ARTICLE

Emerging New Clinical Patterns in the Presentation of Celiac Disease

Grzegorz Telega, MD; Tess Rivera Bennet, MD; Steven Werlin, MD

Objective: To evaluate changes in the clinical presentation of celiac disease in southeastern Wisconsin.

Design: Retrospective medical record review.

Setting: Clinical specialty practice in pediatric gastroenterology.

Patients: The medical records of all patients diagnosed with celiac disease at the Children's Hospital of Wisconsin between 1986 and 2003 were reviewed. Data extracted from the medical records included year of diagnosis, demographics, indications for endoscopy and biopsy, signs, symptoms, and laboratory data. Biopsy specimens were read by the pediatric pathologist and graded according to the Marsh criteria.

Main Exposure: Date of initial diagnosis of celiac disease.

Main Outcome Measures: Presenting symptoms of patients with newly diagnosed celiac disease.

Results: One hundred forty-three patients were diagnosed with celiac disease. The number of patients diagnosed with celiac disease increased from 1 in 1986 to 93 in 2003. The mean age at diagnosis increased from 5.32 years for patients diagnosed before 1995 to 8.70 years for patients diagnosed after 1995. Gastrointestinal symptoms dominated in children younger than 3 years, whereas in children older than 3 years, the majority presented with nongastrointestinal indications. The percentage of patients presenting with gastrointestinal symptoms alone decreased during the study period; 11.2% of patients diagnosed with celiac disease were overweight (body mass index > 90).

Conclusions: Our study provides a unique longitudinal follow-up of clinical practice over a 17-year period. Currently, patients with celiac disease usually do not present with classic symptoms; they are more likely to be asymptomatic school-aged children who belong to a high-risk group.

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Author Affiliations:
Department of Pediatrics, Medical College of Wisconsin (Drs Telega and Werlin), and GI Consultants (Dr Bennet), Milwaukee.

UNTIL RECENTLY, CELIAC disease was considered to be a rare condition, with the highest incidence (1 in 100 to 1 in 300) in European countries, such as Ireland, Sweden, Finland, and Austria.[1,2] It was thought to affect only about 1 in 3000 white individuals in the United States.[3] The classic patient had a constellation of symptoms, including diarrhea, abdominal distention, and failure to thrive.[4] Recent studies have shown that the true incidence of celiac disease in North America is about 0.5% to 1.0%.[5-7] Many, if not most, of these patients are asymptomatic members of high-risk groups, such as patients with diabetes mellitus or thyroid disease and close relatives of patients with celiac disease.[8]

In the last few years at the Children's Hospital of Wisconsin, we have begun screening high-risk patient groups for celiac disease. Despite the fact that the population of the state of Wisconsin and referral population of our institution did not change significantly from 1986 until 2003, there has been a dramatic increase in the number of patients with newly diagnosed celiac disease, many of whom are asymptomatic members of high-risk groups. We hypothesized that the changing pattern of presentation of celiac disease may be due to the introduction of screening of high-risk patients and increased awareness of celiac disease in the community. Between December 1996 and December 1998, all children attending the Diabetes Clinic were offered serological screening for celiac disease as part of a study to determine the frequency of celiac disease in our cohort of children with diabetes. Two hundred eighteen agreed to

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participate. All children with diabetes were routinely screened following completion of the research study. Most children with hypothyroidism, short stature, and Down syndrome were screened beginning in 2000, and all children with these disorders have been screened since 2003.

This change in the pattern of presentation is accepted by pediatric gastroenterologists, yet to our knowledge no study has described this in a quantitative fashion. The aim of this study was to present current data on changes in the clinical presentation patterns of celiac disease in southeastern Wisconsin.

METHODS

The medical records of all patients diagnosed with celiac disease at the Children's Hospital of Wisconsin between 1986 and 2003 were reviewed. Data extracted from the medical records included year of diagnosis, demographics, indication for biopsy, signs and symptoms, complete blood cell count, IgA level, and results of iron studies, liver function tests, and celiac antibody tests. Biopsy specimens were read by the pediatric pathologist on service and were graded according to the criteria described by Marsh.[9] Antibody tests were done by commercial laboratories.

The diagnosis was accepted if the patient fulfilled 1 of the following criteria[10]: (1) Histological evidence of celiac disease (≥Marsh 2) was present in an appropriate clinical setting, such as children with chronic diarrhea and failure to thrive, with resolution of symptoms on a gluten-free diet. (2) The presence of elevated celiac antibody (tissue transglutaminase [tTG] or endomysial [EMA] antibodies) levels in combination with histological evidence of celiac disease (≥Marsh 2). (3) Marsh 1 histological results with positive tTG or EMA antibody findings and clinical or serological evidence of improvement on a gluten-free diet.

Exclusion criteria included lack of a biopsy and Marsh 1 histological results with negative celiac antibody test findings. This study was approved by the Human Rights Review Committee of the Children's Hospital of Wisconsin. Statistical analysis was performed using SPSS 12.0 (SPSS Inc, Chicago, Illinois), and χ^2 test, regression analysis, and analysis of variance were used to determine significance. Ratio analysis was performed and 95% confidence intervals (CIs) were calculated where appropriate.

RESULTS

There were 143 patients diagnosed with celiac disease during the study period; 93 or 64.3% of them were female (**Figure 1**). The number of patients with newly diagnosed celiac disease increased from 1 in 1986 to 93 in 2003 ($P<.001$). Sex distribution did not change significantly during the study period.

The mean age of the patients was 8.37 years (range, 1-17 years). During the study period, the mean age at diagnosis increased from 5.32 years (95% CI, 3.16-7.49) for patients diagnosed before 1995 to 8.70 years (95% CI, 7.85-9.54) for patients diagnosed after 1995 (95% CI for difference of the means, 2.79-3.96). The proportion of patients diagnosed in early childhood (0-9 years of age) decreased significantly from 85.7% for children diagnosed before 1995 to 45.2% for children diagnosed after 1995 (95% CI for difference of the means, 35.4%-46.6%).

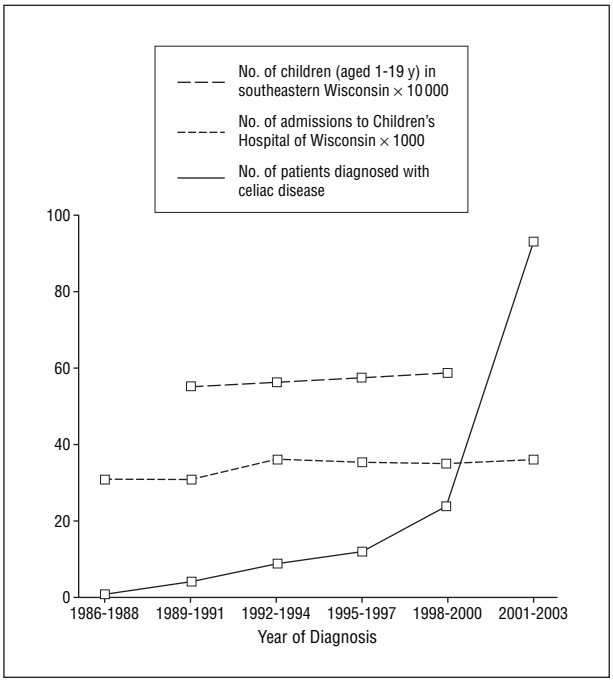

Figure 1. Total number of patients diagnosed with celiac disease by year of diagnosis. The trend was significant as evaluated by exponential regression ($P<.001$). The change in the population of children (aged 0-19 years) in southeastern Wisconsin (×10 000) is based on 1990-2000 census data.

One hundred twenty-two patients or 85.3% had elevated EMA-IgA or tTG-IgA antibody levels. Of the remaining patients, 3 tested positive for anti-gliadin–IgA antibodies and 4 tested positive for anti-gliadin–IgG antibodies. Among the patients who tested positive for anti-gliadin–IgG antibodies, 1 patient had IgA deficiency. In all but 3 patients who were referred for assessment of elevated anti-gliadin antibody levels, anti-EMA or anti-tTG antibody levels were measured. In these 3 patients, the diagnosis of celiac disease was established based on duodenal biopsy results consistent with celiac disease and clinical improvement on a gluten-free diet. Nine patients evaluated with endoscopy without prior serological testing for gastrointestinal symptoms had duodenal biopsy results consistent with celiac disease. All had clinical improvement on introduction of a gluten-free diet and no evidence of alternative disease. In 3 patients, duodenal biopsy results were consistent with celiac disease but the serological testing was done at outside laboratories (as reported by parents) and the results were not available. In these patients, no alternative diagnosis was identified.

Patients were referred for evaluation for celiac disease because of gastrointestinal symptoms (failure to thrive, diarrhea, abdominal pain, bloating, constipation) or problems not related to intestinal disease. Extraintestinal reasons for evaluation included having a condition associated with a high risk of developing celiac disease (type 1 diabetes,[11,12] thyroid disease,[13] Down syndrome,[14,15] family history of celiac disease[16]), abnormal laboratory values (iron deficiency anemia,[17] abnormal transaminase level[18]), and extraintestinal symptoms (short stature,[19] mood disorders,[20] alopecia[21]). High-risk groups

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were screened using anti-tTG or anti-EMA testing. In patients with IgA deficiency, anti-gliadin–IgG testing was used. Some patients presented with a combination of gastrointestinal and extraintestinal symptoms.

While gastrointestinal symptoms predominated in children younger than 3 years, in children older than 3 years, the majority presented with either extraintestinal symptoms alone or with a combination of symptoms. The difference in age composition for symptom clusters was statistically significant ($P<.001$) (**Figure 2**). The percentage of patients presenting with only gastrointestinal symptoms significantly decreased during the study period as an increasing percentage of patients presented with primarily extraintestinal manifestations ($P<.001$); 69.7% (95% CI, 61.6%-76.9%) of patients were diagnosed during evaluation of extraintestinal conditions associated with celiac disease (**Table**). In this group, 59.6% (95% CI, 49.8%-69.4%) had no gastrointestinal symptoms identified or recorded.[22] The most common gastrointestinal symptoms included diarrhea (28.0%; 95% CI, 20.5%-35.4%), failure to thrive (25.4%; 95% CI, 8.0%-32.4%), and abdominal pain (22.5%; 95% CI, 15.5%-29.3%); 11.2% (95% CI, 6.0%-16.4%) of patients diagnosed with celiac disease were overweight (body mass index >90).

With increasing severity of histological injury, there was an increased frequency of presentation with gastrointestinal symptoms (**Figure 3**). The severity of intestinal injury correlated with the type of clinical presentation ($P<.001$). There was no correlation between serological test results and severity of histological changes.

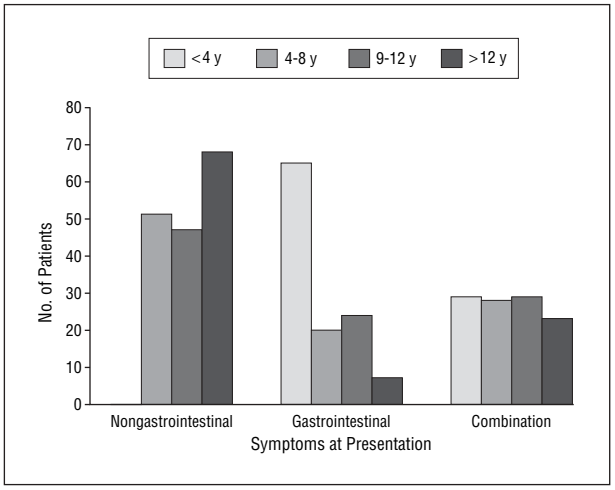

Figure 2. Age distribution of patients diagnosed with celiac disease by type of presentation. The difference was significant as evaluated by χ^2 test ($P<.001$).

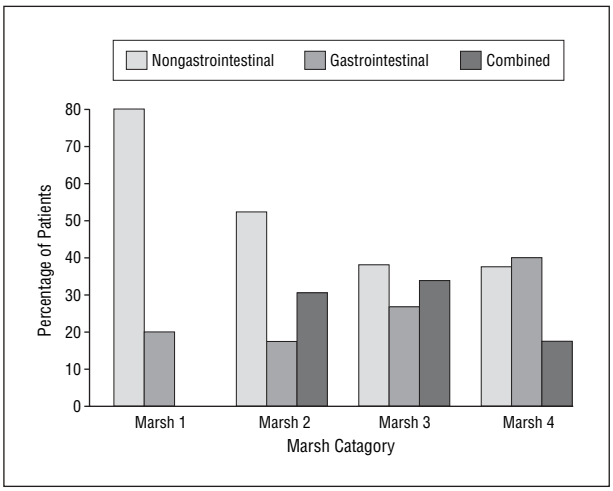

Figure 3. Percentage of patients with extraintestinal and gastrointestinal presentation in relation to severity of histological findings on duodenal biopsy. Bars represent percentage of patients presenting with the particular conditions within each Marsh category (sum is 100% in each category). The difference was significant as evaluated by χ^2 test ($P<.001$).

Table. Presenting Symptoms and Conditions in Patients Diagnosed With Celiac Disease

Condition	No. of Patients	All Patients With Celiac Disease, %	Patients With Condition and No GI Symptoms, %
Non-GI conditions			
Type 1 diabetes mellitus	56	39.4	71.4
Thyroiditis	15	10.6	60
Short stature	13	9.2	38.4
Down syndrome	11	7.7	63.6
Family history of celiac disease	10	7.0	70
Iron deficiency	9	6.3	33.3
Mood disorders	5	3.5	0
Abnormal transaminase levels	1	0.7	0
Alopecia	1	0.7	0
Any non-GI condition[a]	99	69.7	59.6
Gastrointestinal symptoms			
Diarrhea	40	28.2	NA
Failure to thrive	36	25.4	NA
Abdominal pain	32	22.5	NA
Bloating	17	11.9	NA
Constipation	8	5.1	NA
Any GI symptom[a]	81	57.0	NA

Abbreviations: GI, gastrointestinal; NA, not applicable.
[a]Number of patients with any condition is not equal to the sum of patients with a specific condition because some patients presented with more than 1 condition.

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COMMENT

Recent studies have shown that celiac disease is more prevalent in North America than previously thought.[3,5-7,23] We have documented a profound change in the rate of diagnosis of celiac disease at our center. Typically, patients with newly diagnosed celiac disease do not have gastrointestinal symptoms, such as diarrhea, abdominal pain, bloating, or failure to thrive. Patients are diagnosed later, usually when school-aged. The presence of gastrointestinal symptoms correlates with more severe histological damage of the bowel.

Since celiac disease is a genetically determined disease, it is not likely that the change in pattern of the presentation reflects a change in the behavior of the disease. It is unlikely that this increase is due to a change in demographics because the population in the referral area has remained unchanged. According to census data, the population of children (aged 0-19 years) in southeastern Wisconsin increased from 549 410 in 1990 to 586 081 in 2000 (6.71% growth during 10 years).[24]

We believe that the increase in the diagnoses of celiac disease is due to several factors including the availability of screening blood tests and increased awareness of celiac disease by both community physicians and by physicians caring for high-risk patients, which has led to screening of high-risk patients. Another factor that could explain the increase in the diagnoses of celiac disease is the introduction of more accurate and cheaper methods of screening. Anti-tTG antibodies were accepted as a cheaper alternative to anti-EMA antibodies, and human tTG replaced guinea pig tTG as the antigen, improving reliability of the test.

Our study describes patients with newly diagnosed celiac disease in southeastern Wisconsin. Since our study included data from all practicing pediatric gastroenterologists in this area, we believe that we captured the majority of children with histologically diagnosed celiac disease in our catchment area. A limitation of our study is that we could not include patients who may have been diagnosed by adult-care gastroenterologists. Another limitation is that not all biopsy specimens were available for independent review by a pathologist blinded to clinical data.

In adults, the majority of patients with newly diagnosed celiac disease do not have classic symptoms of celiac disease.[25] We have now, for the first time to our knowledge, described a similar change in presenting symptoms in children with newly diagnosed celiac disease. Our study provides a unique longitudinal follow-up of clinical practice over a 17-year period. This allowed us to evaluate whether clinical paradigms reflected changes in our understanding of celiac disease.

Based on these findings, the classic clinical vignette of pediatric celiac disease, which includes malnutrition, diarrhea, bloating, and abdominal pain, should be replaced with the more typical presentation of celiac disease. The patient with celiac disease is an asymptomatic school-aged child who belongs to a high-risk group. Despite improved awareness and screening protocols, many patients with celiac disease may remain undiagnosed. We recommend that primary care physicians implement screening programs in all high-risk populations, including first-degree family members of known patients with celiac disease and patients with Down syndrome, Turner syndrome, type 1 diabetes, thyroiditis, Addison disease, short stature, iron deficiency anemia, and unexplained elevation of aminotransferase levels. A high level of suspicion for celiac disease should be entertained in other autoimmune disorders even if there are no apparent gastrointestinal symptoms.

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Correspondence: Grzegorz Telega, MD, Department of Pediatrics, The Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226 (telega@mcw.edu).
Author Contributions: *Study concept and design:* Telega and Werlin. *Acquisition of data:* Telega and Rivera Bennet. *Analysis and interpretation of data:* Telega and Werlin. *Drafting of the manuscript:* Telega. *Critical revision of the manuscript for important intellectual content:* Telega, Werlin, and Rivera Bennet. *Statistical analysis:* Telega. *Administrative, technical, and material support:* Telega. *Study supervision:* Werlin.
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Announcement

2008 General Pediatrics Certifying Examination

Examination date: October 27, 2008.

Registration for first-time applicants: December 3, 2007, through February 28, 2008.

Late registration for first-time applicants: February 29, 2008, through May 1, 2008.

Registration for reregistrants: February 14, 2008, through May 1, 2008.

Late registration for reregistrants: May 2, 2008, through May 30, 2008.

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All applicants must complete applications online during the registration periods. The requirements for online applications are found on the American Board of Pediatrics Web site: http://www.abp.org. Additional information including eligibility requirements is found on the American Board of Pediatrics Web site. Each application will be considered individually and must be acceptable to the American Board of Pediatrics.

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