

# Etiologies and Predictors of Diagnosis in Nonresponsive Celiac Disease

DANIEL A. LEFFLER, MELINDA DENNIS, BRIAN HYETT, EOIN KELLY, DETLEF SCHUPPAN, and CIARAN P. KELLY

Department of Gastroenterology, Beth Israel Deaconess Medical Center, Boston, Massachusetts

See Barone MV et al on page 1245 for companion article in the April 2007 issue of *Gastroenterology*.

**Background & Aims:** Nonresponsive celiac disease (NRCD) is a common problem affecting from 7% to 30% of celiac patients. Because NRCD comprises varied and potentially morbid entities, efficient and cost-effective patient care requires knowledge of the specific causes of this disorder. The aim of this study was to determine the common etiologies of NRCD in a tertiary referral center. **Methods:** All cases of biopsy examination–proven celiac disease (CD) seen at our institution over the preceding 5 years were included in this study. NRCD was defined as a failure to respond to at least 6 months of treatment with a gluten-free diet or the re-emergence of symptoms or laboratory abnormalities typical of CD while still on treatment with a gluten-free diet. **Results:** A total of 113 patients with NRCD meeting the earlier-described criteria were seen from a total of 603 patients with CD (19%), however, among patients for whom we provided primary specialist care the incidence of NRCD was 10% ( $P < .001$ ). Gluten exposure was the most common cause of NRCD (36%), followed by irritable bowel syndrome (22%), refractory CD (10%), lactose intolerance (8%), and microscopic colitis (6%). The mean immunoglobulin A tissue transglutaminase level in the gluten-exposed group was 67 vs 17 U/mL (normal,  $<20$ ) for other diagnoses ( $P < .05$ ). Weight loss and male sex were highly predictive of refractory CD ( $P < .05$  and  $< .001$ , respectively). **Conclusions:** NRCD is a common phenomenon affecting 10%–19% of celiac patients. A limited number of etiologies account for the majority of cases. Clinical factors may be used to guide evaluation.

Celiac disease (CD) is a small-intestinal inflammatory disease defined by characteristic histologic changes including villous atrophy and increases in intraepithelial lymphocytes. CD is triggered by gluten proteins from wheat, rye, and barley, in genetically predisposed individuals who carry the human lymphocyte antigen (HLA)-DQ2 or -DQ8.<sup>1</sup> Mostly because of the availability of accurate serology-based tests,<sup>2–5</sup> increasing numbers of individuals are being diagnosed with CD, therefore clinicians must be aware of the frequency and common etiologies of incomplete response to gluten withdrawal.

Although the majority of individuals with CD have substantial improvement within the first few weeks of gluten withdrawal, between 7% and 30% continue to have symptoms or clinical manifestations suggestive of CD despite being on a gluten-free diet.<sup>6,7</sup> This clinical problem, which encompasses many distinct diagnoses, is known as nonresponsive celiac dis-

ease (NRCD). NRCD may be defined further as *primary* if there is initial failure to respond to a gluten-free diet or *secondary* if signs, symptoms, or laboratory abnormalities consistent with CD re-emerge after initial normalization while maintaining a gluten-free diet (Table 1).

In smaller studies the most common cause of NRCD was unintentional gluten intake, accounting for approximately 50% of cases of NRCD,<sup>6,8</sup> but etiologies can vary greatly to include lymphoma,<sup>9</sup> small-intestinal bacterial overgrowth (SIBO),<sup>10,11</sup> microscopic colitis,<sup>12</sup> pancreatic insufficiency,<sup>8,12</sup> disaccharidase deficiency,<sup>12</sup> and irritable bowel syndrome (IBS),<sup>8</sup> all of which may present similarly but require very different therapies. Because NRCD comprises a number of potentially severe conditions with disparate treatment and prognosis, efficient and cost-effective care of patients with this syndrome may be challenging.

In contrast to prior investigations, our data allow differentiation of patients referred from outside practices and those receiving primary gastroenterology care through our referral center. In addition, the large number of consecutive patients evaluated allows for a more definitive determination of clinical characteristics, especially as correlated to refractory CD. We sought, therefore, to better define the prevalence of NRCD in current clinical practice in the United States, to identify the range of specific etiologies for this disorder, and to determine which, if any, clinical factors are predictive of the final etiology.

## Methods

A database of all patients seen at our institution from January 1, 2000, to April 1, 2006, coded for CD under the International Classification of Diseases 9th edition code 579.0 was compiled and predetermined clinical data were recorded. From this list, 603 patients were found to have biopsy examination–proven CD. Individuals without definitive evidence of CD in the form of duodenal biopsy examination, or skin biopsy examination in cases of dermatitis herpetiformis, were not included in this study. HLA typing was performed for patients in whom there was doubt regarding the validity of the diagnosis. Analysis of tissue transglutaminase (tTG) titers was performed by enzyme-linked immunosorbent assay with recombinant human antigen (INOVA Quanta Lite human-tTG immunoglobulin [Ig]A; San Diego, CA: sensitivity, 94%; specificity, 99%). For patients with CD, electronic medical records that included all clinician notes, laboratory data, and results of

**Abbreviations used in this paper:** CD, celiac disease; EATL, enteropathy associated T-cell lymphoma; ELISA, enzyme-linked immunosorbent assay; HLA, human lymphocyte antigen; IBS, irritable bowel syndrome; Ig, immunoglobulin; NRCD, nonresponsive celiac disease; SIBO, small intestinal bacterial overgrowth; tTG, tissue transglutaminase.

**Table 1.** Diagnostic Criteria for NRC

Symptoms/signs
Fatigue
Abdominal pain
Diarrhea
Weight loss
Laboratory abnormalities
Anemia
tTG >50% above normal limit

diagnostic tests performed at our hospital and affiliated institutions (Beth Israel Deaconess Medical Center, Joslin Diabetes Center, New England Baptist Hospital, Beth Israel Deaconess Needham, and Beth Israel Deaconess Nashoba) then were searched individually for evidence of NRC and prespecified clinical characteristics, including age at diagnosis, sex, comorbid diseases, and initial IgA anti-tTG level. All entries were reviewed twice for accuracy.

NRC was defined as: (1) referral to a clinician specializing in CD for the evaluation of a lack of response to a gluten-free diet, (2) failure of clinical symptoms or laboratory abnormalities typical of CD to improve within 6 months of gluten withdrawal, (3) recurrence of symptoms and/or laboratory abnormalities typical of CD while on a gluten-free diet (Table 1).

Refractory CD was defined as the persistence of villous atrophy despite strict gluten withdrawal and no evidence of another pathology including overt lymphoma.<sup>13</sup> In addition, selected patients believed to be at high risk were evaluated for T-cell clonality and aberrant T-cell markers, which suggest the presence of more severe type II refractory CD vs the more indolent type I refractory CD.<sup>14,15</sup> For analysis, cases of refractory CD were grouped with ulcerative jejunitis and enteropathy-associated T-cell lymphoma (EATL).

Gluten exposure was determined to be the cause if, during evaluation, likely sources of gluten were elicited and the removal of these sources led to sustained clinical improvement. Lymphocytic colitis was diagnosed in individuals with a grossly normal-appearing colon and more than 20 lymphocytes per 100 epithelial cells on colonic biopsy examination.<sup>16</sup> Disaccharidase deficiency was diagnosed by clinical history with sustained symptom resolution on removal of the specific sugar. SIBO was diagnosed in the setting of significantly increased hydrogen or methane excretion during glucose or lactulose breath testing with sustained clinical response to antibiotic therapy.<sup>17</sup> Eating disorders were defined according to the Diagnostic and Statistical Manual of Mental Disorders-IV<sup>18</sup> criteria. IBS was diagnosed when patients had symptoms meeting Rome criteria<sup>19</sup> in the absence of red flag signs and symptoms and the presence of normal duodenal biopsy specimens. Pancreatic insufficiency was diagnosed when individuals had sustained remission of symptoms in response to the pancreatic enzyme replacement regimen chosen by the treating physician. Other diagnoses in our population were made according to established criteria.<sup>20-24</sup>

With the exception of terminal diseases, diagnosis was considered final if the patient experienced a durable clinical response to directed therapy. Patients seen only a single time were considered lost to follow-up evaluation and no diagnosis was recorded.

A total of 113 consecutive patients meeting the earlier-described criteria were identified. All patients were evaluated by a skilled nutritionist trained in CD. Diagnostic testing was performed according to clinical necessity and the evaluation con-

tinued until a secure diagnosis was reached. In most instances this was followed by subsequent improvement in symptoms and normalization of laboratory abnormalities in cases of non-terminal disease.

Statistical analysis was completed using SPSS for Windows (release 13.0; SPSS Inc., Chicago, IL). A 2-sample *t* test, the Pearson  $\chi^2$  test, and the Fisher exact test were used to compare variables between groups of patients with specific final diagnoses and between NRC and responsive CD. Results were considered significant with a *P* value of less than .05.

This study was reviewed and approved by the Committee for Clinical Investigations at Beth Israel Deaconess Medical Center.

## Results

A total of 113 of 603 (18.7%) individuals with CD were found to have NRC. Of the 113 patients, 74 (65%) were referred by clinicians from outside our institution and the remaining 39 (35%) patients were cared for at our institution from the initial diagnosis of CD onward. NRC accounted for 35% of the 211 new referrals to our celiac center. The majority of the remaining referrals were for either confirmation of diagnosis or general management of previously diagnosed CD. Thirty-nine of the 392 patients (9.9%) with CD who received their primary care at our institution developed NRC compared with 35% of referrals (*P* < .001). Of the individuals receiving primary care at our institution who developed NRC, 25 (64%) were primary in onset. The overall duration of symptoms at initial evaluation was 15.3 months (range, 1-138 mo). For primary and secondary nonresponse the duration of symptoms before evaluation was 31.7 and 7.7 months, respectively.

The mean age at onset of NRC was 42.2 years, which was not significantly different from the mean age at diagnosis of all cases of CD in our population. Gender distribution and the prevalence of comorbid autoimmune disorders were similar between groups. In individuals with NRC, there was a non-significant increase in the prevalence of psychiatric disorders, defined by past diagnosis with one or more mental illnesses, most commonly anxiety and depression, or current prescription of psychoactive medication (Table 2). Of the 34 individuals with psychiatric diagnoses, 22 (64.7%) had B<sub>12</sub> and folate levels checked. Two (9%) were found to have low B<sub>12</sub> levels, whereas folate levels were normal in all individuals.

The reliability of diagnosis is based on repeated visits with persistent clinical improvement. The mean duration of follow-up evaluation was 19.8 months (range, 2-126 mo), the mean number of visits was 5.8 (range, 2-30). Individuals seen only for a single visit were considered lost to follow-up evaluation with no confirmed diagnosis. In this cohort of 113 patients, 14 did not meet the earlier-described criteria at the time of review and were not included in further analysis. Of the remaining 99 individuals, IgA anti-tTG titers were available for 89 patients at the initial evaluation. Of these, 38 patients had increased titers, with levels greater than 20 (42.7%). The group with increased IgA anti-tTG had been on the diet for a mean of 49.2 months compared with 60.5 months for the patients with normal anti-tTG titers (*P* = .50).

Among the 99 with confirmed diagnoses, we found a total of 12 etiologies of NRC. The most common cause was (inadvertent) gluten exposure, accounting for 36% of patients. Other common etiologies of NRC included IBS (22%), refractory CD (10%), lactose deficiency (8%), SIBO (6%), and microscopic co-

**Table 2.** Characteristics of Nonresponsive vs Responsive CD

	Nonresponsive (n = 113)	Responsive (n = 490)	P
Mean age at diagnosis, y	42.2	44.0	.29
% Female	79.6	70.3	.11
Initial IgA tTG (ELISA units)	114.7	103.6	.50
% Comorbid psychiatric condition <sup>a</sup>	31.9	23.7	.09
% Other autoimmune disorder <sup>b</sup>	31.0	23.9	.15
% Outside referral	64.6	27.6	<.0001

<sup>a</sup>Predominantly depression and anxiety.

<sup>b</sup>Predominantly thyroid disease, type 1 diabetes mellitus, and Raynaud's phenomenon.

litis (6%). The remaining 13% consisted of eating disorders, peptic ulcer disease, gastroparesis, Crohn's disease, food allergies, common variable immune deficiency, and duodenal adenocarcinoma. Predominant symptoms in nonresponsive patients included diarrhea (54%), abdominal pain (55%), weight loss (20%), and, to a lesser extent, fatigue (5%). Laboratory abnormalities prompting evaluation were found in 10% and included persistent increases in IgA anti-tTG autoantibody levels and iron-deficiency anemia.

A limited number of factors were found to be predictive of the final diagnosis in NRCD. The most significant of these was recent weight loss per patient report, which was predictive of refractory CD with an odds ratio of 31.1 (95% confidence interval, 5.9-163.1). An increased IgA anti-tTG titer greater than 20 U/mL (the upper limit of normal) was predictive of gluten exposure at an odds ratio of 11.3 (95% confidence interval, 3.7-34.4) and a mean of 67 U/mL (range, 2-135 U/mL). Of the 35 patients with persistent gluten exposure, anti-tTG titers at evaluation were available for 28. Of these, 22 (78%) were increased with tTG levels greater than 20. The absence of abdominal pain also was associated with gluten exposure ( $P < .01$ ).

Beyond the gluten-exposure group, a mean IgA anti-tTG titer greater than 20 U/mL also was found in refractory CD (mean, 45 U/mL; range, 3-127 U/mL) and SIBO (mean, 25 U/mL; range, 1-82 U/mL). IBS was found in 22 of 99 NRCD patients and was associated with the presence of abdominal pain and the absence of diarrhea ( $P < .01$ ). Microscopic colitis and SIBO also were associated with diarrhea ( $P < .05$ ). Female patients had a greater risk of being diagnosed with IBS ( $P = .04$ ), but a decreased risk of refractory CD ( $P = .006$ ) (Table 3). Comparisons of presenting symptoms across diagnoses can be found in Figures 1-3.

### Discussion

In this study we report the incidence, etiology, and clinical characteristics of 113 consecutive NRCD patients seen at our center over the preceding 5 years. Our findings are consistent with those of other reports; however, the larger size of our patient population allows for increased statistical power and for us to make diagnostic predictions based on presenting symptoms. As in past studies,<sup>8</sup> gluten exposure remains the most common cause of NRCD and is the only diagnostic category independently associated with an increased IgA anti-tTG titer. It is difficult to classify purposeful vs inadvertent gluten exposure. During the study period, patients were instructed to avoid all oat products and the majority of patients diagnosed with gluten exposure did not have gross blatant gluten intake, but rather had not been adequately diligent in removing sources of cross-contamination or hidden gluten in restaurant foods, medications, or cosmetics.

Although gluten exposure is prominent, the 35% prevalence rate seen in this study was lower than the 50% previously reported.<sup>8</sup> Although this difference is not yet statistically significant ( $P = .06$ ) and may be a chance finding, the Boston area has a very large and active CD advocacy group and a number of highly skilled celiac nutritionists. These factors may account for a relatively good adherence to a gluten-free diet, which may vary in different regions. This view is supported by the much lower prevalence of NRCD in those patients who were treated in our tertiary center initially compared with patients who were referred to us (9.9% vs 39%,  $P < .05$ ).

**Table 3.** Summary of Final Diagnoses and Associated Characteristics in NRCD

Diagnosis	Number of patients	Mean tTG	Male (%), n = 21	Female (%), n = 78	Predominant symptoms (%)	Primary nonresponse	
						Male (%)	Female (%)
Gluten exposure	35	67 <sup>a</sup>	9 (43)	26 (33)	D (55) A (35) <sup>a</sup> W (15)	4/9 (44)	18/26 (69)
IBS	22	9	1 (5)	21 (27) <sup>a</sup>	D (34) <sup>a</sup> A (91) <sup>a</sup> W (5)	1/1 (100)	13/21 (62)
Microscopic colitis	6	7	0 (0)	6 (8)	D (100) <sup>a</sup> A (17) W (0)	N/A	2/6 (33)
Refractory sprue <sup>b</sup>	10	45	6 (29)	4 (5) <sup>a</sup>	D (70) A (80) W (90) <sup>a</sup>	3/6 (50)	2/4 (50)
Disaccharidase deficiency	8	16	1 (5)	7 (9)	D (67) A (67) W (0)	0/1 (0)	7/7 (100)
Eating disorder	4	34	0 (0)	4 (5)	D (50) A (100) W (0)	N/A	4/4 (100)
SIBO	6	25	2 (9)	4 (5)	D (100) <sup>a</sup> A (67) W (33)	1/2 (50)	2/4 (50)
Miscellaneous <sup>c</sup>	8	14	2 (10)	6 (8)	N/A	N/A	N/A

D, diarrhea; A, abdominal discomfort; W, weight loss.

<sup>a</sup> $P < .05$  vs combined other diagnoses.

<sup>b</sup>Includes refractory sprue, ulcerative duodenitis/jejunitis, and small-intestinal lymphoma.

<sup>c</sup>Duodenal adenocarcinoma (1), diabetic gastroparesis (1), Crohn's disease (1), peptic ulcer disease (2), food allergy (2), common variable immune deficiency (1).

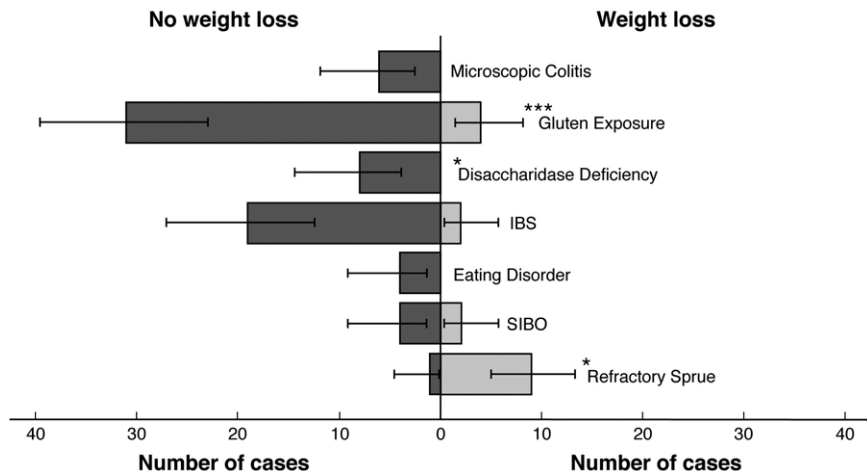


Figure 1. Frequency of weight loss in different diagnoses. \**P* < .05; \*\**P* < .01; \*\*\**P* < .001.

Although we found 12 distinct causes of NRCD, it is notable that gluten exposure and disaccharide deficiency in combination accounted for 43% of all patients. This reaffirms the importance of skilled nutritional counseling in the treatment of CD.<sup>25-27</sup> Further, although the specter of refractory CD is commonly increased, this was found in only 10% of patients with NRCD. Furthermore, the majority of patients with refractory CD were referrals from other institutions and the incidence of refractory CD within our own patient cohort was 0.7%. Of the 10 individuals with refractory CD, 1 had persistent ulcerative jejunitis, 1 had ulcerative jejunitis that progressed to EATL, and 4 had EATL without a prior diagnosis of refractory CD or ulcerative jejunitis. Of note, all 5 individuals with EATL were men. Diagnoses were confirmed by T-cell-receptor  $\gamma$  monoclonality, immunohistochemistry, and evaluation for lymph node involvement. Of the other 4 individuals without EATL or ulcerative jejunitis, 3 had immunophenotyping and polymerase chain reaction for T-cell clonality, which were negative, and the fourth is doing well after a number of years of follow-up evaluation, so these 4 patients were classified as refractory CD type 1.

It is unclear why the men in our cohort were significantly more likely to be diagnosed with refractory CD and exclusively developed EATL compared with women. The scarcity of refrac-

tory CD and EATL has made epidemiologic studies difficult. Only 1 prior study reported a sex-specific incidence of EATL among patients with CD with a calculated incidence of 0.011 and .037 for females and males, respectively, but included only 4 patients.<sup>28</sup> A number of other studies compared rates of intestinal lymphoma with the general population and controlled for sex,<sup>29,30</sup> but did not provide the sex distribution of the celiac population from which the patients were drawn. The age at diagnosis of CD in men and women developing this disorder was 44 and 51, respectively (*P* = NS). However, our data do not permit evaluation of the duration of symptoms before the diagnosis of CD or of dietary compliance. It is possible that the initial diagnosis was delayed in men vs women, or that men were less strict with gluten avoidance, allowing for the development of complicated CD. Although autoimmune enteropathy may masquerade as refractory CD, because this is a rare and poorly defined condition we do not routinely evaluate for this condition in patients with refractory CD.

We found a limited number of clinical factors present at the initial evaluation of NRCD to be associated with specific ultimate diagnoses. Refractory CD was highly associated with weight loss, and, conversely, only a single patient with refrac-

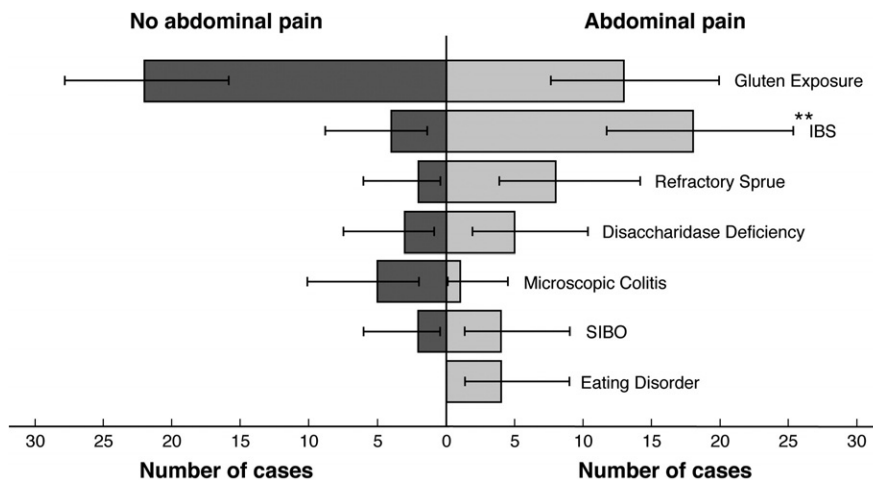


Figure 2. Frequency of abdominal pain in different diagnoses. \**P* < .05; \*\**P* < .01; \*\*\**P* < .001.

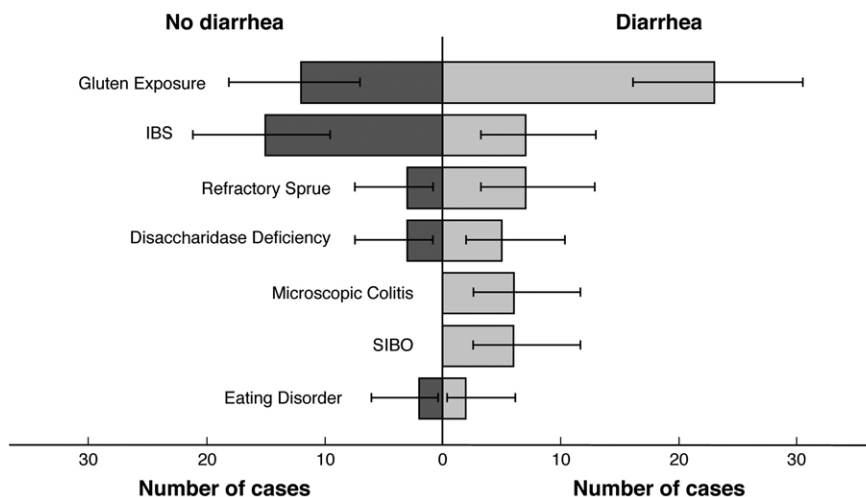


Figure 3. Frequency of diarrhea in different diagnoses. \* $P < .05$ ; \* $P < .01$ ; \*\*\* $P < .001$ .

tory CD did not present with this sign. The IgA anti-tTG titer was increased significantly only in the gluten-exposure group compared with all other groups and this finding should trigger a search for inadvertent gluten exposure. Notably, although not reaching statistical significance, the only other diagnoses that presented with an increased tTG level were SIBO and refractory CD. The reasons for this are unclear and warrant further investigation, although we hypothesize that nonspecific immune stimulation of small intestinal mucosal B and/or T cells may sustain antibody production.

Diarrhea was present in all cases of microscopic colitis and SIBO but was significantly less common in individuals with IBS. The lack of diarrhea in NRCD patients diagnosed with IBS may stem from the well-documented fiber deficiency in the typical gluten-free diet,<sup>31</sup> however, it also is notable that the line between SIBO and IBS has blurred recently<sup>32</sup> and it may be that individuals who in the past would have been diagnosed with IBS now appear more consistent with SIBO. IBS also was associated commonly with abdominal pain whereas gluten exposure was not. The lack of abdominal pain in the gluten-exposure group, which differs from the common complaint of abdominal pain among newly diagnosed CD patients,<sup>33,34</sup> may be explained by the fact that most patients had low-level, unintentional exposure, which may be enough to cause diarrhea and/or laboratory abnormalities without causing pain. All patients underwent esophagogastroduodenoscopy/colonoscopy before diagnosis with IBS. Other imaging modalities including capsule endoscopy, computerized tomography scans, and ultrasounds were performed according to clinical acumen. Of the 22 patients with IBS, 15 (68%) underwent imaging studies, including 9 small-bowel follow-throughs, 8 computerized tomography scans, 6 ultrasounds, and 1 magnetic resonance imaging, all of which were, by definition, normal.

No diagnostic group was significantly different in primary vs secondary nonresponse, however, disaccharidase deficiency presented only in primary NRCD. This is plausible because brush-border enzymes are reconstituted with healing of the intestinal mucosa in treated celiac patients. This finding supports the common practice of limiting lactose intake in CD during the initial weeks to months of dietary therapy.<sup>12,35</sup> In addition, although approximately 20 individuals are known to have un-

dergone a therapeutic trial of pancreatic exocrine hormone supplementation, none responded to this treatment, which contrasts with other studies of NRCD.<sup>8,12</sup> Whether clinical pancreatic exocrine sufficiency is associated with treated or untreated CD currently is unclear and needs to be addressed definitively in future studies. Finally, eating disorders were determined to be the cause of NRCD in 4 patients. While the co-existence of eating disorders with CD has been reported,<sup>36,37</sup> eating disorders as a cause of NRCD is not commonly recognized and is an area deserving of further study.

In general, measured characteristics were similar between individuals with responsive CD and NRCD, except for psychiatric disorders, which trended toward an increase in the nonresponsive group. The reason for this finding is unclear at this time. Possibilities include that pre-existing psychiatric disorders predispose to NRCD because a number of etiologies (gluten exposure, eating disorders, and IBS) may be influenced by psychiatric disorders. Alternatively, psychiatric disorders could be reactive as a result of the stresses associated with NRCD. A third possibility is that the inflammatory and/or nutritional abnormalities of CD are more severe or persistent in NRCD and these may contribute to the evolution of psychiatric disease.<sup>38-40</sup>

There were a number of limitations to this study. First, data were collected retrospectively and patients were evaluated by a number of clinicians. Differences in the diagnostic strategies used by various clinicians may have biased the final diagnoses. However, the end point of clinical improvement with directed treatment suggests that, although different intermediate paths may have been taken, the final diagnoses are reliable. Another limitation could be that the study was undertaken at a tertiary referral center with decreased relevance for a general community practice. However, the fact that there was no significant difference in the prevalence of diagnoses between patients referred to us from outside clinicians and hospitals and those cared for primarily by our physicians suggests that our findings are generalizable. Finally, because we are the only CD referral center in New England, our patient population was limited geographically and there may be variations in etiologies in different regions.

In conclusion, NRCD is a common condition, affecting 19% of patients with CD in our sample, 10% of whom have refractory CD. The calculated incidence of NRCD and refractory CD in our

population is 10% and 0.7%, respectively. Similar to smaller prior studies,<sup>6,8</sup> gluten exposure is the most common etiology of NRCd, and a limited number of other diagnoses make up more than 90% of cases. There is evidence that certain readily available clinical parameters including IgA anti-tTG titer, sex, and the presence of weight loss, diarrhea, or abdominal pain can guide the diagnostic work-up, and these should be considered when evaluating a case of NRCd. With the rapidly growing number of individuals diagnosed with CD, NRCd is likely to become an increasingly common clinical problem in gastroenterologic practice. Further study will have to prospectively evaluate the utility of the predictive factors described in this study.

## References

- Farrell RJ, Kelly CP. Celiac sprue. *N Engl J Med* 2002;346:180–188.
- Dieterich W, Ehnis T, Bauer M, et al. Identification of tissue transglutaminase as the auto-antigen of celiac disease. *Nat Med* 1997;3:797–801.
- Dieterich W, Esslinger B, Schuppan D. Pathomechanisms in celiac disease. *Int Arch Allergy Immunol* 2003;132:98–108.
- Dieterich W, Laag E, Schopper H, et al. Autoantibodies to tissue transglutaminase as predictors of celiac disease. *Gastroenterology* 1998;115:1317–1321.
- Sulkanen S, Halttunen T, Laurila K, et al. Tissue transglutaminase autoantibody enzyme-linked immunosorbent assay in detecting celiac disease. *Gastroenterology* 1998;115:1322–1328.
- O'Mahony S, Howdle PD, Losowsky MS. Review article: management of patients with non-responsive coeliac disease. *Aliment Pharmacol Ther* 1996;10:671–680.
- Wong RC, Steele RH, Reeves GE, et al. Antibody and genetic testing in coeliac disease. *Pathology* 2003;35:285–304.
- Abdulkarim AS, Burgart LJ, See J, et al. Etiology of nonresponsive celiac disease: results of a systematic approach. *Am J Gastroenterol* 2002;97:2016–2021.
- Honemann D, Prince HM, Hicks RJ, et al. Enteropathy-associated T-cell lymphoma without a prior diagnosis of coeliac disease: diagnostic dilemmas and management options. *Ann Hematol* 2005;84:118–121.
- Ghoshal UC, Ghoshal U, Misra A, et al. Partially responsive celiac disease resulting from small intestinal bacterial overgrowth and lactose intolerance. *BMC Gastroenterol* 2004;4:10.
- Tursi A, Brandimarte G, Giorgetti G. High prevalence of small intestinal bacterial overgrowth in celiac patients with persistence of gastrointestinal symptoms after gluten withdrawal. *Am J Gastroenterol* 2003;98:839–843.
- Fine KD, Meyer RL, Lee EL. The prevalence and causes of chronic diarrhea in patients with celiac sprue treated with a gluten-free diet. *Gastroenterology* 1997;112:1830–1838.
- Trier JS, Falchuk ZM, Carey MC, et al. Celiac sprue and refractory sprue. *Gastroenterology* 1978;75:307–316.
- Daum S, Weiss D, Hummel M, et al. Frequency of clonal intraepithelial T lymphocyte proliferations in enteropathy-type intestinal T cell lymphoma, coeliac disease, and refractory sprue. *Gut* 2001;49:804–812.
- Cellier C, Patey N, Mauvieux L, et al. Abnormal intestinal intraepithelial lymphocytes in refractory sprue. *Gastroenterology* 1998;114:471–481.
- Lazenby AJ, Yardley JH, Giardiello FM, et al. Lymphocytic ("microscopic") colitis: a comparative histopathologic study with particular reference to collagenous colitis. *Hum Pathol* 1989;20:18–28.
- Kerlin P, Wong L. Breath hydrogen testing in bacterial overgrowth of the small intestine. *Gastroenterology* 1988;95:982–988.
- Wilson GT, Walsh BT. Eating disorders in the DSM-IV. *J Abnorm Psychol* 1991;100:362–365.
- Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology* 2006;130:1480–1491.
- Burks W, Ballmer-Weber BK. Food allergy. *Mol Nutr Food Res* 2006;50:595–603.
- Kalra I, Sellin JH. Common variable immunodeficiency and the gastrointestinal tract. *Curr Gastroenterol Rep* 2004;6:377–383.
- Luzi G, Zullo A, Iebba F, et al. Duodenal pathology and clinical-immunological implications in common variable immunodeficiency patients. *Am J Gastroenterol* 2003;98:118–121.
- Friedenberg FK, Parkman HP. Delayed gastric emptying: whom to test, how to test, and what to do. *Curr Treat Options Gastroenterol* 2006;9:295–304.
- Hanauer SB, Present DH. The state of the art in the management of inflammatory bowel disease. *Rev Gastroenterol Disord* 2003;3:81–92.
- Lovik A, Fausa O, Motzfeldt K, et al. [Diet among patients with celiac disease. Do patients comply with a gluten-free diet?] *Tidsskr Nor Laegeforen* 1989;109:1153–1155.
- Lovik A, Lundin KE. [Dietary treatment of coeliac disease and dermatitis herpetiformis.] *Tidsskr Nor Laegeforen* 2003;123:3237–3240.
- Case S. The gluten-free diet: how to provide effective education and resources. *Gastroenterology* 2005;128(Suppl 1):S128–S134.
- Cottone M, Termini A, Oliva L, et al. Mortality and causes of death in celiac disease in a Mediterranean area. *Dig Dis Sci* 1999;44:2538–2541.
- Askling J, Linet M, Gridley G, et al. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. *Gastroenterology* 2002;123:1428–1435.
- Catassi C, Fabiani E, Corrao G, et al. Risk of non-Hodgkin lymphoma in celiac disease. *JAMA* 2002;287:1413–1419.
- Thompson T, Dennis M, Higgins LA, et al. Gluten-free diet survey: are Americans with coeliac disease consuming recommended amounts of fibre, iron, calcium and grain foods? *J Hum Nutr Diet* 2005;18:163–169.
- Sharara AI, Aoun E, Abdul-Baki H, et al. A randomized double-blind placebo-controlled trial of rifaximin in patients with abdominal bloating and flatulence. *Am J Gastroenterol* 2006;101:326–333.
- Rashid M, Cranney A, Zarkadas M, et al. Celiac disease: evaluation of the diagnosis and dietary compliance in Canadian children. *Pediatrics* 2005;116:e754–e759.
- Murray JA, Watson T, Clearman B, et al. Effect of a gluten-free diet on gastrointestinal symptoms in celiac disease. *Am J Clin Nutr* 2004;79:669–673.
- Murphy MS, Sood M, Johnson T. Use of the lactose H2 breath test to monitor mucosal healing in coeliac disease. *Acta Paediatr* 2002;91:141–144.
- Yucef B, Ozbey N, Demir K, et al. Eating disorders and celiac disease: a case report. *Int J Eat Disord* 2006;39:530–532.
- Ricca V, Mannucci E, Calabro A, et al. Anorexia nervosa and celiac disease: two case reports. *Int J Eat Disord* 2000;27:119–122.
- Sverker A, Hensing G, Hallert C. 'Controlled by food'—lived experiences of coeliac disease. *J Hum Nutr Diet* 2005;18:171–180.
- Wei J, Hemmings GP. Gene, gut and schizophrenia: the meeting point for the gene-environment interaction in developing schizophrenia. *Med Hypotheses* 2005;64:547–552.
- Pynnönen PA, Isometsä ET, Aronen ET, et al. Mental disorders in adolescents with celiac disease. *Psychosomatics* 2004;45:325–335.

---

Address requests for reprints to: Daniel Leffler, MD, Department of Gastroenterology, Beth Israel Deaconess Medical Center, Dana 501, 330 Brookline Avenue, Boston, Massachusetts 02215. e-mail: dleffler@caregroup.harvard.edu; fax: (617) 667-2767.

Supported by a National Institutes of Health T32 research grant.