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Clinical Characteristics and Prognosis of Legume Allergy in Children

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ABSTRACT

Objective: The knowledge concerning allergy to legumes is limited. We aimed to evaluate the clinical features and prognosis of legume allergy in children.

Materials and Methods: We evaluated patients with legume allergy who were followed up from 2010 to 2017 at the Division of Pediatrics Allergy and Immunology, with their clinical features, laboratory findings, and prognosis.

Results: The median age of the enrolled 37 patients in our study was 7 (interquartile range, 4.3-9.2) years. Twenty-nine (78.3%) were male. Thirteen (35.1%) patients were found to have an allergic reaction against more than one legume. The distribution of legume allergies was as follows: peanut (n=21, 56.8%), lentil (n=16, 43.2%), chickpea (n=13, 35.1%), pea (n=6,16.2%), bean (n=5, 13.5%), lupine (n=2, 5.4%), and kidney bean (n=1, 2.7%), with a total of 64 allergic reactions. The distribution of these different legume allergy reactions was as follows: urticaria and angioedema (n=31, 48.4%), anaphylaxis (n=23, 35.9%), atopic dermatitis (n=6, 9.3%), eosinophilic esophagitis (n=3, 7.8%), and food protein-induced enterocolitis syndrome (n=1, 1.5%). Thirty-two (86.5%) of 37 patients had an allergy to a non-legume food. Tolerance to 50 legume allergies affecting 27 patients being followed up for more than 12 months were given. Eight of the 18 patients with a single legume allergy and 1 of the 9 patients who were allergic to multiple legumes developed tolerance.

Conclusion: Peanut and lentil were the most frequent legumes that caused allergic reactions in our study. The rate of allergies to non-legume foods was high. In patients who were allergic to a single legume, the tolerance rate was 44.4%.

Keywords: Legume allergy, prognosis, children

INTRODUCTION

Legumes causing allergic reactions differ from country to country. Peanut is the most frequent cause in Northern Europe and the United States of America (USA), whereas lentil is the main cause in Spain (1-5). Prevalence, clinical signs, and natural course of legume allergies excluding peanut allergy are not widely studied (6). Lentils are one of the most common foods that cause allergic reactions in children with food allergy in Turkey because they are used frequently (7). Clinical findings and diagnostic issues depend on the underlying mechanism that can be immunoglobulin (Ig)-E mediated, non-IgE mediated, or mixed. The most common route of exposure in legume allergy is ingestion of the legume and it is reported that allergy due to inhalation also occurs. The steam generated during the cooking process of legumes may cause allergic

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symptoms, which is probably related to the heat resistance of the antigen (8,9).

Patients frequently have another legume allergy or an accompanying different food allergy or aeroallergen sensitization (3-8,10). Lentil, chickpea, and pea allergies can be seen in a single patient, which may represent the multiplicity of legume allergies (9-11).

The rate of tolerance development against peanuts ranges from 21.5% to 50% in different studies (12,13). There are two different papers from Turkey that have studied the prognosis for allergies to legumes except peanut. In the first one, the tolerance ratio for lentil allergy was found to be 50% (14). The second paper gave the tolerance ratios for peanut, lentil, pea, chickpea, and beans (10).

In this study, we aimed to evaluate the clinical findings, accompanying food allergy and aeroallergen atopy, and the natural outcome of legume allergy in children.

MATERIALS and METHODS

We included patients who were diagnosed with legume allergy at our pediatric allergy and immunology clinic between 2010 and 2017.

The sociodemographic features, symptoms, type of legume causing the allergic reaction, initial dietary exposure age to legumes, age of symptom onset, mother's exposure to the allergic legume during pregnancy and breastfeeding, diagnostic tests at the initial visit including results of skin prick tests (SPTs), serum-specific IgE levels, results of food provocation tests; existence of any other legume, food or aeroallergen allergy; accompanying allergic-immunologic diseases; family history of allergic disease; follow-up period and development of tolerance data were obtained from patient visits and medical records.

Patients who had not shown up at the hospital for more than six months were called for an evaluation readmission. Skin prick tests and/or serum-specific IgE (sIgE) tests were performed, and open oral provocation tests (OPT) were conducted to determine the tolerance state of the patients. Oral provocation tests were not performed in case of history of anaphylaxis within the last year and if the parents did not give consent. According to the results of OPTs performed at the last controls of the patients, or the statements of the families about the development of a reaction after accidentally or deliberately trying to eat the culprit legume at home, "development of tolerance" and "persistence of allergy" were noted.

Patients with primary immunodeficiency were excluded from the study.

The study was approved by the Ethical Review Committee of University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital. (Date: 14.06.2017, Number: 2017-94)

Diagnosis of Legume Allergy

Diagnosis of IgE-mediated legume allergy: Patients who had only sensitization according to SPT and/or sIgE and did not have a reaction with the culprit legume 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 legume allergy.

Diagnosis of atopic dermatitis (AD): The Hanifin and Rajka criteria are routinely used for the diagnosis of AD and for the diagnosis of legume-triggered AD. The suspected legume is eliminated from the diet (or from the mother's diet for exclusively breastfed patients) for at least 2 weeks while under optimal skin care (15). If symptoms regress, the suspected food is reintroduced to the patient's diet (or maternal diet if breastfed). Patients with symptom exacerbation upon exposure and supporting allergy test results (positive results for both SPT and specific IgE tests) are diagnosed with food-triggered AD.

Diagnosis of food protein-induced enterocolitis syndrome (FPIES): Food protein-induced enterocolitis syndrome was diagnosed according to the diagnostic criteria proposed by the American Academy of Allergy, Asthma & Immunology in the International Consensus Guidelines for the Diagnosis and Management of FPIES published in 2017 (16).

Diagnosis of eosinophilic esophagitis: The eosinophilic esophagitis diagnosis was made according to the guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults (17).

Skin Prick Tests and Food-specific IgE Analysis

Epidermal SPTs were performed using allergen extracts for peanut and soybean (ALK-Abello, Madrid, Spain) along with a positive control (10 mg/dL of histamine phosphate) and a negative control (0.9% sterile saline). Prick-to-prick testing with raw food was performed for

lentil, chickpea, pea, whitebean, lupine, and kidney bean in the patients with a history of symptoms after these legumes. The diameter of the resulting indurations was measured horizontally and vertically. Induration of an average diameter at least 3 mm greater than the negative control was considered positive.

Food allergen-specific IgE antibody measurements were performed using ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) and were considered positive when levels were equal to or greater than 0.35 kU/L.

Food Challenge Tests

Food challenge tests with eliminated foods were performed at least 6 six months after the first challenge. Food challenge tests were performed as open oral food challenges (OFCs) according to the European Academy of Allergy and Clinical Immunology Guidelines (15). All children were examined before food challenge tests. Tests were not performed in patients who had an active infection or who had used antihistamines within the last 7 days. In open OFC tests, legumes were given orally stepwise, increasing doses every 15 minutes. The OFC 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 the challenge test for any allergic reactions and told to continue eating the suspected food. Patients whose OFC results were negative and who tolerated the food at home were considered to have developed tolerance.

Statistical Methods

Statistical analyses were performed using the SPSS 24 software package (SPSS Inc., Chicago, Illinois). Numbers and percentages are reported for discrete variables and means and standard deviations for continuous variables. Values are presented as means and standard deviations for data demonstrating a normal distribution and as medians and interquartile ranges (IQR) for data not demonstrating a normal distribution. The Chi-square (χ^2) test was performed to compare nonparametric data, the Mann-Whitney test for non-normally distributed data, and the independent t-test for normally distributed continuous data. A value of $p<0.05$ was considered statistically significant.

RESULTS

Thirty-seven patients were enrolled in the study, 29 (78.4%) of whom were boys. The median age was 7 (IQR, 4.3-9.2) years at the last follow-up. The median follow-up period was 42 (IQR, 9-56) months.

Sixty-four legume allergies were found in 37 patients. Of these, 21 (56.8%) had peanut allergy, 16 (43.2%) had lentil allergy, 13 (35.1%) had chickpea allergy, 6 (16.2%) had pea allergy, 5 (13.5%) had bean allergy, 2 (5.4%) had lupine allergy, and 1 (2.7%) had kidney bean allergy. No patients had an allergy to soybean.

Twenty-four (64.9%) patients were allergic to one legume, and 13 (35.1%) were allergic to more than one legume. Among these multiple legume allergic patients; six were allergic to 2 different legumes, three were allergic to 3 different legumes, two were allergic to 4 different legumes, one was allergic to 5 different legumes, and one was allergic to 6 different legumes. The clinical and laboratory findings of the patients according to the type of legume allergies are shown in Table I.

Of the 13 multiple legume allergic patients, 8 (61.5%) were allergic to lentils and chickpeas, 6 (46.2%) were allergic to lentils and peas, and 3 (21.3%) were allergic to lentils and peanuts.

The features of allergic reactions against legumes were as follows: of the 64 allergic reactions, 31 (48.4%) were urticaria and/or angioedema, 23 (35.9%) were anaphylaxis, 6 (9.3%) were atopic dermatitis, 3 (4.6%) were eosinophilic esophagitis, and 1 (1.5%) was food protein-induced enterocolitis syndrome (Table I).

The median eosinophil count was 400 (range, 0-2800) at first admission. Seventeen (45.9%) patients' eosinophil count was 500 and over and 2 (5.4%) patients' eosinophil count was 1500 and over.

The median serum total IgE concentration was 428 (IQR: 112-982) IU/mL. Total IgE concentrations were higher than 100 IU/mL in 28 (75.6%) patients, and in 8 (21.6%) patients it was found to be ≥1000 IU/mL.

Thirteen (35.1%) patients had a family history of allergic disease.

In 34 (91.8%) of the 37 patients being followed for legume allergy, the mother had consumed the allergic legume during pregnancy and lactation period at least

Table I. The clinical and laboratory findings of the patients according to the type of legumes.

	Peanut n=21	Lentil n=16	Chickpea n=13	Pea n=6	Bean n=5	Lupin n=2	Kidney Bean n=1
Age at last follow-up (years) median (IQR)	6.5 (4.2-9.2)	6.5 (4-8.5)	7.4 (4.2-18)	7.8 (6.5-14.9)	8.3 (5.2-15)	11.1 (7.4-14.7)	4.7
Gender (F/M)	4/17	4/12	4/9	2/4	3/2	1/1	0/1
Follow-up period (Months) median (IQR)	36 (5-45)	40 (10-58)	41 (23-59)	41 (31-57)	32 (23-49)	46 (30-46)	47
Introduction to diet (months) median (IQR)	19 (11.5-36)	6 (6-12)	9 (6-12)	11 (6-12)	10 (6.5-12)	9 (6-12)	10
Onset age of symptoms (months) median (IQR)	36 (9-67)	12 (6-36)	12 (8-71)	12 (10-48)	42 (10-102)	29 (10-48)	10
Age of diagnosis (months) median (IQR)	48 (17-79)	23 (19-53)	27 (17-71)	60 (6-147)	65 (36-130)	83 (54-112)	72
Skin prick test (mm) median (IQR)	4 (3-5.3)	7 (5-10)	6 (5-16)	12 (6-26)	13 (5 -22)	5 (4-6)	5
Specific IgE (kU/l) median (IQR)	0.3 (0.10- 3)	52 (0.2-153)	21 (3-74)	14 (0.4- 105)	-	-	-
Urticaria and/or angioedema, n(%)	8 (38%)	10 (62.5%)	5 (38.4%)	3 (50%)	3(60%)	2 (100%)	-
Anaphylaxis, n(%)	4 (19%)	6 (37.5%)	7 (53.8%)	3 (50%)	2 (40%)	-	1 (100%)
Atopic Dermatitis, n(%)	5 (23.8%)	-	1 (7.6%)	-	-	-	-
Eosinophilic Esophagitis, n(%)	3 (14.2%)	-	-	-	-	-	-
FPIES*, n (%)	1 (4.7%)	-	-	-	-	-	-
Accompanying non-legume food allergy, n(%)	19 (90.5%)	14 (87.5%)	11 (84.6%)	6 (100%)	5 (100%)	2 (100%)	1(100%)
Aeroallergen sensitization, n(%)	9 (42.9%)	7 (43.8%)	6 (46.2%)	4 (66.7%)	3 (60%)	1 (50%)	1 (100%)

***FPIES:** Food Protein Induced Enterocolitis Syndrome

once per month. Three of the patients' mothers reported that they had never consumed the allergic legume, neither during pregnancy nor during the lactation period.

Thirty-two (86.5%) of 37 patients had allergy to a non-legume food. Seventeen (45.9%) patients were found to be allergic to egg, 8 (21.6%) were allergic to milk, and 7 (18.9%) were allergic to hazelnut. The additional food distribution is listed in Figure 1.

Thirteen (35.1%) patients had accompanying asthma, and 9 (24.3%) had accompanying allergic rhinitis.

According to the minimum 12-month follow-up criteria which relates the clinical course, 27 patients were eligible. Among these subjects, 18 patients had one legume allergy. Eight (44.4%) of these patients who had only one legume allergy developed tolerance. Among these, 5 had peanut allergy, 2 had lentil allergy, and 1 had chickpea allergy.

One of the 9 patients who had multiple legume allergies developed tolerance to all the legumes. The relevant patient who had allergy to peanut and chickpea developed tolerance to both legumes at 45 months of age. The two patients who were allergic to four different types of legumes and one patient who had allergy to 5 and 6 different legumes continued to be allergic to all the legume types.

The tolerance ratio in terms of the legume type were as follows: peanut 8/13 (61%), lentil 3/12 (25%), chickpea 4/11 (36.6%), and pea 1/6 (16.6%) (Figure 2). The tolerance median age was 83 months (IQR 48-116) for peanut allergy, 48 months (three patients being aged 39, 48 and 48 months at the time of tolerance development) for lentils, and 46.5 months (36, 45, 48, 96 months) for chickpea. The only subject with pea allergy gained tolerance at 32 months. Patients allergic to lupines, kidney beans, and beans did not develop tolerance to any of the foods.

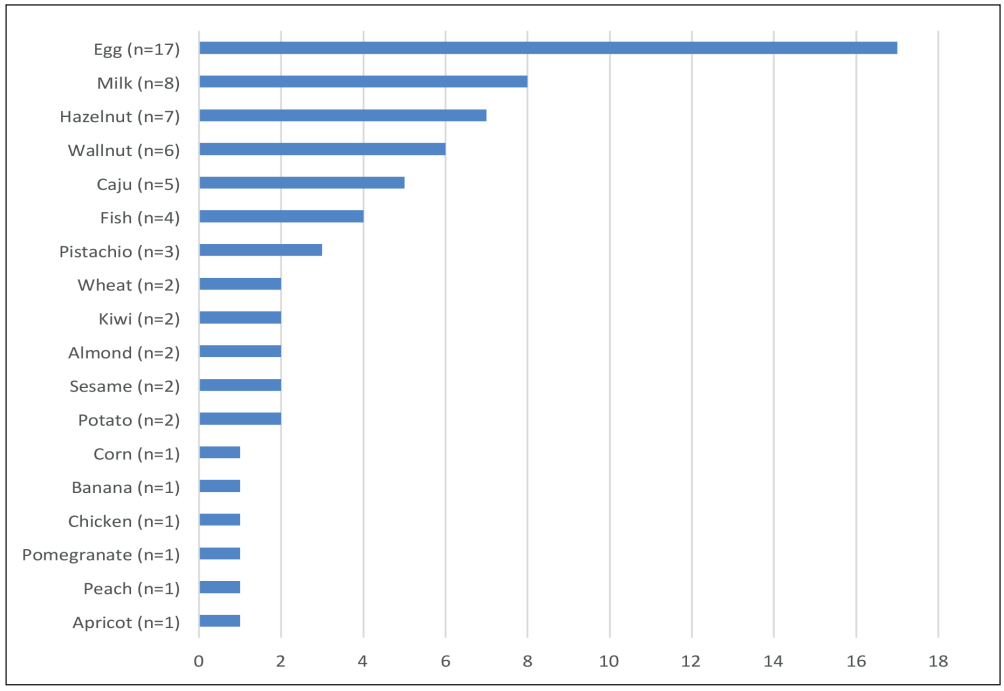

Figure 1. Allergic foods accompanying legume allergy.

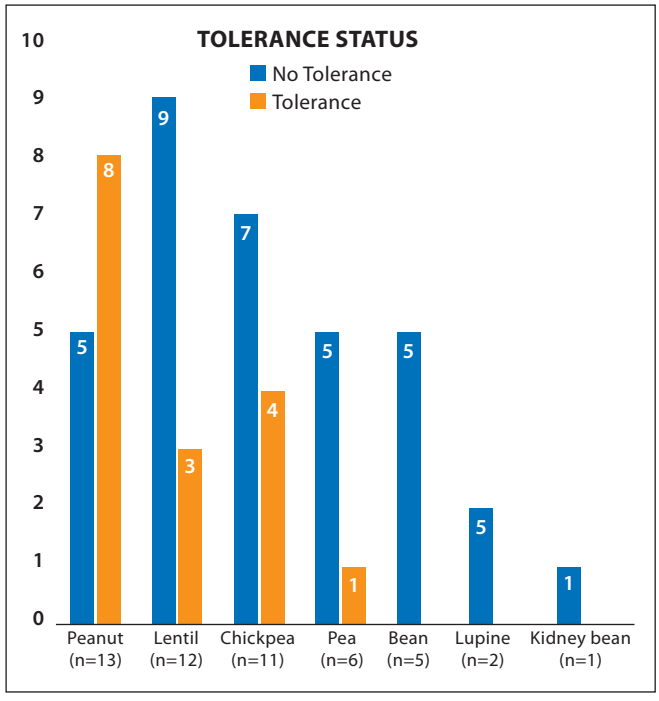

Figure 2. Tolerance status of allergic events in patients with over a year of follow-up

The factors that might influence tolerance of all study patients could not be assessed because of the limited number of subjects. We were able to compare the factors affecting tolerance ratio only in patients with peanut allergy. We could not find any statistically significant difference between patients with persistent peanut allergy and those who developed tolerance (Table II).

DISCUSSION

The culprit for food allergy differs due to the nutritional habits of communities. Legumes are foods frequently consumed in Turkey; they are preferred during the transition to additional feeding in the early period and thus allergic reactions are frequently seen. A study conducted in Turkey in 2011 on 315 patients with IgE-mediated food allergy revealed that 11.7% had peanut (4th frequent) allergy, 7% had lentil (6th frequent) allergy, and 2.5% had chickpea (12th frequent) allergy (7).

There are limited studies on the clinical features and prognosis of legume allergy (6). Sensitivity to legumes varies among countries. Peanut allergy is the first among food allergies and allergies to legumes in Northern Europe and the USA (1). However; in a study conducted in Spain, it was observed that 80% of 54 patients with legume allergies had red lentil allergy, 59% had chickpea allergy, and 50% had allergy to peas (4). In our study, we found food allergy against peanuts in 21 (56.8%) patients, lentils in 16 (43.2%), chickpeas in 13 (35.1%), peas in 6 (16.2%),

Table II. Comparison of Characteristics of Patients with Persistent Peanut Allergy and Those Who Developed Tolerance.

	Patients who developed tolerance, (n=8)	Patients with persistent allergy, (n=5)	p
Concomitant aeroallergen sensitivity, n (%)	5 (62.5)	2 (40)	0.59
Concomitant food allergy, n (%)	7 (87.5)	5 (100)	>0.9
History of anaphylaxis with peanut, n (%)	1 (12.5)	2 (40)	0.51
Age at onset symptoms (months) Median (IQR)	12 (6-80)	36 (11.5-72)	0.37
Peanut-specific IgE level at admission (kU/L) Median (IQR)	0.35 (0.1-5.7)	0.35 (0.3-0.9)	0.29
SPT test diameter performed with commercial peanut antigen at admission (mm) Median (IQR)	3 (0-4)	5 (1.5-11)	0.20

beans in 5 (13.5%), lupines in 2 (5.4%), and kidney bean allergy in one patient.

Symptoms may start in the early stages of life because legumes may enter the diet early in life. In our study, the median age of onset of symptoms according to species of legumes were as follows; 36 months (9-67 months, IQR) for peanuts, 12 months (6-36 months) for lentil, 12 months (8-71 months) for chickpea, 12 months (10-48 months) for peas, 42 months (10-102 months) for beans, 10 months and 48 months in two patients for lupine, and 10 months for kidney bean. The age of symptom onset also varies from country to country. A study conducted in Spain revealed legume allergy onset age as 22 (range, 4-192) months, lentil allergy onset as 15 months, and chickpea allergy onset age as 18 months (3). A Turkish study on lentil allergy revealed the symptom onset age was 16 months (14). Another study from Turkey revealed the symptom onset age for peanut allergy as 43 months, lentil allergy as 18 months, chickpea allergy as 22 months, pea allergy as 20 months, and bean allergy as 21 months (10).

Legume allergy cross-reactions are not uncommon; 24 (64.9%) of our patients displayed allergy to one legume, and 13 (35.1%) displayed sensitivity to more than one legume. Six (16.2%) patients showed allergic reactions to 2 different legume species, 3 (8.1%) had allergic reactions to 3 different legume species, 2 (5.4%) displayed allergy to 4 different legume species, one patient to 5 different legume species, and another patient to 6 different legume species. Similarly, in a study performed in 2008 by Martinez et al. with 44 patients, it was revealed through provocation tests that there was sensitivity to more than one legume in 72.2% of patients (11). Another study performed on 54 patients in Spain found that 78% of patients were allergic to more than one legume (3). Various studies have shown that the presence of a second legume allergy often in the event of lentil allergy with lentil-chickpea-pea allergy coexistence the leading group and lentil-chickpea-pea allergy coexistence with peanut allergy less frequent (11,18). In our study, 10 (76.9%) of the 13 patients with multiple legume allergies had allergy to lentil and chickpea, 6 (46.1%) had allergy to lentils and peas, and 4 (30.7%) had lentil and peanut allergy coexistence. All 6 (100%) individuals with pea allergy also had lentil allergy. This can be explained by the recently discovered fact that the amino acid sequences of the major antigens for lentil and peas, the Len c1 and Pis s antigens, show a similarity of up to 90% (11). There is a need to explain such similarities on a molecular basis.

In our study, 32 (86.5%) of the 37 patients who we evaluated for legume allergies had a coexisting allergy to non-legume food. Seventeen (45.9%) patients were allergic to eggs, 16 (43.2%) were allergic to nuts (hazelnut, almond, pistachio, walnut, cashew nut), and 8 (12.6%) were allergic to cow's milk. In a similar study, 91% of 87 patients had an allergy to another food: eggs 67%, cow's milk 49%, and nuts 71% (10).

Our study revealed that 8 of the 18 patients who were allergic to one legume developed tolerance. Only 1 of the 9 patients who were allergic to more than one legume developed tolerance to all allergic legumes. This patient had peanut and chickpea allergy.

There is limited knowledge about the natural course of legume allergy in the literature. In 2001, 223 patients allergic to peanut were evaluated in the USA. Their ages were 4-20 months and 63% were male. Twenty percent of the patients had developed tolerance to peanut allergy (12). In two different studies, the tolerance rate was approximately 20% (13,19). The paper by Yavuz et al. revealed 50% tolerance in 30 patients whom they followed for lentil allergy; the median age was 3.5 years (14). Another paper by Soyak et al. revealed 22% tolerance in 49 patients with lentil allergy. Our study results displayed symptom improvement in 3 (25%) patients; one was 39 months and the other two were 48 months of age.

In conclusion, the prevalence of lentil allergy in our study was higher than in studies reported in other countries, whereas the prevalence of peanut allergy was relatively lower. We attribute this to the different traditional dietary habits in Turkey. The tolerance rate of legumes in our study was somewhat comparable to rates reported in other studies. However, there is limited data about the tolerance rates of legumes in the literature. Further studies including more patients are needed to better define the tolerance rate of legumes in children.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Authorship Contributions

Concept: **Zeliha Yanginlar Brohi, Hakan Guvenir,** Design: **Zeliha Yanginlar Brohi, Hakan Guvenir,** Data collection or processing: **Ilknur Kulhas Celik, Muge Toyran,** Analysis or Interpretation: **Zeliha Yanginlar Brohi, Ersoy Civelek, Tayfur Ginis, Betül Buyuktiryaki, Can Naci Kocabas, Emine Dibek Misirlioglu,** Literature search: **Zeliha Yanginlar Brohi, Hakan Guvenir, Ilknur Kulhas Celik,** Writing: **Zeliha Yanginlar Brohi, Hakan Guvenir,** Approval: **Zeliha Yanginlar Brohi, Hakan Guvenir, Ilknur Kulhas Celik, Muge Toyran, Ersoy Civelek, Tayfur Ginis, Betül Buyuktiryaki, Can Naci Kocabas, Emine Dibek Misirlioglu.**

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