



A clinical pathway for the diagnosis of sesame allergy in children

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ABSTRACT

Background: Sesame allergy (SA) is a common cause of life-threatening, persistent food allergy, not only in the Middle East and Asia, but increasingly worldwide. Commercially available tests such as extracts for skin testing or specific IgE for sesame or its components in serum, have very limited predictive values. Therefore the diagnosis is dependent on the performance of oral food challenges (OFC), frequently avoided in children, due to time and resource constraints, as well as the risk of anaphylaxis. In the current study we aimed to develop a simple, readily available, clinical tool, able to predict sesame OFC outcomes in children.

Methods: Children with a history of SA were evaluated in the outpatient allergy clinic. All children underwent natural sesame OFC, with an additional baked-sesame challenge offered to children with SA. Clinical data were compared between the sesame tolerant (ST) and SA groups. Machine-learning tools were applied, to create a simple, clinically driven, decision tree analysis (DTA), predicting the outcome of sesame OFCs and the diagnosis of SA.

Results: One hundred four children, mean age 47.2 months, 58% boys were included, with a high prevalence of additional food allergies, atopic dermatitis, asthma, and rhinitis. Following OFC, 56 (54%) were diagnosed as ST and 48 (46%) SA. Among SA children, 85% were able to consume baked-sesame in equal or higher protein amounts compared to natural sesame paste. Compared to ST, SA children had a tendency towards a higher incidence of allergic rhinitis (5% Vs 17%, $p = 0.062$), multiple food allergies (3.6% vs 12.5%, $p = 0.09$) and requiring medical treatment after the initial SA reaction (27% vs 41%, $p = 0.022$). As a group, skin tests with both commercial and natural tahini paste differed significantly between ST and SA (mean wheal in mm, for extract 4.2 vs 13.4, $p < 0.001$ and for natural sesame paste 6.7 vs 24.4, $p < 0.001$). However, the PPV of any individual test was only between 60%–85%. Our exploratory, clinical DTA, predicted OFC outcomes and the presence or absence of Sesame Allergy, with $\geq 96\%$ positive (PPV) and negative (NPV) predictive values.

Conclusion: OFCs remain the gold standard for the diagnosis of Sesame Allergy and are indicated to define ST/SA status even in highly atopic patients with previous immediate allergic reactions to sesame. A decision-tree analysis based on clinical parameters easily available in every

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allergy clinic, can predict the outcome of sesame OFC in the vast majority of children, increasing the safety and availability of such diagnostic procedures.

Keywords: Food allergy, Sesame, Anaphylaxis, Skin prick test (SPT), Machine learning

INTRODUCTION

Sesame seed allergy is a recognized problem worldwide, with typical onset in children younger than 2 years of age.¹⁻³ The prevalence of this allergy varies between populations and with diagnostic criteria and reported to be between 0.1% and 2.2%.⁴⁻⁸ Notably, one or more anaphylactic reactions are reported in up to 70% of sesame allergic patients.^{2,3,7,9,10} Spontaneous tolerance was traditionally estimated to develop in less than 30% of sesame allergic children.¹¹⁻¹³ However, in other groups, a higher rate of spontaneous resolution of natural sesame allergy was reported,^{1,4,5,14,15} while data regarding tolerance to baked sesame seeds, that are ubiquitously used, is scarce.

Similar to other IgE mediated food allergies, persistency of a sesame allergy diagnosis gravely impacts the quality of life of patients and families,¹⁴⁻¹⁶ strengthening the necessity for early and accurate assessment of allergy both to the natural and baked sesame proteins.

The predictive value of sensitization to sesame food proteins as measured by skin tests and/or specific IgE is limited.¹⁷ Thus, oral food challenges (OFCs) are essential for both the diagnosis and follow-up of children with SA,¹⁸⁻²¹ as sensitization alone even in patients with a previous allergic reaction, overestimates the prevalence of "true", challenge confirmed allergy. In this regard, other biomarkers have been explored, such as sensitization to specific allergenic proteins, like Ses i1, or the basophil activation test, both of which may add to the predictive value of skin tests. However, they are costly, not immediately available in most allergy clinics, and not accurate enough to abolish the requirement for OFC. The latter remains the gold standard for diagnosis of food allergy, though it is time and labor intensive, costly, carries the risk of anaphylaxis and therefore commonly postponed.

The ability to predict OFCs outcomes, with a high level of accuracy, from data readily available in every allergy clinic, and thus stratify low and high-risk procedures may enable early and wider use of this tool. Hence, in the current study, we aimed to develop a clinical diagnostic pathway, utilizing such parameters, to predict sesame challenge outcomes.

METHODS

Patients

This study was performed at the Clinical Immunology, Angioedema and Allergy Unit, Sheba Medical Center, between January 2017 and May 2019. Children with a documented history of one or more immediate reactions to sesame seed and positive skin tests were included. Patients were excluded if they had experienced a recent (<12 months) anaphylactic reaction to sesame or if they had a history of recent uneventful consumption of a significant quantity of sesame containing foods. All patients' guardians gave verbal informed consent, and the study was approved by the Ethics Committee of the Sheba Medical Center.

Skin prick tests (SPTs) were performed at the initial evaluation. Patients were required to be off antihistamines for >5 days prior. SPTs to commercial protein (ALK-Abello) and natural sesame paste (commercial tahini – containing 100% ground sesame seeds) were done on the volar surface of the forearm using a skin test applicator (Duotip-test II), along with a positive control (10 mg/mL histamine) and a negative control (saline), and assessed within 15-20 min. Serum samples were analyzed for sesame-specific IgE using an ImmunoCAP fluorescence enzyme immunoassay (Phadia AB, Portage, MI). The detection limit of the assay was 0.35 kU/L. A positive ImmunoCAP test was defined as ≥ 0.35 kU/L.

Oral Food challenges (OFCs) were performed as graded open challenges with increasing

increments every 20 min, and 120 min observation following the final dose. Sesame allergy (SA) was determined if allergic response was observed during OFC or within the 2 h of follow-up. The initial dose was a touch of tahini on the tongue, measured by our dietitian as 10 mg of sesame proteins, followed by doses of 125/250/500/1000/2125 mg of sesame protein. The initial doses of a challenge are dictated in our center by the calculated risk of a severe anaphylactic reaction but also by the final dose required to define age-appropriate regular consumption dose. In the case of sesame paste (tahini) 2 teaspoons, equal to 2400 mg of sesame protein would be a normal consumed quantity. Therefore, an initial 125 mg of sesame protein (1/20 from the total consumed dose) was in fact the first challenge dose.

Sesame tolerant (ST) children did not experience any adverse event during the procedure and consumed more than 4 g of protein. The No Adverse Effect Level (NOEL) in children with SA, was determined at the last tolerated cumulative dose (prior to the dose where an allergic reaction was elicited). In children with a NOEL of <240 mg, an extensively heated and baked sesame oral challenge was offered to the parents. A graded open challenge with extensively heated and baked sesame cookie in divided doses of 7.5 mg, 15 mg, 30 mg, 60 mg and 117.5 mg, a total dose of 240 mg of sesame proteins, was performed to determine the possible tolerance to small amounts of baked sesame protein. The average time between failing natural sesame OFC and performing extensively heated and baked sesame OFC was 4–6 months. Since the age of the subjects was relatively young, it is possible that in the six-month interval between the challenges in some cases there was spontaneous recovery. However, most children's spontaneous recovery from sesame allergy will do that at their toddler years and before the age of 3 years old. The mean age of children at OFC performance in our study was of 47.2 months. So, in most cases these are probably not cases of spontaneous recovery.

Data were collected retrospectively from the electronic medical records including: gender, age of first food allergy reaction, characterization of primary reaction (skin, respiratory and gastrointestinal, severity), treatment of first reaction, age

at prior and current food challenge, prior accidental exposures, (number, timing, and characterization), other food allergies (the diagnosis of additional food allergies was based on either, an immediate type of allergic food reaction in the previous year with a positive prick-prick skin test demonstrating sensitization or a challenge proven immediate type food allergy). Data of skin prick tests results and sesame food challenge results were collected prospectively. This data point was then used within the context of the decision tree analysis, personal atopy, family history of atopy, and measured sIgE value.

Statistics: Statistical analysis was performed using SPSS 25.0 (IBM SPSS ver 25.0) and JMP Pro 15.0 (SAS jmp pro ver 15.0). For all tests, a p-value of <0.05 was considered statistically significant. Continuous variables were described as mean $\pm$ 95% confidence interval (CI), and categorical variables as percentages. Comparisons between groups ST vs. SA were analyzed by ANOVA, chi-square test, or Fisher's exact test as appropriate for categorical variables or non-normally distributed continuous variables. Differences between the groups were assessed by a putative risk score for OFC outcome. Machine learning techniques were used for a decision-tree analysis – this is a non-parametric tool that identifies prediction rules for classifying observations. The algorithm used to construct classification and regression trees²²⁻²⁵ is referred to as “supervised learning”. The trees are based on binary splits of covariates at cutoff values that create maximally separated and homogeneous groups. The cutoff of a split is determined statistically by identifying homogeneous groups that are as distinct as possible. The splits are therefore creating groups with smaller variability than the pre-split original group, with a maximum difference in means between the 2 subgroup splits. Unlike classical logistic regression, decision-tree analysis does not require observations with no missing values. With large data sets, a training set (a subset of the data) is used to construct the tree and a validation set (the remaining subset) is used to assess and validate its performance. In smaller data sets, repeated random allocations of the data used as the exploratory and validation sets is employed to verify the relative robustness of the decision tree

analysis.²² The decision tree used here is exploratory. In confirmatory studies, the data is randomly divided into a training set and a validation set and the tree derived from applying the training data is evaluated with the validation set. Such confirmatory analysis requires larger data sets than the one available in this study. In order to evaluate the classification properties of the decision tree, receiver operating curves (ROC) were calculated (Fig. 1A and B and Fig. 2B). The ROC curve maps sensitivity versus (1-specificity) over a range of cutoff values. The diagonal line corresponds to a random classifier (decision tree). Curves with high sensitivity and high specificity are optimal classifiers. The performance of a decision tree is assessed with the area under curve (AUC) statistic. Random classifiers have AUC = 0.5, perfect classifiers have AUC = 1.

From the clinical standpoint, Decision making in clinical practice often involves the need to make complex and intricate decisions with important long-term consequences. Decision analysis, as described above, is a tool that allows users to apply evidence-based medicine to make informed and objective clinical decisions when faced with complex situations. A decision tree, is used to visually and explicitly represent and model a given problem and help determine the best course of action for a particular patient or group of patients. Two such examples published in recent literature are focused on the diagnostic accuracy of tests for peanut allergy (PA),²⁶ and for the probability of a high threshold in PA children.²⁷ Using this

statistical advanced tool, a decision-maker can inform a preferred method of intervention and explore variables which influence the final outcome.

RESULTS

In this study, 104 children 60 (58%) boys, 6 months to 17 years of age, mean age at OFC performance of 47.2 months (95% CI 39–55), were evaluated (Table 1). All children underwent OFC with natural sesame protein as either sesame paste (tahini) or sesame sweet confection (halva) regardless of their prior reactions and/or size of SPT to sesame. Of which 56/104 (54%) were sesame tolerant (ST) and 48 (46%) experienced an immediate allergic reaction and were defined as sesame allergic (SA). The mean (and 95% CI) amount of sesame protein consumed during OFC was 5.7 (4.1–7.3) gram in tolerant children and 0.9 (0.4–1.4) gram in allergic patients ($p < 0.0001$). During OFC, SA children displayed rash/angioedema (90%), respiratory complaints/symptoms (40%), gastrointestinal (30%) and/or anaphylaxis (47%) and were treated with adrenaline, anti-histamine, and glucocorticoids as appropriate. Notably 22/48 (46%) SA children experienced an anaphylactic reaction and 1 child had an anaphylactic shock that responded to adrenalin. None of the children required hospitalization. The mean “no adverse event level” (NOAEL) in SA children was 0.3 (95% CI 0.15–0.4) gr of sesame protein ($p < 0.0001$). Children with a NOAEL of less than 0.24 gr of sesame proteins (less than 1/5 of a teaspoon of tahini paste) were offered a graduated OFC with an extensively heated and baked (EHEB) sesame cookie. Out of 12 SA children whose parents agreed to this additional challenge 10 consumed uneventfully a greater or equal amount of baked sesame proteins, with a mean baked NOAEL of 0.19 gr (95% CI 0.14–0.24). Two children challenged with the EHEB sesame cookie, developed an anaphylactic reaction requiring adrenaline to smaller amounts of baked sesame. The group that underwent the baked sesame food challenge is small and may not be representative of the entire population of sesame allergic children.

Over all, both SA and ST children were highly atopic, with 65% reporting an additional food

Number of patients	n = 104
Age mean (month) (95% CI)	47.2 (39–55.4)
Male gender	60 (58%)
Atopic dermatitis	54 (52%)
Asthma	21 (20%)
Allergic rhinitis	11 (10%)
Multiple food allergy	68 (65%)
Family member with food allergy	8 (8%)
Family member with atopy	21 (20%)

Table 1. Sesame allergic patients: descriptive of cohort (Between January 2017 and May 2019)

	Sesame food challenge cohort n = 104		Sesame tolerant n = 56	Sesame allergic n = 48	P value
Cohort	Age (in months)		43.2 ± 40.9	51.83 ± 42.5	NS
	Gender Male		33 (59%)	27 (56%)	NS
Concomitant Food Allergy and Atopy	Atopic Disease	Atopic Dermatitis	25 (45%)	29 (60%)	NS
		Asthma	9 (16%)	12 (25%)	NS
	Food Allergy (FA)	Allergic Rhinitis	3 (5%)	8 (17%)	0.062
		Additional Food Allergy	36 (64%)	32 (67%)	NS
		Milk	11 (20%)	5 (10%)	NS
		Eggs	14 (25%)	16 (33%)	NS
		Peanut	17 (30%)	9 (19%)	NS
		Fish	2 (3.6%)	10 (20.1%)	0.005
		Soy	2 (4%)	0 (0%)	NS
		Hazelnut	3 (5%)	7 (15%)	NS
		Pecan	8 (14%)	6 (12%)	NS
		Walnut	9 (16%)	10 (20%)	NS
		Pistachio	4 (7%)	9 (19%)	0.076
		Cashew	4 (7%)	6 (12%)	NS
		Almond	1 (2%)	3 (6%)	NS
		Any Tree Nuts	15 (27%)	18 (37%)	NS
		Multiple FA (>3 +Ses)	2 (3.6%)	6 (12.5%)	0.09
	Family History	Food Allergy	5 (9%)	3 (6%)	NS
		Atopic Disease	12 (21%)	9 (19%)	NS
Initial Allergic Reactions to Sesame	Average Age At First Allergic Reaction (Month)		12.2 (6.2-18.2)	9.5 (6.4-12.5)	NS
	Manifestations	Skin	53 (94%)	41 (85%)	NS
		Respiratory	10 (18%)	12 (25%)	NS
		Gastrointestinal	4 (7%)	4 (8%)	NS
	Treatments	Anaphylaxis	11 (20%)	11 (23%)	NS
		Anti-histamine	15 (27%)	20 (41%)	0.022
		Steroids	4 (7%)	4 (8%)	NS
		Adrenaline	2 (4%)	1 (2%)	NS

Table 2. Demographics and atopic manifestations of. Sesame tolerant (ST) vs. Sesame allergic (SA) children. *ST* sesame tolerant, *SA* sesame allergy, *FA* food allergy, *NS* not significant

allergy, more than 50% with atopic dermatitis and an average of 20% with a diagnosis of asthma (Table 1). SA was associated with a concomitant sensitivity to fish allergens compare to ST (20.1% vs. 4%; $p = 0.005$) though only 10/48 SA children were co-sensitized to fish. A trend towards increased incidence of allergic rhinitis (17% vs. 5%; $p = 0.062$) and sensitivity to multiple foods (12.5% vs. 3.6%, $p = 0.09$) were also observed in SA versus ST children. SA correlated with increased use of antihistamines during the initial allergic reaction (53% Vs 29%, $p = 0.022$; Table 2). Notably, a quarter of children in both groups, reported a history of an anaphylactic reaction, but only 3 of them received adrenaline as part of their treatment.

SPT with commercial sesame extract (ALK-Abello) and with natural sesame paste (tahini) were performed prior to OFC. Both were significantly higher in SA children compared to the ST children (Table 3). However, looking at individual patient's tests, a large overlap was observed between groups, especially for the SPTs using commercial extracts. Moreover, 4/48 (8.3%) SA children exhibited a negative SPT test using the commercial extract, 2 of whom had an anaphylactic reactions during OFC. A better discrimination was obtained using tahini paste SPT (Table 4, and the ROC curves in Fig. 1A and B) with ROC showing an AUC of 0.794 (95% confidence interval: 0.689-0.898) for the commercial sesame extract (Fig. 1A) and an AUC of 0.887 (95% confidence interval: 0.815-0.959) for tahini paste (Fig. 1B). Using logistic regression analysis, commercial Sesame extract SPT had a 91% negative predictive value but only a 44% PPV when compared to OFC outcomes. Whereas,

tahini paste SPT had 89% NPV and an 80% PPV for sesame OFC outcomes.

To maximize the predictive value of pre-challenge data towards sesame OFC outcomes, we created an exploratory decision-tree analysis (DTA) on a subset of 72 children (Fig. 2A) with suspected sesame allergy, who underwent a full clinical evaluation, skin tests with the commercial sesame extract, raw tahini paste, and an open label oral sesame food challenge. Using the whole set of data, the first statistically driven split (the first decision point in the diagnostic algorithm) was determined by a value of 8 mm on the tahini skin test wheal. Out of 31 patients with an SPT wheal of 8 mm or more, 27/31 (87%) had an allergic reaction on challenge, ie, true positive. In this branch of the DTA, the next diagnostic decision point, was determined by the presence or absence of nut allergy. In the subgroup with tahini SPT > 8 mm and nut allergy 15/15 (100%) of patients had an allergic reaction on challenge, driving the predictive value of the DTA to 100% in this group. Similarly, out of the 41 children with an initial SPT wheal to tahini below 8 mm, all 28 children with an initial SPT flare to sesame extract, below 5 mm, were sesame tolerant. Also all the boys in the tahini < 8 mm group were tolerant irrespective of their sesame flare size. This decision tree analysis improved both the negative and positive predictive values (Fig. 2B) with an overall pre challenge probability of $\geq 96\%$, to predict either tolerance to sesame (negative OFC) or true persistent allergy (positive OFC). The decision-tree results were validated utilizing repeated random allocations of the data points used as the exploratory and validation sets, thus increasing the robustness of the classification results.

Test	SA mm (95%CI)	ST mm (95% CI)	p value
Commercial Sesame - wheal	7.0 (5.1-8.9)	2.2 (1.3-3.1)	<0.0001
Commercial Sesame - flare	13.4 (9.8-16.9)	4.2 (2.3-6.1)	<0.0001
Tahini paste - wheal	13.8 (10.9-16.6)	3.8 (2.5-5.0)	<0.0001
Tahini paste - flare	24.4 (20-28.9)	6.7 (4.4-9.0)	<0.0001
Specific IgE to sesame	5.8 (1.0-10.6)	2.3 (0-5.3)	NS

Table 3. SPT and Specific IgE results. SA sesame allergy, ST sesame tolerant, IgE immunoglobulin E, NS not significant

Test	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95%CI)	NPV (95%CI)
Commercial sesame Wheal > 3 mm	87.5% (71-96.5)	62.8% (46.7-77)	63.6% (53.7-72.5)	87% (72.4-94.6)
Tahini paste Wheal >3 mm	100% (91.4-100)	38.6 (24.3-54.5)	60.3 (54.6-65.7)	100%
Tahini paste Wheal >8 mm	65.8% (49.4-79.9)	88.6% (75.4-96.2)	84.4 (69.7-92.7)	77.65 (67.3-86)

Table 4. Diagnostic performances of SPTs. *SPT skin prick test, CI confidence interval*

DISCUSSION

Sesame seed allergy is a serious health concern worldwide with significant impact on the quality of life of children and their families. In Israel, sesame allergy is the third most common cause of food allergy.⁶ Children in Israel are usually introduced to sesame between the ages of 4-12 months. In our cohort, more than 90% of patients had their first allergic reaction before 1 year of age. Although the most common reported manifestations of first allergic reaction are dermatological,^{28,29} in our cohort almost a quarter of patients suffered an anaphylactic reaction. Inappropriately, in the vast majority of anaphylactic reactions, adrenaline treatment was not given. This is, unfortunately, very much in agreement with published data on the treatment of food allergy in young infants worldwide.^{2,30,31}

In the current study, 54% of children with a documented history of an immediate allergic reaction to sesame in infancy, had outgrown their sesame allergy at a mean age of 4 years. This

reinforces the role of OFC in assessing sesame allergy in infants and children and stands in agreement with findings of several recent working groups.^{18,21,32} In contrast, data derived from retrospective studies estimated a much lower resolution rate of sesame allergy. A prospective study that employed serial food challenges in children from about 1 year of age and later at 4 years in the same cohort, was conducted by the Australian HealthNuts study and estimated the natural resolution of sesame allergy at about 30%.^{4,33} These reported discrepancies regarding resolution of SA may have derived from differences between cohorts (eg, genetic, dietary exposure to small doses and/or early introduction of baked sesame proteins) as well as the inclusion criteria to the studies as for example, in this study, we excluded children with overt severe anaphylaxis to sesame in the previous year.

Noteworthy, no data are available regarding tolerance of baked sesame among children that

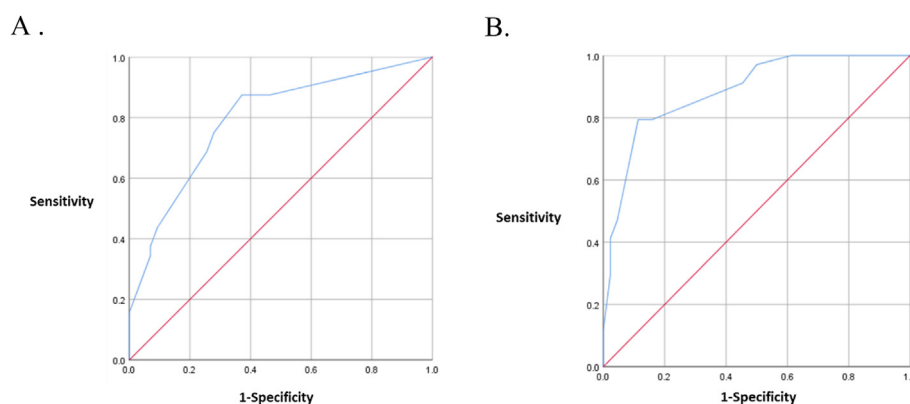
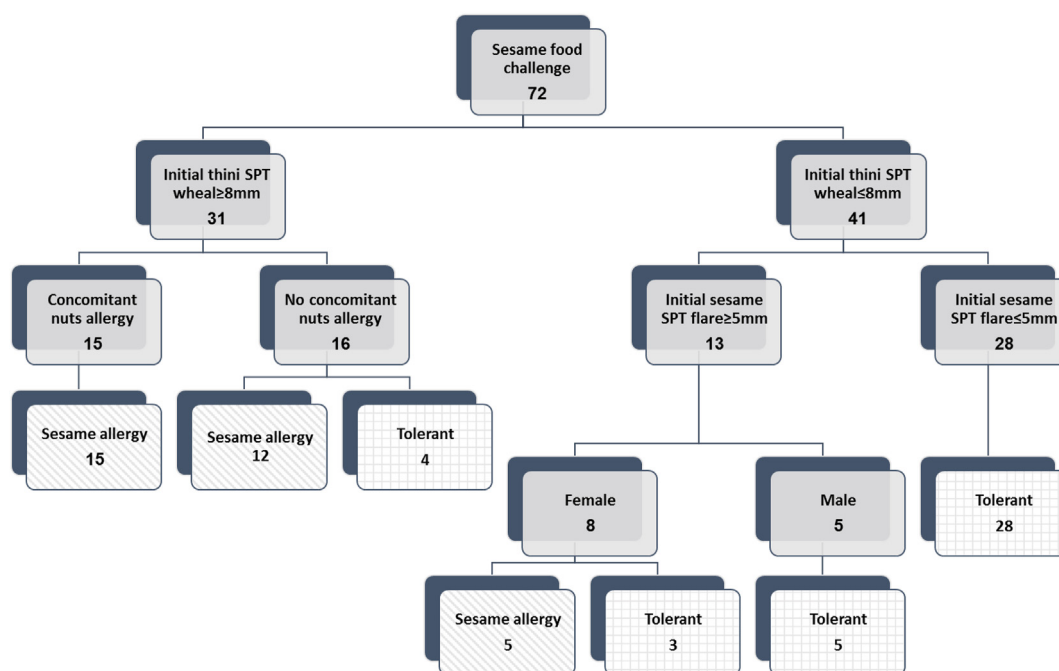


Fig. 1 ROC curves for SPTs with commercial sesame extract or tahini paste in the diagnosis of Sesame Allergy A. ROC for initial SPT with sesame extract B. ROC for initial SPT with tahini paste. ROC receiver operator curve, SPT skin prick test, CI confidence interval, AUC area under the curve. ROC receiver operator curve, SPT skin prick test, CI confidence interval, AUC area under the curve

A



B

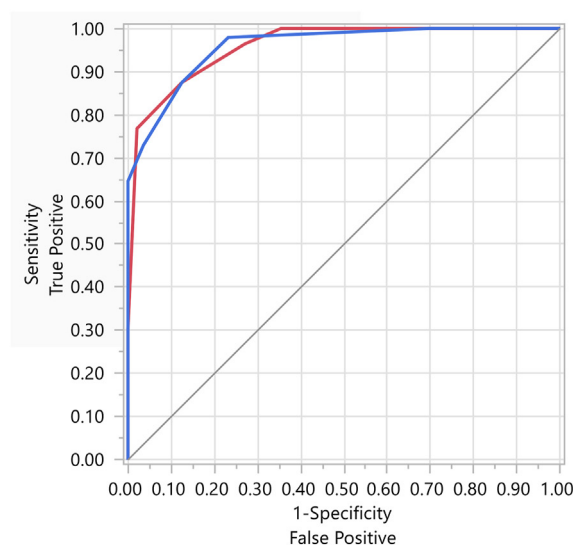


Fig. 2 A. Decision-tree analysis for the diagnosis of Sesame Allergy in Children. B. ROC curve Receiver Operating Characteristic for decision tree. ROC analysis for the decision tree had NPV of 0.9585 and PPV of 0.9585 ROC receiver operator curve, CI confidence interval, NPV negative predictive value, PPV positive predictive value

are allergic to the natural protein. This may be of importance in general and particularly in the era of oral immunotherapy. Most of the sesame allergenic proteins belong to the storage protein families,^{34–36} and storage protein plant-based allergens are resistant to thermal processing. However, there are scarce data specifically

addressing the thermal resistance of sesame allergens, such as 2S albumin and lipid storage proteins. In our study 10 out of 12 (85%) SA children in our cohort could tolerate a higher amount of extensively heated sesame proteins compared to the dose of natural-sesame proteins tolerated during OFC. To the best of our knowledge, this is

Target statement	Meaning equivalence (MEF) included in BOM	Surface similarity (SSF) not included in BOM
<u>Finding 1:</u> Families with children affected by a food allergy to staple foods, including sesame, require specialist evaluation and treatment	Food allergy in children impacts negatively on day to day activities of the whole family	Educating patients on strict avoidance and carrying an epinephrine auto-injector, is completely effective in avoiding accidental exposures in preschool children
	The incidence of accidental exposures to allergenic foods in preschool children is high	
	The currently recommended management of FA in children is: Patient education, strict avoidance and carrying an epinephrine auto-injector	The availability of an adrenalin auto-injector and knowledge of its use in the event of accidental exposure, normalizes the QOL of food allergic families
<u>Finding 2:</u> All children suspected of an allergic reaction to foods should be expeditiously referred to a center that includes appropriate facilities, medical and support staff, experienced in the diagnosis and treatment of children with food allergies as early as possible!	The diagnosis of food allergy in children should be performed soon after the suspected event	Recommending strict avoidance of suspected allergenic foods is the best treatment for all young children with a suspected food allergy
	There are no age limitations on the performance of diagnostic allergy tests, such as skin prick tests or observed food challenges, provided these are performed by well trained and experienced medical teams	Laboratory test such skin tests or specific IgE to food can accurately diagnose food allergy in children
<u>Finding 3:</u> The natural history of Sesame Allergy (SA) in young children is more favorable than previously estimated	A significant proportion of preschoolers with a history of an immediate allergic reaction to sesame, can consume large amounts of sesame safely - ie have resolved their sesame allergy	Food allergy in children always resolves in the first years of life
	Unnecessary avoidance of foods in early childhood may increase the risk for the development of a life threatening food allergy	Early avoidance and late introduction of allergenic foods is beneficial in preventing food allergy in children
<u>Finding 4:</u> A decision tree diagnostic pathway, including clinical and skin test data, can be a very good predictor for sesame allergy/tolerance	Including data such as size of skin test reactions with tahini paste and sesame extract, with clinical data such as gender, and additional food allergies can increase the safety of oral food challenges	If using a decision tree diagnostic pathway indicates a low risk for food allergy, the child can start eating the food at home
	A diagnostic pathway can help with the decision of the appropriate timing and setting for the performance of a food challenge	A decision tree diagnostic pathway can immediately replace the need for performing food challenges
		This decision tree diagnostic pathway predictive value is valid for all populations/ethnic groups at all ages

Table 5. Generalizability of the study findings. BOM boundary of meaning, MEF Meaning Equivalence, SSF Surface Similarity, QOL quality of life, SA sesame allergy

the first report of possible differences in tolerance thresholds of baked versus natural sesame proteins among SA children. However, 2 children, developed an immediate systemic allergic reaction to lower doses of baked proteins, implying that in some patients, a process similar to the Maillard reaction, may play a role in determining the threshold of allergic reaction to baked sesame. In comparison to natural sesame protein food challenge, in which only 1 out of 48 (2%) needed adrenalin; in the baked-sesame food challenge 2 out of 12 (16.6%) needed adrenalin, which might make this procedure very riskier.

The group of sesame-allergic children that agreed to participate in the follow-up study (baked-sesame OFC) had an Average age of 31 months and an average of 1.13 g of sesame protein at sesame OFC failure, in comparison to those who did not agree to participate in the follow-up study (baked-sesame OFC) which had an average age of 47 months and an average of 3.3 g of sesame protein at sesame OFC failure.

As previously published,³² our study confirms that adding a skin prick-prick test with a non-processed natural sesame paste (tahini), improved the accuracy of sesame allergy evaluation. Similarly, but not performed in this study, sophisticated laboratory analyses, such as the basophil activation test²¹ along with sesame specific IgE and/or component specific IgE to Ses i 1^{18,37} could improve the a-priori prediction of OFC outcomes, however, none have resulted in high enough positive predictive values and all three are expensive and not readily available in most allergy clinics. Therefore, we employed only clinical pre-challenge data, in the development of a predictive diagnostic tool with a PPV of 96% and an NPV of 98% for OFCs with natural sesame proteins (Fig. 2A). This tool is easily applied and may enable the early performance, particularly of relatively low risk OFCs. The decision tree takes into account the patient's gender, concomitant nuts allergy, and skin tests with both commercial extract and tahini paste. The algorithm was validated extensively and is now in use in our referral center for the purposes of defining the safety of a proposed OFC with sesame.

Our study has some limitations as it was conducted in a single center, in a fairly homogenous

population, in one geographical/ethnic area. The gold standard food challenge is double blind placebo control. As in most clinical offices, all challenges performed were open labeled, and therefore open to some bias. However, as all children were challenged, irrespectively of medical history and previous or current results of serum specific IgE or skin tests and OFC protocols, and as starting dose and consequent up dosing were quite uniform, we consider such biases to be minimized. Another limitation is the use of tahini paste both for skin testing and challenges, which is not standardized, although has a constant known protein content. Lastly, a relatively small numbers of results were used in the data set from which the decision-tree analysis is derived (72 patients). Thus we have performed additional validations of the proposed algorithm using repeated random allocation of the exploratory and validation sets, to maximize the robustness of the findings. However, the generalization of the model demands further proof of repeatability and reproducibility in different populations and at different ages.

Problems with reproducibility and generalizability of published research are a significant and current concern of the scientific community.³⁸⁻⁴⁰ In order to provide a formalized generalizability of findings we present (Table 5) a methodology developed in the context of pedagogy and teaching, focused on conceptual understanding. Specifically, we apply Meaning Equivalence Reusable Learning Objects (MERLO) statements to define a boundary of meaning (BOM) representing a generalizability of findings in this paper.^{29,41} The BOM represents what can (meaning equivalence) and what cannot (only surface similarity) be inferred from the study and enables researchers to design studies that are capable of challenging or reproducing the published results. MERLO statements are derived from alternative natural representations of a conceptual target statement. These alternatives are classified as meaning equivalence findings (MEF) representing legitimate conclusion of the study or a generalized inference in the opinion of the authors. The surface similarity findings (SSF), are similarly sounding affirmations but their meaning is not supported by the conclusions of the study and are not claimed as generalizable and/or reproducible. Table 5 presents a findings

generalizability table with MEF and SSF columns delineating the BOM. In this study the table was derived qualitatively by domain expert assessment. In statistically designed studies with randomized treatment assignment, the BOM can be evaluated quantitatively with a sign type error indicating a finding statement of the wrong direction. For more on generalization of findings, BOM and S-type error see Ref. ³⁸ In this work Table 5 presents a high level verbal summary of the research findings emphasizing clinical implications.

CONCLUSIONS

In this study, 54% of young children with suspected sesame allergy were found to be sesame tolerant, which emphasize the need for OFCs to verify the status of sesame allergy in children. Additionally, more than 80% of children with persistent SA to natural sesame could tolerate baked sesame protein, alluding to the idea that the content and preparation of the sesame proteins used in challenge procedures may influence the threshold inducing reactions in allergic children. This observation requires further studies regarding both the diagnosis of sesame allergy and the potential for oral immunotherapy of this allergen. Last but not least, utilizing a decision tree analysis model we were able to reliably predict sesame OFC outcomes with both a negative and positive predictive values of >96%. This model may enable allergist/immunologists to greatly improve precision in the management children with a history of sesame allergy.

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Availability of data and materials

Data and materials are available from corresponding author.

Ethics approval

Research was approved by the Sheba Ethical committee.

Author contribution

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Consent for publication

All Authors give their consent for publication.

Declaration of competing interest

None.

Abbreviations

SA, sesame allergy; OFC, oral food challenges; ST, sesame tolerant; DTA, decision tree analysis; PPV, positive predictive value; NPV, negative predictive value; SPT, skin prick tests; NOEL, No adverse effect level; EHEB, an extensively heated and baked; MERLO, meaning equivalence reusable learning objects; BOM, boundary of meaning; SSF, surface similarity findings; ROC, receiver operator curve; CI, confidence interval; AUC, area under the curve

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