Diagnostic tests for food allergy

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ABSTRACT

The diagnosis of food allergy is still based primarily on a detailed medical history and comprehensive physical examination. Clinical or laboratory tests only serve as an add-on tool to confirm the diagnosis. The standard techniques include skin prick testing and *in-vitro* testing for specific IgE-antibodies, and oral food challenges. Properly done, oral food challenges continue to be the gold standard in the diagnostic workup. Recently, unconventional diagnostic methods are increasingly used. These include food specific IgG, antigen leucocyte antibody and sublingual/intradermal provocation tests, as well as cytotoxic food and applied kinesiology and electrodermal testings. These lack scientific rationale, standardisation and reproducibility. There have been no well-designed studies to support these tests, and in fact, several authors have disproved their utility. These tests, therefore, should not be advocated in the evaluation of patients with suspected food allergy because the results do not correlate with clinical allergy and may lead to misleading advice and treatment.

Keywords: food allergy, skin prick test, *in-vitro* specific IgE test, oral food challenge, unproven allergy tests, food specific IgG test, cytotoxic food testing, ALCAT test, sublingual/intradermal provocation tests, kinesiology and electrodermal testing

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INTRODUCTION

Food is an integral part of life and is usually well tolerated. However, adverse reactions to a particular food may occur and present as food intolerance, allergy or hypersensitivity. In most populations, perceived food allergy, based on self-reported surveys, is substantially influenced by the reporter's subjective bias, and often overestimates the prevalence of true food allergy in a population.[1] This perception has led to unnecessary implementation of food avoidance. A survey has shown that up to one-fourth of American households alter their dietary habits unnecessarily because a member of the family is perceived to have food allergies.[2] In Singapore, a questionnaire survey on the prevalence of food allergy in secondary school children also showed that surveys alone overestimated the prevalence of true food allergy in this cohort by at least five- to ten-fold.[3] In contrast to the Western world, where peanuts and tree nuts are common causes of food allergy, the pattern of food allergy in countries in the Asian region is quite different. The prevalence of peanut and tree nut allergy is less common, and food allergies to unique allergens, such as edible Bird's nest in Singapore, chestnuts in Korea, buckwheat in Japan, Korea and China, and chickpeas in India, are commonly reported.[4] Hence, panels of food allergen testings may have a different focus in different populations.

The process of diagnosing and treating food allergy is complex and at times elusive. A thorough medical history-taking and physical examination continue to be the mainstay in the diagnostic process, with laboratory tests used as important adjunct tools to confirm the diagnosis and monitor its course. Although, food allergy may be associated with other forms of allergic diseases, not all patients with eczema or respiratory allergies require an evaluation for food allergy as a trigger of their allergic disease. In fact, only a small proportion of patients with respiratory allergic problems, such as rhinitis and asthma, and up to 35% of young children with severe atopic eczema, have associated food allergies.[5] Of late, several commercial laboratories have offered food allergy tests that do not have scientific basis and have not been validated. Resorting to these unproven diagnostic techniques leads to misdiagnoses and unnecessary withdrawal of foods from the diet. Such elimination diets, if done extensive, may result in inadequate nutrition and dire consequences, especially in children. Thus the purpose of this review article is to provide a useful guide in choosing appropriate ancillary diagnostic tests for patients suspected to have food allergy or hypersensitivity.

Food hypersensitivity is immunologically mediated and can be classified as either IgE-mediated (resulting in classical clinical presentations, such as anaphylactic reactions) or non-IgE-mediated hypersensitivity (exemplified by dietary protein enterocolitis and coeliac disease).[6,7] These reactions are differentiated from other adverse reactions to food namely toxic reactions (resulting from contaminants or toxins synthesised by an organism or the food itself, e.g. snapper or sea bass contaminated with ciguatoxin, scombroid fish poisoning),

Table I. PPV and NPV of food-specific IgE concentration (in kUA/L using Pharmacia CAP-FEIA®)[62] and PPV of skin prick test for predicting reactions in children aged 16 years and below.[14,63]

Food allergen	Food-specific IgE concentration (CAP-FEIA®)		SPT cut-off wheal diameter (mm)/ PPV for positive reaction (%)
	> 95% PPV (kUA/L)	> 95% NPV (kUA/L)	
Egg	6	0.6 (> 90% NPV)	7 (100)
Milk	32	0.8	8 (100)
Peanut	15	< 0.35 (85% NPV)	8 (100)
Fish	20	0.9	
Soybean	65 (50% PPV)	2	
Wheat	100 (75% PPV)	5	

PPV: positive predictive value; NPV: negative predictive value; SPT: skin prick test

and food intolerance due to pharmacological properties of food (caffeine in coffee, alcohol, tyramine in cheese), as well as host-related factors, such as lactase deficiency, galactosaemia or idiosyncratic reactions.

ESTABLISHED DIAGNOSTIC TESTS IN FOOD ALLERGY

Measurement of food-specific IgE using the skin prick test and *in vitro* laboratory techniques

Measurement of fond-specific IgE using the skin prick test (SPT) or *in vitro* assays are useful to establish the presence of IgE sensitisation to specific foods in patients suspected clinically to have IgE-mediated food-allergic reactions.[8, 9]

There are numerous protocols delineating the practical procedure for SPT. One useful reference has been produced by the American Academy of Allergy, Asthma and Immunology.[10] The presence of allergen-specific IgE on cutaneous mast cells results in a positive skin test in the form of a transient "wheal-and-flare" reaction.[11] A wheal of at least 3 mm in diameter, or larger than the diluent control is considered positive.[12,13] In general, the larger the SPT response, the higher the likelihood of clinical relevance. A median wheal diameter greater than 8–10 mm has been correlated with clinical allergy.[14] For example, in infants less than two years of age, SPTs to milk, egg or peanuts with wheal diameters of 8 mm or larger are reportedly more than 95% predictive of true clinical reactivity.[15] It should be noted that 'fresh' allergens are superior to commercially-prepared extracts for labile allergens, such as those of fruits and vegetables.[16,17] The technique of using fresh foods is called the prick-prick test, which refers to the sequence of pricking the fruit or vegetable and then the skin.[17]

SPTs provide a rapid means to detect IgE sensitisation and are highly sensitive but only moderately specific in regard to clinical reactivity, i.e. there is a high rate of false positivity. The positive predictive accuracies of SPTs are less than 50% compared to double-blind placebo-controlled food challenges (DBPCFC).[18] On the other hand, a negative SPT result has more than 95% negative predictive accuracy, and is therefore useful for confirming the absence of an IgE-mediated reaction.[6,8,19,20] Although the SPT is a safe procedure, it is not without risk. In fact, fatal anaphylactic reactions have been noted in exquisitely allergic individuals. Fatality has been reported following a prick-puncture test in a woman with food allergy, allergic rhinitis and poorly-controlled, moderate persistent asthma.[21] It is therefore recommended that emergency equipment and medications are at hand for the procedure.

In vitro tests for food-specific IgE antibodies may also be used to screen patients suspected of IgE-mediated food allergies. This test is preferred when the patient has significant dermatographism or severe skin disorders with limited surface for testing, and for those on antihistamines, or with suspected exquisite sensitivity to certain foods.[8] More recent tests, such as the CAP system fluorescent enzyme immunoassay instead of the radioallergosorbent test, which involves radioactive substrates, are favoured as these tests are more sensitive in detecting low levels of allergen-specific IgE and the cut-off values correlating with clinical allergy have been studied systematically in western populations[12,22,23] (Table I). As in the SPT, a negative result is reliable in ruling out an IgE-mediated reaction to a particular food, but a positive result has low specificity. Additionally, one has to be aware that between 10%–25% of patients with undetectable serum food-specific IgE levels have been reported to have clinically-relevant reactions,[12] and a physician-supervised food challenge may be necessary to confirm the absence of clinical allergy.

When comparing the two diagnostic modalities, SPTs are generally favoured as they are highly reproducible in experienced hands and less costly to perform compared to *in-vitro* testings. It causes minimal patient discomfort and yields results within minutes. The *in-vitro* test, however, may provide better quantitative results (i.e. exact values of specific IgE), and may therefore be more useful for monitoring specific IgE levels over time.

Intradermal skin testing is not recommended for diagnostic evaluation of food allergy because studies

have shown that it has an unacceptably high false-positive rate, i.e. lower specificity. Most importantly, there is no significant increase in sensitivity or predictive value when compared with DBPCFC.[20] Furthermore, this method is associated with a greater risk of inducing systemic reactions, including fatal anaphylactic reactions.[24]

FOOD CHALLENGES

Food challenges provide the most definitive way to diagnose adverse reactions to food. When immune mechanisms other than IgE-mediated hypersensitivity are suspected, as exemplified by food protein-induced enterocolitis syndrome, a food challenge may be the only way of confirming the diagnosis.[25] Oral food challenges may be open, single-blind or double-blind placebo-controlled. Several expert groups have developed protocols for food challenge testings, e.g. the standardised protocol based on consensus from the European Academy of Allergy and Clinical Immunology.[26] Other groups have made modifications to food challenge protocols to include threshold doses for more sensitive individuals who require low-dose challenges,[27] and protocols to include challenges with food additives.[28] In addition, clinical algorithms for children have been developed by Niggemann et al,[29] and a suggested practical protocol has been developed by Sicherer.[30] Food challenge testings have been utilised for both IgE-mediated and non-IgE-mediated allergies. In DBPCFC, the specific food is masked in a vehicle food and then administered in a graded fashion. The active food and an equivalent amount of placebo are given in random order and both tests are performed in a controlled manner.[8,31] This double-blind placebo-controlled oral food challenge represents the gold standard in the diagnosis of food allergy.[8,9] On the other hand, a single-blinded challenge, in which the patient is unaware but the physician is aware of the content of the challenge, is sufficient as a screening tool for reactivity.[9] An open feeding under observation to rule out rare false-negative challenges must be done if the result of the blinded challenge is negative.[32]

When specific IgE has diminished substantially in the course of monitoring a patient's IgE-mediated food allergy, open food challenges may be used to confirm that the patient has outgrown his or her food allergy. Patients should never be advised to resume intake of the specific food at home as the negative predictive value of skin tests and *in-vitro* tests are not 100% foolproof.

Elimination diet

A trial elimination of the suspected food(s) may be attempted prior to the food challenge. This trial elimination diet may take one of three forms: (1) Elimination of one or several foods suspected to be causing the symptoms; (2) Elimination of all but a defined group of allowed foods; and (3) An elemental diet consisting of hydrolysed formula or amino acid-based formulas in infants. The type of elimination diet used depends on the clinical situation, as well as the results of IgE antibody tests. The rationale behind an elimination diet is if true food hypersensitivity is present, then symptoms should disappear when the food is eliminated from the diet, and re-appear when the food is reintroduced, even if disguised. However, elimination diets alone are seldom diagnostic of food allergy, especially in chronic disorders such as atopic dermatitis. Hence, a double-blind placebo-controlled oral challenge is preferred since it is the least prone to bias from patients or investigators.[30]

RESEARCH-BASED TEST

Atopy patch test

This modality is done with the epicutaneous application of intact protein allergens in a diagnostic patch test setting to evaluate cell-mediated responses to various sensitisers. It is considered a potentially-valuable additional armamentarium in the diagnostic workup of food allergy in infants and children, particularly in those with atopic dermatitis, allergic eosinophilic esophagitis and food protein-induced enterocolitis syndrome.[33-36]

Atopy patch tests (APTs) seem to have better specificity but lower sensitivity than those measuring IgE and seem to reflect late-phase clinical reactions.[34,37] This is shown in studies conducted on infants with cow's milk allergy, in which APTs demonstrated an improved utility for determining delayed responses to oral food challenges compared to SPTs, which were better correlated with immediate symptoms.[38] However, a study conducted by Mehl et al concluded that although APTs showed improved overall sensitivity and specificity of outcome predictions when combined with results from the IgE tests, it added only modest diagnostic information in the context of avoiding an oral food challenge.[39] In addition, an APT is time-consuming since it requires two or three visits, demands a highly experienced test evaluator and is more costly than SPTs. Skin reactions, a result of the irritative effects of the application, may confound interpretation. Nevertheless, a ready-to-use APT for cow's milk, Diallertest®, has been favourably evaluated[33] and is commercially available in several countries, including Singapore. However, in general, further evaluation of this test and development of more standardised reagents and guidelines for interpretation are still necessary. Further research into recombinant allergen-based specific

IgE testings to evaluate allergenic epitopes, microarray immunoassays to enable the evaluation of multiple IgE reactivities and cellular basophil activation tests are currently being assessed for future clinical use.[40-42]

INAPPROPRIATE TESTS

Food-specific IgG tests

Tests for food-specific IgG are marketed as IgG radioallergosorbent tests and vary in offering measurements of total IgG toward a food, or IgG4 with or without food immune complex assay. The measurement of such specific IgG antibodies and their subclasses, primarily IgG4, is based on the fact that the titre falls after a period of withdrawal of the specific food antigen. Thus, some physicians opt to use such a modality to diagnose food allergies. Unfortunately, the determination of specific IgG antibodies in serum does not correspond with oral food challenges.[43] Burks et al conducted a study of antibody responses to milk proteins in patients with milk-protein intolerance proved by oral challenge, and found that no increase in IgG antibodies was noted.[44] In another study, Shek et al concluded that food-specific IgG or IgG4 does not add any information to the diagnostic workup of food allergy.[45] Furthermore, most people develop IgG antibodies to foods that they eat, and this is a normal immune response indicating exposure but not allergic sensitisation.[20] Recent studies have shown that the IgG response may even be protective, and thus prevents or protects against the development of IgE food allergy. Hence, there is no convincing evidence to suggest that this test has any diagnostic value for allergy.[46]

Leucocyte cytotoxic tests

Cytotoxic testing, also known as "Bryan's Test", involves observing changes in the shape of white cells when a specific antigen is added to whole blood. It is prone to bias as it depends on subjective interpretation.[47] Cytotoxic testing has been shown to be non-reproducible, lacking in theoretical basis and nonstandardised, and thus cannot be recommended.[48,49] Unfortunately, this test is still used by some practitioners.[31,50]

The antigen leucocyte antibody test (ALCAT), a test for cellular responses to foreign substances, has been used in some countries for the diagnosis of non-IgE-mediated hypersensitivity reactions. This is a modified version of the leucocytotoxic testing, in which changes in the white cell diameter are measured after the white cells are challenged with specific food allergens.[51] Several investigators have reported that the ALCAT test is an inappropriate modality for testing food allergy in clinical practice mainly because of its poor reproducibility, as well as its a lack of scientific and clinical proof of efficacy.[52,53] It is therefore not recommended to be used for diagnosing allergies of any form.

Sublingual and intradermal provocation tests

In this test, the allergen is applied sublingually or intradermally, and then followed by an observation period for a local response. The application of allergen is progressively increased until a wheal appears on the skin (intradermal provocation dose), and the dosage is then decreased until the wheal disappears. This corresponds to the neutralisation dose used to desensitise the patient. Unacceptably high false-positive rates, as well as safety concerns, such as systemic reactions (including fatal anaphylactic responses), are associated with the intradermal allergy skin test and sublingual administration.[20,54] In fact, angiooedema after the application of sublingual drops has previously been reported,[55] and a patient with systemic mastocytosis was reported to have developed severe, life-threatening reactions after undergoing provocation-neutralisation due to a massive mediator release.[54]

Bock et al reported that this test provided no significant increase in sensitivity and predictive value compared to DBPCFC.[9,19] Furthermore, it has not been validated by other studies and has failed to show reliable results, with clinical manifestations reported as random and unrelated to the test itself.[56] Prompt neutralisation of allergic symptoms by administration of the allergen is inconsistent with the current knowledge of the pathogenesis of any form of immunological hypersensitivity, and is therefore, without scientific basis.[57] Position statements from the American Academy of Asthma, Allergy and Immunology and the National Centre for Health Care Technology (UK) have stated that the treatment and diagnosis of allergic disorders using this method is ineffective and implausible.[20,58]

Other inappropriate and unproven tests

Applied kinesiology refers to the study of muscles and the relationship of muscle strength to health. It is based on the fallacious theory that organ dysfunction is accompanied by specific muscle weakness. The patient holds a glass vial containing the offending specific allergen in one hand, while the practitioner tests the muscle strength of the opposite arm by applying light pressure to the forearm. A positive test is obtained if there is a weakening in the muscle strength in the contralateral arm. Two studies have refuted the validity of these tests, stating that there was an absence of inter-tester reliability and that the test had no correlation with the specific IgE, IgG or lactose breath hydrogen testing.[53,59,60]

Electrodermal testing, also known as VEGA testing, is based on the false theory that an allergy produces a change in electrical resistance in the skin. This involves placing the patient in a circuit of machine that uses a galvanometer to measure the skin conductance. A food extract in a sealed glass vial is placed in contact with an aluminum plate within the circuit, which is in contact with the patient's skin. A galvanometer is used to measure the electrical resistance of the skin. A drop in electromagnetic conductivity or a "disordered reading" indicates an allergy or intolerance to that allergen. Double-blind placebo-controlled studies on the test's diagnostic accuracy revealed poor reproducibility of the method. It was ineffective in diagnosing allergies as it could not even distinguish between atopic and non-atopic participants, or between allergens and negative controls.[61]

CONCLUSION

In patients suspected to have IgE-mediated food allergies with an uncertain diagnosis, the SPT and/or serum measurement of specific IgE antibodies to relevant food extracts are important in the diagnostic workup. Both tests have undergone rigorous clinical evaluations in terms of their validity, and have proven to be of high diagnostic value in predicting food allergies. However, the interpretation of these results requires knowledge of the tests' limitations, in particular the false-negative and false-positive results. DBPCFC still remains the gold standard in the diagnostic approach in patients suspected of having food allergy.

The other tests described are unproven or inappropriate. There is little or no scientific rationale, evidence, or standardisation of these procedures. Furthermore, these tests have poor reproducibility, and the results do not correlate with the clinical evidence of allergy. Despite their commercial availability, these unproven tests should not be used in the evaluation of patients with suspected allergic disease since they do not predict true food allergy or hypersensitivity.

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