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Unrecognized Functional Dyspepsia Among Those With Refractory Chronic Constipation: Analysis of a Tertiary Cohort

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Abstract

BACKGROUND AND AIMS: Patients with functional constipation (FC) are frequently dissatisfied with current treatment options which may be related to persistent, unaddressed symptoms. We hypothesized that refractory FC may actually represent functional dyspepsia (FD) overlap. Among adults presenting with refractory FC, we sought to (1) identify the prevalence of concurrent FD and (2) identify the symptoms and presentations most frequently associated with concurrent FD and FC.

METHODS: We assembled a retrospective cohort of 308 patients sequentially presenting to a tertiary neurogastroenterology clinic for evaluation of refractory FC, defined as having failed first-line therapy. Using Rome IV criteria, trained raters identified the presence and characteristics of concurrent FD in addition to demographics, presenting complaints, and psychological comorbidities.

RESULTS: Among 308 patients presenting with refractory FC (average of 3.0 ± 2.3 constipation treatments tried unsuccessfully), 119 (38.6%) had concurrent FD. Aside from meeting FD criteria, the presence of concurrent FD was associated with patient complaints of esophageal symptoms

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Authors' Contributions:

M.P., T.B., I.A., F.R., I.G.F., and C.S. carried out data collection. H.B.M. and M.P. conducted statistical analyses. M.P. and T.B. wrote the manuscript. H.B.M. and K.S. provided substantial editing of the manuscript and supervised the project. All authors edited the manuscript and approved the final draft submitted.

*co-senior authors.

Conflicts of Interest:

These authors disclose the following: K.S. has received research support from Ironwood and Urovant, has served as a speaker for Shire, and has served as a consultant to Arena, Gelesis, GI Supply, and Shire. H.B.M. receives royalties from Oxford University Press for her forthcoming book on rumination syndrome. The remaining authors disclose no conflicts.

Ethical Statement:

The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Reporting Guidelines:

STROBE, SAGER.

(Odds ratio = 3.1; 95% confidence interval, 1.80–5.42) and bloating and distension (Odds ratio = 2.67; 95% confidence interval, 1.50–4.89). Patients with concurrent FD were more likely to have a history of an eating disorder (21.0% vs 12.7%) and were also more likely to present with current avoidant/restrictive food intake disorder–related symptoms (31.9% vs 21.7%).

CONCLUSION: Almost 40% of adult patients referred for refractory FC met criteria for concurrent FD in a tertiary-level cohort. The presence of both FC and FD was associated with greater esophageal symptoms and bloating/distention. Determining presence of concurrent FD may represent an additional therapeutic opportunity in refractory patients who may attribute symptoms to FC alone.

Keywords

Functional Dyspepsia; Functional Constipation; Overlap; Disorders of Gut-Brain Interaction

Introduction

Disorders of gut-brain interaction [DGBI; also known as functional gastrointestinal (GI) disorders] affect approximately 40% of the population globally and may be characterized by specific patterns of GI and extraintestinal symptoms and psychiatric comorbidities.^{1,2} DGBIs can impact any part of the GI tract and concurrent DGBIs spanning anatomic regions are common.³ Awareness of the prevalence of concurrent DGBIs has grown in recent years and the association with increased somatic symptom severity, greater illness anxiety, lower quality of life, and greater work-related impairment is well documented.^{4,5} Repeated consultations, diagnostic investigations, surgeries, and prescriptions are also disproportionately reflected in patients with DGBI overlap syndromes, especially when the concurrent DGBIs involve different GI organ systems.^{6,7}

Functional dyspepsia (FD) and functional constipation (FC) are 2 common DGBIs. Whereas FD is defined by upper GI symptoms, specifically bothersome symptoms most often related to eating such as early satiation, postprandial fullness, epigastric pain, and/or epigastric burning,⁸ FC is localized to the lower GI tract with symptoms including straining, hard stools, and incomplete evacuation.⁹ Despite clear differences in diagnostic criteria, management, physiology, and innervation of the stomach and colon, there are common symptoms (eg, abdominal pain, bloating, distention) which may be shared in both diagnoses. These shared symptoms may lead patients to misattribute symptoms to one condition or the other, based on pre-existing explanatory models (eg, which symptoms developed first, which diagnostic workups were originally prescribed). Such symptom misattribution (eg, attributing bloating to constipation when actually driven by dyspepsia) may lead to selection of treatments targeting only one of the concurrent conditions without management of the other—potentially leading to suboptimal therapy and decreased patient satisfaction. Careful consideration of the presence of shared and distinguishing symptoms may be critical for treatment prescriptions—both pharmacologic and behavioral. However, detailed data on the specific clinical features of concurrent FD and FC are limited to inform precision medicine efforts.

Studies have suggested that FD symptoms are present in 15.4%–33.5% of patients with FC.^{7,10} While significant concurrence of these 2 disorders has been reported, a complete investigation of upper and lower GI symptoms, psychiatric comorbidities, and eating/weight-related problems associated with the presence of FD, specifically in patients with refractory FC, has not yet been described. The interconnectedness of psychological conditions and GI motility disorders is complex and likely multidirectional. Thus, obtaining a more comprehensive description of these potential associations may ultimately provide a greater insight relevant for diagnostic considerations and medical management, particularly for patients who do not respond as well to initial therapy.

Among adults presenting to a tertiary care neurogastroenterology clinic for refractory FC, we sought to (1) identify the prevalence of concurrent FD (which we refer to as FD overlap syndrome) and (2) identify the GI symptoms and other clinical characteristics most frequently associated with FD overlap syndrome presence. We hypothesized that a significant proportion of patients who presented with refractory constipation would describe symptoms consistent with FD but would not carry an official diagnosis, possibly contributing to their failure to respond to typical laxative therapy. Furthermore, since a large proportion of adult patients with FD have difficulty maintaining weight or have significant dietary restriction, we also explored the frequency of eating/weight-related issues in those with FD overlap syndrome.^{11–15}

Materials and Methods

Study Design

Using a clinic-based administrative database, we evaluated a cohort of 308 consecutive patients referred to a neurogastroenterology clinic at a tertiary care academic medical center [Massachusetts General Hospital, Boston, Massachusetts] for refractory FC between July 2016 and August 2020. Refractory constipation was defined by the clinic population, with all patients referred by outside providers after failing at least first-line laxative therapy.

The senior investigators (H.B.M. and K.S.) trained designated project coders (M.P., T.B., I.G.F., A.S., F.R., and I.A.) to systematically review medical records to determine FD symptoms by Rome IV,^{16,17} FD subtypes, and GI symptom duration. Each trained coder was assigned a subset of patients for chart analysis. Regular meetings between the coders and senior investigators throughout the data collection process reviewed the quality of clinical documentation and determined diagnostic consensus on complex cases.

The initial patient encounter with a neurogastroenterologist served as the primary data source with documentation of patient demographics and past medical history. Refractory constipation status was determined by noting the number and type of previously prescribed laxatives. FD overlap syndrome was defined specifically as meeting criteria for Rome IV FD in addition to having a diagnosis of FC.¹⁷ Patients who had documented evidence of postprandial fullness (at least 3 days per week), early satiation (at least 3 days per week), and no evidence of structural disease were classified as having FD postprandial distress syndrome. Patients who had bothersome epigastric pain (at least 1 day per week) or epigastric burning (at least 1 day per week) were classified as having FD epigastric

pain syndrome. We also extracted other patient characteristics including presenting GI complaints—abdominal symptoms (bloating, distension, pain) and esophageal symptoms (reflux, regurgitation, belching, globus, choking, cough, dysphagia, heartburn, chest pain, esophageal spasms), and historical psychiatric diagnoses.

Coders determined eating disorder symptom presence using relevant documentation from subsequent follow-up visits with gastroenterology, nutrition, behavioral health specialists, and primary care. Coders conferred eating disorder symptom presence using the Diagnostic and Statistical Manual of Mental Disorders, fifth Edition criteria including avoidant/restrictive food intake disorder (ARFID), anorexia nervosa, bulimia nervosa, binge-eating disorder, and other specified feeding or eating disorder. Criteria for ARFID included documented evidence of food avoidance or restriction resulting in significant weight loss (or failure to gain weight), significant nutritional deficiency, dependence on enteral feeding or oral nutritional supplements, and/or marked interference with psychosocial functioning. Coders conferred “definite” eating disorder (eg, definite ARFID) when cases met all Diagnostic and Statistical Manual of Mental Disorders, fifth Edition criteria. Coders conferred “potential” when cases met some criteria but not enough information was available to make a full diagnosis. We examined presence of current eating disorder symptoms if either definite or potential diagnosis was conferred (eg, ARFID symptoms).¹⁵

All information obtained from a chart review was stored in REDCap.^{18,19} The Mass General Brigham Human Research Committee provided scientific review and approval for this study.

Statistical Analysis

We calculated the frequency of presenting GI complaints among patients who met Rome IV criteria for concurrent FD and those who did not. We grouped individual presenting complaints into larger categories including abdominal symptoms (bloating, distension, pain), esophageal symptoms (reflux, regurgitation, belching, globus, choking, cough, dysphagia, heartburn, chest pain, esophageal spasms), and historical psychiatric disorders. “Patients who had a history of anxiety or depression, trauma, or an eating disorder at the time of presentation were classified as having a historical psychiatric diagnosis.” We used chi-square tests for categorical variables and independent *t*-tests for continuous variables (which were normally distributed) to examine differences in characteristics of those with and without FD overlap syndrome. We used multivariable logistic regression to evaluate if there was an association between presence of an FD overlap syndrome and patient characteristics that were selected based on univariate screen with *a priori* insertion of presenting GI symptoms and demographics (age, sex, body mass index).

Results

Demographics of Patients Presenting with Functional Constipation

We identified a total of 308 patients who presented to a neurogastroenterology clinic for an evaluation of refractory FC between July 2016 and August 2020. No patients were excluded from the analytic population. All patients in this cohort were referred to a constipation specialist prior to evaluation and had tried an average of 3.0 ± 2.3 constipation treatments

unsuccessfully. Overall, the cohort ranged in age from 17–84 ($M \pm SD = 42.6 \pm 16.8$) years. The majority (82.8%) of patients were female. Most patients (90.6%) identified as White, 10% as Asian, 2.6% as Black or African American, 0.3% as Native Hawaiian or Pacific Islander, and 4.2% as Hispanic/Latino/a. Overlap of FC and FD by Rome IV criteria occurred in 38.6% ($n = 119$) of patients. In this overlap group, 73.9% ($n = 88$) had postprandial distress syndrome, 45.3% ($n = 54$) had epigastric pain syndrome, and 18.5% ($n = 22$) had both epigastric pain syndrome and postprandial distress syndrome.

Presenting Symptoms and Comorbidities Associated with Functional Constipation and Overlapping FD

There were no significant differences in sex, age, or body mass index between those with FC alone and those with FD overlap syndrome (Table 1). Compared to patients with FC alone, patients with FD overlap syndrome were significantly more likely to present with abdominal pain and discomfort (59.7% vs 47.1%, $P = .03$) and abdominal bloating and distension (73.9% vs 55.0%, $P < .001$). Esophageal symptoms were also significantly more common in patients with FD overlap syndrome compared to patients with FC alone (44.5% vs 24.3%, $P < .001$).

We used multivariable logistic regression to explore associations between specific patient characteristics, presenting GI symptoms, and comorbidities associated with the FD overlap syndrome patient population (Table 2). Presence of FD overlap syndrome was associated with the patient-reported esophageal symptoms (Odds ratio = 3.1; 95% confidence interval, 1.80–5.42), bloating, and distension (Odds ratio = 2.67; 95% confidence interval, 1.50–4.89).

As per Table 1, patients with FD overlap syndrome were more likely to have a history of an eating disorder (21.0% vs 12.7%, $P = .05$). Patients with FD overlap syndrome were also more likely to present with current ARFID symptoms (definite or possible ARFID; 31.9% vs 21.7% $P = .05$). Of those ARFID symptoms, and FD overlap syndrome, 28.9% ($n = 11$) had a history of marked interference with psychosocial functioning. Presenting complaints of meal-related fullness (36.8%, $n = 14$) was common as was weight loss or failure to gain weight (42.1%, $n = 16$). Nutritional deficiencies were present in 15.8% ($n = 6$) and 7.9% ($n = 3$) were dependent on nutritional supplementation. Restricted food intake was motivated by a fear of aversive consequences in 55.3% ($n = 21$) and a lack of interest in eating and sensitivity or sensory characteristics of food were both present in 2.6% ($n = 1$).

Discussion

Concurrence of different DGBI is common and while the overall prevalence has been documented in previous studies, data describing the specific characteristics of individuals with concurring FC and FD are limited. In this study of tertiary-level patients referred for refractory constipation, we found that almost 40% of patients met criteria for concurrent FD (FD overlap syndrome) and treatment dissatisfaction among patients with chronic constipation.²⁰ Future research is needed to identify whether or not FD overlap syndrome differentially affects treatment outcomes.

We found a higher proportion of patients with FD overlap syndrome compared to previous series of adult patients.^{3,4,7} A cross-sectional survey study assessing the concurrence of multiple DGBIs found FD overlap syndrome in 33.5% of patients, while a prospective multicenter study reported FD overlap syndrome in only 15.4% of patients.^{7,10} The high rate (40%) of FD among our patient population is likely a reflection of the tertiary nature of our cohort, with patients seeking second and third opinions for their symptoms.

The present study importantly identifies a potential driver of care-seeking in the refractory FC population—namely unrecognized or misattributed dyspeptic symptoms. Patients frequently associate a number of bowel-related complaints with the term “constipation” including pain, bloating, and distension.⁶ Our experience is that many patients presenting with constipation are actually experiencing a variety of symptoms that may or may not be driven by impaired evacuation of colonic contents as evidenced by the presence of esophageal symptoms and bloating/distention in the FD overlap group. In a patient population where these symptoms do not respond to first-line laxative therapies, we have likely selected a population with (1) more severe constipation and (2) patients with concurrent symptoms not adequately treated by laxatives alone—including those with FD.

Recognizing the presence of concurrent DGBIs may present a clinical challenge due to the potential for misattribution of symptoms by both patients and providers. In a retrospective review of a similar tertiary population, 64% of consulters were found to have FD–irritable bowel syndrome overlap by study questionnaire compared with only 23% who were identified as having this overlap based on routine clinical documentation by the clinician.²¹ Thus, overlap syndromes in DGBI patients are likely under-recognized by clinicians and therefore underdiagnosed as well.²¹

Physician awareness of overlap could improve quality of care, prevent unnecessary interventions, and yield more positive health outcomes.⁵ In fact, the coexistence of multiple DGBIs in a single patient has been associated with increased healthcare utilization. A recent survey study by Sperber et al which included 54,127 adults in 26 countries demonstrated that the presence of DGBIs in multiple GI regions is associated with increased psychological comorbidity, healthcare utilization, and disease severity.⁵ In addition, more than half (59%) of current FC prescription users are dissatisfied with their current chronic treatment.²⁰ Identifying causal underlying conditions (such as FD overlap) could prevent patients from enduring trials of multiple constipation agents and their associated side effects. For truly refractory disease, addressing heretofore unrecognized comorbid DGBIs could prevent the rising rates of colectomy for chronic constipation, a procedure with significant postoperative risks and often-disappointing outcomes.^{22,23}

Diagnosing an FD overlap syndrome may also present an ideal opportunity to provide more complete patient education about visceral hypersensitivity.²⁴ Visceral sensory abnormalities are common in DGBI and may contribute to the challenge of identifying the origin of refractory abdominal symptoms for both patients and clinicians.²⁵ Patients with a DGBI in one GI anatomic region frequently have additional symptoms referable to other parts of the gut²⁶ suggesting that visceral hypersensitivity may not respect anatomic boundaries and DGBI of different GI regions may in fact be manifestations of the same underlying

pathophysiology.^{26,27} Patients with FD are known to have decreased sensory thresholds for rectal distension despite a presumed lack of lower GI symptoms on initial presentation.²⁸ In addition, abnormalities in proximal gastric motor and sensory function and impaired postprandial relaxation of the gastric fundus have been demonstrated in patients with slow transit constipation.^{29,30} We see the presence of esophageal symptoms and bloating in the FD overlap syndrome group as potential markers of pan-gut sensory abnormalities.

The increased prevalence of esophageal and abdominal bloating/distension symptoms in the FD overlap syndrome group was accompanied by a numerically increased proportion of those with a history of an eating disorder (21% vs 13%). Moreover, current ARFID symptoms were significantly more common in FD overlap syndrome than FC alone (32% vs 22%) and driven by a fear of aversive experience (eg, extreme fullness, nausea, bloating). The high prevalence of disordered eating symptoms in this FD overlap syndrome population mirrors the high prevalence of eating disorder symptoms, especially ARFID (up to 40%) in the tertiary FD population.¹⁵ Comorbid eating disorders are also associated with more severe FD symptoms in comparison to those without comorbid disease.³¹ There are multiple ways in which FD, FC, and restrictive eating may be associated (Figure). Patients may restrict food intake to prevent onset of constipation-related symptoms. Similarly, symptoms of FD such as early satiation and postprandial fullness may lead to a decreased interest or fear of eating, ultimately resulting in problematic food avoidance/restriction.

We acknowledge several limitations that should be considered in respect to our findings. Because of the retrospective design of this study, it is possible that certain FD cases may not have been captured if the clinician did not specifically inquire about and/or document these symptoms, although our high prevalence suggests that our provider population frequently sought these complaints. With multiple coders, inter-rater reliability could be an important factor and it is possible that minor variances in coding technique could have affected our results. We did however use frequent, structured meetings with the supervising investigators to resolve potential difficulties in assigning diagnoses. In addition, we were also unable to identify whether or not FD overlap syndrome differentially affected treatment outcomes. Finally, patients included in this study visited a single tertiary clinic where frequency of FD overlap syndrome could be artificially inflated. However, we would argue that identifying these cases from a “refractory” population seen in tertiary care is exactly what is needed before these patients move on to ever more expensive and sometimes invasive treatment directed at the wrong issue.

Our findings highlight the importance of recognizing FD-related complaints for patients with refractory FC. Identifying the patient who consults for constipation but reports upper abdominal symptoms or bloating and distention immediately after meals may suggest that FD may be driving some of the symptomology. Commonalities in overlap pathophysiology suggest that certain categories of therapies, indeed, other types of therapies relevant to FD including neuromodulators, and exposure-based behavioral treatments may add our treatment armamentarium and represent future directions for overlap-related research.

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Abbreviations used in this paper:

ARFID	avoidant/restrictive food intake disorder
BMI	body mass index
DGBI	disorder of the gut-brain interaction
EPS	epigastric pain syndrome
FC	functional constipation
FD	functional dyspepsia
IBS-C	irritable bowel syndrome with constipation
PDS	postprandial distress syndrome
SD	standard deviation

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Data Transparency Statement:

Data, analytic methods, and study materials will be made available to other researchers upon reasonable request.

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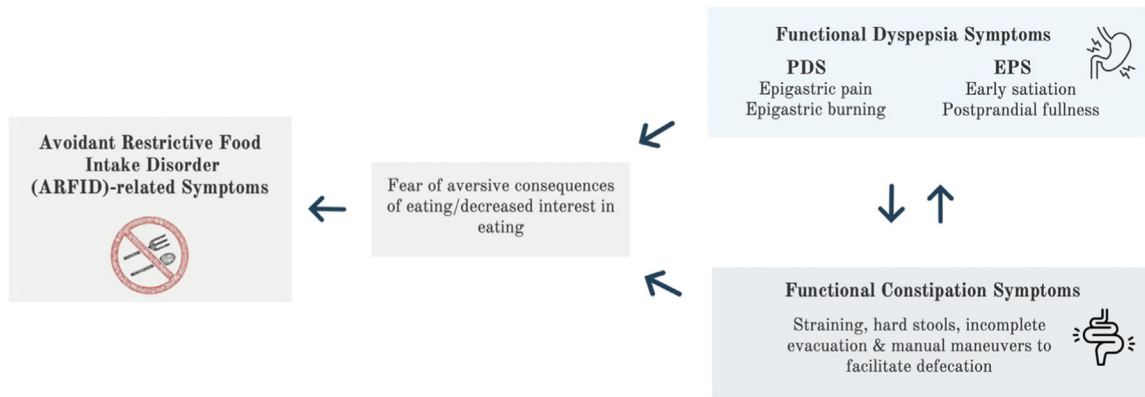


Figure. Associations between FD, functional constipation, and avoidant restrictive food intake disorder. The ways in which symptoms of FD and functional constipation are associated with symptoms of avoidant restrictive food intake disorder are shown.

Table 1.
Demographics and Comorbidities of Patients Presenting With Functional Constipation^a

Variable	Functional constipation with overlapping FD (n = 119)	Functional constipation only (n = 189)	P value
Age at consult, mean (SD), y	41.9 (16.1)	43.1 (17.2)	.57
Sex-female, n (%)	101 (84.9)	154 (81.5)	.44
BMI at consult, mean (SD), kg/m ² ^b	25.2 (6.6)	24.2 (6.2)	.21
Overlapping FD, n (%)			
Postprandial distress syndrome	88 (73.9)		
Epigastric pain syndrome	54 (45.3)		
Presenting symptoms, n (%)			
Eating/weight-related	25 (21.0)	24 (12.7)	.05
Esophageal ^c	53 (44.5)	46 (24.3)	<.001
Abdominal pain/discomfort	71 (59.7)	89 (47.1)	.03
Bloating/distention	88 (73.9)	104 (55.0)	<.001
Average number of constipation agents tried (SD)	3.1 (2.2)	3.0 (2.3)	.72
IBS-C, n (%)	24 (20.2)	32 (16.9)	.47
Historical psychological disorders, n (%)			
History of anxiety or depression	68 (57.1)	90 (47.6)	.10
History of trauma	38 (32.8)	53 (28.0)	.47
History of eating disorder	25 (21.0)	24 (12.7)	.05
Current eating disorder symptoms, n (%)	40 (33.6)	50 (26.5)	.12
ARFID-related	38 (31.9)	41 (21.7)	.05
Other eating disorder-related ^d	20 (16.8)	30 (15.9)	.28

FD, functional dyspepsia; SD, standard deviation; BMI, body mass index; IBS-C, irritable bowel syndrome with constipation; ARFID, avoidant/restrictive food intake disorder.

^aData are expressed as number (percentage) unless otherwise noted. Percentages are rounded.

^bThere were 16 patients with missing BMI.

^cEsophageal symptoms include reflux, regurgitation, belching, globus, choking, cough, dysphagia, heartburn, chest pain, and esophageal spasms.

^dDefined as having symptoms related to any eating disorder other than ARFID: anorexia nervosa, bulimia nervosa, binge-eating disorder, or other specified feeding or eating disorder.

Table 2.
Associations With Overlapping Functional Constipation and Functional Dyspepsia^a

	OR	SE	95% CI	P value
Age	0.99	0.01	0.02–0.46	.915
Female sex, yes/no	0.79	0.37	0.39–1.64	.522
BMI	1.04	0.02	0.99–1.08	.111
Esophageal symptom presence, yes/no	3.10	0.28	1.80–5.41	<.001
Abdominal pain and discomfort presence, yes/no	1.25	0.27	0.74–2.11	.410
Bloating symptom presence, yes/no	2.67	0.30	1.50–4.89	.001
History of eating disorder, yes/no	1.67	0.35	0.84–3.35	.142

Associated with the FD, overlap syndrome with a priori insertion of symptoms, and characteristics (age, sex, body mass index).

^aMultivariate logistic regression was used to determine associations between specific patient characteristics, presenting GI, symptoms, and comorbidities.