Cashew nut allergy

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Abstract

Cashew allergy is one of the most common tree nut allergies, and its prevalence appears to be increasing. Furthermore, ingestion of low doses of cashew is associated with a high rate of severe anaphylactic reactions in allergic children. Over the past decades, the world production of cashew nut has significantly grown, thereby increasing the risk of exposure.

The goal of this topic is to review clinical aspects of allergy to cashew nut, allergic components, cross-reactivity, diagnosis and management.

Introduction

The cashew nut (Anacardium occidentale) belongs to the Anacardiaceae family (figure). It is usually considered as a nut, but is actually a seed and not a nut. The seed is surrounded by a shell and by a layer of toxic oil, the cashew nut shell liquid (CNSL). So cashew nuts must be roasted to be safe to eat. CNSL is a resin, made up of 80% anacardic acid and the rest of cardol and cardanol. Its applications to green chemistry and polymer chemistry are wide. CNSL is not edible, so its use as a chemical feedstock does not compete with the food supply chain. It is used in the manufacture of inks, varnishes, friction elements (brakes and clutches), and can cause contact dermatitis (1).

Half of the cashew nuts is consumed as a snack, whether salted or spiced, alone or in combination with other nuts. The other half is processed as sweets, chocolates, bakery, ice creams, butters, pesto's, etc.

In less than 30 years, world production has grown significantly, from 1 million tons in 1993 to over 5 million tons in 2021. The leading producer is Côte d'Ivoire, in addition to Benin, Nigeria, India and Vietnam.

The average weight of a cashew nut is 1.4 gr. The protein concentration of the roasted cashew nut is 18.8 %. One cashew nut thus contains an average of 260 mg of proteins.

Prevalence

Cashew nut allergy is a common and increasing tree nut allergy. Whilst this may be a real increase, increased cashew nut consumption may be revealing more cases, and more cases may be noticed and declared because of increased awareness of patients and doctors.

There are significant geographical disparities. In the USA, cashew nuts are the main foodstuff involved in allergic reactions to nuts since many years; in Europe, however, hazelnuts were the most frequently involved nut. More recent data from the RAV (Réseau d'Allergo-Vigilance), however, place cashew nuts as the leading nut causing anaphylaxis (2).

In Europe, cashew nuts are the fourth leading cause of anaphylaxis amongst food allergens, after peanuts, milk and egg. We found only a few studies on its prevalence : 41 % of the nut allergic patients in France, 0.08% of children under 4 in the UK (3). Cashew nut allergy is more prevalent in the Asian population, due to earlier exposure in its dietary practices.

Despite a natural history of spontaneous non-healing, recent works have showed that an allergy to cashew nut, even severe, can progress towards spontaneous acquisition of tolerance in 9 to 30% of patients.

Allergens

The major cashew allergens belong to the family of storage proteins. Ana o 1 is a vicilin-like protein, Ana o 2 is a legume-like protein and Ana o 3 is a 2S albumin. These proteins are resistant to heat and gastric proteolysis. Most of patients (> 80%) allergic to cashew nut are sensitized to Ana o 3.

In current practice, only cashew and Ana o 3 specific IgE assays are available. Ana o 2 is included in the 112 allergens of the ISAAC microarray (4).

Cross-reactivity

Both pistachio (Pistacia vera) and mango (Mangifera Indica) belong to the Anacardiaceae family, and are thus botanically related to cashew nut. In vitro reactivity between cashew nut and pistachio has been established by sIgE inhibition tests. Willison et al., 2008, demonstrated that Ana o 1 and Pis v 3 (specific pistachio protein) had large structural homologies (5). Moreover, Uotila et al., 2016, reported that pistachio and cashew nut had the strongest co-sensitization linkages among edible nuts (6). The clinical cross-reactivity has also been proven : the PRONUTS study in 2019 showed that cashew nut and pistachio were the most highly

correlated nut allergies, as almost 80% of children allergic to cashew nuts are also allergic to pistachio (7). This prevalence is similar to that reported in previous studies (IDEAL study, 2016, or NUT CRACKER study, 2018) or by Saba et al., 2020, but higher than the prevalence described by Van der Valk et al. in 2017 (31%) (8-11). Saba et al. demonstrated that in multivariate analysis, low threshold dose to cashew nut is the only significant factor associated with allergy to pistachio in children allergic to cashew nut (8).

There is also a cross-reactivity in vitro between pistachio nut and mango seed (not mango fruit). Mango juice may contain traces of mango pits due to contamination during the industrial process.

Other allergens include a high degree of homology with cashew nut in their allergenic proteins : walnut (Ana o 3/Jug r 1 or Ana o 2/Jug r 4), peanut (Ana o 2/ Ara h 3), soybean (Ana o 2/Gly m 6).

Finally, a study of Savvatianos et al., 2016, established a cross-reactivity between cashew nuts and the seeds of fruits of the Rutaceae family (orange and lemon) (12). Several cases of allergic reactions or anaphylaxis have been reported after consumption of lemon seeds in patients allergic to cashew nuts. Fruit pulp can be eaten without triggering a reaction, as with mango.

Clinical features

Cashew nut allergy often has an early onset, with an average age of 3 years at diagnosis. New dietary habits (early consumption of nut pastes) are likely to lower this average age further.

Allergic reactions to cashew are the same as other food allergies : skin lesions followed by respiratory and gastro-intestinal symptoms. 30% of the anaphylactic cases to cashew have no cutaneous reaction, delaying the diagnosis of anaphylaxis. Cashew nut allergy causes more digestive symptoms than peanut allergy.

Cashew nuts allergens are obviously highly potent and can cause relatively severe reactions. Anaphylactic reactions seem to be more frequent for cashew nut than for peanut (50% and 30%, respectively). Clinical observations reveal that significant reactions may happen for minimal levels of exposure. Studies determining the eliciting doses by double-blind placebo-controlled food challenge test (DBPCFC) show that the ED50 (protein dose at which 50% of the allergic population is likely to react), is 25.4 mg (for any type of symptoms) (13). This corresponds to the protein content of one tenth of a cashew nut. This ED50 is comparable to peanut or hazelnut, but clearly lower than that of egg or milk (>80 mg). The ED05, which is likely to trigger a reaction in 5% of cashew-allergic children, is estimated at 0.32 mg of proteins, or 1.7 mg of cashew.

Diagnosis

As with other foods, cashew nut allergy is diagnosed by history, combined with in vitro specific IgE tests and skin prick tests. These tests do not distinguish between sensitization and clinical allergy. For the diagnosis of allergy, the gold standard remains the oral challenge test. However, as in most cases children have a clear-cut history of anaphylaxis after consumption of cashew nuts, oral food challenges should not be used.

Skin prick tests seem to be superior to sIgE to cashew nut in predicting challenge tests outcome : Corderoy et al., 2011, showed that patients with positive or negative cashew nut challenge tests do not differ in median cashew nut sIgE; in contrast, the SPT was significantly larger in patients with positive challenge tests (14). A cut-off value of ≥ 8 mm gave a 95% positive predictive value for a positive challenge test outcome (15).

Sensitization to cashew nut 2S albumin, Ana o 3, is highly predictive of cashew and pistachio allergy: using 0.16 kU/L as the optimal threshold, they showed that Ana o 3 had a sensitivity of 98% and a specificity of 94% (12).

In addition, Van der Valk et al., 2017, demonstrated that the components Ana o 1,2 and 3 discriminated better between cashew nut allergic and tolerant children sensitized to cashew nut than the skin prick tests (9).

So there are 3 indications for oral challenge tests in cashew nut allergy :
- confirm the allergy to cashew nuts;
- investigate spontaneous acquisition of tolerance, which is possible and probably less rare than previously thought;
- establish a reactive threshold for the implementation of oral immunotherapy.

Bourcier et al. carried out an oral food challenge (OFC) on 36 patients with cashew nut allergy confirmed by skin and biological tests, without an accidental episode over a period of at least 3 years, or with clinical and biological sensitization of fortuitous discovery (allergic skin tests performed in the case of a reaction to another nut or in the context of atopic dermatitis) (16). The average age at the time of the first allergy tests was 3 years and at the time of OFC was 8 years. 15 children tolerated the maximum cumulative dose of 4441 mg and were able to reintroduce cashew nuts immediately into their diet. 15 patients had to continue with a strict avoidance regime. 6 children received oral immunotherapy (OIT).

Oral food challenges are not without risk; they are time-consuming, labor-intensive, stressful and possibly costly. So, Van der Valk et al., 2017, developed a prediction model for cashew nut allergy (9). The Van der Valk score is a predictive score, combining the determination of specific IgE antibodies to Ana o 3, the diameter of the papule in skin tests and the sex of the patients (table). The OFC could thus be refuted in patients with a score ≥ 8 (highly probable clinical reactivity), while children with a low score < 4 would be the preferred target population for an OFC (probability of asymptomatic sensitization or tolerance acquisition).

Table : van der Valk score (6).

Predictor	Value	Score
Gender(girl)		1
Ana o 3(kU/l)	00 - 0.1	0
	0.11 - 0.5	1
	0.51 - 1.5	2
	1.51 - 5	3
	5.01 - 19	4
	19.01 - 60	5
	60.01 - 100	6
SPT(meandiameter(mm))	0 - 2	0
	2.01 - 5.5	1
	5.51 - 9.5	2
	9.51 - 13	3
	13.01 - 17	4
	17.01 - 21	5
	21.01 - 23	6
	24+	7
Total sum score		...

Management

Based on the LEAP study, infant feeding guidelines now recommend introducing peanuts as part of complementary feeding, in order to prevent peanut allergy prevalence. These food allergy prevention guidelines do not include tree nuts, nor cashew nuts in particular. Palmer et al. showed that regular consumption of cashew nuts from 6 months of age was feasible and safe, but they did not determine whether this strategy could reduce the prevalence of cashew nut allergy (17).

The mainstay of therapy in food allergic patients is avoidance of the culprit food. Avoidance of cashew nut is increasingly difficult to achieve, because of the presence of cashew nuts in more and more food products. Furthermore, avoidance of botanically related foods such as pistachio must be advised.

In 2006, Ferdman et al., demonstrated that 27% of children with peanut or nut allergy were unable to recognize the target food (18). Only 25% of the children in this study correctly identified the cashew nut. Therapeutic education therefore has an important place in the management of cashew allergy.

As for other food allergies, a written action plan is essential, including details of evictions and an emergency protocol with instructions for treatment in case of reaction. In the school environment, the entire teaching team should be aware of the evictions, the emergency action plan, the location of the emergency kit with adrenaline and its proper use.

Since a few years oral immunotherapy (OIT) plays a role in the treatment for cashew nut allergy. Several teams have published their protocols and results of oral cashew (and/or pistachio) immunotherapy (19, 20). These protocols appear secure and allow children at high anaphylactic risk to tolerate a high dose of cashew nuts, thus protecting them from anaphylaxis.

In 2022, the NUT CRACKER study demonstrated that cashew OIT is effective in desensitizing most cashew allergic patients; it cross-desensitizes all pistachio and some walnut allergic patients (20). The safety of cashew OIT is similar to OIT for other foods. Low cashew dose consumption is sufficient to maintain full desensitization.

Conflict of interest

The author has no conflicts of interest to declare in relation to the subject matter of this manuscript.

REFERENCES:

1. Haumonté Q, Nguyen V, Thomas H, Pontier J, Corriger J, Barbaud A, et al. L'allergie à la noix de cajou: à propos de 34 observations pédiatriques documentées par un test de provocation orale. Revue Française d'Allergologie. 2017;57(3):264.
2. Réseau d'Allergo-Vigilance Vandoeuvre les Nancy, France [cited 2023 June]. Available from: https://www.allergyvigilance.org.
3. Tariq SM, Stevens M, Matthews S, Ridout S, Twiselton R, Hide DW. Cohort study of peanut and tree nut sensitisation by age of 4 years. Bmj. 1996;313(7056):514-7.
4. van der Valk JP, Dubois AE, Gerth van Wijk R, Wichers HJ, de Jong NW. Systematic review on cashew nut allergy. Allergy. 2014;69(6):692-8.
5. Willison LN, Tawde P, Robotham JM, Penney RMt, Teuber SS, Sathe SK, et al. Pistachio vicilin, Pis v 3, is immunoglobulin E-reactive and cross-reacts with the homologous cashew allergen, Ana o 1. Clin Exp Allergy. 2008;38(7):1229-38.
6. Uotila R, Kukkonen AK, Pelkonen AS, Mäkelä MJ. Cross-sensitization profiles of edible nuts in a birch-endemic area. Allergy. 2016;71(4):514-21.
7. Brough HA, Caubet JC, Mazon A, Haddad D, Bergmann MM, Wassenberg J, et al. Defining challenge-proven coexistent nut and sesame seed allergy: A prospective multicenter European study. J Allergy Clin Immunol. 2020;145(4):1231-9.
8. Saba L, Clerc-Urmès I, Delahaye C, Chevillot E, Jarlot-Chevaux S, Dumond P, et al. Predictive factors of allergy to pistachio in children allergic to cashew nut. Pediatr Allergy Immunol. 2020;31(5):506-14.
9. van der Valk JPM, Vergouwe Y, Gerth van Wijk R, Steyerberg EW, Reitsma M, Wichers HJ, et al. Prediction of cashew nut allergy in sensitized children. Pediatr Allergy Immunol. 2017;28(5):487-90.
10. Elizur A, Appel M, Nachshon L, Levy M, Epstein N, Rigbi N, Golobov K, et al. NUT co reactivity N: Acquiring knowledge for elimination recommendations (NUT CRACKER) study. Allergy. 2018;73(3):593-601.
11. van der Valk JP, Gerth van Wijk R, Dubois AE, de Groot H, Reitsma M, Vlieg-Boerstra B, et al. Multicentre Double-Blind Placebo-Controlled Food Challenge Study in Children Sensitised to Cashew Nut. PLoS One. 2016;11(3):e0151055.
12. Savvatianos S, Konstantinopoulos AP, Borgå Å, Stavroulakis G, Lidholm J, Borres MP, et al. Sensitization to cashew nut 2S albumin, Ana o 3, is highly predictive of cashew and pistachio allergy in Greek children. J Allergy Clin Immunol. 2015;136(1):192-4.
13. Blom WM, Vlieg-Boerstra BJ, Kruizinga AG, van der Heide S, Houben GF, Dubois AE. Threshold dose distributions for 5 major allergenic foods in children. Journal of Allergy and Clinical Immunology. 2013;131(1):172-9.
14. Corderoy T, O'Sullivan M, Nolan R. Skin prick test predicts cashew nut challenge outcome in children with low specific IgE. Internal Medicine Journal. 2011;41:15-6.
15. Ho MH, Heine RG, Wong W, Hill DJ. Diagnostic accuracy of skin prick testing in children with tree nut allergy. J Allergy Clin Immunol. 2006;117(6):1506-8.
16. Bourcier M, Bourrier T. Allergie à la noix de cajou: 36 tests de provocation orale pédiatriques à la noix de cajou avant le rAna o 3. Revue Française d'Allergologie. 2018;58(8):556-63.
17. Palmer DJ, Silva DT, Prescott SL. Feasibility and safety of introducing cashew nut spread in infant diets-A randomized trial. Pediatr Allergy Immunol. 2023;34(6):e13969.
18. Ferdman RM, Church JA. Mixed-up nuts: identification of peanuts and tree nuts by children. Ann Allergy Asthma Immunol. 2006;97(1):73-7.
19. Brocart C, Wintrebert G, Collin S, Schvartz L, Sabouraud-Leclerc D. Immunothérapie orale (ITO) noix de cajou/pistache à propos d'une série de 80 enfants. Revue Française d'Allergologie. 2021;61(4):239.
20. Elizur A, Appel MY, Nachshon L, Levy MB, Epstein-Rigbi N, Koren Y, et al. Cashew oral immunotherapy for desensitizing cashew-pistachio allergy (NUT CRACKER study). Allergy. 2022;77(6):1863-72.