The Race for the Diagnostic Autoantibody in Celiac Disease. And the Winner is...

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Celiac disease is an autoimmune enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. The classical clinical manifestation of malabsorption, diarrhea and weight loss represents only one-third of the entire wide spectrum of gluten-sensitized people [1]. The rest, who constitute the submerged part of the celiac disease iceberg, are asymptomatic individuals, termed *latent* celiac disease patients. However, those with a wide variety of manifestations represent the non-classical celiac population, and are detected by serological screening [2,3]. The advent of new serological markers, such as antigliadin or anti-endomysial antibodies, for the diagnosis and detection of celiac disease has uncovered the previously unrecognized atypical and hyposymptomatic patients.

Furthermore, a new aspect of potential celiac disease has emerged. Consanguinity (first-degree relatives), other autoimmune diseases, and several hereditary genetic disorders (trisomy 21, Turner's syndrome, etc.) have increased incidence of the disease. Other factors such as type of cow's milk formula, breast-feeding, age at gluten introduction, quantity of gluten, and quality of cereals may affect the clinical presentation [4]. In light of the above, and since the definite diagnosis is based on an invasive procedure like endoscopy, a reliable non-invasive screening tool is sorely needed. The use of serological markers to detect those patients who should have a jejunal biopsy is essential.

The three antibodies that were used until recently were antigliadin, antireticulin and anti-endomysial antibodies. Antigluten antibodies are age and gluten intake dependent, and genetically influenced [5–7]. The sensitivity and specificity of immunoglobulin-G antigluten antibody are 82–100% and 50–100% and of IgA antigluten antibody 52–99.9% and 65–100% respectively [8,9].

IgA antireticulin antibodies are more specific (59–100%) than sensitive (30–95%) in celiac disease [9]. The reported sensitivity for IgA AEA in adult patients with untreated celiac disease is 68–100% and in untreated celiac children 85–100%. Its specificity may be as high as 99.7–100% [8–10], thus emerging as the most reliable serological marker for this disease.

Nevertheless, several ethical and technical problems remain. For example, the substrate used for the detection of AEA is monkey esophagus. Since this is an endangered species, an alternative had to be found and the substrate was changed to human umbilical cord. The technical problems, however, are yet to be resolved. The immunofluorescence technique currently used is cumbersome, expensive and inter-observer dependent. In practice, the test is somewhat laborious and not well suited for large-scale screening. Furthermore, the lack of standardization of the AEA assay may lead to unacceptable variability among laboratories that perform this test [11].

A step toward unraveling the puzzle of celiac disease was taken by Dieterich et al. [12] who identified tissue transglutaminase as the antigen recognized by AEA. The detection of IgA autoantibody to tTG in the serum of celiac patients represents a potential tool for the diagnosis and follow-up of the disease [12–15].

In this issue of the Journal, Levine et al. [16] describe an improved enzyme-liked immunoassay that detects serum antitransglutaminase antibodies in celiac children compared to AEA. This study is the first to be published on the celiac disease population in Israel, and the authors should be congratulated. They found a sensitivity and specificity of 90% for antitransglutaminase antibodies compared to 100% and 94% respectively for AEA. They concluded that the tTG-based ELISA test is both sensitive and specific for detection of celiac disease.

The question is, which serological marker for the diagnosis of celiac disease will win the race? The antitransglutaminase antibodies test appears to be more objective but does not reach the reliability of its competitor. However, there is room for improvement. The available antigen used for the ELISA is a commercial guinea pig tTG that is both non-human and impure. The recent cloning of the human tTG is a further advance. The preliminary data suggest that the human tTG-based assay is a highly specific (100%) and, more importantly, sensitive (99%)

AEA = anti-endomysial antibodies

tTG = tissue transglutaminase

screening test [17,18]. Do anti-tTG antibodies have a pathogenic role in celiac disease, or do they function as bystander antibodies in the plethora of autoantibodies found in celiac patients' sera? [19]. Most recently, IgA from sera of untreated celiac patients inhibited fibroblast-induced transforming growth factor-beta 1-mediated differentiation of deep crypt T84 epithelial cells. These IgA, reactive for tTG, significantly inhibited intestinal epithelial cell differentiation and induced epithelial cell proliferation, thus mimicking the gluten-triggered jejunal mucosal lesion in celiac disease [20].

In summary, the new antitransglutaminase antibody is a major step toward improved diagnosis of celiac disease and most probably plays a role in the induction of the intestinal injury. With some technical improvement and the use of humanized antigenic substrate, it stands to win the title of the chosen antibody, to replace the gold standard intestinal biopsy for the diagnosis of gluten-sensitive enteropathy.

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Capsule

Lamivudine: promising new treatment for hepatitis B

Lamivudine is a cytidine dideoxynucleoside analogue that inhibits HBV reverse trasncriptase in order to decrease viral DNA synthesis. After a year of treatment, HBV DNA becomes undetectable by molecular hybridization in 80% of patients; however, supercoiled HBV DNA intermediates within hepatocytes are resistant to treatment and relapse occurs when treatment is stopped. Other drugs, such as famciclovir, lobucavir and adeforvir, are either less potent or have been evaluated less completely than lamivudine. Lamivudine has shown histological improvements in 38--52% of treated patients. It also increases liver function and stops the progression of fibrosis. However, long-term toxicity is not known, and resistance, the major risk of chronic use, may be induced by lamivudine monotherapy. Single-agent therapy is simple, cheap and potentially less toxic than combination therapy, nonetheless synergistic antiviral agents should be explored.

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