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A remarkable food allergy in children: cashew nut allergy

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What is already known on this topic?

- *Recent studies on cashew nut allergy suggest that the prevalence of cashew nut allergy is increasing with raising consumption. Clinical reaction to cashew nuts may be severe, suggesting high potency comparable with other tree nuts and peanuts. The allergenic potential of cashew nuts is an underestimated important healthcare problem.*

What this study adds on this topic?

- *Most of the children in this study were sensitized to cashew nuts without ever consuming cashew nuts in the infancy period. Early onset of moderate-to-severe atopic dermatitis and multiple food allergies are remarkable co-existing conditions in children who have been diagnosed with a cashew nut allergy. Cashew nut allergy is associated with a significant risk of anaphylaxis; therefore, anaphylaxis should be considered when evaluating children with suspected cashew nut allergy.*

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ABSTRACT

Objective: The prevalence of cashew nut allergy is increasing. Clinical reaction to cashew nuts may be severe, including anaphylaxis. In this study, we aimed to evaluate the frequency of cashew nut sensitivity in a group of children with food allergy and the clinical features and course of cashew nut allergy.

Material and Methods: A retrospective chart review was performed on 516 children who presented with food allergy at a pediatric allergy department. Individuals sensitized to cashew nuts were examined.

Results: Cashew nut sensitization was detected in 17 (64.7% male; mean age of symptom onset, 14 months) of 516 patients with food allergy. Skin symptoms were the most frequent clinical presentation, followed by gastrointestinal symptoms. Overall, 29.4% of the patients presented with anaphylaxis. All anaphylactic reactions were developed after the first consumption of cashew nuts. Of the cashew nut–sensitized patients, 82.3% were diagnosed with moderate-to-severe atopic dermatitis, and all of them had multiple food allergies. During the follow-up, 90% of the patients who had cashew nut sensitization and co-existing food allergies to cow's milk and/or hen's egg developed tolerance to cow's milk and/or hen's egg, but none of the patients could tolerate cashew nut ingestion.

Conclusion: Cashew nut is a potent allergen, causing severe allergic reactions that persist long term compared with other food allergies. Early onset of moderate-to-severe atopic dermatitis and multiple food allergies are remarkable co-existing conditions in children who have been diagnosed with cashew nut allergy. Pediatricians should be aware of this emerging food allergy.

Keywords: Anaphylaxis, cashew nut, IgE-mediated allergy, sensitization, tree nut allergy

Introduction

Tree nut allergy affects over 2% of children (1). Recent studies on cashew nuts (CNs) suggest that the prevalence of CN allergy is increasing with raising consumption (2). In the 2017–2018 season, CN production raised by 32% over the previous decade worldwide. The biggest cashew consumers in the world are India, USA, Germany, Netherlands, and the United Kingdom (3). Cashew nut allergy seems to have become a significant problem, not only in these places but also in other regions, because of the increase in consumption over the past years (4). Nuts are frequently consumed as snacks in Turkey. Sunflower seeds are the most commonly consumed snacks, followed by mixed nuts (common constituents of mixed nuts: hazelnuts, pistachios, almonds, walnuts, peanuts, and CNs) in the traditional eating habits of Turkey (5). Parallel to the growing trend of CN consumption throughout the previous 10 years all over the world, we suggest that the rate of CN sensitization is also likely to increase in Turkey as reported in the previous studies (2).

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Cashew nut allergy presents most commonly in the first five years of life (range, 2 months to 27 years), with typical rapid-onset immunoglobulin E (IgE)-mediated symptoms (1, 2). Clinical reaction to CNs may be severe, including anaphylaxis, suggesting high potency comparable with other tree nuts and peanuts (2, 6). The mainstay of therapy in CN allergy is avoidance of CNs; however, this is not easy to provide in patients with CN allergy because it exists in many food products (2). The majority of children allergic to hen's egg or cow's milk often develop tolerance over time, but CN allergy tends to show lifelong persistence similar to other nuts (1).

Although CN allergy is a serious health problem in children, it remains understudied in comparison to peanuts and needs to be underscored as a potent food allergen. In this study, we present the patients who were sensitized to CNs in a group of children with food allergy attending a pediatric allergy clinic. We assessed the clinical features and course of CN allergy.

Material and Methods

A retrospective chart review was performed on 516 children less than 18 years of age who presented with food allergy over a 24-month period at the pediatric allergy department of a tertiary care children's hospital. Food allergy diagnosis was based on the combination of clear-cut history, typical clinical presentation, positive skin prick test (SPT)/specific IgE, or oral food challenge (OFC) test (7).

Skin prick test with CN was not applied to all children (n=516) with food allergy. Among these children, those with a history of allergic reaction to CNs and/or pistachios were evaluated for CN allergy in the clinic, but others were not prick tested with CNs routinely. A total of 17 patients sensitized to CNs (evidence of nut-specific IgE shown by a positive SPT [Stallergenes, France]) were recruited in the study. A positive SPT was defined as a mean wheal diameter at least 3 mm greater than the negative control. We used the ratio defined as histamine equivalent prick (HEP)-index diameter. We divided the average diameter of allergen-induced wheal by the average diameter of histamine-induced wheal.

Tolerance was defined for patients whose first OFC was positive and last OFC was negative during the follow-up. Anaphylaxis was defined according to the clinical criteria reported in "Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology" (8). Hannifin and Rajka criteria were used to confirm the diagnosis of atopic dermatitis (AD) (9). The SCORing Atopic Dermatitis (SCORAD) index is used to assess the severity of AD. Scores below 25 were classified as mild, scores 25–50 were classified as moderate, and scores over 50 were classified as severe AD (10).

Ethical approval was received from Keçiören Training and Research Hospital Ethics Comity (protocol number 2012-KAEK-15/2090). The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Among the descriptive statistics, continuous variables were shown as mean and standard deviation (SD). For data not normally distributed, median with data range (minimum to maximum or interquartile range) was used. Categorical variables are shown as number and percentages. The Mann-Whitney U test was used for the comparison of continuous inter-group values. All analyses were performed with IBM SPSS Statistics, version 15.

Results

A total of 17 patients sensitized to CNs were recruited in the study. Patients were diagnosed with CN allergy with the combination of clear-cut history, typical clinical presentation, and positive SPT or OFC. Patients with a history of anaphylaxis after CN ingestion (n=5) and positive SPT with CN were not challenged. Of 17 patients, four were not challenged because their parents did not approve the OFC. All four patients had a positive SPT with CN with a wheal size greater than 10 mm, which is the reported cutoff value to predict clinical reactivity for CN (11). Cashew nut sensitization was detected in 17 of 66 patients with tree nut allergy. A flowchart of the patients is shown in Figure 1. Demographic and clinical characteristics of patients with CN sensitization are shown in Table 1.

Clinical symptoms after CN intake are shown in Figure 2. Skin symptoms were the most frequent clinical presentation, followed by gastrointestinal symptoms. Of 17 patients, four never consumed CNs. The parents of these four children did not approve the OFC, so they were still on an elimination diet. These four patients had moderate-to-severe AD with multiple food allergies, and two of them had anaphylaxis with hazelnut.

Anaphylaxis occurred in 9 of 66 patients who were diagnosed with tree nut allergy. Of those, five were due to CN ingestion. There was no identified biphasic reaction. None of the anaphylactic reactions required hospital admission longer than 24 hours.

Table 1. Demographic and clinical characteristics of children with cashew nut sensitization

Total	**n (%) (N=17)**
Gender	
Male	11 (64.7)
Mean age (month)*	37 (11–66)
Mean age of symptom onset (month)*	14 (6–30)
Atopic disease	
Atopic dermatitis	14 (82.3)
Anaphylaxis	9 (52.9)
Asthma	5 (29.4)
Sensitization of other tree nut allergy	
Pistachio nut	14 (82.3)
Walnut	9 (52.9)
Hazelnut	9 (52.9)
Almond	5 (29.4)
Sensitization of peanut allergy	5 (29.4)
Co-existing food allergy	
Egg	8
Cow's milk	6
Mean total IgE (ku/L)*	309 (16–2.150)
Mean tryptase level (µg/L)*	6.7 (3.8–10.9)

*Minimum–maximum interval. IgE, immunoglobulin E.

Table 2. Comparison of children with CN sensitization according to the clinical reactions to CN based on anaphylaxis			
Patients	**Patients with anaphylactic reaction**	**Patients with non-anaphylactic reaction**	**p**
Wheal diameter of SPT with CN	20 (10.5–21.5)	6 (5–9)	0.069
Mean HEP-index diameter of CN	1.40 (1.05–1.88)	1.09 (0.88–1.42)	0.268
Total IgE (ku/L)	106 (35–1.643)	74 (38–343)	0.794
Basal tryptase level (µg/L)	8.3 (5.2–8.3)	5.2 (3.8–7.8)	0.154
Absolute eosinophil count (microL)	350 (90–500)	205 (105–487)	0.799

CN, cashew nut; HEP, histamine equivalent prick; IgE, immunoglobulin E; SPT, skin prick test.
All values reported as median (interquartile range).

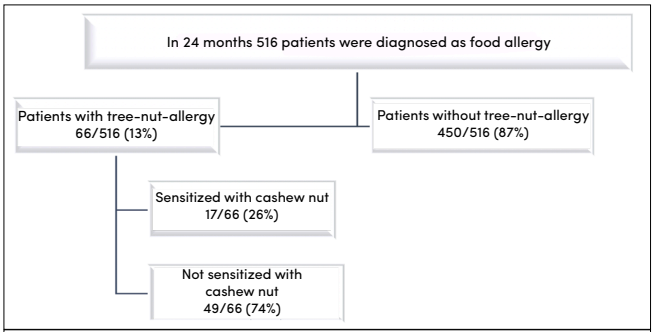

Figure 1. Flowchart of the study

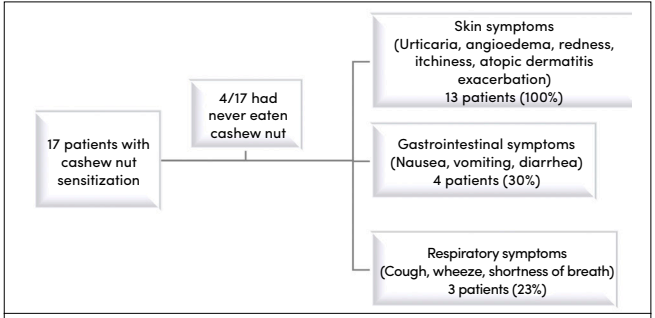

Figure 2. Clinical symptoms after cashew nut ingestion

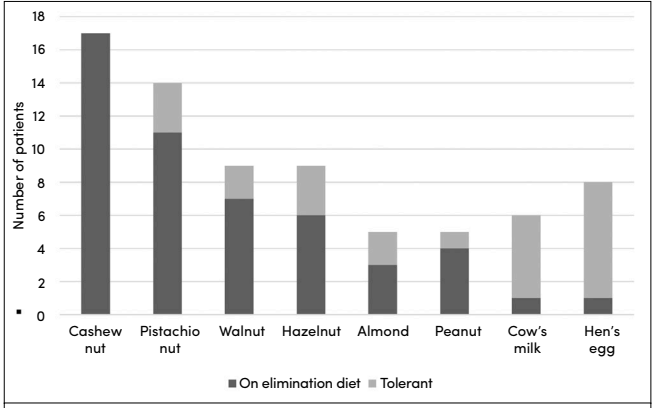

Figure 3. Tolerance acquisition to tree nuts in patients with cashew nut sensitization

Of 17 CN-sensitized children, 14 had AD. According to the SCORAD index, all of these patients were diagnosed as moderate-to-severe AD. All patients with CN sensitization had multiple food allergies. All patients with CN sensitization had co-existing sensitization proven by positive SPT with at least one of the tree nuts, as described in detail in Table 1. Overall, 58.8% of patients with CN sensitization had co-existing challenge-proved food allergies with cow's milk and/or hen's egg.

The mean±SD wheal diameter of SPT with CN was 10.3±6.9 mm. The mean±SD HEP-index diameter of CN was 1.4±0.85. Patients were divided into two groups (patients with anaphylactic and non-anaphylactic CN reactions) according to the clinical reactions to CN based on international anaphylaxis guidelines (8). There was no difference in the HEP-index diameter or SPT mean wheal diameter between these two groups ($p>0.05$). No differences were found concerning total IgE, basal tryptase level, and absolute eosinophil count between the two groups ($p>0.05$) (Table 2).

Patients whose parents refused OFC or patients with positive OFC continued an elimination diet during the follow-up. During the follow-up (minimum–maximum, 6–24 months), none of the patients were re-challenged with CN. Two patients had eaten CNs in the follow-up period accidentally, and IgE-mediated clinic symptoms were observed. All of the patients with CN sensitization had still been on an elimination diet. Of the patients with CN sensitization, 35.2% developed tolerance to some of the other tree nuts (pistachio nut, walnut, hazelnut, almond, peanut) rather than CN, as shown in Figure 3. Of the patients who had co-existing food allergies to cow's milk and/or hen's egg, 90% developed tolerance to cow's milk and/or hen's egg.

Discussion

In this study, results show that CN is causing considerably severe reactions among tree nuts, and CN allergy is associated with a significant risk of anaphylaxis in children. Most of the children were sensitized to CN without ever consuming CNs in the infancy period. Early onset of moderate-to-severe AD and multiple food allergies are remarkable co-existing conditions in children who have been diagnosed with CN allergy.

In our study, we found that 3.2% of the 516 children diagnosed with food allergy were sensitized to CN over a 24-month period. In Sweden, over a 10-year period, the estimated prevalence of CN allergy was 6% of food allergic children (12). We suggest that the difference may be due to the eating habits and frequency of CN consumption in different geographical areas and awareness of the doctors for the diagnosis of CN allergy. In our study, 26% of the nut allergic patients were sensitized to CN. Davoren et al. (6) and Moneret-Vautrin et al. (13) indicated that 12.6% and 41%, respectively, of the nut allergic patients were sensitized to CNs.

The median age of CN reaction was about 24 months in the literature (14). In our study, the age of onset of allergic symptoms to CN varies between 6 and 30 months, with a mean age of 14 months. For CN allergy, the ingestion of CNs seems to be the principal sensitization path, although mechanisms associ-

ated with poor skin barrier function such as AD have also been highlighted as an increasing risk factor for the development of CN allergy (4). Crealey et al. (15) reported that 76% of those reacting to CNs had eczema (65% of those developing it in the first six months of life). Compatibly, most of our patients had moderate-to-severe AD in early life and were sensitized to CNs without ever consuming them. Our patients' data supported the mechanism associated with disrupted skin barrier integrity and transcutaneous sensitization.

Most of the reported clinical reactions to CNs are moderate to severe, and fatalities have also been reported (5). Gastrointestinal symptoms are common after skin involvement and more frequent in comparison to peanut and other tree nut allergies (16, 17). In this study, skin symptoms were the most common, followed by gastrointestinal and respiratory symptoms, which corresponds to previous reports (18). In our study group, five of 17 patients (29.4%) sensitized with CN presented with anaphylactic reaction after ingestion of CNs. Anaphylactic reaction was developed after the first consumption of CNs. Three of these patients were younger than 12 months, and four of them had a history of severe AD. Crealey et al. (15) reported that 53% of children with clinical reaction to CNs presented with anaphylaxis, and Clark et al. (19) reported more severe symptoms (more bronchoconstriction and more cardiovascular symptoms) to CNs compared with peanut allergy. Anaphylaxis occurring without cutaneous features has previously been reported, but none of our patients presented without cutaneous features (6). The SPT's mean wheal diameter, HEP-index diameter, total IgE, basal tryptase level, and absolute eosinophil count did not differ significantly among patients with anaphylactic and non-anaphylactic CN reactions. The small number of patients may limit the analysis. Cetinkaya et al. (20) showed that asthma, egg white allergy, higher serum basal tryptase levels, and female gender were independent risk factors for anaphylaxis in children with tree nut allergies.

The cashew plant *(Anacardiumoccidantale L)*, pistachio nut *(Pistaciavera)*, and mango *(Mangiferaindica)* belong to the Anacardiacea family, and previous studies demonstrated cross-reactivity to CNs and pistachio (21). Of the patients with CN sensitization, 82.3% had co-sensitization with pistachio nut in our group. Because the consumption of mango is very rare in Turkey, mango allergy was not evaluated. van der Valk et al. (22) reported in their study evaluating 29 children that co-sensitization between CNs and pistachio nuts was 98%, but pistachio nut sensitization was clinically relevant in 34% of the children. Unless a negative OFC is demonstrated, avoidance of pistachio nuts must be advised. The other related tree nut allergens should be investigated before avoidance (2).

There were no patients with CN allergy alone; all patients had multiple food allergies in our study. Overall, 58.8% of our patients clinically reacted to another food with cow's milk and/or hen's egg. Recent data show that early-onset severe eczema and egg allergy is a significant risk factor for peanut allergy (23-25). Most of our patients with CN sensitization had early-onset moderate-to-severe eczema, and more than half of them had hen's egg and/or cow's milk allergy. We propose that not only peanut but also CN allergy is alarming for this group of patients.

Over 36 months, all of the patients with CN sensitivity were still on a CN elimination diet, although 90% of these patients developed clinical tolerance to cow's milk and/or hen's egg. During follow-up with patients in whom OFCs were performed, there were no patients who developed tolerance to CNs. Prevention and detection of CN allergy in clinical practice is highly important, because this potent allergen seems to be responsible for the long-lived allergy (1).

This study projects experiences in a tertiary allergy clinic but has some limitations because of the retrospective composition. The most important limitation of the study was the small number of participants. The specific IgE level of CNs was not measured because of the insufficiency of the hospital's laboratory. However, in a recent study, it is indicated that SPT with CN is more predictive than specific IgE for positive OFC (11). Oral food challenges were not performed on the patients whose parents did not give written informed consent. In spite of these facts, it is a real-life study pointing to the life-threatening severe reactions after CN intake in children.

Cashew nut is a potent allergen causing severe and systemic allergic reactions that persist long term compared with other food allergies. Cashew nut allergy is associated with a significant risk of anaphylaxis; therefore, anaphylaxis should be considered when evaluating children with a suspected CN allergy. There is a vigorous prevalence of atopy among CN allergic subjects. Children who have a food allergy to hen's egg and/or cow's milk, with early onset of moderate-to-severe AD, seem to be at risk.

Ethical Committee Approval: Ethics committee approval was received for this study from the ethics committee of Keçiören Training and Research Hospital (2012-KAEK-15/2090).

Informed Consent: Patient consent was not obtained due to the retrospective design of the study.

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