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Failure of introduction of cashew nut after a negative oral food challenge test in children

J.P.M van der Valk, R. Gerth van Wijk, A.E.J. Dubois, H. de Groot, N.W. de Jong,

Drs. J.P.M van der Valk, MD¹

j.p.m.vandervalk@erasmusmc.nl*

Prof. Dr. R. Gerth van Wijk¹

r.gerthvanwijk@erasmusmc.nl

Dr. H. de Groot²

h.deGroot@rdgg.nl

Prof. Dr. A.E.J. Dubois³

a.e.j.dubois@umcg.nl

N.W. de Jong, BEd, PhD¹

n.w.dejong@erasmusmc.nl

* Corresponding auteur

1. *Department of Internal Medicine, section of Allergology, Erasmus MC, Rotterdam, the Netherlands.*
2. *Department of Pediatric Allergology, Diaconessenhuis Voorburg, RdGG, Delft, the Netherlands.*
3. *Department of Pediatric Pulmonology and Pediatric Allergology, University Medical Centre Groningen, GRIAC Research Institute, University of Groningen the Netherlands.*

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Postal address

J.P.M. van der Valk

PO 2040

3000 CA Rotterdam

The Netherlands

+31107040100

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To the editor,

Food challenge tests are helpful in assessing the clinical relevance of sensitisation, as determined by skin prick tests and/or specific IgE measurements. After a negative challenge, the patient is advised to introduce the negatively tested food into the diet. Previous studies with commonly challenged allergens demonstrated, however, that in spite of this advice the rate of introduction after a negative challenge is low (1-3).

We studied the introduction rate after a negative challenge in cashew nut sensitised children, ranging in age from 2 to 17 years. The patients were recruited from the study 'Improvement of Diagnostic mEthods for ALlergy assessment' (IDEAL) with cashew nut allergy in children as a show case (trial number NTR3572). The inclusion and exclusion criteria and detailed study protocol were previously described (4). Briefly, all patients underwent a blood draw for sIgE determination, a skin prick test with cashew nut extract and a double-blind placebo-controlled food challenge (DBPCFC) test with cashew nut. The DBPCFC test consisted of an eight-step incremental dose regime of validated and standardised food challenge materials (5). The children consumed 3180 mg cashew nut protein (22 cashew nuts) if all 8 dose-steps were passed. The

challenge step was repeated if the child experienced subjective symptoms that disappeared in an hour (6). The DBPCFC test was discontinued and considered positive when 1) objective symptoms occurred, or when 2) subjective symptoms re-occurred twice after the same dose of challenge material had been administered, three times consecutively, or when 3) subjective symptoms persisted for more than one hour (7). Repeating these portions was needed to find out whether the subjective symptoms reported by the child were reproducible and caused by the challenged food or coincidental symptoms due to other reasons.

The patient was contacted by telephone one week after the challenge test. The parent and/or the child was informed about the negative result of the challenge test (no cashew nut allergy). Then the physician explained that the cashew nut should be introduced into the diet and the importance of the introduction was explained. Furthermore, the patient was asked whether they thought they would be able to introduce the cashew into the diet, starting with small amounts of cashew nut, and if the response was affirmative, no further action was taken. When the patient and/or the family was not sure whether introduction would be successful, the physician explained the introduction method in more detail and an introduction schedule was recommended. In some cases the parents still felt that the introduction would give problems, then they were referred to a dietician, who again explained the introduction schedule (8, 9). The introduction schedules comprise instructions and photographs with information on the required amounts of specific food for home introduction.

The patients were asked to complete a questionnaire 6 months after the finish of the IDEAL-study (inclusion May 2012-March 2015), with questions concerning the introduction of cashew nut in the diet of the child. The questionnaire was based on the questionnaire used in a study on the introduction rate of hens' egg, cows' milk, hazelnut and peanut, and slightly adjusted for the

IDEAL study (2). The questionnaire contained 14 questions on the successful or failed introduction, symptoms during introduction, the advice received and the understanding of the test result.

Children were divided in 3 groups: those with a successful introduction (starting as well as continuing eating cashew nut on a regular basis) those with a partly successful introduction (consumption of only traces or processed products) and those with a failed introduction (never consumed or only once and never thereafter).

Possible factors influencing successful introduction, which were based on a previous study (i.e. gender, age, symptoms during the DBPCFC test according to the patient, time between the test result and the start of the introduction procedure advice and symptoms during introduction) were recorded (2).

A total of 179 children were included and underwent the DBPCFC of which 36 (20.1%) tests were considered negative. Of these children (or their parents), 30 completed the questionnaire. The mean age of the children was 8.8 years (range 2-17 years), 21 boys (70%) and 9 girls (30%).

Successful introduction was reported in 13 children (43.3%), partly successful introduction in 6 children (20%) and failed introduction in 11 children (36.7%). Possible factors influencing the introduction rate are shown in Table 1. Statistical analysis could not be performed because of the small numbers. Other patients' characteristics and diagnostic test results in the groups of

children with a failed, partly- or successful cashew nut introduction are shown in Table 2. The results do not show obvious differences between the groups nor is there a trend visible.

The main reason for a failed introduction was difficulty in changing the habitual avoidance of this food, followed by fear of the child and aversion to cashew nuts. Parents of one child said they were misinformed. Hence, this child did not introduce the cashew nut in the diet (Fig 1).

More boys (52.4%) than girls (22.2%) had a successful introduction. Younger children had higher rates of successful introduction than older children. These results are comparable with an earlier study (2).

Symptoms from the perspective of the parents during the DBPCFC were rarely reported. One child had skin symptoms and one child had respiratory symptoms.

Although all parents and children received advice to introduce the cashew nut into the diet after the negative DBPCFC, only 22/30 parents of the children (73%) reported to have received the advice. Clearly, from the perspective of the patient, the advice as it was given was in some cases insufficient to result in retention by the patient and/or family.

A higher percentage of parents and/or children, who reported to have received advice to introduce cashew nut into their diet after the food challenge (FC) test, had a successful introduction (11/22 children), compared to the parents and/ or children that did not recall

receiving such advice (2/7 children). Ten children introduced cashew nuts between one week and one month.

Three of the 30 children who completed the questionnaire, reported symptoms during the introduction of cashew nut at home. Two of them reported 'oral allergy' symptoms and one child had respiratory symptoms in combination with gastrointestinal symptoms.

Our study showed a high failed introduction rate of 36.7% after a DBPCFC test with cashew nut. For the purposes of discussion we might even add this to the 20% of patients who had a partly successful introduction to yield an extremely high percentage of 56.7%. Previous studies have reported rates of failed introduction with different allergenic foods in 25%, 28% and 32% of the patients, respectively (1-3). Studies performed by Flammarion et al., Dambacher et al. and Miceli Sopo et al. showed higher rates of successful introduction of 83%, 81% and 71%, respectively (10-12). The first of these studies (10) included only children with cow's milk allergy and in the second two studies, the number of patients with a cow's milk allergy and hen's egg allergy was overrepresented (11,12). A previous study by our group demonstrated that hazelnut and peanut FC test were followed by higher rates of failed introduction (40.6% and 39.5%, respectively) than by hen's egg and cow's milk (13.2% and 9.8%, respectively)(2). The rates of successful introduction for cashew nut in our study was comparable with the rates of successful introduction for peanut and hazelnut. Awareness in patients and the fear of life-threatening reactions as may be caused by nut or peanut allergy, as compared allergenic foods that elicit severe reactions less often, may be the reason for the differences between successful introduction rates of the different allergenic foods (13). Nuts and peanuts are not essential food products and a diet without nuts and peanuts will not lead to missing essential nutrients. It is easier to avoid nuts, in particular cashew nut, because these allergens are less often hidden in

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food products than hen's egg and cow's milk, although one should realise that cashew nuts are becoming increasingly common in processed food products (14). Recently, the LEAP study demonstrated that early introduction of peanut significantly decreased the development of peanut allergy in high risk children, which lead to new consensus guidelines regarding potential benefits of early, rather than delayed, peanut introduction into the diet of this specific group of children (15,16). Introduction of cashew nut into the diet of the sensitised children in the present study might be of great importance. Moreover, the chance of developing an acute allergic reaction after long time elimination is demonstrated by Flinterman et al. (17).

A shortcoming in the study is that we did not define 'continuing eating the cashew nut on a regular basis'. Currently, there are no published protocols with amount and frequency of exposure to the allergenic food which may be considered adequate to prevent the occurrence of allergy. Often daily consumption is recommended, but more research is required to adequately define the minimum exposure parameters which will maintain immunologic tolerance to the food in question.

A previous study by our group demonstrated that age, gender, symptoms during the challenge test, dietary advice and symptoms during introduction significantly influenced introduction rates (2). This study confirms that boys and younger children have a higher successful introduction rate. Concerning advice and introduction rate, in our study 73% of the children received advice after the negative FC test according to the questionnaire compared to 52 % in the abovementioned study (2). Despite the higher rate of children who received advice to introduce the cashew nut in the diet, rates of successful introduction remain low. We speculate that the intention to introduce cashew nut into the diet after a negative challenge may be less than with other allergenic foods. The most frequently reported reason of the parents to consent to the

DBPCFC with cashew nut was to determine the clinical relevance of sensitisation and not to be able to introduce the cashew nut in the event of a negative challenge test.

In our study, only 3 children experienced symptoms at home during the introduction of cashew nuts. This is lower than that found in a previous study by our group, where 28% of the children reported symptoms during home introduction of hen's egg, cow's milk, hazelnut and peanut (2). We used challenge material recipes with higher final dosages than in the previous studies. A child consuming all doses would have eaten 3180 mg cashew nut proteins compared to 350 mg of proteins in the recipes used in the previous studies. This higher final challenge dose may be more reassuring.

In this study, more than half of the children did not successfully introduce the cashew nut into their diet after a negative challenges. This emphasizes the need for introduction protocols and better coaching methods after a negative challenge. It also highlights the need for follow up and attention to this somewhat neglected group in comparison to children with a positive challenge test.

In conclusion, firstly, successful introduction is dependent on the type of the tested allergenic food, age, and gender. Secondly, clear and structured advisory protocols are indispensable, to provide the patient with clear-cut information and a follow-up protocol to measure insure successful introduction of the allergenic food. Finally, we advise physicians to discuss the goals of the DBPCFC with patients prior to the test, to perform the test at the youngest age possible, and to use adequate amounts of protein to reduce the chance of false negative testing which may consequently cause symptoms at home during introduction.

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Table 1. Possible factors associated with a failed introduction after the DBPCFC test with cashew nut

	Successful introduction N (%)	Partial* introduction N (%)	Failed introduction N (%)
Total	13 (43.3)	6 (20.0)	11 (36.7)
Gender			
Girl	2 (22.2)	2 (22.2)	5 (55.6)
Boy	11 (52.4)	4 (19.0)	6 (28.6)
Age			
0-4	3 (75.0)	0	1 (25.0)
4-8	5 (50.0)	3 (30.0)	2 (20.0)
≥ 9	5 (31.2)	3 (18.8)	8 (50.0)
Symptoms during FC according to the parents			
No	13 (46.4)	5 (17.9)	10 (35.7)
Yes	0	1 (50.0)	1 (50.0)
Advice			
Yes	11 (50.0)	5 (22.7)	6 (27.3)
No	2 (28.6)	1 (14.3)	4 (57.1)
Time between the test result and the start of the introduction procedure			
Never started	0	0	7(100.0)
A week	5 (83.3)	1(16.7)	0
A month	5 (62.5)	2(25.0)	1(12.5)
A year	1 (50.0)	0	1(50.0)
Forgotten by patient	2(33.3)	3(50.0)	1(16.7)
Symptoms during introduction			
Yes	0	0	3(100.0)
No	13(61.9)	6(28.6)	2(9.5)
Never started	0	0	6(100.0)

* consumption of only traces or processed products

Table 2. Patients' characteristics and diagnostic test results in the groups of children

	Failed introduction N = 11 (%)	Partly introduction N = 6 (%)	Successful introduction N = 13 (%)
Eczema	3 (27)	3 (50)	7 (54)
Asthma	3 (27)	2 (33)	3 (23)
Hay fever	4 (36)	4 (67)	7 (54)
Other nut allergies			
Yes	5 (46)	4 (67)	8 (62)
No	4 (36)	2 (33)	3 (23)
Unknown	2 (18)		2 (15)
History of cashew nut allergy	6 (55)	2 (33)	7 (54)
SPT cashew nut (HEP-index area)	1.24 (range 0.39- 4.22)	0.30 (0- 1.82)	0.96 (0- 14.25)
sIgE cashew nut (kU/l)	2.16 (range 0- 17.80)	0.77 (range 0.43 – 15.70)	1.30 (range 0- 5.48)

with a failed, partly - or successful cashew nut introduction.

