Serologic Evaluation of Celiac Disease for Patients Younger Than 2 Years of Age

The rising prevalence of pediatric celiac disease[1,2] and the variability in presentation[3] has prompted research and led to the evolution of published guidelines[4-8] regarding recognition and accurate diagnosis. The diagnosis is challenging because celiac disease causes an array of symptoms or no symptoms at all. Also, histopathologic findings of duodenal biopsies consistent with celiac disease are seen in other common and uncommon pediatric intestinal diseases, such as Crohn's disease, viral gastroenteritis, autoimmune enteropathy, and food protein–induced enteropathy,[9-11] and although symptomatic response to gluten-free diet is a defining characteristic of celiac disease, it is subjective and nonspecific.[12,13]

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Serologic evidence of celiac autoimmunity is a crucial piece of the diagnostic puzzle for most patients. Serologic testing has evolved, and currently the recommended initial screening test for celiac disease in children and adults is tissue transglutaminase (TTG) immunoglobulin A (IgA).[5,7] However, observations in pediatric patients raised concerns about lower sensitivity of TTG IgA for detecting celiac disease in infants and young children.[14-16] These concerns underpinned recommendations to obtain complementary serologic testing, especially deamidated gliadin peptide (DGP) immunoglobulin (IgG), to increase screening and diagnostic sensitivity.[7] In this volume of *The Journal*, Khan et al addressed whether TTG IgA is a sufficient screening tool to evaluate for celiac disease in infants and children 24 months or younger.[17] The authors performed a retrospective chart review of patients younger than the age of 24 months with histopathologic findings suggestive of celiac disease at 3 large children's hospitals in the US (Boston Children's Hospital, Nationwide Children's Hospital, and Mayo Clinic). Patients were classified as either having celiac disease or as non-celiac controls based on published diagnostic criteria for celiac disease,[7] including dietary exposure to gluten, positive celiac serology, consistent histopathology, and response to gluten-free diet. Most of the patients had TTG IgA results available (celiac disease, 115/127; controls, 19/23). Of those who had TTG IgA levels available, 97% (112/115) of the patients with celiac disease and none of the controls had elevated TTG IgA levels. These data offer compelling support for TTG IgA and a total IgA as the appropriate initial screening tests to evaluate for celiac disease in infants and children 24 months or younger. Although a high percentage of patients with celiac disease had elevated TTG IgA, several patients with celiac disease (15/127) were diagnosed based on other serologic tests, specifically, IgG-based tests. Thus, clinicians who strongly suspect celiac disease, based on clinical presentation and/or histologic findings, are justified to delve further.

In this study, there was a limited number of patients with celiac disease and negative TTG IgA, making it difficult to assess which complementary serologic tests to obtain in infants and children 24 months or younger. Antigliadin antibody IgA was previously proposed[15] but has since been abandoned.[7] DGP IgG has been proposed[8] because some studies show high sensitivity, especially in patients who are IgA deficient.[18] One study suggested that DGP IgG elevation may precede TTG IgA in screening infants and young children with celiac disease.[19] DGP IgG was the test that secured the diagnosis in 1 of the 3 patients who were TTG IgA negative in the study by Khan et al, but it was elevated in 2 controls as well. For each of these 2 false positives, the level was only mildly elevated, 20.8 and 31.3 (ULN 20 units), and compelling arguments were given to exclude celiac disease for both—one had no clinical or histologic response to a gluten-free diet and the other was never exposed to gluten. Because so few subjects had DGP IgG tested, this study does not provide sufficient data to determine sensitivity and specificity for this test but reinforces concerns about false positives.

A few other interesting findings are reported. First, the data show at least 39% of controls without celiac disease have HLA antigen genotypes that confer celiac risk. This reinforces the maxim that finding risk alleles does not indicate a diagnosis. They also present data that informs the use of endomysial antibody (EMA) which, for those who had the test performed, was negative in all control patients, negative in 13 of 66 (19.7%) patients with celiac disease, and positive in only 53 of 66 (80.3%). These data accord with other studies that indicate high specificity of EMA but inferior sensitivity to TTG IgA.[20]

The main limitations of the study are its retrospective nature and missing serologic information for some patients. These limitations preclude robust comparison of DGP IgG and TTG IgA in this age group. Prospective studies that compare TTG IgA, DGP IgG, and EMA, or perhaps evaluate the utility of subsequent blood draws in patients with mildly elevated serologies, may address questions about the best

DGP	Deamidated gliadin peptide
EMA	Endomysial antibody
IgA	Immunoglobulin A
IgG	Immunoglobulin G
TTG	Tissue transglutaminase

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next serologic test for patients younger than 2 years old with normal TTG IgA and suspected celiac disease based on clinical symptoms or histologic findings. Despite the limitations of this study, it reinforces that TTG IgA was able to identify 97.5% of infants and children younger than 24 months old with celiac disease. TTG IgA may be the test to start, but appreciating that it is not 100% sensitive, it may not be appropriate to stop there. Making a diagnosis of celiac disease in a young child has lifelong implications and requires careful assembly of multiple pieces of a puzzle. Including young children and infants in broad recommendations to obtain TTG IgA as the first test simplifies where to start with the serology piece. ■

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