



## Food Research Institute

UNIVERSITY OF WISCONSIN–MADISON

### **FRESH Seminar: “Update on Food Allergy: New and Old Syndromes”**

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MADISON, Wis. (FRI) – Three topics related to food allergies (alpha-gal reactions, bird-egg syndrome, and celiac disease/gluten sensitivities) were discussed by FRI Affiliated Faculty member Robert Bush, MD at a recent FRESH seminar.

#### **Alpha-gal reactions, IgE, and parasites**

In 2008, a study was published in the *New England Journal of Medicine* that described an unusual anaphylactic reaction to the cancer drug cetuximab. Cetuximab is a chimeric monoclonal antibody in which part of a murine antibody is replaced with a human sequence to prevent humans taking the drug from having an immune response to the drug. The study reported that a very high percentage of patients (25/76) experienced an anaphylactic reaction after taking their first dose of drug. This was very surprising, as a patient would normally have had some prior exposure to a substance to generate such a strong immune response.

The investigators learned that the frequency of the anaphylactic response varied dramatically depending on the geographical home of the patients, with patients from the southeastern U.S. exhibiting the highest frequency of anaphylactic reaction. They also learned that the IgE molecules generated in the patients with the anaphylactic reactions were directed against an oligosaccharide on the Fab portion of the heavy chain of the monoclonal antibody.

The oligosaccharide eliciting the response was identified as galactose- $\alpha$ -1,3-galactose, also known as “alpha-gal.” Alpha-gal is found in many places, including cat IgA molecules, meat-derived gelatin, numerous heat-stable beef proteins, and proteins found in bovine and porcine heart valves (which are used therapeutically to replace defective heart valves in humans). Interestingly, the study also showed many (15/72) control patients who had never taken cetuximab also had serum IgE antibodies against alpha-gal.

In 2009, another study was published describing an anaphylactic reaction occurring in 24 patients in the southeastern U.S. after eating red meat. The reaction was unusual in that it occurred 4–6 hours after eating the meat, whereas most anaphylactic reactions associated with food allergies occur within minutes. The patients were shown to have IgE antibodies that reacted with beef, pork, lamb, cow’s milk, cats, and dogs, but not to chicken, turkey, or fish. Just as in the case of the cetuximab patients, the response was shown to be specific for alpha-gal. The delayed onset of anaphylactic symptoms with meat



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was hypothesized to have been caused by the need for protein digestion to occur before alpha-gal could be released into the serum to trigger the response.

Based on patient history, a number of risk factors for the reaction to red meat was established. A large percentage of the patients had reported being bitten by a tick. Alpha-gal is found in two varieties of ticks: the lone star tick (found in the southeastern U.S.) and the castor bean tick. It is possible that the patients reacting to cetuximab may also have had prior exposure to alpha-gal through lone star tick bites, consistent with the geographical occurrence of the reaction.

IgE, which is responsible for allergic reactions, is believed to protect against parasites. Ticks are major carriers of parasites. The human body may have evolved to have such reactions to alpha-gal as a way to protect against parasites from ticks.

### **Bird-Egg Syndrome**

Bird-egg syndrome is characterized by respiratory symptoms in response to exposure to bird dander as well as gastrointestinal and skin symptoms associated with eating eggs. Some patients also develop a reaction to avian meat. The syndrome is most commonly found in adult females, especially those with pet birds. The condition is distinct from egg-white allergies, which occur primarily children and typically disappear as the child grows up.

Bird-egg syndrome appears to be the result of IgE reactivity to livetin, a protein found in the water-soluble fraction of the egg yolk.

### **Celiac Disease**

Gluten has become a popular food substance to avoid in recent years, although it is not clear if gluten is always the real culprit. Glutens are a class of proteins found in wheat, barley, and rye.

Celiac disease, which affects about 1% of the U.S. population, is the most serious and well-known disease associated with gluten consumption. A similar protein in oats, avenin, is not usually a problem for celiac patients. Celiac disease is an autoimmune disease associated with gastrointestinal symptoms, anemia, and fatigue, and can lead to more serious problems, including anemia, infertility, osteoporosis, gastrointestinal cancers, and neurological conditions. There is a strong genetic predisposition to celiac disease.

Glutens are rich in proline residues and resistant to proteolysis. In patients with celiac disease, some of the peptides from gluten trigger an immune response that also attacks the small intestine mucosa, resulting in loss of intestinal villi. The destruction of the intestinal villi is responsible for the symptoms and complications of celiac disease.

Celiac disease is most definitively diagnosed by intestinal biopsy; however, most cases are diagnosed based on serological tests. Celiac patients show elevations in anti-tissue transglutaminase and anti-



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endomysial IgA antibodies. Additionally, certain HLA markers (HLA-DQ2/DQ8) typically are found in celiac patients. Because celiac disease is IgA- rather than IgE-mediated, skin prick tests done for allergy testing are not of use.

Celiac disease often is confused with wheat protein allergies, but the two conditions are very different. The symptoms of wheat protein allergies are classic allergy symptoms, and the diagnosis is made based on the presence of specific IgE antibodies.

A third condition associated with gluten is gluten intolerance (non-celiac gluten sensitivity). In contrast to celiac disease and wheat allergies, gluten intolerance has no immune cause. Symptoms of gluten intolerance include gastrointestinal problems, headache, foggy mind, aches, etc. Diagnosis typically is made by eliminating the possibility of celiac disease or wheat allergy and/or testing whether the patient improves on a gluten-free diet.

Many patients with gluten intolerance are self-diagnosed. No double-blind, placebo-controlled study has been done to prove gluten itself is causing the symptoms in patients with gluten intolerance. There is some belief that a reaction to fermentable oligo-, di-, mono-saccharides and polyols (FODMAPS) are actually responsible for the symptoms in patients with gluten intolerance.

### *About the Food Research Institute*

*The Food Research Institute (FRI), a part of the College of Agricultural and Life Sciences at the University of Wisconsin–Madison, operates its own laboratories and administers its own research and service programs. The mission of FRI is to catalyze multidisciplinary and collaborative research on microbial foodborne pathogens and toxins and to provide training, outreach and service to enhance the safety of the food supply. To fulfill this mission, FRI conducts fundamental and applied research, provides accurate and useful information and expertise, delivers quality education and training, and provides leadership in identifying and resolving food safety issues to meet community, government, and industry needs.*

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