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Lymphocytic Duodenosis and the Spectrum of Celiac Disease

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Abstract

Introduction: Celiac disease (CD) is a chronic inflammatory disease of the small bowel that is characterized by increased intraepithelial lymphocytes (IELs) and villous atrophy of the mucosa. It is unclear how often intraepithelial lymphocytosis in the absence of atrophy is a manifestation of gluten sensitive enteropathy. The objective of this study was to identify factors that discriminate patients with celiac disease from those with lymphocytic duodenosis (intraepithelial lymphocytosis without villous atrophy). We compared Class 2 HLA type, presenting symptoms, and serology in patients with lymphocytic duodenosis (LD) and CD.

Methods: Retrospective review of 124 systematically assessed patients with LD compared with 454 CD patients with villous atrophy. All patients had duodenal biopsies and Class 2 HLA typing

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No conflicts of interest exist.

Study Highlights

- Lymphocytic duodenosis, AKA duodenal lymphocytosis or non-atrophic lymphocytic enteritis, is commonly reported in duodenal biopsies.
- Lymphocytic duodenosis may be part of the spectrum of gluten-sensitive enteropathy.
- It is not clear how frequently lymphocytic duodenosis is part of the gluten-sensitive spectrum.
- Class II HLA typing, may identify those without the genetic susceptibility for celiac disease.

What is new in this paper?

- A large prospectively evaluated series of patients found to have lymphocytic duodenosis are described.
- Celiac serology is positive in only a small subset of these patients.
- HLA typing identifies one half of patients with lymphocytic duodenosis as not having celiac disease or belong to the gluten-sensitive spectrum.
- Anemia, malaise, rash, and a family history of CD were less common in lymphocytic duodenosis than in celiac disease.
- Fully one half of patients with lymphocytic duodenosis do not belong to the spectrum of celiac disease.

performed. HLA type, symptoms, serology pattern, and response to a gluten free diet were analyzed using univariate logistic regression modeling, adjusted for age and gender.

Results: Half of the (63 [51%]) LD patients lack the Class 2 HLA genotypes encoding DQ2 or DQ8 whereas only 11 (2%) CD patients had neither DQ2 nor DQ8, p<0.001. The genes encoding DQ2 were much more prevalent in CD (91%) than that in LD (37%, p<0.001), however, the rate of carriage of DQ8 did not differ between the two groups (15% versus 15%, p=0.9). While diarrhea and weight loss were equally frequent in both LD and CD patients, LD patients were less likely to be associated with anemia (p=0.007), malaise (p=0.006), skin disorder (p=0.007), or a family history of celiac disease (p<0.001). The LD subjects were much less likely to have tissue transglutaminase or endomysial antibodies than CD (12% or 0% versus 87% and 87%; p<0.001 respectively).

Conclusion: The LD cohort differs significantly in terms of HLA type, serology and clinical features, suggesting that the majority of patients with lymphocytic duodenosis do not belong in the spectrum of celiac disease.

Keywords

sprue; genetics; HLA; pathology

INTRODUCTION

Celiac disease (CD) is a chronic inflammatory disease of the small bowel that occurs with the ingestion of gluten, which can be found in grain products such as wheat, barley, and rye.[1] Upon ingestion of gluten, people with CD mount a T-cell mediated reaction, which can lead to the characteristic mucosal lesions of intraepithelial lymphocytosis and villous atrophy.[2-4] Patients can present with symptoms of malabsorption, such as diarrhea, steatorrhea, weight loss, and nutrient and mineral deficiencies.[3]

Studies have shown there is a genetic component that is crucial to the etiology of celiac disease. For example, people with the gene pair encoding the major histocompatibility complex class II human leukocyte antigen (HLA) DQ2, may be more susceptible to celiac disease.[5,6] Indeed, it has been shown that not only is there an association with celiac disease but that DQ2 or occasionally DQ8 HLA genes are virtually required for celiac disease to occur. The absence of these genes makes celiac disease very unlikely. By evaluating HLA type, we may gain insight into whether someone is more or less likely of having a diagnosis of CD when the initial evaluation of duodenal biopsy neither identifies nor rules out the diagnosis of CD.[7,8] Such a circumstance occurs when the duodenal biopsy reveals an increase in IELs but lacks the villous atrophy and chronic inflammation that characterizes CD. While serology specific for celiac disease has been used as an adjunctive test for CD, their utility in those with minor changes suggestive of CD is limited as most such patients are seronegative.[9,10]

As the awareness of the high frequency of CD increases, more patients undergoing an upper endoscopy are having routine duodenal biopsies taken. While CD may be the most common explanation for biopsies showing villous atrophy with inflammation in the Western populations, LD is becoming a more frequent pathological finding. Lymphocytic duodenosis can also be associated with autoimmune disorders, food protein intolerance, *Helicobacter pylori* gastritis, parasitic infections or NSAIDs use.[11,12] It is not clear what this means clinically and how many patients with this pathological finding belong to the spectrum of gluten sensitive enteropathy. The aim of this study is to report a systematic evaluation of patients who are found to have LD through biopsies obtained clinically and to compare their HLA typing, celiac serology and clinical features with patients with established CD.

METHODS

This retrospective study of 124 patients who had duodenal biopsies with increased IELs (defined as >40 intraepithelial lymphocytes per 100 epithelial nuclei) and normal villous architecture, referred to as lymphocytic duodenosis (LD) (Figure 1) seen systematically evaluated at the Mayo Clinic from July, 1997 to November, 2006.[13] These patients were then compared to 454 patients who had a diagnosis of CD based on duodenal biopsies with >40 IELs/ 100 enterocytes and villous atrophy without other explanation for these changes evaluated during the same time period.(7) As a routine 4 duodenal biopsies were obtained from each patient at index endoscopy. Only patients (total of 578) that had Class 2 HLA typing performed were included. Only one individual per pedigree was used so as to not overpopulate the sample with a single family having similar genes.

The clinical records of all patients in this study were reviewed for the following: age, gender and race, date of diagnosis, residency at time of diagnosis and presenting symptoms (presence or absence of the following: diarrhea, greasy stool, abdominal distention, abdominal cramping, flatulence, ascites, edema, anorexia, weight loss, nausea/vomiting, paresthesia, tetany, bone pain, anemia, malaise, skin disorder, inflamed mouth (canker sores, mouth ulcers), itchy skin, headaches, family history of CD, failure to thrive (persistently below 3rd percentile for weight or <80% ideal body weight), poor increase in height (height <3rd percentile for age), and constipation).

Most of the subjects had serological testing undertaken at Mayo Medical Laboratories. However, a small proportion had these tests done in other labs. Serology testing (EMA, TTg (IgA), TTg (IgG), Gliadin IgA, Gliadin IgG) was reported only if it was completed close to the time of the intestinal biopsy and while the patient was on a normal gluten containing diet. If the patient had been on a gluten free diet subsequent to the biopsy, the response to a gluten free diet (either an objective or subjective response) was recorded. Note that only patients who were on a normal gluten containing diet at the time of the biopsy were included in the study.

The clinical records were abstracted independently by two people (an experienced study coordinator and the primary investigator) to help ensure accuracy.

All patients in the study were seen at the Mayo Clinic and were individuals who sought medical evaluation for clinically significant symptoms. Participants were identified from the Medical Diagnostic Index, Celiac Disease Clinic, and Mayo Clinic Life Sciences System. The majority of the patients were seen in the Division of Gastroenterology and Hepatology. All patients with celiac disease were recruited for a separate study on Epidemiology of celiac disease or had HLA done as part of their clinical care.

HLA Genotyping

Low resolution HLA class 2 gene typing, including both the DR and DQ alleles, was completed on all patients in the study. Some patients also underwent high resolution typing. DNA was extracted from peripheral blood for HLA typing of DR and DQ alleles. Typing methodology was polymerase chain reaction with sequence-specific primers (PCR-SSP), low resolution (One Lambda, Canoga Park, CA) and high resolution (Genovision, West Chester, PA).[14]

Although high resolution typing was not done on all subjects, we were able to extrapolate the DR typing in combination to infer the DQA1 alleles carried. We found this was highly accurate based on 285 subjects who had both high and low resolution typing. Subjects were considered to carry the celiac disease susceptibility genotype only if there was carriage of both of the relevant DQA and DQB alleles.

Serology

Tissue transglutaminase IgA was determined from the ELISA procedure, which is performed with a commercially available ELISA kit using human TTg antigen (The Binding Site, Birmingham UK). The calibrators, controls and diluted patient samples are added to the wells and autoantibodies recognizing the TTg antigen bound during the first incubation. The results were classified as negative, weakly positive or strongly positive.

Endomysial antibodies of the IgA subclass present in the serum bind to the reticulin component of the endomysium of the smooth muscle in monkey esophagus tissue [15] and can be detected by indirect immunofluorescence. In brief, diluted (1:5 and 1:20) serum samples were incubated with air-dried 5 micron cryostat sections of monkey esophagus (The Binding Site, Birmingham UK) for 30 minutes at room temperature. Subsequently, unbound antibody is rinsed free and excess buffer removed by blotting. Substrate-bound IgA antibody is then identified with a fluorescent anti-human IgA (Fab2-specific) conjugate (The Binding Site, Birmingham UK), and the staining pattern examined with a Zeiss microscope with Zeiss IV FL vertical illumination for epifluorescence and a fluorescein filter system (Carl Zeiss Inc. Thornwood, New York). A positive cutoff of 1:5 was selected as normal sera at lower dilutions produced nonspecific substrate staining. Positive staining is identified as a reticulated lace-like pattern surrounding smooth muscle bundles at dilutions of 1:5 and 1:20.

Gliadin testing was done by ELISA using both IgA and IgG isotype using a commercial kit from Scimedix.

The patients' serology testing was only included in this study if it was completed close to the time of the intestinal biopsy and while the patient was still on a normal gluten containing diet.

Statistical Analysis

Descriptive statistics were first used to summarize the data on all subjects, stratified by specific type of disease LD or CD. Categorical parameters were expressed by the number and percentage among the non-missing total, and continuous parameters were represented by the mean and standard deviation. Differences in continuous parameters between the two disease-specific groups were tested using a t-test, while associations between categorical variables and group were assessed using the standard 2-way contingency table method along with a chi-squared test or Fisher's exact test.

Logistic regression was employed to further distinguish between the LD and CD groups, such that prognostic factors associated with higher risk of LD relative to CD (or vice versa) could be identified. A univariate logistic model postulates a relationship between the log odds of response (LD vs. CD) and the prognostic factor under investigation. Odds ratios (OR) were presented to convey the strength of association and quantify the risk of developing one disease versus the other as a function of the corresponding factor. An additional utility of logistic modeling, estimates of effect can be produced while controlling for other covariates that otherwise may confound the response-risk factor relationship. Using multivariate regression adjustment for the factors age and gender, additional ORs were obtained to determine associations independent of those two regular confounders. A significance level of $\alpha=.05$ was used for all analyses.

RESULTS

Demographic Information

There was no statistical difference in gender or age distributions between the LD and CD cohorts. While there was a significantly lower proportion of declared Caucasians in the LD

group, this was due to a greater number of individuals who did not declare their race and ethnicity. Also, a higher majority of patients in the LD cohort were residents of locations other than the southeastern part of Minnesota at the time of diagnosis. [Table 1]

Clinical Symptoms

The majority (65%) of LD patients presented with chronic diarrhea. Furthermore, 43% had abdominal cramping, 37% had weight loss, 33% had abdominal distention, 33% had nausea/vomiting, and 25% presented with constipation. When compared to those individuals with villous atrophy, LD patients were significantly less likely to have anemia, malaise, or skin disorders after adjusting for age and gender. In contrast, LD patients were significantly or marginally more likely than CD patients to have diarrhea and nausea/vomiting , again after controlling for age and gender effects. [Table 2]

HLA Genotype

Most patients with LD lack the HLA types associated with CD. When comparing the rates of allele presence (either one or both alleles) between patients with LD histology and those with celiac disease, DQ2 is significantly less prevalent in the LD group (37% vs. 91%, $p<0.001$). DQ8 rates are not significantly different in the two groups. When compared to the CD cohort, there is a marginally higher proportion of LD patients that have the DQ8 allele without having the DQ2 allele (12% vs. 7%, OR=1.96, $p=0.045$), and a significantly higher proportion without either DQ2 or DQ8 (51% vs. 2%, OR=44.5, $p<0.001$). [Table 3] The profile of patients with celiac disease who did not have either DQ2 or DQ8 is shown in Table 4.

Serology at Time of Diagnosis

Ninety-three percent of the tested CD patients had tested positive for either EMA, TTg or gliadin, while only 27% in the LD cohort tested had some type of serology positivity ($p<0.001$). [Table 5] Of the 313 seropositive CD patients, 308 of those were DQ2/8 positive. Of the 31 seropositive LD patients, 17 of those were DQ2/8 positive. The 14 patients with LD who lacked both DQ2 and DQ8 were positive for gliadin antibodies alone or their level of TTg-IgA was close to the negative threshold. Just 10.8% (n=12) of the LD patients tested were positive EMA or TTg while 90.5% (n=284) of the CD patients tested positive ($p<0.0001$).

Family History

Of the 124 patients with LD, only 10 (8%) had a family history of celiac disease, compared to 97 of 454 (21%) CD patients with a family history ($p<0.001$). Of the 10 LD patients with a family history of CD, only one person had neither a DQ2 nor a DQ8 allele. Among the 97 CD patients with a family history, only two people had neither a DQ2 nor a DQ8 allele. [Table 6]

Response to a Gluten Free Diet (GFD)

Of the 124 LD patients, 36 of them had a documented trial of a GFD with either a positive or negative response that was recorded at follow-up. Twenty-nine of those individuals responded to the diet, whereas 7 did not show any improvement. Of those 29 responders, 14 people had an objective response that included correction of anemia (n=1), reversion of serology from positive to negative (n=5), improvement in biopsy (n=3), reversion of serology and improved biopsy (n=4), and reversion of serology with improved biopsy and correction of anemia (n=1). While all 454 CD patients were advised to follow a gluten free diet, 352 had a documented response to the GFD at follow-up. Of these individuals, 345 had a positive response while 7 people had no response. Those who lacked any symptoms at diagnosis or at least a documented follow up 3 or more months after institution of the gluten free diet were excluded.

Each individual was then assessed for whether they carried at least one pair of the genes encoding the DQ2 or DQ8 serotypes equivalents. [Table 7]

Other Diagnoses

While testing for other possible explanations for LD was not as systematic, 64 subjects had gastric biopsies performed at the time of the index endoscopy, of whom 4 were *Helicobacter pylori* positive. Five of 49 subjects tested had small intestinal bacterial overgrowth based on duodenal aspirates taken at the same time. Other disorders such as microscopic colitis and IBD affected a handful of patients only. In most LD patients with diarrhea, it was assumed that the cause was idiopathic (31.3%), functional or IBS (27.5%) or medication induced (8.8%).

DISCUSSION

Along with the increased awareness of celiac disease as a diagnostic consideration has come a much greater number of duodenal biopsies that require pathological interpretation. The finding of isolated lymphocytic duodenosis is becoming an increasingly common histological finding. The main observation of this systematic study is that patients with lymphocytic duodenosis are substantially different as a group from those with celiac disease. When taken as a group, one half lacks the HLA gene pairs thought to impart susceptibility for celiac disease, and they are much less likely to test positive serologically with any of the tests used to detect for celiac disease. Furthermore, they often lack the objective features specific for malabsorption such as anemia and weight loss. The high rate of diarrhea in this population is likely the result of a selection bias of those who underwent biopsies.

Although the majority of patients with LD differ from those patients with CD, there is a subgroup of LD patients who have features supportive of gluten sensitivity. For example, of the 124 LD patients, there were 46 (37%) who carried the DQ2 alleles. Furthermore, although only 114 out of 124 LD patients had serology tests at the time of biopsies, 12 (10.8%) did have a positive result for EMA or TTg antibody. This attests to the fact that within the population of patients with LD and symptoms, a subpopulation of these are part of the spectrum of gluten sensitive enteropathy and would likely benefit from being treated as such. Those patients who were negative for TTG or EMA antibodies even if they had gliadin antibodies, form a third indeterminate group who carry the at risk genotype and for whom gluten sensitivity remains a possibility but is less certain.

Of our cohort of LD patients, almost two-thirds had neither the DQ2 allele nor the serological evidence for celiac disease suggesting that the majority of LD patients, do not belong on the spectrum of celiac disease. It is likely that lymphocytic duodenosis represents a common inflammatory response of the epithelium to a number of noxious or inflammatory signals. This lymphocytosis could represent a nonspecific, innate response to many luminal noxious factors including bacteria or to inflammatory markers such as *H. pylori*, Crohn's disease or other autoimmune disorders. It is also possible that even certain gluten peptides that are not those involved in the DQ- restricted T-cell mediated adaptive response characteristic of celiac disease, may trigger a response in the surface epithelium.[11,12]

This study is based on a population of patients who sought medical evaluation for clinically significant symptoms and may not necessarily be representative for patients found to have LD in the absence of symptoms, such as asymptomatic family members where gluten sensitive enteropathy is more likely. Another situation where these conclusions may not apply are in those patients with dermatitis herpetiformis wherein even the mild degrees of enteropathy are highly likely to be a manifestation of gluten sensitivity.[16,17] This observational study is limited by not having a randomized therapeutic protocol. A future therapeutic study is needed to determine if and indeed, which symptomatic LD patients will respond to a gluten free diet.

How do our results intersect with the classification of celiac disease? There have been several studies supporting the role of gluten in patients with, LD, or even just electron microscopic changes of the surface of the enterocytes that improve along with symptoms on a gluten free diet.[18] This appears to occur in the context of the CD associated HLA type. In some of these studies the patients have positive serological tests for CD and in others the celiac specific serology is negative.[19,20] Our study suggests that LD segregates into 2 distinct groups. Those patients with LD who are seropositive and carry the celiac disease susceptibility genes, belong to the spectrum of gluten sensitive enteropathy whereas the majority, who lack genetic and serological evidence of celiac disease, do not. A minority of subjects remain for whom gluten sensitivity remains a possible explanation for the minimal histological change and potentially symptoms..

Interestingly, of the 25 LD patients who responded to a gluten free diet, 11 of them did not carry the HLA types associated with celiac disease. The subjective response to a gluten free diet reported by those LD patients who lack DQ2 or DQ8 may be a response to a general reduction in carbohydrate ingestion. However, we cannot discount the possibility that other (non-HLA associated) responses to gluten can occur.[21] Possibly, this may suggest that there are other immune reactions to gluten beyond the standard HLA-restricted types. There may be symptomatic consequences of these innate responses to gluten or other components of cereals.[22] There are reports in the literature that patients with d-IBS may also respond to gluten avoidance, especially in those who are also serum IgG and DQ2 positive.[11,19] Indeed, the combination of LD with the at-risk HLA type suggests that these patients truly belong somewhere on the spectrum of gluten sensitive enteropathy, even though most patients with LD do not belong in that spectrum. Although gluten sensitive enteropathy may explain some cases of lymphocytic duodenosis, there are likely other explanations involved that are yet to be explored.

In summary, lymphocytic duodenosis is an increasingly recognized pathological finding, and our study provides evidence that HLA genotype, celiac serology and clinical symptoms such as anemia, malaise or skin disorders can be used to dissect a well defined minority belonging to the spectrum of gluten sensitive enteropathy from the majority that do not.

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Abbreviations

CD, celiac disease; DH, dermatitis herpetiformis; HLA, human leucocyte antigen; EMA, endomysial antibody; LD, lymphocytic duodenosis.

REFERENCES

1. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. Gastroenterology Dec;2006 131 (6):1981–2002. [PubMed: 17087937]
2. Green PH, Jabri B. Celiac disease. Annu Rev Med 2006;57:207–21. [PubMed: 16409146]
3. Farrell RJ, Kelly CP. Celiac sprue. N Engl J Med Jan 17;2002 346(3):180–8. [PubMed: 11796853]
4. Schuppan D, Dennis MD, Kelly CP. Celiac disease: epidemiology, pathogenesis, diagnosis, and nutritional management. Nutr Clin Care Apr-Jun;2005 8(2):54–69. [PubMed: 16013224]
5. Kaukinen K, Partanen J, Maki M, Collin P. HLA-DQ typing in the diagnosis of celiac disease. American Journal of Gastroenterology 2002;97(3):695–9. [PubMed: 11922565]

6. Lewis C, Book L, Black J, Sawitzke A, Cannon-Albright L, Zone J, et al. Celiac disease and human leukocyte antigen genotype: accuracy of diagnosis in self-diagnosed individuals, dosage effect, and sibling risk. Journal of Pediatric Gastroenterology & Nutrition 2000;31(1):22–7. [PubMed: 10896066] [see comment]
7. Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, et al. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr Jan;2005 40(1): 1–19. [PubMed: 15625418]
8. Murray JA, Rubio-Tapia A, Van Dyke CT, Brogan DL, Knipschield MA, Lahr B, et al. Mucosal atrophy in celiac disease: extent of involvement, correlation with clinical presentation, and response to treatment. Clin Gastroenterol Hepatol Feb;2008 6(2):186–93. [PubMed: 18096440]quiz 25
9. Rostami K, Mulder CJ, Stapel S, von Blomberg BM, Kerckhaert J, Meijer JW, et al. Autoantibodies and histogenesis of celiac disease. Rom J Gastroenterol Jun;2003 12(2):101–6. [PubMed: 12853995]
10. Rostami K, Kerckhaert J, Tiemessen R, von Blomberg BM, Meijer JW, Mulder CJ. Sensitivity of antiendomysium and antigliadin antibodies in untreated celiac disease: disappointing in clinical practice. Am J Gastroenterol Apr;1999 94(4):888–94. [PubMed: 10201452]
11. Wahnschaffe U, Ullrich R, Riecken EO, Schulzke JD. Celiac disease-like abnormalities in a subgroup of patients with irritable bowel syndrome. Gastroenterology Dec;2001 121(6):1329–38. [PubMed: 11729112]
12. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity (‘celiac sprue’). Gastroenterology Jan;1992 102(1):330–54. [PubMed: 1727768]
13. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. European journal of gastroenterology & hepatology Oct; 1999 11(10):1185–94. [PubMed: 10524652]
14. Olerup O, Zetterquist H. HLA-DR typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours: an alternative to serological DR typing in clinical practice including donor-recipient matching in cadaveric transplantation. Tissue Antigens May;1992 39(5):225–35. [PubMed: 1357775]
15. Leonard JN, Chorzelski TP, Beutner EH, Sulej J, Griffiths CE, Kumar VJ, et al. IgA anti-endomysial antibody detection in the serum of patients with dermatitis herpetiformis following gluten challenge. Arch Dermatol Res 1985;277(5):349–51. [PubMed: 4026376]
16. Karpati S. Dermatitis herpetiformis: close to unravelling a disease. J Dermatol Sci Apr;2004 34(2): 83–90. [PubMed: 15033190]
17. Nicolas ME, Krause PK, Gibson LE, Murray JA. Dermatitis herpetiformis. Int J Dermatol Aug;2003 42(8):588–600. [PubMed: 12890100]
18. Picarelli A, Maiuri L, Mazzilli MC, Coletta S, Ferrante P, Di Giovambattista F, et al. Gluten-sensitive disease with mild enteropathy. Gastroenterology Sep;1996 111(3):608–16. [PubMed: 8780564]
19. Wahnschaffe U, Schulzke JD, Zeitz M, Ullrich R. Predictors of clinical response to gluten-free diet in patients diagnosed with diarrhea-predominant irritable bowel syndrome. Clin Gastroenterol Hepatol Jul;2007 5(7):844–50. [PubMed: 17553753]quiz 769
20. Kaukinen K, Maki M, Partanen J, Sievanen H, Collin P. Celiac disease without villous atrophy: revision of criteria called for. Dig Dis Sci Apr;2001 46(4):879–87. [PubMed: 11330428]
21. Jabri B, Kasarda DD, Green PH. Innate and adaptive immunity: the yin and yang of celiac disease. Immunol Rev Aug;2005 206:219–31. [PubMed: 16048552]
22. Yamazaki K, Murray JA, Kita H. Innate immunomodulatory effects of cereal grains through induction of IL-10. J Allergy Clin Immunol Jan;2008 121(1):172–8. [PubMed: 17919702]e3

Table 1

Demographic information

Variable	Frequency		p-value
	LD (N=124) [%]	CD (N=454) [%]	
Female gender, No. [%]	83 [67]	313 [69]	0.67
Age at diagnosis	42.2 ± 14.9	44.9 ± 18.6	0.14
Race			0.008
Caucasian	87 [70]	355 [78]	
Other	5 [4]	3 [1]	
Undeclared	32 [26]	96 [21]	
Residency at diagnosis, No. [%]			0.04
Southeast Minnesota	26 [21]	147 [33]	
Elsewhere	98 [79]	306 [67]	
Unknown	0 [0]	1 [0.2]	

Table 2

Clinical features

Variable	Frequency		Odds Ratio* [p-value]
	LD (N=124) [%]	CD (N=454) [%]	
Anemia	23 [19]	146 [32]	0.50 [0.007]
Malaise	5 [4]	62 [14]	0.27 [0.006]
Skin disorder	5 [4]	61 [13]	0.27 [0.007]
Diarrhea	80 [65]	250 [55]	1.51 [0.050]
Abdominal cramping	53 [43]	166 [37]	1.29 [0.23]
Weight loss	46 [37]	177 [39]	0.96 [0.86]
Abdominal distention	41 [33]	127 [28]	1.25 [0.30]
Nausea/vomiting	41 [33]	97 [21]	1.83 [0.007]
Constipation	31 [25]	81 [18]	1.54 [0.075]

* Adjusted for age and gender.

Table 3

HLA genotypes

DQ Alleles	Frequency		Odds Ratio* [p-value]
	LD (N=124) [%]	CD (N=454) [%]	
DQ2	46 [37]	413 [91]	0.06 [<0.001]
DQ8	19 [15]	69 [15]	1.04 [0.90]
DQ8 without DQ2	15 [12]	30 [7]	1.96 [0.045]
Neither DQ8 or DQ2	63 [51]	11 [2]	44.5 [<0.001]

* Adjusted for age and gender.

Table 4

Profile of celiac disease patients who do not have either DQ2 or DQ8.

Patient	Gender	Age at Dx	HLA Type	Serology Results	Response to GFD
1	M	64	DQ5,6	Excluded	Unknown
2	F	61	DQ5,6	EMA positive	Yes
3	F	76	DQ5,6	Gliadin IgA positive	Yes
4	F	43	DQ5,6	Gliadin IgA positive	Yes
5	F	60	DQ5,7	Excluded	Yes
6	F	4	DQ6,6	TTg IgA negative	Yes
7	F	61	DQ6,6	Excluded	Yes
8	F	72	DQ6,7	TTg IgA negative	Yes
9	M	65	DQ6,7	TTg IgA and Gliadin IgA positive	Yes
10	F	66	DQ7,4	Excluded	Yes
11	F	50	DQ7,9	EMA and TTg IgA positive	Unknown

Table 5

Celiac serology

Serology Type	Frequency		Odds Ratio* [p-value]
	LD (N) [%]	CD (N) [%]	
EMA positivity	0/72 [0]	209/240 [87]	<0.01 [<0.001]
TTg positivity	12/99 [12]	210/237 [87]	0.02 [<0.001]
Gliadin positivity	20/47 [43]	151/169 [89]	0.09 [<0.001]
EMA or TTg positivity	12/111 [11]	284/314 [90]	0.01 [<0.001]
EMA, TTg, or Gliadin positivity	31/114 [27]	313/336 [93]	0.03 [<0.001]

* Adjusted for age and gender.

Table 6

Distribution of genotypes in people with a family history of celiac disease.

CD Susceptible Genotypes	Frequency	
	LD (N=10) [%]	CD (N=97) [%]
DQ2	9 [90]	94 [97]
DQ8	1 [1]	1 [1]
No DQ2 or DQ8	1 [1]	2 [2]

Table 7

Number of individuals in each cohort who had a positive or negative response to a gluten-free diet along with their corresponding presence or absence of DQ2 or DQ8 alleles.

Cohort	Response to GFD	DQ2 or DQ8 positive	DQ2 or DQ8 negative
LD	Yes (N=29)	18 (62%)	11 (38%)
	No (N=7)	4 (57%)	3 (43%)
CD	Yes (N=345)	320 (93%)	25 (7%)
	No (N=7)	7 (100%)	0 (0%)