

Celiac Disease

Clinical Background

Celiac disease or gluten sensitive enteropathy is a non-allergic immune-mediated sensitivity in genetically susceptible individuals to gluten in wheat or related proteins found in barley and rye.

Epidemiology

- Incidence – 1/100-150 in the U.S.
- Age – median is 20s
- Ethnic – mainly affects Caucasians of North European ancestry

Risk Factors

- *HLA DQ2* allele (90-95%)
- *HLA DQ8* (5-10%)
- 75% concordance in monozygotic twins

Pathophysiology

- Inappropriate immune response to gluten in wheat or related proteins in barley and rye
- Celiac lesion may be characterized by increased intraepithelial lymphocytes with crypt hyperplasia and partial, subtotal or total atrophy
- tTG (tissue transglutaminase) has been identified as the major target autoantigen of the endomysial antibody (EMA)
 - tTG is an enzyme that catalyzes the replacement of amide groups of protein and peptide-bound glutamine residues by primary amines (cross-linking) as well as by hydrolysis (deamidation)
- Gliadin, a glutamine-rich protein, has been identified as a specific substrate for tTG
 - Deamidation of gliadin has been reported to improve the overall diagnostic performance of the conventional antigliadin antibody assays

Clinical Presentation

- Clinical manifestations are extremely varied and tend to differ by age group
- General symptoms – anemia, fatigue, weight loss
- Pediatrics symptoms – diarrhea, abdominal distention, malnutrition
 - Symptoms of malnutrition include
 - Short stature
 - Anemia
 - Defects in dentition
 - Failure to thrive
 - Developmental delay
- Adult symptoms – abdominal pain, flatulence, diarrhea, steatorrhea in severe cases
 - Extraintestinal features in adults include
 - Fatigue and malaise (may occur independently of anemia)
 - Neurologic or psychiatric disorders
 - Neuromuscular abnormalities
 - Infertility
 - Mouth ulcers
- Associated conditions
 - Dermatitis herpetiformis

- IgA deficiency
- Increased risk of lymphoma

Treatment

- Gluten-free diet may control celiac disease/gluten sensitive enteropathy and associated risks

Diagnosis

- Indications for testing
 - Chronic diarrhea without infectious etiology
 - Family history of celiac disease
 - Early-onset osteoporosis
 - Autoimmune disease associated with celiac disease (type I diabetes, autoimmune thyroiditis, etc.)
 - Non-autoimmune conditions associated with celiac disease (Down syndrome, Turner syndrome, etc.)
- Laboratory testing
 - tTG antibodies IgA by ELISA
 - Has been reported to have equivalent diagnostic utility as EMA IgA by IFA for celiac disease
 - Sensitivity and specificity about 98%
 - Deaminated gliadin antibodies IgA by ELISA
 - Higher sensitivity/specificity than conventional antigliadin antibody tests
 - May be present without tTG IgA antibodies
 - IgA deficiency
 - If IgA deficiency is suspected, determination of IgA levels prior to antibody testing is recommended
 - If patient is IgA deficient, all antibody testing will need to be performed using IgG tests to prevent under-diagnosis of celiac disease
 - If IgA is deficient and IgG is normal, consider evaluation for immunoglobulin deficiency
 - In some cases, tTG and/or deamidated gliadin IgG antibodies may be present despite detectable levels of IgA
 - If suspicion for celiac disease is strong and tTG IgA is negative, the presence of tTG IgG and DPG (IgA and IgG) antibodies may be clinically relevant
 - Celiac disease dual-antigen screen may be clinically useful in individuals with suboptimal IgA or IgA deficiency
 - HLA testing is not necessary for routine laboratory evaluation of celiac disease – low positive predictive value
 - May be indicated in individuals at risk for celiac disease or individuals who are repeatedly seropositive but biopsy negative
 - The absence of HLA-DQ2 or -DQ8 eliminates the risk for celiac disease
 - F-actin IgA – presence of anti-F actin antibodies in biopsy-confirmed celiac disease patients may indicate intestinal villus atrophy
 - Should be ordered only in patients with confirmed celiac disease by biopsy
- Histology
 - Duodenal biopsy – gold standard for celiac disease diagnosis
 - 4 or 5 samples should be taken to increase probability
 - Intestinal damage is assessed by a modified Marsh score
 - Scores range from 0, 1, 2, 3a to 3c
 - Only Marsh scores 2 and above are considered clinically significant
 - Patient should not be on a gluten-free diet at time of biopsy

- Criteria for diagnosis
 - Positive EMA or tTG IgA serologic test
 - Positive tissue biopsy
 - Complete resolution of clinical symptoms and/or a seronegative response following a gluten-free diet
 - Gluten rechallenge not necessary except in patients who had no initial biopsy or uncharacteristic biopsy

Prognosis

- Anti-actin IgA (F-actin) levels correlate with severity of mucosa damage and may indicate moderate to severe disease

Differential Diagnosis

- Irritable bowel syndrome
- Inflammatory bowel disease
- Malabsorption
- Malnutrition
- Colorectal cancer

Monitoring

- Antibody titers
 - Usually wane after patient adheres to diet
 - Will become elevated again if gluten reintroduced

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Celiac Disease Reflexive Panel 0051065 Method: Nephelometry/Indirect Fluorescent Antibody/Enzyme-Linked Immunosorbent Assay	Preferred panel for celiac disease diagnosis (panel includes IgA, tissue transglutaminase antibodies and deamidated gliadin peptide antibodies)	Test results alone are not diagnostic; biopsy recommended for a diagnosis of celiac disease/gluten sensitive enteropathy Panel not recommended for follow-up testing in confirmed celiac disease patients	
Celiac Disease Dual Antigen Screen with Reflex 2002026 Method: Nephelometry/Indirect Fluorescent Antibody/Enzyme-Linked Immunosorbent Assay	May be indicated for patients with IgA deficiency or suboptimal IgA levels, especially in pediatric patients Panel includes celiac disease dual-antigen screen; tissue transglutaminase antibodies IgA and IgG; and gliadin peptide antibodies IgA and IgG		

<p>Tissue Transglutaminase Antibody, IgA 0097709</p> <p>Method: Enzyme-Linked Immunosorbent Assay</p>	<p>Preferred screening assay for suspected celiac disease patients who are not IgA deficient</p>	<p>Certain individuals, particularly children <3 years, may test negative for tTG IgA antibodies</p> <p>Not recommended for individuals with suboptimal IgA or IgA deficiency</p> <p>Test results alone are not diagnostic; biopsy recommended for a diagnosis of celiac disease/gluten sensitive enteropathy</p>	<p>If positive and celiac disease confirmed, test may be useful in monitoring compliance to gluten-free diet</p>
<p>Deamidated Gliadin Peptide (DGP) Antibody, IgA 0051357</p> <p>Method: Enzyme-Linked Immunosorbent Assay</p>	<p>Certain individuals, particularly children <3 years who test negative for tTG and/or EMA antibodies, may be positive for gliadin IgA and/or IgG antibodies</p>	<p>Test results alone are not diagnostic, biopsy recommended for a diagnosis of celiac disease/gluten sensitive enteropathy</p>	<p>If positive and celiac disease confirmed, test may be useful in monitoring compliance to gluten-free diet</p>
<p>Tissue Transglutaminase Antibody, IgG 0056009</p> <p>Method: Enzyme-Linked Immunosorbent Assay</p>	<p>Screen for celiac disease in patient who is IgA deficient or has suboptimal IgA levels</p>	<p>Test results alone are not diagnostic; biopsy recommended for a diagnosis of celiac disease/gluten sensitive enteropathy</p> <p>Certain individuals, particularly children <3 years who test negative for tTG and/or EMA antibodies, may be positive for gliadin IgA and/or IgG antibodies</p>	<p>If positive and celiac disease confirmed, test may be useful in monitoring compliance to gluten-free diet</p>
<p>Deamidated Gliadin Peptide (DGP) Antibody, IgG 0051359</p> <p>Method: Enzyme-Linked Immunosorbent Assay</p>	<p>Screen for celiac disease in patient who is IgA deficient or has suboptimal IgA levels</p>	<p>Test results alone are not diagnostic, biopsy recommended for a diagnosis of celiac disease/gluten sensitive enteropathy</p> <p>Certain individuals, particularly children <3 years who test negative for tTG and/or EMA antibodies, may be positive for gliadin IgA and/or IgG antibodies</p>	<p>If positive and celiac disease confirmed, test may be useful in monitoring compliance to gluten-free diet</p>

<p>Celiac Disease Dual Antigen Screen 0051689</p> <p>Method: Enzyme Linked Immunosorbent Assay</p>	<p>Screen for at-risk individuals with deficient or suboptimal IgA levels</p>		<p>If positive, individual tTG and gliadin peptide antibody assays must be performed</p>
<p>F-Actin (Smooth Muscle) Antibody, IgA 0051724</p> <p>Method: Enzyme-Linked Immunosorbent Assay</p>	<p>Identify a subset of celiac disease patients with more severe intestinal mucosa damage</p> <p>Monitor disease activity and adherence to gluten-free diet in patients with biopsy-proven celiac disease</p>	<p>Should not be used to screen for celiac disease</p> <p>Does not replace intestinal biopsy for confirming celiac disease</p>	<p>If positive and celiac disease confirmed, test may be useful in monitoring compliance to gluten-free diet</p>

Additional Tests Available

Test Name and Number	Comments
<p>Reticulin Antibody, IgA with Reflex to Titer 0050698</p> <p>Method: Indirect Fluorescent Antibody</p>	<p>Not recommended for celiac disease testing</p> <p>Use tTG testing</p>
<p>Reticulin Antibody, IgG 0098878</p> <p>Method: Indirect Fluorescent Antibody</p>	<p>Not recommended for celiac disease testing</p>
<p>Immunoglobulin A, Serum 0050340</p> <p>Method: Nephelometry</p>	<p>IgA results determine whether to use IgA or IgG tTG and DGP assays</p>
<p>Tissue Transglutaminase Antibody, IgA with Reflex to Endomysial Antibody, IgA Titer by IFA 0050734</p> <p>Method: Enzyme-Linked Immunosorbent Assay/Indirect Fluorescent Antibody</p>	<p>Screen for celiac disease in patients who are not IgA deficient</p> <p>Certain individuals, particularly children <3 years who test negative for tTG and/or EMA antibodies, may be positive for gliadin IgA and/or IgG antibodies</p> <p>tTG IgA and EMA IgA have equivalent diagnostic utility for celiac disease</p>
<p>Deamidated Gliadin Peptide (DGP) Antibodies, IgA & IgG 0051358</p> <p>Method: Enzyme-Linked Immunosorbent Assay</p>	<p>Certain individuals, particularly children <3 years who test negative for tTG and/or EMA antibodies, may be positive for gliadin IgA and/or IgG antibodies</p> <p>Test results alone are not diagnostic; biopsy recommended for a diagnosis of celiac disease/gluten sensitive enteropathy</p>

Additional Information

Antigliadin antibodies may be found in healthy individuals as well as individuals with other inflammatory bowel conditions.

Guidelines

Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. New York State Department of Health - State/Local Government Agency [U.S.]. 2005 January.

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Diagnostic Algorithm(s)

PDF algorithm(s) available at www.arupconsult.com.

Celiac Disease or Gluten Sensitive Enteropathy Testing Algorithm

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