The Many Faces of Celiac Disease: Clinical Presentation of Celiac Disease in the Adult Population

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The major modes of presentation of patients with celiac disease are the classic diarrhea-predominant form and silent celiac disease. Those with silent celiac disease lack diarrhea, although they may present with manifestations of celiac disease that include an irritable bowel syndrome, anemia, osteoporosis, neurologic diseases, or malignancy. A significant proportion of patients are diagnosed through screening at-risk groups including relatives of patients and insulin-dependant diabetics. Nondiarrheal presentations now are seen more commonly than those with diarrhea. Patients with celiac disease have a greater burden of disease than the general population because of autoimmune diseases and malignancies. There is a need for screening studies of patients with conditions associated with celiac disease to determine whether the large numbers of people with undiagnosed celiac disease currently are seeking health care.

Celiac disease traditionally is considered a malabsorption syndrome and usually is taught as such; however, an ever-decreasing fraction of those with celiac disease present in this way. The disease more closely resembles a multisystemic disorder with the intestine as the primary site of the disease.

Three major advances have occurred in our knowledge of the spectrum of the disease that we now regard as celiac disease. First, there were several early published series showing subtle, unusual clinical presentations.[1–5] Second, Marsh,[6] in a landmark publication, showed the pathologic spectrum of celiac disease. He showed the histopathologic picture to be a continuum from normal villous architecture with intraepithelial lymphocytosis, through partial villous atrophy to total villous atrophy. Third, the widespread availability of relatively sensitive and specific serologic tests for celiac disease has allowed for large population-based serologic surveys that have shown celiac disease to be very common[7,8] and has allowed physicians of any subspecialty to test patients for the disease.

Modes of Presentation

The classification of the main modes of presentation of adults with celiac disease into *classic* (diarrhea predominant) and *silent* is accepted widely.[9] The silent group includes atypical presentations and those presenting with complications of celiac disease as well as truly asymptomatic individuals picked up through screening high-risk groups.

Modes of Presentation of Adults With Celiac Disease in the United States

In view of a lack of current information on the clinical presentation of celiac disease in the United States, we obtained data on 1138 people with biopsy examination–proven celiac disease.[10] Our results showed that the majority of individuals were diagnosed in their 4th to 6th decades. Women predominated (2.9:1); however, the female predominance was less marked in the elderly. Diarrhea was the main mode of presentation, occurring in 85%. Most strikingly, symptoms were present a mean of 11 years before diagnosis.

To assess whether the presentation had changed over time, we analyzed the mode of presentation for a series of patients seen in the Celiac Center at Columbia University in New York.[11] There were 227 patients with biopsy examination–proven celiac disease. We noted that women again predominated, in a ratio of 1.7 to 1. The mean age at diagnosis was 46.4 ± 1.0 years (range, 16–82 years) and was similar in men and women. Women were younger and had a longer duration of symptoms compared with the men. The modes of presentation were symptomatic, with diarrhea as the main mode of presentation (62%), with the remainder classified as silent (38%). This latter group included anemia or decreased bone density as presentations (15%), screening first-degree relatives (13%), and incidental diagnosis at endoscopy performed for such indications as reflux or dyspepsia (8%). We compared those diagnosed before and after 1993 (when serologic testing first was seen in patients), and noted a decrease in those presenting with diarrhea, 73% vs 43% ($P = .0001$) and a decrease in the

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duration of symptoms, from 9.0 ± 1.1 years to 4.4 ± .6 years ($P < .001$). These results suggested that the use of serologic testing was responsible for more patients being detected with celiac disease having presented in nonclassic ways after a shorter duration of symptoms. The duration of symptoms before diagnosis still is unacceptably long.

In a population-based study from Minnesota, Murray et al[12] noted a 10-fold increase in the incidence of celiac disease from 1950 to 2001. This was accompanied by a decrease in the clinical severity of the disease, with fewer people with diarrhea and weight loss at presentation. Only 54% had diarrhea at diagnosis whereas 34% complained of abdominal pain and 30% complained of bloating. Obesity was present in 27%.

These studies confirmed that fewer patients present with severe gastrointestinal symptoms, and the clinical face of celiac disease in the United States is diverse, no longer one of a malnourished individual with a malabsorption syndrome.

Many patients with celiac disease, 36% in our series, have had a previous diagnosis of irritable bowel syndrome.[10] In fact, screening of patients seen in an irritable bowel referral center revealed that 5% of those fulfilling strict Rome II criteria for a diagnosis of irritable bowel syndrome had celiac disease.[13]

In most series of patients with celiac disease HLA DQ2 predominates, occurring in 90%–95% of patients. HLA DQ8 occurs in the remainder. In view of the large number of patients seen with milder forms of celiac disease we investigated whether the presence of HLA DQ8, as opposed to HLA DQ2, may account for the severity of the disease. We had the opportunity to compare our patients with a cohort of patients from Paris with celiac disease. We observed that among our New York City patients with celiac disease, HLA-DQ2 homozygotes were less prevalent compared with the Parisian cohort (59% and 79%; $P = .08$). HLA-DQ8 alleles were more prevalent in the New York cohort compared with the Parisian cohort (41% and 21%; $P = .026$), comprising DQ2/DQ8 heterozygotes (27% and 14%, respectively, $P = .08$) and DQ8 homozygotes (14% and 7%, respectively, $P = .08$). There was, however, no difference in the clinical or pathologic parameters of severity when we compared the groups based on HLA type.[14] HLA DQ8 was found more commonly in patients with celiac disease in our cohort than those in European studies.

Iron-Deficiency Anemia

Iron-deficiency anemia was the mode of presentation in 8% of the individuals seen by us.[11] In a study from the Mayo Clinic, celiac disease was identified as the cause of iron deficiency in 15% of those undergoing endoscopic assessment for iron deficiency.[15] In a prospective study of adults, mean age in their 50s, Karnum et al[16] found 2.8% to have celiac disease. However, it is a well-accepted practice that when iron deficiency is discovered in a menstruating female there is usually no alternate source of the iron-deficient state sought. We do not have any data on the prevalence of celiac disease among iron-deficient individuals of different ages.

Decreased Bone Density

A similar percent of patients, 7%, were diagnosed with celiac disease during the evaluation of decreased bone density (osteopenia and osteoporosis).[17] More of the men had more severe osteoporosis than women. Certainly men and premenopausal women with osteoporosis should be evaluated for celiac disease even if they lack evidence of calcium malabsorption, although the yield in menopausal women is low.[18]

Recognition of Celiac Disease at Endoscopy

An increasingly important mode of presentation is the recognition of endoscopic signs of villous atrophy in individuals who undergo endoscopy for symptoms not associated typically with celiac disease. These endoscopic signs include a decrease in duodenal folds, scalloping of folds, and the presence of mucosal fissures. The indications for upper-gastrointestinal endoscopy include dyspepsia, upper abdominal pain, or gastroesophageal reflux. In the latter period of our study, this mode of presentation accounted for 10% of those who were diagnosed with celiac disease.[11] Interestingly, symptoms of gastroesophageal reflux may resolve after starting a gluten-free diet.[19] This is thought to be caused by resolution of an accompanying motility disorder.[20] The endoscopic abnormalities of the duodenal mucosa are not specific or sensitive markers of celiac disease.[15,21]

There is an argument for the routine biopsy examination of the duodenum in anyone undergoing upper-gastrointestinal endoscopy to detect celiac disease, irrespective of the appearance of the duodenal mucosa.[22]

Screening-Detected Celiac Disease

Screening of high-risk groups, especially relatives of patients with celiac disease, is a major mode of presentation. Studies reveal that 5%–10% of first-degree relatives of patients with celiac disease have serologic and biopsy examination evidence of the disease.[6,8] These cases are found in 25% of the families. Not all those detected by screening are asymptomatic.

Another group that frequently is subject to screening is insulin-dependent diabetic patients; as a result celiac disease is detected in about 5%.[23,24]

Atypical Presentations

Among the atypical presentations that we have encountered are neurologic problems. We have found that 8% of those attending a peripheral neuropathy center, for evaluation of peripheral neuropathy, had celiac disease.[25,26] The neuropathy typically is sensory in type, involving the limbs and sometimes the face. Nerve conduction studies frequently are normal; however, skin biopsy specimens reveal nerve damage in small fibers. We also have identified patients with severe ataxia.[27] We have not identified patients with epilepsy, a neurologic manifestation that may be more common in childhood celiac disease.[28]

Other, less common presentations are abnormalities of blood chemistry determinations such as increased serum amylase levels secondary to macroamylasemia,[29] hypoalbuminemia, and marked increase of the sedimentation rate. We have identified patients in whom the erythrocyte sedimentation rate is greater than 100, decreasing to normal on a gluten-free diet. Two patients had been considered to have polymyalgia rheumatica, although temporal artery biopsy specimens were negative, and the patients' symptoms and erythrocyte sedimentation rate responded to a gluten-free diet. These patients attest to the systemic nature of the inflammatory response in celiac disease. We have not identified patients because of the presence of evidence of hyposlenism in blood film (Howell–Jolly bodies),[30] although several patients have had documented platelet counts greater than a million and have received chemotherapy for essential thrombocytosis. We have seen patients referred because of dental enamel defects.[31] Many women diagnosed with celiac disease have a history of infertility. Although there are European studies of screening infertile individuals,[32–34] there have been no such systematic studies in the United States.

Burden of Disease in Patients With Celiac Disease

Patients with celiac disease appear to have a large burden of other diseases. As well as osteoporosis and anemia, patients have an increased rate of autoimmune diseases and malignancies. Among the patients seen at the Celiac Center at Columbia, 30% have at least 1 associated autoimmune disorder; this compares with 3% in the general population.[35,36] This is a comparable figure with the prevalence of autoimmune diseases in an Italian population with celiac disease.[37] The diseases include type 1 diabetes, psoriasis, thyroid diseases, neurologic problems, autoimmune liver diseases, and autoimmune cardiomyopathy.

In addition, the patients seen by us had an increased rate of malignancies compared with the United States general population by using the National Cancer Institute SEER (Surveillance, Epidemiology, and End Results Program) data as a reference.[38] The malignancies that occurred at an increased rate were esophageal carcinoma, small intestinal adenocarcinoma, non-Hodgkin's lymphoma, and melanoma. A gluten-free diet appeared protective against the development of these malignancies, except for non-Hodgkin's lymphoma.

Seronegative Celiac Disease

Not all patients have positive endomysial or tissue transglutaminase antibodies at presentation.[13,39–42] The presence of positive antibodies correlates with the degree of villous atrophy, and possibly the mode of presentation of celiac disease.[39,43–45] Clinically, patients with and without a positive endomysial antibody are similar.[39,40]

Ethnic Origins of Patients With Celiac Disease

Celiac disease is common in populations of European origin. However, the greatest reported prevalence is in a North African refugee population[46] and the disease frequently is recognized in the Middle East and India as well as South America.[47–51] Although not commonly recognized in African Americans, Hispanics, or Asians in North America, there are reported cases of celiac disease identified from these ethnic groups, indicating that the disease should be considered in any ethnic group,[52,53] not only in residents but also immigrants from many diverse countries around the world. Celiac disease truly has an international face.

Summary

In summary, adults with celiac disease in the United States present after a long duration of symptoms, although the duration of symptoms is decreasing. Non–diarrhea-predominant presentations, or those with silent celiac disease, are the most frequent presentation. Those patients that are in the exposed, diagnosed portion of the adult celiac disease iceberg in the United States have a greater burden of diseases than the general public. It remains to be determined whether early diagnosis will decrease this disease burden. In addition, there needs to be systematic study of patients with diseases known to be

caused by or associated with celiac disease in the United States.

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