Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

REVIEW ARTICLE

Systematic review on cashew nut allergy

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To cite this article: van der Valk JPM, Dubois AEJ, Gerth van Wijk R, Wichers HJ, de Jong NW. Systematic review on cashew nut allergy. *Allergy* 2014; **69**: 692–698.

Keywords
allergy; Anacardiaceae; cashew; hypersensitivity.

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Accepted for publication 21 February 2014

DOI:10.1111/all.12401

Edited by: Bodo Niggemann

Abstract

Recent studies on cashew nut allergy suggest that the prevalence of cashew nut allergy is increasing. Cashew nut consumption by allergic patients can cause severe reactions, including anaphylaxis. This review summarizes current knowledge on cashew nut allergy to facilitate timely clinical recognition and to promote awareness of this emerging food allergy amongst clinicians. The goal of this study is to present a systematic review focused on the clinical aspects of allergy to cashew nut including the characteristics of cashew nut, the prevalence, allergenic components, cross-reactivity, diagnosis and management of cashew nut allergy. The literature search yielded 255 articles of which 40 met our selection criteria and were considered to be relevant for this review. The 40 articles included one prospective study, six retrospective studies and seven case reports. The remaining 26 papers were not directly related to cashew nut allergy. The literature suggests that the prevalence of cashew nut allergy is increasing, although the level of evidence for this is low. A minimal amount of cashew nut allergen may cause a severe allergic reaction, suggesting high potency comparable with other tree nuts and peanuts. Cashew allergy is clearly an underestimated important healthcare problem, especially in children.

Although peanut allergy has been on the increase for two decades or more, studies indicate that cashew nut is also becoming an important food allergen (1, 2). The rapid increase in consumption of cashew nuts and the change in eating and cooking habits may be responsible for the increasing significance of cashew nut allergy (2).

In this paper, we summarize the relevant information available on epidemiology, allergen components, clinical features, diagnosis, clinical and *in vitro* cross-sensitization and management of cashew nut allergy.

Data sources and literature search

In our search, we adhered to the methods and procedures of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for reporting this systematic review, excluding irrelevant items. Registration number in PROSPERO is CRD42013004047.

We used Ovid MEDLINE and EMBASE databases to identify relevant articles using the string: (Anacardi*[tw] OR cashew*[tiab]) AND (Hypersensitiv*[tw] OR hyper sensitiv*[tw] OR allerg*[tw]) for Ovid MEDLINE and (Anacardi* OR cashew*): de, ab, ti AND (Hypersensitiv* OR (hyper NEXT/1 sensitiv*) OR allerg*): de, ab, ti for EMBASE. We also checked references to relevant articles ('snowballing').

We aimed to include studies focused on the clinical aspects of cashew nut allergy. We considered only studies in English. There was no restriction on publication date. Mouse model studies were excluded. Initially, all articles on cashew nut allergy or on cashew nuts were included. Thereafter articles on contact dermatitis, genetics, product labelling, poisoning, detection methods and possible medicinal effects of cashew plants were excluded. Forty of 255 articles found with the literature search (244 articles) and by 'snowballing (11 articles) were considered relevant for the review. Of these 40 articles, one article was a prospective study and six articles were retrospective studies. Five of these seven articles focused on clinical symptoms and constitute a major source for this review. In addition, seven case reports about cashew nut were located. The remaining 26 articles are mainly descriptive and not directly related to cashew nuts or cashew nut allergy. This literature selection procedure is shown schematically in Fig. 1.

Apart from this selection, we added literature to describe the characteristics of the cashew nut, the prevalence,

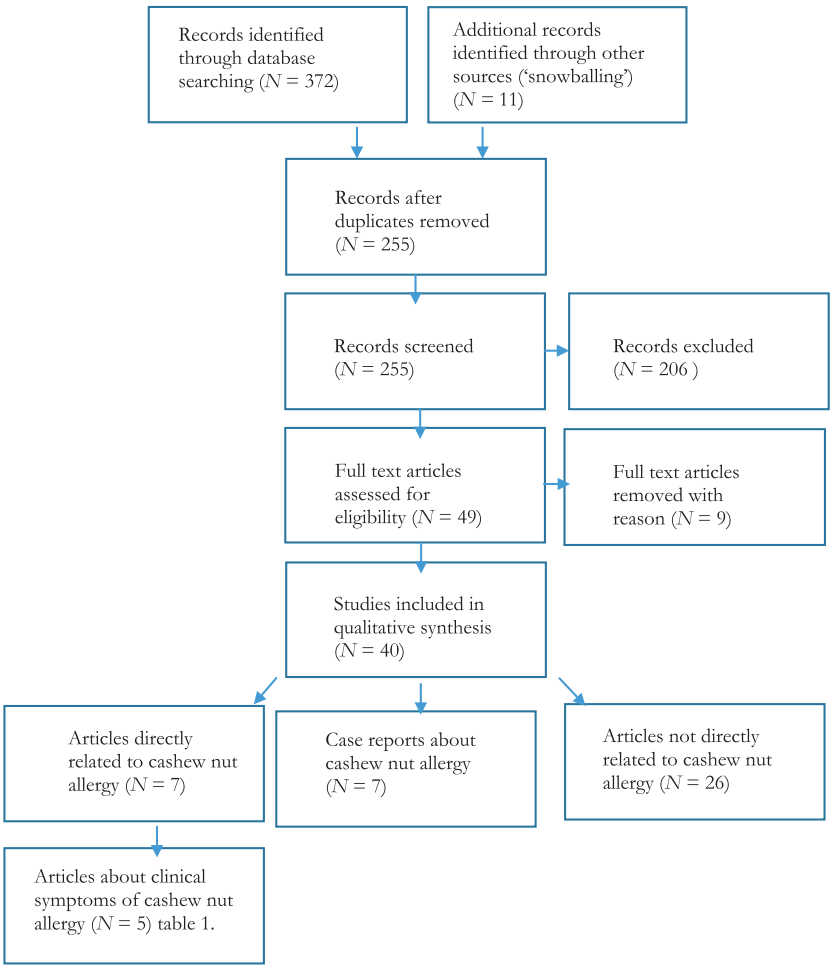

Figure 1 Summary of the search and selection.

allergenic components, cross-reactivity and diagnosis of cashew nut allergy.

Relevant papers

The five relevant studies on clinical symptoms of cashew nut allergy are presented in Table 1. The prospective study by Rance et al. (2) analysed the clinical features and results of skin prick tests (SPT), specific IgE (sIgE) assays and food challenge tests of 42 children with cashew nut allergy without an associated peanut allergy. The study by Davoren et al. (3) described the clinical features, including anaphylactic reactions, to tree nuts and peanuts. Clark et al. performed a retrospective case-matching study in children referred for either cashew nut (47 children) or peanut (94 children) allergy. The severities of the most severe reactions were compared (4). The paper by Hourihane et al. (1) reported the clinical features of cashew nut allergy in 26 paediatric and three adult subjects, whose history of reaction was supported by positive SPT or raised cashew-specific IgE. Grigg et al. (5) performed a retrospective chart review and phone survey to identify the clinical characteristics of cashew nut allergic patients in comparison with peanut allergic patients.

The paper by Corderoy et al. was a retrospective chart review. This study evaluated the mean SPT wheal diameter, cashew sIgE, age at challenge and previous clinical history to determine whether any of these variables predicted the risk of a subsequent reaction during oral food challenges (6). The retrospective study by York et al. (7) investigated the ethnicity of 100 children with a clinical history of cashew nut allergy.

Cashew nut and cashew nut allergy

The cashew nut

The Portuguese discovered the cashew nut in northeastern Brazil in the sixteenth century and exported the cashew nut tree to other continents (8). The cashew nut (Anacardium occidentale) belongs to the Ancardiaceae family. Botanically the cashew nut is actually a seed and not a nut, but historically it has been referred as to a nut. The cashew nut is

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Table 1 Overview of allergen homology, co- and cross-sensitization and co- and cross-reactivity between cashew nut and other food allergens

Allergen	Allergen homology	Co-sensitization (*n*/total)	Serological cross-reactivity	Clinical dual reactivity (*n*/total)	Probable clinical cross-reactivity
Pistachio	Willison (23)	Rance (2) (28/42) Garcia (19) (3/3) Sansosti (22) (1/1) Fernandez (25) (2/2)	Willison (23) Noorbakhsh (20) Hasegawa (13) Parra (21)	Garcia (19) (1/3) Ferdman (26) (1/1)	Noorbakhsh (20) Willison (23)
Mango	–	–	–	–	–
Walnut	Barre (18) Wang (17) Robotham (15)	Rance (2) (4/42)	–	–	–
Almond	–	Rance (2) (10/42)	–	–	–
Hazelnut	Barre (18)	Rance (2) (6/42)	–	–	–
Peanut	Barre (18) Wang (16)	Clark (3) (13/47)	–	–	–
Soybean	Wang (16) Wang (17)	–	–	–	–
Orange seed	–	O'Sullivan (27) (35/100)	–	–	–
Pectin	–	Ferdman (26) (1/1)	Rasanen (35)	–	–
Sesame	Wang (17) Robotham (15)	–	–	–	–
Mustardseed	Robotham (15)	–	–	–	–

– Literature is not found.

kidney-shaped and grows on the bottom of the cashew apple. It is surrounded by a shell as well as a layer of toxic oil. Because of this toxic oil, the cashew nut must be roasted before it is safe to eat. Sixty per cent of cashew nuts are consumed as a snack, and the remaining 40 per cent is processed in products such as butters, pestos, bakery – and confectionary items, sweets, ice creams and chocolates (1, 5, 9). The cashew nut is used especially in the Indian, Thai and Chinese cuisines. In the world production of edible nuts, the cashew nut ranks as third with Vietnam, Nigeria, India and Brazil as the major cashew nut exporters. Cashew nut cultivation is not organized on a plantation scale in most producing countries. The price of the cashew nuts is much higher than that of peanuts and other nuts because of the labour-intensive manner of processing required to turn the raw nut into the edible cashew nut (9).

The world production of cashew nuts has experienced a rapid growth. A tenfold increase has been observed during the last 50 years. The world production of cashew nuts was approximately 1.24 million tonnes in 2000 and increased to approximately 3.58 million tonnes in 2010 (9).

Epidemiology

Many published reports deal with the prevalence of tree nut allergy in general. Although cashew nut allergy is reported as a common tree nut allergy, we found only a few studies on the prevalence of cashew nut allergy (10). The search yielded studies suggesting an increase in cashew nut allergy in children and an increased recognition of cashew nut allergy in clinical practice (2, 3, 5). In a study by Tariq et al. (11), 0.08% of children under 4 in the United Kingdom were found to be sensitized to cashew nuts. Moneret-Vautrin et al. (12) reported that 41% of the nut allergic patients in France were sensitized to cashew nut.

Hasegawa et al. (13) observed relatively more cashew nut allergy in female adults. The study of York et al. (7) indicates that cashew nut allergy may be more prevalent in the Asian population. Forty-one of 100 patients derived from a multicultural paediatric allergy clinic in Leicester (UK) with a clinical history suggestive of cashew nut allergy were from Asian/Asian British background compared with only 21% with a history suggestive of allergy to other nuts. A possible explanation for this finding is that Asian children have earlier exposure to cashew nuts because of dietary practices leading to more cashew nut allergy compared with other populations (7).

Despite the impression that sensitization and clinical allergy to cashew nut are increasing, methodologically rigorous studies documenting this have not yet been performed.

Allergens

The major cashew allergens are Ana o 1, Ana o 2 and Ana o 3. Ana o 1 is a 50 kDa vicilin-like protein resistant to heat and proteolysis. The other two known allergens are Ana o 2, a 33 kDa legume-like protein, and Ana o 3, a 13 kDa 2S albumin (14–16). All three allergens are classified as seed storage proteins. Of patients allergic to cashew nut, 50% (10 of 20 sera) are sensitized to recombinant Ana o 1, 62% (13 of 21 sera) to recombinant Ana o 2 and 81% (21 of 26 sera) to recombinant Ana o 3 determined by Western immunoblotting (14, 15, 17).

Allergens from these families of seed storage proteins are known to be allergenic in other tree nuts, legumes and seeds.

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Clinical cross-reactivity, cross-reactivity *in vitro* and co-sensitization

The cashew nut as well as the pistachio *(Pistacia vera)* nut and the mango *(Mangifera indica)* belong to the Anacardiaceae family and are thus botanically related. A high degree of serological cross-reactivity has been established between cashew nut and pistachio (Pis v 1, Pis v 2 and Pis v 3) by sIgE- inhibition tests. This may be explained by the highly conserved primary and three-dimensional structure of these allergen homologue pairs, present in both cashew nut and pistachio (18–22). Clinical cross-reactivity between cashew nut and pistachio was suggested in the study by Noorbakhsh et al. and the study by Willison et al. (20, 23). Garcia et al. and Quercia et al. (19, 24) also reported clinical cross-reactivity between cashew and pistachio, although sIgE inhibition tests were not performed. Cross-reactivity between pistachio nut and mango seed has also been established by sIgE- inhibition tests. Information on the molecular basis of serological or clinical cross-reactivity between cashew and mango fruit, and on which proteins could be involved, is not available (25). Allergens with a high degree of homology with cashew nut in their allergenic proteins include hazelnut, mustard seed, peanut, pistachio, sesame, soybean and walnut (15–18, 23). Co-sensitization is seen between the cashew nut and almond, hazelnut, orange seed, pistachio, peanut, pectin and walnut (2, 3, 19, 22, 25–27). Sensitization against cashew nut allergy seems to be a primary sensitization rather than a cross-reaction between cashew nuts and pollens. An overview of the homology, clinical cross-reactivity, cross-reactivity *in vitro* and co-sensitization between cashew nut and other allergens is shown in Table 1.

Clinical features

The age of onset of cashew nut allergic symptoms varies between 2 months and 27 years with a mean of approximately 3 years (1, 2, 4, 5).

Most allergic reactions to cashew nut, such as other food allergies, manifest with skin lesions followed by respiratory and gastro-intestinal symptoms (Table 2). The study of Davoren et al. showed cutaneous involvement as the initial

Table 2 Relevant studies on clinical symptoms of cashew nut allergy

Author	Year	Type of study	Number of cases	Children/adults	Symptoms (% and *n*=)
Rance (2)	2003	Prospective study	42	Children	Respiratory 25% (28/112)* Cutaneous 56% (63/112) Gastro-intestinal 17% (19/112)
Davoren (3)	2011	Retrospective chart review	27	Children	Anaphylaxis: 74.1% (20/27)† Respiratory: 15% (3/20) Respiratory, cardiovascular system, skin: 5% (1/20) Respiratory, skin, gastro-intestinal 25% (5/20) Respiratory and skin: 40% (8/20) Respiratory and gastro-intestinal 15% (3/20) Nonanaphylaxis: 25.9% (7/27) Skin 100% (7/7)
Hourihane (1)	2000	Retrospective study	29	Children and adults	Wheeze: 48% (14/29) Collapse/feeling faint: 38% (11/29)
Grigg (5)	2009	Retrospective chart review	16	Children	Anaphylaxis: 50% (8/16)‡ Respiratory: 50% (8/16) Cutaneous: 72.4% (11/16) Gastro-intestinal: 18.8% (3/16) Eye symptoms: 18.8% (3/16)
Clark (4)	2007	Case-matching study	47	Children	Cutaneous: 98% (46/47) Gastro-intestinal: 32% (15/47) Rhino-conjunctivitis: 6% (3/47) Wheeze: 40% (19/47) Laryngeal oedema: 9% (4/47) Cardiovascular: 13% (6/47) Lightheaded: 13% (6/47)

*42 cases, 112 events.

†Defined as a rapidly evolving generalized multisystem allergic reaction characterized by cardiovascular involvement and involvement of other systems (skin and/or gastro-intestinal (5).

‡As defined by the Second Symposium on the definition and management of anaphylaxis (36).

symptom in 100% of the nonanaphylactic cases. The initial symptoms in most anaphylactic patients are respiratory, often combined with skin symptoms. On the other hand, 30% of the anaphylactic cases had no cutaneous reaction which might make it difficult to recognize anaphylaxis (3). Compared with peanut allergy, cashew nut allergy causes more gastro-intestinal symptoms (5).

Cashew nut causes severe allergic reactions similar to responses to other tree nuts and peanut (2, 3, 28) and can be lethal in both adults and children (29). However, some studies reported anaphylactic reactions even more frequently to cashew nut than to peanut (50% and 30%, respectively) (5). This was also found in the study by Davoren et al. of 214 children with peanut or tree nut allergy. Thirty per cent of the peanut and 74% of the cashew nut sensitized patients developed an anaphylactic reaction after ingestion (3). Although being suggestive, this analysis did not correct for other possible factors which might bias these results, such the eliciting doses or a history of asthma.

Clark et al. performed a case-matching study of children with a history of a reaction after cashew nut or peanut ingestion and evidence of sensitization (positive skin prick test). Children with the most severe reaction to peanut ingestion were matched 2 : 1 to children with the most severe reaction to cashew nut ingestion. This study showed no significant differences in clinical features between the cashew nut and peanut group, except asthma (more prevalent in the peanut group).

This study reported that allergic reactions to cashew nuts are often more severe than reactions to peanuts, with more frequent bronchoconstriction and cardiovascular symptoms in the cashew group despite the fact that asthma was a more frequent co-morbidity in the peanut group (4).

At the Royal Children's Hospital in Melbourne, 117 anaphylactic reactions occurred over a 5-year period, more frequently to cashew nut than to peanut (18% and 13%, respectively). However, it is not described whether this difference is statistically significant and the percentages are not adjusted for other risk factors (28).

The study by Davoren et al. showed that five of 27 patients with cashew nut allergy had an allergic reaction after only skin or mucosal contact. One of these five patients developed anaphylaxis (3). This suggests significant reactions even to minimal levels of exposure. Blom et al. determined the eliciting doses in 31 patients with a positive double-blind placebo-controlled food challenge test (DBPCFC) and found that the protein dose, at which 50% of the allergic population was likely to respond (ED50), was 25.4 mg (any type of symptoms) which is comparable to peanut (17.2 mg) and hazelnut (13.5 mg) and clearly lower than that of egg or milk (82.0 and 82.6 mg, respectively) (30). The severity of accidental reactions to cashew reactions could be increased further by the fact that compared with peanut and hazelnut, cashew is more often in particulate form resulting in higher doses. However, further research is necessary.

These data collectively suggest that cashew nut allergy may be considered an exceptionally potent allergen that is a relatively frequent cause of anaphylaxis.

Diagnosis

Corderoy et al. showed that patients with positive or negative cashew nut challenge tests do not differ in median cashew nut sIgE. In contrast, however, the SPT was significantly larger in patients with positive challenge tests. Skin prick tests seem to be superior to sIgE in predicting challenge outcome (6). The reliability of SPT depends on several factors such as age, method of skin prick testing and quality of the extract. A cut-off value of ≥8 mm (SPT) gave a 95% positive predictive value for a positive challenge test outcome (31). However, the size of the study and the population characteristics limit, however, the generalizability of the data. There are currently no studies reporting the relative importance of sensitization to major allergens of cashew in predicting clinical reactivity to cashew nut or the severity of such reactions. A relatively new approach is component-resolved diagnosis, which might be useful to determine sIgE to cashew nut allergens.

Algorithm for the diagnosis of cashew nut allergy

Cashew nut allergy is often diagnosed by history, combined with measuring sensitization by skin prick test and *in vitro*-specific IgE tests. As with other foods, the latter tests do not distinguish very well between clinical allergy and asymptomatic sensitization. For the diagnosis, the gold standard remains DBPCFC, according to international guidelines DBPCFC should not be used in case of a clear-cut history of anaphylaxis after consumption of cashew nuts (32). The fact that this test is time-consuming, labour-intensive, expensive and not entirely without risk has prompted research into the development of models predictive of clinical reactivity based on other parameters.

DunnGalvin et al. developed a prediction model for peanut allergy, which might replace DBPCFC. When validated in the same centre, the model showed an AUC of 0.97 to predict peanut allergy (33). However, this prediction model was not able to predict peanut allergy in a Dutch study (34). A prediction model has not yet been developed for cashew nut allergy.

Management

The mainstay of therapy in food allergic patients is avoidance of the allergic food. This is increasingly difficult to achieve in cashew nut allergic patients because of the increase in cashew nuts in many food products.

Causal treatment for food allergy in form of oral immunotherapy (OIT) is in development. Oral immunotherapy for food such as egg, milk and peanut seems to be a promising way to induce desensitization or tolerance despite the difficulties, such as the side-effects and doses schedule. Possibly OIT can play a role in the treatment for cashew nut allergy in the future.

Furthermore, avoidance of botanically related foods such as pistachio must be advised in case of established cashew nut allergy. More research is needed to better underpin an

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advice on avoidance of botanically related foods with allergenic homology to cashew nut.

Summary and conclusion

Recent studies on cashew nut allergy suggest that the prevalence of cashew nut allergy has increased. Whilst this may be a real increase, increased cashew nut consumption may be revealing more cases, and more cases may be noticed because of increased awareness of patients and doctors. The latter seem less likely given the often severe nature of reactions to cashew nut. The major allergenic proteins described in cashew nuts to date are legume-like proteins and 2S albumins. The DBPCFC test is currently the gold standard to establish cashew nut allergy. Cashew nuts allergens are apparently highly potent and can cause relatively severe reactions. They are a relatively common cause of anaphylaxis and can cause death. Avoidance of pistachio nuts must currently be advised in case of a cashew nut allergy, but advice of avoidance of other related allergens needs further investigation.

In comparison with literature and research focussed on peanut, cashew allergy is clearly an underestimated but important healthcare problem, especially in children.

Further research is urgently needed on this relatively new food allergen, including allergenic content, diagnostic tools and dietary advice for the patients required to prevent severe anaphylactic reactions.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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