How can component- resolved diagnostics help in diagnosing food allergies, such as peanut and/or tree nut allergy in children and adolescents?

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Keywords

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Abstract

Food allergy is the most common cause of anaphylaxis in children. In pre-schoolers under 3 years old, cow's milk and hen's egg are the most common elicitors and most children outgrow this allergy. Tree nuts and peanuts are the next most common triggers of anaphylaxis in both children and adolescents and tend to persist from a very young age into adolescence/adulthood. In this article we will focus on the diagnostic tools for hazelnut and peanut allergy. Skin prick tests and specific IgE antibody titres to allergen extracts alone are generally not sufficient to determine whether an acute reaction can be explained by a specific food allergen. Component resolved diagnostics clearly has added value for the diagnosis of clinically relevant food allergy in children and adolescents.

Allergic diseases are characterized by the occurrence of symptoms upon contact after ingestion, inhalation or skin contact with innocent products, being protein structures, called 'allergens' that cause an immunological reaction. We here only consider type I or IgE mediated allergies. Mechanistically an allergen will be presented to naïve T-cells by allergen-presenting cells that will drive naïve T cells towards T helper 2 cells, instructing B cells to produce IgE antibodies towards those allergens. Circulating IgE antibodies can bind to their receptors on mast cells and/or basophils and upon renewed contact, those cells can degranulate with symptoms as a result (figure 1) (1). However, the presence of circulating specific IgE (sIgE) antibodies on itself is called 'sensitization' and is not necessarily associated with clinical symptoms or symptomatic allergy, neither are positive skin prick tests (2). It is crucial for clinicians to understand the differentiation between allergic sensitization and clinical allergy (in case of symptoms) and to consider both in test interpretation and diagnostic decision making. In clinical practice, IgE mediated allergy can be diagnosed in the first place by a detailed clinical history, followed by skin prick tests and/or blood analysis: sIgE antibody titres to an allergen extract (mixture

Figure 1: "Immunological mechanisms of allergic sensitization. Epithelial cells produce alarmins such as IL-25, IL-33, and TSLP in response to external insults. These cytokines are central regulators of type 2 immunity, as they act on dendritic cells to induce TH2 responses and activate ILC2 cells leading to production of IL-13 and IL-5. Allergens and pathogens that pass skin or mucosal epithelial barriers are captured and processed by dendritic cells (DCs), which in turn migrate to draining lymph nodes, where they present allergen-derived peptides on MHC class II molecules to naïve T cells, which in turn (depending on co-stimulatory and cytokine signals) can differentiate to TH2 cells or TFH cells. TH2 cells produce type 2 cytokines such as IL-4, IL-13, IL-5, and IL-9, and function as effector cells that drive many aspects of allergic inflammatory responses. TFH cells produce IL-21, IL-4, and IL-13 and induce IgE class switch recombination in B cells, plasma cell differentiation and allergen-specific IgE production. Plasma cell produce allergen-specific IgE antibodies that are released into circulation and can bind to FcεRI molecules on mast cells and basophils. Subsequent exposure to allergen can result in mast cell and basophil degranulation".

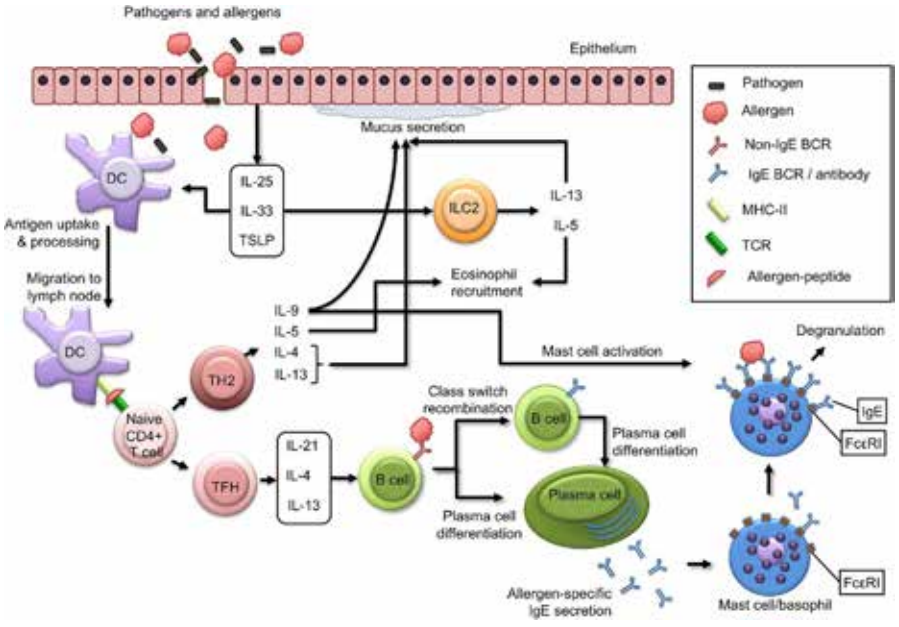
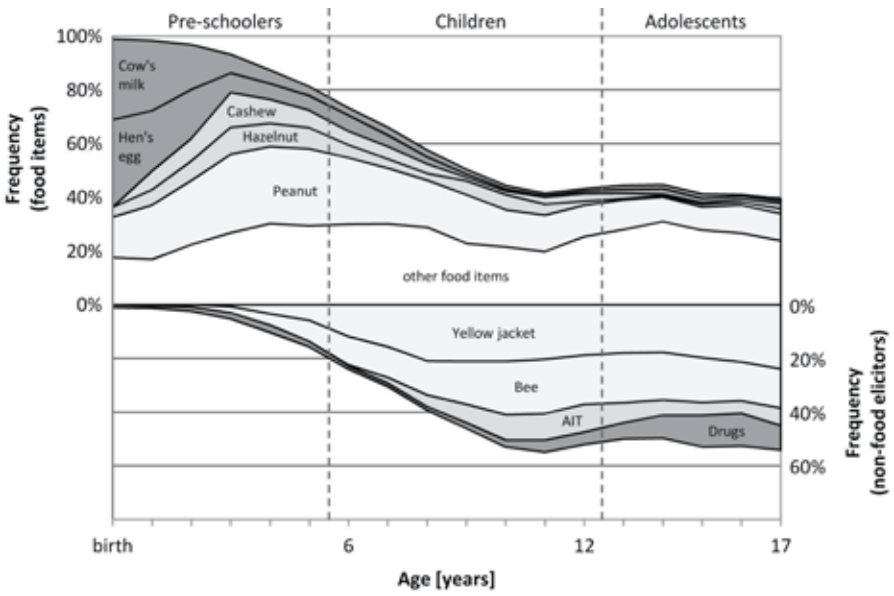


Figure 2: The elicitors of anaphylaxis by age according to the European anaphylaxis registry (7).



of proteins from the allergen) and sIgE antibody titres to specific proteins in an allergen, called allergen components. Multiplex tests such as ISAC® (Immuno Solic-phase Allergen Chip), a multiplex test available since 2008, analyses at the same time sIgE tests against 112 allergen components from 48 different allergen extracts. ALEX® (Allergy Xplorer) tests simultaneously sIgE against 120 allergen extracts and 170 allergen components and is available since 2019 (3). If based on a detailed history no culprit of the allergic reaction can be found, the multiplex test is available, but currently not reimbursed. In research settings the Basophil Activation Test (BAT) and Mast Cell Activation test (MAT) are being developed (4). We define three types of allergens: environmental allergens that can be inhaled, allergens that can be injected (insect venom allergens or drug allergens) and food allergens that can be ingested.

We here will discuss more in detail specific diagnosis of food allergy, as food is globally the most common trigger for anaphylaxis admissions to hospital in children and adolescents (5). According to the food anaphylaxis registry, the most frequent elicitors for an anaphylactic reaction in pre-schoolers under 3 years are cow's milk and hen's egg and most children will outgrow this allergy before the age of 8 and 12 years respectively, provided that they do not present with very high sIgE levels for these food products at diagnosis (6,7). Tree nuts (such as hazelnut) and peanut are the following most frequent elicitors of anaphylaxis in both children and adolescents and they generally persist from a very young age until adolescent/adulthood (fig 2) (7). As these are frequent triggers of anaphylaxis, we have chosen to specifically highlight the diagnostic tools for hazelnut and peanut allergy. To determine if an acute reaction can be explained by a specific food after eating e.g. a complex meal, skin prick tests and sIgE antibody titres to (an) allergen extract(s) are generally not satisfying. Component-resolved diagnostics can further unravel the history and differentiate between primary and secondary food allergy, being an IgE mediated allergy for food and IgE mediated allergy for aeroallergens with secondary cross-allergy to food respectively. We know that primary food allergy can strongly be associated with severe reactions such as anaphylaxis. The most clinical relevant components for a primary hazelnut and peanut allergy are respectively seed storage proteins Cor a 9, Cor a 14 and Ara h 2, Ara h 6 (8,9). Other known major proteins of peanut are Ara h 1, Ara h 3 and Ara h 9 (10). If the child reports mild local oral or throat pruritus without systemic symptoms, when ingesting the food it can be caused by a pollen-food allergy syndrome or oral allergy syndrome (2). Rarely, in 1,7% of the cases, a pollen-food allergy syndrome might even cause an anaphylactic shock (11). Allergen components Cor a 1 and Ara h 8 (PR-10 components) are Bet v 1 structural homologues allergens from respectively hazelnut and peanut (table 1), which can cause a cross-reactivity with the birch tree causing a pollen-food allergy syndrome then called secondary or 'cross-allergy' (10). Therefore, the measurement of allergen components is useful to make the distinction between a primary food allergy and a pollen-food allergy syndrome. If the patient has a positive sIgE antibody titre for hazelnut or peanut extract, birch extract and Cor a 1 or Ara h 8 respectively, in the absence of symptoms after ingestion of hazelnut or peanut, this might be considered as pollen-food cross-reactivity causing cross-sensitization, without cross-allergy. In that case, children should not stop their hazelnut or peanut intake. On the contrary, regarding new guidelines they should be encouraged to further ingest these food proteins (12). New allergies may arise from strict avoidance of all nuts, there are consequences on nutrition and growth, especially in children with other food allergies (13). On the other hand, it is nowadays hypothesized that tolerance induction towards other treenut families might be induced by regular consummation of tolerated treenuts and/or peanuts. Results of a clinical trial designed to prove this hypothesis, are awaiting (14). In case the clinical history is suggestive for a primary IgE mediated allergy to hazelnut or peanut and the clinically relevant antibody titres to the components are negative, we can still not rule out a primary hazelnut or peanut allergy, because not yet all tests towards clinically relevant allergen components are routinely available or certain responsible allergen components within the food proteins might even not yet be defined. An oral food challenge (OFC) remains the gold standard to diagnose food allergies in children. An OFC is labour intensive, the child can be traumatized afterwards and it can lead to anaphylaxis which rarely might be fatal. Enabling an OFC requires a specialized service in a hospital with a highly skilled clinical team and the ability to transfer quickly to intensive care units if needed. On the

Table 1 : Hazelnut and peanut allergen components (10).

Family	Biochemical name	Hazelnut	Peanut
Family	PR10	Cor a 1	Ara h 8
Bet v 1 homologues (PR10)	2S albumin	Cor a 14	Ara h 2, Ara h 6
Prolamin	Non-specific lipid-transfer protein (LTP) (PR14)	Cor a 8	Ara h 9
Prolamin	Legumin	Cor a 9	Ara h 3
Cupin	Vicilin	Cor a 11*	Ara h 1
Cupin	13.01 - 17	4	13.01 - 17
	17.01 - 21	5	17.01 - 21

*Cor a 11 is only available in a multiplex test.

other hand, an OFC can reduce anxiety and improve health-related quality of life, therefore allergy work-up today still relies on OFCs (15). Potential alternatives to an OFC are newer diagnostic tests such as component-resolved diagnostics which were highlighted above but also BAT and MAT are more and more used to diminish the frequency of OFC and to come to a final diagnosis before renewed introduction of the suspected food (4).

We are convinced that a diagnostic work-up for food allergy by component- resolved diagnostics has an added value in clinical practice of specialists of paediatric allergy along with a detailed clinical history, sIgE antibody titres to allergen extracts and/or skin prick tests for diagnosing a clinically relevant food allergy. Since the differentiation of a pollen-food allergy syndrome versus primary food allergy needs component-resolved diagnostics, the limited reimbursement in Belgium of 6 sIgE antibody titres in total should be reconsidered. For example, if sIgE antibody titre for peanut extract is positive, it is our conviction that the available sIgE tests towards all components of peanut should be reimbursed (Ara h 1,2,3,6,8 and 9).

Conflict of interest

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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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.

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