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Nausea in Children with Functional Abdominal Pain Predicts Poor Health Outcomes in Young Adulthood

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Abstract

Background & Aims—Nausea is common among children with functional abdominal pain (FAP). We evaluated the relation of nausea to short- and long-term morbidity in pediatric patients with FAP.

Methods—We performed a prospective study of 871 children with FAP (8–17 years old) seen in a pediatric gastroenterology practice; follow-up data were collected from 396 of the patients 8.7±3.3 years later. Participants were defined as having significant nausea if they reported nausea “a lot” or “a whole lot” within the past 2 weeks. Validated questionnaires assessed abdominal pain, gastrointestinal and somatic symptoms, and depression. Baseline measures, anxiety, and the Rome III criteria were assessed in the follow-up evaluation.

Results—At baseline, 44.8% of the patients reported significant nausea. Those with nausea reported worse abdominal pain, gastrointestinal symptoms, somatic symptoms, and depression than those without nausea ($P < .001$ for all). When the children had reached young adulthood, those with nausea in childhood continued to have more severe gastrointestinal ($P < .001$) and somatic symptoms ($P = .003$) than patients without nausea in childhood, as well as higher levels of anxiety ($P = .02$) and depression ($P = .02$). In the follow-up evaluation, somatic symptoms, depression, and anxiety remained significant after controlling for baseline abdominal pain severity.

Conclusions—Pediatric patients with FAP and nausea have more severe short- and long-term gastrointestinal and somatic symptoms than patients with FAP without nausea, as well as reductions mental health and daily function. Pediatric patients with FAP and nausea therefore need intensive treatment and follow up.

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Keywords

functional gastrointestinal disorder; pediatric nausea; anxiety

Introduction

Functional abdominal pain (FAP) is common among children and adolescents, with a prevalence between 0.3–19%.¹ FAP is associated with comorbid somatic symptoms and frequent medical visits.¹ FAP in childhood may predict future morbidity; longitudinal studies have shown that children with FAP are at increased risk for functional gastrointestinal disorders (FGIDs), anxiety, and depression in young adulthood.^{2,3}

Nausea is a common somatic symptom among pediatric FAP patients—more than a quarter experience nausea daily, while half experience nausea at least twice a week.^{4–6} Despite the absence of identifiable organic etiology, nausea in FAP patients has been associated with higher levels of disability, negative affect, fatigue, and anxiety.^{4,6–9} Currently, there are no empirically supported interventions for pediatric functional nausea.⁷ No studies have prospectively assessed the impact of nausea in pediatric FAP patients. Thus, it is unknown whether comorbid nausea increases risk for poor health outcomes.

The goal of our study was to evaluate the long-term physical and mental health outcomes of pediatric FAP patients reporting clinically significant nausea. We hypothesized that pediatric patients with FAP and nausea (FAP+Nausea), compared to pediatric patients with FAP and no nausea (FAP Only), would report more somatic and internalizing symptoms both at baseline and nine-year follow-up. Additionally, we hypothesized that the FAP+Nausea group, compared to the FAP Only group, would be more likely to meet criteria for a FGID in late adolescence and young adulthood, indicating an increased risk for persistence of FAP.

Methods

Patients

Baseline evaluation—Data was drawn from a larger prospective study of health outcomes in consecutive new patients (ages 8 to 17) evaluated for FAP (duration > three months) in a pediatric gastroenterology clinic. Patients were enrolled in IRB approved studies conducted by Walker and colleagues between 1993 and 2004^{2,3,10–13}. Patients underwent medical evaluation for abdominal pain and were eligible if they had no significant organic etiology for their pain. Those with minor histologic findings of esophagitis and normal endoscopy were not excluded, as histologic findings alone are not sensitive or specific for organic disease.¹⁴ Additional eligibility criteria included: living with parent(s) or parent figure, capable of consent/assent, and no chronic illness or developmental delay. The baseline sample comprised 871 pediatric FAP patients (60% female, 92% Caucasian, mean age = 11.61±2.4 years). Patients and parents provided informed consent/assent and completed questionnaires in the clinic at the time of initial evaluation.

Follow-up evaluation—Patients who agreed to follow-up evaluation were contacted by mail or telephone. Eligibility criteria for the follow-up study included age 12 years or older

at follow up, a minimum of 4 years between initial evaluation and follow up, and no current chronic or life-threatening disease. Seven hundred sixty patients were eligible and 396 patients could be contacted and consented. Four were excluded for incomplete data. Thus, the patient sample at follow-up comprised 392 pediatric FAP patients assessed an average of 8.7 ± 3.3 years after initial evaluation (65% female, 91% Caucasian, mean age = 20.8 ± 3.9 years). For the follow-up study, patients answered questions about their health and current symptoms by means of a telephone interview and online survey. A subset of these patients ($n = 336$) completed a psychodiagnostic interview.

Measures

Gastrointestinal and non-gastrointestinal symptoms—The Children's Somatization Inventory (CSI) assesses the severity of 35 somatic symptoms experienced during the past two weeks^{15,16}. Two subscales were calculated: Gastrointestinal (GI) symptoms and non-GI symptoms. For this study, nausea was excluded from the GI symptom subscale. Patients rated how much they were bothered by each symptom during the past two weeks on a 5-point scale ranging from 0 (not at all) to 4 (a lot). For each subscale, item responses were summed yielding scores ranging from 0 to 32 (GI symptoms) and 0 to 104 (non-GI symptoms). Patients completed the CSI at both baseline and follow-up evaluations.

Nausea—Patients were defined as having clinically significant nausea if they responded “a lot” or “a whole lot” to item #13 on the CSI (“nausea or upset stomach”)¹⁵. Those who reported experiencing nausea “not at all,” “a little,” or “some” were not considered to have clinically significant nausea.

Abdominal pain—The Abdominal Pain Index (API) assesses weekly frequency, daily frequency, duration, and typical intensity of abdominal pain during the past two weeks¹⁷. Patients' responses are converted to a 5-point scale and averaged to yield a mean index score ranging from 0 to 4. Higher scores indicate more severe abdominal pain. Patients completed the API at both baseline and follow-up.

Internalizing symptoms

Depressive symptoms: At baseline, patients completed the Children's Depression Inventory (CDI; ¹⁸), a validated self-report measure of depressive symptoms during the past two weeks. Responses are summed, yielding a total score between 0 and 54, with higher scores indicating higher levels of depressive symptoms.

At follow-up, patients completed the Center for Epidemiological Studies—Depression Scale (CES-D) ¹⁹, a validated adult self-report measure of the frequency of twenty depressive symptoms during the past week. Items are summed, yielding a composite score ranging between 0 and 60. Higher scores indicate greater depressive symptoms.

Anxiety symptoms: At follow-up, the Spielberger State-Trait Anxiety Inventory (STAI)—Trait Scale ²⁰ assessed the frequency of anxiety symptoms. Items were summed yielding a composite score between 20 and 80. Higher scores indicate more anxiety. Anxiety symptoms were not assessed at baseline.

DSM-IV anxiety and depressive psychiatric disorders—Diagnostic criteria for anxiety and depressive disorders were assessed at follow-up with *The Anxiety Disorders Interview Schedule-IV (ADIS): Adult Lifetime and Child and Parent Versions*,²¹ a semi-structured interview administered by a trained clinician and designed to assign both current and lifetime DSM-IV psychiatric diagnoses. A Clinical Severity Rating indicating at least moderate severity/impairment is required for assigning a diagnosis of an anxiety or depressive disorder. Further details on the administration of the diagnostic interviews are provided in Shelby et al., 2013.²

Functional Gastrointestinal Disorders—*The Rome III Diagnostic Questionnaire*²² is a self-report measure used to identify individuals who meet the Rome III symptom criteria for FGIDs. At follow-up, the 24 items assessing symptoms associated with abdominal pain-related FGIDs (irritable bowel syndrome, functional dyspepsia, abdominal migraine, and functional abdominal pain) were administered.

Data Analysis

Analyses were performed using SPSS Statistics, version 18 (SPSS, Inc, Chicago, IL). Descriptive analyses used chi-squared (χ^2) tests. Independent t-tests compared continuous measures with a two-tailed $p < .05$ criterion for significance. Because abdominal pain has exhibited a predictive relation to the long-term outcomes in our study¹¹, we controlled for abdominal pain severity in subsequent analyses to examine the unique impact of nausea in FAP patients. Thus, one-way analyses of covariance (ANCOVA), controlling for baseline abdominal pain severity, examined group differences on continuous baseline and follow-up measures. Logistic regressions, controlling for abdominal pain severity, examined whether the FAP+Nausea group, compared to the FAP Only group, was at increased risk for psychiatric disorders and FGIDs at follow-up.

Results

Baseline Evaluation

At baseline, 391 (44.83%) pediatric patients had significant nausea. There were no differences in gender or race (Table 1); however, FAP+Nausea patients were slightly older at baseline than FAP only patients (12.36 ± 2.53 years versus 11.79 ± 2.43 , $p = .001$). FAP+Nausea patients reported significantly greater abdominal pain severity than FAP Only patients ($t[871] = -12.90$, $p < .001$). Abdominal pain severity was controlled for in subsequent analyses reported below to eliminate this difference as a confounding factor.

Controlling for abdominal pain severity, FAP+Nausea patients, compared to FAP Only patients, reported significantly more GI symptoms ($F[1,869] = 141.70$, $p < .001$) and non-GI somatic symptoms ($F[1,868] = 94$, $p < .001$). The FAP+Nausea group scored greater than the FAP Only group for each individual GI symptom on the CSI: constipation ($F[1,868] = 22.29$, $p < .001$), diarrhea ($F[1,866] = 27.69$, $p < .001$), difficulty swallowing ($F[1,868] = 24.62$, $p < .001$), vomiting ($F[1,868] = 106.14$, $p < .001$), feeling bloated/gassy ($F[1,865] = 37.55$, $p < .001$), and “food making you sick” ($F[1,867] = 64.78$, $p < .001$). Controlling for abdominal pain severity, the FAP+Nausea group, compared to the FAP Only group, reported

significantly greater depressive symptoms ($F[1,854]=26.1$, $p<.001$) and functional disability ($F[1,705] = 44.8$, $p<.001$) at baseline. These results are summarized in Table 2.

Follow-up Evaluation

Nausea at initial evaluation significantly correlated with nausea at follow up ($r = 0.226$, $p<0.001$). FAP+Nausea patients continued to report greater abdominal pain severity at long term follow-up compared to FAP Only patients ($t[389] = -2.92$, $p = .004$). Controlling for baseline abdominal pain severity, the FAP+Nausea group, compared to the FAP only group, reported significantly greater depressive ($F[1,345] = 5.24$, $p = .02$), anxious ($F[1,346] = 5.38$, $p = .02$), and non-GI somatic symptoms ($F[1,389] = 4.64$, $p = .03$) at follow-up. These results are summarized in Table 2. Additionally, the FAP+Nausea group, compared to the FAP only group, were 1.79 (95% CI: 1.07, 3.01) times more likely to meet criteria for a current DSM-IV anxiety disorder and 1.79 (95% CI: 1.11, 2.89) times more likely to meet criteria for a DSM-IV anxiety disorder in their lifetime. Regarding type of anxiety disorder, FAP+Nausea patients, compared to FAP only patients, were 2.61 (95% CI: 1.38, 4.96) times more likely to meet DSM-IV diagnostic criteria for generalized anxiety disorder (GAD) in their lifetime and 2.49 (1.22, 5.10) times more likely to meet diagnostic criteria for GAD at the time of follow-up. Differences between groups for social anxiety disorder approached significance ($p = .052$). Regarding DSM-IV depressive disorders, FAP+Nausea patients were 1.81 (1.10, 2.97) times more likely to meet criteria for a major depressive episode in their lifetime compared to FAP Only patients but the two groups had similarly low rates of DSM-IV depression diagnosis at follow up (8.6% for FAP+Nausea, 3.8% for FAP only).

While the FAP+Nausea group continued to have worse GI symptoms ($t[335] = -3.83$, $p < .001$) and greater functional disability ($t[300] = -3.03$, $p = .003$) than the FAP Only group at follow-up, these differences did not remain statistically significant when controlling for baseline abdominal pain severity ($F[1,389] = 3.37$, $p = .07$ and $F[1,388] = 2.7$, $p = .10$, respectively). The Rome III criteria were administered at follow-up. See Table 3 for the prevalence of FGIDs at follow-up by nausea group. Chi-squared tests indicated these differences were significant. However, logistic regression analyses controlling for baseline abdominal pain severity did not yield significant group differences in the presence Rome III diagnoses at follow-up.

Discussion

This study shows that pediatric patients with FAP and comorbid nausea experience worse abdominal pain, gastrointestinal and extra-intestinal somatic symptoms, depression, and functional disability compared to FAP patients without nausea. Moreover, as adolescents and young adults, FAP patients who reported significant nausea at their initial pediatric gastroenterology evaluation reported significantly greater extra-intestinal somatic symptoms, depression, and anxiety than those who presented without nausea. Additionally, compared to FAP patients without nausea at initial evaluation, those with nausea were more likely to meet diagnostic criteria for past or current anxiety disorders and a past major depressive episode. To our knowledge, this is the first prospective cohort study to report the negative long-term

symptom and mental health outcomes for pediatric patients with FAP who also complain of nausea.

Previously published work on this patient sample has shown that current and lifetime diagnoses of anxiety disorders are substantially higher in adolescents with a history of FAP compared to healthy controls (lifetime: 51% versus 20%; current 30% versus 12%).² The lifetime risk of depressive disorder is also significantly higher in those with FAP (40% versus 16%),² especially those with multiple non-intestinal somatic complaints.¹² In the present study, the subgroup of FAP patients with significant nausea had more depressive symptoms at initial evaluation and more anxiety and depressive disorders at follow up than those with FAP alone. These differences persisted when controlling for abdominal pain severity, suggesting that nausea is an independent factor driving the difference between groups. This is in line with previous studies in children with FAP and nausea that found nausea severity to correlate with anxiety and maladaptive coping.^{4,6}

Our findings suggest that nausea is an independent risk factor for current and future depression and anxiety in FAP. This may be due to chronic nausea being a distressing symptom that permeates multiple areas of physical and psychosocial functioning. It may be difficult for these patients to maintain good nutrition, sleep habits, exercise, and resiliency when they are frequently nauseated. Alternatively, FAP patients with comorbid nausea may represent a phenotype with autonomic nervous system dysfunction that contributes to both nausea and emotional distress. Alterations in autonomic nervous system function have been described in patients with both childhood anxiety and chronic nausea.^{23,24} Autonomic nervous system imbalance should be considered as a possible unifying etiology.

This study demonstrates, for the first time, that children with FAP and nausea are more likely than those without nausea to have FGIDs in adulthood. This increased frequency of FGIDs in adulthood did not remain significant when controlling for abdominal pain at baseline, suggesting that the combination of both nausea and abdominal pain severity may increase risk for persistent FGIDs. Both extra-intestinal somatic symptoms and depression have been identified as predictors for future FGIDs in children with FAP.³ As we report in this study, children with FAP and nausea have a higher burden of somatic symptoms and depression in childhood and young adulthood. These comorbidities may increase risk for FGIDs.

Strengths of this study include its large sample, prospective design, extensive follow up period, use of validated pediatric questionnaires, and inclusion of psychosocial measures. By including only those patients suffering from “a lot” or “a whole lot” of nausea within the prior two weeks, we were able to focus on the most severe phenotype of nausea sufferers. This likely accounts for some of the difference in the prevalence of nausea reported in our study population of children with FAP (45%) than what has been previously reported (53–59%).^{4,6}

There are several limitations to this study. First, while all FAP patients underwent an extensive medical evaluation, the medical evaluation typically did not evaluate two secondary conditions that may be associated with nausea. Specifically, no formal screening

for postural orthostatic tachycardia syndrome (POTS) was performed. Abdominal pain and recurrent nausea are common among children with POTS and it is known to co-exist with FGIDs.^{25,26} We cannot rule out the possibility that some children may have had POTS and not FAP complicated by nausea. We also did not perform gastric emptying studies in all participants to rule out gastroparesis. These studies were ordered at the discretion of the pediatric gastroenterologist based on patient presentation. Gastroparesis symptoms may be non-specific in children and can include nausea and abdominal pain^{27,28}. The prevalence of gastroparesis in children is unknown but based on the low adult prevalence of 0.04–4%²⁹, it is likely that the majority of our cohort would not have had gastroparesis.

Second, we cannot determine the nature of the relation between FAP and nausea. FAP could contribute to the development of nausea or vice versa. Similarly, anxiety could contribute to the development of nausea or result from experiencing chronic nausea. Prospective studies beginning in early childhood are needed to specifically assess the timing of the development of these disorders.

Finally, baseline nausea was assessed at a time when there were no validated measures for pediatric nausea. The Nausea Profile has recently been validated for pediatric assessments; however, this profile does not assess frequency or chronicity.^{9,30} The Baxter Retching Faces Scale provides a pediatric appropriate pictorial scale for nausea severity; however, it has only been validated for acute nausea.²³ Future research should focus on diagnostic tools to better define this patient population and provide a measurement tool for therapeutic trials.

Children with FAP and nausea experience increased morbidity in the short and long term. They are at increased risk for extra-intestinal somatic symptoms, anxiety and depression irrespective of abdominal pain severity. This suggests that nausea is more than just a co-morbid symptom of FAP and may have a different underlying etiology necessitating different forms of treatment.

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Abbreviations

ANCOVA	Analysis of Covariance
CI	Confidence Interval
FAP	functional abdominal pain
FGID	functional gastrointestinal disorder
GI	gastrointestinal
IBS	irritable bowel syndrome

OR Odds Ratio

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Table 1

Demographic characteristics of pediatric FAP patients with and without nausea

	FAP+Nausea	FAP Only
<u>Baseline</u>	n = 398	n = 479
Sex, % female	63.3%	56.8%
Race, n (%)		
Caucasian	348 (91.8%)	431 (92.5%)
African American	18 (4.7%)	20 (4.3%)
Asian	2 (0.5%)	4 (0.9%)
Hispanic	3 (0.8%)	4 (0.9%)
Other	8 (2.1%)	7 (1.5%)
Age at initial evaluation, M $\pm$ SD, years	12.36 $\pm$ 2.54	11.79 $\pm$ 2.43
<u>Follow-Up</u>	n = 179	n = 217
Sex, % female	68.7%	60.8%
Race, % Caucasian	92.1%	90.6%
Follow-up period, mean interval $\pm$ SD, year	8.93 $\pm$ 3.47	9.21 $\pm$ 3.45
Age at follow-up evaluation, M $\pm$ SD, years	20.88 $\pm$ 3.96	20.80 $\pm$ 3.90

Table 2

Means adjusted for abdominal pain severity $\pm$ standard errors by nausea group for baseline and follow-up measures

Variable	FAP+Nausea	FAP Only	η_p^2
GI symptoms (excluding nausea and abdominal pain)			
Baseline	10.04 $\pm$.21	6.17 $\pm$.19	.171 *
Follow-up	4.17 $\pm$.29	3.42 $\pm$.26	.009
Non-GI somatic symptoms			
Baseline	14.96 $\pm$.50	8.24 $\pm$.44	.098 *
Follow-up	10.53 $\pm$.62	8.66 $\pm$.56	.012 *
Depression			
Baseline (CDI)	10.51 $\pm$.35	8.02 $\pm$.31	.030 *
Follow-up (CES-D)	12.09 $\pm$.72	9.80 $\pm$.64	.015 *
Anxiety			
Baseline	N/A	N/A	
Follow-up (STAI)	39.34 $\pm$.81	36.71 $\pm$.73	.015 *
Functional disability			
Baseline	13.96 $\pm$.52	9.03 $\pm$.48	.060 *
Follow-up	5.22 $\pm$.50	4.06 $\pm$.45	.007

* Difference between groups is significant at $p < .05$, GI = gastrointestinal, N/A = not applicable because the measure was not administered at this time point

Table 3

Prevalence of pain-related functional gastrointestinal disorders at follow-up by nausea group

Follow-Up		
FAP+ Nausea (n = 177)		FAP Only (n = 214)
FGID Diagnosis	n (%)	n (%)
Any FGID	85 (48.0)	77 (36.0)
IBS	59 (33.3)	51 (23.8)
FD	43 (24.3)	34 (15.9)
None	92 (52.0)	137 (64.0)

* FGID = functional gastrointestinal disorder, IBS = irritable bowel syndrome, FD = functional dyspepsia, FAP = functional abdominal pain