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EDITORIAL

TREE NUTS ALLERGY: Knowledge, gaps and practical implications

In the current issue of *Allergologia et Immunopathologia*, Pinar Gur Cetinkaya et al. present a retrospective study on the phenotype of children with allergy to peanut and other nuts in the Eastern Mediterranean.[1] Their findings have a number of implications and raise a series of comments.

In the mentioned study, hazelnut followed by pistachio were the most frequently implicated nuts, with data similar to those reported in the EuroPrevall study,[2] in which hazelnut was found to be the nut with the highest sensitisation rate in Europe (9.3%) – albeit with important geographical differences. The lowest frequency corresponded to Iceland (1.3%) and the highest to Switzerland (17.8%). In the European study, walnut was the second most commonly implicated nut, in contrast to the Turkish study, where this position was held by pistachio – reflecting the different consumption habits in each country, and thus the different implications of each type of nut in food allergy. In Spain, no studies have been made on the prevalence of allergy to nuts, and the existing data consist of biased information corresponding to patients visiting paediatric allergy clinics. In the PREVALE study (Prevalence of Food Allergy in Leganés), the cumulative incidence of allergy to nuts in the first three years of life was found to be 0.83%, with walnut accounting for 50% of the cases, followed by peanut (40%) and cashew nut (20%) (data not published).

Co-sensitisation and co-allergy to different nuts is common,[3–5] as evidenced by the study of Pinar Gur Cetinkaya et al., where over half of the children reacted to various nuts – the prevalence moreover being seen to increase with age. Clinical reactivity among different nuts such as walnut, pecan and macadamia is well known. Co-allergy between members of the cashew family is very frequent (80%), in the same way as with other nuts such as hazelnut and walnut[5] – although with some particularities, such as for example the fact that most patients with allergy to pistachio are also allergic to cashew nut because of the close similarity between the major allergens rPis v 3 and rAna o 1;[4,6] however, only 40% or less of those allergic to cashew nut are also allergic to pistachio.[7,8] These combinations of allergy to different nuts are due to the common presence of epitopes with high sequence homology – such scenarios being more frequent the closer the nuts are to each other on the phylogenetic scale.[6] However, co-sensitisation is more common than co-allergy, and this can lead to the introduction of restrictive diets referred to many nuts when the indication is only guided by the results of complementary tests that detect IgE. Although it was almost considered to be axiomatic that up to 30% of all subjects with allergy to peanut could also be allergic to other nuts,[9] it has been seen for example that up to 96% of all children with allergy to peanut and sensitised to walnut exhibit tolerance when exposure tests are made with the other nuts to which they are sensitised.[10] Using only allergy tests to diagnose allergy to nuts implies that such children follow unnecessary avoidance diets, since these tests exhibit a high negative predictive value but a very low positive predictive value in diagnosing food allergies.

It should be mentioned that despite the low frequency of allergy to almond, such allergy constitutes a risk marker for co-allergy of these children to peanut and other nuts – particularly hazelnut and cashew nut.[1,8]

On the other hand, there are experimental data from animal models on the effect of primary allergy to a given food upon the development of allergy to a second food – reinforcing the idea that all nuts should be avoided when a reaction to one of them has occurred.[3] With all these data and following assessment by, and advice from, the paediatric allergologist, the parents and families should be the ones to decide whether or not to exclude all nuts, or to only exclude those nuts clearly defined as being allergic based on the provocation tests.

In the study published in the current issue of *Allergologia et Immunopathologia*, 72% of the cases also presented atopic dermatitis and 50% suffered egg allergy. It has been firmly established that these two allergic comorbidities are risk factors for the development of food allergy,[8,11–13] and indeed they have been regarded as risk factors for allergy to peanut in the LEAP study on the prevention of food allergies.[12] The epithelial barrier dysfunction seen in atopic dermatitis is a clear risk factor for the develop-

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ment of allergic sensitisation, food allergy and other allergic diseases.[14] Epidemiological studies, and recently also studies in animals, have demonstrated the skin – digestive tract connection; damaged keratinocytes produce IL-33, which in the small intestine stimulates the group 2 innate lymphoid cells (ILC2). These in turn produce IL-4 and IL-13, which promote the expansion of activated mast cells, thus incrementing intestinal permeability and the transmission of allergens that can trigger food allergy.

Allergy to nuts has always been related to the clinical severity of the reactions produced.[6] In this study, in up to 41% of the cases the reactions were of an anaphylactic nature and therefore potentially fatal. The predominant role of nuts as a cause of anaphylaxis, particularly in older children, has been well documented[15] and is fundamentally seen in children sensitised to storage proteins commonly found in the Mediterranean setting,[16] particularly 2S-albumins as is the case of Ara h 2 in peanut. The importance, in terms of the severity of the reactions, of proteins associated to oil bodies, such as the oleosins, remains to be established.[17,18] It is necessary to draw attention to this point, because we are witnessing an increase in allergy to members of the cashew family, particularly cashew nut,[19] which is a genuine ''protein bomb'' that frequently produces severe anaphylactic reactions.[20] As paediatric allergologists, we must prescribe and instruct these patients and their families on how to recognise severe allergic reactions, and how to handle and self-administer adrenalin injectors.

Given the exponential increase in food allergy observed worldwide, one of the main objectives of the paediatric allergologist should be the prevention of such allergies. The currently popular (but controversial and not fully demonstrated) ''dual exposure'' hypothesis postulates that skin contact with the food allergen, as well as delayed intake of the food, leads to an increased risk of suffering food allergy.[21] This has led to a series of clinical trials being conducted on the prevention of allergy. In the case of allergy to nuts, it has now been firmly demonstrated by the LEAP (Learning Early About Peanut allergy) trial that allergy to peanut can be prevented in populations with allergy risk through the early introduction of peanut in the infant diet at between 4-11 months of age.[12] In populations without allergy risk, the EAT (Enquiring About Tolerance) study, in the intention-to-treat (ITT) analysis, found no significant differences in allergy prevention between a group in which several foods were introduced early and another group in which introduction took place at the usual age (5.6% versus 7.1%, respectively; $p = 0.32$). Due to the high lack of adherence to the instructions of the study, on performing the per protocol (PP) analysis with those subjects that had complied with the instructions received, a clear decrease in peanut allergy was effectively observed in those children who had started to consume peanut early (0% versus 2.5%; $p = 0.003$).[22]

No prevention studies involving nuts other than peanut are available. Consequently, we can only extrapolate the evidence which the aforementioned studies and other publications have provided on the prevention of allergy to peanut and egg, and to which we add the already known lack of efficacy of delaying food introduction to the diet of the infant. Based on this, it does not seem unreasonable to affirm that the early introduction of these nuts in the diet of the infant could be considered if we seek to prevent the appearance of allergy to nuts. In the study being addressed,[1] a cause for concern is the early onset of allergy to walnut and hazelnut (nine months). On the one hand we must remember that these are the most commonly implicated nuts in our country. So we should ask ourselves: What is the appropriate time to introduce these nuts into the diet of the infant at risk of allergy? On the basis of the existing data, the answer would be closer to 4-6 months of age than to 11 months of age. It must be taken into account that this information referred to earliness in allergy to nuts is only applicable to the Turkish population, where these nuts are very commonly consumed and are found in most homes. This is not representative of the situation in Spain, since for example the previously mentioned PREVALE study found the mean age of onset of allergy to nuts to be 32 months.

It is our responsibility as paediatric allergologists to try to ''flatten the curve'' of the increased incidence of food allergy, providing clear information for the families on the ineffectiveness of delaying complementary feeding, particularly in children at risk of allergy, and firmly stressing the demonstrated efficacy of the early introduction of these foods. As paediatricians, we could be concerned that this measure might result in a shortening of the breastfeeding period – although this has not been seen to happen in the prevention studies published to date.

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References

1. Gur Cetinkaya P, Buyuktiryaki B, Soyer O, Murat Sahiner U, Sackesen C, Sekerel BE. Phenotypical Characterization of Tree Nuts and Peanut Allergies in East Mediterranean Children. Allergol Immunopathol (Madr). 2020, xxxxx.
2. Datema MR, Zuidmeer-Jongejan L, Asero R, Barreales L, Belohlavkova S, de Blay F, et al. Hazelnut allergy across Europe dissected molecularly: A EuroPrevall outpatient clinic survey. J Allergy Clin Immunol. 2015;136:382–91.
3. Kulis M, Burks AW. Effects of a pre-existing food allergy on the oral introduction of food proteins: findings from a murine model. Allergy. 2015;70:120–3.
4. Elizur A, Appel MY, Nachshon L, Levy MB, Epstein-Rigbi N, Golobov K, et al. NUT Co Reactivity - Acquiring Knowledge for Elimination Recommendations (NUT CRACKER) study. Allergy. 2018;73:593–601.
5. Andorf S, Borres MP, Block W, Tupa D, Bollyky JB, Sampath V, et al. Association of Clinical Reactivity with Sensitization to Allergen Components in Multifood-Allergic Children. J Allergy Clin Immunol Pract. 2017;5:1325–34.
6. Eigenmann PA, Lack G, Mazon A, Nieto A, Haddad D, Brough HA, et al. Managing Nut Allergy: A Remaining Clinical Challenge. J Allergy Clin Immunol Pract. 2017;5:296–300.
7. van der Valk JPM, Bouche RE, Gerth van Wijk R, de Groot H, Wichers HJ, Dubois AEJ, et al. Low percentage of clinically relevant pistachio nut and mango co-sensitisation in cashew nut sensitised children. Clin Transl Allergy. 2017;7:8.
8. McWilliam V, Peters R, Tang MLK, Dharmage S, Ponsonby AL, Gurrin L, et al. Patterns of tree nut sensitization and allergy in the first 6 years of life in a population-based cohort. J Allergy Clin Immunol. 2019;143:644–50.

9. Sicherer SH, Sampson HA. Peanut allergy: emerging concepts and approaches for an apparent epidemic. J Allergy Clin Immunol. 2007;120:491–503.
10. Couch C, Franxman T, Greenhawt M. Characteristics of tree nut challenges in tree nut allergic and tree nut sensitized individuals. Ann Allergy Asthma Immunol. 2017;118:591–6.
11. Abrams EM, Chan ES. Prevention of Non-peanut Food Allergies. Curr Allergy Asthma Rep. 2019;19:60.
12. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372:803–13.
13. Robison RG, Singh AM. Controversies in Allergy: Food Testing and Dietary Avoidance in Atopic Dermatitis. J. Allergy Clin Immunol Pract. 2019;7:35–9.
14. Tham EH, Rajakulendran M, Lee BW, Van Bever HPS. Epicutaneous sensitization to food allergens in atopic dermatitis: What do we know? Pediatr Allergy Immunol. 2020;31:7–18.
15. Pouessel G, Jean-Bart C, Deschildre A, Van der Brempt X, Tanno LK, Beaumont P, et al. Food-induced anaphylaxis in infancy compared to preschool age: A retrospective analysis. Clin Exp Allergy. 2020;50:74–81.
16. Pedrosa M, Boyano-Martínez T, García-Ara MC, Caballero T, Quirce S. Peanut seed storage proteins are responsible for clinical reactivity in Spanish peanut-allergic children. Pediatr Allergy Immunol. 2012;23:654–9.
17. Barbarroja-Escudero J, Sánchez-González MJ, Pineda F, Rodríguez-Rodríguez M, Antolín-Amérigo D, Castillo M, et al. Identification of Lipoproteins From Sunflower Seeds in 2 Monosensitized Anaphylaxis Patients. J Investig Allergol Clin Immunol. 2018;28:334–6.
18. Schwager C, Kull S, Behrends J, Röckendorf N, Schocker F, Frey A, et al. Peanut oleosins associated with severe peanut allergy-importance of lipophilic allergens for comprehensive allergy diagnostics. J Allergy Clin Immunol. 2017;140:1331–8.
19. van der Valk JP, Dubois AE, Gerth van Wijk R, Wichers HJ, de Jong NW. Systematic review on cashew nut allergy. Allergy. 2014;69:692–8.
20. Clark AT, Anagnostou K, Ewan PW. Cashew nut causes more severe reactions than peanut: case-matched comparison in 141 children. Allergy. 2007;62:913–6.
21. Lack G. Update on risk factors for food allergy. J Allergy Clin Immunol. 2012;129:1187–97.
22. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl JMed. 2016;374:1733–43.

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