

## Short communication

# Cashew nut causes more severe reactions than peanut: case-matched comparison in 141 children

**Background:** Cashew nut allergy is becoming common, but the risk of severe reactions in comparison with peanut allergy is unknown.

**Method:** A case-matching study of children with a recent history of a reaction after definite nut ingestion, with positive skin prick test. Children whose worst ever reaction was to cashew nut (cashew group), were matched with two children each whose worst ever reaction was to peanut (peanut group) for sex, age of reaction and presentation, amount ingested, and asthma. Severity of the worst clinical reactions to date was compared.

**Results:** A total of 47 children in the cashew group were matched to 94 in the peanut group. There were no differences in clinical features between groups for matching criteria, except asthma (more prevalent in the peanut group).

Wheezing and cardiovascular symptoms were reported more frequently during reactions in the cashew compared with the peanut group: odds ratios (OR) 8.4 (95% CI: 3.2–22.0) and 13.6 (95% CI: 5.6–32.8), respectively. The cashew group received intramuscular adrenaline more frequently: OR 13.3 (95% CI: 5.5–32.2). Overall, the OR for a severe reaction (severe dyspnoea and/or collapse) in the cashew group was 25.1 (95% CI: 3.1–203.5).

**Conclusions:** Previous studies show cashew nut can cause severe reactions; this is the first study to show by case-matching that severe clinical reactions occur more frequently in cashew compared with peanut allergy. The nut type which caused the worst reaction to date should be considered when providing emergency medication.

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Peanut allergy affects 1.5% of children, has an early onset and resolution is uncommon (1, 2). Tree nut allergy is also common and persistent (3–5). Allergy to cashew nuts is increasingly recognized in clinical practice but there are few data on the clinical features with which to inform practice (6).

Management of nut allergy should include a risk assessment, to inform the provision of specific avoidance advice and emergency medication (7). Factors which might influence the severity of future reactions should be taken into account, such as age, severity of the worst reaction to date and amount of nut which caused it, and the presence of asthma (8). The type of nut that caused the worst reaction to date may also indicate increased risk. The majority of reactions to peanut are mild, but it is also the commonest cause of fatal anaphylactic reactions to food (8). Tree nut allergy also has a wide spectrum of severity and overall may be more severe than peanut allergy (9). Previous studies have shown the potential for cashew nut to cause anaphylaxis (6, 10, 11). We compared the severity of cashew and peanut reactions in subject pairs, matched for known and suspected confounding factors.

## Method

A case-matching retrospective study of children whose worst clinical reaction before referral was to either cashew nut or peanut. Diagnosis was based on a history of a typical type 1 hypersensitivity reaction to definite ingestion of either cashew or peanut, with evidence of sensitization to the specific nut type by skin prick test (weal diameter  $\geq 3$  mm). Peanut extract was provided by ALK-Abello, (Madrid, Spain). Cashew nut extract (10% w/v in Coca's solution) was prepared in-house: ground cashew nuts were incubated for 7 days at 5°C with coca's phenol ( $\text{NaH}_2\text{PO}_4$  0.37 mg/ml,  $\text{Na}_2\text{HPO}_4$  1.42 mg/ml, NaCl 2.5 mg/ml (BDH, Poole, UK), phenol 4 mg/ml (Sigma, Gillingham, UK), the suspension was centrifuged and supernatant filtered (0.22  $\mu\text{m}$ ). Children whose worst ever reaction was to cashew nut, were enrolled consecutively from our allergy clinic (cashew group). Children from our allergy clinic whose worst ever reaction was to peanut were matched 2 : 1 to subjects from the cashew group for sex, age at first reaction to cashew nut or peanut, age at presentation, amount of nut exposure during worst reaction, and whether the nut was spat out or vomited (peanut group). Nut exposure was defined (by history) as trace (cutaneous contact, no ingestion), small (ingestion of up to one nut) or large (ingestion of more than one nut). We also attempted to match subjects for the presence of asthma. Symptoms of the worst reaction to date and emergency medication used were obtained by an experienced allergist. Severity of the worst reaction to date was

graded by symptoms (mild = cutaneous features only; moderate = wheeze/laryngeal oedema; severe = severe dyspnoea and/or collapse) (7, 9).

## Statistics

Odds ratios were calculated with 95% CIs. Medians and interquartile ranges (IQR) are shown for data which are not normally distributed. Severity scores of matched pairs are compared with the Wilcoxon matched pairs test. Calculations were made using GRAPHPAD PRISM version 3.00 for Windows, (GraphPad Software, San Diego, CA, USA).

## Results

There were 47 children whose worst ever reaction was to cashew nut (cashew group) who were matched with two peanut allergic subjects each (peanut group;  $n = 94$ ). There were no significant differences in clinical features between cashew and peanut groups for the matching criteria, except asthma (there were too few peanut allergic subjects without asthma to match) (Table 1). There was no difference in median SPT weal diameter to cashew or peanut. No child in the peanut group reported ever having had an allergic reaction to cashew nut. In the cashew group, three subjects reported reactions to peanut which were milder than their cashew reactions. Where data were available, 13/47 (28%) of the cashew group were also sensitized to peanut. Sensitization to other nut types was detected in 17% (eight of 47) of the cashew group and 7% (seven of 94) of the peanut group.

The majority of subjects in both groups had urticaria and/ or angioedema during their worst ever reaction and one-third also had gastrointestinal symptoms (Table 2). Symptoms suggestive of lower airway narrowing were reported more frequently in children from the cashew group (Table 2). The OR of developing cardiovascular symptoms was also higher in the cashew group. Overall, severe reactions (severe dyspnoea and/or collapse) were reported in 22% (10/47) of the cashew group compared

Table 1. Subject characteristics

| Subject characteristics             | Cashew group<br>$n = 47$ | Peanut group<br>$n = 94$ |
|-------------------------------------|--------------------------|--------------------------|
| Male                                | 23 (49)                  | 46 (49)                  |
| Female                              | 24 (51)                  | 48 (51)                  |
| Age at onset median (IQR)           | 3.0 (1.8–5.0)            | 3.0 (2.0–5.2)            |
| Age at presentation median (IQR)    | 5.3 (3.3–8.1)            | 5.3 (3.3–8.1)            |
| Asthma*                             | 19 (40)                  | 61 (65)                  |
| Spat out/vomited immediately        | 16 (34)                  | 19 (20)                  |
| Trace exposure only                 | 4 (9)                    | 7 (8)                    |
| Small amount ingested               | 7 (15)                   | 15 (16)                  |
| Large amount ingested               | 36 (77)                  | 72 (77)                  |
| SPT weal diameter (mm) median (IQR) | 8.5 (6.5–10.0)           | 8.0 (6.5–10.0)           |

Unless otherwise specified, numbers of subjects with percentages in parentheses are shown.

Cashew group = children who is worst ever reaction was to cashew nut; peanut group = children who is worst ever reaction was to peanut. Nut exposure was classified as trace (cutaneous contact only); small (ingestion of up to the equivalent of one nut); large (ingestion of the equivalent of more than one nut) during the worst ever reaction.

IQR, interquartile range; SPT, skin prick test

\*Asthma was more prevalent in the peanut group.

with only 1% (one of 94) of the peanut group (OR 25.1 95% CI: 3.1–203.5; Fig. 1). Only one of 10 subjects with cashew allergy who suffered a severe reaction also had a history of asthma. There were no biphasic reactions.

We compared the emergency treatment given to children in each group during their reactions (Table 3). Approximately one-quarter of reactions resolved without pharmacological treatment and one-half of each group received oral antihistamines. However, children in the cashew group received intramuscular adrenaline much more frequently than those in the peanut group (13% vs 1%: OR 13.2 (95% CI: 5.4–32.3).

## Discussion

Approximately 0.08% of 4-year old in the UK are allergic to cashew nut and referrals for cashew nut allergy have

Table 2. Clinical symptoms and signs experienced during each subject's worst ever reaction

| Symptoms/signs during worst ever reaction     | Cashew group $n = 47$ |    |                        | Peanut group $n = 94$ |    |                 |
|-----------------------------------------------|-----------------------|----|------------------------|-----------------------|----|-----------------|
|                                               | $n$                   | %  | OR (95% CI)            | $n$                   | %  | OR (95% CI)     |
| Cutaneous (urticaria ± angioedema)            | 46                    | 98 | 2.0 (0.2–18.8)         | 90                    | 96 | 0.5 (0.01–4.5)  |
| Gastrointestinal: (abdominal pain ± vomiting) | 15                    | 32 | 1.2 (0.57–0.97)        | 26                    | 28 | 0.81 (0.38–1.3) |
| Rhino-conjunctivitis                          | 3                     | 6  | 3.1 (0.5–19.4)         | 2                     | 2  | 0.3 (0.05–2.0)  |
| Wheeze                                        | 19                    | 40 | <b>8.4 (3.2–22.0)</b>  | 7                     | 7  | 0.1 (0.1–0.3)   |
| Laryngeal oedema                              | 4                     | 9  | 1.4 (0.4–5.3)          | 6                     | 6  | 0.7 (0.2–2.7)   |
| Cardiovascular                                | 6                     | 13 | <b>13.6 (5.6–32.8)</b> | 1                     | 1  | 0.1 (0.01–0.2)  |
| Lightheaded                                   | 6                     | 13 |                        | 1                     | 1  |                 |
| LOC                                           | 0                     | 0  |                        | 0                     | 0  |                 |

Cashew group = children who is worst ever reaction was to cashew nut; peanut group = children who is worst ever reaction was to peanut. Numbers of subjects with percentages and odds ratios with 95% confidence intervals are presented.

Significant OR are shown in bold.

LOC, loss of consciousness; OR (95% CI), odds ratio with 95% confidence intervals.

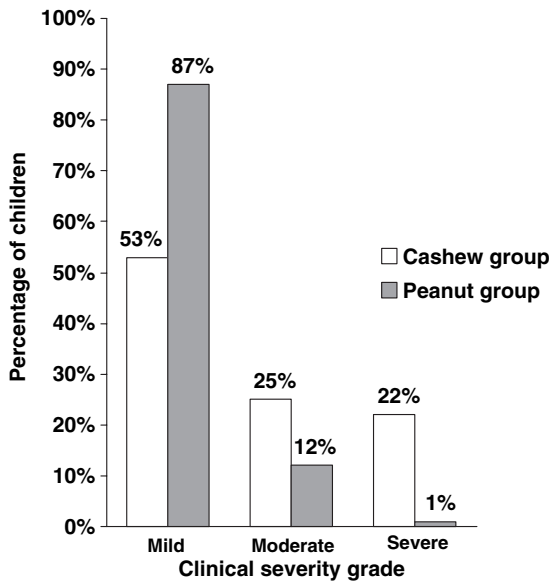


Figure 1. Clinical severity grade of clinical reactions in cashew and peanut groups. Cashew group, worst ever reaction was to cashew nut, peanut group, worst ever reaction was to peanut. Severity of the worst reactions to date was graded according to clinical features (mild = cutaneous features only; moderate = wheeze/laryngeal oedema; severe = severe dyspnoea and/or collapse) (7, 9). Chi-squared test for difference between cashew and peanut groups  $P < 0.0001$ ,  $\chi^2 = 32.0$ .

Table 3. Emergency treatment administered during each subject's worst ever nut reaction

| Treatment received during worst ever reaction | Cashew group $n = 47$ |    |                        | Peanut group $n = 94$ |    |                 |
|-----------------------------------------------|-----------------------|----|------------------------|-----------------------|----|-----------------|
|                                               | <i>n</i>              | %  | OR (95% CI)            | <i>n</i>              | %  | OR (95% CI)     |
| Oral antihistamine                            | 23                    | 49 |                        | 53                    | 56 |                 |
| Intravenous antihistamine                     | 4                     | 9  |                        | 4                     | 4  |                 |
| Intramuscular adrenaline                      | 6                     | 13 | <b>13.2 (5.4–32.3)</b> | 1                     | 1  | 0.07 (0.03–0.2) |
| No treatment                                  | 11                    | 23 |                        | 26                    | 28 |                 |
| No information                                | 3                     | 6  |                        | 9                     | 10 |                 |

Numbers of subjects with percentages and odds ratios with 95% confidence intervals are presented.

Significant odds ratios are shown in bold. Only a single dose was required by subjects who received intramuscular adrenaline.

OR (95% CI), odds ratio with 95% confidence intervals.

increased in recent years (6, 12). There is a need for data on clinical features to inform management. Cashew nut is able to cause severe reactions, but the risk of severe reactions in comparison with allergy to other nut types is poorly understood.

Of 747 children referred to our allergy centre, each child's worst ever reaction to peanut before referral was cutaneous in 64%, involved mild airway narrowing in 24%, and severe dyspnoea and/or collapse in 8% (7). This spectrum is similar to another series of peanut allergic

children and adults where wheeze occurred in 38% and collapse in 7% (13). A study of 1000 peanut and nut allergic subjects showed those with Brazil or hazelnut allergy suffered airway narrowing more frequently than those with peanut allergy (60% and 51%, respectively vs 24%) (9), raising the possibility that tree nut allergy may be more severe.

A study of 30 adults demonstrated the potential for cashew nut to cause severe reactions (43% had airway narrowing and 20% syncope/hypotension) (6). This is in contrast to a series of 42 children where wheeze occurred during only 7% of cashew reactions; there were no cardiovascular symptoms (14). A UK study of children and adults demonstrated a further distinct pattern of cashew reactions, where 48% reacted to contact without ingestion, 48% reported wheeze and 38% suffered cardiovascular symptoms (10). These studies show that reactions to cashew can be at least as severe as those to peanut, although no direct comparison was made. The first study to compare rates of severe reactions between peanut and cashew allergic children showed a higher rate of anaphylaxis in the cashew group (74% vs 31%) (11). The prevalence of respiratory features during cashew reactions varies widely between centres (7% (14), 48% (10), 43% (6), 74% (11), and 40% in the present study), which may be explained by differences in referral patterns and/or patient selection between allergy clinics. In the present study we controlled for this by matching cashew and peanut allergic subjects for known confounding factors. We demonstrated a clear increase in the proportion of respiratory and cardiovascular reactions among children allergic to cashew nut (OR 8.4 and 13.6, respectively). This was reflected by the increased odds of having a severe reaction (OR 25.1) and requiring intramuscular adrenaline (OR 13.2). However, it is worth noting that no child required a second dose of adrenaline.

Following correct diagnosis, children with food allergy should receive a management plan including written information on allergen avoidance and provision of appropriate emergency medication (7). When deciding whether to provide injectable adrenaline, a risk assessment should include consideration of the severity of the worst reaction to date and the presence of concomitant asthma as previously suggested (7). Further, we now suggest that the diagnosis of cashew nut allergy increases the odds of a severe reaction and requiring intramuscular adrenaline and should also be considered in the risk assessment.

It has been suggested that cashew avoidance is easier than peanut avoidance (10, 14); nonetheless it is not straightforward. A recent study showed that 10/37 (27%) of nut-allergic children were unable to correctly identify the type of nut to which they were allergic (15). Cashew nuts are commonly sold as the whole nut alone, or packaged with other nut types. Cashew nuts present a

considerable hazard, being hidden in a wide variety of commonly ingested foods, such as Asian meals, sweets, ice cream, cakes, chocolates and they are increasingly used in commercially prepared pesto sauce instead of pine nuts. Specific information on how to achieve nut avoidance should always be provided.

No food challenges were performed in this study, these would have been unhelpful as we wanted to recruit a group of subjects representative of all severities (we could not challenge children with a history of anaphylaxis). Further, there is no correlation between severity of reactions elicited during challenge or the

dose which elicits them and severity of reactions occurring 'in the field' (16). Subjects were only enrolled if their parents could positively state they had reacted exclusively to cashew and not peanut or vice versa, but there remains a small possibility that they reacted to a contaminating nut.

In summary, this is the first study to employ case-matching to compare severity of peanut and cashew nut allergy and demonstrates increased severity of reactions to cashew nut. Risk assessment for children with nut allergy should include consideration of the nut type which caused the worst reaction to date.

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