

Sesame: An Increasingly Popular Word and Common Food Allergen



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The well-known phrase “open sesame” probably has nothing to do with the plant, being similar in sound to the Hebrew word for secret. Sesame Street, a fictional Manhattan address, is probably even better known, and at least 2 generations of children have been entertained, and educated, by its producers, writers, and cast.

Sesame has been cultivated for more than 4000 years, and has been used mainly as a source of oil, and more recently for tahini, a paste made from ground hulled and toasted sesame seeds. Sesame seed use has been increasing in western diets over the last half century, and it is now one of the most common causes of food allergy and anaphylaxis.^{1,2} Whole sesame seeds, usually found on baked products, appear to be better tolerated, perhaps because of the higher duration and temperature of baking, and perhaps because they are uncrushed and pass through the gut undigested.³ Sesame is usually consumed with other allergenic foods including other seeds and legumes and avoidance can be difficult, given the number of foods and food labels with which it is associated.³ Like allergy to peanut and in contrast to childhood allergies to milk and egg, allergy to sesame is likely to persist. Accurate diagnostic testing is thus critical in evaluation of patients who may have IgE-mediated sesame allergy.

The prevalence of sesame sensitization demonstrated by allergen skin prick testing in a population study among young children was 2.5%, and in that study challenge-proven sesame allergy was found to be 0.8%.² Most of the children thus identified had not been known to have previously consumed sesame. Only peanut and egg sensitivity were more common than sensitivity to sesame. Allergic reactions to sesame appear to have been increasing in frequency, probably due to increasing use of sesame products in foods with increasing popularity of Middle Eastern cuisine. It is unknown whether early exposure to sesame provides the protection now recognized for peanut.⁴

Saf et al⁵ analyzed the diagnostic performance of skin prick test (SPT) and IgE serology in 332 patients, predominantly

children, who had had sesame challenges in their clinic. The indications varied and only 25% had a history of a prior reaction to sesame. Most subjects had no history of sesame ingestion at any time and were avoiding sesame because of positive SPTs carried out during assessment for other food allergies.

In 106 patients, the open oral provocation test (OFC) was positive (ie, the patient failed the OFC). The SPT was positive (>3 mm) in 89%, whereas the ImmunoCAP was positive (>0.35 kU_A/L) in 87%. The specificity of the SPT is low (38%), but for the ImmunoCAP, it is even lower (12%). If we want fewer than 1 of 5 sesame-tolerant patients to have a false-positive diagnostic test, the cutoff should be set at 6 mm for the SPT, and at 7 kU_A/L for the ImmunoCAP. This would result in a decrease in the sensitivity to 54% for the SPT, and to 17% for the ImmunoCAP (see the receiver-operator curves [ROC]⁵). Readers should note that these results may be substantially different in other populations. In this context, the relatively high fraction of subjects without a history of sesame ingestion (included because of other food allergy) may be relevant.

One of our messages is that an ROC curve is clinically not very helpful in a situation like this. The ROC curve has been developed for situations in which only 1 test result is available. However, regarding the sesame results, no complicated statistical evaluation is needed to conclude that neither the SPT nor the sIgE test will do on its own. We need a 2-step approach in which the aim of the initial step is to decide about inclusion. If the test is negative, no further action along this path is taken. If the test is positive, the next step is to exclude false positives. The initial test needs to have a really good sensitivity, but to be useful it should be negative in a substantial fraction of the target population. Low sensitivity may be explained by the absence of important allergens in the test system.

We first need to figure out why 1 of 8 patients with a convincing sesame allergy is negative in the SPT and/or ImmunoCAP. The simplest working hypothesis is that the allergen extract used is deficient in clinically important allergens. For quite some time, allergens were considered to be very special among the many proteins in allergen source materials. However, we have to accept that most allergen sources contain many allergens. To identify missing allergens, we need much more information on the proteomes of allergen source materials, and possibly even about the lipids and glycolipids that may contribute to the allergenicity in oil-rich seeds and nuts.

Just like the cave of the 40 thieves, the sesame pod contains treasures. In addition to several intriguing lipids, some of the seed proteins also appear to have interesting properties that may be relevant for allergenic activity. The investigation of purified allergenic components (molecular allergology) is a logical approach to look for missing allergens. The 2 options are to purify the natural proteins from sesame seeds or to use molecular

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technology to express potential allergens as recombinant proteins. Natural proteins have been mostly tested by immunoblotting. At the moment, the WHO-IUIS Allergen nomenclature website lists 7 sesame allergens from 4 families: the 2S family (Ses i 1 and 2, related to peanut allergens Ara h 2, 6, and 7), the vicilin 7S family (Ses i 3; related to Ara h 1), the oleosin family (Ses i 4 and 5, related to Ara h 12, 13, 14, and 15), and the 11S family (related to Ara h 3). Only 1 recombinant allergen is available (rSes i 1), the use of which was evaluated in 30 patients by Saf et al⁵ and was found to have a sensitivity of 58%. None of the other 6 components have been tested as purified proteins in a quantitative immunoassay. This allergen panel is not suited to estimate how much allergenic activity is unaccounted for in IgE serology and in extracts used for skin tests, as was done for peanut⁶ and walnut.⁷

By way of an example of what kind of surprises to expect when looking for missing sesame allergens, it may be illustrative to report our results on the similar quest for missing peanut allergens. When we tested a pediatric panel for IgE to 6 recombinant peanut allergens (Ara h 1, 2, 3, 6, 8, 9) as well as profilin and cross-reactive carbohydrate determinants, we still found that for some patients the IgE reactivity to peanut extract was higher than the sum of the sIgE to these components.⁶ We looked for additional peanut allergens by immunoblotting of peanut extract and by a radioallergosorbent test–type assay and discovered an IgE-binding component that was poorly detectable by immunoblotting. By mass spectrometry, we identified a small cysteine-rich fragment of the vicilin-type allergen Ara h 1 as a major IgE-binding component. This fragment is largely absent from Ara h 1 in peanut extract, because it is cleaved off inside the peanut.⁸ It is now well established that most nuts and seeds produce such cysteine-rich small protein fragments and that these fragments play an important part in their antimicrobial defense mechanisms. In a recent review, this phenomenon was described as “An Ancient Peptide Family Buried within Vicilin Precursors.”⁹ A characteristic structural feature of this family is the presence of 1 or more quartets of cysteines Cys1-x(3)-Cys2-x(10)-Cys3-x(3)-Cys4, in which Cys1 and Cys4 are disulfide-linked as are Cys2 and Cys3⁹ (in which x(3) indicates 3 variable amino acids (CXXXC) and x(10) a more variable segment of 9–14 amino acids), resulting in a tight alpha-helical hairpin fold. Walnut has 3 and macadamia has 4 such CXXXC-type antimicrobial peptides, whereas the peanut protein has only 1 such sequence.⁸ The degree to which these CXXXC-type antimicrobial peptides are cleaved off from the parent vicilin is unknown, but they should be considered to be independent allergens with properties markedly different from their parent vicilin protein. It is unknown if the 3D structure of the free peptides (alpha-helical hairpin folds) is also present if these peptides are still buried in the nonprocessed parental protein.⁹

As mentioned above, also sesame nuts contain a protein related to Ara h 1: Ses i 3. It presumably is the source of 3 antimicrobial CXXXC-type proteins. However, in the sequence that was initially reported,¹⁰ 1 of the expected 12 cysteines was reported as an arginine. This sequence is still in the official WHO-IUIS allergen nomenclature database. This presumed sequencing error in the initial 2001 report was spotted using much more reliable current DNA-sequencing technologies.¹¹ This illustrates the importance of verifying the older sequence information, as already stressed by others,⁷ but not generally acknowledged.

The treasures in the 1001-Nights' sesame cave will presumably have other surprises than proteins hiding in other proteins. It will take years before we have suitable panels of recombinant allergens that could be used to replace allergen extracts for sesame as well as for many other allergens. We still need more information on the natural allergens, particularly on allergens derived from nuts and seeds. It is important to appreciate the need to carefully check claims on the allergenicity of purified natural allergens. State-of-the-art mass spectrometry should be used to check the post-translational modifications of the natural allergens. Allergenic activity may be found in a fraction that looks pure but may in fact contain well over 10% contamination, often by fragments of parent molecules with very different physicochemical properties. It might be prudent to state that claims based on purified natural proteins should be confirmed with recombinantly produced proteins. The prognoses on the availability for diagnostic purposes of well-defined lipid-associated allergens such as those belonging to the oleosin family are even more uncertain.

What can we do in the mean time? The frequency of false-negative results in basophil activation test bioassays needs to be established in larger trials, but even if the reproducibility and sensitivity are found to be satisfactory, practical issues would still need solving. For the time being, we will need provocation tests if we really want to exclude a sesame allergy diagnosis. Patients with a positive oral provocation test and negative STP and sIgE should be able to help scientists to build a biobank needed to find the missing allergens. New protocols for the preparation of diagnostic allergen extracts for *in vivo* and *in vitro* use are needed, but regulatory constraints may be a major hurdle.

Even when the missing allergens will have been identified and will be available for diagnostic tests, it is likely that we will still need the 2-step protocol: (1) a high-sensitivity initial test based on “synthetic extracts”: mixtures of extracts, semipurified natural components, possibly enriched with recombinant allergens, including a cross-reactive component(s); (2) a second test to increase the specificity of the diagnosis with either a carefully selected small panel of species-specific components, or alternatively a large-scale microarray. The choice between these 2 options will depend on cost-effectiveness, on potential problems due to IgG interference and quantitative accuracy that might be needed if a critical cutoff level is essential for optimal specificity.

As for recombinant allergens, they are undoubtedly the jewels in the sesame cave, but we should keep in mind that the patients are not exposed to such perfect structures. Starting as a freshly produced protein, there is a long and winding road to digested, cooked, aggregated, and otherwise abused allergens in the real world of allergen exposure.

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