CME

Celiac Disease or Non-Celiac Gluten Sensitivity? An Approach to Clinical Differential Diagnosis

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OBJECTIVES: **Differentiating between celiac disease (CD) and non-celiac gluten sensitivity (NCGS) is important for appropriate management but is often challenging.**

METHODS: **We retrospectively reviewed records from 238 patients who presented for the evaluation of symptoms responsive to gluten restriction without prior diagnosis or exclusion of CD. Demographics, presenting symptoms, serologic, genetic, and histologic data, nutrient deficiencies, personal history of autoimmune diseases, and family history of CD were recorded. NCGS was defined as symptoms responsive to a gluten-free diet (GFD) in the setting of negative celiac serology and duodenal biopsies while on a gluten-containing diet or negative human leukocyte antigen (HLA) DQ2/DQ8 testing.**

RESULTS: **Of the 238 study subjects, 101 had CD, 125 had NCGS, 9 had non-celiac enteropathy, and 3 had indeterminate diagnosis. CD subjects presented with symptoms of malabsorption 67.3% of the time compared with 24.8% of the NCGS subjects ($P<0.0001$). In addition, CD subjects were significantly more likely to have a family history of CD ($P=0.004$), personal history of autoimmune diseases ($P=0.002$), or nutrient deficiencies ($P<0.0001$). The positive likelihood ratio for diagnosis of CD of a >2× upper limit of normal IgA *trans*-glutaminase antibody (tTG) or IgA/IgG deaminated gliadan peptide antibody (DGP) with clinical response to GFD was 130 (confidence interval (CI): 18.5–918.3). The positive likelihood ratio of the combination of gluten-responsive symptoms and negative IgA tTG or IgA/IgG DGP on a regular diet for NCGS was 9.6 (CI: 5.5–16.9). When individuals with negative IgA tTG or IgA/IgG DGP also lacked symptoms of malabsorption (weight loss, diarrhea, and nutrient deficiencies) and CD risk factors (personal history of autoimmune diseases and family history of CD), the positive likelihood ratio for NCGS increased to 80.9.**

CONCLUSIONS: **On the basis of our findings, we have developed a diagnostic algorithm to differentiate CD from NCGS. Subjects with negative celiac serologies (IgA tTG or IgA/IgG DGP) on a regular diet are unlikely to have CD. Those with negative serology who also lack clinical evidence of malabsorption and CD risk factors are highly likely to have NCGS and may not require further testing. Those with equivocal serology should undergo HLA typing to determine the need for biopsy.**

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INTRODUCTION

The pathogenesis of celiac disease (CD) is one of the best understood among autoimmune diseases, given our knowledge of the environmental, genetic, and immunologic basis of the disease (1). CD is precipitated by the ingestion of barley, wheat, and rye, which trigger immunohistopathological changes in genetically susceptible subjects (1,2). The gluten-free diet (GFD) remains the cornerstone treatment of CD (1). However, CD is not the sole clinical entity that responds to the GFD (3).

Recently, there has been growing interest in subjects who report gastrointestinal (GI) symptoms responsive to the GFD in the absence of documented CD (4–8). This population shares characteristics of both CD and irritable bowel syndrome, but it does not meet the diagnostic criteria for either disorder (4–6). Consequently, a new disorder known as non-celiac gluten sensitivity (NCGS) has emerged to describe this increasingly frequent presentation to gastroenterologists and primary care practitioners (4–12). Currently, the lack of specific diagnostic criteria preclude the study of NCGS prevalence in the

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general US population, but experts estimate it to be as common or more common than CD (8–10).

Differentiating between CD and NCGS is important for appropriate management and risk stratification, but it is often challenging as there is lack of evidence-based recommendations for the evaluation of patients reporting gluten-responsive symptoms. Whereas CD subjects should maintain a lifelong, strict GFD and limit their exposure to gluten to foods containing less than 20 parts per million (13–15), NCGS subjects can be more liberal and titrate their exposure to gluten as needed to avoid symptoms. Unlike patients with CD, NCGS subjects do not appear to be at a higher risk for long-term complications such as intestinal lymphoma (16,17) or nutrient deficiencies secondary to malabsorption (18,19). Furthermore, there is no indication for screening of family members of those with NCGS. To provide recommendations for the evaluation of gluten-responsive symptoms, we conducted this study in which we first defined NCGS and then developed a clinical model for the differentiation of CD and NCGS. Our study allows us to offer clinicians a clear, stepwise diagnostic algorithm for the investigation and management of patients who report symptoms responsive to gluten exclusion.

METHODS

The Celiac Center at Beth Israel Deaconess Medical Center maintains a secure database (Microsoft Access, Redmond, WA) of all patients with known or suspected CD. We retrospectively reviewed records from 238 patients who presented to our clinic for new evaluation of gluten-responsive symptoms. To be included in the study, subjects had to have durable response to GFD defined as complete or near-complete resolution of GI symptoms on GFD, which persisted across more than one clinic visit separated by 3 or more months, as well as a recurrence of symptoms on consumption of gluten-containing foods. Subjects who had ongoing symptoms on GFD were excluded from analysis, and they all had more likely diagnoses to explain their presentation. Similarly, subjects who were on other exclusion diets such as FODMAP or dairy-free diets were excluded. Records were reviewed for basic demographics, presenting symptoms, and age of the first GI symptom. In addition, records were reviewed for nutrient deficiencies, personal history of autoimmune diseases, and family history of CD. Relevant serologic, genetic, and histologic data were also recorded. Analysis of celiac serologic tests was limited to IgA tissue *trans*-glutaminase antibodies (tTG) and/or IgA/IgG deaminated gliadan peptide antibodies (DGP), provided that they were obtained on a gluten-containing diet (INOVA Diagnostics, San Diego, CA). Results that were above the upper limit of normal were further divided into two categories: borderline positive (or equivocal, between the upper limit of normal and twice the upper limit of normal) and highly positive (greater than twice the upper limit of normal) (20). Genetic testing for CD-related human leukocyte antigen (HLA) haplotypes included HLA DQ2.5 *cis* (DQA^{0501}/DQB^{0201}), HLA DQ2.5 *trans* ($DQA^{0505}/DQB^{0301} + DQA^{0201}/DQB^{0202}$), HLA DQ2.2 ($DQA^{0201}/DQB^{0202}$), and DQ8 ($DQA^{0301}/DQB^{0302}$), and it was performed using high-resolution PCR-sequence-specific amplification (21). Histological testing was considered adequate if four to six biopsies were taken from the duodenum and were interpreted by a specialized GI pathologist (22). Biopsies from the duodenal bulb were interpreted with caution, given the possibility of villous architecture distortion and/or peptic duodenitis (23). NCGS was defined as symptoms durably responsive to a GFD in the setting of negative serology and normal duodenal biopsies on regular, gluten-containing diet (either before starting GFD or after at least 6–8 weeks of gluten challenge) or negative HLA DQ2/DQ8 testing (7,8). Sero-positive CD was defined as elevated IgA tTG or IgA/IgG DGP (borderline or highly positive) and enteropathy on a gluten-containing diet (8). Seronegative CD was defined as Marsh II or Marsh III pathology in subjects who are positive for *DQ2* and/or *DQ8* HLA genes, and who have a negative IgA tTG with a normal total IgA level and, if available, a negative IgA/IgG DGP test, along with a clinical or histological response to the GFD (24). Potential CD was defined as positive serology and normal or Marsh I pathology on a regular diet in the setting of positive HLA DQ2 or DQ8 testing (8). Subjects who had borderline positive serologic tests and Marsh I pathology findings on adequate biopsy sampling were further labeled as "indeterminate" for CD. Finally, non-celiac enteropathy (NCE) was defined as diffuse villous atrophy and two of the following criteria: (i) negative HLA DQ2 and DQ8; (ii) negative celiac serology on a gluten-containing diet, as well as lack of histological improvement on GFD; and (iii) negative CD serology on a gluten-containing diet along with a confident alternate diagnosis such as combined variable immunodeficiency or autoimmune enteropathy (3).

Evaluation of plasma nutrient concentrations included 25-OH vitamin D3 (normal 30–60 ng/ml), iron (normal 30–160 μg/dl), ferritin (normal 13–150 ng/ml), total iron-binding capacity (normal 240–450 μg/dl), vitamin B12 (normal 240–900 pg/ml), and zinc (normal 60–130 μg/dl) using liquid chromatography coupled to tandem mass spectrometry. Iron deficiency anemia was defined as anemia in the setting of low ferritin and high total iron-binding capacity. Vitamin D levels of < 10 ng/ml indicated severe deficiency, whereas mild–to-moderate deficiency was defined as levels between 10 and 30 ng/ml (23). Subjects were considered to have a positive family history for CD if they reported having a first- or second-degree relative with biopsy-proven CD.

Statistical analysis was performed using SPSS for Windows, rel. 13.0. 2004; SPSS, Chicago. Study outcomes were assessed using Fisher's exact test or χ^2-test with Yates correction for discrete variables, and Student's *t*-test as appropriate. This study was approved by the Beth Israel Deaconess Medical Center Institutional Review Board and was in concordance with the general principles laid out by the Standards for the Reporting of Diagnostic accuracy checklist.

RESULTS

Demographic and clinical features

Of the 238 subjects included in our analysis, 125 (52. 5%) had NCGS (as determined by our a priori definitions) and 101 (42.4%)

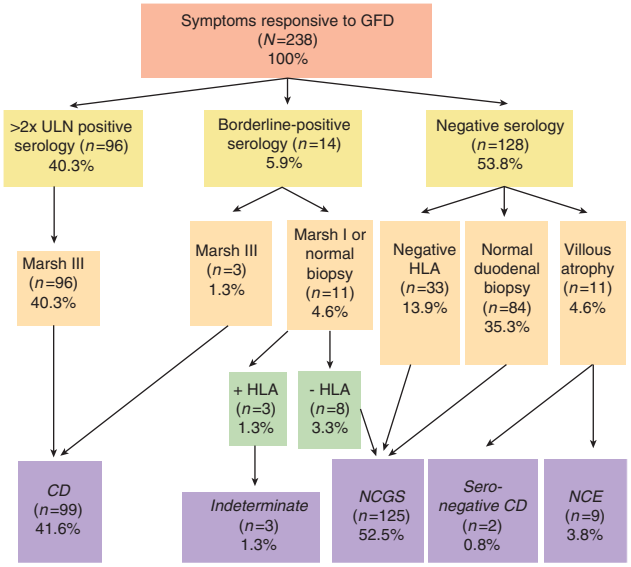

Figure 1. Flowchart of patients presenting with symptoms responsive to GFD. CD, celiac disease; GFD, gluten-free diet; NCE, non-celiac enteropathy; NCGS, non-celiac gluten sensitivity; ULN, upper limit of normal.

had CD. Nine subjects (3.8%) had NCE and three (1.3%) were indeterminate (**Figure 1**). In all, 76.2% and 78.4% of CD and NCGS subjects were female, respectively ($P=0.8$). NCGS subjects had a modest but highly statistically significant earlier recorded age of onset of symptoms compared with CD subjects (38.0 vs. 42.2 years, $P=0.003$). CD subjects presented with symptoms of malabsorption (diarrhea with weight loss or steatorrhea) 67.3% of the time compared with 24.8% of the NCGS subjects ($P<0.0001$). On the other hand, constipation was a fairly common presenting symptom in NCGS subjects (51.2%), but rare in celiac subjects (6.9%). CD subjects were significantly more likely to have a family history of CD (28.7 vs. 12.8%, $P=0.004$), personal history of autoimmune diseases (28.7 vs. 12.0%, $P=0.002$), or nutrient deficiencies (57.4 vs. 18.4%, $P<0.0001$) **Table 1**. When stratified by type and severity of nutrient deficiency, 29.7% of celiac subjects had severe vitamin D deficiency, compared with 0.8% (1/125) of the NCGS subjects ($P<0.0001$). Similarly, iron deficiency anemia was significantly more prevalent in celiac subjects compared with NCGS subjects (19.8 vs. 2.4%, $P<0.0001$). Twenty celiac subjects had documentation of two or more types of nutrient deficiencies compared with only one NCGS subject (**Table 1**). The spectrum of autoimmune diseases seen in our cohort was large and included Hashimoto's thyroditis, Grave's disease, insulin-dependent diabetes mellitus, rheumatoid arthritis, systemic lupus erythromatous, Sojren's syndrome, and other rheumatologic diseases.

Common practice trends

In our analysis, we identified common practice trends in diagnosing patients who report gluten-responsive symptoms. Almost invariably, the initial diagnostic step was celiac serologic testing. On a gluten-containing diet, 128 subjects had negative IgA tTG and/or IgA/IgG DGP, 14 had borderline positive serology results, and 96 had positive results (**Figure 1**). All subjects who had positive serology tests (>2× upper limit of normal) consequently underwent endoscopy with duodenal biopsy, which confirmed villous atrophy consistent with CD.

Table 1. Clinical and demographic differences between CD and NCGS

	Celiac disease (*n*=101)	Non-celiac gluten sensitive (*n*=125)	*P* value
Age of symptoms onset (year)	42.2	38.0	0.03
Female gender	76.2%	78.4%	0.8
Typical celiac symptoms (diarrhea and weight loss) (%)	67.3	24.8	<0.0001
Family history of celiac disease (%)	28.7	12.8	0.004
Personal history of autoimmune disease (%)	28.7	12	0.002
Nutrient deficiency[a] (%)	57.4	18.4	<0.0001
Mild-to-moderate vitamin D deficiency[b] (*n*)	20	19	0.4
Severe vitamin D deficiency[c] (*n*)	30	1	<0.0001
Iron deficiency anemia (*n*)	20	3	<0.0001
Vitamin B12 deficiency (*n*)	5	1	0.1
Zinc deficiency (*n*)	3	0	0.09
Subjects with two or more deficiencies (*n*)	20	1	<0.0001

CD, celiac disease; NCGS, non-celiac gluten sensitivity.
[a]Nutrient deficiency is defined as vitamin D, iron deficiency anemia, vitamin B12, or zinc deficiency.
[b]Vitamin D levels between 10 and 30 ng/dl.
[c]Vitamin D levels less than 10 ng/dl.

All 14 subjects with borderline positive celiac serologies underwent upper endoscopy with duodenal biopsy as the next diagnostic step. Of these, 3 subjects (21.4%) had Marsh III pathology and were confirmed to have CD, whereas 11 subjects (78.6%) had Marsh I or normal biopsies. Consequently, genetic testing was performed in all 11 of these subjects. Eight were negative for both DQ2 and DQ8 and were confirmed to have NCGS. The other three subjects were positive for DQ2 and were labeled as "indeterminate".

Most of the variability in workup was noted in the 128 subjects who had negative serology on gluten-containing diet. Sixty-two subjects underwent genetic testing as the next diagnostic step, whereas 66 subjects underwent endoscopy as their next testing modality. Of the 62 who had genetic testing before endoscopy, 33 subjects lacked celiac genes and were categorized as NCGS without the need for further testing. The other 29 subjects were positive for at least one celiac gene and were categorized as NCGS based on consequent normal duodenal pathology.

Of the subjects who underwent endoscopy before genetic testing, 55 had normal duodenal biopsies and were labeled as NCGS, whereas 11 subjects had Marsh III pathology. On further genetic testing of these 11 subjects, 2 subjects had positive celiac genes

and were labeled as sero-negative CD. These two subjects had complete clinical response to the GFD and improved pathology on subsequent endoscopy. The other nine subjects lacked celiac genes and had persistent diffuse villous atrophy pathology on repeat endoscopic evaluation despite being on GFD. All these subjects underwent further workup that included immunoglobulin quantification, immunohistochemical staining of biopsies, breath testing for small intestinal bacterial overgrowth, stool testing for giardia antigen, and anti-enterocyte antibody testing. In addition, most of them had colonoscopy with random biopsies to evaluate for microscopic colitis. All nine subjects met criteria for NCE. More specifically, four subjects had immune mediated enteropathy, four subjects had combined variable immunodeficiency, and one subject had giardiasis.

In summary, there were 60 subjects in our cohort who had negative serology and negative celiac HLA genes. Of these, 33 subjects (55%) were diagnosed with NCGS without endoscopy based on their durable response to GFD and lack of enteropathy risk factors and alarm signs. Eighteen of the remaining 27 subjects (30%) underwent endoscopy before genetic testing and were diagnosed with NCGS on the basis of normal duodenal biopsies. Finally, nine subjects (15%) were found to have persistent diffuse villous atrophy despite being on a GFD and were labeled as NCE based on further workup (as described above).

Analysis based on our proposed clinical model

We analyzed our cohort using alternative methodology in order to incorporate genetic testing and clinical presentation into the diagnostic model and to assess the yield and appropriateness of tests used in predicting the final diagnosis. Endoscopy with duodenal biopsies had 100% yield for CD in subjects who reported symptoms caused by gluten ingestion and had positive serology testing (**Figure 1**). Had genetic testing been conducted before endoscopy in subjects with borderline serology, endoscopy could have been avoided in 57.1% (8/14) of these subjects. Duodenal sampling revealed Marsh III pathology and established CD diagnosis in three of the remaining six subjects who were positive for celiac genes. The diagnosis remained indeterminate in the other three subjects who had normal or Marsh I pathology (**Figure 1**).

When clinical presentation is taken into consideration, 88 of the 128 subjects with negative serology had no typical enteropathy signs and symptoms or risk factors for CD such as family history of CD or personal history of autoimmune diseases. Although 55 of these 88 subjects (62.5%) underwent endoscopy to rule out CD, all of them had normal duodenal biopsies and were categorized as NCGS. Therefore, clinical presentation alone was predictive of NCGS in 100% of this patient population (**Figure 2**). On the other hand, 40 of the 128 subjects had symptoms or signs of malabsorption or risk factors for enteropathy. Endoscopy established a diagnosis of NCE or sero-negative CD in 27.5% (11/40) of these subjects on the basis of diffuse villous atrophy on duodenal sampling. The other 29 subjects had normal duodenal pathology and were diagnosed with NCGS (**Figure 2**).

The sensitivity, specificity, and positive likelihood ratio of a >2× upper limit of normal tTG or DGP with clinical response to GFD for CD were 97% (confidence interval (CI): 91.5–99%), 100% (CI: 97.3–100%), and 130% (CI: 18.5–918.3), respectively. Similarly, the sensitivity, specificity, and positive likelihood ratio of the combination

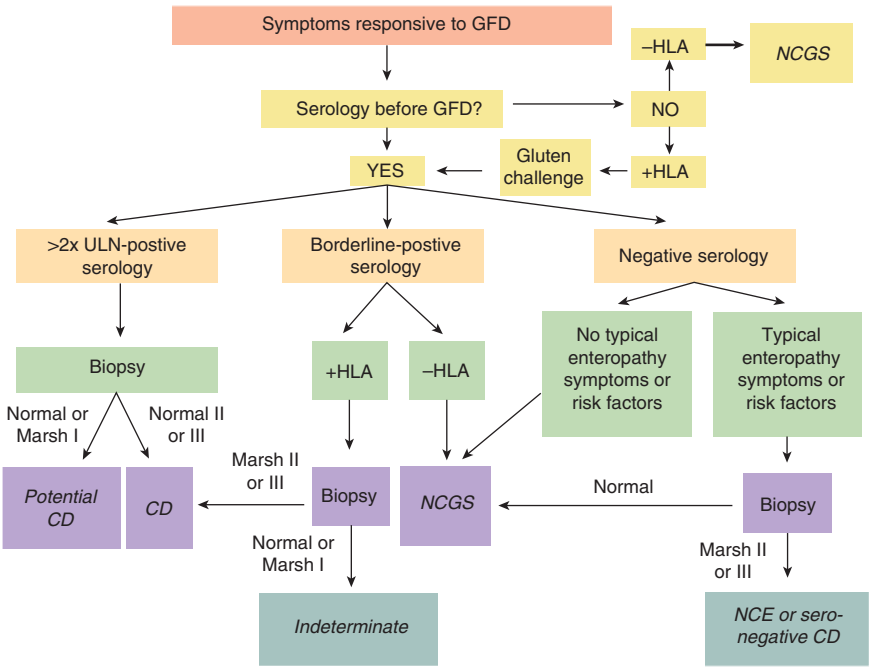

Figure 2. Diagnostic model for symptoms responsive to gluten exclusion. CD, celiac disease; NCE, non-celiac enteropathy; NCGS, non-celiac gluten sensitivity; ULN, upper limit of normal.

of gluten-responsive symptoms and negative tTG or DGP on a regular diet for NCGS were 93.6% (CI: 87.9–96.7%), 90.3% (CI: 83.4–94.5%), and 9.6% (CI: 5.5–16.9), respectively. When individuals with negative tTG or DGP also lacked malabsorptive symptoms and signs (weight loss, diarrhea, and nutrient deficiencies), as well as CD risk factors (personal history of autoimmune diseases and family history of CD), the specificity and positive likelihood ratio for NCGS increased to 100% and 80.9%, respectively.

DISCUSSION

Despite the availability of guidelines for the diagnosis and management of CD (25), many subjects with NCGS continue to be erroneously diagnosed with CD. By conducting this study in a large cohort of subjects with symptoms responsive to the GFD, we aimed to address this emerging clinical issue by formulating and evaluating a simple clinical model that guides clinicians in the efficient differential diagnosis of these subjects.

The first finding of our study was that NCGS and CD subjects present clinically in distinct ways despite the common response to the GFD. NCGS subjects developed symptoms at an earlier age. Constipation accounted for more than 50% of presenting symptoms in NCGS. In addition, only 24.8% of the NCGS subjects presented with diarrhea, weight loss, or nutrient deficiencies, compared with 67.3% of the CD subjects. Patients with CD often present with severe and multiple nutrient deficiencies, especially vitamin D and iron deficiencies, compared with mild isolated vitamin D deficiency observed in NCGS subjects and in the general population.

Our findings confirm the very high specificity of positive specific celiac tests (IgA tTG and IgA/IgG DGP) for CD in subjects who are responsive to the GFD (26). Although multiple past studies have confirmed the high specificity of these tests for CD in the general population, they rarely addressed their diagnostic accuracy in individuals with complete symptom resolution on the GFD. Currently, there is a large clinical practice discrepancy in approaching patients who self-start the GFD and have borderline or negative serology. Hence, in many circumstances, HLA testing and assessment of enteropathy risk factors are overlooked, and endoscopy is the default next step. We found that incorporating personal history of autoimmune disease or nutrient deficiencies and a family history of CD in the diagnostic model is most effective in subjects with negative serology. Those with negative serology who also lack clinical evidence of malabsorption and CD risk factors are highly likely to have NCGS and do not routinely require endoscopy. On the other hand, there is a significant risk (27.5%) that subjects with clinical evidence of malabsorption and/or CD risk factors will have inflammatory changes on small intestinal biopsy despite their negative celiac serology results; hence, an upper endoscopy with biopsy is indicated (**Figure 2).**

Another finding of our study is that in subjects with borderline serology who also lack symptoms of malabsorption or nutrient deficiency, negative HLA DQ2/DQ8 testing can obviate the need for further testing, including endoscopy and biopsy (27). By the same token, negative HLA testing precludes gluten challenge, which is often poorly tolerated and can be associated with high cost and burden. Our findings are in concordance with a recent publication by Coburn *et al.* (28) who found that HLA testing is useful in differentiating between CD and symptoms reported by subjects who self-treat with GFD without an established CD diagnosis. Nonetheless, given the high prevalence of the celiac-associated HLA genes in the general population, and, in some areas, limited access to genetic testing, there is no sufficient evidence to recommend HLA testing as a routine first-line test before celiac serology testing **Figure 2**.

Although the prevalence of HLA genes in the general population is around 40% (29), an interesting observation of our study was that 53% of the NCGS subjects had positive HLA genes. This finding might be attributed to selection bias, as a substantial number of patients seen in our celiac center come for second-opinion visits. In other words, subjects with negative genes in whom the diagnosis of CD is safely excluded may be preferentially receiving their care in community practices rather than tertiary care centers. In addition, 12.8% of our NCGS subjects have a family history of CD. This can be due to increased self-referral to a specialized celiac clinic and can explain the higher prevalence of celiac genes in these NCGS subjects. Finally, a report by Wahnschaffe *et al.* (11) has demonstrated that subjects with positive HLA genes are more likely to respond to the GFD compared with subjects with negative genes.

To ensure the exclusion of clinical entities that mimic NCGS and are responsive to exclusion diets other than the GFD such as low FODMAP or dairy-free diets, we only included in our analysis subjects who reported following a completely regular diet except for gluten exclusion. Although it may be possible to have NCGS and concomitant small intestinal bacterial overgrowth and/or microscopic colitis, the complete resolution of symptoms on GFD precluded further testing for these two entities. Moreover, small intestinal bacterial overgrowth and microscopic colitis are more common in CD, and symptoms of these disorders do not resolve with gluten exclusion alone. In a similar manner, symptomatic lactose intolerance was not highly suspected in most of our NCGS subjects, given the resolution of symptoms despite being on dairy products.

Overall, our proposed model offers an effective and clear approach to the differential diagnosis and management of subjects with symptoms responsive to the GFD, especially in those with borderline or negative serology. On the basis of our model, endoscopy could have been avoided in 61.8% of subjects who had borderline or negative serology and underwent endoscopy for definitive diagnosis. Nonetheless, we note several limitations with our study. First, it was conducted in a tertiary center that receives a large referral number of CD subjects. Hence, the relative prevalence of NCGS to CD might be underestimated compared with the general population risk. Second, the majority of our subjects were White females from a limited geographical area. Therefore, our findings might not be generalizable to the general population. In addition, the pathology slides were interpreted by specialized GI pathologists, which might not be available in all clinical settings.

In conclusion, CD and NCGS present differently despite the response to the GFD. Testing for specific celiac serologies such as IgA

tTG or IgA/IgG DGP on a gluten-containing diet is an important first step. Those with positive serology are highly likely to have CD. Those with borderline serology should undergo HLA typing to determine the need for biopsy. Those with negative serology who also lack clinical evidence of malabsorption and CD risk factors are highly likely to have NCGS and may not require further testing. Further prospective population-based studies that validate this diagnostic algorithm and explore the prevalence and pathogenesis of NCGS are warranted to better understand this emerging and important entity.

CONFLICT OF INTEREST

Guarantor of the article: Toufic A. Kabbani, MD, MPH.

Specific author contributions: Study designs, acquisition of data, analysis and interpretation of data, and drafting of the manuscript: Toufic A. Kabbani; acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical review of the manuscript: Rohini R. Vanga; study designs, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical review of the manuscript: Daniel A. Leffler; acquisition of data: Javier Villafuerte-Galvez, Kumar Pallav, Joshua Hansen, Rupa Mukherjee, Melinda Dennis; study designs, acquisition of data, analysis and interpretation of data, and critical review of the manuscript: Ciaran P. Kelly.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Celiac disease (CD) affects about 1% of the US population and is precipitated by ingestion of barley, rye, and wheat. Gluten-free diet (GFD) is the cornerstone treatment of CD.
- ✓ An emerging and common entity known as non-celiac gluten sensitivity (NCGS) is distinct from CD but is also responsive to the GFD.
- ✓ Several conditions, known as "non-celiac enteropathy" (NCE), can mimic CD and cause villous atrophy. These conditions can also respond to the GFD.

WHAT IS NEW HERE

- ✓ NCGS and CD subjects present in distinct clinical ways despite their common response to GFD. NCGS subjects develop symptoms at a younger age, present more often with constipation, and are less likely to have malabsorptive symptoms, nutrient deficiencies, personal history of autoimmune disease, and family history of CD.
- ✓ IgA *trans*-glutaminase antibodies (tTG) and IgA/IgG deaminated gliadan peptide antibodies (DGP) do not only have very high specificity for CD in the general population, but also in subjects who report symptoms responsive to the GFD. These tests should be the first step in approaching these patients.
- ✓ In subjects responsive to the GFD who have borderline serology, negative human leukocyte antigen (HLA) DQ2/DQ8 testing can obviate the need for further testing including endoscopy.
- ✓ Subjects responsive to the GFD who have negative serology and also lack clinical evidence of malabsorption and CD risk factors are highly likely to have NCGS and do not routinely require endoscopy.

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