

linked to a broad differential diagnosis, including primary immunodeficiencies.⁶

Although generalized erythroderma is an uncommon presentation of zinc deficiency, the deficiency should be considered in patients who have treatment-resistant diarrhea, depression, and erosive dermatitis. Although the triad of zinc deficiency (dermatitis, diarrhea, and alopecia) is only seen in 20% of patients, it is crucial to keep zinc deficiency as part of the differential diagnosis when evaluating patients.⁷ As seen in this case, zinc deficiency should be regarded when evaluating patients with erythroderma, chronic diarrhea, and laboratory evidence of an acquired immunodeficiency, especially in intensive care–associated dermatoses. This case highlights the importance of prompt diagnosis because zinc deficiency and its associated manifestations may respond markedly with adequate supplementation.

Rachel Aviv, MD*
Jennifer Toh, MD†
Rachel Eisenberg, MD†
Sarika Khanna, MD‡
Sunit P. Jariwala, MD†
*Department of Medicine
Kaiser Permanente
San Jose, California

†Division of Allergy and Immunology
Montefiore Medical Center
Bronx, New York

‡Department of Dermatology
Montefiore Medical Center
Bronx, New York
jenntoh@gmail.com

References

- [1] Prasad AS. Impact of the discovery of human zinc deficiency on health. *J Trace Elem Med Biol*. 2014;28:357–363.
- [2] King J, Shames D, Woodhouse L. Zinc homeostasis in humans. *J Nutr*. 2000; 130(5S Suppl):1360S–1366S.
- [3] dos Santos-Valente EC, da Silva R, de Moraes-Pinto MI, Sarni RO, Costa-Carvalho BT. Assessment of nutritional status: vitamin A and zinc in patients with common variable immunodeficiency. *J Invest Allergol Clin Immunol*. 2012;22:427–431.
- [4] Baum MK, Lai S, Sales S, Page JB, Campa A. Randomized, controlled clinical trial of zinc supplementation to prevent immunological failure in HIV-infected adults. *Clin Infect Dis*. 2010;50:1653–1660.
- [5] Mistry N, Gupta A, Alavi A, Sibbald RG. A review of the diagnosis and management of erythroderma (generalized red skin). *Adv Skin Wound Care*. 2015; 28:228–236.
- [6] Relan M, Lehman HK. Common dermatologic manifestations of primary immune deficiencies. *Curr Allergy Asthma Rep*. 2014 Dec;14:480.
- [7] Bologna J, Jorizzo JL, Schaffer JV. *Dermatology*. 3rd ed. Philadelphia: Elsevier Saunders; 2012:737–751.

Development of sesame tolerance and cosensitization of sesame allergy with peanut and tree nut allergy in children



Sesame is an increasingly recognized food allergen with a worldwide prevalence that varies from 0.1% to 0.9% based on self-report, skin prick test (SPT), or oral food challenge (OFC).^{1,2} The median onset of sesame allergy (SA) is 1 year, with 15% to 76% of people developing allergy by 2 years.^{3,4} Most SA manifests with cutaneous signs and symptoms, but anaphylaxis is a common presentation.⁵ SA diagnosis in practice is mainly based on clinical history with a positive SPT result to sesame and/or elevated sesame IgE levels. The few studies investigating sesame IgE levels as a means of predicting clinical reactivity were unable to establish a threshold level with 95% predictive value.^{6–8} Reports of the development of tolerance to sesame vary, from 20% of affected children in Israel⁴ to 33.7% in a US.-based parent survey,³ and there are limited evaluations of sesame IgE before and after development of tolerance.

With the increase in the prevalence of peanut and tree nut (TN) allergy, the risk of potential cross-reactivity among sesame, peanut, and TN needs further characterization. SA occurs in 15% to 54% of patients with self-reported peanut allergy, 8% to 14.8% of patients with TN allergy, and 50% to 54% with both peanut and TN allergy.^{2,7,9} This study aims to describe development of tolerance in patients with SA by OFC and the rates of cross-sensitization with peanut and TNs.

We performed a retrospective medical record review of patients with SA with sesame IgE testing at Texas Children's Hospital Allergy and Immunology Clinic from January 1, 2010, through March 31, 2014. Of 1,645 clinic patients with food allergy, 126 underwent sesame IgE tests. Diagnosis of sesame, peanut, and TN (cashew, hazelnut, walnut, almond, pecan, and Brazil nut) allergy was based on a history of allergic signs and symptoms within 30 minutes after ingestion of food and elevated specific IgE levels (>0.35 kU_A/L) and/or positive SPT results (wheal diameter of >3 mm from negative control; allergen extracts 1:20 w/v). Sesame

sensitization was defined as elevated specific IgE level (>0.35 kU_A/L) and/or a positive sesame SPT result without a history of clinical reaction on sesame ingestion. Fisher exact test, Wilcoxon rank sum test, and linear mixed model statistics were performed. Approval was obtained from the Baylor College of Medicine Institutional Review Board.

Of the 126 patients who underwent sesame IgE tests, 19 had elevated sesame IgE levels, and true SA (sesame IgE with clinical history) was present in 9 patients (0.5% of all patients with food allergy), whereas 6 had sesame sensitization and 4 patients were excluded from analysis because of a lack of history of exposure to sesame. The patients with SA were divided into 2 groups: sesame allergy alone (SAA; $n = 3$) and sesame and peanut allergy (SPA; $n = 6$). Symptoms with ingestion of sesame included hives, pruritus, and eczema exacerbations (Table 1). Most patients had concomitant atopic disease (80% with allergic rhinitis and/or atopic dermatitis but were not different between groups; $P > .05$) (Table 1). Asthma was also not different among the groups ($P = .05$). Sesame IgE levels were significantly higher in patients with SPA ($P = .04$) and SAA ($P = .04$) compared with sesame sensitization. Sesame SPT results were positive in 50% of patients with SPA and 100% of patients with SAA. Peanut allergy and positive peanut SPT results were present in all patients with sesame sensitization. One-third of all patients with SA (SPA and SAA) had a history of TN allergy (2 patients with SPA: 1 with a positive walnut SPT result and walnut specific IgE level of 5.48 kU_A/L and 1 with a positive cashew SPT result; SAA patients: 1 with a positive almond SPT result), and TN sensitization was noted in 56% (Table 1). The sesame IgE in patients with SAA and SPA was 10-fold higher than in patients with sesame sensitization. This median sesame IgE (approximately 10 kU_A/L) was similar to the median sesame IgE in a cohort reported by Maloney et al (sesame IgE, 7.74 kU_A/L).⁶

Five patients developed sesame tolerance on reintroduction of sesame at home or at clinic (Table 2). One patient (patient 3) underwent an additional sesame IgE test before OFC, with results that

Table 1
Clinical and Laboratory Features of the Study Patients^a

Feature	SS (n = 6)	SAA (n = 3)	SPA (n = 6)	P value
Age at diagnosis, median (range), y	3.7 (1.5–5.3)	3.6 (1.7–3.9)	3.5 (1–8)	.86
Sex, M:F	4:2	2:1	3:3	.99
History of eczema	5 (83)	2 (67)	5 (83)	.99
History of asthma	0	1 (33)	4 (67)	.05
History of allergic rhinitis	4 (67)	2 (67)	6 (100)	.36
History of peanut allergy	6 (100)	None	6 (100)	
History of tree nut allergy	0	1 (17)	2 (33)	
Cashew			1	
Walnut			1	
Almond		1		
Tree nut sensitization	2 (33)	2 (67)	3 (50)	
Hazelnut	1		1	
Cashew, walnut, and pecan	1			
Cashew and hazelnut		1		
Cashew and walnut		1		
Cashew, walnut, almond, Brazil nut, and pecan			1	
Cashew, walnut, hazelnut, and pecan			1	
Total IgE, median (range), kU _A /L	313 (22–418)	757 (79–1,434) ^b	1,059 (547–1,352)	.09
Sesame seed IgE, median (range), kU _A /L	1.04 (0.52–5.52)	10.5 (20–47)	11.8 (1.01–26.4)	.04
Positive SPT to sesame seed	0/1 (0)	3/3 (100)	2/4 (50)	.25
Peanut IgE, median (range), kU _A /L	4.6 (1.94–95.1)	0.6 (0.38–0.9)	44.9 (1.3–>100)	.42

Abbreviations: SAA, sesame allergy alone; SPA, sesame and peanut allergy; SPT, skin prick test; SS, sesame sensitization.

^aData are presented as number (percentage) of patients unless otherwise indicated.^bTwo of 3 patients had total IgE levels drawn.**Table 2**
Demographic and Clinical Features of Sesame Allergic Patients

Patient No./Sex/Age at Diagnosis, y	Reported Symptoms With Sesame Ingestion	Timing of Symptoms Within 30 min	Treatment	Sesame Skin Prick Test Result ^a	Sesame IgE at Diagnosis, kU _A /L	Tolerance ^b (Development by OFC)	Age at Tolerance, y
1/M/3.6	Hives, pruritus, eczema flare	Yes	Antihistamine	Positive	2.64	Yes (home)	5.3
2/M/1.7	Hives, pruritus	Yes	Antihistamine	Positive	10.5	Not done	NA
3/F/7	Hives, pruritus	Yes	Antihistamine	Not done	25.6	Yes (clinic)	11.7
4/M/8	Hives, pruritus	Yes	Antihistamine	Positive	5.5	Yes (clinic)	10.5
5/M/2	Hives, pruritus, eczema flare	Yes	Antihistamine	Positive	26.4	Not done	NA
6/F/1	Hives around lips	Yes	Antihistamine	Positive	15.3	Not done	NA
7/M/2	Hives, pruritus, eczema flare	Yes	Antihistamine	Negative	2.69	Yes (clinic)	4.10
8/F/5	Eczema flare, pruritus	Yes	Antihistamine	Negative	1.01	Yes (clinic)	5.3
9/F/3.9	Hives, pruritus	Yes	Antihistamine	Positive	15.1	Not done	NA

Abbreviations: NA, not applicable; OFC, oral food challenge.

^aPositive skin prick test was defined as a wheal greater than 3 mm from negative control.^bTolerance was defined as passing sesame OFC in clinic or after sesame introduction at home.

decreased from 5.5 to 1.14 kU_A/L. Furthermore, 2 other patients with SPA and 1 with SAA had a documented decrease in sesame IgE over time but no OFC. The median decrease in sesame IgE was 12.9 to 2.95 kU_A/L, and the median time for decline was 3 years. The decrease in sesame IgE was a mean of 3.6 kU_A/L/year (95% confidence interval, 5.98–1.15). The mean age of development of tolerance in this cohort was 7.9 compared with 5.9 years in a prior study of SA diagnosis by patient report.³ To date, sesame IgE has not been found to be a good predictor in assessing the probability of a patient passing an OFC. Until larger studies are performed, clinicians could continue monitoring sesame IgE levels, and when a decreasing trend is observed, reaching below approximately 2.0 kU_A/L, a sesame challenge may be considered unless there is a history of anaphylaxis to sesame. Indeed, this is consistent with the report by Zavalkoff et al⁷ of the sesame IgE-negative predictive value between 81% and 99% for 3 kU_A/L or less.⁷

There is a great variability in the estimates of SA prevalence, with a recent increase in the number of countries reporting SA.^{1,5} This study found that SA occurred in 0.5% of patients with food allergy (<0.1% of the population), which is lower than previously reported in the United States.² The natural history of SA is persistence in most patients,⁴ but tolerance developed for a median of 3.3

years in 45% of our cohort, longer than the previously reported parental report time of 1.4 years from first reaction to tolerance.³ This may be because parental report could overestimate the initial SA diagnosis, causing subsequent tolerance to occur with the timing of the confirmation of the absence of the diagnosis. Moreover, the timing of OFC may have delayed the documentation of the development of tolerance.

Cross-reacting allergens (Ses i 3, Ara h 1) may play a role in sesame sensitization, giving false-positive sesame IgE results, resulting in false diagnoses.⁵ Caution should be used in interpreting sesame IgE in peanut allergy because patients with sesame sensitization in this cohort had sesame IgE levels as high as 5.5 kU_A/L. Two-thirds and one-third of patients with SA had peanut and TN allergy, respectively, suggesting that patients with SA may be more likely to have peanut than TN allergy. Patients with SA should have peanut and TN allergy evaluation to identify risk of potential allergic reactions. Although a limitation of this study is the small number of patients in our cohort, there are limited data on the development of sesame tolerance in the United States confirmed by OFC. In summary, patients with SAS may develop tolerance, which may accompany a decrease in sesame IgE levels.

Karen Thursday S. Tuano, MD*
 Kristin H. Dillard, MD*
 Danielle Guffey, MS†
 Carla M. Davis, MD*

*Department of Pediatrics
 Section of Immunology
 Allergy and Rheumatology

Baylor College of Medicine/Texas Children's Hospital
 Houston, Texas

†Dan L. Duncan Institute for Clinical and Translational Research
 Baylor College of Medicine
 Houston, Texas
 CMDavis@texaschildrens.org

References

- [1] Zuidmeer L, Goldhahn K, Rona RJ, et al. The prevalence of plant food allergies: a systematic review. *J Allergy Clin Immunol*. 2008;121:1210–1218.e4.
- [2] Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol*. 2010;125:1322–1326.
- [3] Gupta RS, Lau CH, Sita EE, Smith B, Greenhawt MJ. Factors associated with reported food allergy tolerance among US children. *Ann Allergy Asthma Immunol*. 2013;111:194–198.e4.
- [4] Cohen A, Goldberg M, Levy B, Leshno M, Katz Y. Sesame food allergy and sensitization in children: the natural history and long-term follow-up. *Pediatr Allergy Immunol*. 2007;18:217–223.
- [5] Dalal I, Goldberg M, Katz Y. Sesame seed food allergy. *Curr Allergy Asthma Rep*. 2012;12:339–345.
- [6] Maloney JM, Rudengren M, Ahlstedt S, Bock SA, Sampson HA. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. *J Allergy Clin Immunol*. 2008;122:145–151.
- [7] Zavalkoff S, Kagan R, Joseph L, St-Pierre Y, Clarke A. The value of sesame-specific IgE levels in predicting sesame allergy. *J Allergy Clin Immunol*. 2008;121:1508–1510.
- [8] Permaul P, Stutius LM, Sheehan WJ, et al. Sesame allergy: role of specific IgE and skin-prick testing in predicting food challenge results. *Allergy Asthma Proc*. 2009;30:643–648.
- [9] Stutius LM, Sheehan WJ, Rangsihienchai P, et al. Characterizing the relationship between sesame, coconut, and nut allergy in children. *Pediatr Allergy Immunol*. 2010;21:1114–1118.

Lactobacillus reuteri DSM 17938 plus vitamin D₃ as ancillary treatment in allergic children with asthma



Asthma is a heterogeneous disease usually characterized by chronic airway inflammation.¹ Allergy and asthma prevalence has significantly increased worldwide during the past decades,² and the hygiene hypothesis suggests that reduced exposure to microbial agents could increase the risk of allergic diseases.³ This theory has been recently revisited with an emphasis on the role of microbiota dysbiosis that promotes impaired immunologic tolerance to allergens.⁴ In addition, vitamin D₃ deficiency has been associated with asthma and allergy inception and worsening.⁵ Therefore, many attempts of restoring enteric microbiota with probiotic supplementation and correcting vitamin D₃ deficiency have been performed, but with conflicting results.⁶

Lactobacillus reuteri DSM 17938 reduced bronchial inflammation and significantly increased interleukin 10 in children with asthma.⁷ The combination of *L reuteri* DSM 17938 plus vitamin D₃ improved allergen immunotherapy efficacy.⁸ On the other hand, Kerley and colleagues⁹ recently reported that 15-week vitamin D₃ supplementation in Irish children with asthma decreased school-days missed alone, but there were no other advantageous changes in asthma parameters compared with placebo. Therefore, the aim of this pilot study was to evaluate the effect of a food supplement with *L reuteri* DSM 17938 (10⁸ CFU) plus vitamin D₃ (400 IU) on airways inflammation, asthma control, and lung function in children with mild persistent asthma and allergic to house dust mites (HDMs).

This study was a randomized, double-blind, placebo-controlled trial. In total, 32 children (age range, 6–14 years) were recruited. Inclusion criteria were as follows: (1) diagnosis of mild persistent asthma (documented in the medical records) under good control; (2) monoallergy to HDMs; (3) regular treatment with montelukast (5 mg/d); and (4) serum vitamin 25-hydroxyvitamin D level less than 30 ng/mL. Exclusion criteria were as follows: (1) current (or in the past 8 weeks) therapy with inhaled or oral glucocorticosteroids and/or vitamin D supplement; (2) previous or current allergen immunotherapy; (3) normal serum vitamin D level; (4) chronic intestinal disorders that may interfere with the vitamin D₃ and probiotic pathways; and (5) chronic respiratory disorders.

Patients and their parents signed the informed consent form. The research was approved by the Ethical Committee of the Second Naples University (clinicaltrials.gov Identifier: NCT02734446). The study started in September 2015.

At baseline (T0), patients were visited and the parameters were recorded, including serum vitamin D assay. At randomization (with a ratio 1:1 according to a masked code), children were subdivided in 2 groups. Group A was treated with a solution that contained *L reuteri* DSM 17938 (10⁸ CFU) plus vitamin D₃ (400 IU) 5 drops per day, and group B was treated with a solution that contained placebo (5 drops per day) for 90 days. Children were revisited at the end of treatment (T1) and after a 30-day follow-up (T2). Montelukast treatment was continued throughout the study. Salbutamol spray could be used as symptomatic treatment.

The primary outcome was bronchial inflammation assessed by fractional exhaled nitric oxide. Secondary outcomes were asthma control measured by questionnaire (Childhood Asthma Control Test [C-ACT]) and lung function evaluated by spirometry, considering bronchial reversibility to bronchodilation testing. In detail, forced expiratory volume in 1 second change was expressed as the percentage of the difference between pre-bronchodilation testing predicted values and post-bronchodilation testing values. These parameters were evaluated at all times, but the C-ACT was evaluated at T0 and T1, and serum vitamin D₃ levels were assayed at T0 and T1. Adherence to intervention therapy and montelukast was considered as percentage of taken doses. The Mann-Whitney test and Wilcoxon test were used (STATISTICA, StatSoft Italia, Padova, Italy).

All children completed the study, except 1 in group A and 2 in group B. The 2 groups were statistically homogeneous and comparable at baseline (Table 1). The adherence to intervention therapy and

Table 1
Demographic Data in Group A and B

Variable	Group A (n = 15)	Group B (n = 17)
White ethnicity	15	17
Age, mean (SD), y	8.7 (1.7)	8.5 (1.9)
Males, No. (%)	6 (40)	7 (41)