

IgE mediated legume allergy in east Mediterranean children: A reflection of multiple food allergies

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Abstract

Background: Legumes are nutritionally valuable as an inexpensive protein source, but may cause severe allergic reactions. This study aimed to identify the characteristics of legume allergies (LAs) in Turkish children.

Methods: A total of 87 children (4.9 (3.1–7.0) years) with LAs confirmed by either oral food challenge (OFC) or consistent history were reviewed.

Results: The median age of onset was 19 (12–38) months. The most frequent LA was lentil ($n = 57$, 66%), followed by peanut ($n = 53$, 61%), chickpea ($n = 24$, 28%), pea ($n = 21$, 24%), bean ($n = 7$, 8%), and soybean ($n = 1$, 1%). From these, it was observed that 60% had multilegume (≥ 2) allergies and the age of onset occurred earlier compared with the single LA subgroup (18 (11–30) vs. 28 (17–42) months, $p = .042$). Single LA was present in peanut (51%) and lentil (16%) allergies, but not chickpea, pea, and bean. Fifteen patients had tolerated lentils before their first allergic reaction. The majority of children with LA (91.9%) were allergic to multiple foods including tree nuts (71%), hen's egg (66%), and cow's milk (49%). Seventy-eight patients (89.7%) also presented with atopic comorbidities concerning atopic dermatitis (70%), asthma (40%), and allergic rhinitis (30%). Patients with anaphylactic type of reaction (20%) had higher frequency of aeroallergen sensitization ($p = .001$). Lip dose challenge with legume paste predicted the result of OFC with a diagnostic accuracy of 81.82% and a positive likelihood ratio of 10.8.

Conclusion: In Turkey, LA is a reflection of multiple food allergies and the presence of allergy to a least frequently encountered legume is a sign of multiple LA.

KEYWORDS

bean, chickpea, legume allergy, lentil, Mediterranean region, pea, peanut

1 | INTRODUCTION

Legumes belonging to the Fabaceae (or Leguminosae) family are an inexpensive and important protein source for a considerable portion of the world. Commonly consumed legumes include beans, soybeans, peas, chickpeas, peanuts, lentils, and lupines.

Legumes were reported to cause IgE-mediated allergies. However, legume allergy (LA) is not yet fully characterized due to the paucity of literature with small samples of studies with suspected, self-reported, and probable food allergies. The spectrum of LA differs between regions; peanut and soybean are the legumes most commonly implicated in food allergies, particularly in

Western countries, the United States, and Japan,^{1,2} lentils in the Mediterranean region, and chickpeas in India.³ Understanding LA is possible by documenting its phenotypes in varying populations, especially in those with different traits. In this study, we aimed to document the LA phenotypes in Turkish children.

2 | METHODS

2.1 | Study population

This was a retrospective study of children followed for LA between January 1, 2015, September 30, 2021, at the Pediatric Allergy Division of Hacettepe University Ihsan Dogramacı Children's Hospital in Ankara, which is a referral center for the entire country.

Patients registered to our clinic with the ICD code of "T78.1 Adverse food reactions" were reviewed to identify patients with LA. The diagnosis of LA was based on at least one of the presence of a positive skin prick test (SPT ≥ 3 mm than negative control) and/or positive specific IgE (sIgE ≥ 0.35 kU/L) along with either a positive oral food challenge (OFC) or a consistent and clear-cut history of food-related IgE-mediated symptoms after the ingestion of a culprit legume. There were 120 children diagnosed with LA. Among these, only 87 patients with full/complete data for legume allergy were allocated for the current study. The remaining 33 patients with consistent sensitivity (SPT > 8 mm and/or sIgE > 15 kU/L) were not included to avoid the potential for selection bias. Of the remaining 33 patients, 28 had high sensitivity for one legume, 2 for two, 2 for three, and 1 for four (Table S1). Food allergies other than legumes were based on either a positive OFC or a consistent and clear-cut history or high degree sensitization (SPT or sIgE levels of the culprit food suggesting clinical reactivity with $> 95\%$ positive predictive value (PPV)).

Data including age, gender, initial and subsequent reactions upon exposure to legumes, the presence of atopic comorbidities, other food allergies, family history of atopy, aeroallergen sensitization, absolute eosinophil count, total serum immunoglobulin E (IgE), SPT, sIgE, lip dose challenge (LDC) and OFC results were collected from the electronic database of the clinic. Diagnosis of asthma, allergic rhinitis, and atopic dermatitis was done according to international guidelines.⁴⁻⁶ Eosinophilia was defined as a peripheral blood eosinophil count $\geq 500/\text{mCL}$.⁷

2.2 | Study measurements

Skin prick test was considered positive if the mean wheal diameter was at least 3 mm or larger than the diameter of the negative control as detailed previously.⁸ Histamine, 10 mg/ml, and isotonic sodium chloride solution were used as positive and negative controls, respectively.

Specific IgE for legumes and total IgE were measured by the Immuno-CAP method in the sera of the patients (Thermo Fisher AB).

Key Message

Legume allergy is more likely among children with multiple food group allergies, and a majority of the patients are allergic to more than one legume. In the Eastern Mediterranean region, in contrast to Western countries and the United States, lentil allergy is much more frequent than peanut allergy, and lupine and soybean allergies are scarce. One in three of the lentil-allergic patients have a history of lentil tolerance before an allergic reaction with lentils occurred. Although chickpea, pea, and bean allergies are the less frequently encountered legume allergies, the most frequent legume co-allergy is observed in these children. Lip dose challenge with paste form appears as a promising tool in predicting an oral food challenge outcome.

2.3 | Oral food challenge

2.3.1 | Lip dose challenge

Lip dose challenge was performed as an integral part and the first step of the OFC. The positive outcome of LDC did not abstain us from performing the OFC but enabled us to be more cautious; the interval between the steps was set to 30 min. Dry chickpeas and beans soaked overnight. Legumes (except peanut) were boiled in 200 ml water (100°C) for 20 min, then pulsed until the mixture was ground. Two spoons of olive oil were added to increase skin penetration. For peanuts, paste forms were used. LDC was performed as detailed previously.⁹

2.3.2 | Oral food challenge procedures

Open OFCs were performed for diagnostic purposes or evaluation of tolerance acquisition with cooked lentils, chickpeas, peas, beans, soybeans, and regular forms of peanuts. Children were fed incremental doses of the allergen until the standard dietary dose was reached (approximately 2 gr peanut protein, 4 gr pea and chickpea proteins, and 8 gr lentil and bean protein for patients younger than 4 years, and approximately 4 gr peanut protein, 8 gr pea and chickpea protein, and 16 gr lentil and bean protein for those older than 4 years).¹⁰ Patients were monitored for 2 h after ingestion of the final dose. A positive challenge was defined as IgE-mediated objective hypersensitivity symptoms.¹¹

2.4 | Statistical analysis

The data including ages, eosinophil counts, total IgE, SPT, and sIgE values were given as median and interquartile range due to non-normal distribution. The chi-squared and Mann-Whitney U tests were used

to compare nonparametric values. The statistical tests were two-sided, and a p -value $\leq .05$ was regarded as statistically significant. Statistical analyses also included univariate and multivariate analyses. ORs with relevant 95% CIs were calculated for evaluating the potential associations between various predictors (including current age, presence of asthma, allergic rhinitis, atopic dermatitis, sIgE, and SPT values) and anaphylactic reactions in lentil and peanut allergy.

3 | RESULTS

There were 120 children diagnosed with LA. Among these children, 87 patients with either OFC-proven or consistent history were reviewed and they were defined as clinically reactive to legumes. Male gender ($n = 68$, 78%) was predominant within the study population (Table 1), and the median onset ages of the LA symptoms and last evaluation were 19 (12–38) months and 4.9 (3.1–7) years, respectively. The median follow-up time was 35 months (12–59). A total of 78 patients (90%) had a history of atopic comorbidity; 70% had atopic dermatitis, 40% asthma, and 30% allergic rhinitis. Furthermore, the majority of children (92%) were allergic to multiple food groups (≥ 2) including tree nuts ($n = 62$, 71%), hen's egg ($n = 58$, 67%), cow's milk ($n = 43$, 49%), and seeds ($n = 37$, 46%) (Figure 1).

The most frequently diagnosed LA was lentil ($n = 57$, 66%), followed by peanut (53, 61%), chickpea ($n = 24$, 28%), pea ($n = 21$, 24%), bean ($n = 7$, 8%), and soybean ($n = 1$, 1%). More than half of the patients ($n = 52$, 60%) had multiple (≥ 2) LA, and the age of onset of LA symptoms occurred significantly earlier than in the single LA subgroup (18 months (11–30) vs. 28 months (17–42), $p = .042$) (Table 1).

A total of 163 allergic reactions were reported in the study population (Table 2), and urticaria ($n = 58$) was the most frequent reaction, followed by anaphylaxis ($n = 38$), exacerbation of eczema ($n = 26$), and angioedema ($n = 18$). The highest frequencies of anaphylaxis were observed with lentils ($n = 13$, 34%) and peanuts ($n = 12$, 32%). Patients with an anaphylactic reaction to legumes were older (83 (52–119) vs. 51 (32–80) months, $p = .005$) and had a higher frequency of aeroallergen sensitization (54% vs. 21%, $p = .001$) than patients without anaphylaxis (Table 1).

3.1 | Lentils

Fifty-seven patients were reactive to lentils; 47 had consistent history, and 10 were OFC-proven. The median onset age of the symptoms was 18 (12–32) months (Table 2). Forty-eight of the 57 (84%) patients had multiple LA. Although asthma was significantly higher in the anaphylactic group (54% vs. 23%, $p = .023$) (Table S2), at univariate and multivariate logistic regression analyses, only older age (OR: 1.030, 95% CI: 1.005–1.055, $p = .017$) was likely to be associated with the history of anaphylaxis (Table S3).

Interestingly, 15 of 40 (38%) patients had a history of tolerance to lentils before the first allergic reaction with lentils (17 patients with missing information). The median onset age (IQR) of lentil allergy

symptoms was later (30 (23–43)) vs. 17 months (10–24), $p = .001$, and a family history of atopy was more frequent in this group when compared to the children who had allergic reaction at first consumption of lentils ($p = .043$) (Table S4).

When the co-allergies to other legumes were considered, 41% of lentil-allergic children were co-allergic to chickpeas and peanuts, followed by peas (36%) (Table 3). Of the patients, 33 (58%) had also a tree nut allergy (Table S5).

During the follow-up, tolerance developed in 11 of 49 patients (22%) (8 patients with missing information). The median values of SPT at the time of diagnosis were significantly lower in the lentil-tolerant than in the non-tolerant patients (5.0 mm (4.0–7.0) vs. 9mm (4.5–12.7), $p = .037$) (Table S6).

3.2 | Peanuts

Fifty-three patients were allergic to peanuts: 51 with consistent history and 2 with OFC test positivity. The median onset age of the symptoms was 43 (14–76) months (Table 2).

Of these patients, twenty-six (49%) had multiple LA. Twelve patients (23%) experienced an anaphylactic reaction to peanuts, and these patients were at older ages ($p = .026$) and had a higher rate of allergic rhinitis ($p = .027$) (Table S7). On multivariate logistic regression analysis, higher peanut sIgE was found to be an independent risk factor for the history of peanut anaphylaxis (OR: 1.032, 95% CI: 1.002–1.063, $p = .040$) (Table S8).

When the co-allergies to other legumes were considered, the highest frequencies were observed with lentils ($n = 23$, 43%) and chickpeas ($n = 15$, 28%) (Table 3). Interestingly, forty-six patients (87%) had co-allergies to tree nuts (Table S5).

During the follow-up, 5 of 51 (10%) patients (2 patients with missing information) tolerated peanuts and initial SPTs of these patients were significantly lower than non-tolerants (4.0 mm (1.0–4.5) vs. 12.0 mm (6.0–16.0), $p = .003$) (Table S9).

3.3 | Chickpeas

Twenty-four patients (28%) were allergic to chickpeas, 21 with consistent history and 3 with OFC test positivity. The median onset age of symptoms was 22 (14–42) months (Table 2), and all had multiple LA. The majority were co-allergic to lentils ($n = 23$, 96%), followed by peas ($n = 15$, 63%) and peanuts ($n = 15$, 63%) (Table 2). Furthermore, 14 (58%) were co-allergic to tree nuts (Table S5). During follow-up, tolerance occurred in only one of 21 (5%) patients (3 patients with missing information).

3.4 | Peas

Twenty-one patients were allergic to peas, 16 with consistent history and 5 with OFC positivity. The median onset age of the symptoms

TABLE 1 Demographic features and laboratory test results of the study population and subgroups

	Study population n = 87	Single legume allergy subgroup n = 35 (40%)	Multiple legume allergy subgroup n = 52 (60%)	p	Legume anaphylaxis subgroup n = 24 (28%)	Legume non-anaphylaxis subgroup n = 63 (72%)	p
Male gender, no. (%)	68 (78)	25 (71)	43 (83)	.212	20 (83)	48 (76)	.471
Current age, mo ^a	59 (37–84)	66 (39–90)	59 (37–83)	.482	83 (52–119)	51 (32–80)	.005
Onset age of legume symptoms, mo ^a	19 (12–38)	28 (17–42)	18 (11–30)	.042	16 (11–42)	20 (13–38)	.510
Age at the diagnosis of food allergy, mo ^a	8 (5–18)	9 (6–18)	7 (5–24)	.508	20 (6–27)	8 (5–17)	.178
Atopy in the family, no. (%)	41 (47)	17 (49)	24 (46)	.651	10 (42%)	31 (49%)	.800
Eosinophilia ^b	51 (59)	16 (46)	35 (68)	.036	15 (63%)	36 (57%)	.312
Total IgE, kU/L ^a	518 (265–1452)	495 (205–1045)	584 (334–1599)	.118	377 (259–1552)	618 (304–1433)	.576
Initial symptoms after legume exposure, no. (%)							
Eczema ^c	11 (13)	6 (17)	5 (10)		0 (0)	11 (17)	
Urticaria ^d	38 (44)	14 (40)	24 (46)		6 (25)	32 (51)	
Anaphylaxis	17 (20)	7 (20)	10 (19)		17 (71)	0 (0)	
Angioedema	9 (10)	3 (9)	6 (12)		2 (8)	7 (11)	
Others (nausea, vomiting, cough)	12 (14)	4 (11)	8 (15)		3 (13)	9 (14)	
Coexisting atopic diseases, no. (%)	78 (90)	32 (91)	46 (88)	.697	21 (88)	57 (90)	.614
Atopic dermatitis	61 (70)	24 (69)	37 (71)	.796	11 (46)	50 (79)	.002
Asthma	35 (40)	17 (49)	18 (35)	.218	12 (50)	23 (37)	.191
Allergic rhinitis	26 (30)	13 (37)	13 (25)	.248	13 (54)	13 (21)	.001
Aeroallergen sensitization, no. (%)	26 (30)	13 (37)	13 (25)	.248	13 (54)	13 (21)	.001
Pollen/grass	12 (14)	4 (11)	8 (15)		7 (29)	5 (8)	
Dust mite	6 (7)	2 (6)	4 (8)		2 (8)	4 (6)	
Mold	2 (2)	2 (6)	0 (0)		2 (8)	0 (0)	
Pet dander	8 (9)	4 (11)	4 (8)		3 (13)	5 (8)	
Accompanying other food allergies, no. (%)	79 (91)	33	46	.236			
Cow's milk	43 (49)	14 (40)	29 (56)		10 (42)	33 (52)	.489

TABLE 1 (Continued)

	Study population n = 87	Single legume allergy subgroup n = 35 (40%)	Multiple legume allergy subgroup n = 52 (60%)	p	Legume anaphylaxis subgroup n = 24 (28%)	Legume non-anaphylaxis subgroup n = 63 (72%)	p
Hen's egg	58 (67)	20 (57)	38 (73)		13 (54)	45 (71)	.242
Grain	12 (14)	2 (6)	10 (19)		3 (13)	9 (14)	.392
Tree nuts	62 (71)	29 (83)	33 (63)		17 (71)	45 (71)	.571
Hazelnut	51 (59)	26 (74)	25 (48)		15 (63)	36 (57)	
Cashew	40 (46)	19 (54)	21 (40)		11 (46)	29 (46)	
Pistachios	34 (39)	13 (37)	21 (40)		9 (38)	25 (40)	
Walnut	31 (36)	16 (48)	15 (29)		0 (0)	6 (15)	25 (40)
Almond	3 (3)	3 (9)	0 (0)		9 (38)	3 (5)	
Seeds	37 (43)	15 (43)	22 (42)		8 (33)	28 (44)	.989
Sesame seeds	31 (36)	10 (29)	21 (40)		2 (8)	23 (37)	
Pumpkin seeds	12	7 (20)	5 (10)		0 (0)	10 (16)	
Sunflower seeds	9 (10)	4 (11)	5 (10)		2 (8)	6 (14)	
Poppy seeds	5 (6)	2 (6)	3 (6)		2 (8)	3 (5)	
Fruit	4 (5)	3 (9)	1 (2)		1 (4)	3 (5)	
Fish	4 (5)	1 (3)	3 (6)		1 (4)	3 (5)	

^aMedian (IQR).^bBlood eosinophil count >500/mcL.^cAny flare-up after exposure in addition to the immediate reaction.^dOther than contact urticaria.Bold values denote statistical significance at the $p \leq .05$ level.

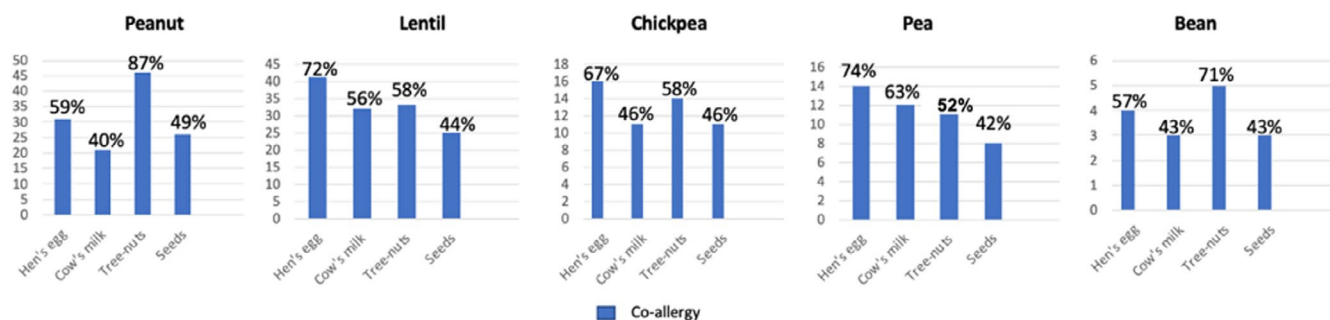


FIGURE 1 Co-allergy rates of legumes

TABLE 2 Legume allergy by type and according to the most severe reaction experienced

	Peanut n = 53	Lentil n = 57	Chickpea n = 24	Pea n = 21	Bean n = 7
Onset age of the symptoms, mo ^a	43 (14–76)	18 (12–32)	22 (14–42)	20 (14–38)	21 (2–83)
Single legume allergy, no. (%)	27 (51)	9 (16)	0 (0)	0 (0)	0 (0)
Allergic reactions (n = 163)					
Anaphylaxis, no. (%) (n = 38)	12 (23)	13 (23)	6 (25)	6 (29)	1 (14)
Urticaria, no. (%) (n = 58)	16 (30)	24 (42)	8 (33)	7 (33)	3 (43)
Angioedema, no. (%) (n = 18)	3 (6)	7 (12)	5 (21)	2 (10)	1 (14)
Eczema, no. (%) (n = 26)	11 (21)	6 (10)	3 (13)	4 (19)	1 (14)
Other, no. (%) (n = 23)	11 (21)	7 (12)	2 (8)	2 (10)	1 (14)
SPT, mm ^a	9.0 (4.7–15.2)	6 (4.0–11.0)	5.0 (3.0–6.5)	5.5 (3.0–8.5)	2.5 (0–4.2)
sIgE, kU/L ^a	17.0 (4.3–49.2)	8.9 (3.3–40.4)	14.9 (6.0–61.8)	19.2 (4.4–90.0)	NA
Tolerance, no. (%) ^b	5/51 (10%)	11/49 (%22)	1/21 (5%)	1/15 (7%)	2/5 (40%)

^aMedian (IQR).^bTolerance status is unknown in 2 patients with peanut, 8 with lentil, 3 with chickpea, 6 with pea, and 2 with bean allergy.

	Lentil	Peanut	Chickpea	Pea	Bean	Soybean
Lentil (n = 57)	X	23 (41%)	23 (41%)	21 (36%)	7 (12%)	1 (2%)
Peanut (n = 53)	23 (43%)	X	15 (28%)	11 (20%)	5 (9%)	1 (2%)
Chickpea (n = 24)	23 (96%)	15 (63%)	X	15 (63%)	5 (20%)	1 (4%)
Pea (n = 21)	21 (100%)	11 (52%)	15 (71%)	X	6 (28%)	1 (5%)
Bean (n = 7)	7 (100%)	5 (71%)	5 (71%)	1 (14%)	X	0 (0%)
Soybean (n = 1)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	0 (0%)	X

Note: []:0%–40%; []:41%–60%; []:61%–75%; []:76%–85%; and []:86%–100%.

TABLE 3 Co-allergy rates among legumes

was 20 (14–38) months (Table 2), and all were also allergic to lentils (100%), followed by chickpeas (n = 15, 71%) and peanuts (n = 11, 52%) (Table 3). Co-allergy to tree nuts was reported in 11 patients (52%) (Table S5). During the follow-up, tolerance occurred in one of 15 (7%) patients (6 patients with missing information).

3.5 | Beans

Seven patients had a bean allergy, 6 with consistent clinical history and one with OFC positivity. All bean-allergic patients had multiple LA. Lentil allergy was observed in all patients (100%), followed by

peanut ($n = 5$, 71%) and chickpea ($n = 5$, 71%). Among legumes, the highest tolerance (40%) was observed in bean-allergic patients.

3.6 | Soybean

Only one patient was allergic to soybean with consistent clinical history.

3.7 | Lip dose challenge

Thirty-three patients underwent LDC before the OFC (Table S10). Of the 19 patients with negative LDC, 14 (74%) passed the OFC while 5 (26%) failed. Furthermore, of the 14 patients with positive LDC, only 1 passed (7%) the OFC, while 13 (93%) failed. LDC had a diagnostic accuracy of 81.82% with a 72.22% sensitivity, a 93.33% specificity, a 92.86% positive predictive value (PPV), a 73.68% negative predictive value (NPV), a positive likelihood ratio (+LR) of 10.8, and a negative likelihood ratio (-LR) of 0.3.

3.8 | Oral food challenge

During the follow-up period (35 months (12–59), 41 OFCs were performed: 20 patients passed, and 21 failed. Among legumes, positive OFC frequency was highest with peas ($n = 5$, 83%) and chickpeas ($n = 3$, 75%). The most frequently tolerated legumes were beans (40%) (Table 2). Anaphylaxis occurred in 4 patients during the OFC, 1 with peanuts, 1 with lentils, 1 with peas, and 1 with chickpeas. The patient who had anaphylaxis during the OFC with peas received three doses of epinephrine and was hospitalized for one day in the intensive care unit.

4 | DISCUSSION

This is the first study to describe clinical features, co-reactivity, and tolerance of LA in the Eastern Mediterranean region. Although it is not routine practice to include peanuts in studies examining LA, we preferred the evolutionary perspective to identify within-group co-allergies. In this study, most of the children were allergic to more than one legume and lentils were the most common LA. Although chickpea, pea, and bean allergies were the less frequently encountered legume allergies, the most frequent legume co-allergy was observed in these children. Multiple food group allergies were present in the majority, and almost one fourth reported anaphylaxis. Lip dose challenge with paste form appeared as a promising tool in predicting an OFC outcome.

There is accumulating evidence that the spectrum of IgE-mediated food allergies differs between populations.^{12,13} In Turkey, chickpeas take the first place in annual per capita consumption of legumes (5.8 kg),¹⁴ followed by lentils (5.6 kg), beans (3.3 kg), peas

(1.1 kg), and peanuts (<0.25 kg).^{15,16} Interestingly, peanuts were the second most common cause of LA, although its lower consumption suggests that it may also be the most allergenic legume. In the literature, the most common LAs are peanuts, lentils, and soybeans in Spain¹⁷; chickpeas and peanuts in Asian countries¹⁸; and peanuts and soybeans in the United States.¹⁶ In Finland, peas were reported as the second most frequent LA after peanuts.¹⁹ These indicate that besides exposure (culinary culture), the allergenicity of the foods plays a role in the development of food allergies.^{12,13}

In our patients with LA, both the onset of allergy mostly occurred very early (in the first two years of life) and almost all patients ($\geq 90\%$) had multiple food group allergies and atopic comorbidities. If we consider atopy in a spectrum from mild to severe, it has led our LA patients to think that they are close to the severe/strong end. Therefore, we suggested that the presence of LA reflects a highly atopic background. Moreover, more than one in three of the lentil-allergic patients had a history of lentil tolerance before an allergic reaction with lentils occurred, considering that early consumption of lentils may not always prevent the development of clinical allergies in infants with a strong atopic background.

Another interesting finding of the present study is that almost 60% of our cohort had multiple LA. For instance, nearly one in two lentil-allergic children had a peanut and chickpea allergy and one-third had a pea allergy. Almost all patients with a chickpea allergy and all patients with a pea allergy were also allergic to lentils. An extensive co-reactivity among lentils, chickpeas, and peas was previously reported in the Mediterranean area.^{20,21} This may be related to the highly atopic background and sensitization to common allergenic molecules/epitopes, such as Len c 1 from lentils, Pis s 1 from peas, and globulin fraction of chickpeas.²²

In our study, over 90% of children had multiple food group allergies and coexisting allergies were common with tree nuts, hen's egg, cow's milk and seeds, the most frequent causes of food allergies in Turkish children older than 2 years.¹² In a Spanish cohort with a similar age group, 31% of the patients had a single food group allergy and co-allergy with hen's egg (28%) was most frequent, followed by fish (24%) and tree nuts (20%).²⁰ In France, 76% of children with pea allergy had a co-allergy to other foods.²³ These findings suggest that LA is more likely among children with multiple food group allergies rather than a single allergy. Interestingly, among legumes, patients with peanut allergy had the highest rate of co-allergies (87%), which was consistent with our previous report.²⁴ In the literature, co-allergy to tree nuts was reported in 28%–50% of peanut-allergic patients.^{25–27} This shows that peanut allergy is a heterogeneous disease and variability between countries may be due to the differences in exposures, genetic backgrounds, and culinary cultures.

Another important finding of the present study was that the rate of having legume co-allergy was much higher in the case of having an allergy to a less frequently allergic legume. For instance, we had only a few cases of bean allergy despite the fact that beans are the third most consumed legume in Turkey (3.3 kg/year). Moreover, beans were tolerated by most of the patients with lentil and peanut

allergies. This suggests that being allergic to a less common legume allergen indicates a high allergic background, and the presence of bean allergy might be the sign of multiple LA. A similar finding has been reported for almond allergy. Almond allergy is the rarest form of tree nut allergy, but the presence of its allergy is a sign of a multiple tree nut allergy.²⁴ Notably, soy allergy alone is very rare also in peanut-allergic children. Also, bean together with soy seems to be of less importance. Furthermore, in legume-allergic children, beginning with beans as part of the supplementary diet instead of lentils, peanuts, or chickpeas may be a safer alternative.

In this study, among the allergic reactions to legumes, almost one in four was anaphylactic type, which occurred mostly with lentils and peanuts. In France, legumes (except peanuts) were the fourth most common reason for food anaphylaxis with a prevalence of 6.8% mostly with lupine and soybean.²⁸ Similar to our findings, a number of studies have reported severe allergic reactions with legumes, especially lentils, peas, and chickpeas.^{29,30}

Currently, OFC is the gold standard for diagnosis; however, this procedure carries inherent risks and is time/labor-consuming. Though LDC is usually the first step of OFC, its utility as a diagnostic test has also been questioned. In this retrospective study, the use of paste forms (LDC paste) of legumes in LDC revealed 81.82% diagnostic accuracy, 72.22% sensitivity, and 93.33% specificity. Vazquez-Ortiz et al.³¹ reported that LDC had a sensitivity of 32% and a specificity of 98%; however, they documented substantial differences between application and evaluation methods. Recently, our study group reported that LDC paste had 54.8% sensitivity and 96.4% specificity in tree nut allergy diagnosis. These figures suggest that when LDC paste is used in a standardized manner, it has the potential to identify patients at risk for more severe reactions, and can reduce the number of OFCs and be used as an integral part of the OFC.

The limitation of this study is that, first, the diagnosis of LA was not completely based on OFC results; however, most had more than one consistent history with a culprit legume, excluding the possibility of mislabeling. Second, this study was conducted in a tertiary referral center where patients were admitted without referral, so we cannot completely exclude the possibility of bias in patient selection. Third, the inclusion of the remaining 33 patients whose clinical reactivity status was not known may alter the results. The other limitations are the relatively small number of patients to make strong conclusions, the lack of data for LA outcome, and molecular allergology. The strength of our study includes the first study on the LA phenotypes from the Eastern Mediterranean region, documentation of atopic comorbidities, co-allergies, natural prognosis, and reporting the utility of LDC paste in children for the first time, and being a real-life practice.

5 | CONCLUSION

In summary, we have shown that LA is more likely among children with multiple food group allergies, and a majority of the patients

were allergic to more than one legume. In the Eastern Mediterranean region, in contrast to Western countries and the United States, lentil allergy is much more frequent than peanut allergy, and lupine and soybean allergies are scarce. In light of annual consumption amounts, we thought that LA development might be the result of the interaction between exposure and personal atopic background.

IRB STATEMENT

The study protocol was reviewed and approved by the Hacettepe University Institutional Review Board (2021/19-13).

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Elif Soyak Aytekin: Data curation (lead); Investigation (equal); Methodology (equal); Resources (lead); Writing – original draft (lead); Writing – review & editing (equal). **Hilal Unsal:** Data curation (equal); Resources (equal). **Umit M Sahiner:** Data curation (equal); Formal analysis (lead); Methodology (equal); Writing – review & editing (supporting). **Ozge Soyer:** Conceptualization (equal); Methodology (equal); Supervision (supporting); Writing – review & editing (supporting). **Bulent Enis Sekerel:** Conceptualization (lead); Methodology (supporting); Project administration (lead); Supervision (lead); Writing – review & editing (lead).

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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