High Prevalence of Nausea in Children With Pain-Associated Functional Gastrointestinal Disorders: Are Rome Criteria Applicable?

Katja Kovacic, Sara Williams, B U.K. Li, Gisela Chelimsky, and Adrian Miranda

ABSTRACT

Objectives: The aim of the study was to determine the prevalence of nausea in pediatric patients with pain-associated functional gastrointestinal disorders (FGIDs), examine the effect on social and school functioning, and examine the applicability of pediatric Rome III criteria.

Methods: A total of 221 pediatric patients (6–18 years of age) with chronic abdominal pain prospectively completed a demographic, history, and gastrointestinal symptom questionnaire adapted from the Questionnaire on Pediatric Gastrointestinal Symptoms (QPGS). The 6-item, revised Pediatric Migraine Disability Assessment Score tool was used to assess the effect of symptoms on school, home, and social disability. Rome III criteria were applied to all subjects.

Results: A total of 183 patients with pain and nausea for a minimum of 2 months were identified. Ninety-six patients were studied after excluding those with vomiting and/or organic disease. Among these, 53% had nausea at least 2 times per week and 28% experienced daily nausea. Frequency of nausea was significantly correlated with poor school and social functioning, and uniquely predicted social disability beyond pain. Although 87% met adult Rome criteria for functional dyspepsia, only 29% met corresponding pediatric Rome criteria. Additionally, 22% met the criteria for irritable bowel syndrome (IBS)-diarrhea, 13% for IBS-constipation, 13% for abdominal migraine, and 31% were classified as having functional abdominal pain. Pediatric IBS-diarrhea and IBS-constipation overlapped in 5% of patients.

Conclusions: Nausea is a prevalent symptom in patients with pain-associated FGIDs and correlates with poor school and social functioning. There is substantial overlap among FGIDs in children with nausea.

Key Words: chronic abdominal pain, functional gastrointestinal disorders, nausea, Rome criteria

(Pediatric functional gastrointestinal disorders (FGIDs) are common among children and adolescents. They represent a diagnostic challenge for pediatricians and gastroenterologists because no biomarker exists and symptoms are often interrelated

Received January 8, 2013; accepted April 6, 2013.

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The authors report no conflicts of interest.

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DOI: 10.1097/MPG.0b013e3182964203

Pain-associated FGIDs include functional abdominal pain (FAP), irritable bowel syndrome (IBS), functional dyspepsia (FD) and abdominal migraine (AM). These disorders can present with a combination of chronic or recurrent symptoms and abdominal pain that is not explained by structural or biochemical abnormalities (7,8). Children with FGIDs have poorer psychosocial functioning than their healthy counterparts and report similar quality-of-life scores to children with inflammatory bowel disease (4). The effect on quality of life and the diagnostic uncertainty of these disorders make them challenging to health care providers, patients, and families. Our understanding of FGIDs has evolved in the last several years and a considerable effort has been made to develop criteria that will allow clinicians to make a diagnosis of FGIDs using specific symptom patterns. Pediatric Rome III criteria were developed as a symptom-based classification tool to more accurately diagnose FGIDs in both adults and children (2). The pediatric criteria were developed much later and often involve different criteria for the same disorder described in adults. Although the criteria for IBS and FAP are similar in both adults and children, FD criteria are significantly different. FD in adults includes symptoms such as postprandial fullness, early satiety epigastric pain, or burning without evidence of structural disease that is likely to explain the symptoms. In children, however, the criteria are limited to persistent or recurrent pain or discomfort centered in the upper abdomen that is not relieved by defecation or associated with the onset of a change in stool frequency or stool form. As in all other FGIDs, the criteria exclude any inflammatory, anatomic, metabolic, or neoplastic process that explains the symptoms. It is important to point out these differences because many children present with the symptoms that are included only in the adult FD criteria. Although abdominal pain is central to many of these disorders, other symptoms such as nausea, headache, and fatigue can add substantial burden.

Chronic nausea in pediatric patients with FGIDs can be disabling and is a symptom that is poorly described in the scientific literature. The absence of a specific scale or measurable sign in children likely leads to the uncertainty in assessment and management of nausea. To our knowledge, there are no studies that describe the prevalence of nausea and its effect on functioning in pediatric patients with pain-associated FGIDs. More studies in children are clearly needed because the lack of evidence may have hampered the development of the pediatric Rome criteria. Although chronic idiopathic nausea is a separate category in the adult Rome III classification (5), no similar category exists for children. We hypothesized that there is a high prevalence of nausea in children with FGIDs and that this could negatively affect social and school functioning.

Our aims in the present study were to examine the prevalence of nausea and other associated symptoms in children with pain-associated FGIDs, to assess the effect of nausea on childhood social...
and school functioning, and to examine the applicability of pediatric and adult Rome III criteria in patients with nausea.

METHODS

Subject Selection

Participants included new pediatric patients ages 6 to 18 years who were referred for evaluation of chronic abdominal pain to the outpatient pediatric gastroenterology clinic at Children’s Hospital of Wisconsin (CHW) between January 2009 and October 2011. The human research institutional review board at CHW approved this study. Eligibility requirements included abdominal pain of at least 2 months duration and no evidence of an inflammatory, anatomic, or metabolic process that explained symptoms.

The study sample was selected as follows. A total of 221 consecutive new clinic patients with abdominal pain completed the intake questionnaire during the study period. Of these, 183 had pain of at least 2 months duration and complete questionnaire data. The medical records of those 183 patients were then reviewed to exclude patients with abdominal pain of organic etiology. Biochemical workup (eg, complete blood cell count) was completed in 89% of patients; 98% of those studies were normal. Values were considered normal or abnormal based on established norms used by the CHW laboratory. In addition, further diagnostic evaluation was performed as indicated by clinical presentation on a subset of patients, including upper endoscopy in 49% and colonoscopy in 22%. Mucosal biopsies were reviewed and were histologically nondiagnostic in 76% and 93% of patients who underwent upper and lower endoscopy, respectively. The remaining patients who did not undergo further workup were diagnosed as having FGID and did not have a change in their diagnosis throughout the study review period, which was an average of 13 months. From this evaluation, a total of 23 patients with organic disorders were excluded (eg, eosinophilic esophagitis, candidiasis, gastric/duodenal ulcer, Helicobacter pylori gastritis), leaving a final sample of 160 patients with pain-associated FGIDs.

The demographics of the final sample (N = 160) were as follows: patients ranged in age from 6 to 18 years, (mean 12.02, standard deviation [SD] 2.94), 68% were girls, and 78% were white, 11% African American, 5% Latino, 1% Asian, 1% Native American, and 4% identified as “other ethnicity.”

Measures

Consecutive new patients completed a demographic, history, and gastrointestinal symptom questionnaire at the time of their first clinic visit. The 5-page questionnaire was adapted from the Questionnaire on Pediatric Gastrointestinal Symptoms (QPGS). This is a validated diagnostic measure based on the Rome II criteria (6). The questionnaire includes specific questions regarding abdominal pain, bowel movements, nausea, and vomiting as well as associated symptoms. Additional data regarding demographics, blood tests, mucosal endoscopic biopsies, and follow-up visits were obtained retrospectively from systematic chart reviews.

The 6-item revised Pediatric Migraine Disability Assessment Score (PedMIDAS) tool was used to assess the effect of symptoms on school, home, and social disability during a 2-month period. The PedMIDAS is a validated instrument, originally developed to assess disability in children with migraine headaches (7). This tool is scored by individual questions: how many full days did the child miss school because of symptoms, how many partial days did the child miss school because of symptoms, how many days did the child function at less than half ability in school because of symptoms (exclusive of missed days), how many days was the child unable to do things at home because of symptoms, how many days was the child unable to participate in extracurricular activities because of symptoms, and how many days did the child function at less than half ability in home and extracurricular activities because of symptoms (exclusive of missed days). Two subscales were created to assess total school functioning disability (sum of items 1–3) and home/social functioning disability (sum of items 4–6). Higher scores indicated more disability.

Statistical Analysis

Data were analyzed in 3 stages: symptom characteristics (frequencies and descriptives), disability (Pearson correlation and hierarchical multiple regression), and Rome III criteria classifications (frequencies). Statistical analysis was performed with SPSS version 19 (SPSS Inc, Chicago, IL). An unadjusted P value of <0.05 was considered significant.

RESULTS

Symptom Characteristics

Overall, the majority of patients had abdominal pain for an interval of 2 to 6 months (34%), with 24% experiencing pain for 7 to 12 months, 19% for 1 to 2 years, and 23% for >3 years. A majority of patients (60%) were reported to have pain on an almost daily basis (5–7 times per week), and a total of 87% of the sample reported pain at least twice per week. During the previous 2-week period, patients rated their average pain-intensity ratings as mean 6.33, SD 2.06, on a 0 to 10 numerical pain-rating scale, with 10 being most severe. Nausea and vomiting frequencies were also examined; nausea without vomiting was present in a majority (60%) of the pain-associated FGID sample (Table 1).

The nausea without vomiting group (nausea alone; N = 96) was further examined. Figure 1 represents a flowchart of the sample selection. Among these patients, 28% had nausea almost daily (5–7 times per week), and a total of 53% had nausea at least 2 times per week (Fig. 2).

Pain-associated symptoms, including headache, early satiety, and fatigue, were common among patients with nausea (73%, 67%, and 61%, respectively). Heartburn and postprandial fullness were prevalent, but less common (Fig. 3).

Disability

PedMIDAS data were examined to determine the degree of disability that was related to nausea frequency among the pain patients with nausea alone (N = 96). First, individual PedMIDAS items were correlated with nausea frequency. Questions 1 (full school days missed), 2 (partial school days missed), and 4 (unable to do home activities) were significantly correlated with nausea frequency (r = 0.33, P < 0.01; r = 0.27, P = 0.01; and r = 0.31, P < 0.01, respectively) so that increased disability was related to higher nausea frequency. Second, 2 subscales were created to examine school functioning versus home/social functioning. Both

<table>
<thead>
<tr>
<th>TABLE 1. Frequency of nausea and vomiting in patients with pain-associated functional gastrointestinal disorders (N = 160)</th>
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<tbody>
<tr>
<td>Nausea (%)</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
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</table>
school functioning and home/social functioning scales were significantly related to nausea frequency, \( r = 0.28, P < 0.05 \) and \( r = 0.30, P < 0.05 \), respectively.

Finally, hierarchical multiple regression analyses were conducted to examine the contribution of pain and nausea frequency to school and social disability among the nausea-alone pain patients. Pain frequency was entered on the first step and nausea frequency on the second step to examine the unique contribution of nausea to disability prediction. Two analyses were conducted with this model: the first with the school disability subscale of the PedMIDAS as the dependent variable, and the second with the social disability subscale of the PedMIDAS as the dependent variable. Results of the regression analyses are presented in Table 2. Pain frequency accounted for a significant proportion of variance in school disability (10%), but not social disability (5%). The addition of nausea frequency accounted for an increase of 5% of the total variance in school disability (\( P = 0.06 \)) and a significant increase of 7% of the total variance for social disability, above and beyond what was accounted for by pain.

Rome III Classification

Patients with pain-associated FGIDs and nausea were classified based on Rome III criteria. Among the patients with nausea, the prevalence of FD when the pediatric Rome III criteria were applied was 29%. Conversely, if the adult Rome III criteria for FD were applied, the prevalence of FD increased to 87%. Furthermore, 22% of patients with nausea met pediatric Rome III criteria for IBS-diarrhea subtype. Of these patients, none met the criteria for pediatric FD, whereas 76% also met criteria for adult FD. When applying the Rome III criteria for IBS-constipation subtype, 13% of patients with nausea met the criteria. Of these, none met the criteria for pediatric FD and 100% met the adult FD criteria. Pediatric IBS-diarrhea and IBS-constipation subtypes overlapped in 5% of the nausea patients (Fig. 4).

There was a low prevalence of AM (13%) based on Rome III criteria among patients with nausea. Within that group, 17% also met criteria for pediatric FD and 100% met the adult FD criteria. Because the Rome criteria limit the classification of childhood FAP to those who do not qualify for any other FGID, only 31% of nausea patients with abdominal pain could be classified as FAP.

DISCUSSION

The present study demonstrates that nausea is a common associated symptom in pediatric patients with pain-associated FGIDs. To our knowledge, this is the first study to report on the high prevalence of nausea and its association with adverse effect on school and social functioning. Our findings suggest that nausea could be an independent indicator of adverse quality-of-life outcomes. In this patient population, significant overlap was found...
within the disorders using the Rome III, and no pediatric criteria specifically address the presence of nausea, suggesting that the criteria may need to account for this important symptom in future revisions.

For a child or adolescent, chronic nausea is associated with substantial physical and psychosocial distress as well as school absences and limitations in home and social functioning. It constitutes a diagnostic dilemma for physicians because there are limited data on clinical features, diagnostic tools, and effective treatments for nausea. This study highlights nausea as a more common symptom in patients with pain-associated FGIDs than previously acknowledged. The limited reports of childhood nausea, the absence of applicable Rome criteria, and the fact that more than half of our abdominal pain cohort also experienced nausea suggest that this is an understudied condition.

Among children in our cohort with nausea and a pain-associated FGID, there was a high frequency of nausea episodes; 53% of patients experienced nausea at least 2 times per week and 28% experienced daily nausea. Nausea frequency was related to school and home/social functioning, such that greater frequency of nausea was related to poorer overall functioning. Furthermore, regression analyses indicated that nausea frequency was predictive of social disability, beyond the effects of pain frequency on functioning. The results also show that symptoms such as headache, fatigue, early satiety, and postprandial fullness are prevalent among patients with nausea and abdominal pain. Heartburn is less common in this patient cohort but is nevertheless prevalent. These symptoms have not yet been incorporated in the pediatric Rome criteria. In fact, the FD criteria are fairly different between adults and children. It is important to note that the pediatric FD criteria do mention ‘‘discomfort’’ as a symptom. Although discomfort could have been intended to incorporate nausea, the term is too vague and the present study shows that children are able to understand the term ‘‘nausea.’’. Because early satiety and postprandial fullness are both integral parts of the adult Rome III criteria for FD (5), we analyzed the data applying both adult and pediatric criteria. It is plausible to consider that our patients may experience FD described in adults. Our analysis shows that 87% of patients met the adult Rome III criteria for FD, whereas only 29% of patients met pediatric Rome III criteria. According to pediatric Rome III criteria, IBS needs to be excluded to make a diagnosis of FD. This likely also accounts for part of the inconsistency. A study by Chogle et al (8) on the reliability of Rome III criteria in children also indicates that the criteria need further refinement. The authors found only 50% agreement rate (intrarater reliability) among pediatric gastroenterologists for using the pediatric Rome III criteria in the clinical setting. This may reflect a lack of experience in using the classification system or poor agreement with physician diagnosis, which was replicated in a study by van Tilburg et al (9). It may also simply reflect the multifactorial nature of FGIDs and the fluctuation of symptoms that make it difficult to apply criteria that defines all conditions accurately.

Overlap among various FGIDs based on the Rome III criteria has been consistently reported not only in the adult but also in the pediatric literature (10–16). The separation of IBS from FD has been previously questioned because these 2 disorders may be different manifestations of a single entity (11,15,17). This illustrates the complexity of diagnosing FGIDs and the difficulties associated with developing a diagnostic tool without the use of biomarkers. Furthermore, the high association of nausea, abdominal pain, and headaches suggests that perhaps some of these children may experience AM. As in chronic migraine headaches, it is plausible that AM could evolve from episodic to chronic (18). Because we did not subject all patients who were clinically classified as FGID to endoscopic biopsy to establish a diagnosis, it is possible that a small number may in fact experience abdominal pain that is not ‘‘functional.’’ We minimized the potential for verification bias by using an alternate criterion standard of follow-up to determine whether those patients in the FGID group who were not subjected to biopsies may have been misdiagnosed (19). None of the FGID patients in our study experience a change to an ‘‘organic’’ disorder after an average of 13 months of follow-up, strengthening the initial diagnosis. We also excluded patients with nausea that reported vomiting. Although this was done to improve patient characterization, it may have inadvertently improved our study because vomiting has been found to be a risk factor for mucosal inflammation in children with FD (20).

Another disorder to consider in subjects with chronic nausea and abdominal pain is postural orthostatic tachycardia syndrome (POTS). Although mainly characterized by orthostatic symptoms and palpitations, patients manifest a variety of comorbidities. Gastrointestinal symptoms are common and POTS often coexists with FGIDs (21–23). A study by Olha et al (21) found that 79% of pediatric patients with POTS report abdominal pain and 60% report recurrent nausea and vomiting. Recognizing the association between FGIDs and autonomic dysfunction and obtaining a detailed history of nausea and orthostatic symptoms are important part of the diagnosis and management of patients with chronic abdominal pain. The present results also suggest that nausea is not solely restricted to patients with foregut symptoms as generally thought. Nausea and its effect on quality of life should be assessed when evaluating patients with IBS, a disorder classically thought of as limited to the lower gastrointestinal tract. Previous studies have implicated gastric

### TABLE 2. Hierarchical regression of pain and nausea frequency predicting school and social disability

<table>
<thead>
<tr>
<th>Variable</th>
<th>$R^2$</th>
<th>$\Delta R^2$</th>
<th>$F$</th>
<th>df</th>
<th>$B$</th>
<th>SE</th>
<th>$\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain frequency: school</td>
<td>0.10</td>
<td>6.96*</td>
<td>1, 64</td>
<td>9.30</td>
<td>3.53</td>
<td>3.53</td>
<td>0.31*</td>
</tr>
<tr>
<td>Pain frequency: social</td>
<td>0.05</td>
<td>3.03</td>
<td>1, 58</td>
<td>8.39</td>
<td>4.82</td>
<td>4.82</td>
<td>0.22</td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea frequency: school</td>
<td>0.15</td>
<td>3.55</td>
<td>1, 63</td>
<td>3.66</td>
<td>1.94</td>
<td>1.94</td>
<td>0.22</td>
</tr>
<tr>
<td>Nausea frequency: social</td>
<td>0.12</td>
<td>4.26*</td>
<td>1, 57</td>
<td>5.33</td>
<td>2.58</td>
<td>2.58</td>
<td>0.26*</td>
</tr>
</tbody>
</table>

* $P < 0.05.$

![FIGURE 4. Rome III criteria overlap. Percentages reflect fraction of the nausea and abdominal pain patient cohort. FD = functional dyspepsia; IBS = irritable bowel syndrome.](image-url)
sensory motor dysfunctions in the pathophysiology of some FGIDs (24). In this regard, it should be noted that although delayed gastric emptying could also account for a significant number of patients with nausea and pain, it was beyond the scope of this study and was not investigated.

A limitation of our study is that the questionnaire was not originally designed to categorize patients based on exact Rome III criteria. For example, we classified the change in frequency of bowel movements as IBS-diarrhea if the patients had ≥3 bowel movements per day. Similarly, patients were classified as IBS-constipation if they had ≤3 bowel movements per week. We used the pediatric FD cutoff for symptom duration of minimum 2 months when classifying patients as adult FD, which actually requires 3 months of symptoms. This may have resulted in slight overestimation of the adult FD criteria. Also, although Rome criteria for AM require episodic abdominal pain lasting for at least 1 hour, we chose patients who had pain for 2 to 4 hours or more. Because of this, some patients with AM may have been misclassified as FAP and we may have underestimated the prevalence of AM in our cohort. Although there was an association between nausea and poor school and social functioning, we cannot conclude a cause and effect relation, and despite statistical significance, the r values obtained (0.27–0.33) suggest a weak correlation. The low variance of disability predicted by pain and nausea frequency (9%–11%) suggests that other factors also contribute to disability. Another limitation of our study is that the patient cohort was not entirely representative of the US population, with some ethnic groups underrepresented.

In summary, this is the first study to report nausea as a highly prevalent and debilitating symptom in patients with pain-associated FGIDs. Our findings suggest that chronic nausea is associated with adverse effects on social and school functioning. The physical and psychosocial burden of chronic nausea coupled with chronic abdominal pain appears to have a larger effect on health outcomes and quality of life than previously appreciated. Consideration may need to be made to redefine diagnostic criteria for pediatric FGIDs, particularly as it relates to nausea in the FD criteria, and possibly include chronic idiopathic nausea as a separate category in children.

REFERENCES