

Functional GI Disorders Are Prevalent Among Pediatric

Patients with Persistent Asthma

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Short Running Title: Functional GI Disorders and Asthma

Abstract

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Aim: Functional gastrointestinal disorders (such as functional abdominal pain, irritable bowel syndrome and functional dyspepsia) are a common cause of chronic GI symptoms in children. Prior studies demonstrated a high comorbidity of functional GI disorders (FGIDs) among patients with asthma. However, data exploring specific disease characteristics within the US populations are scarce. This study aimed to assess the prevalence and comorbidities of FGIDs among pediatric asthma patients at a university-affiliated urban community hospital.

Methods: This prospective, cross-sectional study assessed FGID prevalence, asthma control, and symptoms of anxiety among pediatric patients with persistent asthma. The validated diagnostic pediatric ROME-III questionnaire was used to assess FGIDs. The Asthma Control Test assessed asthma control. The Beck Anxiety Index assessed symptoms of anxiety. Higher BAI scores corresponded with increased anxiety.

Results: Among 110 enrolled patients, eighteen (16%) met diagnostic criteria for FGIDs, 10 of which were consistent with a functional abdominal pain disorder. Patients with FGIDs had a significantly lower mean ACT score ($M=11.5\pm4.9$) compared to patients without FGIDs ($M=14.8\pm5.3$) ($P=0.03$;Cohen's $d=0.6$). FGID patients had significantly higher anxiety scores ($M=34\pm11$) than those without FGIDs ($M=14\pm13$)($P<0.01$). Asthma control predicted presence of an FGID ($OR=0.9$ 95%CI[0.80-0.99]; $P=0.03$). However, after adjusting for anxiety, asthma control no longer predicted FGID presence ($aOR=0.9$ 95%CI[0.83-1.05]).

Conclusions: This study suggests a high prevalence of functional GI disorders among patients with persistent asthma. Moreover, patients with FGIDs had poor asthma control and increased anxiety. Clinicians should consider FGIDs in patients with poor asthma control and assess for anxiety as indicated.

Keywords: FGIDs; Functional Abdominal Pain Disorders; Functional Upper GI Tract Disorders

Introduction:

Functional gastrointestinal disorders (FGIDs) are a common cause of unexplained abdominal pain and other gastrointestinal symptoms in children. These symptoms can be severely debilitating and are correlated with a high rate of impairment in daily function and school absence. Pediatric FGIDs have also been associated with a lower quality of life.¹ A subgroup of FGIDs, specifically those including functional abdominal pain disorders, are associated with psychiatric comorbidity such as anxiety and traumatic life events.²

A large population-based retrospective study, conducted in the UK, with nearly 30,000 primary care patients, found a higher prevalence of asthma and other types of atopy among patients with FGIDs compared to control subjects without FGIDs.³ This association has been previously established among adults by others in the UK^{4, 5} and in the US.⁶

Unfortunately, data is lacking regarding specific disease characteristics of patients that screen positive for an FGID in the US pediatric population. The objective of this study was to assess the prevalence and comorbidities of pediatric asthma patients who screen positive for FGIDs in an urban US primary care setting. This assessment is important because most children

with chronic abdominal symptoms who present to their primary care setting may meet criteria for a diagnosis of FGIDs and can be managed in that setting without any further diagnostic testing if there are no additional warning signs. Finally, addressing FGIDs in patients with asthma may broaden our understanding of risk for poor asthma control among patients.

Methods:

Study Design

This was a prospective, cross-sectional study to assess the prevalence and comorbidities of pediatric asthma patients who screen positive for FGIDs. Our primary objective was to assess the frequency of patients who would qualify for a diagnosis of FGIDs among our asthmatic population. In addition, we aimed to characterize the differences between patients who would meet criteria for FGID compared with patients who did not. Finally, we examined differences in asthma control between these two groups.

Inclusion Criteria

Inclusion criteria included an age range of 4-20 years and an existing diagnosis of persistent asthma (as defined by daily inhaled corticosteroid use). Patients were required to have at least one electronic medical record (EMR) encounter on file in our system.

Exclusion Criteria

Patients were excluded if they did not have an existing diagnosis of persistent asthma (as defined by daily inhaled corticosteroid use), as recorded in our EMR and verified by the patient. Subjects were also excluded if the patient or their parents were unable to read and complete study surveys in either English or Spanish, which was verified by trained study personnel.

Clinic Setting

Patients and parents were recruited for this study during a clinical visit to the emergency department (ED), pediatric inpatient unit, or ambulatory clinics (which included primary care clinics and an asthma clinic) at a university-affiliated urban community hospital. Patients were included if they presented for assessment due to any symptom, even if a visit had no relationship to an asthma related complaint. The study was approved by our local institutional review board (IRB).

Study Visit

Patients were enrolled from June 2016 to April 2017. During the study visit, patients and/or parents completed a battery of 3 questionnaires which focused on FGID symptoms, asthma control, and comorbid anxiety. Children 12 years of age and older completed a patient-administered questionnaire. Alternatively, parents of patients below the age of 12 years completed a parent-administered questionnaire. Questionnaires were available based on preference in both English and Spanish. All participants were consented and or assented prior to study enrollment.

Study Instruments

FGIDs

Functional gastrointestinal disorders were screened with the “Questionnaire on Pediatric Gastrointestinal Symptoms – Rome III version” (QPGS-RIII).⁷ This questionnaire has a parent and child self-reported version and was developed to assess for symptoms associated with FGIDs.⁷ This questionnaire has been previously validated for use in both English and Spanish.^{7,8} This questionnaire was modified to include FGIDs superior to the umbilicus, including upper functional abdominal pain disorders such as irritable bowel syndrome (IBS), functional

abdominal pain syndrome (FAP Syndrome), functional abdominal pain (FAP), and functional dyspepsia (FD)), as well as other functional upper GI tract disorders, including aerophagia, cyclic vomiting syndrome (CVS), and adolescent rumination syndrome. The questionnaire includes scoring instructions with diagnostic criteria for each FGID which are based on provisional recommendations by the Rome III Child and Adolescent Committee. The authors obtained written permission to use both the English and Spanish questionnaire for study purposes by the Rome Foundation.

Asthma Control

Asthma control was assessed with the asthma control test (ACT).⁹ This test provides a quantitative continuous score based on symptoms, ability of physical activity, and frequency of rescue medication usage. Beside the regular asthma control test, the validated childhood asthma control test (C-ACT) was used for children below the age of 12 years.⁹ The ACT ranges from 5-25 and the C-ACT ranges from 0-27, with the higher number reflecting better asthma control.⁹ Among both indices, a score of 19 or less suggests that asthma is not well-controlled.⁹

Anxiety

Comorbid symptoms of anxiety were assessed with the Beck Anxiety Inventory (BAI).^{10, 11} The BAI is a 21-item, validated questionnaire that assesses for anxiety symptoms in children using a 4-point Likert scale. The total score ranges from 0-63, with a higher score indicating greater anxiety.

Statistical analysis

Descriptive statistics were compared between patients with and without FGIDs. Chi square and Fisher exact tests were used to assess categorical variables. Independent t-tests and the

Mann-Whitney U test were used for parametric and non-parametric continuous samples.

Logistic regression was used to assess predictors of FGIDs, adjusted for specific variables that demonstrated significant bivariate correlation with outcome. A two-tailed test with a p-value of <0.05 was considered significant. This was a pilot study with no prospective data available regarding the impact of asthma control on FGID symptoms. Effect sizes of mean differences were calculated with Cohen's d test to confirm that adequate power was achieved. All statistical analyses were performed with IBM SPSS Statistics Version 20 (Armonk, NY).

Results:

Enrolled Patients

One hundred twenty-two patients were invited to participate in the study; 110 patients agreed to participate and were included in our overall analysis (Figure 1). Sixteen percent (18/110) of this group met diagnostic criteria of an FGID based on their QPGS Rome III answers. Of patients who met FGIDs, one third was pre-adolescent and two-thirds were adolescents. (can you identify the exact age breakdown of adolescent vs non)

Patient Demographic Data

Overall, mean age was 10 ± 4.6 years (mean $\pm$ SD) and ranged from 4-20 years of age (Table 1). The majority of patients, 86%, were of African American and/or Hispanic race and/or ethnicity. The majority of patients, 81%, were insured by Medicaid. Notably, most patients had a registered address in which the zip code was associated with a median household income of less than \$25,000 per year, as reported by the US Census Bureau.¹²

Demographic data were compared between FGID and non-FGID groups. Patients with FGIDs were more likely to be female (72%) compared to patients without FGIDs (45%) ($p<0.03$). No other patient demographic data differed between the two groups.

Questionnaire Demographic

There were no significant differences between those patients with FGIDs and those without FGIDs regarding demographic data (Table 1). Overall, a minority of families (13%) preferred to complete a Spanish questionnaire. Sixty-seven percent of questionnaires were completed by parents, which was pre-determined by the cut-off age stipulated in the methods section. Of interest, the majority of questionnaires (55%) were completed in the pediatric emergency department (PED), which is most likely the result of a higher than average patient census in the emergency department compared to other settings in our institution. However, there was no difference in the percentage of FGIDs diagnosed in the PED compared to other settings.

Disease Characteristics

Comorbid disease characteristics were reviewed after the patient visit, and included allergies, eczema, and allergic rhinitis/allergic conjunctivitis. These specific atopies have been demonstrated to have higher associations with FGIDs as documented in prior studies.³ In this study we did not find higher incidences of individual atopies. This was expected as all enrolled patients had asthma as underlying atopy. Of note, only one patient was found to have a histologically confirmed GI disease by chart review. Though this patient had been diagnosed eosinophilic esophagitis, they did not meet diagnostic criteria for a FGID.

As patients with FGIDs have a higher likelihood of comorbid psychiatric disorders, including anxiety and depression, the overall psychiatric history was assessed using the EMR. Fifteen

percent of patients had a comorbid reported psychiatric history. There were no differences between the FGID and non-FGID groups.

Individual FGID Diagnoses

Eighteen patients met criteria for a FGID diagnosis. Among this group, there were a total of 23 individual FGID diagnoses. Two patients qualified for 3 simultaneous FGIDs, and 1 patient qualified for 2 simultaneous FGIDs (Table 2). Of the 23 FGID diagnoses, 10 were identified as functional abdominal pain disorders, of which irritable bowel syndrome was the most common ($n=5$) and functional dyspepsia the least common ($n=1$) (Table 2). Thirteen diagnoses were made among other functional upper GI tract disorders, including aerophagia ($n=9$) and cyclic vomiting ($n=4$).

Asthma control and Anxiety

The secondary outcomes, asthma control and anxiety scores, were compared between patients with FGIDs and patients without FGIDs. Patients with FGIDs had lower mean Asthma Control Test score (11.5 ± 4.9) than patients without FGIDs (14.8 ± 5.3 ; $p = 0.03$). This reflects lower asthma control among FGID patients compared to patients without FGIDs. Furthermore, this difference indicated a medium effect size (Cohen's $d = 0.6$). Finally, patients with FGIDs had significantly higher anxiety scores (34 ± 11) compared to patients without FGIDs (14 ± 13) ($p < 0.01$).

Predictors of FGIDs

Of the 3 variables that were significantly different between FGID patients and non-FGID patients, (sex, asthma control, and anxiety), all were significant predictors of FGIDs using bivariate logistic regression (Table 3). Patients with FGIDs were 3 times more likely to be female

than patients without FGIDs (OR 3.2; 95% CI 1.06-9.82; $p < 0.05$). Of note, the secondary outcomes appeared to be bivariate predictors as well. Regarding asthma control, patients with FGIDs had an OR of 0.9 (95% CI 0.80-0.99; $p = 0.03$) compared to the non-FGID group. As a higher asthma control score indicates worse control, this suggests that patients with FGIDs were less likely to have well controlled asthma than their non-FGID peers. Alternatively, this indicates that lower asthma control scores predicted FGIDs. Furthermore, patients with FGIDs were more likely to be more anxious than patients without FGIDs (OR 1.1; 95% CI 1.02-1.10; $p < 0.01$).

Using multivariate analysis, 2 of the 3 variables (female and degree of anxiety) remained independent predictors for FGIDs. Under these parameters, asthma control was no longer a significant independent predictor (Table 3 – multivariate predictors). FGID patients were 3 times more likely to be female than patients without FGIDs (aOR 3.3; 95% CI 1.00-10.56; $p < 0.05$). Furthermore, patients with FGIDs remained slightly more anxious than non-FGID patients (aOR 1.1 95% CI 1.01-1.10) consistent with the bivariate analysis. In contrast, asthma control was no longer a predictor for FGIDs when adjusted for anxiety and sex (female) (aOR 0.9; 95% CI 0.83-1.05; $p = 0.23$).

Discussion:

We found a high prevalence of patients with functional GI disorders (16%, $n=18$) among a population of pediatric patients with persistent asthma at an urban university-affiliated community hospital. Of the 18 patients who qualified for FGIDs, we identified 23 individual FGID diagnoses. This estimate is similar to prior research. More specifically, the recent study by Jones et al.³ found a prevalence of FGIDs up to 15% (of IBS and functional dyspepsia in

particular) among adult asthma patients in a primary care setting in the UK. In that retrospective study, 19% of patients with asthma had multiple FGIDs.³ A recent study examined FGIDs by maternal administration of the QPGS among an online sample of pediatric patients. Independent of disease comorbidities or type of FGIDs, the authors found a FGID prevalence of 23% overall among this cohort of pediatric patients.¹ A meta-analysis of pediatric functional upper GI disorders found that functional dyspepsia was the most common FGID, with 3-27% and a prevalence of cyclic vomiting syndrome of only 2-3%.¹³ While the prevalence rates found in our study are generally comparable to the previous studies, no other pediatric study has examined FGIDs as a whole or specifically limited to functional upper GI tract disorders among asthma patients, limiting our ability to directly compare our results with prior research.

Using bivariate analysis, this study also found that patients with FGIDs were more likely to be female, have increased levels of anxiety, and exhibit poor asthma control compared to patients without FGIDs. Initially we found that poor asthma control scores also predicted FGIDs. In addition, increased increased anxiety scores were a predictor of FGIDs.

Though poor asthma control was identified initially as a significant predictor variable, it was no longer a significant independent predictor after controlling for anxiety and sex on multivariate analysis. As our study included a relatively small sample size, this result could theoretically be attributed to a type II error, particularly given the difference between the means of asthma control had a medium effect size. Green (1991),¹⁴ documented that a sample size of 107 subjects would be required for an adequately reliable regression calculated using the most conservative estimation procedures. As our total sample size appears to be adequately powered to detect difference in this regression (n=110), it is therefore less likely

that this outcome would be attributed to a type II error. Instead, it is more likely that the effect seen is accurate; patients' sex and anxiety drive differences in rates of FGIDs.

Our study had several limitations. This study examined the prevalence and characteristics of functional upper GI tract disorders (FGIDs) among pediatric patients with asthma. FGIDs were assessed using the validated QPGS questionnaire to determine whether patients met criteria for an FGID. This questionnaire is one of the accepted methods to diagnose FGIDs in a research setting. In a clinical setting, certain patients with symptomatic "red flags" require further diagnostic evaluation (such as esophagogastroduodenoscopy) to exclude any upper GI tract organic GI diseases. In contrast, this extensive clinical evaluation is not routine practice in a research setting.^{1, 3, 13} One could argue that it would be ideal to obtain GI histology for all patients to determine diagnostic clarity, as a rigorous search to exclude organic diseases are particularly important among atopic patients. However, the role and prevalence of inflammatory disease in eosinophilic GI disease is unclear.^{4, 6} Alternatively, another argument could be made that it would not be ethical to expose these pediatric patients to an invasive work-up of endoscopy (including anesthesia) for the purpose of screening for FGIDs among otherwise healthy asthma patients. As a result, it is unknown if some of our patients qualifying for a FGID had another underlying GI disorder that would impact the results established by this study. We suggest that this outcome is possible but less likely, given that the electronic medical records of all patients in our study were comprehensively reviewed at time of the data analysis. At this time, only one patient required a previous GI evaluation during which eosinophilic esophagitis was found, but this patient did not qualify for an FGID based on the questionnaire responses. Furthermore, as the role of inhaled corticosteroids on FGIDs is unclear, we only

included patients who were prescribed daily dosing of inhaled corticosteroids to limit the risk of a heterogeneous sample. However, we did not adjust for medication adherence, seasonal variations or individual changes in the living environment or individual exposure to allergens, each of which could further confound differences in asthma control found between the groups. While we did not adjust for these individual differences, we assumed that the majority of our patients will have similar exposures, as this study was performed at a community hospital and the majority of patients had a zip code on file that was within close proximity to the hospital and limited to one borough of New York City.

Another study limitation included using a questionnaire that was used to collect answers about symptoms. While we prospectively assessed FGIDs based on these validated questionnaires, there could have been some recall bias based on assessment methods. In addition, we did not utilize the entire QPGS-Rome III, as we were particularly interested in upper GI tract diseases and wanted to minimize the question burden of participants. As a partial version of the QPGS-Rome III was subsequently used which excluded FGIDs below the umbilicus, this could have led to underestimation of the prevalence of overall FGIDs found.

Finally, after data collection was completed, we noted that the majority of patients were recruited and enrolled in the emergency department. Theoretically, it could be that the acuity of patient symptoms may have reflected the higher acuity setting of the emergency department. That said, we did not find a difference between FGIDs found in the PED as compared to other less acute settings, suggesting that this concern may be less relevant.

Conclusion

This study found a relatively high prevalence of upper GI tract FGIDs among pediatric asthmatic patients. We also found that patients with FGIDs had higher anxiety scores and were more likely to be female. This study demonstrates that it is feasible to screen for FGIDs while assessing for asthma control and anxiety in a clinical research setting. It is important for pediatricians to be aware that FGIDs and asthma co-exist. General pediatricians are usually the first to detect these symptoms, and the American Academy of Pediatrics (AAP) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recently published guidelines that promote the diagnosis and management of FGIDs by primary care pediatricians. These guidelines reinforce that most pediatric FGIDs can be safely managed by a pediatrician without the need for involvement of a gastroenterologist or further GI studies (e.g. endoscopic evaluation) if red flags are absent.¹⁵ Future research should examine if improvement in management of asthma control and anxiety could contribute to a decrease in FGID symptoms and improve other related outcomes such as quality of life. Finally, using the new Rome IV Criteria and change in classification of certain FGIDs, future prospective research should also evaluate the role of the new Rome IV criteria in pediatric asthma patients with comorbid gastrointestinal symptoms.

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Table Legend

Table 1. Comparison of Demographics Between Patients With and Without FGIDs

Table 2. Frequency of Individual FGIDs

Table 3. Bivariate and Multivariate predictors of FGIDs

Table 1. Comparison of Demographics Between Patients With and Without FGIDs				
	Total (n=110)	FGIDs (n=18)	No FGIDs (n=92)	<i>p</i> Value
Patient Demographics				
Age (Mean $\pm$ SD)	10 $\pm$ 4.6	12 $\pm$ 5.6	10 $\pm$ 4.4	NS
Pre-adolescent (%)	45%	12%	88%	
Adolescent (%)	55%	20%	80%	
Sex (% , F)	49%	72%	45%	<0.03
Ethnicity				
AA/Hispanic (%)	86%	83%	86%	NS
Insurance:				
Medicaid (%)	81%	83%	80%	NS
Income				
<25K (%)	90%	89%	90%	NS
Questionnaire demographics				
Language (Spanish) (%)	13%	6%	14%	NS
Parent-completed (%)	67%	56%	70%	NS
Setting:				
ED (%)	55%	44%	57%	NS
Inpatient (%)	26%	11%	21%	
Outpatient (%)	19%	44%	23%	
Comorbidities				
Atopy				
Allergies (%)	30%	33%	29%	NS
Eczema (%)	37%	33%	38%	NS
Allergic Rhino-conjunctivitis (%)	61%	50%	63%	NS
Behavioral				
Psychiatric History (%)	15%	28%	12%	NS

F - female; SD – Standard Deviation.

Table 2. Frequency of Individual FGIDs	
	N = 18 (16%)
Functional Abdominal Pain Disorders	10
- IBS	5
- FAP Syndrome	2
- FAP	2
- Functional Dyspepsia	1
Other Functional Upper GI Tract Disorders	13
- Aerophagia	9
- Cyclic vomiting syndrome	4
- Adolescent rumination syndrome	0

Table 3. Bivariate and Multivariate Predictors of FGIDs			
	OR	95% CI	<i>p</i> Value
Asthma Control	0.9	0.80-0.99	0.03
Anxiety	1.1	1.02-1.10	<0.01
Sex (Female)	3.2	1.06-9.82	<0.05
	aOR	95% CI	<i>p</i> Value
Asthma Control	0.9	0.83-1.05	0.23
Anxiety	1.1	1.01-1.10	<0.01
Sex (Female)	3.3	1.00-10.56	<0.05

OR – Odds Ratio; aOR – Adjusted Odds Ratio; 95% CI – 95% Confidence Interval

Figure Legend**Figure 1.** Flow diagram of patient enrollment