Celiac disease

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Wheat flour had been suspected as the cause of celiac disease in children by the Dutch pediatrician WK Dicke (1) during feeding studies in the 1930s. He became convinced of the observations during World War II when Holland was occupied by German forces. Children with celiac disease who had improved on a diet supplemented with tulip bulbs became ill when the occasional rusk became available. Furthermore, at the end of the war, when Swedish bread was airlifted into Holland, the children became ill again. During the 1950s, further feeding studies in a number of European centres showed that the toxic substances were the prolamins in wheat (gluten), rye (secalin) and barley (hordein). There has been a long debate about the toxicity of oats, but the most vigorous studies to date show that they are safe (2,3). Thus, treatment with a diet lacking wheat, barley and rye has become a universal practice. With earlier definitions of celiac disease, rechallenge with gluten was required to demonstrate histological relapse. This is now rarely done, but this experience with rechallenges served to establish that 'once a celiac, always a celiac'. Thus, without a single placebo controlled, randomized, clinical trial, a lifetime of gluten-free diet has become the standard recommendation.

Why certain individuals are susceptible to gluten and the mechanisms by which this results in intestinal inflammation are still unclear. More than 90% of patients with celiac disease possess human leukocyte antigen (HLA)-DQ2, and most of the remainder possess HLA-DQ8. Other non-HLA genes may also be involved, but three published sibling pair linkage studies (4-6) did not agree on the location of these genes in the genome. Many attempts have been made to determine which sequence of alpha-gliadin is toxic (gliadin is an alcoholic extract of gluten that can be separated into alpha, beta, gamma and omega fractions by electrophoresis). Two recent studies have independently, using different methodologies, identified a sequence that appears to be a dominant peptide for inducing a T-cell response (7,8). This response is DQ2-restricted but only occurs once a specific glutamine within the sequence is converted to glutamate by tissue transglutaminase. This enzyme has been identified as

the antigen to which the antiendomysial antibody is directed and appears to be crucial in the initiation of both T-cell and B-cell responses to wheat proteins.

Antiendomysial antibodies are detected by immunofluorescence with the use of monkey esophagus or human umbilical cord, and stain the endomysium of smooth muscle. They have been shown to be more than 90% sensitive and specific for untreated celiac disease. Antibodies disappear from serum within a year of being on a strict gluten-free diet, and hence can be used as a test for compliance. With the identification of transglutaminase as the antigen, a number of ELISAs have been developed to replace the more labour-intensive immunofluorescent assay. These tests will allow easier diagnosis of celiac disease – in particular for screening high risk populations. So far, the ELISA appears to give results equivalent to those from tests using antiendomysial antibody, as shown by a variety of studies (9-13), including a study from Vancouver, British Columbia, published in this issue of *The Canadian Journal of Gastroenterology* (pages 669-672).

The apparent prevalence of celiac disease has undoubtedly increased since the availability of reliable antibody tests, and the true prevalence appears to be approximately 0.5% in Europe and North America. Early diagnosis and, hence, early introduction of a gluten-free diet are particularly important for preventing osteoporosis later in life (14). This makes screening of high risk groups even more important; screening of patients with type I diabetes, which is known to be associated with celiac disease, revealed 10% to have transglutaminase antibodies (15). Gillet et al (pages 669-672) report the results of screening a large cohort of patients with primary biliary cirrhosis. Although not all patients with positive antibodies had had a biopsy, all five who had biopsies were shown to have celiac disease. On the basis of published data (see above), it seems likely that most of the remaining patients with positive antibodies will also turn out to have celiac disease – an important observation in a disease such as primary biliary cirrhosis in which osteoporosis is common. Clearly, it is important to screen populations of patients with 'idiopathic' osteoporosis.

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REFERENCES

1. Dicke WK. Investigation of the harmful effects of certain types of cereal on patients with celiac disease (Thesis). Utrecht, 1950.
2. Janatuinen EK, Pikkarainen PH, Kempainen TA, et al. A comparison of diets with and without oats in adults with celiac disease. *N Engl J Med* 1995;333:1033-7.
3. Hardman CM, Garioch JJ, Leonard JN, et al. Absence of toxicity of oats in patients with dermatitis herpetiformis. *N Engl J Med* 1997;337:1884-7.
4. Zhong F, McCombs CC, Olson JM, et al. An autosomal screen for genes that predispose to celiac disease in the western counties of Ireland. *Nat Genet* 1996;14:329-33.
5. Houlston RS, Tomlinson IP, Ford D, et al. Linkage analysis of candidate regions for coeliac disease genes. *Hum Mol Genet* 1997;6:1335-9.
6. Greco L, Corazza G, Babron MC, et al. Genome search in celiac disease. *Am J Hum Genet* 1998;62:669-75.
7. Arentz-Hansen H, Korner R, Molberg O, et al. The intestinal T cell response to alpha-gliadin in adult celiac disease is focused on a single deamidated glutamine targeted by tissue transglutaminase. *J Exp Med* 2000;19:603-12.
8. Anderson RP, Degano P, Godkin AJ, Jewell DP, Hill AV. In vivo antigen challenge in celiac disease identifies a single transglutaminase-modified peptide as the dominant A-gliadin T-cell epitope. *Nat Med* 2000;6:337-42.
9. Williams AJ, Annis P, Lock RJ, Unsworth DJ, Gale EA, Bingley PJ. Evaluation of a high-throughput second antibody radiobinding assay for measuring IgA antibodies to human tissue transglutaminase. *J Immunol Methods* 1999;228:81-5.
10. Lock RJ, Pitcher MC, Unsworth DJ. IgA anti-tissue transglutaminase as a diagnostic marker of gluten sensitive enteropathy. *J Clin Pathol* 1999;52:274-7.
11. Miller A, Paspaliaris W, Elliott PR, d'Apice A. Anti-transglutaminase antibodies and coeliac disease. *Aust N Z J Med* 1999;29:239-42.
12. Amin M, Eckhardt T, Kapitza S, et al. Correlation between tissue transglutaminase antibodies and endomysium antibodies as diagnostic markers of coeliac disease. *Clin Chim Acta* 1999;282:219-25.
13. Bazzigaluppi E, Lampasona V, Barera G, et al. Comparison of tissue transglutaminase-specific antibody assays with established antibody measurements for coeliac disease. *J Autoimmun* 1999;12:51-6.
14. McFarlane XA, Bhalla AK, Robertson DA. Effect of a gluten free diet on osteopenia in adults with newly diagnosed coeliac disease. *Gut* 1996;39:180-4.
15. Lampasona V, Bonfanti R, Bazzigaluppi E, et al. Antibodies to tissue transglutaminase C in type I diabetes. *Diabetologia* 1999;42:1995.