Children with Functional Nausea—Comorbidities outside the Gastrointestinal Tract

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Objective To detail common comorbidities and procedures performed to evaluate functional nausea in children.

Study design In total, 63 children age 7-18 years seen in a tertiary care pediatric clinic who met Rome IV criteria for functional nausea prospectively completed an Intake Questionnaire, the Pediatric and Parent-Proxy PROMIS-25 Profile v 2.0, the Pediatric and Parent-Proxy Pediatric Sleep Disturbance-Short Form 4a, and the COMPASS 31 orthostatic intolerance scale to assess comorbidities. Medical records were reviewed for diagnostic tests performed to evaluate nausea and for additional comorbidities. Summary statistics were used to determine the most common comorbidities and diagnostic yield of the procedures. Intraclass correlation coefficients assessed agreement between parent and child reports on the PROMIS scales.

Results Patients with functional nausea experienced multisystem comorbidities. A majority reported abdominal pain, headache, orthostatic intolerance, fatigue, disturbed sleep, anxiety, constipation, allergies, and vomiting. Agreement between parent-proxy and child report of symptoms on PROMIS scales was good to excellent (intraclass correlation coefficients = .78-.83; all $P < .001$). Patients underwent extensive diagnostic testing: 96 endoscopic procedures, 199 radiologic tests, and 4 cholecystectomies. Most of the procedures were not diagnostically informative.

Conclusions Children with functional nausea have comorbidities outside the gastrointestinal tract that warrant evaluation. Gastrointestinal diagnostic tests were of low-yield in identifying a cause. Understanding the relationship with comorbidities may provide insight into etiologies for the nausea and define clinical phenotypes to better tailor care. *(J Pediatr 2020;225:103-8)*.

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Functional nausea, a prevalent and poorly understood symptom in children and adolescents, is subjective in nature, and because of this, it can be challenging for patients to articulate their symptoms. It may be overlooked by clinicians compared with more obvious symptoms such as vomiting and abdominal pain. The etiology is likely multifactorial with a wide spectrum of presentations. Based on Rome IV criteria, a patient must experience the following for at least 2 months: bothersome nausea as the predominant symptom experienced at least 2 times per week, unrelated to meals, as well as not consistently associated with vomiting, and not attributable to another medical condition.[1]

Reports have increasingly recognized nausea as a common symptom seen in pediatrics.[2-4] It often occurs concurrently with other functional gastrointestinal disorders (FGIDs) particularly functional abdominal pain.[3] For example, in patients with chronic abdominal pain and chronic nausea, 29% met criteria for pediatric functional dyspepsia, 22% for irritable bowel syndrome with diarrhea, 13% for irritable bowel syndrome with constipation, and 31% met criteria for functional abdominal pain.[2] The same study found that nausea was also associated with fatigue, early satiety, and headache.[2] In a prospective study, patients with functional abdominal pain who also reported nausea had significantly worse abdominal pain and somatic symptoms.[3] Orthostatic intolerance (OI) and anxiety are also commonly associated with functional nausea. In a cohort of patients with OI, 56% had primary presentations of nausea.[4] Adolescents with chronic nausea were found to have a higher rate of anxiety than those with abdominal pain alone, with a prevalence of 70% in one study.[5] Tarbell et al found that nausea was significantly associated with state and trait anxiety, OI during a tilt test, and decreased heart rate variability which suggests underlying autonomic dysregulation.[6] These multiple comorbidities can complicate the medical

CT	Computed tomography	HUT	Head-up tilt
EGD	Esophagogastroduodenoscopy	ICC	Intraclass correlation coefficient
EHR	Electronic health record	MRI	Magnetic resonance imaging
EoE	Eosinophilic esophagitis	OH	Orthostatic hypotension
FGID	Functional gastrointestinal disorder	OI	Orthostatic intolerance
GI	Gastrointestinal	POTS	Postural orthostatic tachycardia syndrome
HIDA	Hepatobiliary iminodiacetic acid		

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evaluation of patients with functional nausea and potentially lead to unnecessary tests and procedures.

Gastrointestinal (GI) diagnostic work-up for functional symptoms such as nausea and chronic abdominal pain may include a range of invasive and noninvasive tests including endoscopy, radiologic studies, and surgical exploration.[7] Oftentimes, these strategies are low-yield in elucidating the cause for the symptoms and can be associated with potential complications.[7] Thus, we sought to comprehensively evaluate the multiple comorbidities associated with functional nausea and the diagnostic yield of procedures performed in these patients.

Methods

Patients with a chief complaint of functional nausea were identified from a pediatric subspecialty gastroenterology clinical registry between February 2018 and August 2019 who met inclusion criteria for this institutional review board approved study. Patients age 7-18 years were screened for a visit diagnosis or chief complaint of nausea. Subjects were included if they met Rome IV criteria for functional nausea. Children who were not English speakers or who had other major medical or developmental disorders were excluded. Parents and children signed a consent/assent prior to study enrollment.

Medical Record and Questionnaire Review

Comorbidities were assessed by review of (1) the medical record, including the physician's note at the first appointment summarizing the patient's current symptoms and health history; (2) relevant information from visits with other providers obtained from the electronic health record (EHR) or original records; (3) an intake questionnaire where parents/patients reported current symptoms and past medical history filled out prior to their first visit, and (4) self and parent-proxy report on PROMIS symptom scales[8] as well as the COMPASS 31 OI subscale.[9] Pediatric and Parent-Proxy PROMIS-25 Profile v 2.0 assessed current symptoms in patients age 7-17 years (anxiety, depression, fatigue, pain interference, and pain intensity).[10,11] The pain intensity measure is a 1-10 numeric scale completed by parent and child that does not currently have normative data. The Pediatric and Parent-Proxy Pediatric Sleep Disturbance-Short Form 4a evaluated sleep difficulties. For the PROMIS scales, total scores were converted to *t* scores standardized so that 50 represents the mean for the US population with SD = 10. As the fixed length forms of the PROMIS scales were used, any scale with a missing participant response was not included in the data analyses, as per scoring guidelines. Higher scores indicate more of the domain being measured. It should be noted that the PROMIS questionnaires inquire about symptoms experienced by the patient in the past 7 days, whereas data from the chart reviews had variable time frames for the child and parent reports. Thus, the PROMIS questionnaires reflect the current incidence of the symptoms, whereas the chart review provided an index of the prevalence of the symptoms. In addition, a validated question on illness impact on school attendance from the National Health Interview Survey was administered.[12] Our review is based on the most prevalent comorbidities derived from the symptom assessment methods described above. Demographic data were obtained from the Intake Questionnaire. (Categories and methods for data abstraction detailed in **Table I**; available at www.jpeds.com).

Diagnostic Procedures and Tests

We reviewed procedures patients underwent to assess nausea and related symptoms and their results. Information was obtained from (1) the intake questionnaire detailing past procedures; (2) clinic notes from the child's first visit with the program; (3) prior visit notes from other providers within the institution; (4) diagnostic procedures done within the institution before the first visit; (5) EHR records for studies done outside of the institution before the first visit; and (6) scanned external medical records from the EHR. The amalgamation of sources was done to provide the most comprehensive picture of the patient's procedural history. The GI-related procedures investigated included esophagogastroduodenoscopy (EGD) with biopsy, colonoscopy with biopsy, cholecystectomy, hepatobiliary iminodiacetic acid (HIDA) scan, gastric emptying scan, abdominal radiograph, abdominal ultrasonography, abdominal magnetic resonance imaging (MRI) (inclusive of magnetic resonance enterography, and magnetic resonance angiography), abdominal computed tomography (CT), and upper GI radiograph. Findings of the procedures were also recorded. Findings for the radiologic studies were interpreted according to the radiologist's report with additional evaluation by a pediatric gastroenterologist for select studies. For tests that assessed stool burden, a stool burden of moderate or above was considered abnormal. Patients with eosinophilic esophagitis (EoE) were excluded from the analysis of GI procedures because it was not discernable which tests were done as routine screening for EoE and which were done for investigation of nausea. Patient records were also analyzed for autonomic testing including head-up tilt (HUT) tests. HUT tests were considered abnormal if they met the American Autonomic Society criteria for postural orthostatic tachycardia syndrome (POTS) or orthostatic hypotension (OH).[13] For other autonomic procedures, results were considered abnormal based on the final procedure report.

Study Procedures

A clinical research coordinator oversaw administration of the questionnaires at clinic visits. A research assistant and the principal investigators reviewed the patient's medical records, questionnaires, tests and procedures according to the methods described previously (**Table I**). Data from these reviews were entered into REDCap (Research Electronic Data Capture), a secure web-based data storage platform.

Statistical Analyses

Data were exported from the REDCap database and evaluated for the presence of comorbid symptoms and conditions,

including GI, psychological and general medical symptoms to obtain a comprehensive understanding of the patient's health. Data analyses were performed with SPSS v 25 (IBM, Armonk, New York). Summary statistics were used to calculate the symptoms and conditions most frequently comorbid with functional nausea. Summary statistics were also used to assess the most common procedures and tests used to evaluate nausea as well as the findings from these studies. Intraclass correlation coefficients (ICCs) assessed parent-child concordance on the PROMIS symptom scales. ICC values were interpreted as follows: 0.40, poor agreement; 0.41-0.60, moderate agreement; 0.61-0.80 good agreement; and 0.81 and higher, excellent agreement.

Results

Sixty-three patients (49 female, 78%) with a mean age (±SD) of 14.5 ± 2.8 years (range 7-18) meeting Rome IV criteria for functional nausea were included. Most patients were Caucasian (n = 61; n = 2 did not indicate race), with 9 patients reporting Hispanic ethnicity.

Aside from gastroenterology, 32 patients saw at least 1 subspecialist in cardiology or neurology for the comorbidities associated with functional nausea.

Comorbid Symptoms

Forty comorbid symptoms were investigated using the methodology detailed in Table I. Of these symptoms, those present in at least 25% of patients are described. As shown in Table II, 18 comorbid symptoms occurred in over 25% of the subjects. The most prevalent symptoms were abdominal pain, headache, OI, fatigue, disturbed sleep, anxiety, allergies, and vomiting. Of the subjects with OI, 15 were diagnosed with POTS and 7 with OH. Child report of OI on the COMPASS 31 was on average 6.06 out of 10 (n = 51, SD = 2.53), with higher scores indexing more severe OI.

Table II. Most common comorbidities

Comorbid symptoms	Number (%)
Abdominal pain	59 (93.7)
Headache	52 (82.5)
Orthostatic Intolerance	51 (81.0)
Fatigue	47 (74.6)
Disturbed sleep	45 (71.4)
Anxiety	37 (58.7)
Constipation	36 (57.1)
Allergies	34 (54.0)
Vomiting	32 (50.8)
Poor appetite	31 (49.2)
Joint pain	29 (46.0)
Hypermobility	23 (36.5)
Weight loss	22 (34.9)
Diarrhea	19 (30.2)
Syncope	17 (27.0)
Urinary symptoms	17 (27.0)
Depression	16 (25.4)
Dysphagia	16 (25.4)

To further assess and validate the self-report of symptoms, patients and their parents completed PROMIS questionnaires. The scores for each scale are reported in Table III. ICCs were used to evaluate agreement between parents and children on the following symptoms: fatigue, anxiety, depression, pain interference, pain intensity, and sleep disturbance. Agreement was good to excellent (ICCs = .78.83; all significant at $P < .001$). Child and parent-proxy report of fatigue, sleep disturbance, and pain interference were greater than 1 SD above the referent population norms, all meeting the cut-off for moderate symptoms. The average parent proxy-report and child report of pain intensity was moderate (parent-proxy mean = 5.45, SE = 0.22, n = 53; child mean = 5.85, SE = 0.23, n = 53). Child and parent-proxy reports of anxiety and depression met criteria for moderate severity. The parent-proxy fatigue score met the cut-off for severe symptoms.

Missed School

Of the subjects (n = 37) who completed a National Center for Health Statistics question regarding the number of school days missed in the past year, 75.7% had missed 11+ days of school. We examined the remaining subjects' (n = 26) medical records for notes about missed school and found that 13 were homebound or had missed multiple weeks in the past year, 9 missed occasionally or did not miss school, and 4 subjects were missing notes on school attendance or not applicable. Taken together, 69.5% of subjects missed more than 10 days of school due to their symptoms (not including those whose records were missing or not applicable) compared with a national average of 4.0% for all children age 5-17 years and 27.1% for all children with a current health status of fair or poor.[14]

Diagnostic Tests and Surgical Procedures

When considering endoscopic, radiologic, and surgical intervention, patients had a median of 4 procedures performed (range 0-32). Of these, a median of 1 (range 0-11) had abnormal findings.

Patients underwent 64 EGDs, of which 28 identified some pathology. Of the 28 abnormal endoscopies, only 6 specific diagnoses were made: *Helicobacter pylori* (n = 2), polyps (n = 2), celiac disease (n = 1), and lactase deficiency (n = 1). The remaining findings included non-EoE esophagitis (n = 10), unspecified gastritis (n = 6), chronic

Table III. Parent-proxy and child PROMIS scores

	Parent-proxy score		Child score	
PROMIS 4-item scale	Mean (SE)	Parent n	Mean (SE)	Child n
Depression	55.97 (1.37)	54	52.30 (1.26)	55
Anxiety	58.09 (1.57)	54	57.13 (1.41)	53
Pain interference	63.70 (0.94)	53	62.29 (1.17)	53
Sleep disturbance	64.82 (0.89)	53	63.20 (1.01)	54
Fatigue	66.63 (1.38)	52	62.68 (1.39)	51

inflammation (n = 1), inflammation in the duodenum (n = 1), healing duodenal ulcer (n = 1), candida infection (n = 1), polypoid lesion (n = 2), and inconclusive findings (n = 2). One upper endoscopy was excluded as it was performed for caustic ingestion and, therefore, unrelated to previously reported symptoms. Patients also underwent 32 colonoscopies, of which 5 informed diagnoses of Crohn's disease (n = 1), rectal ulcers (n = 2), chronic nonspecific inflammation (n = 1), and mild proctitis (n = 1).

There were 4 cholecystectomies performed in our patient cohort. The indications for cholecystectomy were biliary dyskinesia (50%), possible gallbladder sludging (25%), and symptomatic cholelithiasis (25%). Postoperative findings indicated only 1 abnormal gallbladder with evidence of cholecystitis and gallstones.

Radiologic Procedures

A total of 199 radiologic procedures were performed on 53 patients. Thirty-four out of 59 abdominal radiographs identified: moderate to severe constipation (n = 32), a small calcification (n = 1), and spina bifida occulta (n = 1). There were 63 abdominal ultrasonographies performed on 36 subjects. Of the 6 abnormal ultrasonographies, findings included an unspecified cyst (n = 1), duplicated right renal collecting system with mild hydronephrosis (n = 1), bilateral ovarian enlargement (n = 1), hepatomegaly (n = 1), and splenomegaly (n = 2). Three out of 20 gastric emptying scans demonstrated delayed emptying. There were 18 upper GI series performed in which only one was considered abnormal, showing mildly diffuse gastric fold thickening. Seven out of 19 abdominal CT scans had abnormal findings, including intussusception (n = 2), mesenteric lymphadenopathy (n = 2), moderate colonic gas and stool (n = 2), and a nonspecific cystic structure (n = 1). There were 10 abdominal MRIs performed, which included abdominal MRI with contrast, magnetic resonance enterography, and magnetic resonance angiography. Two out of 10 abdominal MRIs were abnormal, revealing mild thickening of the distal rectum and focal stenosis in the proximal celiac artery suggestive of median arcuate ligament syndrome. There were 10 HIDA scans, with 3 abnormal findings: decreased gallbladder ejection fraction (n = 2) and bile reflux (n = 1). Although this report focused on GI radiologic procedures, nausea and its comorbid symptoms can be associated with intracranial pathology. Nineteen patients underwent 18 brain MRI/magnetic resonance angiographies and 6 head CTs that were normal except for 4 incidental MRI findings (eg, benign pineal cyst).

We were unable to collect reports for all studies performed as we did not have access to all reports. There were 3 missing endoscopy reports and 5 missing radiologic reports. If the diagnosis or conclusion of a report was not definitive, it was considered inconclusive. Two upper endoscopies and 16 radiologic procedures (2 abdominal radiographs, 7 abdominal ultrasonographies, 3 gastric emptying scans, 1 upper GI series, 1 HIDA scan, 1 abdominal CT scan, and 1 abdominal MRI) were considered inconclusive.

Autonomic Procedures

Eighteen patients underwent autonomic testing as part of their work-up for orthostatic symptoms. Nine out of 19 HUTs (47.4%) were abnormal, meeting criteria for POTS (n = 3) or OH (n = 6). Thirty additional autonomic diagnostic procedures were performed. They included quantitative sudomotor axon reflex test, deep breathing, Valsalva maneuver, and thermoregulatory sweat testing. Of those 30 autonomic tests, 5 (16.7%) were abnormal.

Discussion

This study demonstrated that patients with functional nausea suffer from multisystemic comorbidities involving GI, cardiovascular, psychiatric, neurologic, musculoskeletal, urologic, and constitutional symptoms. Relative to these symptoms, patients receive an extensive diagnostic GI work-up involving endoscopy and radiologic testing that are low-yield in informing a diagnosis and treatment plan.

Eighteen comorbidities occurred in over 25% of the patients studied. Within the GI domain, abdominal pain occurred in all but 4 patients. This finding replicates earlier data on patients with functional abdominal pain that showed high rates of comorbidity with nausea[2,3] and underscores the importance of screening for nausea and abdominal pain together in a clinical setting. Constipation and vomiting were also commonly reported in patients.

Most of the comorbid symptoms, however, occurred outside of the GI tract including headaches, fatigue, OI, disturbed sleep, anxiety, allergies, joint pain, and hypermobility. Eighty percent of patients reported headaches. Because of limitations with self-report, we did not differentiate between headaches and migraines. However, there have been associations found between FGIDs and migraine headaches,[15] and chronic nausea and migraine.[5] Future studies are needed to assess these associations in the context of functional nausea specifically. Our results further replicated findings that OI and anxiety were common in patients with chronic, unexplained nausea.[5,6] Fatigue and disturbed sleep were reported in over 70% of patients. This finding is consistent across other pain-related FGIDs, with studies showing that severity of sleep disturbance is associated with functional impairment.[16] Finally, joint hypermobility was prevalent within this patient population. This finding is also corroborated by studies of other complex FGIDs, and the comorbidities experienced with joint hypermobility share considerable overlap with those experienced by children with functional nausea.[17,18]

In addition to relying on patient or parent report of symptoms, we prospectively assessed non-GI comorbidities observed in other FGIDs using the COMPASS 31 and PROMIS scales. Child report of OI on the COMPASS 31 indicated this patient population on average experienced moderate to high OI. Furthermore, the PROMIS questionnaires revealed that our patient population experienced significantly worse fatigue, disturbed sleep, and pain interference than referent

populations. All symptoms measured met the PROMIS cut-offs for at least moderate severity. The pain interference scale provided an assessment of how functionality is impaired by pain. This reduced functionality may contribute to the finding that nearly 70% of our patients missed more than 2 weeks of school a year because of their symptoms, significantly higher than the national average for children their age, even those with chronic medical conditions.

This study underscores the importance of a holistic approach to clinical care for patients with functional nausea that incorporates identification of non-GI comorbidities and psychosocial aspects of the condition. These comorbidities are not typically screened for in a GI clinic but may contribute to the etiology of the nausea and can significantly impact the clinical course. For example, studies have shown that treating migraine in patients with FGIDs can reduce GI symptoms,[19] and treating OI in pediatric patients with chronic nausea reduced nausea symptoms.[20,21] Systematically screening for these common comorbidities can help to better define the clinical phenotypes of patients with functional nausea and may also provide insights into treatment options.

Patients with functional nausea are more likely to undergo an extensive diagnostic work-up that focuses primarily on GI symptoms with little attention to the comorbidities. There were a variety of diagnostic tests performed, ranging in invasiveness from an abdominal film to gallbladder removal. Most of the diagnostic tests did not reveal a clear cause for the nausea. Although the EGDs did have a higher rate of identifying any pathology, <10% of EGDs informed a specific diagnosis. The colonoscopies and cholecystectomies also had low diagnostic yields; 14% of colonoscopies found evidence of Crohn's disease, rectal ulcers, and inflammation, and only 1 of the 4 gallbladders removed showed pathologic abnormality. Radiologic tests, except for abdominal radiographs, had similarly unimpressive diagnostic yields, ranging from approximately 10% to 36%. These nonspecific findings did not inform treatment of the nausea, as all patients continued to have nausea at the time of first clinic visit.

Two tests were particularly effective in identifying abnormal findings: the abdominal radiograph and HUT. More than 50% of the abdominal radiographs performed had identified moderate or above stool burdens. This result corroborates our other finding that over one-half of the study sample reported constipation. Despite these radiograph findings, it is not routinely recommended to use abdominal radiography in the diagnosis of constipation.[22] Forty-seven percent of HUTs resulted in a diagnosis of either POTS or OH. There may be a selection bias in this case as the ordering physician had a high suspicion based on clinical symptoms of OI. Such findings support the routine evaluation of OI in a patient history and suggest that a more targeted diagnostic approach, using testing as an adjunct to clinical suspicion, could reduce unnecessary testing.

Low-value care is a common problem facing pediatric patients with FGIDs. Kovacic et al examined the diagnostic imaging done for patients with chronic nausea and found that 84% of those patients had an extensive imaging work-up, as defined by any imaging done in addition to an abdominal ultrasonography and upper GI contrast study. They found that 80% of patients with chronic nausea also had extensive laboratory tests, and 93% underwent endoscopy with 98% of those endoscopies returning normal results.[5] Among the reasons providers order extensive diagnostic testing may include parental concerns. For example, in cases of constipation, a radiograph may validate a diagnosis of constipation.[23] Similarly, for recurrent abdominal pain, negative tests can reassure families of the absence of a more serious underlying condition.[24] Although these procedures are generally considered safe, the benefit relative to health risk comes into question if they provide only marginal benefit in delineating the underlying cause of symptoms.

In addition to risk of harm, patients and the healthcare system face the financial burden of these diagnostic tests. One study on pain-predominant FGIDs found that the average cost per patient for the extensive diagnostic work-up was $6104.30.[7] Low-value care stemming from overtesting and unnecessary procedures amounts to an annual cost of $17.2-27.9 billion.[25] These findings will allow physicians to engage in a more targeted diagnostic approach and minimize cost and risk for the patient.

This study had several limitations. First, not all symptoms were systematically assessed. We assigned patients questionnaires to measure relevant comorbidities, however, through this study we identified additional comorbid symptoms that should be prospectively assessed. Further, a portion of the study (chart review) was retrospective in nature. Although we used a wide variety of search methods, including parent and child report, clinic notes, and clinical data from other institutions, our data was limited by what had been documented in the EHR. Furthermore, in identifying GI procedures as part of the work-up for nausea, it was not always documented whether the procedure was done to assess nausea alone. It was difficult to completely differentiate as nausea was so highly comorbid with other symptoms such as abdominal pain or vomiting. Furthermore, although we listed all findings reported from the GI tests, the procedure report did not indicate whether those findings were of clinical significance to the nausea.

Given the wide range of cardiovascular, psychological, neurologic, and constitutional symptoms and the limited yield of invasive GI measures, future studies should consider assessment of these comorbid symptoms to better characterize these patients. Use of the recently developed Nausea Severity Scale[26] could help improve our evaluation of this understudied, aversive symptom. A systematic assessment approach will be essential to improve our understanding of the relationship of functional nausea to its comorbidities. Better definition of the multiple presentations of functional nausea will provide the opportunity to move beyond descriptions of the condition toward the development of empirically derived phenotypes that are associated with specific etiological factors. ■

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Table I. Comorbidity search methods

Comorbid symptoms	Definitions or search methods
Abdominal pain	Search for abdominal pain
ADHD	Search for attention deficit hyperactivity disorder, ADHD
Allergies	Refer to Intake Questionnaire's list of any food, seasonal, or environmental allergies
Anxiety	Search for anxiety
Asthma/Lung disorder	Refer to Intake Questionnaire's review of systems category for any mention of problems with asthma/lungs
ASD	Search for autism, ASD
Auto-immune	Search health history for auto-immune disorders such as: Hashimoto thyroiditis, lupus, celiac disease, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), rheumatoid arthritis, Sjogren syndrome, multiple sclerosis, type I diabetes, inflammatory bowel disease, small fiber neuropathy
Blood disorders	Refer to intake questionnaire's review of systems hematology category, which broadly asked about blood disorders, and included any reported issue ranging from bruising, hemochromatosis or anemia
Cardiac	Refer to intake questionnaire's review of systems cardiac category and included any diagnosed cardiac defect other than tachycardia, OH, and POTS to avoid redundancy with other comorbid symptom categories
Chronic pain	Search health history for chronic pain disorder such as: chronic pain amplification syndrome, neuropathic pain, hyperalgesia, chronic regional pain syndrome, fibromyalgia, visceral hypersensitivity
Concussion	Search for concussion
Connective tissue disorder	Search health history for report of connective tissue disorders other than Ehlers-Danlos syndrome to avoid redundancy with the hypermobility category.
Constipation	Search for constipation
CVS	Search for cyclic vomiting, CVS
Depression	Search for depression
Diarrhea	Search for diarrhea
Disturbed Sleep	Refer to both Intake Questionnaire and medical chart to identify any report of difficulty sleeping
Dysphagia	Include if parents answered "yes" to the Intake Questionnaire question "Does your child have trouble swallowing?"
EoE	Search for eosinophilic esophagitis, EoE
Fatigue	Search for fatigue
GERD	Search for gastroesophageal reflux, GERD
Gastroparesis	Search for gastroparesis
Headache	Search for headache or migraine
Hypermobility	Search for Ehlers-Danlos, EDS, hypermobility; confirmed with Beighton scores found in patient chart: patients were considered hypermobile if their Beighton score was >4, and if there was no Beighton score, referred to the Intake Questionnaire for report of hypermobility.
Hypertension	Search for hypertension, HTN, high blood pressure
IBS	Search for irritable bowel syndrome, IBS
Joint pain	Refer to Intake Questionnaire's review of systems "muscle/bone/joint" category which asked about pain or hypermobility for report of any joint pain, pain, or aches
Kidney disease	Refer to Intake Questionnaire's review of systems "urinary" or "endocrine" categories which asked about urinary tract infections or chronic infections, and thyroid, diabetes respectively, for report of any problems.
Liver disease	Refer to health history for any mention of liver problems
ODD	Search for oppositional defiant, ODD
OI	Search for Orthostatic intolerance, dizziness, OI, orthostatic hypotension, OH, postural orthostatic tachycardia, POTS
Poor appetite	Search for poor appetite, loss of appetite, decreased appetite
Raynaud disease	Search for Raynaud
Sleep disorder	Refer to EHR and health history for diagnosed sleep disorder such as insomnia (either diagnosed via sleep study, or treated with significant prescriptions), apnea, narcolepsy, or a non-restorative sleep disorder
Syncope	Search for syncope, faint, fainting
Tachycardia	Search for tachycardia, excluded all mention of POTS
Urinary issues	Refer to intake questionnaire review of systems urinary category which asked specifically about urinary tract infections or chronic infections, and included if patient reported a history of, or current, enuresis, or recurrent (>1) urinary tract infections.
Vomiting	Include if parents responded "yes" to the Intake Questionnaire question "Does your child vomit?"
Weight gain	Include if parents responded "yes" to the Intake Questionnaire question "Has your child gained weight recently?"; Also checked the amount to confirm the gain in EHR but did not exclude any for the amount gained.
Weight loss	Include if parents responded "yes" to the Intake Questionnaire question: "Has your child lost weight recently?"; Also checked the amount to confirm the loss in EHR but did not exclude any for amount lost.

ADHD, attention deficit hyperactivity disorder; *ASD*, autism spectrum disorder; *CVS*, cyclic vomiting syndrome; *EoE*, eosinophilic esophagitis; *GERD*, gastroesophageal reflux disorder; *IBS*, irritable bowel syndrome; *ODD*, oppositional defiant disorder; *OI*, orthostatic intolerance.