

Pediatric Nonceliac Gluten Sensitivity: A Gluten-related Disorder Treatment Center Experience

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ABSTRACT

Objective: The aim of the study was to identify the prevalence and clinical characteristics of children with nonceliac gluten sensitivity (NCGS) presenting to a tertiary care center specialized for evaluation of gluten-related disorders.

Methods: The medical records of all patients aged 0 to 18 years who presented to our center over a 4-year period (July 2013–June 2018) and consented to participate in our research registry were reviewed. Patients meeting the clinical criteria for NCGS were reviewed in detail.

Results: Among 500 pediatric patients who volunteered to participate in the registry during the study period, we identified 26 (5.2%) with NCGS. Both gastrointestinal and extraintestinal symptoms associated with gluten ingestion were common with abdominal pain (57.7%), bloating (53.9%), rash (53.9%), diarrhea/loose stool (42.3%), and emotional/behavioral issues (42.3%) emerging as the predominant complaints. In addition, children with NCGS demonstrated a high personal history (61.5%) and family history (61.5%) of concomitant allergic/atopic disease.

Conclusions: Even within our highly specialized population of patients with a suspected gluten-related disorder, pediatric NCGS is relatively uncommon. The estimated prevalence and clinical features mirror those previously reported in a similarly highly selective population of adults. In the absence of celiac disease, clinical suspicion for NCGS should arise in a child with gastrointestinal and/or extraintestinal complaints alleviated with gluten removal and considered in symptomatic patients with associated allergic/atopic disease. Proper and adequate exclusion of celiac disease and other potential causes of the clinical complaints is essential to justify adoption of the gluten-free diet according to an appropriate stringency and with dietitian supervision to avoid nutritional deficiencies.

Key Words: children, nonceliac, wheat

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What Is Known

- The estimated prevalence of nonceliac gluten sensitivity is 6%, although the exact prevalence is unknown due to lack of a validated biomarker.
- The symptoms of nonceliac gluten sensitivity include myriad gastrointestinal and extraintestinal complaints.
- Most reports of nonceliac gluten sensitivity focus on adults with little data available pertaining to nonceliac gluten sensitivity in pediatric age.

What Is New

- The prevalence and clinical presentation of nonceliac gluten sensitivity in pediatric patients presenting for evaluation at a specialized clinic for gluten-related disorders mirror that which has previously been reported in a similar nonceliac gluten sensitivity.
- Children with nonceliac gluten sensitivity demonstrate a high comorbid personal and family history of allergic/atopic disease.

Nonceliac gluten sensitivity (NCGS) is a heterogeneous clinical entity in which patients without celiac disease (CD) experience gastrointestinal or extraintestinal symptoms in direct relation to ingestion of gluten-containing grains. It is presumed to be a persistent clinical condition affecting an estimated 6% of the adult population with varied incidence by geographic region (1,2). Unlike the gluten-sensitive enteropathy CD, a biomarker indicating the active state of disease has yet to be identified, posing difficulty in estimation of an exact prevalence. Moreover, although >99% of patients with CD possess the human leukocyte antigens (HLAs) DQ2 and/or DQ8, these genetic markers are observed in only 50% of patients with NCGS (3).

Due to lack of a validated biomarker, NCGS presents a complicated diagnostic process which is presently based upon adequate exclusion of CD or wheat allergy (WA) as the causative agent of clinical symptomatology. Absence of the HLA DQ2/DQ8 antigens is a helpful modality in the algorithm to exclude CD. Clinical trials attempting to identify a biomarker of active disease are underway and use a double-blind crossover gluten challenge to confirm the diagnosis of NCGS, although this approach lacks clinical feasibility (4).

The clinical presentation of NCGS is variable with patients reporting intestinal and extraintestinal symptoms. The key pathologic indicator for the condition involves symptoms temporally associated with gluten ingestion that resolve with gluten removal

and recur with gluten reintroduction. Reports in adult patients suggest gastrointestinal complaints including abdominal pain, bloating and bowel irregularity, and extraintestinal complaints of a “foggy brain”—describing difficulty concentrating or thinking clearly—headache, joint and muscle pain, fatigue, depression, and anemia (5). Cutaneous manifestations appearing similar to eczema and not classified as dermatitis herpetiformis that are alleviated with removal of gluten from the diet have been also reported (6).

The gluten-free diet (GFD) has gained staggering popularity in recent years, emphasizing the importance of distinguishing consumers for whom the diet is a true medical necessity (7). The broad popularity of the GFD may actually reflect the proportion of individuals with NCGS given that many GFD consumers report the diet to be effective at controlling or alleviating specific symptoms (8). The GFD has also been adopted to ameliorate symptoms of other disorders or diseases, most notably of which is the prospect of improving behavioral outcomes in children with autism spectrum disorders (ASDs) (9–11). Other conditions hypothesized to benefit from gluten removal include irritable bowel syndrome, Tourette syndrome, inflammatory bowel disease, rheumatoid arthritis, and fibromyalgia, among others (12–16).

Although various studies of NCGS have been conducted in adults, very little data exist pertaining to NCGS in children (17,18). Given this, we sought to identify the prevalence of NCGS in our highly selective pediatric population and the clinical characteristics of children with NCGS presenting for evaluation at our tertiary gluten-related disorder treatment center.

METHODS

We reviewed the medical records of all patients aged up to 18 years who were seen at our center over a 4-year period (July 2013–June 2018) and consented to participate in our research registry. Our center is specialized for evaluation of gluten-related disorders and all presenting patients are invited to take part in our research registry which includes provision of consent for medical record review. All patients provided written informed consent indicating permission for use of their medical information. Ethical approval was obtained from the Partners Human Research Committee Institutional Review Board at Massachusetts General Hospital.

Data were extracted directly from the patient electronic medical record including physician notes, laboratory values, and pathology reports. Patient-completed and/or parent-completed (on behalf of the child) intake forms from the first new-patient appointment were considered in conjunction with physician-verified information from the electronic medical record to gain an accurate understanding of each patient’s symptoms and medical history. The personal and family medical history of patients identified with NCGS was reviewed in detail.

Data were analyzed using SPSS (IBM SPSS Statistics for Mac, Version 24.0. IBM Corp, Armonk, NY) and are presented as frequency, mean, and standard deviation. Statistical tests between groups were limited to chi squared analysis with a cutoff of $P < 0.05$ considered statistically significant.

RESULTS

During the study period, 500 pediatric patients aged between 7 months and 18 years (mean = 10.3 ± 4.5) visited our tertiary care center and consented to participate in our research registry. The majority of patients presenting to our center were girls ($n = 297$, 59%), white ($n = 452$, 90.4%), and non-Hispanic ($n = 477$, 95.4%). Non-white patients included those who identified as Asian ($n = 9$, 1.8%), mixed race ($n = 9$, 1.8%), other race ($n = 9$, 1.8%), or with unknown race ($n = 21$, 4.2%). Among this population, we identified

TABLE 1. Clinical evaluation for exclusion of celiac disease in children with nonceliac gluten sensitivity

	Negative	Positive	Not done
Serological testing (tTG IgA)	22 (84.6)	0	4 (15.4)
Serological testing (EMA)	11 (42.3)	0	15 (57.7)
Endoscopy with duodenal biopsy	12 (46.2)	0	14 (53.8)
Genetic testing (HLA DQ2/DQ8)	10 (38.5)	6 (23)	10 (38.5.)

Data are presented as n (%). “Negative” results for endoscopy with duodenal biopsy indicate normal duodenal mucosa.

EMA = endomysial; HLA = human leukocyte antigen; TG = tissue transglutaminase.

26 (5.2%) patients aged 2 to 18 years (mean = 8.42 ± 4.1) who fulfilled the clinical criteria for NCGS based on the London Consensus Criteria (2) and will be the focus of further discussion. A diagnosis of NCGS was suspected but not confirmed for an additional 18 (3.6%) patients due to incomplete clinical follow-up. Patients with NCGS were predominantly white ($n = 23$, 88.5%), boys ($n = 17$, 65.4%), and non-Hispanic ($n = 25$, 96.2%). The race/ethnicity of non-white patients included those who identified as Asian ($n = 2$) and Hispanic ($n = 1$).

A diagnosis of CD was excluded for all patients in a manner consistent with the guidelines for NCGS set forth by Catassi et al (19). Most patients ($n = 16$, 61.5%) were evaluated clinically with multiple tests to exclude CD and are discussed below according to the most definitive modality of exclusion. With the exception of HLA typing, all tests were performed while adherent to a gluten-containing diet. The overall frequencies for each modality of clinical evaluation for CD are reported in Table 1. Twelve (46.2%) patients underwent upper endoscopy and were found to have normal duodenal mucosa and another 6 (23%) patients tested negative for HLA DQ2/DQ8. The remaining 8 (30.8%) patients had negative IgA anti-tissue transglutaminase antibodies ($n = 2$ in combination with negative IgA anti-endomysial antibodies). For these 8 patients, total IgA levels were normal ($n = 4$), not obtained ($n = 2$), or not specified ($n = 2$). In addition, IgE-mediated WA was excluded in 7 patients (26.9%); in 2 cases the negative test was documented in a physician note but not available for review in the medical records. All patients reported symptoms temporally associated with gluten ingestion and relieved by gluten removal from the diet. Patients additionally were required to report symptom relapse with reintroduction of gluten into the diet to meet the criteria for NCGS. This included patients who voluntarily undertook a gluten challenge (purposefully ingesting gluten) with physician supervision and those who reported complaints associated with accidental ingestions.

Clinical Presentation

A variety of gastrointestinal and extraintestinal symptoms were reported with gluten ingestion among NCGS patients in our sample. Symptom frequencies are described in Figure 1. Overall, 24 (92.3%) patients reported at least 1 gastrointestinal complaint, and 21 (80.8%) reported at least 1 extraintestinal complaint with most patients experiencing both ($n = 19$, 73.1%). The most common gastrointestinal symptoms included abdominal pain, bloating, and diarrhea/loose stool. Common extraintestinal complaints included rash, emotional or behavioral issues, muscle/joint pain, and fatigue. Emotional and behavioral issues reported included trouble focusing, moodiness, anxiety, impulsivity, low mood/depression, “acting out,” and overall parent-reported “behavioral issues.”

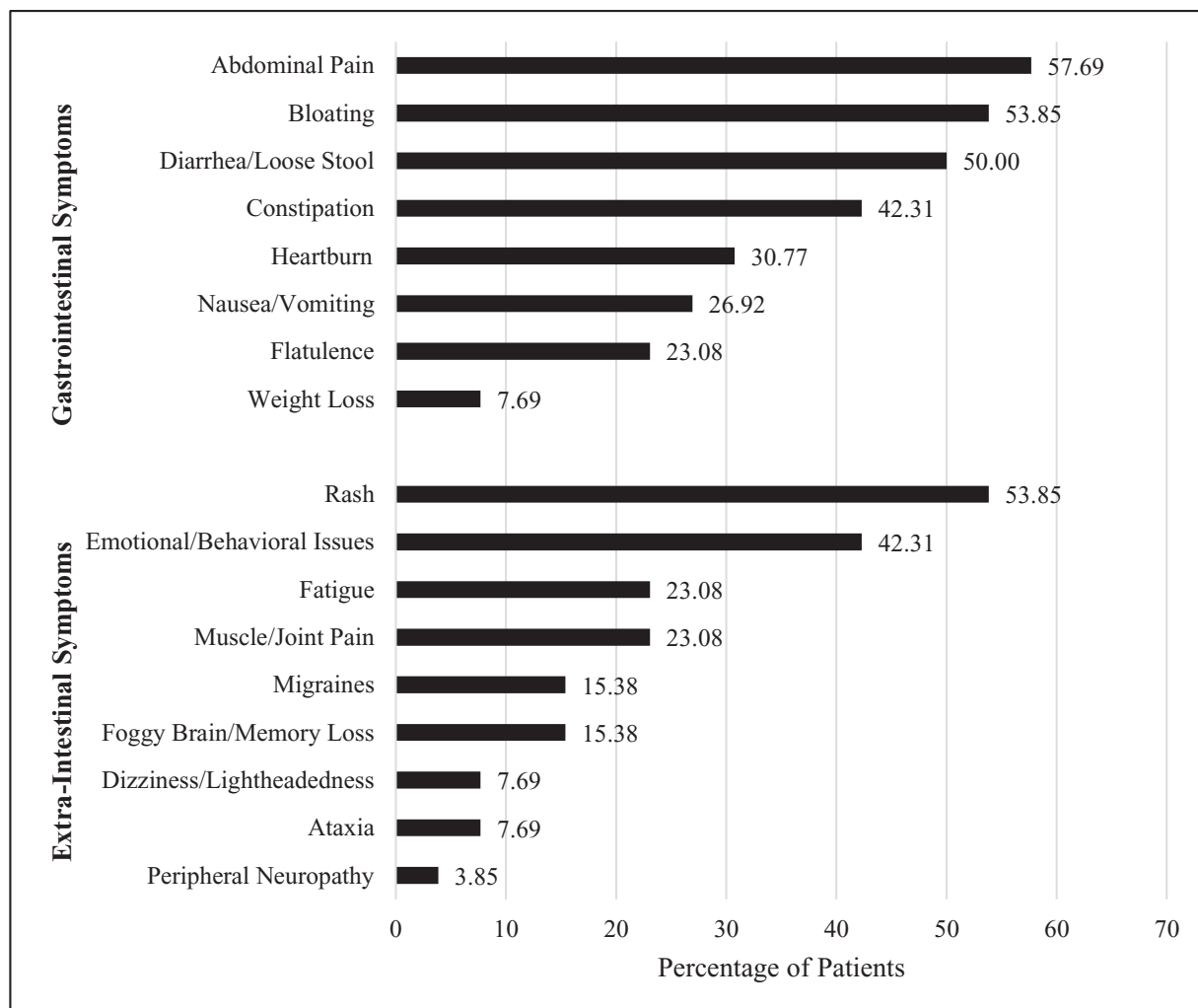


FIGURE 1. Frequency of gastrointestinal and extraintestinal symptoms in pediatric patients with nonceliac gluten sensitivity (NCGS). Symptoms are listed on the vertical axis. Horizontal bars indicate the percentage of patients with NCGS reporting each symptom.

An association with atopic disease was noted with 16 (61.5%) patients reporting an associated allergic/atopic condition (asthma = 10, food allergy = 8, hay fever = 8, eczema = 7). This is higher than what has been reported in the general US population for eczema (6.7%), asthma (21.8%), and food allergy (6.7%) (20). Although 14 children reported rash in association with gluten ingestion on their intake forms, only those with eczema documented by a physician ($n = 7$, 26.9%) in the medical record were classified as such. Food allergies included milk, egg, soy, peanuts, and other fruits and vegetables (peaches, apple, squash, cherries, mango) with most food-allergic patients ($n = 7$, 87.5%) reporting multiple food allergies. Notably 3 (11.5%) patients reported all 4 conditions of food allergy, eczema, asthma and hay fever and 4 (15.4%) patients reported 3 of the 4 conditions suggesting a small subgroup of patients with a hyperallergic phenotype. NCGS children diagnosed with at least one concomitant allergic condition did not differ from nonallergic patients in their symptom presentation except regarding diarrhea/loose stool and flatulence. Patients diagnosed with an allergic condition were more likely to present with diarrhea ($P = 0.016$) compared to nonallergic children (68.8% vs 20%). We also examined the family medical history of NCGS patients for allergic conditions. Sixteen (61.5%) patients were found to have

at least 1 first-degree relative diagnosed with an allergic/atopic condition considering asthma, eczema, food allergy, and hay fever. The overall family history of allergic/atopic conditions among NCGS patients is depicted in Figure 2. Food allergies were the most common allergic manifestation with 14 (53.8%) NCGS patients having an affected first-degree relative (parent = 7, 7, sibling = 4, both = 3).

Six children within our sample had a documented diagnosis of ASD. The clinical features of these children are described in Table 2. Emotional/behavioral issues associated with gluten ingestion were not over-represented in the ASD group ($P = 0.664$), and children with ASD did not differ in clinical presentation on the basis of any individual symptom.

DISCUSSION

Although literature regarding NCGS as a clinical entity in children is scarce (17,18), data from our retrospective study of a highly selective cohort, presenting for care at a tertiary center specializing in gluten-related disorders, mirror that which has been reported in adults from a similarly selective population. Previous work by our group identified 347 adult patients (6% of patients seen) with NCGS who presented to our gluten-related disorders

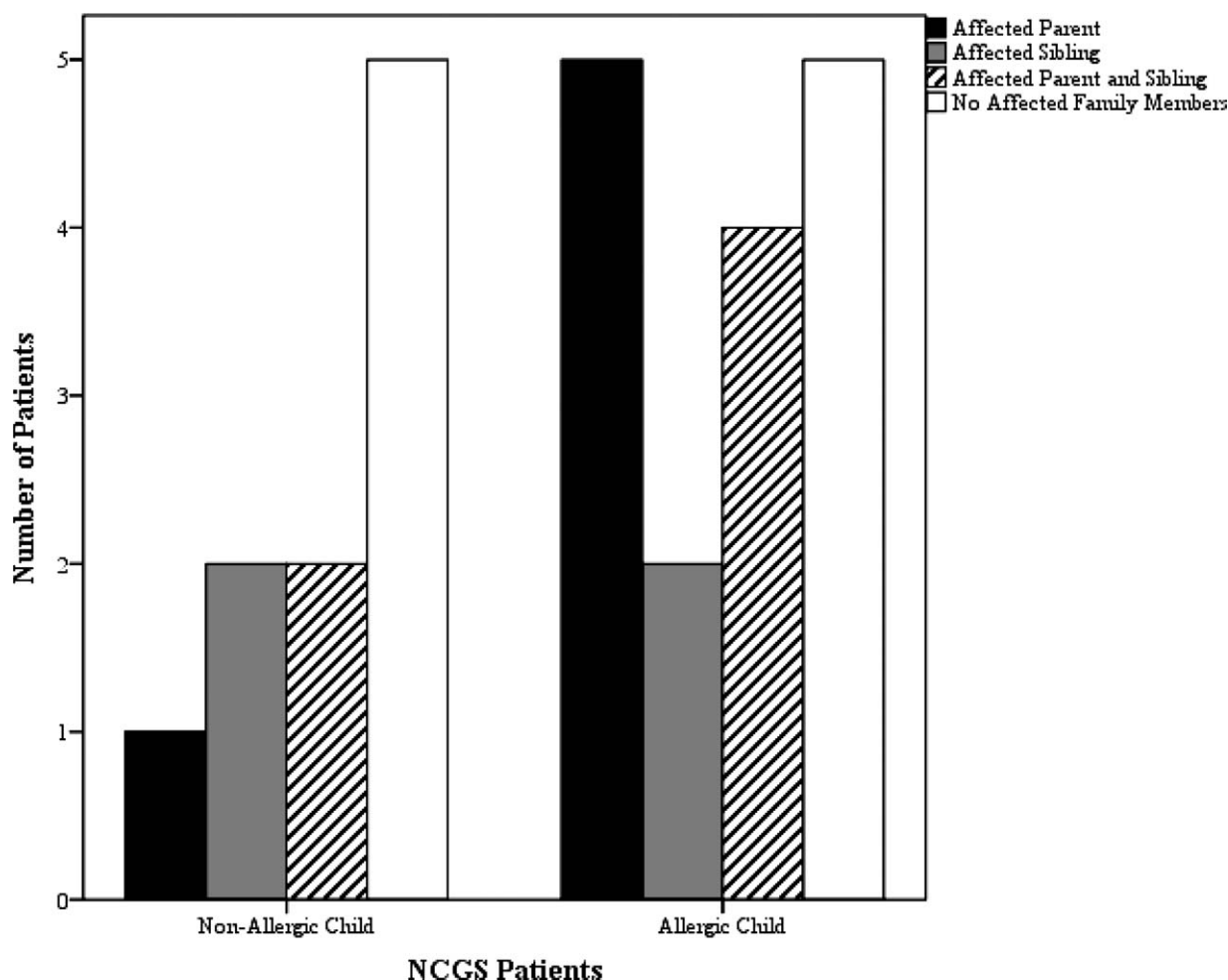


FIGURE 2. Family history of allergic/atopic conditions in children with nonceliac gluten sensitivity (NCGS). “Allergic” children are personally diagnosed with asthma, eczema, food allergy, and/or hay fever while “nonallergic” children carry none of these diagnoses. Parents and siblings of pediatric NCGS patients are counted as affected if they are diagnosed with asthma, eczema, food allergy, and/or hay fever.

clinic most commonly with symptoms of abdominal pain, rash, headache, “foggy mind,” fatigue, and depression (2). Presumed to be an “adult-limited condition,” the average age of onset for NCGS has been reported as 40 years with a range between 17 and 63 years (21). This, however, appears to be due to limited literature pertaining to NCGS in children as, to our knowledge, there are only 2 previously published studies (17,18). A case series of 15 children in Italy reported a clinical picture of NCGS predominated by gastrointestinal complaints (17). A second study used the double-blind placebo-controlled crossover gluten challenge in children to identify those with NCGS (18). Children from the double-blind cohort by Francavilla et al (18) with confirmed NCGS demonstrated both gastrointestinal and extraintestinal symptoms which were similar to symptoms reported by our patients.

The majority of children with NCGS in our study demonstrated concomitant allergic/atopic disease including asthma, eczema, food allergies, and hay fever and also had a high prevalence of family members with these conditions. NCGS is suspected to be one of many non-IgE-mediated food allergic gastrointestinal conditions (22,23). Irrespective of this, an association with IgE-mediated allergic conditions has, however, emerged. It has been reported that individuals with NCGS and cow’s milk protein hypersensitivity are more likely to also be diagnosed with atopic disease compared

to those with irritable bowel syndrome (23). Mansueto et al proposed 2 subtypes of NCGS patients: those with NCGS alone and those with “multiple foods hypersensitivity, including NCGS” who report intolerance to wheat, cow’s milk protein, and many other foods (24). Our data highlight the importance of the connection between atopy and NCGS in that allergic children with NCGS are more likely to present with diarrhea and flatulence compared to nonallergic children. Moreover, a strong family history of allergic conditions was reported in our sample with cumulatively only 5 children (19.2%) reporting no personal or family history of atopy. Considering this, either a family or personal history of food allergy should be investigated as factors that predispose children to NCGS.

Although the pathophysiological mechanisms of disease in NCGS are still being investigated, the condition notably differs from CD in that the classic intestinal enteropathy associated with CD is absent. This enables patients with NCGS to embrace a GFD as needed according to their symptoms compared to patients with CD who must be diligent regarding cross contamination. Accurate diagnosis of NCGS and evaluation by a gastroenterologist to definitively exclude CD is of the utmost importance to ensure that the GFD is followed properly. Ongoing counseling and observation from a dietitian is essential given that individuals adherent to the GFD are at risk for deficiencies in zinc, magnesium, iron, calcium,

TABLE 2. Clinical features of children with nonceliac gluten sensitivity and an autism spectrum disorder

Age	Sex	Exclusion of celiac disease	Gastrointestinal symptoms	Extraintestinal symptoms
3	Male	Genetics Serology	Abdominal pain Diarrhea/loose stool Flatulence	Rash
4	Male	Serology	Constipation	Emotional/behavioral issues Foggy brain/memory loss Muscle/joint pain
4	Male	Genetics Serology	N/A	Emotional/behavioral issues Foggy brain/memory loss
5	Female	Endoscopy	Diarrhea/loose stool Flatulence	N/A
11	Male	Serology	Abdominal pain Bloating Constipation Weight loss	Fatigue Rash
12	Female	Endoscopy Serology	Abdominal pain Bloating Diarrhea/loose stool Flatulence Heartburn/GERD	Emotional/behavioral issues Rash

The age, sex, modality of exclusion of celiac disease (CD), and gastrointestinal and extraintestinal complaints associated with gluten ingestion for each patient with nonceliac gluten sensitivity (NCGS) and an autism spectrum disorder (ASD). Exclusion of CD based on serology indicates negative testing for IgA anti-tissue transglutaminase (tTG) antibodies while adhering to a gluten-containing diet. "Genetics" indicates absence of the HLA DQ2 and DQ8 antigens. "Endoscopy" indicates that an upper gastrointestinal endoscopy with duodenal biopsies was performed while on a gluten-containing diet demonstrating normal duodenal mucosa.

folate, and dietary fiber (25). In addition, new evidence supports that a GFD in the absence of medical necessity should not be encouraged due to alterations to cardiac risk factors (26,27). Finally, the role of the dietitian becomes even more essential when the diet is to be embraced in pre-pubertal children as this is a critical period for maximal growth and development (28).

Given that this was a retrospective chart review, there are limitations to our study. No activities were undertaken for purposes of the research and thus patients were not uniformly evaluated. Upper endoscopy was not performed in all patients, which could result in underdiagnosis of other gastrointestinal conditions which could explain the clinical complaints. A double-blind placebo-controlled crossover challenge with gluten would have been optimal to confirm the diagnosis of NCGS but was not clinically feasible. Previous work by Francavilla et al (18), examining 1114 patients with chronic gastrointestinal symptoms and negative testing for CD and WA, applied a double-blind crossover approach to diagnose NCGS. Upon further examination, the authors found that only 36 patients demonstrated a correlation between symptoms and gluten exposure, and only 11 of the 28 patients who underwent the double-blind challenge ultimately met diagnostic criteria for NCGS (18). This work, which ruled out NCGS in more than 60% of suspected cases, suggests that a significant proportion of our patients would no longer satisfy the diagnostic criteria for NCGS following application of a double-blind crossover design, therefore suggesting that our cohort overestimates the prevalence of NCGS even in this already selective population. Another limitation to our study is that IgE-mediated WA was definitively ruled out in only 26.9% of NCGS patients, whereas the remaining patients were not tested. To firmly establish the diagnosis of NCGS, physicians should test for WA. Finally, a small number of patients seen at our clinic were excluded from this cohort given the inability to adequately exclude CD and confirm the diagnosis of NCGS. This difficulty in classification of patients who clearly experience symptoms associated with gluten ingestion is an important issue

for pediatricians to consider in future practice. Even an empirical short-term trial of the GFD in an attempt to alleviate a patient's symptoms should not be initiated without proper exclusion of CD as the causative pathology. Without proper exclusion of CD, the GFD would need to be adopted in the most stringent manner; vigilance regarding even a crumb of cross contamination would be necessary to ensure that, in the event of an active celiac-associated intestinal enteropathy, the patient is not inflicting further injury. Such dietary stringency and hypervigilance in particular has been shown to have deleterious effects on the quality of life of patients with CD (29). A final limitation of our study is that information was gathered retrospectively from the medical record and thus its accuracy or reliability is not ensured.

The lack of literature pertaining to NCGS in pediatric age may lend physicians to assume that the condition is not observed clinically. Although it is uncommon, the prevalence of NCGS among pediatric patients evaluated at our specialized clinic for treatment of gluten-related disorders was 5.2% over a 4-year period. Given that we are a tertiary care center providing specialty care for gluten-related disorders, this number is higher than what would be expected in routine pediatric practice or at general pediatric gastroenterology centers. Future studies should aim to describe the prevalence of pediatric NCGS across various populations to further understand the prevalence.

Although the literature regarding NCGS is steadily evolving, many questions regarding this condition remain. Are individuals with NCGS responding aberrantly to gluten or some other component of wheat? Is gluten truly to blame, or can the condition result from other fermentable oligo-, di-, monosaccharides, and polyols? Is the condition transient? Does an association exist between NCGS and allergic disposition? Overall, future research is warranted to better define and understand NCGS in children and adults. For now, an adept provider who identifies NCGS as the underlying cause of a patient's myriad possible gastrointestinal and extra-intestinal complaints should be applauded for providing the child and family relief

from both physical suffering and costly specialty-care appointments and evaluations.

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