



Sesame allergies: clinical significance, diagnosis, and therapy

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Abstract

Background Sesame (*Sesameum indicum*) belongs to the pedalium family (Pedaliaceae) and is used primarily in the preparation of food, especially in oriental and Asian cuisine. As a so-called emerging allergen, it is becoming increasingly relevant in the everyday routine of physicians active in the field of allergology in the wake of the globalization of dietary habits and the general trend towards vegetarian and vegan lifestyles. Due to the increased occurrence of anaphylactic reactions to sesame, the European Union has included sesame in the list of food allergens requiring labeling. In addition to its use in private and industrial food preparation, sesame is also utilized in the cosmetics and pharmaceutical industries.

Materials and methods This paper is an overview of selected scientific articles and is based on research in PubMed and specialist databases.

Results Immediate-type IgE-mediated reactions (type I according to Coombs and Gell), as well as delayed-type contact allergic reactions (type IV according to Coombs and Gell), to products containing sesame and sesame oil have been described. The clinical spectrum is broad and ranges from contact urticaria and dermatitis to fatal anaphylaxis. Important allergens in immediate-type allergy include albumins, vicilins, oleosins, and globulins; relevant contact allergens include sesamol, sesamin, and sesamol. The diagnostic work-up for suspected sesame allergy includes skin tests, which should preferentially be carried out with native allergens due to their higher sensitivity and specificity, as well as determination of sesame-

specific IgE antibodies. However, lipophilic oleosins in particular are underrepresented in analytical methods. Differentiated, component-based IgE diagnostic testing is desirable. Oral provocation is the gold standard, whereby it is important to ensure low and safe initial doses as well as adequate maximum doses.

Conclusion Beside diagnostic measurements including skin tests, detection of IgE antibodies and oral provocation tests, the education of patients with sesame allergy is of particular importance. This serves, firstly, to prevent recurrence of allergen exposure and, secondly, should contain information on self-management in the case of repeated reactions. The value of oral tolerance induction and preventive measures such as early introduction as a dietary supplement remains to be clarified in the future.

Keywords Sesame · Sesame seeds · Sesame oil · Oleosins · Allergy · Anaphylaxis · Cross-reactivity

Abbreviations

AGATE	Working Group on Anaphylaxis Training and Education (<i>Arbeitsgemeinschaft Anaphylaxie—Training und Edukation</i>)
BAT	Basophil activation test
DEGS	Study on Adult Health in Germany (<i>Studie zur Gesundheit Erwachsener in Deutschland</i>)
IgE	Immunoglobulin E
kDa	Kilodalton
NPV	Negative predictive value
OPT	Oral provocation test
PPV	Positive predictive value
WDEIA	Wheat-dependent exercise-induced anaphylaxis

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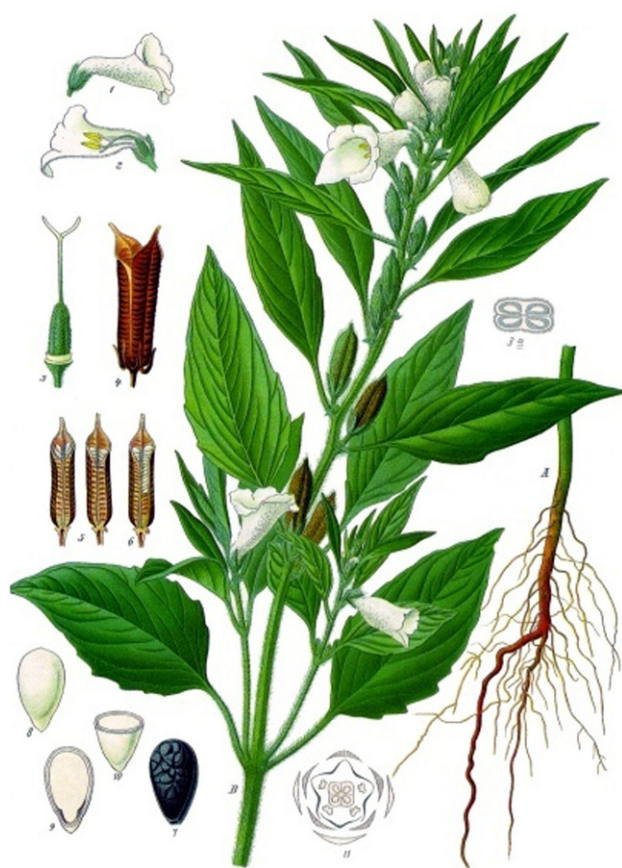


Fig. 1 *Sesamum indicum* from [2]. A Root; B blossoming and fruit-bearing plant; 1 flower seen from the side; 2 flower in longitudinal section; 3 pistil; 3a pistil in cross section; 4 ripe fruit splitting open; 5/6 capsule halves separated from each other and opened; 7 black sesame seeds; 8 white sesame seeds; 9 seeds in longitudinal section; 10 seeds in cross-section; 11 diagram

Introduction

Sesame (*Sesameum indicum*) is a plant belonging to the pedaliaceum family (Pedaliaceae). It is an annual herbaceous plant (Fig. 1) that usually grows to a height of 10–120 cm and occasionally to as much as 180 cm. The seeds ripen in a fruit capsule that reaches a length of approximately 2–8 cm, its width varying between 0.5 and 2 cm. Sesame seeds are typically around 3–4 mm long, ovate, and flattened, measuring around 2 mm wide and 1 mm thick. The size, shape, and color of seeds can vary considerably according to botanical species. The color of the seeds of the world's most widely traded sesame species is creamish-white. Other common colors include yellowish-brown, brown, golden-yellow, reddish, gray, and black [1].

The occurrence and use of sesame or sesame components

Due to its high lipid content, sesame has been utilized as an oleaginous fruit for thousands of years.

The seeds have an approximately 17% protein content [3, 4]. In 2005, sesame seeds were included in the European Union list of food allergens subjected to declaration. Other countries like Canada, Australia, and New Zealand also legally require sesame to be labeled as a food allergen [5]. Terms used as synonyms for sesame include, among others, *ajonjolí*, *benne*/benne seed, *gingelly*, *sesamol*/sesamolina, *Sesamum indicum*, *sim sim*, *tahina*/tahini, or *teel*/til [6]. It is used in industrial and private food preparation, e.g., as a seed or (due to its more intense taste than unrefined) oil for the preparation of Mediterranean, oriental, or Asian dishes. [6–8]. Typical sesame-containing convenience foods include vegetarian ready meals, confectionery and bakery products, breakfast cereals, soups, marinades, salad dressings, sauces, chutneys, as well as protein bars and snacks [6]. Traces of sesame can also find their way into various foodstuffs, such as loose bakery products, during the food production and preparation process. However, this mode of accidental allergen exposure via contamination is an exception.

The most frequent anaphylactic reactions following the consumption of sesame-containing foods have been described in children after eating hummus and tahina/tahini, and in adults after eating burger rolls, (full grain) bread, halva, hummus, tahina/tahini, sesame oil, oriental food, and sesame-containing bars [9]. Thus, the triggering foodstuffs are usually products known to contain sesame. A study conducted in Australia investigated 1355 packaged articles from a supermarket in Melbourne for allergen labeling. Sesame was found to be listed as an ingredient in 6.1% of the products and a precautionary allergen label relating to sesame was found on 27.5% of the products. As such, it was the third most frequent allergen with a precautionary allergen label. Common foodstuffs with a label indicating sesame as a potential ingredient included spicy (86%) and sweet (71.1%) pastries and bread products (73.3%) [10].

Furthermore, sesame is also used as (mostly refined) oil in the pharmaceutical and cosmetics industries [6, 8]. For example, sesame oil can be found in injectable drugs such as sex hormones, neuroleptic drugs, and vitamin D preparations, as well as oral medications such as dronabinol-containing Marinol® capsules [8, 11]. Other (chemically modified) components of sesame, such as hydrolyzed sesame protein (INCI), are also used in the cosmetics industry as skin care and hair conditioning agents [12]. Typical sesame-containing agents include moisturizing oils, ointments, creams, lotions, lip balms, soaps, shampoos, and cosmetics for application to the eye area [6].

Epidemiology

The incidence and prevalence of anaphylactic reactions to sesame varies worldwide according to region

and dietary habits. The latter is estimated to be 0.1–0.2% in countries where sesame is used as a food-stuff [13]. In Israel, sesame is the third most common cause of IgE-mediated food allergies and the second most of food-induced anaphylactic reactions in children aged less than 24 months. There, the prevalence of allergies to food containing sesame is 0.18–0.2% [14] at the age of 1–24 months and 0.13% at the age of 4–18 years [15], with the mean age of first manifestation in children and adolescents being 1 year [16]. Retrospective studies in Lebanon showed sesame sensitization in 3.79% of infants, 2.65% of children, and 1.91% of adults with food-induced IgE-mediated allergic reactions in their previous history, whereby anaphylaxis was the only clinical manifestation in the sesame-allergic patient population [17].

Allergic reactions to sesame have also been described in Western countries in the last five to six decades. This is presumably due to the globalization of dietary habits and increased sesame consumption in the Western world, as well as a trend toward vegetarian and vegan diets. In particular Middle Eastern cuisine and Mediterranean dishes contain sesame or components of sesame. Examples here include the dessert Halva or the sesame-based paste tahina (also known as tahini), which is an ingredient of hummus [6]. The Study on Adult Health in Germany (*Studie zur Gesundheit Erwachsener in Deutschland*, DEGS1) conducted between 2008 and 2010 found the prevalence of sesame sensitization (independent of the actual data on allergic reactions) to be 6.5% [18]. According to data in the anaphylactic registry Anaphylaxie.net from European and non-European centers, sesame is the twelfth most common food allergen (in 52 of 3308 food-allergy sufferers) and of equal relevance in children ($n=27$) and adults ($n=28$). If one looks at the registry data only for Germany, Austria, and Switzerland, sesame is the thirteenth most common food allergen and is responsible for 26 of 2098 documented cases of food-induced anaphylaxis (69% in Germany, 23% in Switzerland, and 8% in Austria). More precisely, 15 reactions affected adults, 11 affected children, with a total of 73% showing severity level 3 and 23% severity level 2 according to Ring and Messmer (as of 5.09.2017, personal correspondence from Dr. Dölle and Prof. Worm; further information at www.anaphylaxie.net). The prevalence of sesame allergy was found to be 0.79% [15] in British children, and 0.8% in Australian children aged up to 12 months; however, the latter analysis was based on reactions in the patient history and took in account also reactions delayed by up to 1 day [19]. A telephone survey found an age-independent prevalence of 0.1% in the US [20]. In 2002, the French national database for the detection of clinically confirmed allergic reactions (CICBAA) showed a prevalence of 2.14% in children and as much as 5.81% in adults [21]. Sesame-containing foods were responsible for 3% of life-threatening allergic reactions in France [22]. On the basis of this

data, sesame seeds were included in the European Union list of food allergens subjected to declaration in 2005 [5].

Sesame allergy usually develops in childhood or adolescence. In one survey, only 13% of respondents reported being over 16 years of age at the time of initial manifestation [9]. However, individual case reports certainly provide evidence of initial onset also in adulthood [23]. Risk factors for the development of sesame allergy include atopy (especially atopic dermatitis) and other food allergies, in particular to tree nuts and peanuts [7, 9]. In most cases, IgE-dependent sesame allergy persists: one study revealed that allergic reactions resolved in only around 20% of patients after an average of 6.7 years [16]. Another study found that tolerance developed in nine of 30 children after 2.8 years on average [24]. A study conducted in Texas reported tolerance development in 45% of sesame-allergic children at a median age of 3.3 years, accompanied by decreased allergen-specific IgE [25].

Pathophysiology and symptoms

A distinction can be made between two types of sesame allergy: immediate-type and—albeit extremely rare—delayed-type allergic reactions. The former are generally attributed to IgE-mediated sensitization to sesame proteins, the latter to T-cellular hypersensitivity to proteins in the lignin-like protein group found in sesame oil [23, 26, 27]. Various subtypes of immediate-type reactions have been described following consumption of sesame seeds (and products derived from them), as well as sesame oil and foods containing sesame oil. These range from oral contact urticaria (oral allergy syndrome) to extremely severe, even fatal, anaphylactic reactions [6, 13]. The latter can also occur in the form of summation or stress-induced anaphylaxis [6, 28]. Furthermore, asthmatic reactions due to allergen inhalation exposure when handling sesame have been reported [6, 29]. Pathophysiologically, these reactions are consistent with IgE-mediated anaphylaxis; however, there are also case descriptions in which sesame-specific IgE antibodies were not detected [30].

In addition, numerous case reports describe contact allergic reactions to sesame oil or preparations containing sesame oil [26, 27, 31, 32]. Sesame oil is used in various forms of popular medicine as a topical preparation, e.g., in traditional Chinese medicine to treat a variety of inflammatory skin disorders or leg ulcers [32]. It is attributed with analgesic, antioxidant, antibacterial, and anti-inflammatory properties, among others [33].

Allergens

As part of allergen diagnostics, it is important to differentiate between immediate-type allergens and contact allergens in sesame. With regard to IgE-mediated

Table 1 Single allergens of the sesame seed in immediate-type reactions (modified from [6])

Sesame allergen	Major group	Molecular weight (SDS-PAGE)	Relevance
Ses i 1	2S Albumins	9 kDa	Detected in 10 out of 10 patients (immunoblot with full antigen) [35]
Ses i 2	2S Albumins	7 kDa	Detection in 6 of 20 sesame-allergic patients (immunoblot with full antigen) [36]
Ses i 3	7S Vicilins	45 kDa	Detection in 15 of 20 sesame-allergic patients (immunoblot with full antigen) [36]
Ses i 4	Oleosins	17 kDa	Detected in 29 of 32 patients (immunoblot with extracted sesame oil bodies) [37]
Ses i 5	Oleosins	15 kDa	See Ses i 4 [37]
Ses i 6	11S Globulins	52 kDa	Detected in 13 of 25 patients (immunoblot with full antigen) [38]
Ses i 7	11S Globulins	57 kDa	Detected in 10 of 24 patients (immunoblot with full antigen) [38]
Ses i 8	Profilins	14 kDa	Rarely clinically relevant [39]

reactions, eight allergen components have been characterized more precisely to date: the 2S albumins Ses i 1 and 2, the 7S vicilin Ses i 3, the oleosins Ses i 4 and 5, and the 11S globulins Ses i 6 and 7 (Table 1). Ses i 8 is a panallergen in the profilin group. According to current knowledge, there is no commercially available test kit for the detection of IgE antibodies against these individual allergens as yet. In a collective of 10 sesame-allergic subjects, an Italian working group described other potential major allergens that have not yet been further characterized. For example, in immunoblot studies, 10 sera displayed reactivity at 20 kilodalton (kDa), while seven of 10 showed reactivity at 32 kDa. Individual sera also showed weaker reactivity at 28, 43, 48, and 67 kDa [34].

This variability in IgE sensitization profiles to different sesame allergen groups can likely be explained by cultural, dietary, genetic, and botanical differences. Furthermore there appear to be geographical differences in sensitization patterns due to the differing presence of cross-reactive pollen and foods. A study on six sesame-allergic Dutch patients found the oleosins Ses i 4 and 5 to be the main allergens in five of six subjects, while four of six had parallel (less pronounced) sensitizations to the storage proteins from the group of 7S and 11S globulins. All patients in whom oleosin was identified as the major allergen showed (severe) anaphylactic reactions, whereas one patient with oral allergy syndrome exhibited no reactivity to this allergen fraction [40].

Cross-reactivities to various allergens are seen; examples include tree nuts and peanuts. For instance, children sensitized to these foods in the skin prick test show positive reactions to sesame significantly more often than non-sensitized children. Furthermore, the probability for children with a previous history of allergic reactions to tree nuts and peanuts to exhibit an allergy to sesame seeds is significantly increased (OR=10.2, 95% confidence interval (CI): 2.7–38.7, $p<0.001$; [41]). An example of a cross-reactive allergen is the 7S vicilin Ses i3, which displays 80% sequence homology to Ara h 1 in peanut [23]. Clinically, cross allergies between sesame seeds and a variety of foods such as kiwi, peanuts, poppy grain, rye seeds, and tree nuts have been described [6]. Corresponding cross-reactivities have also been shown in

laboratory tests (tree nuts to hazelnuts, black walnuts, macadamia, cashew nuts, pistachios) [23, 42]. Inhibition tests in a patient with oral allergy syndrome following sesame consumption revealed 94% and 88% cross-inhibition of IgE reactivity to sesame by cashew nuts and hazelnuts, respectively. The authors suspect this to be due to profilin sensitization. It was possible to detect 21% cross-inhibition by grass pollen, but not by hazelnut in a patient with a previous history of sesame anaphylaxis and serological detection of oleosins as major allergens [40]. Two out of three children with sesame allergy in a Texas cohort were concomitantly allergic to peanuts and one out of three was allergic to tree nuts (walnut, cashew nut, and almond). Allergies or sensitizations to peanuts or tree nuts (e.g., cashew nuts, walnuts, and hazelnuts) were also frequently detected in sesame-sensitized patients without clinically manifest sesame allergy. While cross-reactive allergens from these nuts were shown to be responsible for potentially false positive results in skin prick testing and the determination of sesame-specific IgE antibodies, median sesame-specific IgE was found to be 10-fold higher in patients with manifest sesame allergies than in individuals only sensitized to sesame [25]. On the whole, although there is a wide range of molecular cross-reactivities, their clinical relevance is not always clear (Table 2).

In addition to immediate-type allergens, sesame oil also contains a number of potential contact allergens. These are mainly suspected in the unsaponifiable fraction of sesame oil (containing, e.g., lignine-like proteins such as sesamol (up to 0.54%), sesamin (up to 1.0%) and sesame oil (up to 0.1%), [31]), since no delayed-type reactions to peanut and olive oil, which contain the same triglycerides as sesame oil, were seen in a patient collective with contact allergy to sesame oil [45]. Sesamol and sesamin have been identified as the main triggers of contact allergic reactions to sesame-containing external agents [26, 27, 31]; however, delayed-type reactions to sesamol have also been described [26]. For example, 12 of 13 subjects with contact allergy to sesame oil tested positive to sesamol and sesamin in patch testing with purified individual proteins, while eight of these 13 subjects tested positive to sesamol [26]. However,

Table 2 Molecular cross-reactivity (from [43, 44])

Food	2S Albumins	7S Vicilins	Oleosins	11S Globulins
Green kiwi <i>Actinidia deliciosa</i>	Act d 13	–	–	Act d 12
Cashew <i>Anacardium occidentale</i>	Ana o 3	Ana o 1	–	Ana o 2
Peanut <i>Arachis hypogaea</i>	Ara h 2, Ara h 6, Ara h 7	Ara h 1	Ara h 10, Ara h 11, Ara h 14, Ara h 15	Ara h 3
Brazil nut <i>Bertholletia excelsa</i>	Ber e 1	–	–	Ber e 2
Pecan nut <i>Carya illinoensis</i>	Car i 1	Car i 2	–	Car i 4
Chickpea <i>Cicer arietinum</i>	Cic a 2S albumin	Cic a 1	–	Cic a 6
Hazelnut <i>Corylus avellana</i>	Cor a 14	Cor a 11	Cor a 12, Cor a 13	Cor a 9
Walnut <i>Juglans regia</i>	Jug r 1	Jug r 2	–	Jug r 4
Pistachio <i>Pistacia vera</i>	Pis v 1	Pis v 3	–	Pis v 2, Pis v 5
Sweet almond <i>Prunus dulcis</i>	Pru du 2S albumin	–	–	Pru du 6
Soybean <i>Glycine maxima</i>	Gly m 8	Gly m 5	24-kDa protein 18-kDa protein	Gly m 6
Buckwheat <i>Fagopyrum esculentum</i>	Fag e 2	Fag e 3	–	–

high-performance liquid chromatography (limit of detection, 0.0005%) was unable to detect sesamol, which is formed by chemical reactions, e.g., during storage operations or processing from sesamol [27, 46, 47], in some sesame oil extracts [27].

Diagnostic methods

Skin prick tests can be carried out with commercially available aqueous sesame allergen skin prick test solutions (obtainable from various manufacturers) to diagnose IgE-mediated sesame allergy. However, the validity of this method is limited, since a positive or negative result is not a reliable predictor for the presence or absence of sesame allergy. For example, a study on 33 sesame-allergic individuals aged between 2 and 12 years found a sensitivity of 71% and a specificity of 58% for skin prick testing with sesame allergen solution, as well as a positive predictive value (PPV) of 31% and a negative predictive value (NPV) of 88%. PPV reached 90% only for an average wheal diameter of >6 mm [48]. Other working groups identified a median wheal diameter of >8 mm as a 95% positive predictor for the presence of sesame allergy diagnosed by oral provocation test (OPT) [49, 50]. Therefore, native skin prick tests with sesame seeds, sesame paste (tahina/tahini), or sesame oil is recommended as an alternative or an adjunct [51–53]. The resulting increase in sensitivity is likely due to the better demonstration of fat-soluble allergens, particularly oleosins, in the oily test medium or the lack of individual allergen loss in other preparation processes of (commercial) test solutions. For example, although

10 patients aged between 25 and 72 years with a history of partially severe and repeated sesame-induced anaphylaxis tested negative to an aqueous sesame allergen solution, nine patients were positive to native skin prick tests. Immunoblotting detected sensitization to the oleosins Ses i 4 and/or Ses i 5 in these patients, whereas sesame-specific IgE antibodies could be demonstrated in only two of these cases [51].

An Italian working group described an “immediate contact test” with a 10-mm × 10-mm filter paper soaked in sesame oil as a useful diagnostic method. Three adult, serologically IgE-negative patients that had experienced anaphylaxis to sesame-containing foods were investigated. They were negative in skin prick tests with two commercial test extracts and native skin prick tests with sesame oil; only one patient tested positive to an aqueous elution of freshly ground sesame. In contrast, all showed urticarial skin reactions to sesame oil in the immediate contact test after 20 min [54].

IgE analysis forms the second pillar of allergy diagnostic testing. However, its validity in the investigation of sesame allergy is also subject to considerable limitations. For example, the detection of sesame-specific IgE antibodies in the ImmunoCAP assay showed a sensitivity of 71%, a specificity of 31%, a PPV of 22%, and an NPV of 80%. Of the sesame-allergic individuals diagnosed using OPT, 29% had sesame-specific IgE levels of <0.35 kilounits of allergen-specific antibodies per liter (kUA/l) [48]. However, a retrospective Canadian analysis found no IgE-negative (sesame-specific IgE titer below 0.35 kUA/l) patients among sesame-allergic children [55]. This particular study found a PPV

of 74.1% for a sesame-specific IgE level of $\geq 7 \text{ kU}_A/\text{l}$ [55]. Another study found a PPV of 86% at an allergen specific IgE-titer from $50 \text{ kU}_A/\text{l}$ upwards [49].

The benefits of additional component-based diagnosis were recently investigated. This analysis revealed that sensitization to Ses i 1 is closely associated with clinically manifest sesame allergy. The sensitivity and specificity of rSes i 1 IgE antibodies was 86.1% and 85.7%, respectively [53]. The hope is that these assays will soon be commercially available.

Other experimental laboratory diagnostics include the cellular basophil activation test (BAT) [56] and the identification of sesame-binding antibodies by immunoblotting [34, 34–39, 51]. Utilizing BAT, a Dutch working group was able to successfully differentiate anaphylactic reactions from less severe clinical reactions consistent with oral allergy syndrome. Whereas all patients with anaphylaxis and predominant sensitization to the oleosin fraction tested positive in the BAT, one patient with oral allergy syndrome only tested negative; the authors identified a known tree nut allergy as the cause of the oral symptoms [40].

The gold standard in sesame allergy diagnosis is the double-blind placebo-controlled oral provocation test (OPT), for which a wide variety of test protocols exist. Depending on patient history and previous clinical responses, the safest possible initial dose, an adequate maximum single dose, and a tailored cumulative total dose should be selected [6]. In a study on sesame-allergic individuals that had experienced anaphylactic reactions of severity levels 1–4, an initial dose of 1 mg of sesame meal was administered and the amount gradually increased to a maximum of 7010 mg. At a protein content of approximately 17%, this is equivalent to 0.17–1200 mg of sesame protein. It was found that the lower threshold for a verifiable allergic reaction was 1.03 mg sesame protein. The authors of the latter study pooled their findings with those of four other previously published studies. They were able to determine a lowest amount of 1.02 and a maximum of 3078 mg sesame protein to provoke an allergic reaction. Therefore, a test protocol with a lower threshold dose of 1 mg (equivalent to approximately 6 mg sesame seeds) and an upper threshold dose of at least 3000 mg sesame protein (equivalent to around 17–18 g sesame seeds) is recommended [4]. Since stress-induced allergic reactions to sesame consistent with summation anaphylaxis are also possible [28], testing with cofactors can be indicated in the case of negative OPT and persisting suspicion. The selection of cofactors should be guided by patient history and can be based, e.g., on test protocols for MDEIA or wheat-dependent exercise-induced anaphylaxis (WDEIA) (see for instance [57]).

In the case of suspected delayed-type allergy to sesame oil or sesame oil-containing external agents, patch tests with pure sesame oil is recommended [58]. A case study showed no irritant reactions to patch testing with sesame oil in 20 control subjects. The sus-

pected external agents can also be tested natively, if necessary in a dilution series. In the case of a positive test reaction, the individual ingredients of the product should be tested [32].

Treatment and prevention

With regard to the treatment of anaphylactic reactions to sesame, the reader is referred to the currently valid S2 guideline on the acute therapy and management of anaphylaxis [59]. Following the clinical manifestation of sesame allergy, all patients should be provided with an anaphylaxis passport and an emergency plan, as well as an emergency kit, and made familiar with their use. Affected patients—and, where necessary, their immediate environment—should receive medical information on prevention, early recognition of repeat reactions, and self-management in this event. The indications for use of the emergency set should be explained, as should be correct patient positioning according to the situation and how to place an emergency call. Ideally, information on the self-management of allergic reactions should be repeated and deepened in a structured and certified training program (e.g., AGATE training program) [59]. In a recent study on 115 North American children with sesame allergy, anaphylaxis occurred in approximately 62% of initial manifestations. The annual rate of accidental re-exposure in this patient population was 15.9%. Re-exposure occurred, among other places, at home, at school, in restaurants, at a friend's house, and in a car, with reactions being more severe in two cases, milder in four cases, and similar to initial manifestations in 10 cases. Anaphylaxis self-management was deemed inadequate in this study [60]. Possible sources of exposure (see above) should be highlighted—and explicit reference made to the “hidden” occurrence of sesame—in the context of prevention counseling, and additionally by means of more detailed nutrition counseling if necessary. Accidental allergen intake via, e.g., sesame-“contaminated” foodstuffs is an exception. It is much more the case that the allergy-eliciting foods are generally known to contain sesame [9]. Finally, a description of the amount of sesame sufficient to trigger anaphylaxis can increase awareness among those affected. For example, at a weight of about 3.2 mg per sesame seed (equivalent to around 0.544 mg sesame protein) and a lower trigger threshold of 1.02 mg, two sesame seeds may be sufficient to trigger an anaphylactic reaction in highly sensitized patients [61].

Since sesame allergy persists in the majority of affected individuals [16, 24], the question arises as to the possibility of therapeutic tolerance induction. In a study on allergen-specific immunotherapy for food allergies, six patients suffering from both peanut and sesame allergies underwent oral immunotherapy with peanut and sesame, thereby increasing the tolerated amount of sesame by ten-fold compared with the ini-

tial OPT threshold [62]. However, since immunotherapy was carried out with a variety of foods that are also cross-reactive, and given that patient numbers were low, it is currently not possible to clearly estimate the value of oral immunotherapy for the causal treatment of sesame allergy.

In addition to oral tolerance induction in sesame-allergic individuals with anaphylaxis, prophylactic sesame exposure for the primary prevention of allergies is also discussed, especially given the fact that the majority of sesame allergies manifest in infancy and childhood [9]. A study conducted on 1303 UK infants at increased risk of allergies investigated the early introduction of six highly allergenic foods, including sesame (in addition to cow's milk, peanut, hard-boiled chicken egg, wheat, and white fish such as cod). These foods were administered in addition to breastfeeding from the age of 3 months onwards in the intervention group, while the control group did not receive any additional dietary supplements, but was exclusively breastfed during the first 6 months of life. The intention-to-treat analysis revealed no significant difference between the two groups in the rate of allergies to at least one of the foods administered (5.6% in the intervention group versus 7.1% in the control group). Although the per-protocol analysis demonstrated significant advantages to the early introduction of peanut (allergy prevalence 0% versus 2.5%) and chicken's egg (allergy prevalence 1.4% versus 5.5%), similar effects in relation to sesame allergy were not seen [63].

As described above, many sesame-allergic individuals suffer from atopic dermatitis [9]. This information should also be evaluated through the prism of the dual-allergen exposure hypothesis, which assumes sensitization to food allergens via skin contact with food proteins due to impaired skin barrier function [64]. In 2014, 619 exclusively breastfed infants in the UK were screened for the development of food sensitization. Skin prick testing was carried out with cow's milk, egg, cod, wheat, sesame, and peanut. Children with atopic dermatitis were sensitized to the entire allergen group significantly more often (adjusted odds ratio (OR)=6.18; 95% CI: 2.94–12.98; $p<0.001$); however, positive reactions (skin prick test wheal >3 mm) to sesame were not observed in this patient population [65]. Further research into this question with regard to sesame is required, e.g., in populations with more frequent and early consumption of sesame-containing foods. As a precaution, food-based external agents should be avoided in the case of known skin barrier disorders, not only due to the possibility of immediate-type, but also because of the risk of delayed-type contact allergic sensitization [32]. Particularly external agents that do not contain refined sesame oils should be critically evaluated in this regard.

Conclusion

Sesame allergy represents a growing medical problem, particularly due to increasing nutritional exposure in Western countries. It manifests primarily as IgE-mediated anaphylaxis. Delayed-type contact allergic reactions also occur rarely, although different sesame allergens are relevant to the respective forms. Skin tests should preferably be performed with native sesame. At present, the lack of recombinant allergens available for IgE analysis represents a relevant gap in diagnostic options. Therefore, OPT remains the gold standard for the diagnosis of immediate-type sesame allergy, whereby it is essential to ensure that safe minimum and sufficiently high maximum doses of sesame protein are applied. Patients should be informed in detail about potential sources of exposure. Open questions which need to be addressed are the effectiveness of oral tolerance induction and the possible protective effects of the early introduction of sesame in preventing the development of sesame allergy.

Conflict of interest S. Mühlenbein and W. Pfützner declare that they have no competing interests.

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