Trends in the Presentation of Celiac Disease

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ABSTRACT

PURPOSE: Screening studies have revealed that celiac disease is common in the United States; however, there are scant data on the mode of presentation. We analyzed the trends in clinical presentation over the last 52 years in a large cohort of biopsy-proven patients seen in 1 center.

SUBJECTS AND METHODS: Patients (n = 590) were divided into 6 groups based on the year of diagnosis (1952-2004). Groups were compared for trends in age at diagnosis, childhood diagnosis, duration of symptoms, mode of presentation (diarrhea, bone disease, anemia, incidental at esophagogastroduodenoscopy, screening), and presence of malignancy.

RESULTS: Diagnosis was at an older age since 1980 (P = .007), and there was a significant negative linear trend in patients presenting with diarrhea (P<.001) over time and a positive linear trend in asymptomatic patients detected on screening (P<.001). There was a significant negative linear trend in patients with a malignancy (P = .02) and duration of symptoms before diagnosis of celiac disease (P = .001), although only the subgroup without diarrhea had improvement in delay of diagnosis of celiac disease (assessed by a shorter duration of symptoms) (P = .05). Comparison of patients with and without diarrhea showed no significant difference in age (42.9 years vs 43.7 years, P = .59), gender (29.3% M vs 34.6%, P = .59), and presence of childhood disease (8.0% vs 9.8%, P = .43) or malignancies (9.8% vs 8.9%, P = .71).

CONCLUSION: There is a trend toward fewer patients presenting with symptomatic celiac disease characterized by diarrhea and a significant shift toward more patients presenting as asymptomatic adults detected at screening. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Celiac disease; Clinical presentation; Trends

Celiac disease is caused by a genetic intolerance to gluten, the main storage protein of wheat, and similar proteins in rye and barley.1 Celiac disease was originally described as a pediatric syndrome of diarrhea, steatorrhea, and weight loss.2 This symptomatic presentation in which gastrointestinal manifestations predominate is known as the “classic” presentation. However, adult presentations are now more common than pediatric presentations, and nondiarrheal symptoms, referred to as silent or atypical presentations, are becoming more frequently encountered.3,4

Celiac disease, once considered a rare disease in the United States, is now recognized to occur in approximately 1% of the population.5 The incidence of those diagnosed with celiac disease has increased,3 although the majority of patients with the condition remain undiagnosed. To demonstrate trends in clinical presentation of patients with celiac disease over time, we analyzed the mode of presentation for a large cohort of patients diagnosed over the last 52 years.

METHODS

Study Design and Subjects
All patients presenting to the Celiac Disease Center at Columbia Presbyterian Medical Center in New York City between 1981 and 2004 were entered into a database that was anonymized to protect patient privacy. Patients seen before 1990 were retrospectively entered; subsequent data were entered prospectively. Data including age, gender,
date of diagnosis, age at initial diagnosis, presence or absence of small bowel biopsy, duration of symptoms before diagnosis, and mode of presentation were collected. There were 6 major modes of presentation: patients with the classic presentation of diarrhea; patients with iron-deficiency anemia; patients with reduced bone mineral density; patients diagnosed because of recognition of findings at endoscopy performed for reasons other than assessment of malabsorption/diarrhea or iron-deficiency anemia; patients diagnosed as a result of screening family members of affected individuals; and patients presenting with a variety of other clinical manifestations including abdominal pain, constipation, weight loss, neurologic symptoms, dermatitis herpetiformis, macroamylasemia, hypoproteinemia, elevated sedimentation rate, insulin-dependent diabetes mellitus, increased thyroid hormone-replacement requirement, and liver disease.

Patients included in the study were adults (age >16 years) with biopsy-proven celiac disease and in whom the diagnosis was confirmed by a clinical or histologic response to a gluten-free diet. Intestinal biopsies of patients not diagnosed at our institution were obtained and reviewed for confirmation of the diagnosis. Patients were divided into 6 groups based on the year of diagnosis of celiac disease (1952-2004):

- Group 1, diagnosis before 1981;
- Group 2, diagnosis between 1981 and 1985;
- Group 3, diagnosis between 1986 and 1990;
- Group 4, diagnosis between 1991 and 1995;
- Group 5, diagnosis between 1996 and 2000;
- Group 6, diagnosis after 2000.

The 6 groups were compared for trends in age at the time of diagnosis, diagnosis of childhood celiac disease, duration of symptoms before establishing the diagnosis, presenting symptoms (diarrhea, bone disease, anemia, symptoms discovered incidentally, symptoms discovered by screening, and symptoms with other clinical manifestations), and presence of malignancy. Subgroup analysis was performed to compare the trends in clinical presentation in patients with and without diarrhea.

**Statistical Analysis**

Statistical analyses were performed using the SPSS software package (SPSS Inc, Chicago, Ill). One-way analysis of variance was used to compare the continuous variables between the 6 groups. If the difference was statistically significant, then the least significance difference method was used to detect difference in specific groups. Bonferroni correction was applied for multiple comparisons. Yates’ corrected chi-square test was used to compare dichotomous variables. Fisher exact test was used where appropriate. Continuous variables and categorical data in the 6 groups were compared for linear trend.

**RESULTS**

**Clinical Features and Modes of Presentation of Patient Population**

A total of 590 patients with biopsy-proven celiac disease were included in the study. The patients were predominantly women (401 women and 189 men, ratio 2.1:1). Mean age at diagnosis was 43.4 ± 17.4 years (range 16-83 years). The mean age at diagnosis was similar in men and women (44.9 ± 18.7 years and 42.7 ± 16.8 years, respectively; P = 0.16). Of the 590 patients, 25.1% had a known family history of celiac disease, and 9% were initially diagnosed in childhood and subsequently rediag- nosed as adults.

The mean duration of symptoms before diagnosis was 4.6 ± 7.5 years (range 0-60 years). Although women had a longer mean duration of symptoms when compared with men, this difference was not statistically significant (4.9 ± 7.7 years vs 3.8 ± 7.1 years, P = .08). Diarrhea was the presenting manifestation in 46.7%. Patients presenting with other symptoms including abdominal pain, constipation, weight loss, neurologic symptoms, dermatitis herpetiformis, macroamylasemia, hypoproteinemia, elevated sedimentation rate, insulin-dependent diabetes mellitus, increased thyroid hormone-replacement requirement, and liver disease comprised 17.8% of the group. Bone disease and iron-deficiency anemia constituted 7.1% and 10%, respectively. Celiac disease diagnosed incidentally at upper gastrointestinal endoscopy for conditions other than diarrhea or anemia (mainly dyspepsia or gastroesophageal reflux) comprised 6.6% of the cases. Serologic screening of asymptomatic relatives of patients with celiac disease detected 11.9% of cases. Overall, malignancy was present in 55 (9.3%) of patients. Thirty-five of these patients had a malignancy diagnosed an average of 7.5 years (range: 0.25-26.83 years) before the diagnosis of celiac disease. Five patients were diagnosed simultaneously with celiac disease and a malignancy. Fifteen patients had a malignancy diagnosed an average of 5.78 years (range: 0.33-28.25 years) after receiving a diagnosis of celiac disease.

**Trends Analysis of Changing Presentation with Time**

The majority of patients in our study were diagnosed after 1995 (Table 1). There was a significant negative linear trend in the proportion of patients presenting with diarrhea over
time, with a steady decline from 91.3% of patients diagnosed before 1981 to 37.2% of patients diagnosed after 2000 (\(P < .001\)) (Figure 1). Conversely, there was a statistically significant positive linear trend in patients detected on screening, 0% of patients in groups 1 to 4 and a mean of 15.2% for the last 2 groups (\(P < .001\)). There was no statistical significance over time in patients presenting with bone disease, anemia, or incidentally at endoscopy. Although there was wide variation between the groups with regard to the percentage presenting with “other” clinical manifestations, this difference was not statistically significant (\(P = .9\)). However, this group comprised 19.2% of patients in the last 14 years. A summary of the presentations is shown in Figure 2.

In addition, patients were diagnosed at an older age since 1980 (\(P = .007\)), and there was a significant negative linear trend in the percentage of patients who had a childhood diagnosis (\(P = .03\)). Likewise, malignancy declined from 22% in group 1 to 5% in the latest period of the study, resulting in a negative linear trend (\(P = .02\)) in the prevalence of malignancy over time. When comparing those with malignancy with those without malignancy, there was no statistical difference in the duration of symptoms in any of the groups (Table 2).

On comparison of the 6 groups, there was a highly significant negative linear trend in the duration of symptoms before diagnosis of celiac disease (\(P = .001\)) (Figure 3). Subgroup analysis also revealed that although there was a statistically significant improvement in the delay of diagnosis of celiac disease (assessed by a shorter duration of symptoms before the establishment of the diagnosis) in patients without diarrhea (\(P = .05\)), there has been no significant difference over time in delay of diagnosis in patients with diarrheal symptoms (\(P = .3\)) (Table 3). Com-

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### Table 1 Clinical Presentation of Patients with Celiac Disease between 1952 and 2002

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>23</td>
<td>14</td>
<td>33</td>
<td>60</td>
<td>288</td>
<td>172</td>
</tr>
<tr>
<td>Age (y)</td>
<td>30.5</td>
<td>40.3</td>
<td>45.0</td>
<td>44.0</td>
<td>44.0</td>
<td>42.0</td>
</tr>
<tr>
<td>Childhood celiac disease (%)</td>
<td>30.0</td>
<td>7.0</td>
<td>6.0</td>
<td>6.7</td>
<td>9.0</td>
<td>7.5</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>91.3</td>
<td>71.4</td>
<td>72.6</td>
<td>58.3</td>
<td>42.4</td>
<td>37.2</td>
</tr>
<tr>
<td>Incidental diagnosis (%)</td>
<td>0</td>
<td>0</td>
<td>6.1</td>
<td>5.0</td>
<td>9.0</td>
<td>4.6</td>
</tr>
<tr>
<td>Screening (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>17.0</td>
<td>12.2</td>
<td>12.2</td>
</tr>
<tr>
<td>Bone disease (%)</td>
<td>0</td>
<td>0</td>
<td>15.1</td>
<td>3.3</td>
<td>7.3</td>
<td>8.1</td>
</tr>
<tr>
<td>Anemia (%)</td>
<td>4.3</td>
<td>7.1</td>
<td>3.0</td>
<td>11.7</td>
<td>9.4</td>
<td>12.7</td>
</tr>
<tr>
<td>Others (%)</td>
<td>4.5</td>
<td>21.4</td>
<td>3.0</td>
<td>21.6</td>
<td>14.6</td>
<td>26.0</td>
</tr>
<tr>
<td>Malignancy (%)</td>
<td>21.7</td>
<td>0</td>
<td>15.2</td>
<td>10.0</td>
<td>10.4</td>
<td>5.2</td>
</tr>
<tr>
<td>Delay in diagnosis* (y)</td>
<td>11.0</td>
<td>10.6</td>
<td>6.4</td>
<td>4.6</td>
<td>4.2</td>
<td>4.0</td>
</tr>
</tbody>
</table>

*Delay in diagnosis is defined as duration of symptoms before establishing the diagnosis of celiac disease.

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Figure 1 Percentage of patients with celiac disease with initial presentation of diarrhea. There has been a statistically significant negative linear trend over time.
Comparison of patients with and without diarrhea showed no statistically significant difference in age at presentation (42.9 years vs 43.7 years, \( P = .59 \)), male sex (29.3% vs 34.6%, \( P = .59 \)), presence of childhood disease (8.0% vs 9.8%, \( P = .43 \)), and presence of malignancies (9.8% vs 8.9%, \( P = .71 \)).

**DISCUSSION**

Serologic screening studies from several countries have demonstrated celiac disease to be common, occurring in approximately 1% of the population.\(^{6-8}\) This far exceeds the prevalence of clinically diagnosed celiac disease,\(^9\) indicating that the majority of those with celiac disease are currently undiagnosed. In addition, there have been only 2 recent studies describing the clinical presentation of celiac disease in the United States.\(^{3,4}\) In each of these studies, there was recognition that fewer patients are presenting with diarrhea. This has been attributed to the increasing use of serologic tests to facilitate diagnosis. These tests have only been in clinical use in the United States since the early 1990s. However, we noted that the trend in the decrease in the percentage of patients presenting with diarrhea started before the widespread use of serologic testing.

Accompanying the trend toward a decreasing percentage of patients presenting with diarrhea over time, there was an increasing percentage of patients presenting with silent or atypical celiac disease (ie, lacking diarrhea or malabsorption).\(^{10,11}\) This latter group included those diagnosed because of bone disease, anemia, and recognition at endoscopy performed mainly for reflux-type symptoms. Also included in this group were patients with even more atypical symptoms such as constipation and neurologic symptoms, which in fact comprised 19% of patients over the last 14 years of the study. In addition, we observed that a growing number of celiac disease diagnoses occurred as a result of screening first-degree relatives of affected individuals in the absence of diarrhea. Most of these patients were truly asymptomatic.\(^8\) Overall, these patients with silent celiac

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**Figure 2**  Summary of clinical presentation of celiac disease. The different modes of presentation as a percentage of the total patients in each group. The other category includes those presenting with abdominal pain, constipation, weight loss, neurologic symptoms, dermatitis herpetiformis, macroamylasemia, hypoproteinemia, elevated sedimentation rate, insulin-dependent diabetes mellitus, increased thyroid hormone replacement requirement, and liver disease.

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**Table 2**  Duration of Symptoms in Patients with Malignancy versus Patients without Malignancy

<table>
<thead>
<tr>
<th></th>
<th>Malignancy</th>
<th>No malignancy</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Duration of symptoms (y)</td>
<td>N</td>
</tr>
<tr>
<td>Group 1</td>
<td>5</td>
<td>17.0 ± 11.7</td>
<td>18</td>
</tr>
<tr>
<td>Group 2</td>
<td>0</td>
<td>8.6 ± 6.7</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>5</td>
<td>5.0 ± 8.5</td>
<td>28</td>
</tr>
<tr>
<td>Group 4</td>
<td>6</td>
<td>1.7 ± 1.5</td>
<td>51</td>
</tr>
<tr>
<td>Group 5</td>
<td>29</td>
<td>5.5 ± 8.3</td>
<td>253</td>
</tr>
<tr>
<td>Group 6</td>
<td>9</td>
<td>3.9 ± 4.6</td>
<td>151</td>
</tr>
</tbody>
</table>
disease were less sick because they did not have the classic malabsorptive symptoms. It is unclear why the silent form of celiac disease is the most common one observed but may be related to the widespread use and duration of breastfeeding in the United States and the relative delay in the age at which gluten is introduced into the diet. Both of these factors prevent the development of celiac disease in infancy and most likely delay the presentation of the disease into adulthood.\textsuperscript{12-14} Breastfeeding practices and delayed exposure to gluten also may contribute to the older age of diagnosis of celiac disease seen in patients presenting to our center after 1980, as well as the statistically significant decrease over time in the percentage of patients with celiac disease bearing a childhood diagnosis.

Thus, these trends data demonstrate a change in the presentation of celiac disease. Patients tend to be female, older, and less likely to present with diarrhea. We also recognize that since 1981, there has been a reduction in the duration of symptoms and a marked trend toward earlier diagnosis of celiac disease. On closer analysis, we noted that the duration of symptoms before diagnosis of celiac disease decreased in the subgroup who did not have diarrhea on presentation. This can be attributed to a combination of factors, including increased physician awareness of subtle manifestations of the disease and more widespread use of upper gastrointestinal endoscopy with biopsy and serologic testing.\textsuperscript{15,16} The lack of reduction in duration of symptoms for those presenting with diarrhea suggests that physicians who see patients with diarrhea do not initially consider celiac disease even when the classic presentation is present.

Previous studies have demonstrated an increased rate of malignancies, including non-Hodgkin lymphoma, squamous cell carcinoma of the esophagus, melanoma, and adenocarcinoma of the small bowel in patients with celiac disease when compared with the general population.\textsuperscript{17,18} In our current study, we observed a negative linear trend in malignancy rates when comparing patients who presented in the earlier time periods with those in the latter part of the

![Figure 3](image_url)

\textbf{Figure 3}  
Delay in diagnosis of celiac disease. There has been a declining trend in duration of symptoms before celiac disease diagnosis over time.

<table>
<thead>
<tr>
<th>Group</th>
<th>No diarrhea ($P = .05$)*</th>
<th>Diarrhea ($P = .3$)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Duration of symptoms (y)</td>
</tr>
<tr>
<td>Group 1</td>
<td>2</td>
<td>10 ± 14</td>
</tr>
<tr>
<td>Group 2</td>
<td>4</td>
<td>4.7 ± 3</td>
</tr>
<tr>
<td>Group 3</td>
<td>9</td>
<td>3.2 ± 4</td>
</tr>
<tr>
<td>Group 4</td>
<td>23</td>
<td>3.7 ± 4.3</td>
</tr>
<tr>
<td>Group 5</td>
<td>160</td>
<td>2.3 ± 4.8</td>
</tr>
<tr>
<td>Group 6</td>
<td>98</td>
<td>1.7 ± 3</td>
</tr>
</tbody>
</table>

*P value = significance in trend relating to duration of symptoms before diagnosis of celiac disease.
study. This occurred despite the trend toward later age of presentation. Because there was no difference in the rate of malignancy between those with and without diarrhea, the reduced cancer rate over time cannot be attributed to the presence of milder disease.

Thus, irrespective of the mode of presentation, the risk of developing a malignancy for patients with celiac disease decreased over the study period. This observation may, however, be secondary to the shorter duration of observation for patients in the latter period of our study. However, against this is the fact that the majority of the malignancies in the earlier time periods occurred before the diagnosis of celiac disease. Further evaluation of patients with malignancy compared with those without malignancy revealed no statistical difference in duration of symptoms in any of the 6 groups.

Currently all patients diagnosed with celiac disease are advised to adhere to a gluten-free diet, irrespective of the mode of presentation. This is mainly to prevent the development of worsening symptoms such as diarrhea and complications such as anemia, osteoporosis, and malignancies. However, we noted in this study that the age of presentation of those with and without diarrhea was similar, suggesting that patients without diarrhea may not progress to a diarrhea-predominant syndrome. In addition, there seems to be a decreasing risk for patients to develop a malignancy. It is unclear why some individuals with celiac disease become extremely ill and others remain totally asymptomatic. Our data emphasize the need to develop a long-term study of observing the natural history of silent celiac disease in asymptomatic patients.

In recognition of the lack of clinical data on celiac disease in the United States, our study represents a large cohort of patients diagnosed over a relatively extensive period of time (52 years). The major bias in our observations is because of our status as a tertiary referral center, which may have resulted in us seeing more patients with atypical presentations.

CONCLUSION
Celiac disease is becoming increasingly recognized in the adult population without diarrhea, with a larger percentage of patients presenting as asymptomatic individuals often detected by screening affected families. The atypical forms are, in fact, becoming the typical. The natural history of this milder form of celiac disease has not been determined.

References