Red Flags in Children with Chronic Abdominal Pain and Crohn's Disease–A Single Center Experience

Khalil El-Chammas, MD[1], Angela Majeskie, MS[1], Pippa Simpson, PhD[2], Manu Sood, MD[1], and Adrian Miranda, MD[1]

Objective To compare history and symptoms at initial presentation of patients with chronic abdominal pain (CAP) and Crohn's disease (CD). Red flags are used to help determine which patients with CAP are likely to have an underlying disease such as CD. However, red flags have not been validated and pediatric studies are lacking.

Study design Patients seen in the outpatient Pediatric Gastroenterology Clinic at Children's Hospital of Wisconsin between 2005 and 2008 prospectively completed a demographic, history, and symptom questionnaire. Patients with abdominal pain for at least 1 month and no evidence of organic disease were compared with patients diagnosed with CD confirmed by mucosal biopsies.

Results Data were collected on 606 patients (128 with CD and 478 with functional gastrointestinal disorders). Patients with functional gastrointestinal disorders had more stressors ($P < .001$), were more likely to have a positive family history of irritable bowel syndrome, reflux, or constipation ($P < .05$), were more likely to have vomiting but less likely to have hematochezia, weight loss, and problems gaining weight ($P < .05$); wake from sleep and joint pain were no different between groups. Anemia, hematochezia, and weight loss were most predictive of CD (cumulative sensitivity of 94%).

Conclusion The presence of anemia, hematochezia, and weight loss help identify patients with CAP who require further work-up and referral to a pediatric gastroenterologist. Furthermore, waking from sleep or joint pain occurred similarly between groups and should not be considered as "red flags." *(J Pediatr 2013;162:783-7)*.

Pain associated functional gastrointestinal disorders (FGIDs), including irritable bowel syndrome (IBS), functional dyspepsia, and functional abdominal pain affect a large percentage of children. The hallmark of these disorders is chronic abdominal pain (CAP) that is intermittent or constant without any evidence of anatomic, metabolic, infectious, or inflammatory pathology.[1] A community based study demonstrated that 38% of children experience abdominal pain weekly, and 23% of them miss school for 2 days on average.[2] Up to 89% of pediatric patients with CAP are diagnosed with a functional disorder that results in a substantial social and economic burden.[3,4]

Children with FGIDs have also been shown to suffer from comorbid psychological conditions including stress and anxiety.[5,6] Moreover, it has been suggested that a positive family history of FGIDs increases a child's risk for developing such disorders.[7] Unlike organic causes of abdominal pain, the absence of valid or accurate biomarkers for FGIDs renders it a diagnosis of exclusion after organic causes have been ruled out. Clinicians and researchers have previously relied on symptoms to identify patients with FGIDs, and criteria such as Rome III were developed to aid clinicians in making a positive symptom diagnosis and reduce excessive and often unnecessary diagnostic testing.[8,9] Unfortunately, most clinicians do not feel comfortable simply relying on the criteria or are unaware that they exist.[10,11] Excluding organic causes of CAP remains a challenge for pediatricians, particularly given the heterogeneity of FGID symptoms, as well as reporting disparities among patients and parents.[12,13]

In pediatric patients with CAP, Crohn's disease (CD) is often considered in the differential diagnosis and is often missed because of the nonspecific nature of the intestinal and extra-intestinal symptoms that often overlap with FGIDs.[14-16] Identifying certain characteristics or "red flags" that can assist the pediatrician in detecting CD in patients with abdominal pain would be important because it could limit unnecessary diagnostic testing in those with FGIDs and potentially prevent a delay in the diagnosis of CD. The weight of such "red flags" in relation to FGIDs in children has not yet been reported.

Our aims were to compare the clinical characteristics and red flags in patients with FGIDs to those with CD. Specifically, we hypothesized that patients with pain associated FGIDs have different clinical characteristics than patients with CD, and only some of the commonly used "red flags" are useful in differentiating FGIDs from CD.

AUC	Area-under-the-curve
CAP	Chronic abdominal pain
CD	Crohn's disease
CHW	Children's Hospital of Wisconsin
FGID	Functional gastrointestinal disorder
IBS	Irritable bowel syndrome
PPV	Positive predictive value
ROC	Receiver operating characteristic

From the [1]Division of Pediatric Gastroenterology, Department of Pediatrics, Medical College of Wisconsin; and [2]Department of Pediatrics, Section of Quantitative Health Sciences, Medical College of Wisconsin, Milwaukee, WI

The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2012.09.014

Methods

Patients presenting to the outpatient Pediatric Gastroenterology clinic, at the Children's Hospital of Wisconsin (CHW), for evaluation of abdominal pain between 2005 and 2008 prospectively completed a detailed demographic, history, and symptom questionnaire. The questionnaire was filled out at the first visit by all families and included specific questions regarding clinical symptoms, family history, past medical history, and social history including stressors. Additional data regarding demographics, symptom history, blood tests, mucosal biopsies, and follow-up visits were obtained retrospectively from systematic chart reviews. Patients with abdominal pain for at least 1 month and no evidence of organic disease were considered to have FGIDs and were included in the study. Only patients with confirmed CD by bowel mucosal biopsies were included in the study. In addition to biochemical work-up in all patients diagnosed with FGIDs, diagnostic evaluation also included upper endoscopy in 41% and colonoscopy in 32%. Mucosal biopsies were reviewed retrospectively and were histologically nondiagnostic in all patients who underwent endoscopy. The remaining patients who did not undergo endoscopy had a normal biochemical work-up and did not have a change in their FGID diagnosis after an average of 2-year follow-up. Patients with organic disorders other than CD such as eosinophilic esophagitis, peptic ulcer disease, pancreatitis, cystic fibrosis, lactose intolerance, celiac disease, and ulcerative colitis, were excluded from this study. The human research Institutional Review Board at CHW approved this study.

Blood tests in both patients with FGIDs and those with CD included complete blood count, albumin, asparate aminotransferase, alanine aminotransferase, and erythrocyte sedimentation rate. Values were considered normal or abnormal based on established norms used by CHW laboratory based on age.

Data Analyses

Age is summarized as the median and IQR because the data are skewed. Patients with FGIDs and CD were compared with a non parametric Mann–Whitney test. The χ^2 analysis was used to evaluate the significance of differences in reported history and the symptoms between patients with FGIDs and CD. Tree analysis was performed using the Gini method for classification (optimization function). A classification tree optimizes a function, which aims to make each subgroup different from the other subgroups. It enables identification of the interactive association of variables with the outcome of interest in a nonparametric fashion. All 29 variables were included, the maximum number in a node for splitting was 15, and the minimum number in any node was 5. Twenty percent of cases were selected for validation (test set), and the remaining data were used to develop a model (development set). Bootstrapping of 10 trees with 10% excluded each time, rather than pruning, was used to select an optimal tree. Sensitivity for each level of the tree is provided. A receiver operating characteristic (ROC) curve with an area-under-the-curve (AUC) summarizes the predictive value of the tree. An AUC of 1 would be best indicating 100% sensitivity and 100% specificity. An AUC of 0.5 can be obtained by chance. Sensitivity and specificity is provided for all combinations of the top 3 predictors in the tree. Statistical analysis was performed with SPSS v. 19 (SPSS Inc, North Carolina) and Salford Systems CART (Salford Systems, San Diego, California). An unadjusted P value of $<.05$ was considered significant.

Results

A total of 606 patients were included in this study. There were 478 patients with FGIDs and 128 patients with CD. The median (IQR) age at diagnosis of FGIDs patients was 11 (9-14) years compared with 13 (12-15) for patients with CD, $P < .001$. There were more females among patients with FGIDs (65%) than CD (41%), $P < .001$. The FGID population included: Caucasian 404 (85%), African American 23 (5%), Hispanic 15 (3%), and other 36 (7%). The population with CD included: Caucasian 107 (84%), African American 13 (10%), Hispanic 1 (1%), and other 7 (5%).

Patients with FGIDs identified stressors related to school, social, or family more often than patients with CD ($P < .001$; Figure 1). Similarly, headaches were more common in patients with FGIDs ($P < .001$). Compared with CD, patients with FGIDs more commonly had a positive family history of IBS ($P = .030$), reflux ($P = .044$), or constipation ($P = .032$) (Figure 2).

Patients with FGIDs had a lower OR of experiencing hematochezia, weight loss, and problems gaining weight, and had a higher OR of experiencing vomiting, compared with patients with CD ($P < .001$) (Figure 3).

Tree analysis of FGIDs and patients with CD involved 29 variables including erythrocyte sedimentation rate, sex, race, pain causing waking from sleep, abdominal pain location (upper and lower), number of stools per day, hematochezia, soiling, vomiting, headache, fever, changes in weight (including weight lost, no weight loss, loss up to 5 pounds, loss up to

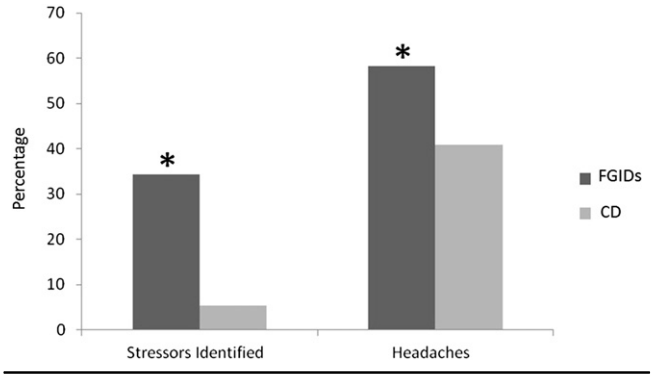

Figure 1. Bar graph showing percentage of FGIDs and CD patients that identify stressors. *$P < .05$.