CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Delay in Diagnosis of Celiac Disease in Patients Without Gastrointestinal Complaints

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ABSTRACT

PURPOSE: The purpose of our study is to investigate the delay in diagnosis of patients with biopsy-proven celiac disease in those who present with gastrointestinal complaints vs nongastrointestinal complaints at our tertiary care center. Celiac disease is an autoimmune disorder that affects approximately 1% of the population worldwide. Celiac disease can have variable clinical presentations; it can be characterized by predominately gastrointestinal symptoms, or it may present without any gastrointestinal symptoms.

METHODS: We retrospectively reviewed the charts of 687 adult patients who carried the diagnosis of celiac disease. Patients included had biopsy-proven celiac disease and were categorized based on presence or absence of gastrointestinal symptoms prior to their diagnosis.

RESULTS: There were 101 patients with biopsy-proven celiac disease that met inclusion criteria. Fifty-two patients presented with gastrointestinal symptoms and 49 had nongastrointestinal complaints. Results from Mann-Whitney statistical analysis showed a median delay in diagnosis of 2.3 months for the gastrointestinal symptoms group and 42 months for the nongastrointestinal group ($P < .001$); 43.2% of patients with nongastrointestinal symptoms had abnormal thyroid-stimulating hormone, as opposed to 15.5% in the gastrointestinal symptom group ($P = .004$). Of patients with nongastrointestinal symptoms, 69.4% had anemia, compared with 11.5% of the gastrointestinal symptom group ($P < .001$). The majority of patients in the nongastrointestinal symptom group, 68%, were noted to have abnormal bone density scans, compared with 41% in the gastrointestinal symptom group. No sex differences were noted on chi-squared analysis between the 2 groups ($P = .997$).

CONCLUSIONS: Although there is growing awareness of celiac disease, the delay in diagnosis for patients without gastrointestinal symptoms remains prolonged, with an average delay of 3.5 years.

 • The American Journal of Medicine (2017) 130, 1318-1323

KEYWORDS: Anemia; Celiac disease; Delay in diagnosis; Gastrointestinal

Celiac disease is an autoimmune disorder that affects approximately 1% of the population worldwide.[1] As many as 6 of 7 cases of celiac disease remain undiagnosed.[2] This discrepancy falls in line with the widely accepted "celiac iceberg" concept and may be due to the fact that patients have variable presentations of celiac disease. Manifestations of celiac disease range from typical gastrointestinal complaints characterized by malabsorption and diarrhea, to more silent forms in patients without overt gastrointestinal complaints. Nongastrointestinal presentations may include anemia, thyroid dysfunction, osteoporosis, liver function test abnormalities, and skin manifestations such as dermatitis herpetiformis. The variable presentations create a clinical challenge to physicians in reaching an early diagnosis. As a result, delay in diagnosis is not uncommon and does not go without consequence. Undiagnosed celiac disease can lead to osteoporotic fractures, infertility, unnecessary surgical procedures including bowel resection, and malignancy.[1] As the majority of cases of celiac disease can be treated with a strict

Funding: None.

Conflict of Interest: None.

Authorship: All authors had access to the data and all had a role in writing the manuscript.

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0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2017.05.027

gluten-free diet alone, adherence to this diet can reverse the risk for adverse clinical outcomes.

The primary aim of this study was to investigate the delay in diagnosis in patients with classical gastrointestinal manifestations vs nongastrointestinal manifestations. Secondary objectives included understanding the biophysical profile of patients who have nongastrointestinal complaints.

CLINICAL SIGNIFICANCE

- There is a mean delay in the diagnosis of celiac disease of 3.5 years in patients who present with nongastrointestinal symptoms.
- Specifically, patients with thyroid abnormalities, anemia, or bone mineral density loss should be screened for celiac disease.

MATERIALS AND METHODS

Using the Loyola University Medical Center institutional-based electronic medical record system (EPIC), we used International Classification of Diseases, Ninth Revision codes to obtain data on patients who carried the diagnosis of celiac disease. We reviewed 687 adult charts spanning over 12 years. Inclusion criteria included adult patients (age >18 years) who had biopsy-proven celiac disease based on Marsh Classification. Those who were excluded were patients diagnosed as having celiac disease without biopsy, self-reported "gluten allergy," and patients with insufficient data. The initial presenting symptoms of the patients who met inclusion criteria were reviewed. Results from endoscopic evaluation and histopathology were reviewed. Data collected included variables such as race, sex, age, body mass index, iron, ferritin, hemoglobin, mean corpuscular volume (MCV), vitamin B12, folate, 25-hydroxy vitamin D (25-OH vitamin D), thyroid-stimulating hormone (TSH), aspartate aminotransferase, and alanine aminotransferase. Mann-Whitney tests and chi-squared statistical analyses were used, with P values $\leq .05$ reaching statistical significance.

RESULTS

A total of 101 patients with biopsy-proven celiac disease met inclusion criteria. The patients that were included were divided into their presenting symptoms to either gastrointestinal complaints or nongastrointestinal complaints (Table 1). Gastrointestinal complaints included patients presenting with nausea, vomiting, abdominal pain, diarrhea, constipation, and bloating. Nongastrointestinal complaints were defined as extraintestinal manifestations such as anemia, abnormal liver function tests, dermatological findings, TSH abnormality, and fatigue. A total of 52 patients initially presented with gastrointestinal symptoms, and 49 had nongastrointestinal complaints. Results from Mann-Whitney statistical analysis showed a median delay in diagnosis of 2.3 months for the gastrointestinal symptoms group and 42 months for the nongastrointestinal group ($Z = -5.525$, $P < .001$) (Table 2). This period includes time from the first visit to a physician due to celiac disease-related symptoms to diagnosis via endoscopy with biopsy.

Clinical Presentation

Patients with gastrointestinal symptoms presented to their primary care provider or gastroenterologist with complaints ranging from nausea, bloating, diarrhea, constipation, gastroesophageal reflux disease, or abdominal pain. Patients with nongastrointestinal symptoms presented to their primary care provider with fatigue, anemia, TSH abnormality, liver function test abnormality, dermatitis herpetiformis, or abnormal bone density scans. The average age for patients with gastrointestinal complaints was 44 years old, as compared with 49 years old in the nongastrointestinal group ($P = .051$) (Figure 1). Of those in the nongastrointestinal group, 69.4% (34/49) had anemia as their initial complaint, compared with 21.2% (11/52) of the gastrointestinal symptom group ($P < .001$). Anemia was the most common sign for the nongastrointestinal group, with the mean hemoglobin level 11.40 g/dL (Table 3). The median MCV for the gastrointestinal group was 89, and 84.3 for the nongastrointestinal group ($P = .012$) (Figure 2). Iron levels did differ, with gastrointestinal group levels averaging 57 ug/dL and nongastrointestinal group levels at 35 ug/dL ($P = .051$).

Bone Mineral Density

Patients in the nongastrointestinal group were also diagnosed with celiac disease following evaluation of bone density. Abnormal bone scans (osteopenia or osteoporosis) were found in 68% (13/19) when compared with 41% (7/17) in the gastrointestinal group ($P = .101$) (Figure 3). Eight percent (4/49) of the patients from the nongastrointestinal group were diagnosed with celiac disease after further investigation following their abnormal bone scan. Thirty-six patients from our cohort had a documented bone density scan; 62 patients had 25-OH vitamin D levels checked.

Thyroid Function Test

A total of 43.2% (19/44) of patients with nongastrointestinal symptoms were found to have abnormal TSH, as opposed to 15.5% (7/45) ($P = .004$). Abnormal TSH was defined as TSH <0.4 u/mL or TSH >4.6 u/mL. Within the nongastrointestinal group, 36.3% (16/44) of the nongastrointestinal group were hypothyroid and 0.07% (3/44) were hyperthyroid. All 7 patients with abnormal TSH in the gastrointestinal symptom group had hypothyroidism.

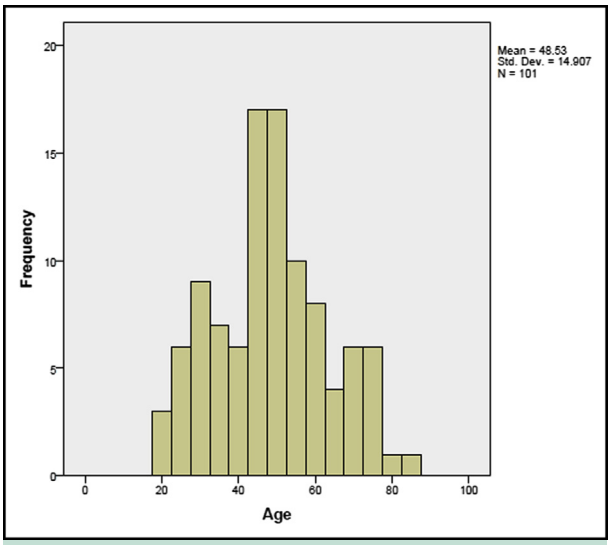

Figure 1 Age distribution.

Liver Function Test and Skin Manifestations

Five patients presented with skin manifestations. A total of 4 were found to have classic dermatitis herpetiformis, and 1 patient had rosacea. Three patients had elevated aspartate aminotransferase/alanine aminotransferase on presentation and were later diagnosed with celiac disease once primary liver pathology was ruled out.

Race and Sex

No sex differences were noted on chi-squared analysis between the 2 groups ($P = .997$). Thirty-three percent (16/49) of the nongastrointestinal group were male and 67.3% (33/49) were female, compared with the gastrointestinal group, in which 32.7% (17/52) were male and 67.3% (35/52) female. Race in our nongastrointestinal cohort was 82% white and 18% non-white. An almost equal distribution of whites presented with gastrointestinal complaints, with 78% being white and 22% non-white ($P = .343$).

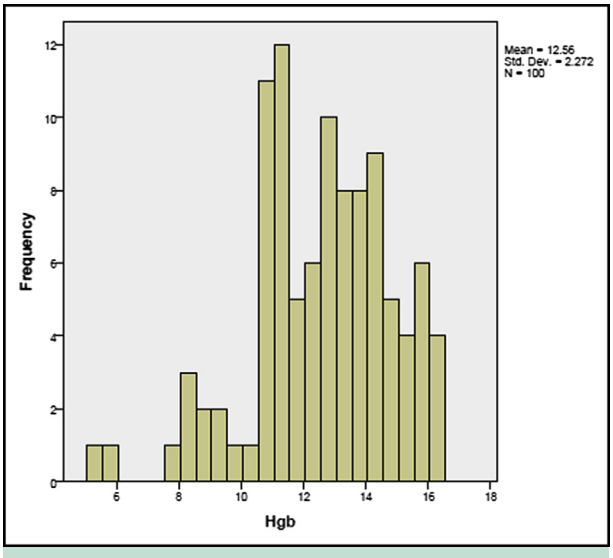

Figure 2 Hemoglobin at presentation.

DISCUSSION

The clinically silent forms of celiac disease are not uncommon, and as a result, physicians should be prepared to encounter more patients with nongastrointestinal complaints.[3] There has been an overall decrease in the prevalence of gastrointestinal complaints over the past 2 decades, in part because of increased awareness in the general public as well as the use of antibody screening by health care providers.

Delays in diagnosis of celiac disease have been observed in the past. Green et al[4] performed a national survey of 1612 patients with celiac disease; 1138 patients reported having biopsy-proven celiac disease. The patients had, on average, a delay in diagnosis of 11 years. Eighty-five percent of patients who completed the survey reported having diarrhea as the presenting symptom.[4] Zipser et al[5] conducted a nationwide survey from 1993 through 2001 of patients with biopsy-proven celiac disease. They obtained a response rate of 1032 with a median age at diagnosis of 46 years old. The adult patients reported that there was a median number of 12 months of symptoms from first presentation to their physician until biopsy diagnosis, and 21% reported symptoms for over 10 years prior to diagnosis.[5] In this study, the patients reported fatigue, abdominal pain, bloating or gas, and anemia as the most frequent presenting symptoms.[5] Similarly, we observed a median delay in diagnosis of 2.3 months for the gastrointestinal symptoms group and a median delay of 42 months for the nongastrointestinal group.

Anemia is a well-known complication of celiac disease and is one of the leading signs of the disease. A recent study found up to 85% of patients with celiac disease have anemia on presentation.[6] Moreover, anemia without overt malabsorption was found to be the most common presenting feature of celiac disease in the UK.[7] The pathophysiology of

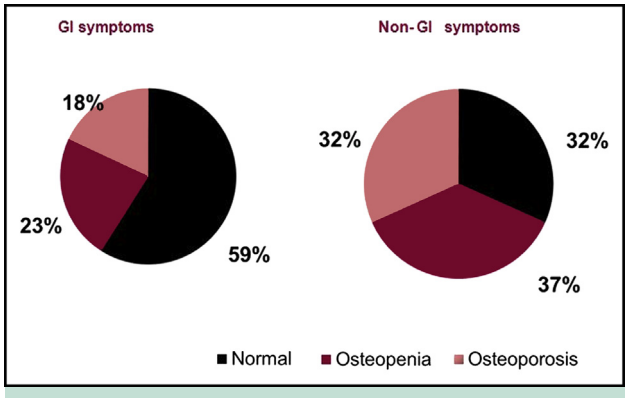

Figure 3 Bone mineral density. GI = gastrointestinal.

Table 1 Demographics

	GI Symptoms n = 51	Non-GI Symptoms n = 49	*P* Value
White	78% (n = 40/51)	86% (n = 42/49)	NS
Male (%)	33% (n = 17/52)	33% (n = 16/49)	NS
BMI (mean)	26.1	24.250	NS
Age, y (mean)	44	49	NS

BMI = body mass index; GI = gastrointestinal; NS = not significant.

anemia in celiac disease is due to malabsorption of iron within the gastrointestinal tract due to villous atrophy in the distal duodenum and jejunum. Absorption of dietary iron occurs at these sites, with transferrin a divalent metal transporter pathway regulating small bowel iron uptake. Patients have been found to be anemic for up to 12 years prior to having an established diagnosis of celiac disease.[7] The degree of villous atrophy has been found to predict a higher likelihood of micronutrient deficiencies.[8]

Our study demonstrated that a large portion of our cohort from both the nongastrointestinal and gastrointestinal groups had anemia. Anemia was the most common presenting sign of celiac disease for the nongastrointestinal group, with a mean hemoglobin level of 11.40 g/dL. Thirty-four of 49 (69.4%) had anemia as their initial sign of celiac disease, compared with 21.2% (11/52) of the gastrointestinal symptom group ($P < .001$). This is in concordance with prior studies, where it has been estimated that the overall prevalence of anemia at the time of diagnosis of celiac disease has been observed to be between 12% and 69%.[9-13] The median MCV for the gastrointestinal group was 89, and 84.3 for the nongastrointestinal group ($P = .012$). Harper et al[8] reviewed 405 celiac disease patients and found iron deficiency anemia in approximately 26%, folate deficiency in nearly 12%, and B12 deficiency in 5%.[8] They concluded that anemia in celiac disease is multifactorial in etiology, and nutritional deficiencies alone do not explain its etiology. Our study supports these findings in that the type of anemia observed was nonspecific, with some of our patients having variations in their MCV.

Many studies have recognized an increased incidence of low bone mineral density in patients with celiac disease compared with nonceliac disease patients of the same age and sex.[14,15] Osteoporosis is found in greater prevalence in patients with celiac disease. McFarlane et al[15] studied a group of 55 patients with celiac disease and found that 50% of male patients and 47% of female patients had

Table 2 Delay in Diagnosis of Celiac Disease Based on Presenting Symptoms

Symptoms	Geometric Mean	Median (mo)	*P*-Value
GI	2.30	2.29	<.001
Non-GI	20.86	42	<.001

GI = gastrointestinal.

Table 3 Hemoglobin on Presentation in Celiac Disease Patients Based on Symptoms

Symptoms	Geometric Mean (Hemoglobin g/dL)	Median (Hemoglobin g/dL)	*P*-Value
GI	13.24	13.60	<.001
Non-GI	11.44	11.40	<.001

GI = gastrointestinal.

osteoporosis.[15] Stenson et al[16] determined that the prevalence of celiac disease in osteoporotic individuals is high enough to warrant serologic screening of all osteoporotic patients for celiac disease. In our study, 35.6% of patients diagnosed with celiac disease had a dual-energy X-ray absorptiometry scan completed. Four of our patients were diagnosed with celiac disease during evaluation for low bone mineral density. Interestingly, the prevalence of low bone mineral density was higher (68%) in patients with nongastrointestinal symptoms compared with those with gastrointestinal symptoms (41%). This may be due to the delay in diagnosis. Identifying these patients early in the disease process is essential, especially as adherence to a gluten-free diet has been shown to improve bone mineral density.[14,17-19]

One striking observation seen in our cohort was the degree of abnormal thyroid function test. Autoimmune thyroid disease is a well-documented finding seen in patients with celiac disease. Thyroid disease co-existing with celiac disease has been documented to be anywhere from 2%-14%. Reunala and Collin[20] followed 383 patients with celiac disease for an average of 10 years. They found that 6% had autoimmune thyroid disease. Collin et al[21] found that 5.4% of 335 adult celiac patients had autoimmune thyroid disease. In another study by Collin et al,[22] 83 patients with autoimmune thyroid disorders were screened for celiac disease and a frequency of 4.8% was found.[22] The rate of thyroid disorder has been observed to be as high as 14% in celiac disease patients.[23] In our cohort, 43.2% (19/44) of patients with nongastrointestinal symptoms were found to have abnormal TSH, as opposed to 15.5% (7/45) ($P = .004$) of patients with gastrointestinal symptoms. The majority were found incidentally, but some patients were diagnosed with celiac disease after abnormal thyroid dysfunction was discovered. The relationship between autoimmune thyroid disease and celiac disease is not well understood, but it is thought to be partly due to a common genetic predisposition, specifically, the major histocompatibility complex II class human leukocyte antigen DQ2 and DQ8 haplotypes that are over-represented in many autoimmune diseases.[24] Our findings further emphasize the importance in evaluating for celiac disease in patients with other autoimmune disorders.

Celiac disease traditionally has been thought of as an ailment that affects predominantly whites, however, we noted there was significant racial variability in our cohort, with 18% of patients being non-white. In particular, 11% of

our patients were Hispanic, 3% African American, 3% other race, and 1% Asian. The prevalence of celiac disease in ethnic minorities is considered rare. Brar et al[25] reviewed 700 patients spanning 23 years of data with biopsy-proven celiac disease and found a total of 9 patients were African American, which represented 1.3% of their cohort. Two patients presented with gastrointestinal manifestations and 7 were diagnosed with celiac disease after presenting with nongastrointestinal complaints.[25] The decreased prevalence may partially be due to lack of evaluation. In a study by Lebwohl et al,[26] rates of duodenal biopsies during esophagogastroduodenoscopy for classical symptoms of celiac disease were measured. They found African Americans and Hispanics were less likely to undergo duodenal biopsies. African American patients underwent duodenal biopsy in 28% of upper endoscopy, compared with 44% for whites ($P < .001$). They concluded that endoscopist behavior could play a role in the low prevalence rate of celiac disease in minorities.[26] Our study showed 11% of patients were Hispanic, which far exceeds the prevalence rate that has been observed in previous studies.[27-29] Although celiac disease continues to remain rare in ethnic minorities, it is evident from our study that clinicians and endoscopists need to maintain a high level of suspicion for celiac disease regardless of race and sex.

To our knowledge, this is the first study that compares the different modalities of presentations among patients with biopsy proven celiac disease. Duodenal biopsies are considered the gold standard for the diagnosis of celiac disease, and a strength of our study is that all patients who were analyzed had biopsy-proven celiac disease. Of the 687 patients that were captured in our study, only 101 had biopsy-proven celiac disease. The remaining 586 patients were excluded given the lack of duodenal biopsy and insufficient data. In addition, there were many patients who were excluded on the basis of having self-reported "gluten allergy," otherwise known as nonceliac gluten sensitivity. This is an emerging entity that has gained popularity among the general population.[30] Moreover, this diagnosis can be made only after exclusion of celiac disease. This is of importance, and clinicians need to make this distinction as nonceliac gluten sensitivity does not carry the same natural disease progression of celiac disease, and differs in management and surveillance.[31] The retrospective nature of our study, which inherently comes with limitations, includes reliance on providers for accurate record keeping; therefore, indications for endoscopy were reliant on the symptoms that were documented by the physician. One cannot exclude variations of symptoms that can fluctuate throughout the course of disease leading up to the diagnosis. There are also many other conditions in which celiac disease occurs more frequently than in the general population that we didn't account for. These variables include other nongastrointestinal manifestations such as peripheral neuropathy, oral aphthous ulcers, unexplained weight loss, developmentally synchronous enamel loss, amenorrhea, epilepsy or ataxia, and unexplained male or female infertility.[31] These variables were not included in our study and should be investigated further in future studies. Nearly one-third of our total cohort had thyroid disease co-existing with celiac disease. As observed in our study, the symptomatology of celiac disease and clinical presentations have now shifted from overt malabsorption seen in the past to having patients present with atypical features that represent only the tip of the "celiac iceberg."

Serological screening tools and awareness of disease have all contributed to the shift in symptomatology given that nongastrointestinal complaints were almost as common as gastrointestinal symptoms at presentations. Providers need to maintain a high clinical level of suspicion when encountering patients who present with unexplained anemia, history of thyroid disease, and abnormal bone density scan. Our study shows that these variables, when present, warrant further evaluation for celiac disease in order to ensure that an underlying diagnosis of celiac disease is not being overlooked for several years.

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