Food Allergy: Unproven diagnostics and therapeutics

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ABSTRACT

Food allergy or intolerance is often attributed by patients as the cause of many symptoms unknown to be directly related to food ingestion. For immunoglobulin E (IgE) mediated food allergy, diagnostic modalities are currently limited to the combination of clinical history, evidence of sensitization with food-specific IgE testing and skin-prick testing, and oral food challenge. Many patients find an appeal in the promise of identification of the etiology of their symptoms through alternative food allergy or intolerance diagnostic modalities. These patients may seek guidance from allergists or their general providers as to the legitimacy of these tests or interpretation of results. These tests include food-specific serum IgG or IgG4 testing, flow cytometry to measure the change in leukocyte volume after exposure to food, intradermal or sublingual provocation-neutralization, electrodermal testing, applied kinesiology, hair analysis, and iridology. In addition, there are some unconventional therapeutic modalities for adverse reactions to foods, including rotary diets. None of these have been supported by scientific evidence, and some even carry the risk of severe adverse reactions. It is important that we offer our patients evidence-based, accurate counseling of these unproven modalities by understanding their methods, their paucity of credible scientific support, and their associated risks.

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Various symptoms are perceived by patients to be a food allergy. History; sensitization assessed *via* food-specific serum immunoglobulin E (IgE) and skin-prick testing; and the diagnostic criterion standard, oral food challenge (OFC), are the only credible methods used to assist in a true food allergy diagnosis. However, there are unproven diagnostic modalities that patients use or are interested in. There currently are no methods for accurately identifying food intolerances, an entity frequently confused by patients for true food allergy. Numerous marketed unproven testing methods are alleged to identify adverse reactions to food. Although some of these include validated laboratory methods, they have not been shown to consistently correlate with disease or they may be used inappropriately. Unfortunately, this could have harmful consequences, including increased costs, inappropriate food elimination, possible nutritional deficiencies, or misdiagnosis.

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FOOD-SPECIFIC SERUM IgG TESTING

Food-specific IgG and IgG4 tests are advertised to diagnose adverse reactions to foods. The tests are typically ordered as an extensive panel of foods. Although these tests are available to be ordered by physicians, they can even be purchased directly by the patient, and are sometimes covered by Health Savings Accounts or Flexible Spending Accounts. There are advertisements asserting that the presence of food-specific IgG can play a role in an array of symptoms not classically associated with true food allergy, including headaches, chronic fatigue, skin issues, gastrointestinal symptoms, hyperactivity, and joint pain.

There have been studies that suggest the use of food-specific IgG guided diets but these have had many methodologic problems, including a lack of control groups; inappropriate, sham diet; lack of randomization; lack of blinding; ill-defined measures of improvement; or no correlation with double-blinded-placebo controlled OFC.[1,2] Alternatively, there was a study that attempted to correlate IgG levels with 97 patients who were morbidly obese and who reported gastrointestinal intolerance to milk or wheat; no association was found between their symptoms and IgG level.[3]

Although laboratory testing for food-specific IgG can be done in a valid and reliable manner, IgG antibodies to food are found in essentially all people who are healthy and asymptomatic; this is thought to be a physiologic immunologic response to regularly ingested foods. In one study, 98% of children who were healthy showed evidence of IgG response to cow's milk protein by 2 years of age.[4] Food-specific IgG has also been correlated with tolerance to foods.[5] Currently, there is no role for food-specific IgG or IgG4

testing in the diagnosis of adverse reactions related to foods, with the rare exception of food-induced pulmonary hemosiderosis (Heiner syndrome),[6] and their role, if any, in gastrointestinal disorders, *e.g.,* Irritable Bowel Syndrome has yet to be elucidated.

CYTOTOXIC TESTING

Cytotoxic testing, including the Alcat test (antigen leukocyte antibody test), claims to identify foods that cause "potentially harmful immune system reactions" by using flow cytometry to measure the change in leukocyte volumes in response to food exposures.[7] The test result is considered positive if there is any change in cellular morphology after incubation with food. However, no evidence supports the accuracy or reproducibility of the laboratory tests themselves,[8] and it is unclear how this finding could represent a cause for the numerous conditions it claims to diagnose. Current literature does not support the use of this assay, and there are no recently published peer-reviewed studies on this method to our knowledge.[7]

PROVOCATION-NEUTRALIZATION

Provocation tests involve intradermal injection or, sometimes, sublingual drops of food extracts, followed by observation for any symptoms and measurement of the local response. A positive test result involves any reported symptom in this observation period. In a double-blinded, placebo controlled study, there was no significant difference in patients who reacted to an antigen compared with patients who reacted to placebo.[9]

Pulse testing is sometimes included in provocation-neutralization, although it may also be used alone. Pulse testing involves measuring changes in the heart rate in response to a sublingual drop, intradermal injection, or OFC. An individual is considered allergic to a food if the pulse changes by 16 beats per minute from baseline during the observation period after exposure. No blinded clinical trials have been done with this technique to our knowledge.[2] Neutralization is used as the "treatment," which involves subsequent injections of the "offending allergen" to "neutralize" the response; this is not only not validated and immunologically implausible but also carries a risk of severe adverse reaction in patients with true IgE-mediated allergy or systemic mastocytosis.[10]

ELECTRODERMAL TESTING

Electrodermal testing involves measuring skin conductance by using a galvanometer in an electrical circuit created with an electrode in the patient's hand, another electrode somewhere else on the patient's body, and a sealed vial of food extract in contact with an aluminum plate but not touching the patient. A decrease in conduction with a certain vial of food extract is considered positive and indicative of allergy to that food.[11] Although no studies have been done with this technique specifically for food allergy, a study has been done with inhalant allergens. This method could not differentiate between individuals who were allergic and individuals who were not allergic based on positive skin-prick testing results and was not reproducible.[12]

APPLIED KINESIOLOGY

In applied kinesiology, or muscle-response testing, a patient holds a vial that contains a food allergen and a practitioner applies light pressure to the opposite arm to test muscle strength. The test result is considered positive if decreased strength is noted. This diagnostic technique is allegedly related to using muscle response as a manifestation of energy balances.[13] Results of studies have shown that this method is no more reliable than the rates expected by chance or random guessing, although use in the diagnosis of food allergy specifically has not been evaluated.[14]

HAIR ANALYSIS

Hair analysis for food intolerances is advertised, although the laboratory methods for this testing are unknown. A study has been done with hair samples of control patients who were asymptomatic; the samples were sent to multiple different laboratories that offered this testing. Results produced many "positives" in these patients who were asymptomatic, with discrepancies among the different laboratories.[15]

IRIDOLOGY

Iridology is the examination of the iris for changes in colors, patterns, or other characteristics that may be related to changes in health status. Although advertised as a method to diagnose food allergies, there are no studies that examined this claim. There is evidence that iridologic style analysis could not assist in the diagnosis of bronchial asthma.[16]

UNPROVEN THERAPUETICS

Although most of the abovementioned diagnostic procedures are used to guide dietary elimination, there are some unproven therapeutic techniques in addition to neutralization discussed previously. Rotary diets, or a 4-day rotation diet, involve splitting foods into biologic groups and is sometimes used as a treatment based on results of food-specific IgG testing. The patient is supposed to eat all members of a specified food group on a 4–7 day rotating cycle and eliminate any food with a positive IgG value, with the goals of preventing continued sensitization to specific foods and of attaining tolerance by continued elimination, or

as prophylaxis. There are no studies that assessed the effectiveness of this technique.[6]

The Nambudripad allergy elimination technique (NAET) is adapted from acupuncture and touted as a natural, noninvasive treatment for food allergies that target energy blockages and imbalances. It uses muscle response testing for a diagnosis and then the patient is treated with acupressure or acupuncture while the allergen is held by the patient. Muscle-response testing is subsequently repeated, and, if the muscle strengthens, then the patient is instructed to avoid the allergen for a day and then to reintroduce it. It does not make any distinction between IgE-mediated allergies and food intolerances.[17] There are no studies that evaluated these claims of NAET as a food-allergy treatment. There is a concern of anaphylaxis should a patient with a true IgE-mediated food allergy seek this treatment and then be told to reintroduce the trigger at home.

There are also various homeopathic and medicinal herb remedies. One is Food Allergy Herbal Formula 2, which is a combination of herbs used in traditional Chinese medicine. It was shown in studies to eliminate anaphylaxis in murine models of peanut allergy up to 5 weeks after treatment, associated with suppression of T-helper type 2 responses.[18] Although human clinical trials demonstrated safety and encouraging *in vitro* immunomodulatory effects, efficacy at the dose and duration in the trials was not established.[19]

UNNECCESSARY OR INAPPROPRIATE TESTING

Although specific IgE testing can be useful to identify sensitization within specific clinical contexts, it is important to highlight that large food panel testing without clinical correlation of suspected IgE-mediated allergic reaction is unnecessary and inappropriate. A positive food serum specific IgE value or skin-prick testing result indicates sensitization to a specific protein but does not always correlate with clinical allergy diagnosed with the criterion standard of an OFC.

One study showed that only 2.5% of individuals sensitized to a major food allergen had clinical symptoms proven by OFC,[20] and another study demonstrated that only 33% of infants who demonstrated sensitization to peanuts and 55% of infants who were egg sensitized had symptoms consistent with IgE-mediated food allergy with OFC.[21] Because these tests have a poor positive predictive value, one could anticipate discovering numerous false-positive results if food-specific panels are performed without the direction of a clinical history consistent with IgE-mediated food allergy.

Misdiagnosis of food allergies has been associated with using multiple food allergen specific IgE panels is not benign. It can result in needless dietary elimination that could possibly be harmful for the patient and lead to higher health-care costs.[22] In children, panel testing and subsequent elimination diets could potentially put them at risk for nutritional deficiencies or affect growth.[23] There is also a theoretical concern that a lack of exposure to a previously tolerated food based on panel-guided elimination could potentially lead to the development of clinical reactivity on re-exposure to the avoided food.

The practice parameters advises that, when considering a diagnosis of food allergy, foods suspected of causing a reaction should be the focus of testing. Specific IgE test results are not diagnostic of food allergy in isolation, and the practice parameter emphasizes that large food-specific IgE panel testing should be avoided.[24] The poor positive predictive value of this testing allows for misinterpretation, misdiagnosis, and inappropriate food avoidance, and indiscriminate use of food-specific IgE testing can result in harmful consequences for our patients and should not be used without the appropriate clinical context.

CONCLUSION

These unproven, or even disproven, methods for the diagnosis and treatment of food allergy and intolerances are not without consequence and can affect quality of life, lead to needless restrictive diets, or be used to inappropriately explain the etiology of multiple symptoms, which potentially leads to a delay in a proper diagnosis. Nonetheless, these methods are used by or are advertised to patients, so it is important to be educated on what other modalities exist and their lack of scientific evidence so that patients can receive thoughtful and accurate counseling and advice.

CLINICAL PEARLS

- Patients often inquire about unproven diagnostics and even therapeutics for adverse reactions to food, so it is important to be aware of these techniques and the literature to provide evidence-based counseling.
- Some modalities, such as food-specific IgG, may involve validated laboratory techniques but that have not been consistently proven to correlate with symptoms or disease.
- Cytotoxic testing, provocation-neutralization, electrodermal testing, applied kinesiology, hair analysis, and iridology lack any scientific evidence to support their use as diagnostic methods for food allergy or intolerance.
- Therapeutics such as neutralization, rotary diets, and NAETs are not only unproven but may be dangerous because they do not differentiate between IgE-mediated food allergy and other adverse

reaction to foods. Food Allergy Herbal Formula 2 showed promise in murine models but efficacy was not established in human clinical trials.

- Large panels of food-specific IgE should not be performed without appropriate clinical context due to a poor positive predictive value, which leads to misinterpretation and unnecessary dietary elimination.

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