

JAMA Diagnostic Test Interpretation

Antitissue Transglutaminase IgA for Celiac Disease Testing

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A 23-year-old woman presented for assessment of positive celiac disease serologic testing. The testing was performed at the patient's request because her 15-year-old brother was diagnosed with celiac disease. Based on her test results, the patient was advised to commence a gluten-free diet. However, she believed that a small intestinal biopsy would be appropriate to confirm her diagnosis and sought another opinion.

The patient did not report any symptoms. She was the eldest of 6 children who were healthy except for the 1 sibling with celiac disease. Her mother had a history of thyroid cancer. Results of her physical examination were normal except for dental enamel defects (with both color and structural changes; **Figure**). Her body mass index (calculated as weight in kilograms divided by height in meters squared) was 21, and her level of 25-hydroxyvitamin D was low at 18 ng/mL (reference range, 20-50). There was no evidence of other vitamin or mineral deficiency, anemia, or thyroid dysfunction.

Celiac disease testing revealed antitissue transglutaminase (anti-tTG) IgA 124 U (reference range, 0-19).



Figure. Dental enamel defects showing both color and structural changes (arrowheads).

HOW WOULD YOU INTERPRET THESE TEST RESULTS?

- A.** Antibody testing should be repeated.
- B.** Celiac disease is unlikely because of the absence of symptoms.
- C.** The test results are consistent with celiac disease. No further testing is needed.
- D.** The test results are suggestive of celiac disease. Upper endoscopy with duodenal biopsy is required to confirm the diagnosis.

Answer

D. The test results are suggestive of celiac disease. Upper endoscopy with duodenal biopsy is required to confirm the diagnosis.

Test Characteristics

Anti-tTG is a common initial serologic test for celiac disease. Using duodenal villous atrophy as the criterion standard, the sensitivity of anti-tTG is 98% (range, 78%-100%), and the specificity is 98% (range, 90%-100%).¹ False-negative results can occur in patients with selective IgA deficiency, those following a gluten-restricted diet, and in patients with seronegative celiac disease.² Based on a US population prevalence of celiac disease of 0.7% to 0.8%, the positive predictive value of anti-tTG testing in an unselected population is 33%.³ However, among high-risk groups (such as first-degree relatives) the positive predictive value of anti-tTG testing is 72%.¹

Patients with any elevation in anti-tTG value should undergo esophagogastroduodenoscopy while maintaining a gluten-containing

diet to determine whether they have celiac disease.^{4,5} Guidelines issued by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)⁶ identify a subset of children for whom the diagnosis of celiac disease can be made without a confirmatory biopsy. According to these guidelines, these children must be symptomatic with an elevated anti-tTG value greater than 10 times the upper limit of normal, have a second confirmatory serologic test (antiendomysial antibody), and an HLA haplotype of DQ2 or DQ8, compatible with celiac disease.⁶ These European guidelines have not been adopted in US pediatric guidelines⁵ and do not apply to adults. Moreover, this patient is asymptomatic with an anti-tTG elevation that is less than the threshold specified by the ESPGHAN criteria.

Symptomatic patients with a high likelihood of celiac disease should undergo duodenal biopsy regardless of anti-tTG testing, given its imperfect sensitivity. This serologic test is instead valuable in determining, among patients at low or intermediate risk of celiac disease, the need for confirmatory duodenal biopsy.

Application of Test Result to This Patient

This patient was screened for celiac disease based on her family history. A meta-analysis found a pooled prevalence of 7.5% in first-degree relatives.⁷ First-degree relatives may be offered screening even if asymptomatic due to the protean manifestations of celiac disease, including effects on bone density that may not be clinically noted until severe. Screening at-risk groups is the mode of presentation in 25% of children and 10% of adults with celiac disease.⁸ Although the patient was asymptomatic, her dental enamel defects may be a manifestation of longstanding celiac disease.⁹

If a patient's biopsy shows villous atrophy, the diagnosis is confirmed and a gluten-free diet should be prescribed under the guidance of an expert dietitian. A normal biopsy or less-specific histologic abnormalities, such as increased intraepithelial lymphocytosis with normal villous architecture, suggests either that the anti-tTG showed false-positive results or that the patient has potential celiac disease, which has an unpredictable natural history and may evolve into the full clinical phenotype over time.¹⁰

Alternative Diagnostic Testing Approaches

The antibody to deamidated gliadin peptide (DGP) has a sensitivity (88%) and specificity (95%) that are somewhat lower than that of anti-tTG. The DGP antibody has an IgG subtype that can be useful in testing for celiac disease among patients with selective IgA deficiency.¹

Another approach to the asymptomatic first-degree relative is to choose not to test for celiac disease. Although routine screening of first-degree relatives is recommended by the North American

Society for Pediatric Gastroenterology, Hepatology, and Nutrition,⁵ guidelines for adults state that testing asymptomatic first-degree relatives is "reasonable but controversial," given the uncertain natural history of untreated asymptomatic celiac disease and is appropriate for shared decision making.⁴

Patient Outcome

Findings from the upper gastrointestinal endoscopy showed reduced duodenal folds and scalloping of folds. Duodenal biopsy revealed total villous atrophy consistent with celiac disease. The patient began a gluten-free diet under dietitian guidance. At 6-month follow-up, she remains asymptomatic.

Clinical Bottom Line: Anti-tTG Testing in First-Degree Relatives of Patients With Celiac Disease

- First-degree relatives of patients with celiac disease have an increased prevalence of celiac disease (7.5%).
- Given the potential for false-positive and false-negative serologic testing, an esophagogastroduodenoscopy with duodenal biopsy is recommended for patients with an elevated anti-tTG.
- The natural history of asymptomatic celiac disease is uncertain. Screening of first-degree relatives is offered because of the protean manifestations that may not be clinically apparent until severe.
- After the diagnosis of celiac disease is confirmed by duodenal biopsy, treatment should be initiated with a strict gluten-free diet under the guidance of an expert dietitian.

ARTICLE INFORMATION

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