Celiac Disease

Celiac disease is an autoimmune digestive disease in response to antigens present in flour gluten. (Dermatitis herpetiformis is an autoimmune skin disease in response to dietary gluten.) Celiac disease is frequently an inherited disorder and is particularly common in individuals of European descent. While frequently diagnosed in Europe (in Italy children are routinely screened by age 6), it is probably underdiagnosed in the United States where the prevalence may be as great as 1 in 250.\(^1\) It is rare in individuals of Chinese, Japanese, or African heritage. Individuals at increased risk of celiac disease include those with:

- Family history of celiac disease or dermatitis herpetiformis
- Type 1 diabetes mellitus
- Thyroid disease
- Down syndrome
- Chronic diarrhea
- Unexplained short stature
- Infertility
- Anemia
- Lactose intolerance

Patients may not always present with the classic symptoms of a malabsorption syndrome (abdominal pain, bloating, weight loss, diarrhea, and foul smelling loose stools). Other presenting symptoms include fatigue, chronic nausea, infertility or fetal loss, bone pain, dental anomalies, and (in children or infants) failure to thrive. Some patients may be asymptomatic.

Serologic tests are very helpful in screening for celiac disease and identifying patients who are candidates for small intestinal biopsy. Patients with celiac disease (and dermatitis herpetiformis) develop autoantibodies that can be measured both to assist in diagnosis and monitor response to the disease. Most of the autoantibodies are IgA antibodies, but some are IgG antibodies. In order of diagnostic utility the autoantibodies are discussed below.

*Tissue transglutaminase (tTG)* (Mayo Medical Laboratories #82587, $104) Primary autoantigen recognized by endomysial antibodies in celiac disease. An ELISA test that recognizes only IgA antibodies. This is the test of choice for most patients undergoing screening serologic testing for celiac disease. False positives may be seen in patients with other autoimmune diseases, particularly autoimmune hepatitis.

*Endomysial antibodies (EMA)* (Mayo Medical Laboratories #9360, $139) Highly specific (few false positives) and sensitive, but labor intensive and more subjective (direct immunofluorescence microscopy). Has a longer turnaround time than tTG. Patients with autoimmune hepatitis may have strong anti-smooth muscle antibodies, which may evaluation for endomysial antibodies difficult and produce an “indeterminate” result. (Nevertheless, this test is the test of choice in patients known to have autoimmune hepatitis who are suspected of having celiac disease.) Detects only IgA antibodies.

*IgA and IgG Gliadin antibodies* (Mayo Medical Laboratories #81766, $162) Less sensitive and specific than tTG and EMA, but detects IgG as well as IgA antibodies. May be helpful in patients with IgA deficiency who are suspected of having celiac disease.
Reticulin antibodies  No longer recommended.  Less sensitive and specific than tTG and EMA.

Serologic testing for celiac disease requires that the patients be on a normal gluten-containing diet, as all of the antibody levels decline following institution of a gluten-free diet.  As tTG and EMA detect only IgA antibodies, false negative results may occur in patients with IgA deficiency.  If the patient has clinical symptoms and a negative test result, quantitative IgA (quantitative immunoglobulins) may be helpful in evaluating the patient.

### Celiac Disease Algorithm*

* Adapted from an algorithm devised by Joseph A. Murray, MD (Mayo Clinic gastroenterologist)²

(These tests may also be used in the evaluation of patients with dermatitis herpetiformis. In this setting, both the EMA and tTG are recommended to maximize sensitivity as the antibody pattern is more variable.)

A positive test, coupled with the appropriate clinical symptoms, is highly suggestive of celiac disease. However, small intestinal (duodenal/jejunal) biopsy is still recommended to confirm the diagnosis. The classic histopathologic features of celiac disease are villous atrophy with crypt hyperplasia of the small intestinal mucosa. An increase in lamina propria chronic inflammatory cells might also be observed. This histologic pattern (often referred to as “sprue”) is not specific for celiac disease, but as celiac disease is the most common cause of this pattern in the Western world, the two terms have, in effect, become synonymous.³ A recent paper described that gluten sensitivity may be suspected in biopsies that lack the characteristic features described above.⁴ The authors report that increased numbers of intraepithelial lymphocytes distributed evenly along the villous mucosal surface (particularly if 12 or more lymphocytes were observed in the tips of several villi) was associated with gluten...
sensitivity. This finding was not specific, and “clinical correlation was necessary.” (Surprised?) In an accompanying editorial, it was suggested that small intestinal biopsies with this pattern should be signed out as “lymphocytic enteritis” or “increased intraepithelial lymphocytes suggestive of gluten-sensitive enteropathy”. “As with all ‘medical biopsies’, there is no substitute for good communication between pathologist and clinician in order to integrate the clinical, laboratory, histologic findings for the most accurate classification of the patient’s disorder.”

John D. Benson, MD

References


PI-Linked antigen replaces the Sugar-Water test

Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a disease that results in hemoglobinuria. It is manifested most prominently by dark-colored urine in the morning. The term “nocturnal” refers to the belief that hemolysis is triggered by acidosis during sleep and activates complement to hemolyze an abnormal red cell membrane. The fact of the matter is that hemolysis occurs throughout the day and is not actually paroxysmal, but the urine concentrated overnight produces the dramatic change in color. PNH results in chronic hemolysis, thrombosis, and pancytopenia and in some patients, acute or chronic myeloid leukemias.

Pathophysiology: PNH is a hematopoietic stem cell disorder which affects erythroid, granulocytic and megakaryocytic cell lines. The abnormal cells in PNH have been shown to lack glycosyl-phosphatidylinositol (GPI)-linked proteins on red cell, white cell and megakaryocytic membranes. The corresponding gene PIGA (phosphatidylinositol glycan class A) is in the X chromosome. The absence of CD59 on cell membranes is strong evidence for PNH. The red cells are sensitive to intravascular hemolysis by complement that results in anemia and hemoglobinuria. The lack of CD59 on platelet membranes induces aggregation and is highly thrombogenic, particularly in the venous system.

Lab Tests: The sugar-water (sucrose hemolysis) test is based on evidence that red cells in patients with paroxysmal nocturnal hemoglobinuria (PNH) are more susceptible to hemolysis in low ionic strength media than normal red cells. The sugar-water test was the primary screening test for PNH for many years. It is now replaced by a more sensitive and specific test that detects the acquired red cell membrane defect responsible for hemolysis. The sugar water test is no longer offered at Rex Lab. Urine hemosiderin examination detects iron in cells in the urine in hemolytic conditions but is not specific and may be positive in patients who have been transfused or have hemochromatosis.

Immunophenotyping of peripheral blood cells by flow cytometry has replaced the sugar water test. The test detects the presence or absence of CD14 (monocytes), CD55 (neutrophils), and CD59 (red cells and neutrophils) on peripheral blood cells. The Mayo Reference Lab offers the test for approximately $200. The test may be ordered through the Rex Lab as PI-linked antigen, blood (81156). Blood is drawn in a yellow-top tube (ACD) and sent overnight to Rochester, Minnesota (Mon. – Fri. only). The results are accompanied by an interpretive report and are available in 3 days. The CPT code is 88180 x 4.
References


Minimum Specimen Requirements for Quantitative Hepatic Iron

Mayo Medical Laboratories recently reported that up to 3% of all specimens submitted for quantitative iron measurement are inadequate to permit analysis.1 We have had reasonably good success in this regard with specimens submitted from our laboratory. Mayo recommends the minimum sample sizes listed below for a specimen sent for quantitative iron analysis only. We would suggest at least 2-3 times that amount so that histology and qualitative iron assessment can be performed initially. If little stainable iron is present (or if the iron is distributed predominantly in reticuloendothelial cells), quantitative iron analysis for evaluation of hemochromatosis is not indicated.2 If quantitative iron studies are desired, please indicate this on the histology requisition at the time the specimen is submitted. Specimens may be submitted in formalin. If the tissue is of borderline adequacy, the attending pathologist may discuss optimal specimen handling with the submitting physician prior to further processing.

<table>
<thead>
<tr>
<th>Type of Biopsy</th>
<th>Minimum Specimen Size (Iron Study Only)</th>
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<tbody>
<tr>
<td>18 gauge needle</td>
<td>0.3 x 10-20 mm (1/2” in length)</td>
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<tr>
<td>14 gauge needle</td>
<td>1.0 x 5-10 mm (1/4” in length)</td>
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<tr>
<td>Wedge biopsy</td>
<td>10 mg</td>
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References


For further information, call the Laboratory (784-3040). Telephone extensions are: Pathologists’ Direct Line (3201), Sharon Logue (Lab Director 2400), Robin Ivosic (Microbiology Lab Manager 3053), Elaine Patterson (Core Lab Manager 3054), Jackie Okoth (Core Lab PM Manager 4248), Diane Young (Anatomic Pathology Manager 3888), Nga Moore (Customer Service Manager 3396)