

New Strategies for Diagnosis and Management of Celiac Disease

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Celiac disease is a gastrointestinal disorder characterized by inflammation, leading to injury to the mucosal lining of the small intestine. The inflammation occurs when gliadin, a protein found in such gluten-containing foods as wheat, rye, and barley, is ingested by genetically susceptible individuals. The mucosal damage and subsequent malabsorption of nutrients leads to various complications. Researchers estimate that more than 2 million people in the United States have celiac disease—a prevalence that is greater than was previously believed. Approximately 60,000 Americans are diagnosed annually with celiac disease. Until recently, diagnosis has been complicated by the fact that the indicators of celiac disease are nonspecific. However, because of the development of new, easy-to-administer serology tests, diagnosis has become much less complicated. After conducting a review of the literature, the authors recommend a serologic testing sequence for diagnosis of celiac disease and urge that adults and children with an assortment of symptoms be tested for this disease. Common signs and symptoms of celiac disease include anemia, arthralgia, fatigue, infertility, neuropathy, and weight loss, in addition to such gastrointestinal symptomatology as abdominal pain, anorexia, bloating, constipation, and diarrhea. The only treatment for patients with celiac disease remains a gluten-free diet.

In the not too distant past, celiac disease was rarely included in differential diagnoses. Instead, this gastrointestinal disorder was usually considered just another uncommon medical condition. However, with the advent of new diagnostic technologies, researchers have discovered that the prevalence of celiac disease in the United States ranges as high as 4.54% in close relatives of individuals with the disease, similar to the prevalence reported in Europe.¹ More than 2 million people in the United States—or approximately 1 in 140 individuals—are likely to have celiac disease.^{1,2} Previous estimates had placed the celiac disease-prevalence rate in the United States at 1 in 3000 people.² Approximately 60,000 Americans are diagnosed annually with celiac disease.²

Thousands of patients in the United States suffer needlessly from celiac disease. Yet, these patients are not without symptoms—though the symptoms may be subtle. For this reason, physicians need to consider celiac disease in their differential diagnoses for many of their patients. The goals of the present article are to increase physician awareness of celiac disease and to outline a strategy for diagnosis and treatment to benefit the greatest number of patients.

Methods

The United States National Library of Medicine's MEDLINE database was searched for English-language articles on celiac disease published between January 1996 and December 2003. Key terms used in the search were *celiac disease*, *gluten-sensitive enteropathy*, *serological testing*, and *treatments*. After pertinent articles were identified, a group of healthcare providers who had an interest in the identification of patients with celiac disease was organized. This group, which consisted of the authors, met on several occasions to formulate practitioner guidelines for the identification of patients with this disorder. These guidelines were based on a review of 60 articles.

Pathogenesis

Celiac disease occurs in genetically susceptible individuals who ingest gluten, a protein found in certain grains. In these individuals, gluten causes an abnormal T cell-mediated immune response and inflammatory injury to the mucosa of the small intestine, resulting in malabsorption of nutrients.² The gliadin fraction of gluten is mainly responsible for this intestinal damage.¹ Approximately 97% of individuals with celiac disease have genetic markers on chromosome 6 called HLA

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(human leukocyte antigen) DQ2 and HLA DQ8, compared with 40% of the general population.³ Because of this genetic predisposition, an individual's intolerance to gluten is lifelong and self-perpetuating.^{4,5}

Presentation

In untreated patients with celiac disease, there may be different clinical signs and symptoms depending on the particular patient (Figure 1).^{1,2} Therefore, it has been difficult for clinicians to diagnose the condition and for epidemiologists to accurately estimate its prevalence. Patients most commonly have gastrointestinal symptoms, including abdominal distention, anorexia, chronic diarrhea, steatorrhea, and weight loss.⁶ The disease can also assume various extraintestinal manifestations, such as osteoporosis.⁷ Many patients with celiac disease have few or no outward symptoms, but certain biochemical signs of malabsorption are indicative of the disease (eg, deficiencies in folate and iron).⁸

Signs and Symptoms (Adults)

- Abdominal pain*
- Arthralgia
- Chronic diarrhea*
- Infertility or recurrent spontaneous abortion*
- Iron deficiency anemia*
- Irritable bowel syndrome
- Peripheral neuropathy
- Persistent fatigue/malaise
- Weight loss*

Signs and Symptoms (Children)

- Abdominal distention/bloating
- Chronic diarrhea*
- Delayed puberty
- Growth failure

Associated Conditions

- Autoimmune disorders
- Dermatitis
- Down syndrome
- Epilepsy
- Idiopathic dilated cardiomyopathy
- Immunoglobulin A deficiency
- Immunoglobulin A nephropathy
- Microscopic colitis
- Osteoporosis or other bone diseases
- Thyroid disease
- Turner syndrome
- Type 1 diabetes mellitus

* Cause of condition is unexplained.

Figure 1. Common signs, symptoms, and associated conditions of celiac disease.^{1,2} Any particular case of celiac disease may include one or more of the listed signs and symptoms. Children's signs and symptoms may also include the signs and symptoms listed for adults.

In patients in which gastrointestinal symptoms are minor or absent, cutaneous manifestations may provide the only clue to diagnosis.⁶ The most common cutaneous manifestation of celiac disease is dermatitis herpetiformis (Figure 2), which affects approximately 25% of patients with the disease, according to Collin et al.⁷ Dermatitis herpetiformis is a skin disorder associated with bullous eruptions on the knees, elbows, buttocks, and back. Hill et al⁴ estimate that 90% of patients with dermatitis herpetiformis have gluten-sensitive enteropathy.

Autoimmune disorders are commonly associated with celiac disease.⁹ Ventura et al¹⁰ report that the prevalence of autoimmune disorders in patients with celiac disease is directly proportional to the patients' duration of exposure to gluten. Longer exposure to gluten is linked to a higher incidence of such autoimmune disorders as autoimmune hepatitis, autoimmune thyroid disease, connective tissue diseases, and type 1 diabetes mellitus.¹⁰ Patients with celiac disease also have an increased risk of esophageal cancer, melanoma, non-Hodgkin lymphoma, and small intestine adenocarcinoma.¹¹

Some patients with celiac disease develop neurologic manifestations, most commonly ataxia and peripheral neuropathy.¹² Marignani et al¹³ associated celiac disease with primary biliary cirrhosis and other autoimmune diseases of the liver. Osteopenia/osteoporosis is a common complication of celiac disease.¹⁴

Children with celiac disease may exhibit a more classic clinical picture than adults. Infants with celiac disease typically first show symptoms between the ages of 4 and 24 months, with abdominal distention, diarrhea, edema, impaired growth, pallor, and vomiting.² The onset of symptoms often coincides with the addition of cereals to the diet.¹⁵ However, there is usually a latent interval, lasting from months to years, between the introduction of gluten to the diet and the development of clinical manifestations of the disease.¹⁵

Children with severe celiac disease who remain untreated may have short stature, pubertal delay, iron and folate deficiency with anemia, and rickets.² Atypical signs of celiac disease (eg, arthralgia, elevated transaminase levels, recurrent abdominal pain, and behavioral disturbances) are usually seen in older children or adolescents who do not have obvious symptoms of malabsorption.²

Diagnosis

The assortment of symptoms experienced by individuals with celiac disease can describe many patients who enter the office of the family physician. Because of these variable and sometimes subtle manifestations, celiac disease is underdiagnosed in the adult population in the United States.¹⁻³

The best approach to diagnosing celiac disease appears to be a systematic process of case identification, targeting those patients with signs, symptoms, or conditions associated with celiac disease.¹ When such patients are identified, appropriate serologic testing can begin (Figure 3).



Figure 2. Dermatitis herpetiformis appears as grouped papulovesicles (0.2–0.6 mm diameter) in several 1-centimeter-wide clusters on the exterior surface of a patient's elbow. Mild postinflammatory hyperpigmentation is also noted. Focal excoriation correlates with the patient's pruritus. (Photo used with permission of Robert Brodell, MD.)

New Recommendations for Celiac Disease Initial Serology Tests*

Serology Test	Test Purpose
IgA-tissue transglutaminase	Performed to identify candidates for duodenal biopsy Sensitivity: 85%–92% Specificity: 93%–98%
Total serum IgA	Performed to identify individuals with IgA deficiency

* Serology tests should be performed before eliminating gluten from patient's diet.

Figure 3. New recommendations, by Westerberg et al, for initial serology tests for celiac disease include immunoglobulin A (IgA)-tissue transglutaminase and total serum immunoglobulin A.

To confirm a physician's suspicion that a patient has celiac disease, we recommend a multistep, cost-effective approach to serologic testing (Figure 4). The first step is to conduct tests for both immunoglobulin A-tissue transglutaminase (IgA-tTG) and total serum IgA. The test for total serum IgA is suggested because there is a high prevalence of IgA deficiency in patients with celiac disease.¹⁶

If results of both of these tests are negative, celiac disease is unlikely. However, if the tests are negative but a high clinical suspicion for the disease remains, we suggest testing for IgA antibody to endomysial antibody (IgA-EMA). If results of either the IgA-tTG or the IGA-EMA test are positive, the patient should be referred to a gastroenterologist for a definitive diagnosis, which may include a duodenal biopsy.

If the IgA-tTG test results are negative, but total serum IgA levels are low—suggesting an IgA deficiency—we recommend testing for immunoglobulin G (IgG). If results of this test are negative, celiac disease is unlikely. A positive finding in the IgG test should be followed by a tissue biopsy of the small intestine.

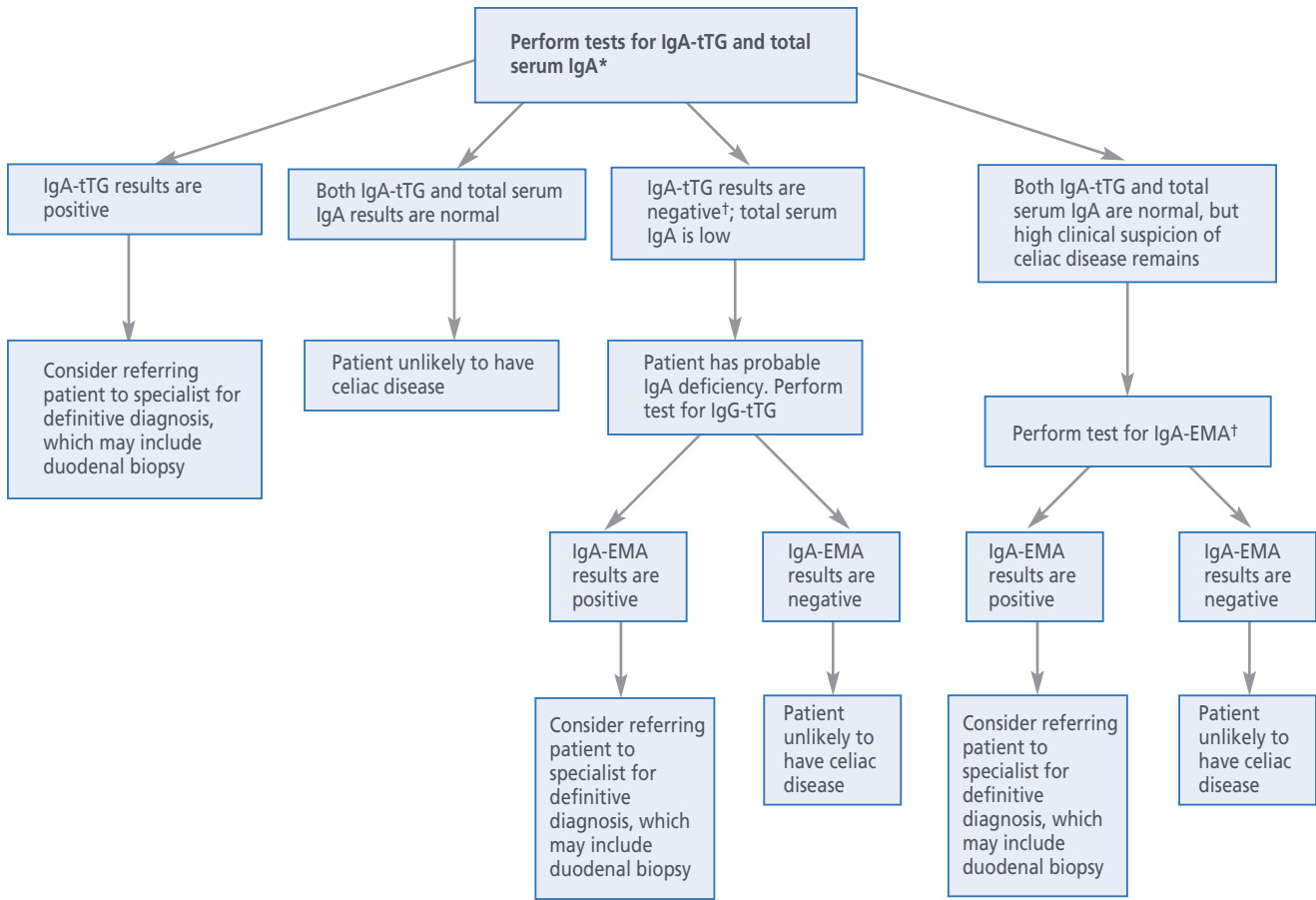
Many children under 2 years of age lack EMA and tTG antibodies, resulting in false-negative testing.^{2,17} Because of this possibility, tests for IgA antigliadin antibodies (IgA-AGA) and IgG antigliadin antibodies (IgG-AGA) should be added to the diagnostic protocol for these individuals. These antibodies are the most useful serologic markers in symptomatic children younger than age 2.² However there are limitations to using the IgA-AGA and IgG-AGA tests for celiac disease because these antibodies may also be found in healthy individuals and in individuals with other inflammatory bowel

conditions.² Thus, serologic testing for very young children—particularly those under the age of 5—is unreliable and requires further study.³

All serology tests should be performed *before* eliminating gluten from the diet. This is because the results of any later serologic analyses would be altered by such a diet.¹⁸ The use of immunosuppressants would also alter the results of serologic analyses, so these medications, too, should be avoided until after testing.¹⁸ If a gluten-free diet is eventually recommended, serologic testing is useful for monitoring adherence and response to the diet.²

The tTG and EMA tests have excellent sensitivity and specificity. A recent screening study by Maki et al¹⁹ of 3634 schoolchildren in Finland (7–16 years) found that each of these tests alone was approximately 95% sensitive. The combination of the tests resulted in a sensitivity and specificity of 100% and 99%, respectively.¹⁹ Russo²⁰ found that the combination of IgA-AGA, IgG-AGA, and EMA tests resulted in 100% sensitivity and negative predictive values, with no false-negatives, in pediatric patients referred for duodenal biopsies (N=95).

Although it is not conclusive whether screening the general population for celiac disease should be undertaken, it is clear that physicians must consider testing in asymptomatic individuals who are at highest risk of developing the disease. This includes patients with first-degree relatives who were diagnosed with celiac disease. Some experts^{2,21–25} also recommend that individuals with autoimmune disorders (eg, autoimmune liver disorders, type 1 diabetes mellitus), functional dyspepsia, idiopathic dilated cardiomyopathy, irritable



* Serology tests should be performed before eliminating gluten from patient's diet. Children younger than 2 years should be tested for IgA-antigliadin antibodies.
 † According to the National Institutes of Health Consensus Development Conference Statement,³ the IgA-tTG and IgA-EMA tests "have equivalent diagnostic accuracy."

Figure 4. New recommendations, by Westerberg et al, for steps in the use of serologic testing for the diagnosis of celiac disease. EMA indicates endomysial antibodies; IgA, immunoglobulin A; IgG, immunoglobulin G; and tTG, tissue transglutaminase.

bowel syndrome, unexplained fatigue, and certain neurologic disorders be evaluated for celiac disease.

Figure 5 illustrates the pretest and posttest probabilities that individuals with various associated medical conditions—as well as individuals in the general asymptomatic population—have celiac disease.^{19,26} Clinicians should consider testing in any population whose pretest probability is elevated compared with the general asymptomatic population. When antibody tests are inconclusive, testing for the genetic markers HLA DQ2 and HLA DQ8 can accurately identify those at greatest risk.³ It would be highly unlikely for an individual

with a negative test result for these genetic markers to have celiac disease.³

A diagnosis of celiac disease may seem obvious from results of serologic testing, but tissue biopsy remains the gold standard for diagnosis. In current practice, most biopsies are performed during upper endoscopy because this technique is more reliable than previous capsule-biopsy techniques.² Biopsy specimens should be obtained from the second or third section of the distal duodenum to avoid the architectural distortion produced by Brunner's glands (glandulae duodenales) or peptic duodenitis.²

Probabilities That Individuals in Symptomatic and Asymptomatic Populations Have Celiac Disease, %*

Associated Condition	Pretest Probability	Posttest Probability†
■ Symptomatic Population		
□ Autoimmune liver disorders	9	96
□ Fatigue, unexplained	3.3	90
□ Functional dyspepsia	3.2	90
□ Idiopathic dilated cardiomyopathy‡
□ Irritable bowel syndrome	3.3–11	85–97
□ Neurologic disorders‡
□ Type 1 diabetes mellitus	4.5–6.2	92–95
■ Asymptomatic Population		
	0.5–1	50–70

* Probabilities given as percentages of individuals with associated conditions who also have celiac disease.
 † Posttest probabilities are estimations made using a nomogram, assuming a likelihood ratio for the combination of serology tests calculated from data based on Maki et al.¹⁹
 ‡ Exact probabilities are not known, but it is known that they are elevated vs the general population.

Figure 5. Pretest and posttest probabilities that patients with various medical conditions also have celiac disease (given as percentages of patients with associated conditions who have celiac disease), compared with the general asymptomatic population.^{19,28}

The classic lesion in untreated patients with celiac disease is characterized histologically by the absence of absorptive villi and by hyperplasia of crypts in the gastrointestinal tract.² These tissue changes are associated with an increased number of intraepithelial lymphocytes, as well as an increase in lymphocytes and plasma cells in the lamina propria.² The extent and severity of symptoms and malabsorption is directly influenced by the degree of enteropathy.²

Treatment

As previously mentioned, the only treatment for patients with celiac disease remains a gluten-free diet. This literally means “no gluten.” A so-called “wheat-free” product is not necessarily gluten-free, because rye and barley also contain gluten proteins. (Recent studies suggest that most oats do not contain proteins that are harmful to patients with celiac disease.^{27,28})

Individuals with celiac disease should be wary of salad bars and buffets, where the foods can easily become cross-contaminated. Medications, vitamins, and mineral supplements may contain gluten as an inactive ingredient.¹ Because there is no government regulation regarding inactive ingredients, the amount of gluten in such products can vary widely. Patients must also be aware of such ingredients as vegetable gum and modified food starch, both of which may contain gluten.

Physicians should encourage their patients with celiac disease to discuss foods with a registered dietitian or to con-

tact the American Dietetic Association’s Consumer Nutrition Hotline at (800) 366-1655 or hotline@eatright.org. Patients can also be referred to various consumer-friendly Web sites to learn more about celiac disease (Figure 6).

Finally, it is important that physicians warn patients that following a gluten-free diet is not easy. Gluten-free foods may be more expensive and less appealing to personal tastes than food that patients are used to eating. Patients may also feel less willing to socialize for fear of eating the wrong foods. They need to understand that this lifestyle change must be a lifelong commitment—not a quick fix to a problem. Although a gluten-free diet may be difficult to follow, its benefits have been well documented, in cases of both intestinal and extraintestinal manifestations of celiac disease.^{25,26,29,30}

In a prospective cohort study designed to evaluate the clinical and nutritional profile of children diagnosed with celiac disease (N=41), Patwari et al²⁹ reported that a gluten-free diet led to rapid improvement in clinical symptoms and in nutritional and hematological parameters. In another cohort study, involving patients with irritable bowel syndrome, Shahbazkhani et al²⁶ reported that all of the individuals diagnosed with celiac disease who adhered to a gluten-free diet (n=11) showed significant improvement in symptoms.

Among individuals with celiac disease who have mainly extraintestinal manifestations, adherence to a gluten-free diet has been shown to result in an improvement of

Resources for Patients With Celiac Disease

- American Dietetic Association—Find a Nutrition Professional
<http://webdietitians.org/cgi/findanrd3.cgi>
- Celiac Disease Foundation
<http://www.celiac.org>
- Celiac Disease and Gluten-Free Diet Support Center
<http://www.celiac.com>
- Celiac Spru Association/United States of America, Inc
<http://www.csaceliacs.org/>
- National Digestive Diseases Information Clearinghouse
<http://digestive.niddk.nih.gov/ddiseases/pubs/celiac/index.htm>
- North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
<http://www.naspgn.org/sub/diseaseinfo.asp>
(Scroll to celiac disease PDF file.)

Figure 6. Online resources recommended by Westerberg et al for patients with celiac disease.

symptoms.^{25,30} Curione et al²⁵ reported that among three patients with celiac disease and idiopathic dilated cardiomyopathy, the two individuals who adhered to a gluten-free diet showed improvement in echocardiographic parameters, as well as in cardiologic symptoms and quality of life. By contrast, the individual who did not adhere to the gluten-free diet had a worsening in echocardiographic parameters and cardiologic symptoms, making supplementary drug therapy necessary.²⁵ In a prospective cohort study of patients with celiac disease and neurologic disorders (N=55), Yolita et al³⁰ found that transaminase concentrations returned to normal within 6 months in four patients who followed a gluten-free diet.

Conclusion

Celiac disease is more prevalent than previously believed, affecting approximately 1% of the US population. Patients who have this condition may experience a variety of symptoms, which are not limited to gastrointestinal problems.

Physicians need to be readily receptive to including celiac disease in their differential diagnoses of patients. Physicians should be especially sensitive to those patients who have the nonspecific complaints of arthralgia, myalgia, and fatigue, because celiac disease can easily remain undiagnosed in these individuals.

Diagnostic tests for celiac disease are readily available today—and less expensive than they were in the past. These

tests have a high degree of sensitivity and specificity. Once celiac disease is diagnosed, a patient can benefit from a gluten-free diet, which promotes symptom relief and an improved quality of life. Proper diagnosis and treatment can help avoid the potentially serious long-term consequences of celiac disease.

Healthcare providers must become more familiar with celiac disease, a sometimes forgotten condition, to better serve their patients.

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