CME review

Spice allergy

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Objectives: To provide a review on spice allergy and its implementation in clinical practice.

Data Sources: PubMed searches were performed using *spice allergy* as the keyword for original and review articles. Selected references were also procured from the reviewed articles' references list.

Study Selection: Articles were selected based on their relevance to the topic.

Results: Spices are available in a large variety and are widely used, often as blends. Spice allergy seems to be rare, reportedly affecting between 4 and 13 of 10,000 adults and occurring more often in women because of cosmetic use. No figures were available on children. Most spice allergens are degraded by digestion; therefore, IgE sensitization is mostly through inhalation of cross-reacting pollens, particularly mugwort and birch. The symptoms are more likely to be respiratory when exposure is by inhalation and cutaneous if by contact. Studies on skin testing and specific IgE assays are limited and showed low reliability. The diagnosis primarily depends on a good history taking and confirmation with oral challenge. The common use of spice blends makes identifying the particular offending component difficult, particularly because their components are inconsistent.

Conclusion: Spices are widely used and contain multiple allergens, yet spice allergy is probably markedly underdiagnosed. There is a need for reliable skin testing extracts and serum specific IgE assays. Currently, the diagnosis depends on a good history taking and well-designed titrated challenge testing. Until immunotherapy becomes developed, treatment is strict avoidance, which may be difficult because of incomplete or vague labeling.

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INTRODUCTION

Since ancient times, spices and herbs have been widely grown by many countries, particularly in Southeast Asia, with India being the largest producer by far. Certain spices are so precious that some were even locked in special boxes. The historical role of the spice trade is demonstrated by the commonly taught story of Marco Polo and the spice route to India, as well as the serendipitous discovery of America by Columbus as he searched for an alternative route to India.

Information summarized in this review on spice allergy was derived from a PubMed literature search and from articles procured from the reviewed articles' references lists. Because the subject was sparsely addressed in the medical literature, the search went back for more than 20 years. In addition, online sources, particularly Wikipedia.org, were used to gather common names of spices.

DEFINITION OF SPICE

A few terms need to be defined, particularly the similarities and differences between *spices* and *herbs*. Historically, plants were categorized as *herbs* based on medicinal concoction derived from plant root, leaf, bark, flower, fruit, or seed. Nowadays, the definition of *spices* varies in different references (Table 1). For example, the *Oxford English Dictionary*

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Table 1. Definitions of Spices and Herbs

Source	Spices	Herbs
Oxford English Dictionary	Can be any various aromatic, vegetable product used to season or flavor foods	A seed-producing annual, biennial, or perennial that does not develop persistent woody tissue but dies down at the end of a growing season. Any plant with leaves, seeds, or flowers used for flavoring, food, medicine, or perfume
Culinary definition	Are aromatic seasonings obtained from the bark, buds, fruit, root, and seeds of various trees and plants	Usually come from the leafy part of the plant
American Spice Trade Association	Any dried plant product used primarily for seasoning purposes	Included broadly with spices

differentiates between *spices* and *herbs* based on purpose of use, whereas the general culinary definition differentiates the 2 based on the part of the plant from which it is derived. The American Spice Trade Association, on the other hand, simplifies the definition by merging *herbs* into *spices*.

For the purpose of this review, the term *spice* refers to any plant product used primarily for food seasoning. It would be impossible to provide a complete list of substances used as spices, but the most familiar are listed in Table 2. Blends of various spices are being increasingly used, with variations in their individual components and proportions. Common examples of commercial preparations are given in Table 3.

EPIDEMIOLOGY OF SPICE ALLERGY

Studies on spice allergy are limited and were primarily on adults whose exposure to spices is more than in children. In a series of adults with food allergy,[1] spice allergy was found in 2%. In another series of 589 children and adults with food allergies, the Cercle d'Investigations Cliniques et Biologiques en Allergologie Alimentaire[2] reported that 6.4% of the adults were diagnosed as having spice allergy based on challenge testing or a strong history. None of 402 children was diagnosed as having spice allergy, although the results of skin prick testing (SPT) with 12 spices were positive in 10.8% of instances. Therefore, based on a 2% food allergy prevalence in adults, spice allergy prevalence may be 0.04% to 0.13% in the general adult population (ie, affects between 4 and 13 of 10,000 subjects).

Because spices are ingredients in cosmetics, women are more likely to develop spice allergy, particularly allergic contact dermatitis.[3,4] The degree and duration of an exposure are high risk factors, particularly in certain occupations, such as spice factory workers, butchers, bakers, chefs, restaurant workers, and florists.[5–9]

Table 2. Common Spices by Individual Names Alphabetically[a]

Allspice	Garlic	Saffron
Anise	Ginger	Sage
Basil	Horseradish	Savory
Bay leaf	Jalapeno pepper	Sesame seed
Caraway seed	Licorice	Star anise
Cardamom	Lovage	Tarragon
Cayenne pepper	Mace	Thyme
Celery seed	Marjoram	Turmeric
Chervil	Mint	Vanilla
Chicory	Mustard seed	Wasabi
Chili	Nutmeg	
Chives	Onion	
Cinnamon	Oregano	
Clove	Paprika	
Coriander	Parsley	
Cumin seeds	Peppercorn (black, green,	
Dill	pink, white)	
Fennel	Poppy seed	
Fenugreek	Rosemary	

[a] Additional spices are available worldwide, depending on the geographic area and dietary culture.

BIOLOGIC EFFECTS OF SPICES

Spices are primarily added to food for flavoring and taste enhancement. However, some hot spices (black pepper, paprika, cayenne, and chili) contain irritant and pharmacologically active substances that can compromise the protective barrier function of the mucosa.[10] Furthermore, certain components may have specific actions; for example, piperine in black pepper inhibits paracellular ion transport by producing cellular swelling.[11] Other components in hot spices may enhance their own paracellular transport across the intestinal epithelial layer via substances such as capsaicin, which is found in paprika, chili, and cayenne pepper. In addition, the plant may contain detergent-like substances, such as saponin, which also affect the epithelial barrier.[12] The hotter the spice, the more likely it acts as an adjuvant for sensitization by promoting a transport of molecules less than 70 kDa, which is capable of inducing sensitization.[11]

EXPOSURE TO SPICES

Exposure to spices can be through ingestion, inhalation, or skin contact. Ingestion is mostly responsible for sporadic cases and is the main route in certain populations where

Table 3. A Selection of Common Commercial Spice Blends and Their Components[a]

Spice blend	Components
Bay seafood seasoning blend	Bay leaves, black pepper, cardamom, celery, cloves, ginger, mustard, nutmeg, paprika, pepper, salt
Cajun seasoning	Black pepper, chili powder, garlic powder, nutmeg, onion powder, parsley flakes, red pepper (cayenne), salt
California style garlic blend	Cottonseed, garlic, parsley, soybean oil
Creole seasoning blend	Bay leaves, black pepper, chili powder, garlic, onion, oregano, paprika, red pepper, salt, thyme
Curry powder, general	Cinnamon, cloves, coriander, cumin, nutmeg, onion, peppercorns, turmeric,
Curry powder, Indian	Red chili, coriander, cumin, mustard seeds, black peppercorns, fenugreek, curry leaves, ginger, turmeric
Curry powder, Japanese	Turmeric, coriander, cumin, cardamom, black pepper, chili (cayenne) pepper, clove, fennel, cinnamon, star anise, allspice, nutmeg, fenugreek, bay leaf, sage, oregano, cocoa powder, coffee powder
Curry powder, Thai	Chili pepper, garlic, lime peel, galangal, coriander, lemon grass, black pepper, cumin, fennel, mace, shallots
Five-spice powder blend	Allspice, anise seed, cinnamon, cloves, fennel seed, ginger, pepper
Greek seasoning	Cinnamon, cornstarch, garlic, nutmeg, onion, oregano, parsley, pepper, salt
Ground seasoning blend	Celery seeds, onion powder, salt
Italian seasoning	Basil, coriander, marjoram, oregano, parsley, rosemary, sage, thyme
Ketchup	Allspice, cinnamon, cloves, garlic, onion powder, sugar, tomatoes, vinegar
Ketchup, hot	Cider vinegar, garlic, jalapeno chili, onions, oregano, salt, tomato paste, tomatoes
Lemon pepper	Black pepper, celery seed, citric acid, cornstarch, garlic powder, lemon oil, onion, salt, sugar
Masala powder	Coriander, cumin, garlic powder, paprika, ginger, mango powder, mint, chili powder
Poultry seasoning	Black pepper, cloves, marjoram, nutmeg, rosemary sage, thyme
Season-all	Black pepper, celery seed, chili pepper, coriander, garlic, nutmeg, onion, paprika, salt
Taco seasoning	Chili powder, cornstarch, cumin, garlic, onion, oregano, red pepper, salt
Thai seasoning	Basil, chili peppers, cinnamon, coriander, cumin, garlic, ginger, lemon peel, lime oil, paprika, red pepper, star anise, tomato, white pepper

[a] Adapted from Scholl and Jensen-Jarolim,[11] www.cdkitchen.com, www.justhungry.com, www.articlesbase.com, and www.wikipedia.org.

consumption of spices is high. Inhalation is the main route among workers in the spice trade (farms, factories, groceries). Skin contact is mostly in certain occupations, such as cosmetic handlers, food handlers, butchers, restaurant chefs, and sporadically among homemakers and cosmetic users.[9,13–15] After sensitization, usually low doses are needed to elicit a reaction, with exposure that can be trivial.

MANIFESTATIONS OF REACTIONS TO SPICES

Spices have been reported to cause a variety of reactions that can be nonimmunologic or immunologic and vary according to the route of exposure.

Nonimmunologic Manifestations

Intense exposure to spices can cause irritant effects, most obvious in occupational settings. Chronic skin contact often causes irritant contact dermatitis, whereas inhalation may cause sneezing, rhinorrhea, ocular itching, conjunctival injection, tearing, or cough. Non–IgE-mediated intolerance to spices has been reported by Jensen-Jarolim et al,[16] who could not detect spice specific IgE in some patients with cutaneous reactions to spices, without pollen allergy.

Immunologic (Hypersensitivity) Manifestations

IgE Mediated. IgE-mediated reactions to spices are similar to those to food in general (Table 4). Exposure through inhalation would most likely cause rhinoconjunctivitis, asthma, or, at minimum, a reactive airway. Ingestion typically presents with urticaria, angioedema, anaphylaxis, gastrointestinal syndromes, or other systemic symptoms. In a case report, urticaria, angioedema, rhinoconjunctivitis, and bronchospasm developed during handling of coriander and fenugreek.[17] Another report showed aniseed-induced nocturnal tongue angioedema due to aniseed liqueur ingestion.[18]

Several cases of systemic anaphylaxis have been reported after ingestion of various spices.[17,19–21] A celery-mugwort-birch-spice syndrome was described in a patient with food-dependent, exercise-induced anaphylaxis.[22] In a patient who developed asthma by inhalation of spice dust, the results of skin testing and specific IgE were strongly positive to curry, coriander, and mace.[23] Leukocytes from a healthy donor, after passive sensitization with the patient's serum, released a substantial amount of histamine on challenge with those spices' extracts. Spices were found to be the culprit in some

Table 4. Manifestations of Immunologically Mediated Reactions to Spices

IgE mediated	Non–IgE mediated
Urticaria	Irritant contact dermatitis
Angioedema	Perioral dermatitis
Rhinorrhea	Stomatitis
Conjunctivitis	Allergic contact dermatitis
Wheezing Anaphylaxis	Systemic allergic contact dermatitis

patients who were evaluated for IgE-mediated reactions to foods.[24]

Non–IgE Mediated. Non–IgE-mediated immunologic reactions are mainly of type IV hypersensitivity (T cell mediated). Occupational allergic contact dermatitis from cinnamon, including 1 case by airborne exposure, has been reported.[25] In a cook with contact dermatitis to garlic, patch testing induced a local reaction at 20 minutes and a delayed reaction after 24 hours to both fresh garlic and diallyl disulfide, a low-molecular-weight garlic ingredient, which is compatible with protein contact dermatitis involving both type I and type IV reactions.[26]

Phototoxic cutaneous reactions may occur by exposure to sunlight of the skin areas that had contact with spices. The most commonly implicated spices are parsley and parsnip. These spices contain furocoumarins that on exposure to UV-A induce a local reaction.[27] The eruption is primarily erythematous and can be associated with vesicles or bullae. It appears after 1 to 2 days and subsides in a few to several days, leaving a hyperpigmentation that may last for a few weeks.

In addition to exposure by skin contact, some patients with contact dermatitis may develop a recurrence after ingestion of the specific spice, either recurrence of lesions in the same local area or generalized (systemic allergic contact dermatitis).[28] It appears several hours to a couple of days after ingestion and subsides within several days.

MAIN ALLERGENS IN SPICES

Spices contain a variety of proteins with potential allergenicity, several of which have been identified and characterized (Table 5).[29–32]

Pathogenesis-related proteins (PRPs), a combination of unrelated protein families, are 1 of the main allergens in spices and function as part of the plant defense system. These defense proteins are induced under stress conditions, such as the presence of microbial pathogens, and enable plants to resist biotic and abiotic stressors. An archetype of PRPs is Bet v 1, which is a major birch pollen allergen and belongs to the PR-10 group of PRPs. Bet v 1 was found to inhibit the binding IgE in serum samples of patients with reactions to a variety of spices (anise, fennel, coriander, and cumin), indicating an important role for that allergen in type I hypersensitivity to these spices.[16]

Profilins, an example of which is Bet v 2, constitute a family of conserved proteins with molecular weights ranging from 12 to 15 kDa. They are present in all eukaryotic cells and function as mediators of membrane-cytoskeleton communication.[29] Profilin sequences are highly conserved among plants, with 70% to 80% identical residues in sequences of different species, and profilin-specific IgE was shown to cross-react between pollen and food.[30]

Cross-reactive carbohydrate determinants (CCDs) are carbohydrate structures from many different glycoproteins. The

Table 5. Allergens Identified in Spices[a]

Plant protein	Allergen structure	Examples
Plant defense system	Pathogenesis-related proteins (PRPs)	All are Bet v 1 homologues
	PR-10: intracellular PRP	Api g 1 (celery)
		Cor s 1 (coriander)
		Cum c 1 (cumin seeds)
		Foe v 1 (fennel)
		Pet c 1 (parsley)
		Pim a 1 (anise)
	PR-14: nonspecific lipid transfer protein (nsLTPs)	Onion
		Saffron
Structural proteins	Profilins	All are profilin homologues (Bet v 2)
		Api g 4 (celery)
		Cap a 2 (bell pepper/paprika)
		Cor s 2 (coriander)
		Cum c 2 (cumin seeds)
		Foe v 2 (fennel)
		Pet c 2 (parsley)
		Pim a 2 (anise)
Prolamin	2S albumins	Ses i 2 (sesame)
		Sin a 1 (yellow mustard seed)
		Bra j 1 (oriental mustard seed)
	nsLTPs (PR-14)	Onion
		Saffron
Cupin	7S globulin (vicilins)	Ses i 3 (sesame seeds)
		Fenugreek

[a] From Scholl and Jensen-Jarolim,[11] Vieths et al,[29] Breiteneder and Radauer,[30] Egger et al,[31] and Gomez-Gomez et al.[32]

immunogenicity of CCDs was reported to be strong by some studies[33,34] but not by others.[35]

Lipid transfer proteins belong to the PR-14 group of PRPs and participate in the plant's cuticle formation.[30] As the name implies, they transfer phospholipids from liposomes to mitochondria. They are heat stable and resistant to pepsin digestion.[36] As a result, they are the most commonly implicated allergens in Rosaceae fruits in patients from the Mediterranean area without a prerequisite of sensitization to birch pollen.

Seed storage proteins are exemplified by 2S albumins, which are the major allergens in sesame seed and mustard, and 7S globulin (vicilins), which are major allergens in sesame and fenugreek.[30]

FACTORS AFFECTING SPICE ALLERGENICITY

Spices added to food can be raw, fresh, or dried. As with other foods, allergenicity of spices vary according to the protein's immunogenicity, which may be affected by processing, particularly heating (boiling, roasting, toasting, frying). Heat may reduce the allergenicity of conformational epitopes or enhance it by exposing epitopes that were hidden in the protein molecule. Information on this issue is very limited on spices.

Hot spices, such as paprika, chili, or jalapeno pepper, are routinely processed by drying and grinding. These procedures destroy Bet v 1 homologues and profilins to a large extent, particularly in paprika.[11] A 23-kDa allergen in paprika and related chili peppers has been identified as a P-23 PRP (osmotin), which resists processing. The major allergen Bet v 1 is labile to digestion,[29] which explains cases of oral allergy syndrome without systemic symptoms after ingestion.

IgE reactivity of Bet v 1 and its homologues in foods is mostly conformation dependent. Celery tubers contain both heat-stable and heat-labile allergenic components; in a descending order, heat resistance of celery allergens was highest for CCDs followed by Api g 4 and least for Api g 1.[37] On the other hand, most patients allergic to raw celery reacted to dried celery.

The allergenicity was maintained in dried spices of the Apiaceae family (anise, fennel, cumin, and coriander).[11] The immunogenicity of Bet v 1 and profilin homologues remains intact in roasted poppy seeds. Cross-reactivity between sesame seeds and poppy seeds was found to be very high. Poppy seeds share epitopes with sesame, which is usually dried but often gets toasted on bread.[38]

Heat-resistant IgE reactivity has been demonstrated for CCDs on glycoproteins in celery.[39] High-molecular-weight spices of Apiaceae and Solanaceae expressing CCDs seem to be more resistant to food processing, including grinding, roasting, and cooking. Germin-like protein in dried black pepper retained its capability of IgE binding despite being processed through drying and grinding.[40]

Freeze-drying may alter the allergenicity of spices. Lyophilized spices produced even stronger SPT reactions than the corresponding whole spice extracts.[41]

CROSS-REACTIVITIES OF SPICES

Spices may cross-react with other spices, certain pollens, or certain foods.

Cross-reactivity Among Spices

Information about cross-reactivities among spices is very limited, even within the same botanical family. Clinical and in vitro cross-reactivity has been demonstrated between oregano and thyme, both of the Labiatae family, in a patient who had a systemic allergic reaction to both.[42]

A study of serum samples from 3 patients with work-related asthma in a spice mill demonstrated a 50-kDa cross-reacting allergen between onion and garlic.[9] In a case of a spice seller who had anaphylaxis after the ingestion of paprika but tolerated the other members of the Solanaceae family, serum specific IgE and basophil histamine release tested positive to all Solanaceae plants.[43] However, radioallergosorbent test inhibition studies showed that the particular paprika antigenic determinant recognized by the patient's serum was not shared by the rest of the solanaceous plants.

On the other hand, cross-reactivity among botanically unrelated spices may occur. In a patient who developed rhinitis and asthma after 1 year of using spices in preparing sausage, the SPT result was positive to paprika (dry powder of *Capsicum annuum*, a Solanaceae) and mace (*Myristica fragrans*, a Myristicaceae), and using enzyme-linked immunosorbent assay inhibition assays, a partial cross-reactivity was demonstrated between paprika and mace.[14]

Cross-reactivity With Pollen

For most patients with spice allergy, serologic and clinical cross-reactivities with certain pollens have been reported. In particular, mugwort and birch pollen sensitization represent an increased risk of progression to spice allergy. Ebner et al[44,45] demonstrated that almost every spice tested contained profilin and Bet v 1 homologous proteins. This finding suggests that, except in occupational settings, allergy to spices is rarely a consequence of sensitization through ingestion of the specific spice but rather secondary to sensitization to certain pollens. Patients with spice allergy are often young adults sensitized to mugwort and birch pollen, sharing cross-sensitization with variety of vegetables.[31] An often described condition is the celery-mugwort-spice syndrome, which later became celery-birch-mugwort-spice syndrome. The main allergens responsible for cross-reactivities are homologues of the birch pollen allergen (Bet v 1), the panallergen profilin, and the seed storage proteins germin-like protein and 2S albumins.[11,31] Individuals sensitized to those aeroallergens are at risk of allergy to spices from the following botanical families, in descending order: Apiaceae, Solanaceae, Lamiaceae, Asteraceae, Papaveraceae, Brassicaceae, and, to a much lower extent, Piperaceae, Myrtaceae, Myricaceaea, Orchidaceae, Lauraceaea, Zingiberaceae, and Alliaceae.

The recent use of recombinant allergens increased our understanding of the molecular basis of the observed clinical IgE cross-reactivities. Some studies revealed that the closer the pollen plant family to the spice family, the more likely cross-reactions occur.[16,46] Some molecules have important functions in the plant cell (eg, defense) and are expressed even in distantly related plants. Among these are profilin and Bet v 1 homologues, which seem to be responsible for many cross-reactivities.[45] Bet v 1 homologues have been detected in the botanical family of Apiaceae, comprising celery, carrot, and many popular spices, such as cumin, anise, and fennel.[16] High conservation of Bet v 1 homologues and profilins in the Apiaceae family may be an important cause of cross-reactions within the family and also with pollen.[3,19]

An example of a profilin homologous protein is Cap a 2, which is present in paprika, belonging to the *Capsicum* genus.[47] Expression of the Bet v 1 homologue and the P-23 PRP, which are relevant for IgE binding, vary with the strain of bell pepper.[48] Furthermore, cross-reactivity between bell pepper and latex allergens has been reported.[49] Germin-like proteins have been identified as an allergen in black pepper and are abundant in many food plants, probably including a variety of spices.[50,51]

Cross-reactivity With Foods

A strong correlation has been demonstrated between seed storage 2S albumin proteins and anaphylaxis to sesame.[52] Seed storage proteins constitute a major class of allergens in most edible seeds and nuts (mustard, sesame, peanut, Brazil nut, and walnut).

Cottonseed, a frequent component of certain spice blends (eg, California style garlic blend), has been demonstrated in vitro to cross-react with 2 walnut allergens, Jug r 1 (2S albumin seed storage protein) and Jug r 2 (vicilin-like protein).[53,54] Cottonseed allergen is usually present in chewy foods, such as donuts and certain candy or pastry.

Mustard is a member of the Brassicaceae family, and cross-reactivity exists between rapeseed allergen Bn III napin and the mustard allergen Sin a 1.[55]

Spice cross-reactivity can occur with other foods in the same family. Fenugreek, a legume that is often incorporated in curry, contains the allergens 7S-vicilin and 11S-legumin, which were partly sequenced and revealed considerable homologies to peanut Ara h 1 and Ara h 3, respectively, which can be responsible for clinical cross-reactivity.[56]

DIAGNOSTIC APPROACH

A detailed history taking is of utmost importance in suspecting spice as the cause of an allergic reaction, particularly in patients with occupational exposure. In sporadic cases, it is prudent to rule out allergy to common foods first. If the patient is known to have allergy to certain foods, suspect the presence of such food as a contaminant or incorporated under an unfamiliar name in the food that caused a reaction. In this regard, complete labeling and careful reading of the ingredients would provide valuable clues. Spice allergy should also be suspected in patients who had reactions to fragrances or to multiple unrelated foods or to certain food(s) when commercially prepared but not when prepared at home. The use of a diary to record foods or circumstances that preceded the appearance of symptoms might be of help.

SPT with hot spices is of limited value because of their irritant effect. Testing healthy control subjects would help in determining the optimal nonirritant concentration. Limited information is available on the reliability of commercial skin testing extracts. In 1 study, SPT was performed with native spices (4 mg in 50 μL of saline) and with extracts that were dialyzed to get rid of irritant components.[20,41] The authors reported that the results did not correlate well with the clinical findings. Spice extracts, except white pepper, elicited positive skin test reactions in only half of those with positive skin reactivity to native spices.[41] Prick-to-prick technique would be optimal for fresh spices or when extracts are not commercially available.

Patch testing is used for delayed-type hypersensitivity reactions. Again the optimal concentration is unknown and may vary from one spice to another. A series of 55 patients with contact dermatitis were patch tested for sensitivity to a group of spices at concentrations of 10% and 25% in petrolatum.[21] A concordant positive result of the 2 concentrations was most common with ginger, nutmeg, and oregano. In only 3 of the 55 patients, the result of patch testing was clinically relevant, indicating a low reliability of those concentrations. Therefore, a 25% concentration might be too low for patch testing.[57] In a series of approximately 1,000 patients investigated in a dermatology clinic for occupational skin disease, only 5 were diagnosed as having allergic contact dermatitis to spices.[5] The causative spices were garlic, cinnamon, ginger, allspice, and clove. The patients also had allergic patch test reactions to foods: tomato, lettuce, and carrot. They found that patch testing with spices "as is" is useful, but testing with dilutions was not reliable.

Serum specific IgE testing to some spices is offered by some laboratories, but the degree of reliability has not been sufficiently ascertained. Niinimaki et al[41] found poor clinical correlation with the result of serum specific IgE determined by a commercial laboratory or by an assay developed in their laboratory.

The corollary is that skin testing with spices is generally of low reliability. If spice allergy is suspected despite a vague medical history and negative skin test and/or specific IgE testing result, a spice-free diet may be tried for a few weeks. This may necessitate avoidance of all commercially prepared foods (restaurants or packaged). If definite improvement in symptoms occurs, placebo-controlled challenge tests can be performed by common spices to be selected as guided by the patient.

Oral challenge testing,[58,59] preferably in a blind, placebo-controlled fashion (using opaque capsules), is needed to confirm the diagnosis of type I hypersensitivity. Initially, spice blends or mixtures are used, and if the results are positive, testing with individual components would reveal the specific ingredient. The quantities used should be individualized according to the suspected quantity that caused the reaction and to what is commonly incorporated in a meal. A suggested start dose can be 10 to 50 mg, depending on the anticipated reaction, and then may be doubled at 20- to 30-minute intervals until reaching a cumulative dose equivalent to at least what is usually ingested of that particular spice by the patient, which can be 200 mg to 1 g. The procedure should be designed and done under direct medical supervision. The patient should be closely monitored for the development of symptoms and prompt appropriate treatment.

MANAGEMENT

Symptomatic Treatment

Until the causative specific spice is identified, the patient should avoid the suspected spice and receive treatment for any existing symptoms. Self-injectable epinephrine should be prescribed to patients who have a history of severe acute symptoms.

Avoidance

Once the diagnostic evaluation is complete and the causative spice is identified, the spice should be strictly avoided. The patient should be cautioned regarding packaged foods or eating in restaurants. Reading food labels should be emphasized, although these labels may not be complete. Hence, it would be prudent to avoid any food that potentially may contain spices, particularly by highly allergic patients. Such patients should wear MediAlert identification and have self-injectable epinephrine readily available.

A major obstacle to complete avoidance is the fact that many spices are incorporated in prepared or packaged food, and sometimes the manufacturers or chefs do not want to reveal their "secret recipe." Furthermore, spice blends are common and their components are inconsistent. The US Food and Drug Administration does not regulate spices because they are considered to be generally recognized as safe, which is primarily based on toxicity effect and not on allergenicity potential.[60] In addition, the label may enlist a vague term such as *spice* or *natural flavoring*. Complete and clear food labeling is being increasingly demanded by allergy patients and advocates. Actually, the directive 2003/89/EC of the European Parliament and Council amending directive 200/13, adopted on November 10, 2003 (OJ L308 of 25.11.2003), indicates that all ingredients should appear individually on the label, regardless of the quantity.[11] It is hoped that a complete and standardized nomenclature be used for food labeling.

We did not encounter any trials of immunotherapy with spice or the effect of immunotherapy with cross-reactive pollens. With the pending development of safe, effective immunotherapy protocols for food allergy, trials of immunotherapy with spices might follow.

Spices in Products Other Than Food

To avoid spices that cause allergic symptoms, patients must be vigilant about spice exposure. Besides food, spices are used as ingredients in numerous products, such as peppermint or cinnamon oil used to flavor toothpaste, dental products, or alcoholic drinks. Massage oil contains oil of cinnamon and cloves. Spices such as star anise, sesame seed, vanilla, and rosemary are frequently incorporated in fragrances, cosmetics, and body oils. Patients allergic to Balsam of Peru or related fragrance mixes may react to spices and flavorings, such as cinnamon (cinnamyl alcohol), vanilla, cloves, caraway, curry, allspice, anise, and ginger.[41,61]

CONCLUSION

According to the limited information available, spice allergy seems to be uncommon, although it probably is underdiagnosed. There is a definite need for more studies to update and to expand our knowledge on this area. Spice allergy may be affecting between 4 and 13 of 10,000 adults but would vary geographically, depending on dietary habits and prevalence of cross-reacting pollens. Women are at a higher risk because of cosmetic and fragrance use. Symptoms may be respiratory, dermatologic, gastrointestinal, and rarely anaphylaxis. The main allergens responsible are PRPs, profilins, CCDs, lipid transfer proteins, 2S albumin, germin-like proteins, and other high-molecular-weight proteins. Most spice allergens are degraded by digestion, and hence sensitization is mostly through inhalation of the spice or of cross-reacting pollen.

A suspicion of spice allergy depends primarily on a thorough history taking. SPT and serum specific IgE testing are generally of low reliability. A definitive diagnosis requires well-designed challenge testing. For contact dermatitis, patch testing, though not standardized, might be helpful.

In addition to symptomatic pharmacotherapy, treatment is basically strict avoidance. Such avoidance can be a major task, considering the widespread use of spices, the unknown components of spice blends, and hidden exposures in cosmetics and commercially prepared foods. It is hoped that immunotherapy protocols are developed in the future.

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