

# Comparing pediatric cashew oral food challenges practice between London and Geneva

To the Editor,

Cashew (*Anacardium occidentale*) is considered a seed belonging to the *Anacardiaceae* family growing on the bottom of the cashew apple.<sup>1</sup> Cashew allergy is increasing, and it is one of the most common nut allergies in the United Kingdom<sup>2–6</sup> and in Switzerland.<sup>7</sup> Physicians and patients should be aware of cashew's potential cross-reactivity to other allergens in a wide range of foods, that can represent possible clinically relevant allergic triggers, for example, pistachio or pink peppercorn.<sup>8</sup>

Children allergic to cashew need to strictly avoid the food and carry appropriate emergency medications as severe allergic reactions are possible. Given the risk of severe reactions and its impact on quality of life, a rigorous diagnosis of cashew allergy is required. The oral food challenge (OFC) to cashew remains the gold standard diagnostic investigation. However, protocols are not universally standardized, even if they are increasingly described.

In an OFC, the allergen is administered in titrated doses that are increased at set intervals until reaching an age-appropriate target dose, if tolerated. There are many variables in this process including patient-related factors, allergy clinic resources, challenge protocols, and the form in which food is eaten.<sup>9</sup> Audit of routine clinical service aims to improve clinical practice. However, information is rarely exportable to other geographic populations, due to several factors, such as different patient characteristics and allergy clinic protocols. Data regarding the comparison of the real-life practice OFCs between different centers are lacking for common food allergens other than peanut. Indeed, a previous analysis on the comparison of the practice of peanut OFC between London and Western Switzerland pointed out several interesting similarities and differences.<sup>10</sup> In the current work, we carried out a retrospective, observational, and bicentric database-based study to compare the practice of cashew OFCs between two tertiary level pediatric centers in London and Geneva. Detailed information on the methods can be found in the Appendix S1 section.

During the period taken into consideration, a total of 144 cashew OFCs were performed: 90 in London and 54 in Geneva, with 88 (males 59.09%; mean age  $\pm$  standard deviation, SD  $6.00 \pm 4.36$  years) and 54 patients (males 59.26%; mean age  $\pm$  SD  $6.57 \pm 3.32$  years) involved, respectively. Table 1 presents general patient characteristics, cashew serum-specific Immunoglobulin E (sIgE) levels, and key outcomes of the cashew OFCs. British and Swiss population

demonstrated comparable features in terms of gender and age ( $p$ -value not statistically significant, n.s.). Concerning sensitization, the mean  $\pm$  SD cashew sIgE levels recorded were also similar in London and Geneva ( $1.56 \pm 3.69$  kU/L and  $2.36 \pm 8.67$  kU/L, respectively;  $p$ -value n.s.).

Among the 144 cashew OFCs, there was a lower rate of positive tests in London compared to Geneva, with 15/90 (16.67%) versus 22/54 (40.74%) positive OFCs, respectively ( $p < .05$ ). Table 2 presents general characteristics, cashew sIgE levels, and key outcomes of patients with positive OFCs. Among positive cashew OFCs, differences were noted in rates of anaphylaxis, being lower in London compared to Geneva (3/15, 20.00% versus 16/22, 72.73%, respectively,  $p < .05$ ). However, British and Swiss populations demonstrated comparable features in terms of clinical manifestations and their onset during cashew OFC ( $p$ -value n.s.).

Regarding the medications used to treat the reactions, populations in London and Geneva demonstrated comparable use of adrenaline, antihistamines, and bronchodilators ( $p$ -value n.s.), but a lower use of corticosteroids was recorded in London than in Geneva, in 1/15 (6.67%) versus 9/22 (40.9%) of positive cashew OFCs, respectively ( $p < .05$ ). Prednisolone was used as a corticosteroid in the two centers. Furthermore, first generation antihistamines were used in London but not in Geneva.

In the same centers, when assessing differences for peanut, we found the children in the British cohort were younger than the Swiss cohort ( $p < .05$ ).<sup>10</sup> The target cumulative peanut protein dose in the OFC design was higher in London. The mean peanut sIgE level was lower in the British cohort ( $p < .05$ ), and a lower occurrence of positive OFCs was demonstrated when compared to Geneva ( $p < .05$ ). These differences in peanut OFC outcomes were hypothesized to arise due to London performing them more on peanut-sensitized patients with no history of exposure to the food, in contrast to Geneva performing them more on patients sensitized to peanut and with a history of reaction to the food.<sup>10</sup> A clinical service that undertakes OFCs needs to set their optimal target service-positive OFC rate, which in London is lower than in Geneva.<sup>10</sup> A higher rate of OFCs may also be associated with a greater proportion of anaphylactic reactions. Of note, all of the anaphylaxis cases which occurred in London were recorded in patients who were candidates to perform a cashew OFC with a single top dose only (supervised feed), which was at the discretion of the clinician who evaluated the patient and

TABLE 1 General patient characteristics, cashew sIgE levels, and key outcomes of the cashew oral food challenges.

|                                                        | London                                      | Geneva                                    | p-value |
|--------------------------------------------------------|---------------------------------------------|-------------------------------------------|---------|
| Cashew OFCs                                            | 90                                          | 54                                        | –       |
| Patients (gender, %)                                   | 88 (52 males, 59.09%; 36 females, 40.91%)   | 54 (32 males, 59.26%; 22 females, 40.74%) | n.s.    |
| Age, mean $\pm$ SD (range) years                       | 6.00 $\pm$ 4.36 (0.85–16.23)                | 6.57 $\pm$ 3.32 (1.31–17.70)              | n.s.    |
| Sensitization: cashew sIgE, mean $\pm$ SD (range) kU/L | 1.56 $\pm$ 3.69 (0.00–31.20); n sIgE nd = 7 | 2.36 $\pm$ 8.67 (0.07–63.90)              | n.s.    |
| Positive OFCs (%); with anaphylaxis (%)                | 15 (16.67%); 3 (3.33%)                      | 22 (40.74%); 17 (31.48%)                  | <.05    |
| Negative OFCs (%)                                      | 71 (78.89%)                                 | 31 (57.41%)                               | <.05    |
| Inconclusive OFCs (%)                                  | 4 (4.44%)                                   | 1 (1.85%)                                 | n.s.    |

Note: Data expressed as mean  $\pm$  standard deviation.

Abbreviations: n sIgE nd, number of serum-specific Immunoglobulin E not determined; n.s., not significant; OFC, oral food challenge; SD, Standard Deviation; sIgE, serum-specific Immunoglobulin E.

TABLE 2 General characteristics, cashew sIgE levels, and key outcomes of patients with positive cashew oral food challenges

| Positive cashew OFCs                                                               | London                                     | Geneva                                    | p-value |
|------------------------------------------------------------------------------------|--------------------------------------------|-------------------------------------------|---------|
| Positive food provocations; with anaphylaxis                                       | 15; 3                                      | 22; 17                                    | <.05    |
| Patients (gender, %)                                                               | 15 (6 males, 40.00%; 9 females, 60.00%)    | 22 (12 males, 54.55%; 10 females, 45.45%) | n.s.    |
| Age, mean $\pm$ SD (range) years                                                   | 6.28 $\pm$ 5.09 (0.87–15.38)               | 6.64 $\pm$ 3.29 (2.29–15.04)              | n.s.    |
| Sensitization: cashew sIgE, mean $\pm$ SD (range) kU/L                             | 0.93 $\pm$ 1.15 (0.01–3.22); n sIgE nd = 1 | 4.25 $\pm$ 13.45 (0.07–63.90)             | n.s.    |
| Time between first exposure and clinical manifestations, mean $\pm$ SD (range) min | 15.93 $\pm$ 16.94 (0.00–51.00)             | 15.45 $\pm$ 23.85 (0.00–80.00)            | n.s.    |
| Clinical manifestations                                                            |                                            |                                           |         |
| Skin                                                                               | 13/15 (86.67%)                             | 15/22 (68.18%)                            | n.s.    |
| Upper respiratory                                                                  | 6/15 (40.00%)                              | 11/22 (50.00%)                            | n.s.    |
| Lower respiratory                                                                  | 7/15 (46.67%)                              | 9/22 (40.91%)                             | n.s.    |
| Gastrointestinal                                                                   | 10/15 (66.67%)                             | 17/22 (77.27%)                            | n.s.    |
| Cardiovascular                                                                     | 3/15 (20.00%)                              | 2/22 (9.09%)                              | n.s.    |
| Medications                                                                        |                                            |                                           |         |
| Adrenaline                                                                         | 2/15 (13.33%)                              | 4/22 (18.18%)                             | n.s.    |
| Antihistamines                                                                     | 15/15 (100.00%)                            | 20/22 (90.91%)                            | n.s.    |
| Cetirizine                                                                         | 12/15 (80.00%)                             | 20/22 (90.91%)                            | n.s.    |
| Chlorpheniramine                                                                   | 10/15 (66.67%)                             | –                                         | –       |
| Bronchodilator                                                                     | 1/15 (6.67%)                               | 4/22 (18.18%)                             | n.s.    |
| Prednisolone                                                                       | 1/15 (6.67%)                               | 9/22 (40.91%)                             | <.05    |

Note: Data expressed as mean  $\pm$  standard deviation.

Abbreviations: n sIgE nd, number of serum-specific Immunoglobulin E not determined; n.s., not significant; OFC, oral food challenge; SD, Standard Deviation; sIgE, serum-specific Immunoglobulin E.

was generally based on negative or low sensitization to cashew. This suggests that an incremental OFC regimen may be a safer practice, even in those considered at lower risk of reactivity.

A lower initial dose of 0.03 g of cashew protein was used in Geneva in comparison with London, where the initial dose was of 0.1 g of cashew protein. Interestingly, 5/22 (22.73%) cashew OFCs resulted positive at a lower initial dose of 0.03 g of cashew protein in Geneva, which was not used in London. The target cumulative dose

of cashew protein used in the protocols was similar, being 3.80 g and 4.43 g in British and Swiss cashew OFCs, respectively. Moreover, the cashew product used for OFC differed between and within centers, being influenced by product's availability, and patients and/or parents' preferences (Appendix S1 section).

Interestingly, although a lower occurrence of positive cashew OFCs and anaphylaxis were recorded in London than in Geneva, British and Swiss populations demonstrated comparable use of

adrenaline. This fact may be explained by the occurrence of mild clinical manifestations of anaphylaxis, but this hypothesis may not be further validated because a limitation of our study was the absence regarding the recording of the severity of reactions. Other limitations of our work were missing data concerning, for example, cashew OFC indications or patients' characteristics, the limited number of patients included and its retrospective, observational, and bicentric database-based nature, which may be associated with selection issues as well.

In conclusion, although patient cohorts had similar IgE sensitization, between two large tertiary allergy centers in Europe, the outcomes differed with a lower proportion of positive cashew OFCs and anaphylaxis occurring in London compared to Geneva. While the children had similar target cumulative dose of cashew protein used in the protocols, cashew OFCs were performed according to departmental protocols in a nurse-led modality in different countries, which could alter their outcomes, also in the context of the limitations mentioned above. Differences in OFC indications, as previously hypothesized to explain differences in peanut OFC outcomes between the two same centers,<sup>10</sup> may also explain these findings. Indeed, it appears evident how OFC indications may vary according to medical decision and patient/family demand.

There is a need for validated OFC protocols for use in regular allergy practice. However, this is influenced by the challenge positive ratio goal for each center, so shared decision-making with patients and their families, and clear rationale for undertaking challenges is required. Hence, further publications of real-life practice OFCs for common food allergens around the world are needed.

## AUTHOR CONTRIBUTIONS

All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interests to disclose in relation to this paper.

## DATA AVAILABILITY STATEMENT

Aggregate analyses are available on reasonable request to the corresponding author.

## ETHICAL APPROVAL

Approval was obtained from Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust (project number 9796) and from Geneva's Regional Research Ethics Committee (project number 2018-02010).

## INFORMED CONSENT

An accurate, informed written consent form filled out by the family with the agreed decision was then signed by the person with parental responsibility.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.