

EDITORIAL

Where Are All Those Patients With Celiac Disease?

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Celiac disease is considered to occur in ~1% of the U.S. population. It is, however, markedly underdiagnosed. In this issue, Fasano and his colleagues have continued their work in demonstrating just where all these patients are. Their current study explores a case finding policy in the primary practice setting. They identified patients who exhibited either symptoms that could be attributed to celiac disease, or had an associated condition. In this population, 2.25% had celiac disease. The study emphasizes the need for physician education in both the prevalence of celiac disease and the wide availability of the serological tests that can facilitate the diagnosis of celiac disease.

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Dr. Alessio Fasano and his colleagues have, in their current article (1) continued their work demonstrating that celiac disease occurs in North America, and is in fact as common as in Europe. Initially, they performed a blood donor study demonstrating that one in 250 healthy blood donors in the Baltimore area had positive endomysial antibodies (EMAs) (2). The EMA is virtually 100% specific for celiac disease (3). They subsequently screened 13,145 subjects, including at-risk individuals such as relatives of those with celiac disease or patients with diarrhea as well as subjects at average risk for celiac disease. In the at-risk groups, the prevalence of celiac disease was 1:22 (4.5%) in first-degree relatives, 1:39 (2.6%) in second-degree relatives, and 1:56 (1.8%) in symptomatic patients with diarrhea, while the prevalence in those without risk factors was 1:133 (0.8%) (4).

In their current paper, they screened individuals seeking health care from a variety of primary practice settings in the United States and Canada. In this study, patients with symptoms of celiac disease or with associated conditions were offered testing. Initially, tissue transglutaminase IgA antibodies were measured. If positive, an EMA was performed and the positive patients were offered an intestinal biopsy. This study resulted in a 42-fold increase in the diagnoses of celiac disease in the involved practices. The prevalence of celiac disease among those screened was 2.25%. The symptoms or reason for screening were irritable bowel syndrome, diarrhea, abdominal pain, bloating, constipation, anemia, fatigue, and a variety of autoimmune diseases, especially thyroid diseases and type 1 diabetes, abnormal liver function tests, infertility, and epilepsy and ataxia. Other at-risk groups included relatives of those with celiac disease and Turner and Down syndrome patients. IBS symptoms, iron deficiency anemia, and thyroid disorders are commonly known risk factors that may lead to celiac disease screening, and chronic fatigue is a common symptom reported by patients. The prevalence of celiac disease, in Fasano's study, was elevated among pa-

tients with gastrointestinal symptoms (~3.5%), thyroid disorders (~9%), iron deficiency anemia (~3.5%), and fatigue (~2.5%).

Celiac disease is considered to be a worldwide disorder, occurring in Europe and countries populated by Europeans, including South America, Australasia, and South Africa. It is, however, becoming an increasing problem in developing countries and in particular the Middle East, North Africa, and Northern India (5).

While the rate of diagnosis is increasing in the United States (6), it is considered to lag behind in many European countries, despite the similar prevalence. It is estimated that less than 5% of those with celiac disease in the United States are currently diagnosed. In view of this high rate of underdiagnosis compared to European countries, an NIH Consensus Development Conference was convened in 2004 (7). The consensus statement used the figures of 0.5–1% for the prevalence of celiac disease in the United States and recommended increased screening strategies through case finding, similar to those employed in Fasano's recent study.

Several studies have shown that patients with celiac disease experience a long duration of symptoms prior to diagnosis (8–10). This diagnostic delay has also been noted for children; in fact, in our study, the duration of symptoms prior to the diagnosis of celiac disease in children was almost half their life (11). This diagnostic delay was associated with a high rate of patient/parent dissatisfaction and the use of multiple different physicians prior to diagnosis (8, 11).

Why is celiac disease underdiagnosed in the United States? The problem appears to be one of physician awareness. The diagnosis, once considered, is relatively easy to obtain (12). The blood tests are quite sensitive and specific (13). If positive, a duodenal biopsy clinches the diagnosis. Most physicians are not aware of the prevalence, or the diverse clinical manifestations of the disease. Celiac disease is in the "Malabsorption" chapter of most textbooks; however, it more closely resembles a multisystem disorder with an

impact on almost any organ system (14–16). As an example, the single greatest source of new referrals to our celiac disease center at Columbia University in New York is from neurologists, specifically from neurologists that deal with patients who have a peripheral neuropathy or ataxia (17–19).

What is a reasonable approach to the diagnosis of celiac disease? First, the disease must be considered as part of a differential diagnosis, after that the diagnosis is reasonably easy and accurate in the great bulk of individuals with the disease (12). The duodenal biopsy is still the gold standard in diagnosis. Positive serological tests (usually the tissue transglutaminase antibodies) result in endoscopic duodenal biopsies that reveal varying degrees of villous atrophy and intraepithelial lymphocytosis. The serological screening tests for celiac disease, used currently by all laboratories, employ human tissue transglutaminase (H-tTG) as the antigen in assays that detect IgA tTG antibodies. The sensitivity and specificity of these assays are around 90%, though in the clinical practice setting, the performance of the test is not as great as in the research laboratory (20).

There are several issues concerning the serological tests used in the diagnosis of celiac disease. These include the presence of selective IgA deficiency resulting in negative IgA-based serologies (IgG tTG and IgG antigliadin antibodies will be positive), the lack of adequate sensitivity and specificity of antigliadin antibodies prompting recommendations that they no longer be included in serologic panels (21), the less than 100% specificity of the IgA anti-tTG compared to the serological gold standard, the EMA with its virtual 100% specificity, and the realization that the serologic tests may all in fact be negative in the presence of celiac disease, especially with lesser degrees of villous atrophy (22). It is of interest that in the current study of Catassi *et al.* the anti-tTG assay was used as a screening test. Biopsy was only performed if the EMA was positive. It is, however, my current practice to use the anti-tTG IgA and IgG, together with a total IgA level in patients in whom there is a suspicion of celiac disease. The EMA is used as a confirmatory test when the diagnosis is questionable. In those at high risk/suspicion for the diagnosis, I will perform a biopsy irrespective of the results of the serologic tests.

While regarded as the gold standard, the biopsy is not 100% sensitive or specific (23). The problems are both in the quality of the histological specimens (number of pieces, orientation, and preparation artifact) as well as the quality of the pathological interpretation. An expert pathological opinion is imperative, especially if the pathology report does not correlate with the clinical or serological data. In cases in which the diagnosis is questionable, there is an important role for assessing the presence of HLA DQ2 or 8, or the alleles that are required for DQ2, because without them celiac disease cannot be present (24)! Video capsule endoscopy has an expanding role in the diagnosis of celiac disease, especially in those unwilling or unable to undergo endoscopy or in those in whom a negative biopsy appears to be a false negative result (25).

Endoscopists should be aware of how common celiac disease appears to be. One can argue for the role of routine duodenal biopsy, especially in this era of open access endoscopy where a detailed family or personal history is not required (26). Certainly, duodenal biopsy should be performed at least more liberally, especially when one is aware of the study of Harewood *et al.* who, in their analysis of the CORI database, demonstrated that less than 10% of those undergoing endoscopy for an indication of diarrhea, weight loss, or iron deficiency actually had a duodenal biopsy performed (27).

It is tempting to blame the lack of interest of the pharmaceutical industry in celiac disease as the root cause of the lack of research and physician knowledge or interest in celiac disease in the United States (as was suggested in a front page article in the *Wall Street Journal*) (28). It is obvious that the practice of gastroenterology as a subspecialty is currently focused on procedures and pharmaceutically driven diseases such as GERD, *H. pylori*, hepatitis C, IBD, and IBS. There is no constant reminder by drug representatives about celiac disease. Interestingly, that may change, because there is an emerging interest in the development of therapies that could offer either a supplement or even an alternative to the rigorous gluten-free diet (29, 30).

Celiac disease is common in the United States; it is, however, markedly underdiagnosed. Physician awareness is the main problem with the primary care physician, the most likely candidate to recognize the patient who possibly has celiac disease, test for it, and refer for endoscopy. It is clear from a study in Northern Ireland that the primary care physician is the most likely source of the increase in the rate of diagnosis of celiac disease in that country (31).

Gastroenterologists in the United States need to increase their own awareness of celiac disease and educate their referring doctors about the prevalence, diverse clinical manifestations of the disease, and the availability of the serologic tests. While the NIH-sponsored Consensus Development Conference on Celiac Disease was published online and as a supplement to *Gastroenterology*, there was no funding to provide the report directly to primary care physicians in the United States (7, 21). Education about celiac disease surely must start in medical schools, continue in residency training programs, and be part of postgraduate educational programs, both specialist and primary care. The high rate of patient dissatisfaction from those finally diagnosed with celiac disease provides an impetus for this.

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