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A one-year investigation of nut allergy cases in children referred to the allergy clinic of the children's medical center

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Abstract--Background: The prevalence of allergy to tree nuts is spreading worldwide. Allergy to tree nuts causes more severe clinical symptoms and anaphylaxis attacks are more likely. The present study was conducted in order to investigate the cases of tree nut allergy among children referred to the allergy clinic of the Children's Medical Center in a period of one year (from the beginning of 2018 to its end). Methods: There were 1920 children with a history of atopic disease (asthma, allergic rhinitis, atopic dermatitis, chronic urticaria) with a history of type I allergic reactions. Eighty seven patients with skin, digestive, respiratory symptoms or anaphylaxis after consuming tree nuts were included in the study. A skin test was performed for most of these people, and in some cases, the serum specific IgE level against the desired nuts was requested, and after confirming the positive history of allergy by the mentioned tests, a questionnaire containing 26 questions was completed by the parents to complete the information. Findings: The prevalence of allergy to tree nuts in the studied population was 4.5%. Allergy to almonds is at the top with a frequency of 62.1%. Totally, 55.2% of the patients were males. The average age of the subjects studied was 42.29 ± 40 months and the

average age at the time of the first allergy was 11.67 ± 12.09 months. The interval between the consumption of nuts and the onset of symptoms in most people was between a few minutes and an hour (62.2%). Additionally, 47% of them showed allergy to more than one type of nuts. Besides, 23 people (26.4%) harbored allergic reactions to sesame. Most of the people studied (52.9%) reacted to only one type of nuts. The prevalence of atopic dermatitis among the subjects of this study was 83.9%. Moreover, 93.1% of people reacted to other foods besides tree nuts. Egg had the highest relative frequency among other allergenic foods (67.8%). Conclusion: The situation of allergy to tree nuts is different in different regions of the world. Additionally, its prevalence varies from 0.05% to 4.9% (Our recorded prevalence was in the range). However, so far, a limited number of studies have been conducted in this field in the Asian region, especially Iran. Therefore, the practical use of the results of such studies is to carry out more and more comprehensive research and use the best methods of diagnosing food allergies, including food challenge tests.

Keywords--food allergy, children, prevalence, demographic characters, Iran.

Introduction

Safe foods play an important role in the development of the communities (1-5). Today, the increasing prevalence of food allergies has become a global issue. The global prevalence of food allergy ranges from 0.4 to 6% (6). The prevalence of allergies in children is higher than adults, so that it is 8% in children under 3 years of age, while in adults it is 2% on average (6). In addition to the higher prevalence of allergies in children, the negative effects of food abstinence on children's growth and development are also evident (7). In general, more than 90% of food allergies in children follow the consumption of cow's milk and its derivatives, eggs, soybeans, wheat, peanuts, tree nuts, fish and seafood (8). One of the 6 main allergenic food categories in children are tree nuts, which consist of walnuts, almonds, hazelnuts, and pistachios. Tree nut allergies affect about 0.6% to 1.2% of the general population of the United States and this rate among children is 1% based on the self-report of parents (9).

Compared to other major allergenic food groups, nuts can cause more severe IgE-dependent hypersensitivity reactions that may occur after consuming very small amounts and even within minutes of consumption. It varies from urticaria, angioedema, and vomiting to severe and life-threatening anaphylactic reactions (10). Another important and distinctive feature of this category of food is that, unlike other allergenic food items, such as milk and eggs, which often resolve spontaneously during the early years of life, they often tend to persist into adulthood (11). Another importance of tree nut allergy is that cross-reactions between their types are common. So that about 37% of patients with an allergy to one type of tree nut may react to other types as well (12).

Currently, the only treatment available in cases of tree nut allergy is the use of nut-free foods and the possibility of quick access to self-injected epinephrine. Of course, it is not possible to follow the general principle of avoiding all foods containing nuts. It is because of some reasons, such as the presence of cross reactions, problems related to the information on the food label, or the presence of hidden allergens in some ready-made commercial foods (13). Therefore, according to the distinctive and special characteristics of tree nut allergy, including the intensity and severity of clinical symptoms, the tendency to continue until adulthood, and the different prevalence of allergy to each type of tree nut according to the geographical region and due to the fact that no extensive study has been done in this field in Iran, we decided to investigate the prevalence of tree nut allergies in the Children's Medical Center Hospital as a referral center.

Materials and methods

Study design

In this cross-sectional study, a detailed biographical history was taken from all the visitors to the Allergy Clinic of the Children's Medical Center (on Sundays, in the morning), during a period of one year (from the beginning to the end of 2018), in order to find possible cases of allergy to tree nuts based on the patients' self-report.

Samples

Random sampling was done for this purpose. All children suffering from one or more types of atopic diseases (including asthma, allergic rhinitis, atopic dermatitis, and chronic urticaria) referred to the allergy clinic of the Children's Medical Center (on Sundays, in the morning) during the beginning of 2018 until the end of it. Occurrence of non-immunological reactions and types of non-IgE-dependent immunological reactions following consumption of tree nuts were determined as exclusion criteria. To calculate the sample size in this study, considering a 10% error and a 60% prevalence of walnut allergy, the sample for this study is determined to be at least 85 people (8) (according to the following formula).

$$x = \frac{z_1 - \frac{\alpha^2}{2}p(1-p^2)}{d^2}$$

$$z_1 - \frac{\alpha}{2} = 1.96$$

$$p = 60\% \quad 1 - p = 40\% \quad d = 10\%$$

Procedure

After the self-reporting of parents, skin prick test or serum specific IgE measurement against tree nuts was performed for children whose parents had a history of clinical manifestations of type I allergic reactions following the consumption of one or more types of tree nuts. If, in the skin test performed with the standard nut extract mentioned in the patient's history, villi with a diameter

of more than 3 mm and flare with a diameter of more than 5 mm compared to the negative control (after 15 min from the time of test), was formed, the test is considered positive. Positive control tests were performed with histamine and negative control with normal saline. In cases where, for any reason, such as positive dermographism, severe eczema, age of the patient (less than 6 months) and the use of drugs, such as antihistamines or corticosteroids to control the underlying atopic disease and the impossibility of temporarily stopping them for testing and or sometimes the lack of some extracts, serum specific IgE measurement was requested. If, depending on the test method, the antibody level is significant (for example, in the RIDA method, more than 0.35 KU/L), it is considered positive. Cases with positive tests, along with the typical history of clinical symptoms of type I hypersensitivity reactions following consumption, are considered as people with allergies to different types of tree nuts. For these people, a questionnaire including individual demographic information and 26 questions related to the topic are designed to be completed by parents.

Statistical analysis

The data obtained from this study were subjected to statistical analysis using SPSS version 22 statistical software (14-18). Qualitative data analysis is done using chi-square test and if necessary Fisher exact test and quantitative data analysis is done using paired t-test and Mann-Whitney test if necessary. P value less than 0.05 is considered significant (19-25).

Results

Demographic characters

Table 1 shows the demographical characters of the studied population. The total number of patients referred to the Allergy Clinic of the Children's Medical Center in the period of one year was 1920 people, of whom 87 people were diagnosed with tree nut allergy and entered the study and filled the questionnaire form. Therefore, the prevalence of allergy to tree nuts in this study was equal to 4.5%. In this study, 87 people with tree nut allergy were studied. Totally, 48 (55.2%) allergic patients were boys and 39 (44.8%) were girls. The mean age at the time of the first allergy was 11.67 ± 12.09 months. The gap interval between the consumption of nuts and the onset of symptoms in most cases was between a few minutes and an hour (62.2%). Totally, 46 people reported the history of consuming nuts individually. In only one case, the infant was an 18-month-old boy with an underlying disease of atopic dermatitis, who developed hives after eating almonds and hazelnuts, and experienced skin erythema and exacerbation of eczematous skin lesions after topical application of almond oil. Totally, 64% of patients had an allergic reaction to cooked nuts. Additionally, 47% of them reported allergy to more than one type of nuts, Furthermore, 23 cases (26.4%) harbored allergic to sesame. The relative frequency of anaphylaxis following the consumption of tree nuts was 10.3%.

Table 1
Demographical characters of the studied population

Variable	Frequency from a total of 87 cases (%)
Sex	
Male	48 (55.2)
Female	39 (44.8)
Age (Mean±SD) (month)	40 (42.29)
Lowest	8
Highest	240
Gap between nut consumption and occurrence of allergy	
Immediately after a few minutes	26 (29.9)
A few minutes to an hour	54 (62.1)
A few hours	7 (8)
Age at the first allergy (Mean±SD) (month)	12.09 (11.67)
The lowest	5
The highest	84
Allergic reaction to cooked nuts	
Yes	56 (64.4)
no	7 (8)
Food containing cooked form is not given to the child	24 (27.6)
Allergy to sesame	
Yes	23 (26.4)
no	40 (46)
Sesame was not among the examined food items	24 (27.6)
Eating nuts individually	33 (37.9)
In combination with other foods	5 (5.7)
Individually and in combination	46 (52.9)
Single and non-edible use	1 (1.1)
Non-food use (soap, shampoo, lotion)	-
Allergy to more than one type of nut	
Yes	41 (47.1)
no	46 (52.9)
History of anaphylaxis	
Yes	9 (10.3)
no	77 (88.5)

Type of nuts and occurrence of allergy

Table 2 shows the allergy occurrence amongst the types of consumed nuts. Almonds caused allergies in 62.1% of people. Also, walnuts, hazelnuts and pistachios caused allergies in 51.7, 27.6 and 23% of people, respectively.

Table 2
Relationship between type of nuts and occurrence of allergy

Nut types	Occurrence of allergy (%)
Almonds	54 (62.1)
Walnut	45 (51.7)
Hazelnut	24 (27.6)
Pistachio	20 (23)

Prevalence of allergy to more than one type of nuts in cases with underlying atopic disease

Table 3 shows the prevalence of allergy to more than one type of nuts in cases with underlying atopic disease. The prevalence of allergy to more than one type of nut in people with asthma was equal to 45%. The prevalence of allergy in people with underlying diseases of atopic dermatitis and allergic rhinitis was 45.2 and 44.4%, respectively. Also, half of the people with measles were allergic to more than one type of nut

Table 3
Prevalence of allergy to more than one type of nuts in cases with underlying atopic disease

Underlying atopic disease (N)	Allergy to more than one type of nuts (%)
Asthma (24)	11 (45)
Dermatitis (73)	33 (45.2)
Rhinitis (9)	4 (44.4)
Urticaria (4)	2 (50)

Classification of people according to the number of nuts causing allergies

Figure 1 shows the classification of people according to the number of nuts causing allergies. Most of the people studied (52.9%) reacted to only one type of nuts. 33.3% of people were allergic to 2 types of nuts, 10.3% to 3 types of nuts and 3.4% to all 4 types of nuts.



Figure 1. Classification of people according to the number of nuts causing allergies

Allergic symptoms of patients by type of symptoms

Table 4 shows the allergic symptoms of patients by type of symptoms. The relative frequency of allergic skin, digestive, respiratory and other symptoms in the studied subjects was 88.5, 14.9, 24.1 and 6.9% respectively.

Table 4
Allergic symptoms of patients by type of symptoms

Allergic symptoms	Frequency (%)
Cutaneous	77 (88.5)
Gastrointestinal	13 (14.9)
Respiratory	21 (24.1)
Others	6 (6.9)

Distribution of allergy against other food stuffs

Table 5 shows the distribution of allergy against other types of foodstuffs. We found that 6.9% of people were allergic to tree nuts only, and 93.1% reacted to other foods in addition to tree nuts. Egg had the highest relative frequency among other allergenic foods in people (67.8%). Other allergenic foods in the studied subjects included peanuts (33.3%), cow's milk (52.9%), wheat (27.6%), seafood (17.2%), soy (20.7%) and sesame (21.8%).

Table 5
The distribution of allergy against other types of foodstuffs

Foodstuffs	Distribution of allergy (%)
Tree nut	6 (6.9)
Peanut	29(33.3)
Egg	59 (67.8)
Cow milk	46 (52.9)
Wheat	24 (27.6)
Seafoods	15 (17.2)
Soy	18 (20.7)
Sesame	19 (21.8)

Discussion

Food safety and hygiene is one of the most critical issues in the last century (26-30). The present study as the first report in Iran, was done to assess the distribution of food allergies amongst the children referred to the health centers, Iran. Our findings showed that the prevalence of tree nut allergy in this study was 4.5%. Among the types of nuts, almonds are the most allergenic with a frequency of 62.1%, followed by walnuts (51.7%), hazelnuts (27.6%) and pistachios (23%). Diverse researches have been conducted in this field globally. Based on the results of a systematic review study conducted by McWilliam et al. (31) from 1996 to 2014 with the help of searching similar articles in 3 electronic databases, 36 studies with the same topic as our study have been conducted in the world, mainly (24 their case) was on children. 18 of them were related to Europe, 8 related to England, 5 related to America, 3 related to Asia and the rest related to Australia and Canada. IgE to tree nuts confirmed by oral challenge was 2% (only 7 studies have used this gold standard diagnostic test). While based on the results of other studies, this rate varies from 0.05% to 4.9%. It has been that the result of our study is also in this range with a prevalence of 4.5%. According to the results of another review article published Weinberger and Sicherer (32), in two studies conducted in European countries where only confirmed cases of allergy were investigated using the food challenge test, the overall prevalence of allergy to tree nuts 3.4% has been reported, which is very close to the result of our study.

Differences in the overall prevalence of tree nut allergy in different regions, in addition to differences in genetic factors and environmental risk factors, can be caused by variations in study design methods and sample size. Regarding the prevalence of allergies to each type of tree nut, the results are completely different depending on the geographical region. Because in each region, according to the specific nutritional culture of that region, factors such as the amount of consumption of each type of nut, The food composition containing nuts or the age at which nuts are consumed for the first time in children's diet are different. For example, among European countries, allergy to walnuts is more common in Spain than in Greece and the Netherlands, because Walnut consumption in Greece is 8 times more than the Netherlands and 9 times less than Spain (33). In most of the studies conducted in Europe, hazelnut is known to be the most common nut allergen with a prevalence of 17-100%, while in America, walnut ranks first with a prevalence of 20-30%. In England, as in our study, allergies

Almonds were the most abundant (33%). In our country, almonds are one of the most consumed types of tree nuts and one of the main foods in the beginning of complementary feeding of infants at 6 months of age is almond milk. In other studies, including Asian studies, the prevalence of allergies by different types of nuts has not been investigated (31).

In our study, the average age of people's first allergic reaction to tree nuts was 11.67 ± 12.09 months, while this rate was 36 months in another study conducted by Fleischer (2007) (34) and 62 months reported by Dreskin and Stitt, (2020) (35). The possible explanation for this difference is that almond allergy is the most common in our study, and as mentioned before, the main food containing almonds in our country is almond butter, which is generally one of the first foods at the beginning of nutrition. Supplementation of infants begins at the age of less than 1 year. Therefore, the average of the first allergic reaction is around 1 year. The present survey had some limitations. Considering that the patients were selected based on self-report in the first stage, it is important to obtain a detailed history from the parents of the patients in order to find allergic clinical symptoms related to the consumption of nuts. This may not be easily possible due to the large number of daily visits to the clinic and its limited time. In order to facilitate this task, it is possible to use a larger number of people taking the history in addition to the regular colleagues of the clinic.

Another important issue is the methods of diagnosis and confirmation of allergy to tree nuts. Sometimes, during the project, we encountered a shortage of some standard extracts of nuts. One of the reasons for conducting a serum test to check the specific antibody against the relevant nuts was such cases. Also, if other new diagnostic methods such as CRD and BAT were affordable and available for all patients, the diagnostic capability would increase based on more details. One of the other implementation limitations of this research was the impossibility of doing the oral challenge due to the corona virus epidemic. This test is the gold standard for diagnosing food allergies. But since it requires hospitalization of patients in the ward, it cannot be performed in the current situation where all elective hospitalizations are canceled. Also, this study was conducted only in the children's medical center, which is of course known as a referral center throughout Iran, while in the future, if a similar study is conducted as a multicenter in several geographical areas of Iran, the results will be valuable. had Because, as seen from the review of similar studies, the frequency of allergies to different types of tree nuts is different according to different geographical regions.

Conclusion

The overall prevalence of tree nut allergy in our study population is 4.5%, with almond allergy at the first place with a frequency of 62.1%, followed by walnut allergy (51.7%) and hazelnut. 27.6%) and pistachio (23%). The reported figures for the general prevalence of allergy to tree nuts and the frequency of allergy to each type of nut are different around the world and depend on several factors, including: the age of the study subjects (children or adults), the study design method (Inclusion criteria and method of selecting people and sample size), geographical region and nutritional culture that governs that region (age of

starting to consume nuts for the first time in infants, different food combinations containing nuts, consumption of nuts during pregnancy and breastfeeding by the mother). Unfortunately, no comprehensive study has been done in this regard in our country, and beyond that, even in the Asian continent, less studies have been conducted than in other regions of the world. Therefore, conducting more studies in all age groups and in different regions of the country is necessary. With diversity in study design methods, it can help to clarify the situation of allergy to tree nuts in Iran in the future.

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