

EDITORIAL

Allergy to nuts: how much of a problem really is this?

During the last decade, there has been mounting concern over the avoidable morbidity and mortality associated with allergy to nuts [1]. Studies in the UK [2] and USA [3] indicate that the prevalence of peanut allergy is around 0.5–0.6% of the unselected population. These data are based on self-reported symptoms. Perceived food allergy is far higher than can be proved on double blind placebo controlled food challenge (DBPCFC), which is considered a gold standard for the diagnosis of food allergy. However, the situation may be different with nut allergy because of the acute onset of relatively well-defined symptoms. The false positive rate (allergy to nut on questionnaire, not proven on challenge) is less than 20% [4,5] suggesting that the prevalence rates from the questionnaire studies are generally reliable. Studies using DBPCFC to confirm the presence of peanut allergy are few [4–6] and so far no study has reported prevalence of this condition in an unselected population, confirmed by oral challenge.

Approximately 125 people die each year in the USA secondary to food-induced anaphylaxis [7]. Allergy to peanut is the most common cause of food-related anaphylaxis [8]. This is, in theory at least, avoidable mortality. It has also been suggested that the incidence of peanut allergy has increased in recent years [9]. Although tree nut allergies are considerably less common, severe systemic reactions to hazelnut [5], brazil nut [10], pistachio nut [11], pine nut [12] and others [13], have been described.

Peanut contains multiple allergens, of which six can be described as major allergens, including Ara h1 and Ara h2 [14]. In a study by Clarke et al. [15], over 70% of subjects reacted to protein bands of 63 and 17 kDa, consistent with Ara h 1 and Ara h 2, respectively, confirming the importance of these two proteins as major allergens. The major allergen of Brazil nut is a 2S albumin of 9 kDa, the presence of which correlates with clinical reactivity [16].

Allergy to peanut starts early in life and in the majority of cases persists into adult life [2,8,17,18]. Although peanut allergy is slightly more common in children, symptoms are usually more severe in adults [2,19]. Most of the patients have a positive family history of atopy and themselves have evidence of other atopic diseases [18,19]. Allergy to nuts is characterized by acute onset of a severe, potentially life threatening reaction with minimal contact [10,20]. In a double blind placebo controlled peanut challenge study, the total reactive dose was estimated to be less than 100 mg in 25% of cases [6]. The reaction often happens where immediate medical help is not available [17].

Apart from anaphylactic reactions, exposure to nuts, in some sensitized subjects may also cause exacerbation of atopic dermatitis or an attack of asthma [21]. Nut-allergic subjects are usually very atopic, with sensitization to other foods and aeroallergens [21]. Subjects allergic to peanut are commonly allergic to one or more tree nuts [2,17]. Most patients with symptoms suggesting nut allergy have specific IgE to more than one nut. Fatal reactions have occurred when eating nuts not known to have caused reactions on previous occasions.

The diagnosis of peanut allergy should not be taken lightly. Under-diagnosis can of course be dangerous but over-diagnosis can lead to stress for the whole family. The severity of symptoms varies from a mild rash to potentially fatal anaphylaxis. Indeed some children are sensitized to peanut and tree nuts, but do not manifest any clinical reaction on exposure [22]. Tariq et al. [23] reported sensitization on skin test to peanut in 1% of an unselected population of 4-year-olds, but only half had experienced a clinical reaction. Attempts have been made to identify the value of skin prick test positivity and weal size. In an analysis of 95 peanut challenges [24], Hill et al. identified a cut-off of 8 mm mean weal diameter, above which the challenges were invariably positive.

In this issue of *Clinical and Experimental Allergy*, Pucar et al. [25] report on the usefulness of skin prick test and the need for peanut challenge in children presenting to a paediatric allergy clinic with a possible reaction to peanut. Over a 4-year period, 140 peanut challenges were performed. They did not challenge children with a convincing history and positive skin test to peanut, as the risk was considered to be unacceptable. Peanut challenges were open and a brief protocol was followed if the skin tests were negative. We suspect the investigator presumed that challenges in these children would be negative. This is a retrospective study and the challenges were not double blind. Despite this, some very useful conclusions can be drawn: (a) that peanut challenge is a relatively safe procedure (of the 18 positive challenges, none required hospital admission and only four were treated with epinephrine), (b) a negative skin prick test, with a reliable extract, nearly always excludes the diagnosis, and (c) in those who have never knowingly been exposed to peanut, but had a positive skin prick test, there is a 30% risk of clinical reaction to peanut (six of 16 children were positive on peanut challenge). A positive skin prick test to peanut should be further investigated with challenge in a safe environment unless

the history is highly suggestive of an acute allergic reaction.

Severe allergic reaction to the first known exposure to peanut is relatively common [17,19]. This indicates a high frequency of occult sensitization, presumably due to the small amount of peanut or peanut oil hidden in various foods [26]. As peanut allergy is closely associated with a personal and family history of atopy, it may be argued that first-degree relatives of nut-allergic patients should be offered skin prick test. If positive to peanut, there is 30% risk of a clinical reaction on exposure, as is reported in the study of Pucar et al. [25]. These can be identified with a peanut challenge and appropriate avoidance measures instituted to prevent an allergic reaction in an uncontrolled environment.

Once nut allergy is diagnosed, complete avoidance of nuts and nut-containing substances remains the only method of preventing allergic reactions. This is not always possible as small amounts are present in a large number of foods and even an indirect contact may initiate a reaction. In a questionnaire study, almost 50% of peanut-allergic subjects had experienced a reaction during the previous 12 months [19]. The difficulty of peanut avoidance was highlighted recently by Sicherer et al. [27], who reported a number of allergic reactions to peanut during commercial flights, requiring treatment with adrenaline. The reactions were either due to accidental ingestion or caused by indirect skin contact or inhalation, as other passengers were eating peanuts. Those involved in the preparation and packaging of food must avoid contamination of foods with nuts, during production, storage, cooking and serving.

Following an education programme, Rance et al. [28] reported less allergic reaction and more appropriate use of adrenaline. The programme consisted of educating the patient and family in their understanding of nut allergy, recognition of hidden foods, reading labels, recognition of earliest signs and the use of epinephrine as a rescue treatment. Constant vigilance usually succeeds and hospital admission and adrenaline treatment are not often required, but this comes at a price. There is a major impact on the quality of life of the individuals and their family. Most patients with severe nut allergy live under a constant threat of an inadvertent exposure and consequent severe reaction. Parental anxiety is obvious when children start school, as the risk of accidental exposure increases. They may not be allowed to go to parties or eat with friends. This may lead to social, psychological and educational problems [29]. Novel agents to block the IgE mediated reaction, such as humanized monoclonal anti-IgE antibody or DNA vaccine, hold promise, but their effectiveness in nut allergy has yet to be investigated.

Heritability of peanut allergy was investigated using a twin study model and estimated at 81% [30]. It has,

however, been suggested that exposure to peanut *in utero* and during infancy may increase the risk. An earlier age of onset may be causally related to increased consumption of peanut by pregnant and nursing mothers [4,19]. This led to advice from the UK Department of Health that pregnant and lactating women, who were atopic themselves, or whose partners or children were atopic, should avoid eating peanuts. Avoidance was also recommended for the child up to the age of 3 years [31]. This notion was supported by a recent study by Frank et al. who studied 25 peanut-allergic and 18 control children. Consumption of peanut by the mother during pregnancy, and its early introduction to the infant's diet, increased the likelihood of peanut sensitization [32].

Allergy to nuts is a serious condition and should be managed with appropriate care, with support given to the patients and their families. Both patients and their physicians will welcome improved methods of diagnosis, avoiding the need for oral challenge. Advances in molecular biology and genetics may lead to better treatment options available to the patient. The interesting phenomenon of sensitization without clinical reactivity needs further investigation as a means of inducing tolerance, which is the norm for young children with cow's milk and egg allergy.

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