IgG Allergy Testing

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There is no question that the foods people eat have a big impact on their health and quality of life. The discussion about adverse food reactions and the health problems associated with them has grown in quality and intensity over the last several decades. From some of our earliest concerns about the impact of cholesterol and fats on health, interest has expanded to include food allergies, propelled forward by the clinical ecology movement. 1

Food allergies are becoming more prevalent in today’s society. It’s estimated that 6% of children and 3-4% of adults may have IgE-mediated food allergies.2, 3 For those with food allergies that are not IgE-mediated and associated with delayed hypersensitivity reactions, estimates are more difficult to determine. Some suggest that between 45-60% of people may be affected. 4, 5 Food allergies are implicated in a wide variety of conditions, including migraine, irritable bowel syndrome, inflammatory bowel disease, eczema, psoriasis and recurrent infection. 6

Agreement about what constitutes food allergy is clouded, however, by confusion about terminology and there is disagreement on how to define, evaluate, and diagnose it. 7, 8 Allergy has come to be defined in conventional medical circles as IgE-mediated reactions.

Despite this narrow viewpoint, patients themselves are convinced that foods trigger symptoms. Self-diagnosis of food allergies is common and there is an increasing trend toward diets to address food allergies, including elimination and challenge and rotation diets.

Testing for adverse food reactions serves many important purposes and provides significant benefit to the patient. Serum testing for food allergies provides a quick response to patients’ questions about food allergies. The written reports given to patients include reference ranges along with instructions to follow in eliminating offending foods. When compliance is high, patients report improvement in symptoms, elimination of long-standing health issues, and, in general, a more satisfying quality of life.

Types of Hypersensitivity Reactions

A food allergy is an abnormal response to a food protein triggered by the immune system. The development of food allergies is dependent on a number of factors, including exposure to the allergenic food, the number of times the food is consumed, and the integrity of the gastrointestinal system.

Specifically, there are four different types of reactions that may occur when a person is exposed to an allergen.

Reactions mediated by IgE are referred to as Type I, in which mast cells and basophils release histamine when exposed to an allergen. This immediate reaction is both serious and potentially life threatening and characteristic of
what we think of as the typical ‘atopic’ or allergic reaction to IgE-mediated antigens. Symptoms generally associated with IgE-mediated reactions include congestion, angioedema and urticaria, and often require life-long avoidance of the substance in question. Airway constriction may occur during severe anaphylactic reactions when vascular integrity is compromised and is a frequent cause of mortality.

Some allergies are primarily atopic, like hay fever or peanut allergy 9 and confirmed by elevated levels of IgE in serum. In the Multicenter Allergy Study, researchers discovered that IgE antibodies to egg were the earliest to be detected in infancy, followed by antibodies to milk. Rates of sensitization were highest at infancy, at 10%, decreasing to 3% by age 6. However, inhalant allergy sensitization developed much later, with rates of sensitization increasing with age. Sensitization to inhalant allergens increased from 1.5% at age 1 to 26% by age 6. 10

In Type II hypersensitivity reactions, attachment of the allergen causes antibody-mediated tissue destruction. This reaction is considered “cytotoxic” because it has a direct effect on the integrity of the cell.

Type III reactions are mediated by a mixed group of antibodies, though IgG antibodies are most prevalent. Immune complexes activate complement, triggering the release of inflammatory cytokines. The resulting inflammatory cascade contributes to many undesirable health symptoms, including joint pain, chronic headaches, fatigue, eczema, and psoriasis, many of which are associated with food allergy. Type III reactions are considered to be “delayed” because of the time required to form the immune complexes. Symptoms of exposure may develop many hours to days later and make diagnosis of a food-related allergy very challenging.

The last type of hypersensitivity reaction is Type IV, in which killer T-cells become cytotoxic when activated by an antigen. These cytotoxic cells target bacteria, viruses, tumor cells, or other cells of the body. Type IV reactions may also be involved in some delayed hypersensitivity reactions, such as celiac disease, in which there is a reaction to the gliadin fraction of grains and wheat gluten. Type IV reactions may cause damage to the mucosal lining of the gut or contribute to other protein wasting conditions, like celiac disease, ulcerative colitis, Crohn’s disease, and leaky gut.

IgG versus IgE Reactions

Testing for food allergies commonly involves serological tests to detect immunoglobulin G4 (IgG4), which is most likely to develop with exposure to food proteins. Blood IgG4 is tested against a number of foods using enzyme-linked immunosorbent assay. Testing generally involves exposing the patient’s serum to up to 96 commonly eaten foods and measuring IgG4 and IgE antibodies.

The accuracy of IgG antibody testing is, however, an area of contention in the conventional medical community. Because serum samples may show elevated IgG4 results without the patient demonstrating any clinical symptoms, it’s suggested that IgG4 has both protective as well as harmful properties. 11 Detractors point out that IgG4 lacks any histamine-releasing properties and that there are few controlled studies on the diagnostic value of food-specific IgG4, making it of little value as a predictor of allergy. The latest discussion revolves around IgG levels as reflecting immunological tolerance, or repeated exposure to foods 12, 13 and not hypersensitivity.
Besides clinical experience that demonstrates patients improve from elimination and rotation diets based upon IgG antibody testing to specific foods, many clinical studies have been done in recent years involving IgG food-related antibodies. Patients with many distressing health conditions have experienced significant improvement as a result of specific IgG testing.

**IgG Antibodies Detectible Before IgE**

IgG antibodies to food are often detectible before IgE antibodies are elevated for common allergic inhalants in children who appear at first to be non-atopic. In a cross-sectional prospective study of the relationship between IgG in foods and IgE in known allergens, researchers found that, when IgG levels were measured in 120 atopic and 144 non-atopic children, the atopic children had higher IgG levels, particularly for egg white, orange, and milk. These levels correlated with an increased risk of IgE-mediated allergy to cats, dogs, mites, milk and eggs. 14

Sensitization to foods as an increased risk of sensitization to inhalant allergens has been substantiated in a prospective study of 397 IgE-negative children, ages 1-5. Children who were initially IgE-negative for antibodies to mites, dogs and cats were assessed for IgG antibodies to foods. Two years later, 12.8% of the children showed IgE sensitization to dog, cat or mite antibodies along with increased IgG antibody levels for a combination of wheat-rice or orange. It was concluded that elevated levels of IgG to orange and wheat-rice, along with other factors, increased the risk of IgE-mediated allergies to inhalants. 15

In recent years, clinical studies demonstrating that IgG antibody testing is an effective and reliable testing method have been conducted in children and in patients with migraine, irritable bowel syndrome (IBS), and gluten sensitivity.

**IgG Food Antigen Studies in Children**

In one study of IgG antibodies to food, 30 overweight children were evaluated against 30 children of normal weight to see if IgG antibodies predisposed them to low-grade inflammation and atherogenesis. IgG antibodies to foods, C-reactive protein (CRP), and intima media thickness of the carotid arteries were measured. Results showed that the obese children had higher IgG antibodies to foods than the children who were of normal weight. Researchers concluded that IgG antibodies were associated with systemic inflammation, suggesting the possibility that obesity and atherosclerosis were associated with IgG food antibodies. 16

To determine whether delayed hypersensitivity reaction to foods might be a factor in the development of chronic diarrhea in children, researchers measured IgG antibodies and prescribed an elimination diet to children in 4 different groups. IgG levels were highest for milk and lowest for pork in each of the study cohorts. Symptoms improved for 65 of the 82 children within 1 week to 3 months of dietary intervention. It was concluded that food allergy was a major factor in the development of chronic diarrhea in children, with food-specific IgG assessment an important component of early management. 17

**Migraine**
Migraine has often been attributed to food allergy in many studies, but extensive evaluation using IgG antibodies has not been done. In a recent study, 56 patients with migraine were evaluated for their serum IgG antibodies to 108 different food allergens using enzyme immunoassay. When titers were assessed, patients with migraine had elevated IgG levels that were statistically significant when compared to the control group. Researchers also found that elimination diets based upon foods to which patients had elevated IgG levels were successful in controlling symptoms of migraine without pharmaceutical intervention.

Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome (IBS) is a complex disorder in which patients experience abdominal pain and discomfort with frequent bouts of diarrhea or constipation. Treatment is challenging and many traditional methods used to predict it are disappointing, with diagnosis based on exclusion in most cases. While IBS may have many causes, patients remain convinced that dietary intolerance and food sensitivities are at the root of the problem. When certain foods are eliminated from the diet of IBS patients, they improve, making dietary modification through elimination of specific foods and food challenge an effective strategy.

In a very clear, double-blind, randomized, controlled study, 131 participants between the ages of 18 and 75 with uncomplicated IBS were enrolled with two outcome measures. The first was to assess what would happen to symptom severity when participants were put on elimination diets based upon their IgG antibodies to foods. The second objective of the study was to measure changes in symptom severity when foods were reintroduced in the diet.

IgG antibodies were measured using an enzyme-linked immunosorbant assay (ELISA) test designed to measure antigens to 29 different foods. Patients were assigned to groups to receive either a “true” or a “sham” elimination diet based upon detected IgG antibody levels. Symptom severity was assessed for each patient prior to the study, along with atopic status. On average, most study participants had had symptoms of IBS for 10 years and, on average, had elevated IgG titers to 6-7 foods.

At the end of the 12-week study, symptom severity decreased by 10% in those on the true diet. While improvement was greatest among participants on the true diet, there was some improvement noted in symptom severity for those on the sham diet, suggesting there was some small placebo effect.

In participants who were fully compliant with the true diet and had the highest level of sensitivity to foods as demonstrated by their IgG titers, there was a 26% improvement in symptom severity. This was not true for participants with high sensitivity who were on the sham diet, however.

When foods with high IgG antibody titers were reintroduced to the diet, symptom severity increased in those on the true diet by 83% and by 31% in the sham group.

In another study involving 25 participants with irritable bowel syndrome (IBS), dietary modification was determined following measurement of their IgG4 antibody levels to specific foods. IgG4 antibody levels were assessed for beef,
pork, lamb, chicken, fish, shrimp, yeast, tomatoes, peanuts, milk, eggs, cheese, wheat, rice, potatoes, and soybeans and foods with titers over 250 mcg/l were eliminated from the diet for 6 months. The highest titers were recorded for beef, pork, lamb, eggs, milk, and wheat. When assessed at 6 months, study participants reported reduced pain and pain frequency, reduced bloating, improvement in bowel habits, and improvement in quality of life. 23

More recently, a study comparing IgG, IgE and total IgE antibody titers was conducted in patients with IBS and functional dyspepsia (FD). Serum IgG and IgE antibody titers were measured for 14 foods, including tomatoes, wheat, crab, codfish, eggs, corn, mushrooms, milk, port, rice, shrimp, beef, chicken and soybeans. As in similar studies, there were no significant levels of food-specific IgE antigens. However, IgG levels were elevated for crab, egg, shrimp, soybean, and wheat as compared to controls in patients with IBS. In patients with FD, IgG antibodies were significantly higher for egg and soybean. While there were elevations in IgG food-specific antigens, there was no correlation to symptom severity. 24

In yet another study, 108 study participants with IBS were tested for their sensitivity to 16 foods using IgG4 and IgE titers and skin prick testing. Study participants had the highest IgG4 titers to wheat, beef, and lamb, with no significant results reported for potatoes, rice, fish, chicken, yeast, tomato, or shrimp. In contrast, IgE titers were not elevated in study participants or controls and skin prick testing showed only one positive result in 5 of 56 patients. Researchers concluded that there is a possible pathophysiological basis for the IgG4 antibodies detected in patients with IBS. 25 While the mechanism may not yet be clarified, mucosal inflammation and immunological reactivity appear to be a factor in IBS and deserve further study. 26

Treatment with elimination and rotation diets has also been shown to be effective for IBS patients who are not responsive to other forms of therapy. In an open label pilot study, 25 patients with diarrhea dominant IBS 27 were first screened for their serum IgG4 and IgE titers, along with mold antigen panels. All patients had baseline antibody abnormalities and were given elimination diets based upon their antibody levels and asked to follow them for up to 4 weeks. After the elimination phase, foods were challenged and reintroduced in a rotation diet if there were no symptoms. Any food causing symptoms was eliminated from the diet for an additional 6 months. Study participants were given probiotics for 4 months out of the 6-month trial period.

At the end of the trial period, patients reported improvement in stool frequency and quality of life scores. Most patients sustained their clinical improvement one year after the trial ended, reporting few symptoms and continued adherence to the rotation diet. 28

Eliminating foods based upon IgG4 levels in patients with IBS has been determined by other researchers to be a very valuable treatment modality. 29

Celiac Disease and Non-celiac Gluten Sensitivity

No discussion of allergy testing would be complete without addressing gluten sensitivity and gluten intolerance. Celiac disease, also known as gluten-sensitive enteropathy, is a food intolerance that affects individuals with a genetic predisposition to react to gliadin, a gluten protein found in wheat, barley, and rye. While the exact mechanism
is unknown, exposure to these proteins causes an inflammatory reaction and increased intestinal permeability leading to symptoms of diarrhea, malabsorption, and irritable bowel syndrome. Chronic exposure leads to atrophy of the villi of the small intestine. To date, the only effective treatment for celiac disease is a gluten-free diet.

Definitive diagnosis of celiac disease is confirmed through biopsy of the small intestine, with serological testing for anti-gliadin (AGA), IgA and IgG, anti-endomysial (EMA), and anti-tissue transglutaminase (tTG) antibodies conducted as part of the diagnostic evaluation. Serum IgG antibody testing for gluten/gliadin antibodies is done using an FDA-approved ELISA.

Research has shown that gluten sensitivity may, in fact, occur without villous atrophy being apparent. Other tissues may be targeted in gluten-sensitive individuals, manifesting as autoimmune diseases or skin conditions, such as dermatitis herpetiformis. Some have recommended that early diagnosis, using serum anti-gliadin IgG testing before tTG or EMA levels are elevated and before villous atrophy has occurred, can help identify those who are at risk and prevent progression of the disease through gluten avoidance.

There is a large group of people in our population, however, who react to gluten and are “gluten sensitive” and do not have celiac disease. Clinical evidence suggests that a gluten-free diet in these individuals, based upon serum IgG levels, reduces symptoms and improves health in a vast majority of those assessed. Preliminary studies are now underway to identify the mechanism with which gluten affects the body in those who are gluten sensitive but without identifiable celiac disease.

**Food Allergy Testing**

Allergy serum and bloodspot tests measure total IgG through ELISA/EIA, which includes all the subclasses of IgG. Sera is added to a 96-well plate containing different food antigens and then evaluated for classic antigen/antibody interactions. Accurate testing requires the patient to eat a wide range of foods within 3 weeks of assessment for IgG exposure to be present. The test provides a report of whether the levels of antibody to the various foods suggest that each one is “safe” to eat, best to eat in moderation, or to avoid entirely.

Other types of testing, such as skin tests, which are reliable for the detection of IgE to environmental allergens, are not reliable for the detection of food allergies.

A further refinement in food allergy testing is the development of the bloodspot test, which requires only a tiny amount of blood for testing of 45-95 food antigens. The patient pricks a finger with a lancet and then places drops of blood on a blood spot collection card. The card is air-dried and returned to the laboratory for assessment of IgG4 antibodies to food via ELISA assay. IgG4 results are ranked according to their concentrations in the blood and then ranked according to those results, such as safe, moderately safe, or avoid. These results can then be used to design therapeutic elimination or rotation diets.

**Conclusion**
While the mechanism associated with IgG-mediated food allergy may as yet be unknown, the results achieved from serum IgG assessment are very clear and provide a valuable means of designing effective treatments.

References

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