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Letter to the Editor

Oral food challenge with a mix of tree nuts to partially liberalize the diet in pediatric IgE-mediated tree nut allergy

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SUMMARY

In selected cases of IgE-mediated tree nut allergy, a specific type of tree nuts (TN) must be avoided, and other specific types may be reintroduced into the children's diet. The risk of allergic reactions and fear of the parents not being allowed to reintroduce these types of specific TN at home necessitate multiple oral food challenges. The study aims to demonstrate the effectiveness of a chosen mixed oral food challenge to specific nuts to liberalize part of the diet of children with IgE-mediated tree nut allergy (IMTNA) and a low risk of allergy. A retrospective study evaluated the efficacy of a chosen oral mixed nuts challenge (OMNC) to assess the tolerance to specific TN in children with pediatric IMTNA following an exclusion diet for all types of TN. Eight children were selected, and all passed an OMNC using a chosen mix of TN. OMNC avoids multiple challenges, saves time, reduces costs, and positively impacts the psychosocial and nutritional context. Performing an OMNC in low-risk allergic children seems a safe and effective procedure to rule out IMTNA to specific types of TN and partially liberalize the childrens' diet.

KEYWORDS: Tree nut allergy, oral food challenge, open mixed nut challenge

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Almonds, Brazilian nuts, cashews, hazelnuts, pecans, peanuts, pistachios, and walnuts are responsible for tree nut allergy, a common allergy that affects approximately 2% of children [1]. The age of onset is between 9 months and 5 years, with a peak between 2 and 3 years [1].
Tree nuts are generally offered after weaning and more frequently after the first year of life in chopped form or as grains [2]. Unlike other allergies, such as milk or egg allergy, that occur early in life and generally resolve spontaneously, tree nut allergy is often permanent [3]. Only 10% of allergic patients are estimated to have spontaneous remission, predominantly occurring by age 6 [4]. Depending on the sensitization to the different nut allergens, five molecular patterns can be distinguished: 1. Primary sensitization to an allergen: the patient has high serum immunoglobulin E (sIgE) values towards a specific nut; there is no close correlation between sIgE levels and clinical reactivity and severity. In this case, the clinical indication is avoidance only of the culprit food [5,6]; 2. Co-sensitization to at least two primary allergens is a condition of polysensitization to multiple nuts with elevated sIgE levels to various tested allergens. The clinical indication is avoiding all nuts; introducing a tree nut to which the patient is not sensitized in a protected environment is recommended [5,6]; 3. Primary sensitization to at least one allergen and IgE-mediated cross-reaction to another botanically related allergen (high level of protein sequence homology): the patient is sensitized to more than one tree nut from

the same botanical family (cashew-pistachio; walnut-pecan) with similar sIgE levels. The clinical recommendation is to avoid only these nuts [5,6]; 4. Primary sensitization to at least one allergen and IgE cross-reaction to another non-botanically related fruit (low/moderate degree of protein sequence homology): the patient is clinically allergic to some tree nuts (with high levels of specific sIgE) but sensitized to others (without clinical reaction and usually with lower levels of specific sIgE) [5,6]; 5. Primary sensitization to a pollen and IgE cross-reactivity between PR-10 and LTP present in nuts: among the PR-10s, Betv1 is one of the main pan-allergens found in birch pollen [5,6]. Betv1 exhibits amino acid homology with allergens present in walnut (Jug r 5), hazelnut (Cor a 1) and peanut (Ara h 8) inducing cross-reaction phenomena [5,6,7]. Diagnosis of tree nut allergy can be performed through medical history, in-vivo and in-vitro tests, and Oral Food Challenge (OFC) [7,8]. A medical history must be assessed deepening the age of onset of symptoms and their duration, the culprit food, the quantity consumed and its processing, and the route of exposure [8]. Personal and family history of allergic reactions must also be investigated, as well as risk factors that increase the probability of developing an allergy [8]. First, it is necessary to evaluate the genetic predisposition: a first-degree family member with a food allergy increases the risk of being allergic by 40% [4]. As in-vivo tests, skin prick tests (SPT) are performed with standardized nut extracts and supported by prick-by-prick (PbP) testing with raw nuts [1]. A cutaneous response greater than 8 mm has a low sensitivity and high specificity and provides a positive predictive value (PPV) > 95% [1]. There are different values based on the type of nut and the SPT negative predictive value (NPV). Specific studies have found an NPV of 95% for peanuts, but population-dependent values are not generalizable [1]. In in-vitro tests, the detection of specific IgE antibodies in the blood is predictive of sensitization to a specific tree nut allergen, and can be used to confirm allergies in cases of a suggestive medical history [7]. Serum IgE $\geq$ 0.35kU/l is usually considered a positive result [1]. Regarding hazelnut allergy, hazelnut sIgE $\geq$ 15 KU/L has a PPV of 57%. On the other hand, hazelnut sIgE < 0.35 KU/L has a negative predictive value (NPV) of 95% [1]. OFC is the gold standard in diagnosing food allergy and is used to confirm or exclude it [8]. In the case of tree nut allergy, it can be performed to assess the tolerance to specific types of tree nuts, partially liberalizing the child's diet [1]. The European Academy of Allergy and Clinical Immunology (EAACI) Guidelines suggest not performing OFC in patients with a convincing clinical history of allergy with positive SPT and/or positive sIgE for the suspected food and in patients with a suggestive clinical history and SPT or specific sIgE above the cut-off [7]. The management consists of avoiding the food involved in the allergic reaction and indicating a specific allergic reaction plan for the patient [1]. It is important to prescribe a specific elimination diet for each child, avoiding unnecessarily restricted diets [1]. It has been demonstrated that the elimination diet can contribute to social isolation, fear of anaphylaxis and a decreased quality of life [3]. This Food Allergy-specific anxiety, which also affects parents, leads to impaired family functioning and an unhealthy relationship with food [4], even inducing some patients with multiple allergies to continue following an elimination diet despite the possibility of liberalizing it because of consolidated eating habits [9]. Finally, families with an allergic child face high healthcare costs: research shows a greater number of medical visits for years and high costs for drugs [4]. Considering the medical and social impact of food allergy on the quality of life of children and their families, the role of the pediatric allergist is to search for a cost-effective method to liberalize the diet in the shortest time, ensuring high levels of safety. In tree nut allergy, a single open mixed nut challenge (OMNC) can discriminate between multiple and single nut allergies, avoiding unnecessarily restricted diets in selected patients. We performed a retrospective, observational study to evaluate the efficacy of a chosen OMNC and assess the tolerance to specific nuts in children with tree nut allergy. Pediatric patients with a known diagnosis of IgE-mediated tree nut allergy without a history of anaphylaxis and following an exclusion diet for all types of nuts who attended Pediatric Allergy Units in Mantua and Verona, Italy, between 2021 and 2022, were included in the study. The home reintroduction of specific tree nuts represented the exclusion criteria. Children underwent an OMNC to assess their potential tolerance to specific types of tree nuts. We assessed the specific culprit tree nut related to IgE-mediated food allergy, and the low risk of allergic reactions was evaluated for each type of tree nut by negative assessment of medical history and in-vivo and in-vitro tests (SPT, PbP and sIgE). SPT, PbP and sIgE were performed in children within one year before the OFC. SPT and PbP wheals greater than 3 mm and sIgE levels $\geq$ 0.35 kU/L were considered positive [5,6]. The content of the mix used in ONMC was chosen case-by-case for each patient. Children were given increasing doses of nuts up to the liberalizing dose for each type of tree nut. Data was collected from electronic patient records. Eight children (5 males and 3 females) were selected. Based on the pattern of allergic sensitization, four patients (50%) had primary sensitization to an allergen, 2 (25%) had co-sensitization to at least two allergens, 2 (25%) had primary sensitization to an allergen and an IgE cross-reaction to another botanically related nut (Tab. I). All children enrolled underwent SPT, PbP, and sIgE, which were negative for all nuts used in the chosen OMNC. Children who underwent the mixed nut challenge had a mean age of 10.1 years (range: 5.4-17.1). Elimination diets for tree nuts were based on (multiple) sensitizations together with known other food allergies or severe eczema, respectively, in 14 (74%) and 3 (16%) children. All children with a low suspicion of allergic reaction underwent OMNC using a chosen mix of tree nuts, and everyone (100%) passed the OMNC. They were instructed to reintroduce all types of tree nuts contained in the ONMC into their home diet. After two months, the children's parents were contacted by phone, who confirmed that none had allergic symptoms after eating nuts tested during the OFC. This study demonstrates that OMNC avoids multiple challenges and successfully liberates diet in children sensitized to one or more tree nuts with a low clinical risk of an allergic reaction. This approach allows the reintroduction of all excluded nuts in a shorter time and facilitates family management. Food products often do not list the individual nuts on the label, which can cause difficulty in

TABLE I. Features of patients and their pattern of allergic sensitisation.

Gender	Age (year)	Culprit food	The pattern of allergic sensitization	Comorbidity
Male	1	Walnut	Primary sensitization to an allergen	Allergic rhinitis
Male	4	Hazelnut	Primary sensitization to an allergen	Atopic dermatitis
Female	2	Walnut	Primary sensitization to an allergen	Atopic dermatitis
Male	4	Walnut	Primary sensitization to an allergen	None
Female	4	Walnut Hazelnut	Co-sensitization to two allergens	Allergic rhinitis
Female	6	Hazelnut Peanut	Primary sensitization to an allergen and an IgE cross-reaction to another botanically related tree nut	Asthma
Male	3	Walnut Hazelnut	Co-sensitization to two allergens	Asthma
Male	7	Walnut Peanut	Primary sensitization to an allergen and an IgE cross-reaction to another botanically related nut	None

managing children's diets [9]. It is questionable whether single challenges are appropriate in terms of advice to parents since packaged foods contain traces of multiple nuts [9]. OMNC saves time and reduces costs for multiple challenges and burden on the healthcare system. There is conflicting evidence that introduction at home may be justifiable in children without allergic sensitization (negative SPT, PbP, sIgE) and previous symptoms after ingestion without performing an OFC [9]. Ball et al. demonstrated that not all patients with negative SPT are confident to reintroduce suspected food at home for fear of reactions [10]. This study enrolled 145 children with peanut or tree nut allergies for an OFC [10]. In patients with peanut IgE-mediated allergy and negative SPT to tree nuts, OFC to tree nuts was negative, while 31.2% of patients with positive SPT reacted to OFC [10]. In patients with a specific tree nut allergy, OFC to peanuts and/or other tree nuts was performed: 7.9% with negative SPT and 38.4% with positive SPT reacted to the OMNC [10]. In other words, a reaction in children with a tree nut allergy to peanut or another tree nut may happen independently of the SPT result [10]. The study by Rancé et al. evaluated the concordance between a prick test and a positive OFC. It was 58.8% with commercial extracts and 91.7% with fresh foods, which are more effective in detecting sensitivity to food allergens [11]. Tree nuts have a high energy intake and good nutritional profile thanks to their content of vitamins (B vitamins, vitamin E) and fatty acids such as omega 3 [2]. Eliminating nuts from the diet seems to not expose the child to nutritional deficits because alternative food sources guarantee an adequate intake of micronutrients [1]. Considering the global impact of food allergies on the lives of children and their families, the pediatric allergist's role is fundamental in finding a cost-effective method to liberalize the diet in the shortest time while ensuring high levels of safety. A limit of the current study is the small sample size due to the low incidence of nut allergy and the short time frame for enrolment. Furthermore, the initial exclusion of nuts from the child's diet was based on parents' self-reported symptoms, and thus some patients may not have been considered for the study. Finally, a limit of OMNC is the difficulty of identifying the culprit nut in case of a positive test. This study confirms that OMNC may be a safe and effective method to test for IgE-mediated tree nut allergy in selected patients, avoiding repeated OFCs and reducing time and healthcare-associated costs. It is possible to discriminate between multiple tree nut allergies and a single nut allergy, avoiding unnecessary restricted diets in selected patients. Further studies on larger samples are needed to confirm our preliminary results.

Ethical consideration

Not applicable.

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Conflicts of interest statement

The authors declare they have no conflict of interest for this work.

Authors' contribution

Conceptualization L.P.; resources G.C. and S.M.; writing-original draft preparation G.C., S.M., L.P., L.V., writing-review and editing L.P., L.T., G.F., G.P.; supervision L.P., L.T., G.F., G.P.; All authors have read and agreed to the published version of the manuscript.

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