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Food-Related Contact Dermatitis, Contact Urticaria, and Atopy Patch Test with Food

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Abstract

A wide variety of foods may cause or aggravate skin diseases such as contact dermatitis, contact urticaria, or atopic dermatitis (AD), both in occupational and private settings. The mechanism of action underlying allergic disease to food, food additives, and spices may be immunologic and non-immunologic. The classification and understanding of these reactions is a complex field, and knowledge of the possible reaction patterns and appropriate diagnostic test methods is essential. In addition, certain foods may cause worsening of atopic dermatitis lesions in children. The atopy patch test (APT) is a well-established, clinically useful tool for assessing delayed type reactions to protein allergens in patients and may be useful to detect protein allergens relevant for certain skin diseases. The APT may even detect sensitization against allergens in intrinsic atopic dermatitis patients, who show negative skin prick test and negative in vitro IgE test results against these allergens. Native foods, SPT solutions on filter paper, and purified allergens in petrolatum have been used for APT. The European Task Force on Atopic Dermatitis (ETFAD) has worked on standardizing this test in the context of AD patients, who are allergic to aeroallergens and food. This recommended, standardized technique involves test application at the upper back of children and adults; use of large, 12-mm Finn chambers; avoidance of any pre-treatment such as tape stripping or delipidation; standardized amounts of purified allergens in petrolatum; and use of the standardized ETFAD reading key. The APT may not be the best working or best standardized of all possible skin tests, but it is the best test that we currently have available in this niche.

Keywords Food allergy · Contact dermatitis · Atopy patch test · Contact urticaria · Reading key

Abbreviations

ICD	Irritant contact dermatitis
ACD	Allergic contact dermatitis
AD	Atopic dermatitis
APT	Atopy patch test
CU	Contact urticaria
DBPCFC	Double-blind placebo-controlled food challenge
ETFAD	European Task Force on Atopic Dermatitis
SCD	Systemic contact dermatitis
SPT	Skin prick test
PACD	Photoallergic contact dermatitis
PCD	Protein contact dermatitis
PTCD	Phototoxic contact dermatitis
PT	Patch test

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Introduction

Foods and spices are capable of inducing immediate type allergy as well as delayed type reactions. Many different food allergens are implicated in causing contact allergies. There are different types of contact dermatitis known (see Table 1): irritant contact dermatitis (ICD), hapten-induced allergic contact dermatitis (ACD), systemic contact dermatitis (SCD), protein contact dermatitis (PCD), contact urticaria (CU), photoallergic contact dermatitis (PACD), and phototoxic contact dermatitis (PTCD) [12]. Affected body parts are those in contact with food, such as hands, lips, and face. Employees in the food processing industry are at a higher risk of developing contact allergies to foods [81, 84].

While contact dermatitis is mainly caused by direct or indirect contact to food, worsening of atopic dermatitis (AD), especially in children, may also be caused by ingestion of food. In order to diagnose contact allergy to food, or worsening of AD due to food consumption, understanding of the different reaction types and diagnostic testing methods is essential. Immediate type hypersensitivity can be detected by

Table 1 Allergens, route of application, and resulting skin disease

Systemic / Topical	Type I allergy	Type IV allergy
Hapten		Contact dermatitis Systemic contact dermatitis
Protein	Contact urticaria Protein contact dermatitis Urticaria Anaphylaxis	Atopic dermatitis Protein contact dermatitis Atopic dermatitis Systemic contact dermatitis

using specific IgE or skin prick tests (SPT) [9]. In order to diagnose delayed type reactions against intact protein allergens, a special patch test (PT) procedure has been developed using protein allergens in an optimized PT setting [19, 92]. The atopy patch test (APT) with food is used predominantly, though not exclusively, in patients with AD to reveal clinically relevant protein allergen sensitization associated with delayed worsening of eczematous skin lesions.

Contact Dermatitis to Food

Irritant Contact Dermatitis to Food

ICD is the most frequently encountered adverse food reaction of workers in the food processing industry [84]. ICD is the result of the direct toxic effect of an agent in contact with the skin. ICD is reflected by a non-immunologic response and occurs soon after contact with the agent. Clinical symptoms may occur within 24 h after contact. Pre-damaged skin (i.e., by wet work or concomitant skin diseases) favors the development of ICD. Acute ICD usually derives from one single cause, whereas other irritant dermatitis usually results from more than one cause.

Most lesions of irritant dermatitis are localized on areas, which are in direct contact with the agent, such as hands, fingertips, or face. Clinical symptoms show a wide variation and may range from only slight scaling over erythema and wheals to blisters and deep burns. Symptoms may sometimes even be hard to distinguish from clinical symptoms of ACD. Burning and itching of concerned body parts accompany the skin lesions.

Foods that are most likely to cause ICD are citrus juices, carrots, corn, garlic, mustard, onion, potatoes, and radish [24, 50, 61, 75]. Food additives that irritate the skin are, among others acetic acid, ascorbic acid, calcium acetate, calcium sulfate, lactic acid, potassium bicarbonate, potassium iodide, potassium bromate, and yeast [6, 12].

Allergic Contact Dermatitis to Food

ACD to food is considered to be relatively rare [12]. ACD is defined as a type IV delayed hypersensitivity reaction. Skin lesions develop within 6–48 h after contact to the offending allergen and subside within several days [6].

Direct contact to fruits, vegetables, and spices is the most common cause of ACD in response to food [6, 12]. Oleoresins in fruits and vegetables are the most frequent allergens causing ACD, with urushiol being the responsible allergen. Well known in the USA for being an allergen in poison oak and poison ivy, it is also contained in mango sap, fruit skin, leaf, or stem of the mango tree. Contact to urushiol from mango most frequently leads to dermatitis of the perioral region. Urushiol is also contained in the seed of the female ginko tree, where it may cause perioral and perianal dermatitis upon ingestion. Food industry workers are at high risk for developing ACD. The most common foods causing ACD in cooks, caterers, chefs, and produce workers are spices, such as garlic, paprika, clove, jamaika pepper, cinnamon, nutmeg, and ginger. Other common causes are bay laurel leaf and vanilla. Twenty out of approximately 60 spices and their essential oils can cause ACD [12].

Systemic Contact Dermatitis to Food

SCD may occur, once a sensitized person is exposed to the allergen orally, transcutaneously, intravenously, or by inhalation.

Clinical symptoms may be indistinguishable from other types of contact dermatitis. The entity may also present with clinically characteristic features. Clinical aspects of SCD may include dermatitis in areas of previous exposure, such as flare ups of previous dermatitis, and previously positive PT sites. SCD may also manifest on previously unaffected skin with vesicular hand eczema, flexural dermatitis, or a maculopapular

rash. SCD may be associated with general symptoms, such as headache, malaise, rhinitis, conjunctivitis, gastrointestinal complaints, or anaphylaxis. Symptoms appear several hours to a couple of days after ingestion of sufficient quantities of the offending allergen and subside within several days [17].

The pathomechanisms of SCD include specific type IV T cell responses and type III reactions, as well as unspecific cytokine release. It is believed that the hematogenous spread of the allergen causes cutaneous reactions. The diagnosis of SCD is confirmed by closed PT, which is reliable and safe [12].

Plants, spices, preservatives, fragrances, and metals may cause SCD. Garlic, onion, quinine tonic water, cashew nutshell oil, and emulsifiers such as gums and propylene glycol are known to cause food-related SCD [30, 80]. Herbals such as chamomile, laurel, and goldenrod may also lead to SCD [23, 68, 71]. SCD has been noticed in patients sensitized to Balsam of Peru. Balsam of Peru is a resin extracted from the *Myroxylon pereira* tree, native mainly to El Salvador. *Myroxylon pereirae* contains naturally occurring flavors such as cinnamic acid, cinnamaldehyde, cinnamic alcohol, methyl cinnamate, benzyl cinnamate, vanillin, and eugenol. Any of the above mentioned ingredients might cause SCD. The most commonly affected body areas are hands, face and anogenital area [2]. Patients with contact dermatitis to *Myroxylon pereirae* may develop SCD from other spices, flavorings, and food. Table 2 gives an overview of foods containing *Myroxylon pereirae*. There have been open studies that show that the elimination diet of *Myroxylon pereirae* improves the dermatitis in over 50% of sensitized patients [59, 70, 82]. Also cobalt, chromium, and nickel can provoke SCD. Patients sensitized to nickel may react to food containing nickel in doses of 5 mg or more. The normal daily ingestion ranges from 150 to 500 μg and depends on the type of food and the food production manner. Table 3 shows foods rich in nickel. A nickel-reduced diet is indicated in patients with severe SCD, if the elimination or reduction of nickel uptake by other means, such as avoidance of tobacco smoke, does not lead to sufficient improvement. The diet should be followed for 1–2 months, and then the patient should be reevaluated, to see if continuation of the diet should be maintained. A quarter of patients benefit from prolonged nickel-reduced diet [4, 83].

Table 2 Food possibly containing relevant amounts of *Myroxylon pereirae* (Balsam of Peru)

Alcoholic drinks: wine, beer, gin, vermouth
Chocolate
Citrus fruits: oranges, lemons, grapefruit, bitter oranges, mandarins
Flavor enhancers: baking products, sweets, chewing gum, tea
Ice cream
Lemonades: Cola drinks
Pickled vegetables: beetroot, cucumber
Perfumed products: perfumed tea, tobacco
Spices: chili, cinnamon, cloves, vanilla, curry, allspice, aniseed, ginger

Protein Contact Dermatitis to Food

In 1976, the term "protein contact dermatitis" was introduced by Niels Hjorth and Jette Roed-Petersen as a novel category of occupational hand dermatitis in addition to ICD and ACD [32]. It was described as eczematous reaction caused by proteins. Initially only patients with positive scratch test results and negative PT were considered to belong to the new entity of contact dermatitis [32]. Later on the definition was extended to patients with positive immediate or delayed reactions in SPT, scratch tests, or PT or no reaction in skin tests at all. At present, also cases with type IV sensitivity to proteins are regarded as PCD.

The lesions of PCD are usually restricted sharply to the area of protein contact. The fingertips show often the first signs of eczematous dermatitis. Clinical symptoms may occur 30 min after contact to the offending allergen and may include itching and stinging [28]. PCD may directly lead to eczematous skin lesions, such as tiny eczematous vesicles but may also begin as CU resulting in eczematous dermatitis [28]. PCD patients suffering from chronic recurrent hand eczema may heal rapidly after avoiding the causative allergen [28].

The pathogenesis behind PCD is not fully understood, but considered to be a combination of immediate type I and delayed type IV reactions [36]. Specific IgE seems to play an important role.

The clinical diagnosis is made if hand dermatitis is associated with a history of immediate reaction to the causative allergen. SPT or scratch tests, specific IgE diagnostics, and PT are performed to confirm the diagnosis. Whereas SPT or scratch tests are usually positive, closed PT shows only occasionally positive results. Even if PT is positive, the diagnosis depends on the demonstration of a positive immediate

Table 3 Food possibly containing relevant amounts of nickel

Hazelnut
Cocoa, dark chocolate
Fruits: almonds, dates, figs, pineapple, plums, raspberries
Grains: bran, buckwheat, whole grain bread, millet, oats, brown rice, sesame seeds, sunflower seeds
Peanuts
Seafood: crab, mussels, oysters, salmon, shrimps
Baking powder
Liquorice
Soya
Vegetables: beans, cabbage, leeks, lentils, lettuce, spinach

reaction [12]. Specific IgE diagnostics may be helpful, but are not as sensitive as SPT or scratch tests are. Nevertheless IgE diagnostics should be performed when possible [8]. If standard tests are negative, the rub test or the open application test may be alternatives. The allergens are preferentially rubbed into or placed on previously affected skin, as positive test results will occur more likely if the causative allergen is applied to previously affected skin [31].

PCD is most frequently induced by occupational exposure; only few cases of non-occupational PCD have been reported.

A wide variety of food may induce PCD [33, 39]. The food allergens found most frequent in patients suffering from PCD are fish or shellfish. Fruit and vegetables like almond, aubergine, asparagus, banana, bean, chamomile, carrot, cauliflower, celery, coriander, chicory, cucumber, endive, lettuce, hazelnut, horseradish, kiwi, lemon, maize, mushrooms, onion, pineapple, potato, tomato, watercress, and caraway, as well as spices like curry, parsnip, paprika, and parsley, and also flour may cause PCD. Meat products like beef, pork, mutton or horse, as well as dairy products are also described to cause PCD [8].

Contact Urticaria to Food

In food-induced CU, the area in contact with the offending substance will react with transient wheals and pruritus. Erythema and edema develop immediately at the site of contact and subside within 45 min. Immunological and non-immunological CU can be differentiated [85].

Non-immunological Contact Urticaria

Non-immunological CU is more common than immunological CU. It is rarely associated with systemic reactions. Direct activation of mast cells, resulting in release of histamine and possibly the release of other vasoactive substances such as substance A, bradykinin, prostaglandins, and leukotrienes are believed to cause the reaction [12].

Foods associated with non-immunological CU are foods that cause direct mast cell activation and release of histamine, such as alcohol, strawberries and tomatoes, and foods that contain histamine, such as matured cheeses, pickled herring, pineapple, red wine, sauerkraut, contaminated tuna, and yeast. Other common causing agents include flavoring agents, preservatives, and other food additives found in soft drinks, chewing gums, and baked goods, such as benzoic acid, sorbic acid, cinnamic acid, cinamic aldehyde, and *Myroxylon pereirae* (Balsam of Peru) [6, 93].

Immunological Contact Urticaria

Immunological CU occurs in sensitized persons, when lipophilic substances, present in certain foods, penetrate the skin—preferentially through the hair follicles. The interaction with preformed IgE in tissue mast cells and circulating basophils leads to their activation, with subsequent release of histamine and other vasoactive substances inducing the urticarial skin lesion. The reaction may clinically manifest as localized urticaria, but also as generalized urticaria, which may be associated with angioedema. Other systemic symptoms may include rhinitis, asthma, and anaphylactic shock [3, 25, 93].

Foods known to cause immunological CU include fish, shrimp, meat, eggs, spices, milk, oats, and tree nuts as well as peanuts [7, 22, 26]. Diagnosis of immunologic CU can be carried out with fresh products using skin tests for type I allergy such as SPT, scratch tests, or open PT, and by determination of specific IgE. The oral challenge is often negative, as the composition of allergens is altered by digestion and cooking [12].

Photocontact Dermatitis to Food

Both visible and UV light may be a relevant co-factor for food-induced skin disease. The mantle diagnosis of photocontact dermatitis can be subdivided into a photoallergic contact dermatitis (PACD) and a phototoxic contact dermatitis (PTCD) type of photocontact dermatitis.

Phototoxic Contact Dermatitis

PTCD is more common than PACD. PTCD or phytophotodermatitis occurs after exposure of the allergen-exposed skin to sunlight, mainly in the UV-A range (320–400 nm). Body parts in contact with food containing photoactivated chemicals are affected. UV light converts the substances into direct toxins for keratinocytes [17].

Furocuomarines (psoralens) are, among other substances, responsible compounds for causing PTCD. These compounds are contained in celery, carrot, lime, lemon, orange, fig, and grapefruit. Most often a linear pruritic dermatitis in areas exposed to the sun, leading to hyperpigmentation in the course, lasting for months, can be observed [12].

Photoallergic Contact Dermatitis

PACD to foods is considered rare. The pathology behind the reaction is a T cell-mediated immune response, as it is the case in ACD. The allergen is activated by sunlight or artificial UV-A light. Cases of patients reacting to garlic have been reported [72].

Atopic Dermatitis Triggered by Food

AD is a frequent, highly pruritic, chronic, or chronic relapsing, inflammatory skin disease, which is diagnosed on clinical grounds. AD is characterized by a typically age-

related pattern of skin lesions combined with intense pruritus [90]. The diagnostic criteria published by Hanifin and Rajka are used most frequently, and based on 3 out of 4 major criteria combined with 3 out of 21 minor criteria. Typical morphology and distribution, chronic or chronically relapsing course, pruritus, and atopic personal or family history form the four major criteria [27].

The etiology of AD is multifactorial and involves genetic risk factors, as well as activation of the innate and adaptive immune system and environmental trigger factors [91]. The pathology underlying AD includes loss-of-function mutations of the profilaggrin gene, reduced skin ceramide content, imbalance of T cell subpopulations, alterations in the dendritic cell populations, and dysfunctional tight junctions, which cause skin inflammation and an impairment of the skin barrier witnessed by an increased transepidermal water loss [86]. The poor skin barrier function allows penetrance of allergens [11]. Aeroallergens and food allergens are the most important allergens for AD [79]. One third of the children with AD report food-related worsening of their AD [16]. As avoidance of the causative allergen can lead to improvement of skin lesions, identification of causative allergens is of utter importance [77]. While SPT and specific IgE reflect early clinical reactions, the APT has a high predictive capacity for late-phase clinical reactions [54]. Important food allergens are, among others, hen's egg, milk, and wheat [54].

Diagnosis of Food-Related Skin Disease

Apart from taking an in-depth personal history and evaluating the patient's clinical picture, in vivo and in vitro tests are needed to establish a diagnosis of food-related skin disease. Depending on the issue being addressed, different types of skin tests may be of use. Specific IgE diagnostics may be of use if the patient's history is suggestive for an immediate type reaction to foods. The gold standard of diagnosing food allergy is the double-blind placebo-controlled food challenge (DBPCFC), but skin tests and serum analysis may be helpful in addition.

Double-Blind Placebo-Controlled Food Challenge

The gold standard of diagnosing food allergy is the DBPCFC [5]. Prior studies have shown that the patients' history alone is not specific in those cases [14, 55]. The DBPCFC is indicated in patients showing worsening of eczema after food consumption.

An elimination diet of approximately 5 to 7 days or an oligo-allergen basis diet of 7 to 14 days must be observed prior to and during the oral provocation tests with suspected foods. The ratio of placebo and verum should be at least 1 to 2, and the volume of all test preparations should be equal. The dose of food is usually raised every 30 to 60 min, until the maximum dose or a clinical reaction is reached. The maximum dose reflects the age-appropriate portion, e.g., one egg or 150 ml milk per day. The observation time follows the reaction type and should be at least 48 h in delayed responses such as AD. As a consequence, only one food item can be tested per week in AD patients. Repeated food provocations over a period of several days and with higher concentrations of suspected food might be needed to exclude false negative test results. A worsening of the SCORAD index of at least 10 to 15 points is required for a clear-cut positive food provocation test with relevance to AD [10, 52].

Skin Tests for Immediate Hypersensitivity

The SPT is the standard diagnostic tool to detect immediate type allergies and an important tool of investigation in CU and PCD. Only limited foodstuffs are available as commercial standardized allergen dilutions. A modification from the standard SPT is the prick-to-prick method. It is used especially for testing fresh foodstuffs: the fresh food is pierced with a SPT lancet and immediately afterwards, the skin is pricked with the same SPT lancet. The test reading is done similarly to the SPT [9, 95].

Scratch testing is an alternative for testing IgE-mediated immediate type reactions to foods, when only non-standardized allergens are available. Five millimeters of long scratches are made with a SPT lancet. Histamine dihydrochloride, 10 mg/ml, serves as positive and saline or 0.1 N sodium hydroxide as negative control. The longest diameter of the wheal transversal to the scratch is measured. Skin reactions at least the size of the positive control are regarded as clinical significant [29].

The open application test, also known as the contact urticaria test, is used to detect non-immunologic and immunologic reactions. It is usually performed on the skin of the upper back or on the outer aspects of the upper arms. Test substances are spread onto 3 × 3 cm areas. Test results are read after 20, 40, and 60 min. Allergic reactions tend to appear faster than non-allergic reactions. The substance itself and the vehicle used determine the maximal reactivity. Erythema and edema are evaluated and documented separately [94].

Rub testing is used to enhance the reactivity in comparison to the open application test. Here, the suspected food or test substance is rubbed ten times with moderate pressure onto healthy or previously affected skin. In the skin application food test, the causative food is put on 4-cm gauze and is either applied to the back with acrylic tape, or put in large Finn chambers for 30 min. The results are followed up for 30–40 min. Both testing methods may be used in cases of suspected food contact allergy [57].

Atopy Patch Test

Definition

The APT is defined as an epicutaneous patch test procedure using protein allergens known to elicit immediate type, IgE mediated reactions, in which the test sites are evaluated for an eczematous, delayed type reaction after 48 and 72 h [67]. The test procedure is somewhat similar to a standard hapten PT, but the nature of allergens differs: intact protein allergens or fresh food products are used in the APT, which are also used to demonstrate IgE-mediated immediate type sensitization in SPTs, whereas haptens are used in standard PTs [41]. In the following, the focus of our review is on food-related APT.

History of APT with Protein Allergens

The date of birth of hapten PT reaches back to the late nineteenth century: The German dermatologist Jadassohn introduced the "Funktionelle Hautprüfung" or "Läppchentest" in 1895 as diagnostic tool for patients with contact dermatitis. Jadassohns co-worker Bloch continued this work and proposed a standardized test series.

In 1937 Rosenberg and Sulzberger were the first to report the application of native proteins in PT [44]. Mitchell and Platts-Mills from the USA further conducted more extensive PT series with aeroallergens in AD patients and controls in 1982, but there was not a standardized definition of the test method or positive reactions at that time [49]. During the following years, various modifications of the APT method would coexist, differing for example in aspects of pre-test tape stripping, abrasion of stratum corneum, or addition of sodium lauryl sulfate to improve the penetration of the test allergen through the epidermis [1, 34, 60, 65, 66, 74].

In 1989, Ring coined the term "atopy patch test" [67]. The APT was standardized in a series of multicenter studies mostly lead by Darsow regarding the allergen concentration, vehicle, time intervals, and preparation of test site in order to develop a reliable diagnostic tool in AD patients for the clinical routine [18, 19, 21, 41]. The resulting protocol of the European Task Force of Atopic Dermatitis (ETFAD) based on avoidance of tape stripping, use of purified protein allergens in petrolatum, large Finn chambers, and readings at 48 and 72 h (Table 5) is currently the best standardized and most reliable protocol regarding sensitivity, specificity, and reproducibility [19, 21]. Other research groups published protocols that differ in one or more aspect, including preparation of the test site, period of time of test application, and allergen preparation [15, 37, 51, 53, 54]. Different results may be reached with quite small changes in protocols, hence the standardization of aeroallergen and food allergen test protocols by the ETFAD was an important contribution and has led to better comparability in multicenter trials.

The first publication about APT with foods was published in 1989. It described a commercial test kit named DIMSOFT, which had been used since 1980 and is now discontinued. The APT of individual foods suspended in dimethylsulfoxide had also been used as a screening method for sensitivity to foods [13]. Langeland described in 1980 the use of a PT in atopic patients with egg allergen prepared in a cream—the concentration was up to 1000 times higher than those used for SPT [45]. Later on, working groups studied the APT with milk and cereals in AD patients [35, 63, 64]. Variations in the applied methodology led to quite diverse percentages of positive APT results. The sensitivity and specificity of the test results would be evaluated against food challenge results, but even these would not all be appropriately standardized for the provocation of eczematous skin lesions [78].

The spectrum of commercially available, standardized APT substances has declined during the last years. As the higher production costs for standardized APT substances are not accompanied by an increased reimbursement for the performing physician, availablility of the APT is at present mostly restricted to academic institutions.

Immunology of the APT

AD is a T cell-based, dendritic cell-mediated chronic inflammatory skin disease, which may be associated with IgE-mediated immune dysregulation [47, 88]. The skin barrier of AD patients is impaired in both seemingly healthy and visibly inflamed skin. Therefore, proteins may penetrate the stratum corneum and act as allergens when taken up by Langerhans cells with low expression of the high-affinity IgE receptor (FcεRI) or inflammatory dendritic epidermal cells (IDEC) with a high level of FcεRI expression [89].

A positive APT reaction is reflected by a lymphohistiocytic infiltrate in histopathology, which closely resembles the early stages of an AD lesion [92]. The early stage of an APT reaction is characterized by an influx of IDEC into the skin lesion, which are detectable in addition to normal Langerhans cells already after 48 h [43]. In contrast, the disease-specific phenotype of the epidermal dendritic cell populations develops only after weeks [43].

The infiltrating Th2 cells secrete interleukin 4 and 13 already 24 h after application of the APT. Inflammatory dendritic epidermal cells are detectable 48 h after APT application in the lesions, and the pattern of infiltrating T cells shifts towards Th1 cells with secretion of Interferon-γ. This can also be observed in chronic AD lesions [69]. The role of IgE-bearing Langerhans cells in the development of the APT lesion is emphasized by the observation of extrinsic AD patients, who are APT positive for house dust mites and carry IgE on their Langerhans cells even in non-lesional

skin [46]. Type I allergy to the allergen causing positive APT results seems not to be a requirement, as intrinsic AD patients lacking specific IgE to house dust mite allergen may show positive APT results to house dust mite [42]. AD patients with allergen-specific peripheral blood lymphocytes show positive APT results more often than those patients without [87].

Clinical Indication for the APT

The most common skin disease associated with food allergy in children is AD. The sensitization to food allergens associated with eczematous skin lesions is not adequately assessed with performing IgE-based diagnostics such as SPT and/or specific serum-IgE alone. The APT can address this unmet clinical need, as shown by a number of studies:

Kekki et al. studied the relevance of APT with foods for the detection of food allergy in correlation with oral food challenge and SPT in atopic infants. They showed that an APT with food improved the accuracy of skin testing in the diagnosis of food allergy in infants with AD. There are cases of challenge-proven food allergy in children published, who did not show specific IgE in their serum, but a positive APT result [40]. Similar cases are published for house dust mite allergic adult AD patients [42].

Strömberg found the ATP to be more sensitive than the SPT in diagnosing food allergy in children with AD, especially in those under 2 years of age [76]. An APT with hen's egg, cow's milk, cereals, and peanut may improve the identification of food allergy in patients with suspected food allergy and negative SPT and specific IgE, in patients with severe or persistent AD and unknown trigger factors, and in AD patients with multiple IgE sensitizations of unknown clinical relevance [79]. There is a need of further APT studies investigating more foods, and of the APT in other food-related diseases.

Technical Aspects of the APT

The APT is performed in a similar technique to a standard PT for contact allergy to haptens, but the high molecular weight of the protein allergens in the APT calls for certain modification of the basic technique. The ETFAD has developed and published a standardized APT protocol for testing purified aeroallergens and food allergens in petrolatum (Table 5) [41].

Test Materials and Vehicles for APT

Native foods, SPT solutions on filter paper, and purified allergens in petrolatum have been used for APT [92]. As the APT with fresh food and SPT solutions is not well standardized, and there are different methods of preparing the allergens, these modifications may lead to variable results (Table 4). Most of the APT studies performed have investigated only cow's milk, hen's egg, and wheat. Testing of food dissolved in vehicles and testing of native food essentially led to similar results.

Niggemann et al. diluted food allergens tested (cow's milk, hen's egg, soybean, and wheat) in a 1:10 solution in parallel to exclude false positive results by irritative reactions. They found 18 out of 77 (23%) positive results in the diluted APT. These reactions were observed in those patients with the strongest reaction to the undiluted ATPs. All of the mentioned patients reacted with eczemas in the DBPCFC. They concluded that the APT results are not biased by unspecific, irritative reactions and that native foods are suitable for performing APT [51].

These results confirmed earlier work of Darsow et al., showing that higher protein concentrations and petrolatum as a vehicle would yield the best results with aeroallergens [20]. Unluckily, the availability of standardized APT substances has declined during the last years, calling for alternatives to be evaluated [92]. As long as there is no validation data available for commercial SPT extracts, the EAACI recommends to use fresh food instead of SPT solutions for the APT [79].

Application Site of the APT

There are no published studies comparing different body regions for APT application. The back is generally chosen in children and adults (Fig. 1) [79].

Chamber Material and Chamber Size

All APT studies, apart from the Diallertest study, use round aluminum chambers (Finn Chamber, Epitest Ltd., Oy). Niggemann et al. compared standard (6 mm) and large (12 mm) chamber sizes in a comparative study involving 30 children, who underwent 55 DBPCFC. Significantly better results could be achieved with the larger, 12-mm chambers. The authors recommend to use 12-mm test chambers for an APT with food, even in infants and small children with small backs [56]. Other study groups found good correlations between DBPCFC and APT with 8-mm chambers, but did not compare chamber sizes [35, 40, 76].

Reay-To-Use APT

Kalach et al. compared a ready-to-use APT with a conventional Finn chamber APT for cow's milk allergy in AD children. A mixture consisting of two thirds of a powdered cow's milk product and one third of a hypoallergenic infantile cow's milk formula was diluted in water. One drop was applied to Finn

Table 4 Variation in published APT techniques for food allergens

	Polulation age	Test area	Pre-treatment	Chamber size	Test substance	Allergen concentration	Allergen	Reading time
Darsow [96]	Children and adults	Upper back	None	12-mm Finn chambers	Purified allergen in petrolatum	Standardized	Egg white, wheat flour, celery	At 48 and 72 h
Niggemann [97]	Children	Back	None	12-mm Finn chambers	Native foods in water	Not standardized	Cow's milk, hen's egg, wheat, soybean	At 48 and 72 h
Kalach [98]	Children	Back	None	11 mm/26 mm Diallertest®	Cow's milk protein/cow's milk formula	Standardized	Milk	At 72 h
Langeveld-Wildschut [99]	Not described	Back	10 tape strippings	Not described	Not described	10,000 units/ml	House dust mite, grass pollen	At 24 and 48 h
Fogg [100]	Children	Back	None	12-mm Finn chambers	Not described	Not described	Cow's milk, soy, egg, wheat, rice, oat	At 72 h

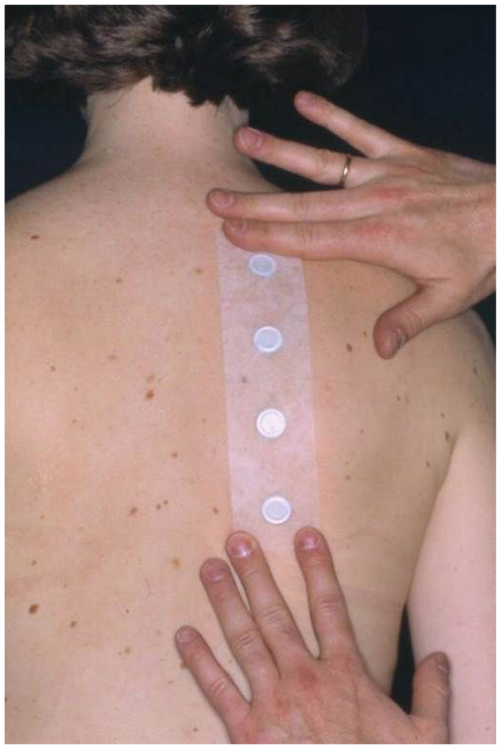

Fig. 1 Application of the APT

chambers or to the ready-to-use APT and put on the children's backs. The authors found that the ready-to-use APT would exhibit a higher sensitivity (76 vs 44%) and test accuracy (82.9 vs 63.4%) in challenge-proven cow's milk allergic atopic children compared to the conventional test. Both test methods exhibited a high specificity and positive predictive value [38].

Age Dependency

The spectrum of allergens triggering AD flares is known to change from mostly food allergens during childhood to mostly aeroallergens in adults. In consequence, the APT with aeroallergens has been mostly studied in adults, whereas APT with food has been studied more in infants and children.

One study found no significant difference regarding sensitivity, specificity, negative, and positive predictive value of APT with foods in five different age groups (< 11 months being the youngest, > 60 months the oldest age group) confirmed by DBPCFC [58]. Another study group reported that positive APT testing with food is more frequent in patients younger than 2 years than in the patients above 2 years of age [76]. Seidenari et al. investigated the APT with peanuts in children and adults using the same study design. Positive APT results were more frequent in patients < 6 years of age. The APT sensitivity proved to be higher than the SPT sensitivity, especially in patients aged 12 years and younger [73]. In conclusion, younger patients show positive APT results more

frequently than adolescents or adults, which may be a consequence of the weaker skin barrier during childhood age [79].

Duration of Application before Reading

Regarding the occlusion time, one study group compared results obtained after 24-h occlusion period with those obtained after 48 h. They performed 64 open oral food challenges in 48 children with the median age of 14 months. The 48-h occlusion time led to better results regarding sensitivity, specificity, positive predictive value, and negative predictive value of the APT [18, 62]. Darsow et al. also found that readings after 24 h led to much worse results than readings after 48–72 h in 314 AD patients with both aeroallergen APT and food APT and recommend readings after 48–72 h (Fig. 2) [18]. Therefore, the standardized ETFAD procedure for APT recommends an occlusion time of 48 h, as well as large Finn chambers for the APT [41].

Reading Key for APT Reactions

The reading of APT reactions does not follow the usual three-step reading key for a hapten PT. Older publications on the APT were mostly based on a five-step reading key. Following the consensus meeting of the ETFAD taking place in Barcelona on October 15, 2003, a new, four-step reading key is used (Table 5) [41].

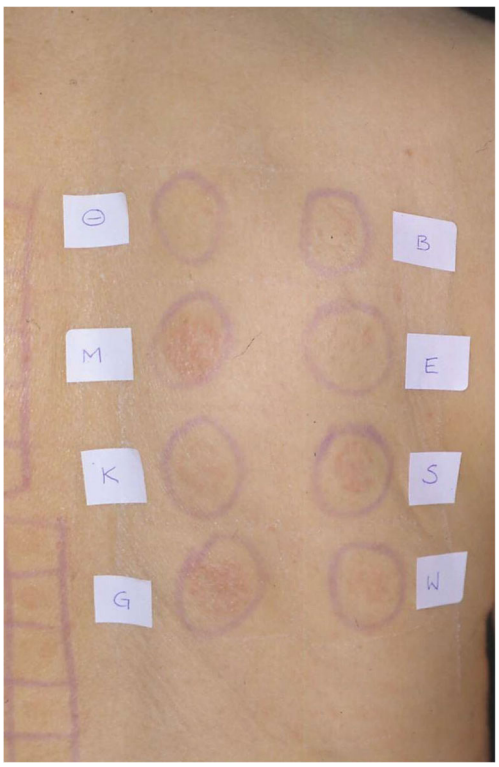

Fig. 2 Positive APT reaction

Sensitivity, Specificity, and Reproducibility of APT Reactions

Benchmark data for the APT regarding sensitivity, specificity, and reproducibility of the procedure may vary largely with seemingly small changes of the test procedure chosen, the patient group studied, the clinical definition of the condition to be identified, and number of test substances to be reproduced. While the relevance of positive APT reactions to food allergens can be shown by food provocation tests, the relevance of an APT reaction to aeroallergens relies strongly on the patient's history.

In consequence, published data from different institutions may be difficult or even impossible to compare.

The sensitivity of the APT for late-phase clinical reactions was 76%, and the specificity was 95% in a study by Niggemann et al. [54]. Of the 133 performed oral food challenges with allergen, 77 were assessed as positive. Specific serum IgE was detected in 86% of the food challenges, whereas the SPT was positive in 83% and the APT in 55% of these cases.

Table 5 ETFAD inclusion/exclusion criteria, protocol, and reading key for APT

ETFAD inclusion/exclusion criteria for APT	
Test site free of topical steroids for 7 days	
Test site without ultraviolet treatments for 4 weeks	
Patient free of oral steroids	
Patient free of oral cyclosporin A of oral tacrolimus	
Avoidance of antihistamines for 5 days (to be evaluated)	
ETFAD protocol for APT	
Test area is upper back	
No tape-stripping or acetone treatment	
12-mm Finn chambers on Scanpor tape	
Purified allergen in petrolatum as test substance	
Allergen concentration standardized in biologic units or µg/mL major allergen content	
Reading at 48 and 72 h	
ETFAD reading key for APT (ETFAD consensus meeting, October 15, 2003)	
–	Negative
?	Only erythema, questionable
+	Erythema, infiltration
++	Erythema, few papules
+++	Erythema, many or spreading papules
++++	Erythema, vesicles

Finn chambers (Epitest Ltd. Oy, Tuusula, Finland); Scanpor tape (Alpharma AS, Norgesplaster, Vennesla, Norway)

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While specific IgE correlated with immediate type reactions, a positive APT was associated with late phase reactions [54]. They also investigated whether the combination of specific IgE, SPT, and APT could improve the diagnostic value in atopic patients suffering from hen's egg and cow milk allergies. Concerning cow's milk allergy, the APT was the best single predictive test with a positive predictive value of 95%. The combination of specific IgE and APT or positive SPT and APT improved the positive predictive value to 100%. Evaluating hen's egg allergy and wheat allergy, the APT was also the best single predictive test with a positive predictive value of 94%. A combination of tests did not optimize the positive predictive value. They concluded the DBPCFC to be redundant in patients with suspected cow's milk or hen's egg allergy [51].

Majamaa et al. evaluated the relevance of different skin tests and the concentration of cow's milk-specific IgE antibodies in correlation with oral cow's milk challenge in 143 infants (< 2 years old) with suspected cow's milk allergy. Seventy two of the performed food challenges were positive. Of these infants, 26% showed elevated specific IgE to cow's milk, 14% were SPT positive, and 44% had a positive APT for cow's milk. Fifty infants showed late phase reactions of either eczematous or gastrointestinal type. The SPT was mostly negative in patients with positive APT. Hence, the APT was a more sensitive method than the SPT or specific IgE to detect cow's milk allergy [48].

Isolauri and Turjanmaa showed an association between reaction type and result of SPT and APT in 138 children aged 2 to 36 months who were challenged with cow's milk in either an open or double-blind, placebo-controlled setting. The challenges were interpreted as positive in 54% of children, and 51% of these children elicited delayed-type eczematous lesions. A good correlation was found regarding reaction type and test type: children reacting to milk challenge with acute-onset reactions were test positive to milk via SPT in 67%, whereas APT were mostly negative. On the other hand, APT was positive in 89% of children reacting with delayed eczematous reactions, while SPT was negative. The authors proposed to perform both SPT and APT in order to enhance the diagnostic accuracy [35].

Darsow et al. could show an allergen-specific concordance of clinical history and APT in 77% (hen's egg), 78% (wheat flour), and 79% (celery) of test reactions. The sensitivity regarding the clinical history was only 30–33%, whereas the specificity was 91% [21].

Summary and Conclusion

Skin contact to foods is common, both in occupational and private settings. Cutaneous exposure to foods, food additives, and spices may cause immunologic and non-immunologic skin reactions. The incidence of food-induced contact allergy, CU, and food allergy-triggered AD is not known exactly, but probably underreported. To confirm a diagnosis of food allergy, knowledge of the possible reaction patterns and appropriate diagnostic test methods is essential. Certain foods may cause worsening of AD lesions in children, especially in severely affected children. The APT is a well-established, clinically useful tool for assessing delayed type reactions to protein allergens in patients. In the context of AD patients allergic to food and aeroallergens, the APT may be useful to detect type IV allergy against protein allergens relevant for the patient. The APT may not be the best working or best standardized of all possible skin tests, but it is the best test that we currently have available in this niche. The availability of standardized test preparations is limited, but may increase with a better reimbursement for this test.

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