

Serological Testing for Celiac Disease

Background: Celiac disease (CD) is an autoimmune enteropathy triggered in susceptible individuals by the ingestion of gliadin, a component of gluten. Gluten is found in many cereals (particularly wheat, but also rye, barley and probably oats), and is ubiquitous in the normal Western diet. The disease may present at any age, from infant to adult. The clinical picture of CD varies from the classical presentation of malabsorption and malnutrition, to a milder form in which increased peristalsis or flatulence is the only consequence of gliadin ingestion. In addition, patients with subclinical CD exhibit a variety of vague, non-specific manifestations (Table 1).

Table 1. Clinical Manifestations of CD

Gastrointestinal: *Early onset* (< 2yrs) - diarrhea, poor weight gain, abdominal distention, muscle wasting, apathy; *Late onset* - diarrhea, nausea, vomiting, abdominal pain, bloating, weight loss

Musculoskeletal: short stature, osteoporosis, dental enamel defects, arthritis, myopathy

Mucocutaneous: dermatitis herpetiformis, recurrent aphthous stomatitis, vasculitis

Hematologic: anemia, leukopenia, thrombocytopenia

Reproductive: infertility, recurrent fetal loss, delayed puberty, menstrual irregularities

Neurologic: epilepsy, cerebellar ataxia, peripheral neuropathy, dementia

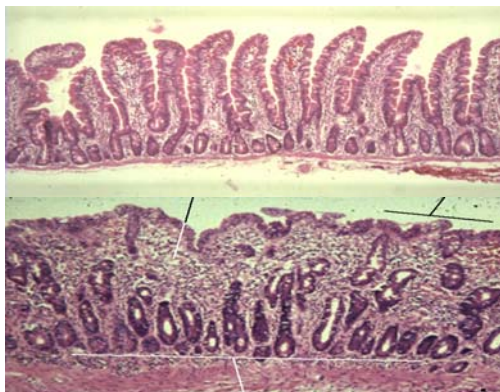
Autoimmune: myocarditis, thyroiditis

Miscellaneous: elevated transaminases, lassitude/weakness, intestinal lymphoma

Normally, as digested food passes through the small intestine, nutrients are trapped and absorbed by the villi (Figure 1). In CD, these villi are atrophied, reducing their ability to absorb nutrients. Over time, lesions appear in the mucosal lining of the small intestine with the extent of damage corresponding to the degree of malnourishment. Treatment for CD requires interaction with a skilled dietitian, education about the disease, adherence to a gluten-free diet for life, and identification and treatment of nutritional deficiencies.

Prevalence: Population-based studies in the US using serological and small intestinal biopsy indicate that CD is in the range of 0.5 to 1.0 percent, similar to estimates

Figure 1. Upper image reveals normal intestinal villi. Lower image reveals flattened mucosa with inflammatory cell infiltrates and crypt hyperplasia.



in Europe and considerably more common than previously thought. Certain ethnic groups may be at lower risk than Caucasians, but there are limited data at present. At risk clinical populations include: first degree relatives of biopsy-proven CD patients, patients with type 1 diabetes mellitus, Down syndrome, Turner syndrome, Williams syndrome, selective IgA deficiency, and various autoimmune disorders.

Diagnosis: Critical to diagnosing CD is the need to recognize the myriad clinical manifestations of the disease. There is no one test that can definitively diagnose or exclude CD in all cases. In the US, the estimated time from first symptoms to diagnosis averages 10 years. Fortunately, there are a variety of laboratory and histopathologic results to assist the physician. All diagnostic testing should be performed while the patient is on a gluten-containing diet.

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(Source: American College of Gastroenterology)

Historically, the diagnosis of CD was based on histological studies of the jejunal biopsy. However, cases of latent and even active CD have been shown to exhibit normal histopathology. Furthermore, cases of malabsorption syndrome or parasitic infections have also been shown to mimic CD histology.

HLA DQ2/DQ8 testing appears to be a useful adjunct in the diagnosis of CD. The sensitivity of this test is

between 90-95%; however, since nearly 40% of the general population and an even higher proportion of high-risk subjects also carry these markers, the specificity is not ideal. Its greatest diagnostic utility appears to be its negative predictive value.

As these limitations have been recognized, serum antibody testing have gained broader acceptance in screening for CD and in follow-up of patients with the disease to evaluate their compliance to a gluten-free diet. Due to its high sensitivity and specificity, serological testing is now recommended by the NIH as the first step in pursuing a diagnosis of CD.

Autoantibodies and CD: Patients with CD produce various autoantibodies, including anti-endomysial (EmA), anti-tissue transglutaminase (tTG), anti-gliadin (AGA), and anti-reticulin antibodies as part of the immune response. IgA antibodies usually predominate although patients may also produce IgG. Among CD patients, roughly 3% will have IgA deficiency and only produce IgG autoantibodies. Therefore, as the tTG and EmA tests detect only IgA, patients with negative test results but a clinical picture of CD should be tested for total IgA to rule out a deficiency. Autoantibodies to tTG and EmA are highly specific and sensitive for the diagnosis of CD. These two tests detect predominantly IgA antibodies whereas the AGA test detects both IgA and IgG isotypes. No IgM class antibodies to these antigens are detected in patients with CD; hence there is no need for this study. tTG is the prominent autoantigen in CD and is responsible for the reactivity seen in EmA testing. It is expressed in many cell types both intra- and extra-cellularly and is the enzyme for which gliadin is the major substrate. AGA antibodies were the first to be described and have been widely published; however, there are frequent false positives in other gastrointestinal diseases and their sensitivity is not as great as tTG or EmA (Table 2). A recent consensus report from the NIH indicates that AGA tests are not to be routinely recommended, but may be useful in cases of IgA deficiency.

Biopsy revealing the typical small intestine lesion in conjunction with positive serology provides presumptive evidence for CD. When followed by a favorable clinical response to a gluten-free diet a definitive diagnosis is confirmed.

Table 2. Diagnostic specificity of serological markers

Test	Sensitivity	Specificity	Comments
<i>EmA-IgA</i>	100%	100%	Subjective interpretation, rare false positives
<i>tTG-IgA</i>	90-95%	98%	Automated, objective interpretation. Levels drop with successful treatment
<i>AGA-IgA</i>	52%	86%	Relatively insensitive
<i>AGA-IgG</i>	86%	78%	Helpful in CD patients with IgA deficiency

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Source: National Institutes of Health – Consensus Development Conference Statement on Celiac Disease, June 2004.

Methodology

For AGA testing, FBR utilizes separate ELISA tests that detect IgA and IgG antibodies to gliadin (CPT code 83520 x 2 units). For EmA testing, FBR utilizes indirect immunofluorescence (CPT code 86256). For tTG, FBR utilizes ELISA that detects IgA antibodies (CPT code 83520).

Ordering Information

Check the appropriate box(es) on the General Requisition form. Testing is performed weekly.

Specimen: 2 mL of nonhemolyzed, nonlipemic serum
Storage and Shipping: Room temperature (or 4°C if delayed more than 48 hours)

Price: Refer to FBR's Fee Schedule

Further Information

For additional clinical information, please contact Robert F. Ritchie, M.D.; for technical information, contact Thomas B. Ledue, BA, or Wendy Y. Craig, Ph.D.

References

- Murray JA. The widening spectrum of celiac disease. *Am J Clin Nutr* 1999;69:354-65.
- Fasanto A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology* 2001;120(3):636-51.
- NIH consensus development conference statement on celiac disease: <http://consensus.nih.gov/cons/118/118celiacPDF.pdf> (accessed Sept 2004).