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CLINICAL PEARLS UPDATE#3

Wheat, Glutens, Gliadins, and Delayed Food Allergies

September 15, 2003

Dear Colleague:

Gluten, gliadin, and wheat delayed hypersensitivity / allergy responses are linked to the enteropathy associated with coeliac syndromes and cause suffering for 2-plus million Americans. Successful comprehensive management using LRA by ELISA/ACT[®] tests and treatment plans are illustrated in the attached 'case report.'

Functional, *ex vivo* lymphocyte response assays (LRA by ELISA/ACT) offer the most advanced tests available for determination of the individual's responses to the widest available range of substances tested by any lab in the world.

We are grateful for the opportunities to be of service to you and your patients.

Sincerely,

Russ Jaffe, MD, Ph.D., CCN, NACB
Lab Director

Wheat proteins are collectively called "gluten." Immunoreactive wheat / gluten-related antigens include: glutenin (gluten polypeptide), gliadin (prolamines), and a variety of wheat glycoproteins.

Wheat / gluten-related antigens are found in:

- wheat, including Kamut and such wheat-derived grains as spelt, teff, and triticale,
- rye,
- barley,
- oats,
- malt, and
- bran.

Thus, if one is immunoreactive to gluten or gliadin (in contrast to other wheat antigens) then it is wise to substitute for all gluten-containing grains if enteropathy is diagnosed or clinically suspected and until immune tolerance is restored.

Gluten is not found in grasses such as:

- corn,
- rice,
- wild rice,
- quinoa,
- millet,
- amaranth, and
- buckwheat.

This assumes that one is tolerant to and not immunoreactive to these items. LRA by ELISA/ACT tests can determine which items are immune tolerant and which are immune reactive for each individual.

Below are abstracts of two recent articles that illustrate the need for comprehensive, advanced, functional tests that measure the key T lymphocyte as well as distinguish reactive from protective antibody responses for better, sustained successful outcomes.

Mowat AM. Coeliac disease--a meeting point for genetics, immunology, and protein chemistry. *Lancet* 2003;361(9365):1290-1292.

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CONTEXT: Coeliac disease is caused by a genetically determined, specific immune response to antigens present in wheat gluten. This immune response may be focused on a limited region of the alpha gliadin component of gluten, and previous studies have suggested that the generation of epitopes for recognition by CD4+ T cells requires deamidation of the protein by tissue transglutaminase. However, it had not previously been shown that candidate epitope peptides could be generated from gluten *in vivo*, or that these epitopes were selective products of physiological digestion of gluten by tissue transglutaminase. Starting point: Lu Shan and colleagues (*Science* 2002; 297: 2275-79) have recently shown that a 33-mer peptide containing known peptide epitopes is generated by digestion with intestinal enzymes *in vivo* and *in vitro*, producing a highly stimulatory antigen for CD4+ T cells. The resulting peptide is resistant to further digestion of a gliadin by intestinal brush border enzymes



and is a highly specific substrate for deamidation by tissue transglutaminase. Because the 33-mer peptide is not present in cereal proteins that do not cause coeliac disease, Shan and colleagues suggest that generation of this peptide in vivo underlies the specific association between gluten, immune responsiveness, and tissue transglutaminase in coeliac disease. In addition, the 33-mer peptide can also be produced by digestion of gluten by bacterial prolyl endopeptidases, suggesting possible future strategies for generating non-toxic varieties of gluten. Where next? It is now important to determine whether this 33-mer peptide and this pathway account for all immune recognition of wheat gluten in coeliac disease and to explore if the tissue transglutaminase homologues found in other organisms can be used to produce non-toxic preparations of wheat.

Lee SK, Lo W, Memeo L, Rotterdam H, Green PH. Duodenal histology in patients with coeliac disease after treatment with a gluten-free diet. *Gastrointest Endosc* 2003;57(2):187-191.

Department of Surgical Pathology and Medicine, Columbia University College of Physicians and Surgeons, New York, New York, USA.

BACKGROUND: The diagnosis of coeliac disease requires characteristic histopathologic changes in an intestinal biopsy with clinical improvement in response to a gluten-free diet. Endoscopy with procurement of biopsy specimens is often performed to document response to the diet, but there are little data on the appearance of treated coeliac disease. This study examined the endoscopic and histopathologic appearance of the duodenum of patients with coeliac disease whose diet was gluten-free.

METHODS: A cohort of 39 adult patients (mean age 52 years, range 20-74 years) with biopsy-proven coeliac disease was retrospectively reviewed. All had responded clinically to a gluten-free diet that they had maintained for a mean of 8.5 years (range 1-45 years). The endoscopic and histopathologic appearances of the duodenal mucosa were reviewed. Blinded review of the diagnostic (initial) and post-treatment biopsy specimens was also performed to assess response of individual patients to the diet.

RESULTS: The endoscopic appearance was normal in 23%, reduced duodenal folds were present in 46%, scalloping of folds in 33%, mucosal fissures in 44%, and nodularity in 33%. There was more than 1 abnormality present in 46%. Histology was normal in only 21%. The remainder had villous atrophy (69% partial, 10% total). Paired (diagnostic and follow-up) biopsy specimens were reviewed blindly for 12 patients. The mean (SD) intraepithelial lymphocyte count fell from 61 (22) to 38 (17) (normal <30 per 100 epithelial cells), and the crypt-to-villous ratio improved although it did not normalize.

CONCLUSIONS: Despite a good clinical response, abnormal endoscopic and histopathologic appearances persist in the majority of patients with coeliac disease treated with a gluten-free diet.

Note: We believe the comprehensive optional treatment guide, available for inclusion with LRA by ELISA/ACT tests, if requested, provides the best current therapy for sustained remissions and intestinal repair. Enteropathy reflects cumulative repair deficits in the intestinal mucosa that comprehensive management may reverse, restoring healthy digestive and mucosal function.

