factors associated with referral for EGD and factors that predict positive biopsy findings in pediatric patients with CAP have not been identified empirically.

Our first aim was to assess the symptoms and psychosocial characteristics associated with the EGD referral. In this study of consecutive patients evaluated for CAP, 28% were

referred for EGD. In the only other published study of which we are aware, Croffie et al (14) reported a higher referral rate (49%), perhaps because the sample was younger and included preschoolers. In our sample, upper abdominal symptoms significantly predicted referral for EGD.

Dyspeptic symptoms were most predictive of EGD referral for girls, whereas esophageal symptoms were most predictive of EGD referral for boys. Scores on psychosocial measures (depressive symptoms, disability, family stress) did not significantly predict EGD referral. However, we cannot rule out the possibility that the combination of upper abdominal symptoms, psychosocial variables, and other factors (eg, insurance status) influenced physicians' decisions to refer patients for EGD.

Biopsy results were positive at 1 or more sites for 45% of those referred for EGD, with boys being significantly more likely (57%) than girls (37%) to have positive histopathological findings at 1 or more sites. The overall diagnostic yield in our sample was similar to that reported by Kokkonen et al (15) (45%) and Thakkar et al (16) (46%) but higher than that reported by Hyams et al (17) (38%). The higher rate of positive biopsy findings among boys in our sample is consistent with a recent report by Thakkar et al (16), based on a cross-sectional PEDS-CORI database review of 727 patients, that male patients with abdominal pain were more likely to have positive diagnostic findings from EGD procedures.

When the site of biopsy was taken into account, we found that positive histopathological findings in our sample were overrepresented in the esophagus (35%) compared with the stomach (13%) and duodenum (3%). Moreover, the rate of positive esophageal biopsy findings was significantly higher in boys (47%) than in girls (27%). In addition, boys were twice as likely as girls to have histopathological evidence of eosinophilic esophagitis. This finding may be explained in part by the fact that in our sample, esophageal symptoms predicted EGD referral in boys but not in girls. However, a higher rate of eosinophilic esophagitis in male patients has previously been observed in adult (18) and pediatric (20–22) populations.

The higher rate of positive esophageal biopsy findings in comparison with other sites (stomach, duodenum) is again similar to the study by Thakkar et al (16) of patients with CAP. Other pediatric studies (15,17,19) reported a higher rate of positive biopsies in the stomach and duodenum. This discrepancy could be due to differences in patient population. For example, Hyams et al (17) focused on adolescent patients with dyspepsia, whereas our sample consisted of children with chronic abdominal pain refractory to medication.

Previous studies of patients with CAP have not investigated the utility of patient-reported symptoms in predicting EGD biopsy results. We found that vomiting significantly predicted positive biopsy findings, but only for boys. This finding may be due to differences in reporting of vomiting or a possible increased prevalence of reflux in boys. Further study with comparisons of gastric pH by sex is warranted. However, these findings suggest that boys with CAP who report vomiting should be referred for EGD with biopsy.

A unique feature of this study was the prospective examination of the relation of children's depressive symptoms and family stress to their EGD biopsy results. Among girls, increased depressive symptoms significantly predicted a positive esophageal biopsy finding. Among boys, increased family stress significantly predicted a positive esophageal biopsy finding.

The mechanism linking psychosocial variables such as depression and stress to gut inflammation is not well described. However, it is known that stress disrupts mucosal secretory and barrier functions in the gut (20,21), permitting penetration of antigens and initiating inflammatory responses. Activation of the inflammatory response system, in turn,

provokes neuroendocrine and brain neurotransmitter changes that are interpreted by the brain as stressors, and may contribute to the development of depression (22). Once depression develops, it enhances the activation of the innate immune system (23). This inflammatory response system activation model (24) may thereby explain the increased rate of positive histopathologic findings in girls with increased depressive symptoms and boys with increased family stress. Additional research is needed to replicate our finding linking depression and stress to histopathological damage in pediatric patients and to identify mechanisms that may explain this association.

Although increased depressive symptoms did not increase the referral for EGD in girls, higher depression was associated with positive biopsy results for those girls who were referred for biopsy. If these findings are replicated, it suggests that increased depressive symptoms in girls should be considered in the decision process regarding EGD referral for girls.

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FIG. 1.
Percentage of patients with negative, equivocal, or positive esophageal biopsy results by sex.

FIG. 2.
Esophageal biopsy results by sex for patients who reported vomiting.

FIG. 3.
Comparisons of the median depressive symptom scores and composite biopsy score by sex.

FIG. 4.
Comparisons of the median family stress scores and composite biopsy score by sex.

TABLE 1

Sex differences in reporting each gastrointestinal symptom in the preceding 2 weeks

	Males (n = 174), no. (%)	Females (n = 287), no. (%)	Total (N = 461), no. (%)	P
Pain in stomach or abdomen	128 (73.6)	230 (80.1)	358 (77.7)	0.100
Nausea or upset stomach	121 (69.6)	215 (74.9)	336 (72.9)	NS
Food making patient sick	58 (33.3)	132 (46.0)	190 (41.2)	0.007
Feeling bloated/gassy	43 (24.7)	98 (34.2)	141 (30.6)	0.033
Constipation	49 (28.2)	79 (27.5)	128 (27.8)	NS
Loose stools/diarrhea	52 (29.9)	72 (25.1)	124 (26.9)	NS
Pain in heart or chest	36 (20.7)	60 (20.9)	96 (20.8)	NS
Vomiting	34 (19.5)	52 (18.1)	86 (18.7)	NS
Difficulty swallowing	22 (12.6)	36 (12.5)	58 (12.6)	NS
Lump in throat	25 (14.4)	29 (10.1)	54 (11.7)	NS

TABLE 2

Sex differences according to biopsy site and biopsy finding

		Males, no. (%)	Females, no. (%)	Total (%)	P
Esophageal	Negative	16 (30.2)	35 (49.3)	51 (41.1)	0.043
	Equivocal	12 (22.6)	17 (23.9)	29 (23.3)	
	Positive	25 (47.2)	19 (26.8)	44 (35.5)	
Gastric	Negative	44 (83.0)	59 (83.1)	103 (83.1)	0.950
	Equivocal	2 (3.8)	2 (2.8)	4 (3.2)	
	Positive	7 (13.2)	10 (14.1)	17 (13.7)	
Duodenal	Negative	48 (90.6)	67 (94.4)	115 (92.7)	0.414
	Equivocal	(3.8)	3 (4.2)	5 (4.0)	
	Positive	(5.7)	1 (1.4)	4 (3.2)	