Evaluation of Clinical Symptoms and Clinical Course in Pediatric Patients with Tree Nut Allergy

Kuruyemiş Alerjisi Olan Çocuklarda Klinik Bulgular ve Doğal Seyrin Değerlendirilmesi

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ABSTRACT

Objective: Tree nut allergies (TNA) are an important health problem can cause severe reactions such as anaphylaxis and the frequency of improvement with age is low. This study aims to evaluate the clinical features and tolerance development of TNAs.

Material and Methods: In our study, the clinical characteristics, laboratory findings and tolerances of the patients who were followed with allergy to tree nuts between 2010-2017 in the Department of Pediatric Immunology and Allergy of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital were evaluated.

Results: A hundred and twenty eight (73.4% male) patients were included in the study with a median age of 61 (min-max:4-209) months. Of the patients, 109(85.2%) were hazelnuts, 60(46.8%) were allergic to walnuts, 47(36.7%) were allergic to pistachios, 37(28.9) were allergic to almonds, 22(17.2%) were allergic to cashew nuts.Presenting reaction was anaphylaxis in 47 (36,7%) patients. The median value of the follow-up period was 56.3 (16.3-134.2) months.Of the 128 patients, 37(29%) have overgrown all TNAs, 9 (7%) have outgrown some of TNAs and TNAs of 70(54.6%) patients persisted. Twelve patients (9.4%) couldn't evaluated. Forty-two percent of patients with single TNA, 31.5% of patients with multi-TNA has developed tolerance within follow-up period.

Conclusion: Tolerance development to TNA seems to be encouraging. Therefore, regular monitoring of these patients is important.

Key Words: Children, Prognosis, Symptoms, Tree nut allergy

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Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: The study was approved by the ethical review committee of the University of Health Sciences, Ankara Child Health and Diseases, Hematology, Oncology Training Research Hospital (EC number:2017-128).

Contribution of the Authors / Yazarların katkısı*: *HASBEK E: Constructing the hypothesis or idea of research and/or article, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***KULHAS I:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***DIBEK MISIRLIOGLU E:*** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***CIVELEK E:*** Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study. ***GINIS T:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Reviewing the article before submission scientifically besides spelling and grammar. ***CAPANOGLU M:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study. ***KOCABAS CN:*** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, ***TOYRAN M:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study.

How to cite / *Atıf yazım şekli* : Hasbek E, Kulhas Celik I, Dibek Mısırlıoglu E, Civelek E, Ginis T, Capanoglu M, et al. Evaluation of Clinical Symptoms and Clinical Course in Pediatric Patients with Tree Nut Allergy. Turkish J Pediatr Dis 2022; 16: 42-48.

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Received / Geliş tarihi : 21.12.2020
Accepted / Kabul tarihi : 12.02.2021
Online published : 07.04.2021
Elektronik yayın tarihi
DOI: 10.12956/tchd.840929

ÖZ

Amaç: Kuruyemiş alerjileri (KA), anafilaksi gibi ağır reaksiyonlara neden olabilmeleri ve yaşla düzelme sıklıklarının az olması nedeni ile önemli bir sağlık sorunudur. Çalışmamızda kuruyemiş alerjilerinin klinik özellikleri ve tolerans gelişiminin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmamızda T.C. Sağlık Bilimleri Üniversitesi Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim ve Araştırma Hastanesi Çocuk Alerji Kliniği'nde 2010-2017 yıllarında kuruyemiş alerjisi nedeni ile izlenen hastaların klinik özellikleri, laboratuvar bulguları ve prognozu değerlendirildi

Bulgular: Çalışmaya ortanca yaşı 2.5 yıl (min-maks: 1-17) olan yüz yirmi sekiz (%73.4 erkek) hasta alındı. Hastaların 109'unda (%85.2) fındık, 60'ında (%46.8) ceviz 47'sinde (%36.7) antep fıstığı, 37'sinde (28.9) badem, 22'sinde (%17.2) kaju fıstığı alerjisi vardı. Kırk yedi (%36.7) hastada başvuru reaksiyonu anafilaksiydi. Takip süresi ortanca 56.3 (min-maks:16.3-134.2) aydı. Yüz yirmi sekiz hastanın 37'sinde (%29) tüm KA'leri düzelmişken, 9'unda (%7) bazı KA'leri düzelmiş 70 (%54.6) hastada ise KA devam etmiştir. On iki hasta (%9.4) değerlendirilemedi. Tekli KA'li hastaların %42'si, çoklu KA'li hastaların %31.5'i takip süresi içinde tolerans geliştirmiştir.

Sonuç: Kuruyemiş alerjilerine tolerans gelişimi cesaret verici görünüyor. Bu nedenle bu hastaların düzenli takibi önemlidir.

Anahtar Sözcükler: Çocuklar, Prognoz, Semptomlar, Kuruyemiş alerjisi

INTRODUCTION

Tree nut allergy(TNA) is an important health problem because it can cause severe reactions that can be lethal and also decreases the quality of life of children with allergies and their families. Tree nuts are the cause of 18-40% of all cases of anaphylaxis and with peanuts they account for the 70-90% of anaphylactic fatalities due to food allergy (1,2). The frequency of reactions with TN is reported to be increasing (3).

Current treatment of TNA is avoidance of the allergenic food, but children, especially at school age are at high risk of accidental exposure to TNs. Anxiety due to the possibility of anaphylactic reactions, efforts to avoid the allergen, disbelief of being ready to use adrenalin auto-injectors are burdens on the patient and the families (4). Parents can over protect their food allergic children and this may interfere with child's development of autonomy and social skills (5).

Tree nuts are reported to have beneficial effects for the health of children. They are widely available and accidental ingestion is common as they are included in many take-home foods (3). These points make the avoidance of TNs harder

Resolution rate of allergic reactions to tree nuts are considered to be low and they are presumed to continue until adulthood in most of the cases (3). However, the results of TNAs in the pediatric age group were obtained from a limited number of studies. In our study, we aimed to evaluate the clinical features of the patients who were followed with the diagnosis of TNA and to evaluate the clinical course of the patients.

MATERIALS and METHODS

The study included patients diagnosed with tree nut allergies between 2010 and 2017 at the Pediatric Immunology and Allergy Clinic of our hospital. Patients who had only sensitization according to skin prick test(SPT) and/or specific IgE(sIgE) and did not have a reaction with the culprit TN were not included in the study. Patients with symptom exacerbation upon exposure or after open oral provocation test(OPT) and supporting allergy test results (positive results for SPT or sIgE tests) were diagnosed with TNA.

Patients' sociodemographic characteristics, complaints, type of allergic reactions, age of symptom development; mother's consumption of TNs in the period of pregnancy and lactation; maternal smoking during pregnancy; laboratory tests at the time of diagnosis, other TNs/ food /aeroallergen sensitivity, accompanying allergic/immunological disease; history of allergic disease in the family; follow-up period, clinical course information was recorded in standard form from patient records and interviews with patients. Patients whose last control has been more than 6 months ago were invited to the clinic and allergy tests (SPT and/or sIgE) were repeated if patient gave informed consent. Patients who consumed the culprit TN at home without any reaction were considered to develop tolerance and who developed reaction were considered to have ongoing TNA.OPT was planned to patients who did not have a reaction in the previous 6 months and who did not consume the culprit TN during this period when consent was taken from parents

Patients with primary immunodeficiency were excluded from the study.

The study was approved by the ethical review committee of the University of Health Sciences, Ankara Child Health and Diseases, Hematology, Oncology Training Research Hospital (EC number:2017-128).

Tree nuts are selected for SPT based on clinical history (suspected food-induced allergy symptoms on previous ingestion of the food or maternal dietary history if breastfed). Prior to SPT, vital signs of each child were measured, physical examinations were performed and recorded. Antihistamines were discontinued one week prior to tests. SPT was performed on the dorsal in younger children, and on the inner side of the forearm in older children. Histamine was used as a positive and saline was used as negative control. The test was accepted positive if the edema diameter that occurred after 15 minutes was greater than 3 mm larger from the negative control.

SPTs were performed using allergen extracts (ALK-Abello,Madrid,Spain) when available. Prick to-prick testing with raw food was done for hazelnut, walnut, pistachio, almonds and cashew nut.

Serum sIgE for hazelnuts, pistachios, cashews, walnuts, almonds and TN mix (peanuts, hazelnuts, Brazil nuts, almonds, coconut) was measured by the ImmunoCAP (PhadiaAB, Uppsala, Sweden) system. The IgE serum levels above 0.35 kU/l was considered positive.

The provocation tests and protocols were performed following the World Allergy Organization (WAO) Food Allergy Working Group and the European academy of allergy and clinical immunology (EAACI) Group Guidelines (6)

Open OPTs were performed using freshly prepared food by an experienced nurse under the supervision of a pediatric allergist. The dosing intervals were 15 minutes (7). Patients were followed for any allergic reaction and OPT was stopped and considered positive if any objective signs and symptoms were documented. Patients with negative results were observed for at least 2 hours after OPT and told to continue receiving the suspected food and admitting to the hospital in case of any reaction at home.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL). The normal distribution of the data was evaluated by Kolmogorov-Smirnov test. Numerical variables without normal distribution were shown as median (min-max). Categorical variables were expressed as numbers and percentages. Mann Whitney U test was used for comparison of numerical variables between two groups, and Kruskal Wallis H test (posthoc: Dunn tests test) was used for comparison between three groups.

RESULTS

Three patients with immunodeficiency were excluded from the study and 128 patients were included of which 73.4% (n=94) were male. The median age at the last follow-up was 61 (4-209) months. The median value of the follow-up period was 56,3 (16.3-134.2) months.

Symptom onset ages according to the types of tree nuts; 36 (4-213) months for hazelnut, 44 (5-214) months for walnut, 34 (5-197) months for pistachio, 36 (5-214) months for almond, and 35 (2-213) months for cashew.

A total of 275 tree nut allergy cases were observed in 128 patients (109 hazelnuts, 60 walnuts, 47 pistachio, 37 almond, 22 cashew allergy). Presenting reaction was urticaria in 124 (96.8%), angioedema in 54 (42.2%), anaphylaxis in 47 (36.7%) and atopic dermatitis in 51 (39.8%) patients. Eosinophilic esophagitis in 2 (%1.8) patients and FPIES in 2 (%1.8) patients. Detailed characteristics of each hypersensitivity reaction according to the type of nuts are given in Table I.

Table I: Clinical and demographic characteristics of patients according to tree nuts.

	All Patients n=128	Hazelnut n=109	Walnut n=60	Pistachio n=47	Almond n=37	Cashew n=22
Gender (n) female /male	34/94	32/77	15/45	14/33	11/26	4/18
Follow up period (months) median (min-max)	12.3(0.03-85.3)	58.5 (16 -104)	58.1 (16.3-102.8)	50.8 (16.4-99.9)	36.7 (16.8-100)	51 (20.7-97.8)
Age at diagnosis (months) median (min-max)	40.2(0.03-217.2)	34 (4-214)	38.6 (5-214)	33.6 (5-197)	39.0(5-214)	35.2 (2-214)
Initial skin prick test (mm) median (min-max)	7 (3-20)	7.3 (3-18)	6.5 (3-18)	8.3 (3-18)	9 (3-22.5)	6.5 (3-16.5)
Initial specificIgE (kU/l) median (min-max)	1.5 (0.1-157)	1.8 (0.4-157)	1.52 (0.35- 150)	-	3.91 (0.82-43.5)	10.76 (1.15-48.2)
Urticaria, *	124 (96.8)	102 (93.6)	58 (96.7)	45 (95.7)	36 (97.3)	22 (100)
Angioedema, *	54 (42.1)	43 (39.4)	31 (51.7)	27 (57.4)	20 (54.1)	14 (63.6)
Anaphylaxis, *	47 (36.7)	38 (34.9)	41 (68.3)	24 (51.1)	15 (40.5)	9 (40.9)
Atopic dermatitis, *	51 (39.8)	42 (38.5)	29 (48.3)	26 (55.3)	18 (48.6)	9 (40.9)
Eosinophilic esophagitis, *	2 (1.5)	2 (1.8)	2 (3.3)	2 (4.3)	2 (5.4)	1 (4.5)
FPIES, *	2 (1.5)	2 (1.8)	-	-	-	-
Accompaning non-TN food allergy, *	58 (71.6)	42 (38.5)	30 (50)	20 (42.6)	16 (43.2)	15 (68.2)
Aeroallergen sensitization, *	47 (36.7)	34 (31.2)	27 (45)	15 (31.9)	14 (37.8)	8 (36.4)
Tolerance development, *	46 (35.9)	38 (34.8)	18 (30)	8 (21.6)	12 (32)	1 (4.5)
Age of tolerance (months) median (min-max)	25.7(4.87-205)	49.2 (12.2-229)	67.9 (17.8-204.0)	69.7(18.5-102)	48.7 (12.1-156)	-

:** *n (%),* ***FPIES: *Food Protein Induced Enterocilitis Sendrom,* ***TN:*** *Tree Nut*

Table II: Comparison of Patients with One and More Tree Nut Allergy.

Variables	Population n=128	TN Allergy		p
		Single n=52	Multiple n=76	
Age at diagnosis (months) median (min-max)	33.8 (1.77-214)	28.6 (1.77-205)	35.8 (4.87-214)	0.985
Gender, * Female Male	34 (26.6) 94 (73.4)	12 (23.1) 40 (76.9)	22 (28.9) 54 (71.1)	0.543
Breastfeeding duration(month) median (min-max)	15 (0.3-42)	15 (2.5-24)	18 (0.3-42)	0.686
Onset of complementary food (month) median (min-max)	6 (2-24)	6 (2-12)	6 (3-24)	0.933
Onset of formula consumption (month) median (min-max)	9.5 (1-24)	7 (4-22)	10 (1-24)	0.260
Allergic disease in the family, *	58 (45.3)	21 (40.4)	37 (48.7)	0.372
Food allergy except tree nuts, *	90 (70.3)	27 (51.9)	63 (82.9)	<0.001*
Anaphylaxis, *	47 (36.7)	7 (13.5)	40 (52.6)	<0.001*
Eosinophil count median (min-max)	400 (100-4900)	300 (100-1400)	400 (100-4900)	0.147
Percentage of eosinophils (%) median (min-max)	4.1 (0.1-24)	3.4 (0.2-14)	4.5 (0.1-24)	0.077
Serum total IgE level (IU/mL) median (min-max)	205 (9.5-2454)	138 (9.5-1990)	258 (13.3-2454)	0.406
Aero-allergen sensitization, *	43 (33.6)	17 (32.7)	26 (34.2)	0.998
Tolerance status (tolerance to at least one TNA)	46 (36)	22 (42.3)	24 (31.5)	0.46
History of allergic disease,*	59 (46.1)	16 (30.8)	43 (56.6)	0.007*

***:**n (%)*

Table III: Comparison of Patients presented with Anaphylaxis and Other Symptoms.

Variables	Initial symptom		p
	Anaphylaxis n=47	Others n=81	
Age of onset (month) median (min-max)	24.1 (5.7-209)	34 (2-213)	0.24
Gender Male Female	37 (78.7) 10 (21.3)	57 (70.4) 24 (29.6)	0.40
Breastfeeding duration(month) median (min-max)	15 (1.5-42)	16.5 (0.3-36)	0.97
Onset of complementary food (month) median (min-max)	6 (3-24)	6 (2-18)	0.71
Onset of formula (month) median (min-max)	10 (1-24)	9 (3-22)	0.57
Allergic disease in the family, *	22 (46.8)	36 (44.4)	0.85
Food allergy except TNs, *	37 (78.7)	53 (65.4)	0.16
Eosinophil count median (min-max)	300 (100-2200)	400 (100-4900)	0.60
Eosinophils percentage (%) median (min-max)	3.9 (0.1-20.2)	4.2 (0.3-24)	0.78
Serum total IgE level (IU/mL) median (min-max)	195 (13.3-1990)	290 (9.5-2454)	0.22
Aeroallergen sensitization, *	22 (46.8)	21 (25.9)	0.02†
TN consumption in pregnancy, * (once in a week or more frequent)	31 (66.0)	38 (46.9)	0.41
Concomitant of allergic disease, *	29 (61.7)	30 (37.0)	0.01†

***:**n (%), †p <0.05 shows statistical significance.*

Table IV: Comparison of tolerance development of patients with tree nut allergy.

Variables	Tolerance to at least one TN n=46	No tolerance development n=68	p
Age of onset (month) median (min-max)	25.7 (4.87-205)	35.8 (2-214)	0.58
Gender, * female male	9 (23.1) 37 (76.9)	21 (28.9) 47 (71.1)	0.543
Breastfeeding Duration(month) median (min-max)	18 (2-36)	14 (0.3-42)	0.714
Onset of complementary food (month) median (min-max)	6 (3-24)	6 (2-18)	0.78
Onset of formula (month) median (min-max)	9 (1-24)	10 (2-21)	0.929
Food allergy except TNs, *	28 (60)	56 (82)	0.016*
Anaphylaxis, *	20 (43.4)	25 (36.7)	0.55
Eosinophil count median (min-max)	400 (100-2200)	400 (100-4900)	0.52
Eosinophils percentage median (min-max)	3.6 (0.1-16.2)	4.4 (0.2-24)	0.28
Serum Total IgE level(IU/mL) median (min-max)	138 (9.5-1600)	240 (21-2454)	0.160
Aero-allergen sensitization, *	18 (39)	22 (32)	0.54
Frequency of TN consumption in lactation: once in a week or more, *	22 (47.8)	34 (50)	0.57
Concomitant allergic disease, *	19 (41.3)	29 (42.6)	0.52

***:** *n (%)*

Of the patients, 90 (70.3%) had food allergy other than TNs: 53 (41.4%) egg allergy, 36 (28.1%) milk allergy, and 32 (25.0%) peanut allergy. Forty three patients (33.6%) had sensitization with aeroallergens: 38 (29.7%) pollen, 8 (6.3%) house dust mite, 7 (5.5%) animal dander, 5 (3.9%) mold, 4 (3.1%) cockroach sensitization.

Of the 128 patients with accompanying allergic diseases, 36 (28.1%) had asthma, 24 (18.8%) had allergic rhinitis, and 51 (39.8%) had atopic dermatitis .

The mean IgE value at the time of initial admission was 205 (14-2454) IU/mL. The median value of the eosinophil percentage was 4.1 (0.1-24) and the median eosinophil count was 400 mm3 (100-4900).

Fifty two (40.6%) of our patients had a single TNA (37 hazelnuts, 7 walnuts, 4 pistachios, 3 cashew nuts and 1 almonds); 76 (59.3%) had multiple TNA. Twenty-six patients (34.2%) had allergy to 2 TNs, 3 TNA were detected in 17 patients (22.4%), 4 TNA in 22 (28.9%), and 5 TNA in 11 patients (14.5%). When multiple TNA patients were compared to single TN allergic patients, frequency of other food allergy (82.9% vs 51.9%;p<0.001), presence of anaphylaxis (52.6% vs 13.5%;p<0.001) and presence of accompanying allergic disease (56.6% vs 30.8%; p=0.007) were higher in the multiple allergic group (Table II).

Of the 52 patients with single-TNA, 22 (42.3%) developed tolerance [18 (81.8%) hazelnuts, 3 (13.6%) walnuts, 1(4,6) pistachio]. Of 75 patients with multiple TNAs 24 (32%) developed tolerance to at least one of the TNs during follow-up period (20 (26.6%) hazelnuts, 11 (14.6%) almonds, 15 walnuts (20%), 7 (9.3%) pistachio and 1 (1.3%) cashew nuts). The ratio of tolerance development to at least one of the TNs did not differ between patients with multiple and single TN allergies (p=0.46) (Table II).

Anaphylaxis was defined in 36.7% of all patients (38 hazelnut allergy, 41 walnut allergy, 24 pistachio allergy, 15 almond allergy and 9 cashew nuts allergy). Frequency of aeroallergen sensitization (46.8% vs 25.9%; p=0.02) and accompanying allergic disease (61.7% vs 37%; p = 0.01) were more frequent in the anaphylaxis group (Table III).

Our 128 patients had 275 TNA cases. Of these cases, 123 had reaction with the culprit TN in the previous 6 months, so these were not evaluated and labeled as “did not develop tolerance”;63 had consumed the culprit TN at home without reaction and were labeled as “had developed tolerance”. Forty-eight TNA cases had anaphylaxis in the previous 12 months. We couldn’t contact 8 patients. So, we couldn’t evaluate these patients’ tolerance status. Four parents refused OPT. Twenty OPTs were performed, 6 OPTs resulted positive and 14 OPTs resulted negative. Thus these 14 cases were also labeled as

"developed tolerance". Consequently, 77 of 275 TNA cases (28%) ended with tolerance development. Of the 128 patients, 37 (29%) have overgrown all TNAs, 9 (7%) have outgrown some of TNAs and TNAs of 70 (54.6%) patients persisted. Twelve (9.4%) couldn't evaluated.

When patients were compared according to tolerance development, frequency of food allergy except TNs was higher among patients who had not developed tolerance (p=0.016) (Table IV). Tolerance development was most frequently present in reactions to hazel nut (34%) and almond (32%). Median ages of children developing tolerance varied between 48.7 months for almond and 69.7 months for pistachio. Frequencies of and ages at tolerance development based on the type of TNAs are given in Table I.

When patients with hazel nut allergies were compared according to tolerance development, it was determined that presence of accompanying TNA (p=0.012) and food allergy other than TNs (p=0.032) were less frequent and initial sIgE levels were lower (p=0.013) among patients who had developed tolerance. When patients with walnut allergy were compared according to tolerance development, only initial sIgE level was lower among patients who had developed tolerance (p<0.001).

DISCUSSION

In the present study, the characteristics of 128 patients with 275 TNAs were presented. Hazel nut and walnut allergies were the most common. Leading presenting symptom was urticaria and anaphylaxis was defined in 36.7%. Accompanying food allergies and concurrent allergic diseases were common. Seventy-seven of 275 TNA cases (28%) ended with tolerance development. Of the 128 patients, 46 (36%) have outgrown at least one of TNAs they had.

Frequency of TNA and type of TNs causing sensitization differs from country to country, probably due to nutritional habits and genetic differences (5). In previous studies it has been reported that chest nut and cashew nut allergies were the most common type in USA and Brasilia while hazel nut and chest nut were common in European countries (8). In accordance with previous studies from our country and other countries hazel nut and chest nut allergies were the most common TNAs in our study (9,10).

Anaphylaxis is the most critical symptom of TNA. Couch et al.(11) reported that anaphylaxis was the first presenting symptom in 28% of patients with TNA. In our study, 47 patients (36.7%) were admitted with anaphylaxis symptoms and it was most common for chestnut allergic patients (68.3%). Among patients whose first symptom was anaphylaxis, concomitant allergic disease (p=0.01) and aeroallergen sensitization (p=0.02) were higher than patients presenting with other symptoms. In a recent study from our country, 48.9% of 184 children with TNA were reported to have anaphylaxis as presenting symptom and female gender, having concomitant egg allergy and asthma were defined as risk factors (12). When patients have accompanying food allergies and allergic diseases, higher risk of anaphylaxis should be kept in mind.

Patients with TNA commonly have reactions with more than one type of TNs. In a retrospective multicenter study evaluating 109 patients who underwent OPT for TN sensitization, 54 (49.5%) patients had other TNA (11). In our study, 76 (59.3%) of our patients were observed to have multiple TNA and presence of other food allergies, accompanying allergic diseases and frequency of anaphylaxis as a presenting symptom were more common among patients who had multiple TNA. Sufficient data were not found in the literature regarding the risk factors for multiple TNA.

Reactions with food other than TNs are also common among patients with TNA. The incidence of non-TN food allergy was reported as 66.4-78% in two previous studies and peanut (60%), egg (42%) and milk (9%) were the most common accompanying non-TNAs (11,13). In our study, 90 (59.3%) of our patients had non-TN food allergy; the most common allergens were egg (41.4%), milk (28.1%) and legumes (41.4%). Other allergic diseases are also, common in patients with TNA (11,13). In our study, 28% of our patients had accompanying asthma, 39.8% atopic dermatitis and 18.8% allergic rhinitis. Also one third of our patients had aeroallergen sensitization.

Tolerance development is considered to be low for TNAs. However, as far as we could reach, there is scarce data about the frequency of tolerance development. The only study we could find is by Fleischer et al. (13) They have examined 278 patients aged between 3-21.6 years, 101 of them had reactions and skin test and/or sIgE positivity. These patients had 115 allergic reactions with TNs, cashew was the most frequent allergen. Of these patients, only 20 had undergone OPT and 9 had passed. Thus, they have reported that at least 8.9% of their patients had developed tolerance. Tolerance to at least one TNA was much higher, 36% in our study and tolerance rate ranged between 34.8% for hazel nut and 4.5% for cashew. In the study by Fleischer et al. (13), 81 of 101 patients could not be examined for tolerance development and this may have affected their results. Also, frequency of TNs causing reactions was very different from our study in their population. Hazel nut and walnut allergies were rare while cashew allergy was the most frequent (30%). For cashew allergy, tolerance development was less frequent and age of tolerance development was the highest in our study.

In the study conducted by Fleischer et al. (13), it was reported that there was lesser improvement in patients with additional tree nut allergy and additional food allergy. Accordingly, children who had developed tolerance to hazel nuts, less frequently had concurrent TNAs and other food allergies in our study. Furthermore, accompanying allergic diseases were less

frequent and initial sIgE levels were lower among these patients. Therefore, in patients with accompanying TNAs with additional food allergy and allergic diseases, the likelihood that the allergy may continue for a longer period should be considered during the follow-up period.

Our study was a observational study and this may have limited its results. Some of our patients were younger and had lower follow up periods, may be too low for tolerance development. A prospective study, with a detailed follow-up may give better results and we are hoping to share the results of our ongoing prospective study soon. But we think that the data gathered by this study is valuable as a large group of proven TNA patients were examined and detailed clinical and laboratory characteristics as well as tolerance status was determined.

According to our data we suggest that at least one third of TNA cases can develop tolerance at a mean age of 4-5 years, and thus children with TNAs should be followed-up for tolerance development.Additional TNAs, accompanying allergic diseases and other food allergies are common so patients should also be evaluated for these conditions.

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