

Case Report

MACADAMIA NUT ALLERGY: 2 CASE REPORTS AND A REVIEW OF THE LITERATURE

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ABSTRACT

We report on 2 patients with anaphylaxis from Macadamia nut. Temporal relationship between consumption of the nut strongly suggested the diagnosis. Clinical suspicion was supported by the presence of positive specific IgE and/or the positive skin test and/or and the basophil activation test.

CASE REPORTS

Case 1

A 55-year-old man was referred to our outpatients' clinic because of an in-flight episode of generalised urticaria, rhinoconjunctivitis, hoarseness, angio-oedema of lips, eyelids and larynx and dyspnoea within half an hour after an apparently first consumption of a whisky and Macadamia nuts. He was successfully treated with

intramuscular antihistamines and intravenous corticosteroids. Detailed history taking, quantification of specific IgE (sIgE) and skin tests confirmed an atopic status with an allergy for tree pollen. However, there was no indication of an IgE-mediated food allergy (in particular a birch pollen associated food allergy or other nut allergies). Specific IgE for Macadamia nut (f345, ImmunoCAP FEIA, Uppsala, Sweden) was negative. The patient refused a skin test for Macadamia nut.

Flow cytometric analysis (FACSCalibur, BD Immunocytometry Systems, San Jose, CA, USA) of activated basophils was performed using Alexa Fluor 448-coupled anti-IgE (Sigma-Aldrich, Chemic GmbH, Steinheim, Germany) and phycoerythrin-conjugated anti-CD63 (Pharmingen, BD Biosciences, Erembodegem, Belgium). The test included a negative control (stimulation with buffer only), a positive control (anti-IgE, Pharmingen BD), and virgin as well as roasted Macadamia nut extract (serial dilution 0.1 up to 100 µg/mL). To exclude non-specific basophil activation, the test was also performed in 2 healthy control individuals who tolerated Macadamia nuts and had negative sIgE and skin prick tests for the nut. Upon challenge with the Macadamia nut, basophils of the patient showed a manifest up-regulation starting at 1% (spontaneous CD63 expression) up to 89% and 87% for the highest stimulation concentration of virgin and roasted nut, respectively (Fig). In contrast, expression of CD63 on basophils from the 2 control individuals remained unchanged (< 1%) (Fig).

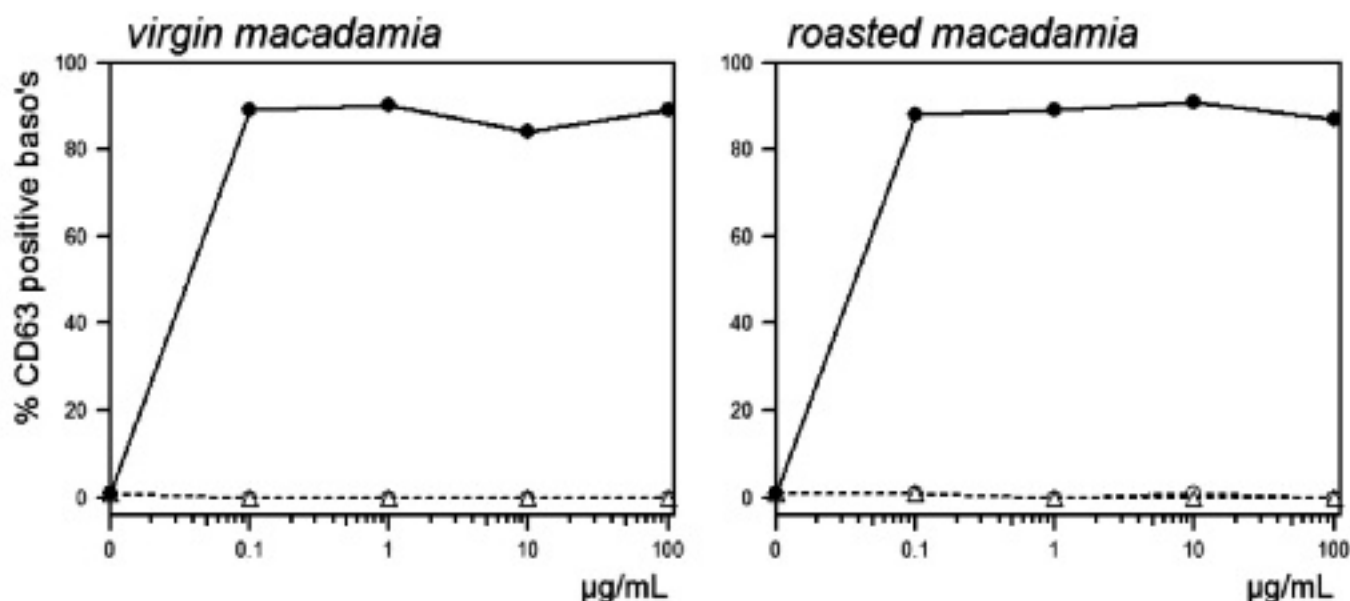
Finally, in order to establish the sensitization profile of the patient, we performed component resolved diagnosis by microarray ((ISACTM, Phadia, Uppsala, Sweden). Briefly, microarray reaction sites were incubated with 20 µL of undiluted patients' serum for 2 hours in order to capture allergen-specific sIgE antibodies by

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Percentage of CD63 positive basophils in the patient (closed symbols) and in two control individuals tolerant for macadamia nut (open symbols) for stimulation with roasted and virgin nut.

their corresponding allergen. Subsequently, the microarray slides were rinsed and washed with buffer solution in order to remove unbound serum sIgE. After drying, complexes of allergen-bound specific IgE were stained with a secondary, fluorescence-labelled anti-human IgE for 1 hour at room temperature protected from light. After a second rinsing and washing procedure, the obtained fluorescence signals were scanned using a laser scanner (LuxScan 10K, CapitalBio, Beijing, China). Analysis of the corresponding digitised microarray image data was performed with ImmunoCAP ISAC software and image information was transformed into numerical data according to calibration sera of known IgE content. Numerical data were expressed as ISAC Standardized Units (ISU/L). Results of relevant genuine and cross-reactive compounds are summarised in the table. Only sensitisation for major birch (*Betula verrucosa*) pollen allergen Bet v 1 and its homologues in hazelnut (Cor a1, *Corylus avellana*) and apple (Mal d1, *Malus domestica*) was demonstrable.

Case 2

A 5-year-old girl was admitted to our outpatients' clinic because of a pronounced oral allergy syndrome with pruritus and swelling of the oropharynx and lips as well as a generalised erythema, almost immediately after eating a Macadamia nut. She was successfully treated with antihistamines. History revealed no atopic status and no prior nut or peanut allergies. It was unclear whether she had ever eaten Macadamia

nuts. Specific IgE for Macadamia nut was 3.76 kUa/L. Skin prick testing with virgin and roasted Macadamia resulted in a wheal and flare reaction of 6/25 mm diameter. Unfortunately, the patient demonstrated a non-responder status in the basophil activation test, i.e. cells did not respond to stimulation with the positive control and nut extract. Such a non-responder status is observed in about 5-10% of the patients.

Results of component resolved diagnosis by microarray are summarised in the table. Only sensitisation for homologues of the major birch pollen allergen and profilins was demonstrable.

Both patients were advised to carefully scrutinize the labeling of prepacked foods and to carry an antihistamine and an auto-injectable epinephrine preparation.

DISCUSSION

Tree nut allergy is a well-known and increasing health issue in adults (1;2) as well as children (3). Nuts mostly incriminated are hazelnuts, almonds and walnuts. Based upon telephone questionnaires in 471 individuals, approximately 9% of patients with severe nut and seed allergy reported an allergic reaction to food while on an airplane. Some reactions were very serious and potentially life-threatening. Individuals usually did not inform airline personnel about their previous bad experiences. In addition, the quality of

Table 1

Individual results for relevant genuine en cross-reactive allergen compounds

Allergen	(Sub)family	PT 1	PT 2	Normal value
rBet v 1	Bet v 1 homologues	17.6	2.47	0
rMal d 1		5.32	0.66	0
rCor a 1		7.12	0.51	0
rBet v 2	Profilins	0	0.33	0
rPhl p 12		0	0.35	0
rPhl p 1	Grass group 1	0	0	0
rPhl p 5	Grass group 5	0	0	0
nArt v 1	Defensin	0	0	0
nArt v 3	Lipid transfer protein	0	0	0
rCor a 8		0	0	0
rPru p 3		0	0	0
rAra h 1	7S vicilin	0	0	0
rAra h 2	2S albumin	0	0	0
rAra h 3	11S globulin	0	0	0

Bet v 1: major allergen from *Betula verrucosa* (birch), Mal d 1: major allergen from apple (*Malus domestica*), Cor a: *Coryllus avelana* (hazelnut), Phl p 1 and Phl p 5: genuine markers for sensitisation from *Phleum pratense* (Timothy grass), Art v: *Artemisia vulgaris* (mugwort), Pru p: *Prunus persica* (peach), Ara h: *Arachis hypogaea* (peanut).

r: denotes a recombinant protein, n: purified natural protein.

Numerical data were expressed as ISAC Standardized Units (ISU/L)

information, about flying with food allergies, available from customer service departments of/for the airlines was found to be highly variable and, in some cases, incomplete or inaccurate (4).

Although IgE-mediated allergy from Macadamia nuts remains anecdotal (5-11), its prevalence might rapidly increase because of gain in popularity. In particular, Macadamia nuts are becoming more frequently available in nut mixes, cereals, ice cream and are now being sold in countries which did not previously import them. Macadamia is becoming an increasingly popular ingredient in baked goods, as is cold pressed Macadamia oil (6). Nut oils may pose a threat to patients with allergy, depending on the method of processing. IgE reactivity to proteins in Macadamia oil has been reported, based upon testing of sera (12) and skin tests (10) from patients with Macadamia allergy. On October 12, 2007 Dairy State Foods voluntarily recalled a quantity of 7 oz. Minnie's Bake Shop Chocolate Chunk Cookies, as these cookies could have contained undeclared Macadamia nuts (from: http://www.fda.gov/oc/po/firmrecalls/dairystate10_07.html).

The symptoms of Macadamia nut allergy are highly heterogeneous and vary from an oral allergy syndrome (OAS) with local oropharyngeal discomfort to severe life-threatening anaphylaxis. In an American survey of 115 allergic reactions to nuts, 5 reactions to Macadamia nuts were reported (4%): 3 moderately severe and 2 severe systemic ones (13). Anaphylaxis following

contact with Macadamia nut has been reported in an infant (14). Occupational dermatitis from Macadamia nut shells was described in 15 nut sorters at a Macadamia nut processing plant. The nature of the allergen was not found but was thought to be confined to the shell, as opposed to the plant leaf or kernel (15). We report on two patients with systemic reactions to the Macadamia nut.

Macadamia is a genus of nine species of flowering plants in the family Proteaceae, native to eastern Australia (seven species), New Caledonia (one species *M. neurophylla*) and Sulawesi in Indonesia (one species, *M. hildebrandii*). The genus is named after John Macadam, who first described the genus (16). Only *Macadamia integrifolia* and *M. tetraphylla* are of commercial importance. The remainders of the genus possess poisonous and/or inedible nuts, such as *M. whelanii* and *M. ternifolia*; the toxicity is due to the presence of cyanogenic glycosides.

The "Macadamia nut" is not truly a nut but a seed (17). A 17.4 kDa protein appears to be the major allergen and is present in raw and roasted extracts (5).

Diagnosis of a nut allergy generally relies upon a compelling history corroborated by positive sIgE and/or skin test results. In the absence of a commercially available skin test extract, most physicians rely upon quantification of sIgE to confirm their clinical suspicion. Unfortunately, on several occasions it has been demonstrated that quantification of sIgE for Macadamia yields false negative results (9;11), an observation

that was confirmed in our adult patient. Alternatively, patients might refuse skin tests, particularly when they have experienced a severe reaction.

The principals and applications of the BAT have recently been extensively reviewed elsewhere (18). Allergens that cross-link membrane-bound specific IgE (sIgE) molecules, induce basophils not only to secrete and generate a variety of quantifiable bioactive mediators (e.g. histamine and leukotrienes), but also to up-regulate the expression of different intracellular and cell membrane markers such as phosphorylated p38 MAPK (mitogen-activated protein kinase), CD63 and CD203c. With respect to food allergy the BAT has been validated in primary food allergies (e.g. the fish parasite *Anisakis simplex* and the giant shrimp *Macrobrachium rosenbergii* and pollen-related food allergies. In individual patients the BAT confirmed the diagnosis of an allergy to coriander, lychee, and mandarin.

We report on 2 patients with anaphylaxis from Macadamia nut. Clinical suspicion was supported by the presence of positive specific IgE and/or the positive skin test and/or and the basophil activation test. Component resolved diagnosis by microarray demonstrated mainly sensitisation to the major birch pollen allergen homologues. No sensitisation for prolamins (lipid transfer proteins, 2 S albumins) or cupins (7S vicilins, 11S globulins) was demonstrable.

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REFERENCES

1. Teuber SS, Beyer K. Peanut, tree nut and seed allergies. *Curr Opin Allergy Clin Immunol* 2004; 4:201-3.
2. Crespo JF, James JM, Fernandez-Rodriguez C, Rodriguez J. Food allergy: nuts and tree nuts. *Br J Nutr* 2006; 96 Suppl 2:S95-102.
3. Skripak JM, Wood RA. Peanut and tree nut allergy in childhood. *Pediatr Allergy Immunol* 2008; 19:368-73.
4. Comstock SS, DeMera R, Vega LC, et al. Allergic reactions to peanuts, tree nuts, and seeds aboard commercial airliners. *Ann Allergy Asthma Immunol* 2008; 101:51-6.
5. Sutherland MF, O'Hehir RE, Czarny D, Suphioglu C. Macadamia nut anaphylaxis: demonstration of specific IgE reactivity and partial cross-reactivity with hazelnut. *J Allergy Clin Immunol* 1999; 104:889-90.
6. Falk M, Katelaris CH, Fulcher DA. Macadamia allergy. *ACI International* 2000; 12:240-2.
7. Pallares DE. Allergy to macadamia nut. *Ann Allergy Asthma Immunol* 2000; 85:385-6.
8. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol* 2003; 112:1203-7.
9. Lerch M, Egger C, Bircher AJ. Allergic reactions to macadamia nut. *Allergy* 2005; 60:130-1.
10. Inaba Y, Yagami A, Suzuki K, Matsunaga K. (Allergy to macadamia nut). *Arerugi* 2007; 56:699-702.
11. Knott E, Gurer CK, Ellwanger J, Ring J, Darsow U. Macadamia nut allergy. *J Eur Acad Dermatol Venereol* 2008; 22:1394-5.
12. Teuber SS, Brown RL, Haapanen LA. Allergenicity of gourmet nut oils processed by different methods. *J Allergy Clin Immunol* 1997; 99:502-7.
13. Fleischer DM, Conover-Walker MK, Matsui EC, Wood RA. The natural history of tree nut allergy. *J Allergy Clin Immunol* 2005; 116:1087-93.
14. Yamada H, Shimizu A, Tsuchiya T, Yoshihara S. (Case of infant with anaphylaxis due to macadamia nuts). *Arerugi* 2007; 56:1306.
15. Knight TE, Hausen BM. Dermatitis in a nutshell: occupational exposure to *Macadamia integrifolia*. *J Am Acad Dermatol* 1996; 35:482-4.
16. von Mueller FJH. Account of some new Australian plants. *Trans Phil lost Victoria* 2 1857;62-77.
17. Hartung ME, Storey WB. The development of the fruit of *Macadamia ternifolia*. *J Agric Res* 1939; 59:397-406.
18. Ebo DG, Bridts CH, Hagendorens MM, Aerts NE, De Clerck LS, Stevens WJ. Basophil activation test by flow cytometry: present and future applications in allergology. *Cytometry B Clin Cytom* 2008; 74:201-10.