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ORIGINAL ARTICLE

Gastroenterology: Celiac Disease

The prevalence and predictive factors of overlapping disorders of gut–brain interaction and celiac disease in children

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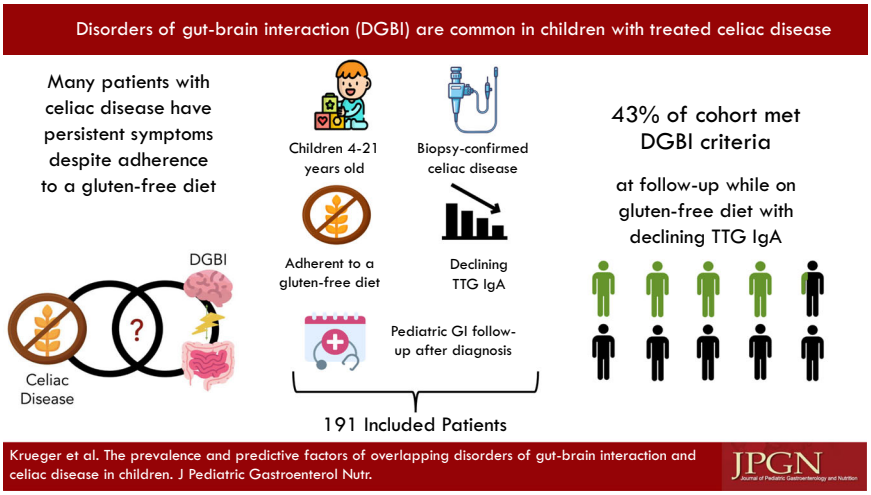
Abstract

Objectives: Disorders of gut–brain interaction (DGBI) are increasing in prevalence; however, diagnosis remains challenging in the setting of organic diseases. While adult studies have shown overlap between DGBI and celiac disease (CeD), no United States studies have assessed DGBI prevalence using Rome IV criteria in pediatric CeD. This study aims to report DGBI prevalence in pediatric CeD patients adherent to gluten-free diet (GFD) with declining serologies and identify common DGBI subtypes and predictive factors for developing DGBI.

Methods: Single-center, retrospective study of children (4–21 years old) with biopsy-proven CeD who were evaluated for DGBI based on Rome IV criteria. Patients who were adherent to a GFD, demonstrated tissue transglutaminase immunoglobulin A (TTG IgA) decline, and had at least one visit 9–24-months after diagnosis with a pediatric gastroenterologist were assessed for the presence or absence of gastrointestinal symptoms at all subsequent follow-up visits. Predictive factors associated with DGBI diagnosis were evaluated.

Results: Of the 191 pediatric patients included, 43% ($n = 83$) met Rome IV DGBI diagnostic criteria. Functional constipation (27/83, 33%) and functional abdominal pain (24/83, 29%) were the most common DGBI. Abdominal pain, constipation, and vomiting at initial presentation as well as comorbid joint hypermobility, headaches, and chronic musculoskeletal pain increased risk of developing DGBI after serological decline.

Conclusions: DGBI are common in pediatric CeD patients adherent to a GFD with declining TTG IgA. Clinicians should have a high index of suspicion for DGBI in CeD patients with persistent symptoms despite strict GFD adherence to facilitate diagnosis and management.



KEYWORDS
functional abdominal pain, functional constipation, gluten-free diet, pediatric, Rome IV

1 | INTRODUCTION

Celiac disease (CeD) is an autoimmune condition triggered by the ingestion of gluten characterized by small intestinal inflammation and villous atrophy which can lead to a wide range of gastrointestinal and extra-intestinal manifestations. It is estimated that 1 in 100 North Americans have CeD.[1] The clinical presentation of CeD is diverse, particularly in children. Among children with CeD, gastrointestinal symptoms are common at presentation, with abdominal pain reported as the most common while other common symptoms include constipation, diarrhea, nausea/vomiting, and flatulence.[2]

Disorders of gut–brain interaction (DGBI), previously referred to as functional gastrointestinal disorders, are a group of conditions characterized by chronic or recurrent gastrointestinal symptoms not fully explained by structural or biochemical abnormalities. These disorders result from complex interactions between the central nervous system, the enteric nervous system, and other factors, including gut motility, visceral hypersensitivity, immune function, gut microbiota, and psychosocial influences, and are widely understood in the context of a biopsychosocial framework.[3] While these conditions have long been present, only relatively recently have these conditions been more carefully evaluated.[4] The Rome IV criteria, established by the Rome Foundation and published in 2016, provide the current diagnostic guidelines for DGBI[5] and address limitations of prior guideline iterations.[6]

The diagnosis and management of DGBI is challenging given overlapping symptomology of DGBI subtypes with each other[7] and the overlap of DGBI with organic gastrointestinal conditions. Furthermore, diagnosing DGBI based solely on clinical symptoms has its own challenges, with a 2022 commentary suggesting modifying the Rome IV criteria to be more amenable to clinical practice by including symptom description as "bothersome" and focusing on the impact on patient quality of life rather than frequency and duration of symptoms.[8]

Given the variable presentation of CeD and overlap with DGBI symptoms, diagnosing DGBI in CeD patients can be challenging.[9] This overlap is highlighted by the American College of Gastroenterology's recommendation to perform serologic testing for CeD as a part of the clinical management guidelines for irritable bowel syndrome (IBS), one of the most common DGBI.[10]

What is Known

- Disorders of gut–brain interaction (DGBI) are increasingly prevalent and significantly impact patient quality of life.
- DGBI and celiac disease (CeD) share many similar symptoms.

What is New

- Forty-three percent of pediatric CeD patients with tissue transglutaminase immunoglobulin A decline and gluten-free dietary adherence met Rome IV DGBI diagnostic criteria.
- Functional constipation and functional abdominal pain were the most common DGBI subtypes in pediatric CeD patients.
- New or persistent symptoms despite CeD serologic improvement should prompt consideration of DGBI to improve management.

Diagnosing DGBI in CeD patients is difficult as tissue transglutaminase (TTG) immunoglobulin A (IgA) typically declines after adopting a gluten-free diet (GFD), but might take 2 years or more to normalize,[11] and clinical assessments about ongoing symptoms are needed before normalization. However, there are no studies evaluating the overlap between DGBI and CeD in US children. Better understanding this overlap is critical given that (1) the prevalence of DGBI is increasing, with studies suggesting approximately one-third of adults[12] and 25% of children aged 4–18 years old[13] meet DGBI diagnostic criteria and (2) the consequences of delayed or missed DGBI diagnosis are numerous, including increased healthcare costs and utilization.[14]

In this single-center US study, we aimed to establish the prevalence and subtypes of DGBI seen in pediatric CeD and assess predictive factors among children with CeD who ultimately were diagnosed with DGBI to facilitate improved diagnosis and care of these patients.

2 | METHODS

A retrospective chart review from 2016 to 2024 was conducted on 191 pediatric CeD patients receiving care at Cincinnati Children's Hospital Medical Center (CCHMC), a tertiary pediatric hospital located in Cincinnati, Ohio.

Patients with biopsy confirmed CeD diagnosis 4–21 years old who (1) had an initial visit with a pediatric gastroenterologist at CCHMC between 2016 and 2024, (2) had at least one follow-up visit in the 9–24-month period after diagnosis, and (3) demonstrated sustained decline in TTG IgA levels after implementing a strict GFD were included in the study. For this study, sustained TTG IgA decline required at least two declining TTG IgA values, a 90% decline from baseline, or normalization of TTG IgA. Patients were excluded if they were diagnosed with CeD before being seen at CCHMC, did not have follow-up visits at CCHMC after diagnosis, were not adherent to a GFD, and/or did not demonstrate a sustained TTG IgA decline as defined. Biopsy-proven CeD diagnosis required a Marsh-Oberhuber score of 3,[15] either through explicit scoring by the reading pathologist on the biopsy report or if the report noted increased intraepithelial lymphocytes, villous blunting and either presence of crypt hyperplasia or no mention of crypt hyperplasia. Demographic and anthropometric data, medication and dietary treatment, family history, serology levels, and endoscopy results were extracted from the electronic health record (EHR).

Anthropometric and symptomatologic data was obtained for the patient's initial visit with a pediatric gastroenterologist and for the first follow-up visit that occurred during the 9–24-month period after diagnosis. Based on expert opinion, symptom information was not collected on any visits in the 9-month period immediately following diagnosis to provide time for clinical improvement on a GFD. However, the first follow-up visit in the 9–24-month period after diagnosis and all subsequent visits with a pediatric gastroenterologist were reviewed to assess for new or persistent symptoms and GFD adherence.

Patients were classified into two groups. (1) The control group (no-DGBI group) consisted of CeD patients who demonstrated TTG IgA decline, were asymptomatic at the 9–24-month follow-up visit, and remained asymptomatic at all subsequent visits. (2) The DGBI group included CeD patients with TTG IgA decline but who had persistent or new onset symptoms satisfying Rome IV criteria at any visit at least 9 months after diagnosis.

2.1 | Statistical analysis

Median and interquartile range were reported for continuous demographic variables whereas count and percentage were reported for categorical variables. Fisher Exact Test was used to evaluate predictive factors for developing DGBI. The Wald method was utilized to report odds ratios (ORs) and 95% confidence intervals (CIs). All statistical analyses were performed in R Studio[16] and a p-value of less than 0.05 was considered statistically significant.

To achieve adequate statistical power, the study aimed to include approximately 200 CeD patients with an estimated DGBI prevalence of 30%. For a sample size of 200 observations, a Two-Sided Exact Test using Binomial Enumeration as the power calculation method provided 90% power to detect a difference between 20% and the hypothesized 30%. Using the Clopper-Pearson exact method and assuming the 30% prevalence rate for this sample size, a 95% CI of the estimated prevalence rate would have a width of about 12.8%. For sample prevalence between 22.7% and 37.3%, the 95% CI would have similar widths.

2.2 | Ethics statement

All aspects of the study were approved by the Institutional Review Board at CCHMC.

3 | RESULTS

Of the 663 patients with CeD diagnosis seen at CCHMC from 2016 to 2024, 191 met inclusion criteria. The cohort was majority female ($n = 125$, 65%), Non-Hispanic ($n = 187$, 98%), and White ($n = 182$,

TABLE 1 Demographic information, common presenting symptoms, and common comorbid conditions for the 191 included celiac disease patients.

Age at diagnosis Median (interquartile range) in years	**11 (6.09)**
Sex	***N* (%)**
Male	66 (35)
Female	125 (65)
Electronic health record race	
White	182 (95)
Black or African American	3 (1.5)
Asian	2 (1.0)
Middle Eastern	1 (0.5)
Native Hawaiian and Other Pacific Islander	1 (0.5)
Not reported	2 (1.0)
Electronic health record ethnicity	
Non-Hispanic	187 (98)
Hispanic	1 (0.5)
Unknown	3 (1.5)
Most common symptoms at diagnosis	
Abdominal Pain	123 (64)
Constipation	68 (36)
Nausea	39 (20)
Diarrhea	31 (16)
Vomiting	31(16)
Asymptomatic	38 (20)
Comorbid conditions	
Psychiatric diagnoses[a]	65 (34)
Type 1 Diabetes	30 (16)
Headaches	29 (15)
Musculoskeletal pain	25 (13)
Joint hypermobility syndrome	18 (9)
Thyroid conditions	9 (4.7)
Eosinophilic esophagitis	5 (2.6)

[a]Psychiatric diagnoses = depression, anxiety, attention deficit hyperactivity disorder, bipolar I or II disorder, anorexia nervosa, bulimia nervosa, and posttraumatic stress disorder.

95%). The median age at diagnosis was 11 years (interquartile range = 6.09 years) (Table 1). Common exclusion reasons included not meeting diagnostic biopsy criteria, not having follow-up at CCHMC, having a CeD diagnosis before being seen at CCHMC, or not having a follow-up in the 9–24-month period after diagnosis (Figure 1).

The most common presenting symptoms at CeD diagnosis were abdominal pain (64%), constipation (36%), and nausea (20%). Thirty-eight patients (20%) were asymptomatic at the initial visit. One-third of patients had at least one documented psychiatric comorbidity (34%), with anxiety (19%), attention deficit hyperactivity disorder (12%), and depression (10%) the most common. Type 1 diabetes was the next most common comorbid condition (16%), followed by headaches (15%), musculoskeletal pain (13%), and joint hypermobility syndrome (9%). Fifteen percent endorsed a family history of DGBI, with functional dyspepsia/gastroparesis and IBS the most common subtypes.

Overall, 83 (43%) patients met Rome IV DGBI criteria, which was significantly higher than the 30% hypothesized, while 108 (57%) did not meet DGBI criteria. There was no statistically significant difference in age at diagnosis, baseline TTG IgA, race, or ethnicity between groups. However, the DGBI group had a significantly lower BMI z-score at presentation compared to the no-DGBI group (median 0.04 vs. 0.34, two-sample *t*-test assuming equal variances, $p = 0.03$). Functional constipation (27/83, 33%) was the most common DGBI identified, followed by functional abdominal pain (24/83, 29%), functional nausea (19/83, 23%), IBS (12/83, 14%), and functional dyspepsia/gastroparesis (10/83, 12%). Among patients who were symptomatic at presentation, 54% (83/153) eventually met DGBI criteria. Nearly three-quarters (61/83, 73%) of the DGBI group had persistence of the same gastrointestinal symptoms from their presenting visit whereas one-quarter (22/83, 27%) had new-onset symptoms that were not present or differed from the reported symptoms at CeD diagnosis. Only two (2/38, 5.2%) asymptomatic patients at presentation developed a DGBI (both diagnosed with functional nausea). Of note, only 14 patients in the DGBI group (17%) had a DGBI diagnosis listed as a medical problem in the EHR, whereas the majority were classified with DGBI through fulfilling Rome IV criteria based on visit notes. Four patients (4.8%) in the DGBI group underwent auricular percutaneous electrical nerve field stimulation and six (7.2%) underwent pyloric botulinum toxin injection and dilation. Use of gastrointestinal-directed medications was common in this group, with cyproheptadine (21/83, 25%), hyoscyamine (19/83, 23%), and dicyclomine (10/83, 12%) the most prescribed. Over one-third (66/191, 35%) saw the behavioral medicine and clinical psychology (BMCP) team at CCHMC, with the majority (39/66, 59%) from the DGBI group.

Presenting symptoms, diagnostic severity, comorbid conditions, and family history were evaluated to determine predictive factors of developing DGBI (Table 2). Patients with abdominal pain (OR 3.09, 95% CI [1.57–6.31]), constipation (OR 2.19, 95%CI

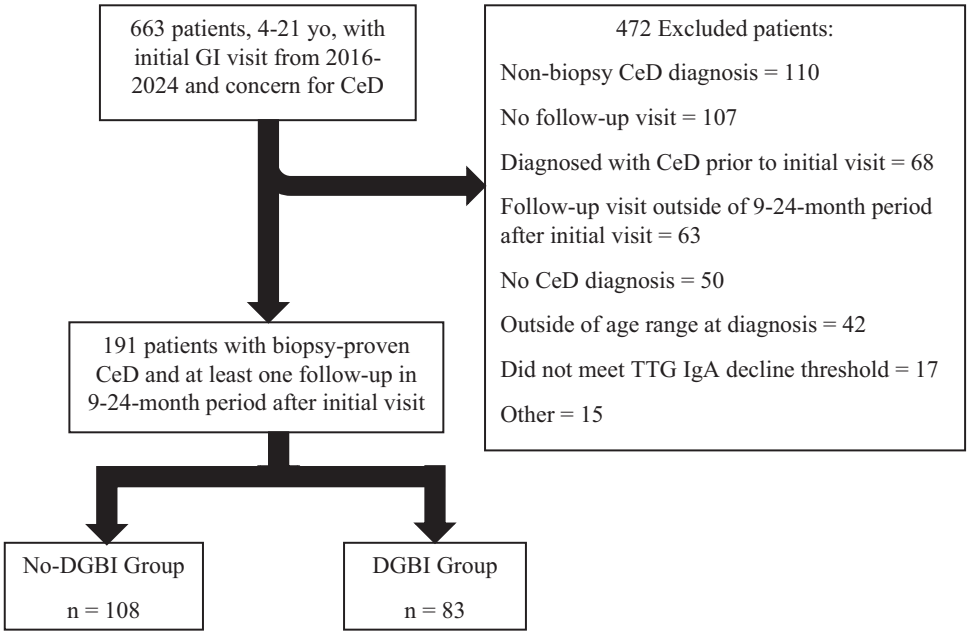


FIGURE 1 472 of the 663 patients identified through Epic query from 2016 to 2024 with an initial gastrointestinal (GI) visit at Cincinnati Children's Hospital Medical Center and concern for celiac disease (CeD) were excluded. Of the 191 patients included, 83 subjects met Rome IV criteria for a disorder of gut–brain interaction (DGBI) while 108 did not meet DGBI criteria. TTG IgA, tissue transglutaminase immunoglobulin A.

[1.15–4.20]), vomiting (OR 2.36, 95%CI [1.01–5.74]), and nighttime pain awakening (OR 9.76, 95%CI [1.21–447.23]) at the initial visit were more likely to develop a DGBI **(**Figure 2). The severity of diagnostic biopsy based on Marsh criteria (Marsh 3a vs. 3b vs. 3c when explicitly stated by the reading pathologist) was not associated with an increased likelihood of DGBI diagnosis, however, those with complete villous blunting described in the pathology findings were at increased risk of DGBI (OR 2.28, 95%CI [1.22–4.29]). Having comorbid joint hypermobility syndrome (OR 5.23, 95%CI [1.56–22.74]), headaches (OR 3.47, 95% CI [1.40–9.23]), chronic musculoskeletal pain (OR 3.20, 95%CI [1.22–9.08]), and chronic muscle pain (OR 5.61, 95%CI [1.08–55.60]) were associated with an increased risk of developing DGBI. The presence of any comorbid psychiatric diagnosis was a significant predictor of developing DGBI (OR 2.08, 95%CI [1.09–4.01]), however, there was no statistically significant single psychiatric condition that was predictive when evaluated separately. Comorbid type 1 diabetes was associated with a decreased risk of developing a DGBI (OR 0.27, 95%CI [0.087–0.74]). Use of neuromodulation treatment with IB-stim ($p = 0.03$**),** pyloric botulinum toxin injection and dilation ($p = 0.006$), and emergency department visits (but not hospitalizations) for gastrointestinal complaints after CeD diagnosis (OR 4.23, 95%CI [1.01–25.08]) were significantly associated with DGBI diagnosis. Sex, race, ethnicity, and presence of any family history of DGBI did not significantly increase the risk of DGBI diagnosis.

4 | DISCUSSION

This single center retrospective study is the first comprehensive study evaluating the overlap of DGBI based on Rome IV criteria and CeD in US pediatric patients. In this study, nearly half (43%) of CeD patients with sustained decline in TTG IgA levels on a strict GFD met clinical criteria for a DGBI. These findings fill an important knowledge gap, as the most prominent US study evaluating DGBI in children excluded patients with CeD[13] while other studies evaluating pediatric CeD and DGBI were done in non-US populations.[17,18]

The prevalence reported here is similar to a study of adults with CeD who were adherent to a GFD that reported over 50% met criteria for a functional gastrointestinal disorder[19] and is higher than previously reported pediatric prevalence rates.[17,18] A prospective Italian pediatric cohort study found that IBS and functional constipation were more common among patients with CeD who were on a GFD for at least 1 year and had normalization of serologic markers as compared to healthy controls.[17] An older study of pediatric patients from Italy found that 28% of patients demonstrated functional gastrointestinal disorders, though this was based on Rome III criteria.[18] Further, it has been shown that even with adherence to a GFD, a significant proportion of pediatric patients experience ongoing gastrointestinal symptoms,[20] something that may be attributable to undiagnosed DGBI.

The most common DGBI subtype among our pediatric CeD cohort was functional constipation (27/83,

TABLE 2 Results of statistical analyses utilizing Fisher Exact test to evaluate predictive factors of developing a disorder of gut–brain interaction (DGBI) in pediatric celiac disease (CeD) patients adherent to a gluten-free diet with declining tissue transglutaminase immunoglobulin A.

Variable	Subcategory	DGBI group *N* (%)	No-DGBI *N* (%)	Odds ratio estimate	95% Wald confidence limits	*p* value
Sex	Male	26 (31.33)	40 (37.04)			0.45
	Female	57 (68.67)	68 (62.96)			
Abdominal pain at initial visit	Present	65 (78.31)	58 (53.70)	**3.09**	**(1.57–6.31)**	**0.0005**
Constipation at initial visit	Present	38 (45.78)	30 (27.78)	**2.19**	**(1.15–4.20)**	**0.014**
Diarrhea at initial visit	Present	17 (20.48)	14 (12.96)			0.17
Weight loss reported at initial visit	Present	12 (14.46)	11 (10.19)			0.51
Nausea reported at initial visit	Present	19 (22.89)	20 (18.52)			0.47
Vomiting reported at initial visit	Present	19 (22.89)	12 (11.11)	**2.36**	**(1.01–5.74)**	**0.031**
Regurgitation reported at initial visit	Present	12 (14.46)	7 (6.48)			0.09
Bloating reported at initial visit	Present	10 (12.05)	10 (9.26)			0.65
Post-prandial distress present at initial visit	Present	12 (14.46)	7 (6.48)			0.09
Blood in stool reported at initial visit	Present	8 (9.64)	5 (4.63)			0.25
Nighttime pain awakening reported at initial visit	Present	7 (8.43)	1 (0.93)	**9.76**	**(1.21–447.23)**	**0.022**
Restricted eating reported at initial visit	Present	5 (6.02)	0 (0)		**1.22**	**0.014**
Marsh 3A on diagnostic biopsy	Yes	10 (12.05)	19 (17.59)			0.32
Marsh 3B on diagnostic biopsy	Yes	12 (14.46)	13 (12.04)			0.67
Marsh 3C on diagnostic biopsy	Yes	3 (3.61)	5 (4.63)			1
Partial villous blunting on diagnostic biopsy	Yes	26 (31.33)	40 (37.04)			0.45
Complete villous blunting on diagnostic biopsy	Yes	46 (55.42)	38 (35.19)	**2.28**	**(1.22–4.29)**	**0.0079**
Comorbid type 1 diabetes	Yes	6 (7.32)	24 (22.22)	**0.27**	**(0.087–0.74**	**0.005**
Comorbid thyroid conditions	Yes	4 (4.82)	5 (4.63)			1
Psychiatric comorbidity	Yes	36 (43.37)	29 (26.85)	**2.08**	**(1.09–4.01)**	**0.021**
Family history of DGBI	Yes	17 (20.48)	12 (11.11)			0.10
Behavorial medicine clinical psychology visit	Yes	39 (46.99)	27 (25)	**2.64**	**(1.38–5.14)**	**0.0021**
Comorbid joint hypermobility syndrome	Yes	14 (16.87)	4 (3.70)	**5.23**	**(1.56–22.74)**	**0.003**
Comorbid dysautonomia	Yes	1 (1.2)	0 (0)			0.43
Comorbid postural orthostatic tachycardia syndrome	Yes	3 (3.61)	3 (2.78)			1
Comorbid noncardiac dizziness	Yes	2 (2.41)	0 (0)			0.19
Comorbid sleep disturbances	Yes	2 (2.41)	0 (0)			0.19
Comorbid headaches	Yes	20 (24.10)	9 (8.33)	**3.47**	**(1.40–9.23)**	**0.004**
Comorbid musculoskeletal pain	Yes	17 (20.48)	8 (7.41)	**3.20**	**(1.22–9.08)**	**0.010**
Comorbid muscle pain	Yes	8 (9.64)	2 (1.85)	**5.61**	**(1.08–55.60)**	**0.021**
Integrative treatment	Yes	0 (0)	1 (0.93)			1
Behavioral therapy	Yes	10 (12.05)	3 (2.78)	**4.76**		**0.018**

TABLE 2 (Continued)

Variable	Subcategory	DGBI group *N* (%)	No-DGBI *N* (%)	Odds ratio estimate	95% Wald confidence limits	*p* value
Neuromodulation treatment with IB-Stimulation	Yes	4 (4.82)	0 (0)		**(0.87)**	**0.034**
Pyloric botulinum toxin injection and dilation	Yes	6 (7.23)	0 (0)		**(1.59)**	**0.0061**
Hospitalizations after CeD diagnosis for gastrointestinal symptoms	Yes	5 (6.02)	1 (0.93)			0.087
Emergency department visits after CeD diagnosis for gastrointestinal symptoms	Yes	9 (10.84)	3 (2.78)	**4.23**	**(1.01–25.08)**	**0.033**

33%) which aligns with prior studies. Other common DGBI subtypes included functional abdominal pain, functional nausea, IBS, and functional dyspepsia/gastroparesis.

It is important to note that among those who were symptomatic at presentation, over half met DGBI criteria after CeD diagnosis and management. Further, the majority of patients who met DGBI criteria did so through having the persistence of the same gastrointestinal symptoms that were present at CeD diagnosis. This raises the question as to whether the symptoms at presentation were due to CeD, DGBI, or both, though definitive DGBI diagnosis cannot be made until workup and management of organic etiologies has been completed. This highlights one of the challenges facing clinicians, and this is made more difficult in CeD as post-diagnosis surveillance relies heavily on serologic monitoring which has limitations, including a lack of published data regarding expected rate of TTG IgA decline or time to normalization that correlates clinically. Further, TTG IgA has low sensitivity in detecting persistent villous atrophy.[21] Nonetheless, TTG IgA screening is minimally invasive and repeat endoscopy is not routinely recommended in the clinical management of CeD in children.

Therefore, in patients with new or residual gastrointestinal symptoms despite improvement and/or normalization of TTG IgA values while on a GFD after CeD diagnosis, DGBI should be considered. This finding should prompt clinicians to screen for DGBI at each visit and explicitly diagnose DGBI when indicated to facilitate appropriate management. Further, these findings could facilitate improved counseling for patients at CeD diagnosis. Clinicians could consider discussing that while symptoms related to CeD should improve on a GFD, some symptoms may persist, especially if they have an increased likelihood of having a comorbid DGBI. Such counseling may prevent the misattribution of persistent symptoms to ongoing gluten exposure and mitigate hypervigilance.

The other aim of this study was to identify predictive factors to aid clinicians in identifying this cohort. We found that it was rare for a patient to develop DGBI if they were asymptomatic at CeD diagnosis. Abdominal pain, constipation, vomiting, and nighttime pain awakening at initial presentation were significantly associated with increased likelihood of developing a DGBI after appropriate management of their CeD. The exact etiology of this association is unclear, but perhaps it is the severity and impact on quality of life of these symptoms at CeD diagnosis that may predispose these individuals to more persistent symptoms or hypervigilance of symptoms and thus DGBI diagnosis. Furthermore, restricted eating at presentation was associated with an increased likelihood of meeting DGBI criteria, and the DGBI group had significantly lower BMI z-scores at presentation. Together, these findings may suggest that this cohort is at risk for nutritional deficiencies which again stresses the importance of early identification of this cohort. In addition, we found that having complete villous blunting on diagnostic biopsy increased the likelihood of having a DGBI. Intuitively, it is possible that complete villous blunting can lead to greater nerve sensitization and subsequently higher rates of DGBI. It is also possible that complete villous blunting is slower to recover, which could account for lingering symptoms due to malabsorption or be related to longer duration of gut injury, and thus more chances for nerve sensitization, though further investigations are required. This finding is somewhat in opposition to prior reports that while more severe villous blunting in children with CeD was associated with worse anemia and growth disturbances, it was not associated with poorer long-term outcomes or perceived quality of life, though it did not specifically look at DGBI.[22]

In addition, several comorbid conditions were shown to have an increased risk of DGBI in our cohort including joint hypermobility syndrome, which aligns with prior studies demonstrating an increased prevalence of CeD in children with joint hypermobility syndrome.[23] Headaches, chronic musculoskeletal pain, and the presence of any comorbid psychiatric condition were also shown to have an increased risk of DGBI in pediatric CeD patients. While not causative, presence of these presenting symptoms or comorbid conditions should prompt clinicians to have a heightened

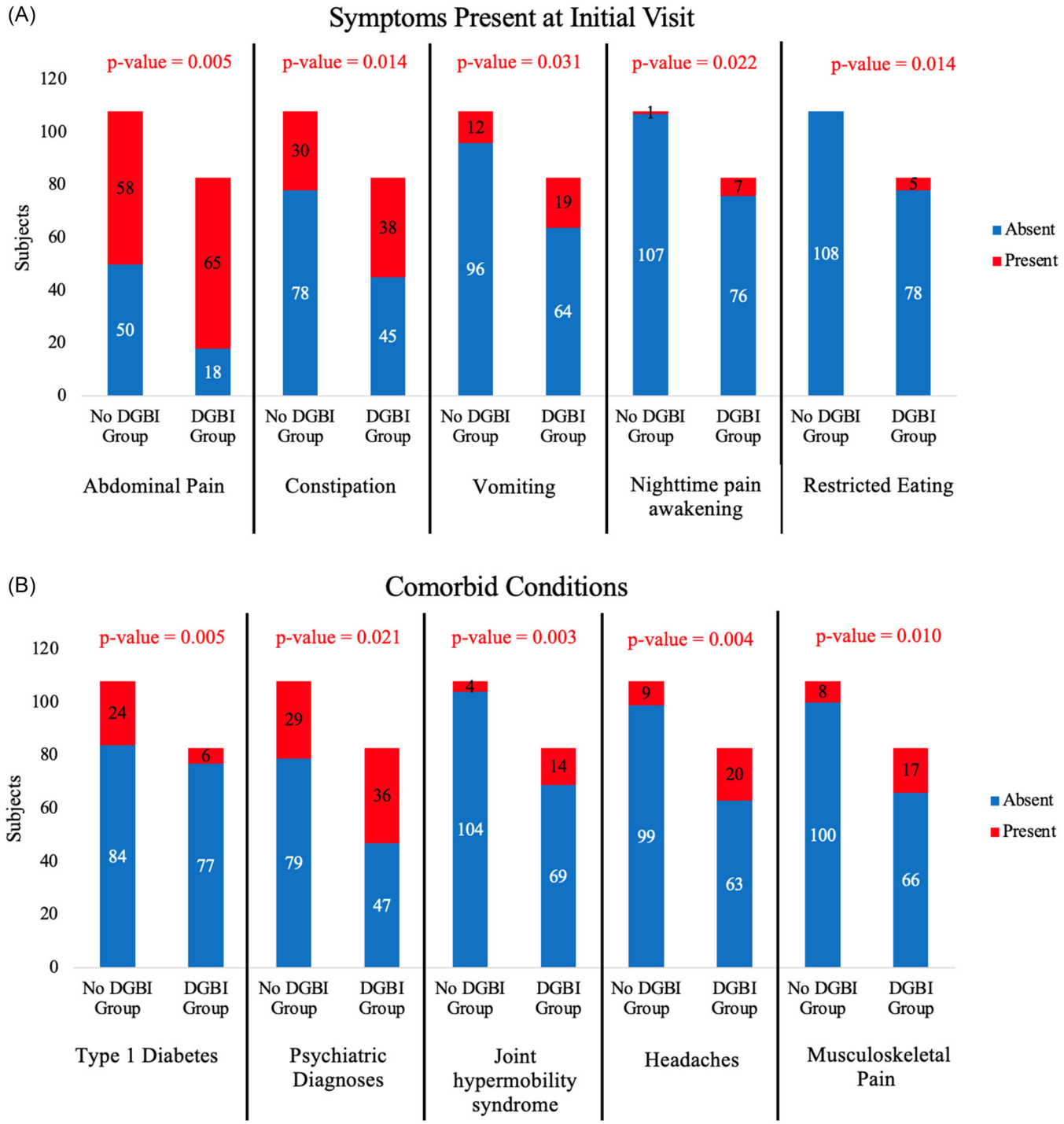


FIGURE 2 Symptoms present at initial visit (A) and comorbid conditions (B) associated with a statistically significant increased or decreased risk of disorder of gut–brain interaction (DGBI) diagnosis.

awareness for potential comorbid DGBI and offers an opportunity for expectation setting that some higher risk patients may have persistent gastrointestinal symptoms due to non-CeD etiologies.

This study is not without limitations, many of which are inherent to retrospective studies. First, though this was a single-center study, it was conducted at a large pediatric healthcare center and had a similar cohort composition to prior multicenter studies. Second, this was a retrospective study of patient records seen by many different gastrointestinal providers. This makes the study susceptible to inconsistencies in documentation and differences in practice (such as timing of TTG IgA monitoring after diagnosis). Nonetheless, all

patients were seen by gastroenterology trained providers at a single institution with similar department practice habits, and charts were reviewed in a standardized fashion. As addressed previously, monitoring of TTG IgA is imperfect, though it is the current standard of care in the field. Finally, there were a significant number of patients who were excluded given the lack of follow-up visit with a pediatric gastroenterologist. It is possible that these patients did not follow-up due to a lack of persistent symptoms. If this were the case, it may subject this study to over-reporting of the prevalence of DGBI in this cohort. However, it is known that DGBI are increasing in prevalence, and this study demonstrates the possibility of DGBI as the cause of persistent symptoms in children with treated CeD rather than persistent CeD in the small intestine that clinicians should be aware of.

5 | CONCLUSION

This study suggests DGBI are common in pediatric patients with CeD despite adequate adherence to a GFD and declining TTG IgA values. Further research is needed to understand how best to monitor patients with CeD after diagnosis, and whether "remission" is something that can be determined based on serology, endoscopy, and/or symptoms. Future multicenter prospective studies evaluating the prevalence and overlap of DGBI in children with CeD are also needed to better understand this interplay. In the meantime, this study underscores the importance of evaluating for and diagnosing DGBI when appropriate in children with adequately managed CeD to promote comprehensive care for patients.

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CONFLICT OF INTEREST STATEMENT

Key Opinion Leader - Kate Farms, Consultant - Ironwood. All the other authors declare no conflicts of interest.

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