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Assessment of food allergies in patients under two years of age with skin manifestations referred to pediatric immunology and allergy outpatient clinic

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ABSTRACT

Objectives: In the first two years of life, patients with cutaneous manifestations with suspicion of food allergy are frequently referred to clinicians in daily practice. The aim of this study was to investigate the frequency of food allergy (FA) in infants presenting with cutaneous manifestations.

Methods: Patients aged <2 years with suspected food allergy and cutaneous manifestations who were admitted to the pediatric immunology and allergy outpatient clinic at Sincan Training and Research Hospital were included. Demographic, clinical and laboratory features of patients were recorded. The severity of atopic dermatitis (AD) was classified using the SCORing AD index.

Results: The study included 217 children with a median age of 9.7 months (IQR 5.8-13.6) (55.8% males). AD (77.9%) was the most common skin manifestation in all patients. Other cutaneous manifestations were urticaria/angioedema (12.4%) and flushing (9.7%). 23 (13.6%) patients were classified as moderate-severe AD and 146 (86.4%) patients as mild AD. The age at diagnosis is lower in the moderate-severe AD group [9 months (IQR 4-15)] compared to the mild AD group [14 months (IQR 9-18)] (P=0.011). In all AD patients, food allergy was detected in 54 (32%) patients. The percentage of food allergy was higher in the moderate-severe AD group (82.6%) than in the mild AD group (24%) (P=<0.001). Multiple FA was shown in 13 (7.7%) patients and the percentage of Multiple FA was higher in the moderate-severe AD group (21.7%) than in the mild AD group (5.5%) (P=0.018). When the most common food allergies were compared, hen's egg and cow's milk allergy were found to be higher in the moderate-severe AD group [(56.5%) vs. (47.8%)] than in the mild AD group [(18.5%) vs. (9%)] (P=<0.001 and P<0.001, respectively). Forty oral food challenges (OFC) tests were performed on patients who were found to have food sensitivity and all passed. In 58 (26.7%) patients, food allergy was identified and food elimination was started. In 54 (24.8%) patients with AD culprit food was eliminated from the diet. No food allergy was found in any patient presenting with flushing. Cow's milk allergy was found in two patients and hen's egg allergy in two patients who presented with urticaria.

Conclusions: We identified food allergy in only one out of every four patients presenting with suspected food allergy and cutaneous manifestations. Correct evaluation of hypersensitivity reactions to foods is important to avoid unnecessary food elimination from infants' diet.

Keywords: Skin manifestations, atopic dermatitis, childhood, food allergy

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The skin is one of the most common targeted organs in food hypersensitivity reactions. Clinical manifestations are classified into IgE-mediated reactions (flushing, urticaria, angioedema), cell-mediated reactions (dermatitis herpetiformis and contact dermatitis) and mixed IgE-mediated and cell-mediated reactions (atopic dermatitis [AD]) [1, 2]. AD is the most common inflammatory cutaneous disease characterized by pruritic, repetitive lesions [3]. Immunological, genetic, and environmental factors play an important role in the pathophysiology of AD, which is thought to cause skin barrier disorder and chronic inflammation in the skin [4]. The effect of food allergy on the pathogenesis and severity of this condition is controversial. In AD, the allergic sensitization process called atopic march is thought to occur in the form of food allergy in early childhood [5, 6]. Food allergens can cause urticarial lesions, pruritus, and eczematous exacerbations, especially in susceptible infants [7]. Particularly, patients with severe atopic dermatitis in the early ages should be evaluated for food allergy. It is necessary to perform a skin test and/or determine the serum level of specific IgE antibodies to confirm food allergen sensitization [8]. The compatibility of the history and laboratory findings with the allergy clinic in the patient should be questioned. The diagnosis should be confirmed by oral food challenges (OFC) tests [2, 9]. In the first 2 years of life, parents perceive a higher rate of food hypersensitivity than objectively assessed food hypersensitivity [10]. Therefore, in case of suspicion of food allergy, the patient should be examined in detail and allergy tests should be performed to avoid unnecessary food elimination. In this study, we aimed to investigate the frequency of food allergy in infants presenting with skin manifestations and suspected food allergy.

METHODS

Study Population

The study included children aged <2 years with suspected food allergies who were admitted to the pediatric immunology and allergy outpatient clinic at Sincan Training and Research Hospital between December 2023 and September 2024. In this retrospective study, there were 317 patients with suspected food allergies, and patients with gastrointestinal symptoms and other food allergy symptoms were excluded. A total of 217 patients with cutaneous manifestations were analyzed. Cutaneous manifestations were categorized as urticaria/angioedema, flushing, and atopic dermatitis [11]. From the patients' medical records, we collected information regarding gender, age, presenting symptoms, absolute eosinophils count, skin prick test (SPT), sIgE, total serum IgE, and OFC results.

Multiple food allergy (≥2 allergens) was specified as more than one type of food group. The diagnosis of AD was defined according to international guidelines and the diagnostic criteria of Hanifin and Rajka. SCORing AD (SCORAD) index was used to assess the severity of AD. Patients with a SCORAD index <25 were categorized as mild AD; patients with a SCORAD index between 25-50 were categorized as moderate AD; and patients with a SCORAD index >50 were categorized as severe AD [3, 12]. In this study, patients were categorized into two groups as "mild" and "moderate-severe" according to the severity of AD.

Study Procedures and Measurements

In the routine practice of the pediatric immunology and allergy outpatient clinic, SPT was performed with common food allergens (cow's milk, egg white, egg yolk, wheat, walnut, hazelnut, peanut, sesame, lentil) in case of suspected food allergy. SPT with food allergen extracts [Lofarma®, (Italy)] was applied on the volar surface of the forearm or back along with negative and positive controls and measured after 15 minutes. Positive results were defined as a mean wheal diameter 3 mm greater than the negative control. The Immuno-CAP method (Thermo Fisher Scientific, Uppsala, Sweden) was used to measure allergen-specific IgE levels in serum, and specific IgE (≥0.35kU/L) was considered positive.

OFCs were made based on the physician's clinical judgment in conjunction with detailed clinical history and results of allergy tests. OFCs were performed according to national guidelines that were consistent by administering step by step of food protein at intervals of 15 to 30 minutes based on the quantity of protein contained in the food [13]. In the case of positive SPT and/or sIgE, the diagnosis of food allergy was based

on either a positive OFC or a clear and clear-cut history of IgE-mediated symptoms after exposure with food or in the presence of a positive SPT and/or sIgE suggesting clinical reactivity with >95% positive predictive value (PPV) for each food allergen [Cow's milk: SPT ≥8 mm than the negative control and/or sIgE ≥ 15kU/L and for Egg white: SPT ≥7 mm than the negative control and/or sIgE ≥ 7kU/L] [14, 15].

This study was made in accordance with the declaration of Helsinki principles. Ethics committee approval was obtained from Ankara Ataturk Sanatorium Training and Research Hospital Ethics Committee for this retrospective study (Decision number: 2024/189)

Statistical Analysis

IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Descriptive analysis was used to characterize the patients. Pearson's Chi-square ($\chi 2$) test or Fisher's exact test was used for between-group comparisons. Levels are shown as the median and interquartile range for data not normally distributed. The Mann-Whitney U test or Kruskal-Wallis test was used to compare values. All statistical tests were two-sided, and the value of statistical significance was set at $P<0.05$.

RESULTS

Study Population

The study included 217 patients presenting with cutaneous manifestations among 317 children with a prediagnosis of food allergy (Fig. 1). All patients were <2 years of age with a median age of 9.7 months (IQR 5.8-13.6) (55.8% males) (Table 1). AD (77.9%) was the most common skin manifestation in all patients. Other cutaneous manifestations were urticaria/angioedema (12.4%) and flushing (9.7%).

Evaluation of Allergy Tests

SPT with food allergens was performed in 209 (96.3%) patients and 76 (35%) patients had positive SPT. The most prevalent allergen sensitivities included egg white (15.2%), egg yolk (9.7%), cow's milk (12.4%), sesame (4.1%), peanut (3.7%), and wheat (4.1%). Allergen sIgE was performed in 76 (35%) patients and 87 (40%) positive allergen sIgE were detected. Of these, 39 (18%) were egg white sIgE positive and 29 (13.4%) were cow's milk sIgE positive. The median value egg white sIgE level was [1.87 kU/L (Min-Max 0.41-95)] and cow's milk sIgE [1.95 kU/L (Min-Max (0.54-24)] (Table 1).

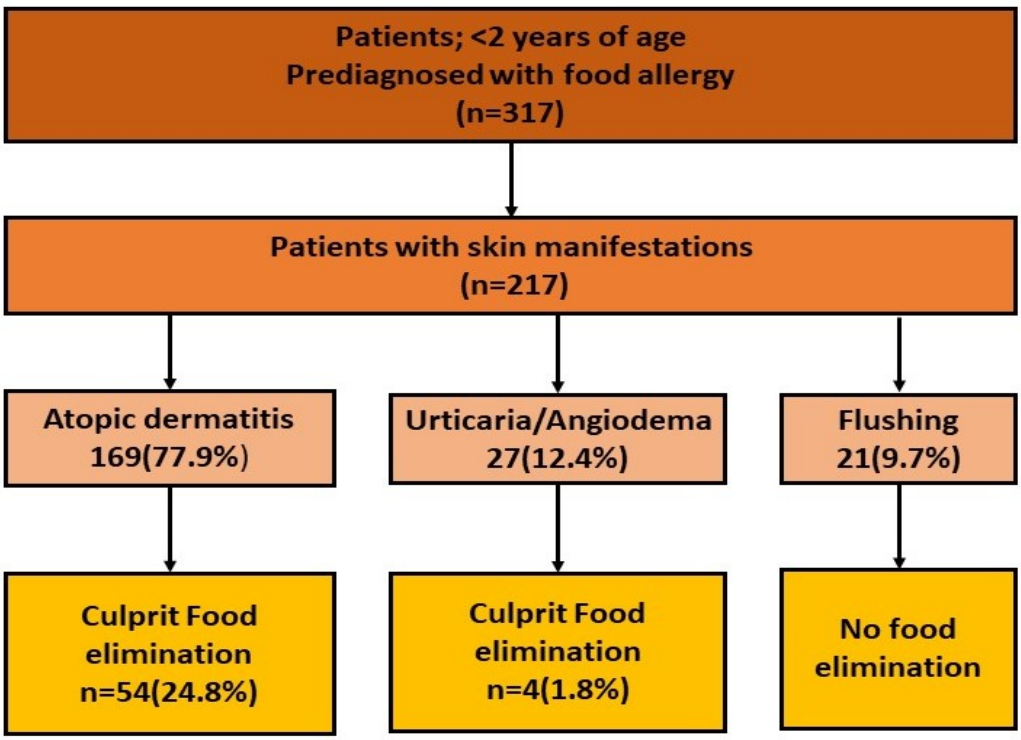

Fig. 1. Flow chart of analyzed patients according to skin manifestations.

Table 1. The characteristics of the study group (n=217)

	Data
Age (month)	9.7 (5.8-13.6)
Gender-male, n (%)	121 (55.8)
Presenting symptoms, n (%)	
Eczema	169 (77.9)
Urticaria / Angioedema	27 (12.4)
Flushing	21 (9.7)
Food sensitivity with SPT, n (%)	
Egg white	33 (15.2)
Egg yolk	21 (9.7)
Cow's milk	27 (12.4)
Wheat	9 (4.1)
Sesame	9 (4.1)
Peanut	8 (3.7)
Walnut	8 (3.7)
Hazelnut	5 (2.3)
Lentil	3 (1.4)
Laboratory values	
Eosinophil (cells/µL)	330 (200-540)
Total IgE (kU/L)	19 (5.7-80)
Egg white sIgE (kU/L)	1.87 (0.41-95)
Egg yolk sIgE (kU/L)	2.1 (1.02-41)
Cows' milk sIgE (kU/L)	1.95 (0.54-24)

Data are shown as median (IQR=interquartile range) (Mininum-Maximum) or n (%). SPT=Skin Prick Test

Patients with Atopic Dermatitis

One hundred sixty-nine (77.9%) patients had current atopic dermatitis with a median age of 9.4 months (IQR 5.3-14). Twenty-three (13.6%) patients were classified as moderate-severe AD and 146 (86.4%) patients as mild AD. The age at diagnosis is lower in the moderate-severe AD group [9 months (IQR 4-15)] compared to the mild AD group [14 months (IQR 9-18)] (P=0.011). In all AD patients, food allergy was detected in 54 (32%) patients. The percentage of food allergy was higher in the moderate-severe AD group (82.6%) than in the mild AD group (24%) (P<0.001). Multiple FA was shown in 13 (7.7%) patients and the percentage of multiple FA was higher in the moderate-severe AD group (21.7%) than in the mild AD group (5.5%) (P=0.018). When the most common food allergies were compared, hen's egg and cow's milk allergy were detected to be higher in the moderate-severe AD group [(56.5%) vs. (47.8%)] than in the mild AD group [(18.5%) vs. (9%)] (P<0.001 and P<0.001, respectively). There was no difference between moderate-severe AD and mild AD subgroups in terms of gender and total IgE levels (Table 2).

Patients with Food Allergy

Forty oral food challenges were performed on patients with food sensitivity and all of them passed. OFC was performed with hen's egg (47.5%), tree nuts (22.5%), and cow's milk (15%), respectively. OFC was not made in 58 (26.7%) patients with both SPT results and/or allergen-specific IgE values much above the cut-off values and have a consistent and clear-cut history of IgE-mediated symptoms within 2 hours after the exposure to food. As a result, in 58 (26.7%) patients, food allergy was identified and the culprit food was eliminated. Among these patients, 54/58 (93%) were diagnosed with AD. No food allergy was found in any patient presenting with flushing. Cow's milk allergy was found in two patients and hen's egg allergy was found in two patients who presented with urticaria. Hen's egg allergy was diagnosed in 31 (53.4%) patients and cow's milk allergy was diagnosed in 15 (25.8%) patients. Both hen's egg and cow's milk allergy were detected in 11 (19%) patients. Walnut allergy was found in three patients, peanut allergy in three patients, wheat allergy in two patients, and sesame allergy in three patients (Fig. 2). These foods were eliminated from the diet of these patients.

DISCUSSION

Food allergy is an increasing health problem, especially in infants and young children. In this study, infants with cutaneous manifestations and suspected food allergies were evaluated. Food allergy was identified in a quarter of the patients and culprit foods were eliminated from the diet. The most common cutaneous manifestation was AD and hen's egg was the most culprit food.

The clinical spectrum of food allergy is broad, skin manifestations are the most common clinical symptom among them. Urticaria, angioedema, and flushing are

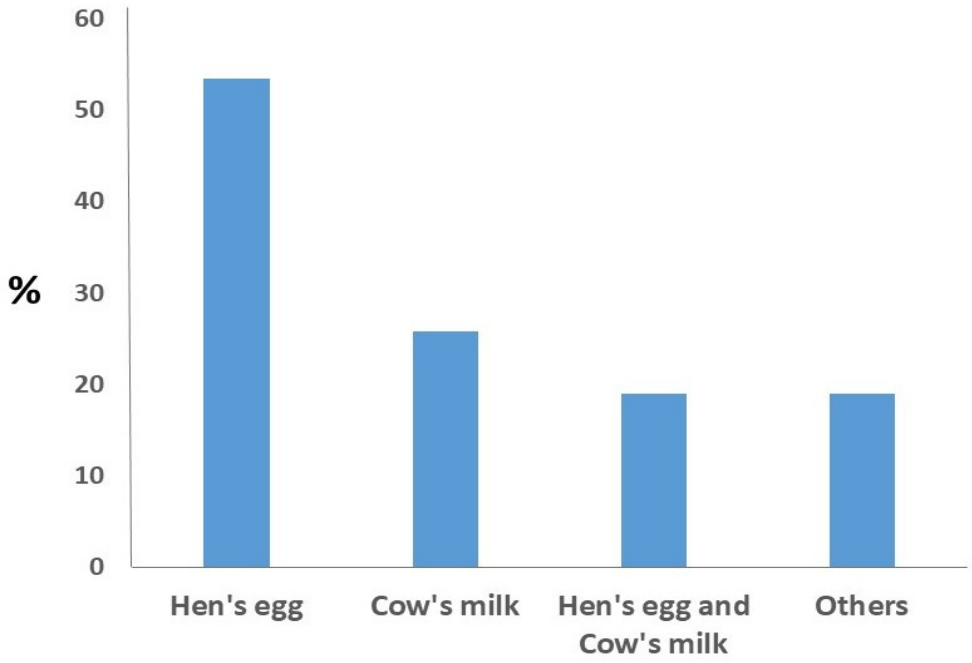

Fig. 2. **Food allergies in the study group**

categorized as immediate symptoms. Exacerbation or worsening of eczema (AD) and exanthema are delayed symptoms [11]. In a study conducted in our country, eczema was the most common diagnosis (36.8%) when the reasons for the first consultation to the physician in food allergy were analyzed. In the same study, 23.7% were found as urticaria and angioedema [16]. In our study, AD (77.9%) was the most common cutaneous manifestation in all patients and urticaria/angioedema was in the second place.

The correct diagnosis of IgE-mediated food allergies is very important. It is based on a combination of a detailed medical history, allergen-specific IgE investigation with SPT and specific IgE in serum, elimination diet followed by OFCs. In this study, we found positive SPT in 35% of patients and positive allergen sIgE in 40% of patients. Many studies have attempted to determine the true diagnostic value of SPT and it

Table 2. **The characteristics of the atopic dermatitis patients and its subgroups according to severity of atopic dermatitis**

	AD (n=169)	Moderate-Severe AD (n=23)	Mild AD (n=146)	P value
Age (month)	9.4 (5.3-14)	9 (4-15)	14 (9-18)	**0.011**
Gender-male, n (%)	98 (58)	15 (65.2)	83 (56.8)	0.450
FA, n (%)	54 (32)	19 (82.6)	35 (24)	**<0.001**
Multiple FA, n (%)	13 (7.7)	5 (21.7)	8 (5.5)	**0.018**
Hen's egg, n (%)	40 (23.7)	13 (56.5)	27 (18.5)	**<0.001**
Cow's milk, n (%)	24 (14.2)	11 (47.8)	13 (9)	**<0.001**
Other food allergy, n (%)	13 (7.7)	5 (21.7)	8 (5.5)	0.007
Eosinophil (cells/µL)	330 (200-547)	460 (312-680)	310 (182-517)	0.053
Total IgE (kU/L)*	19 (5.7-90)	26 (4.8-164)	17.5 (5.8-84)	0.475

Data are shown as median (IQR=interquartile range) or n (%). FA=food allergy, AD=atopic dermatitis

has become clear that a negative test excludes food allergy 90% of the time, whereas a positive test result does not confirm the diagnosis of food allergy, but is instead a case of sensitization [14, 17, 18]. The probability of being allergic increases with increasing skin prick test wheal diameter, and therefore some studies have established diagnostic decision levels for some allergens with a cut-off of 95%-100% positive predictive value (PPV). In vitro, s-IgE testing is another way to investigate IgE-mediated food allergies. As with SPT, there is a similar relationship between the concentration of specific s-IgE and the likelihood of a clinical reaction to the specific food. Several reports have aimed to determine precise diagnostic predictive values. Undetectable s-IgE values are associated with a low risk (10-25%) of reaction to food, with the risk increasing with increasing s-IgE levels. The levels also vary depending on the kind of allergen [14].

Atopic dermatitis is one of the most prevalent skin disorders in children. Patients with AD have a higher risk for food allergies than those without AD [19]. Previous studies that investigated the association between AD and food allergy have shown that severe and earlier onset AD is associated with the development of food sensitization and food allergy at an early age [20-22]. In our study, similar to the literature, age at diagnosis was found to be lower in the moderate-severe AD group compared to the mild AD group. It was shown that food sensitization was significantly higher in children with the moderate-severe AD group and SCORAD index was higher in patients with food allergy, in a report performed in our country [23]. Studies have shown that the prevalence of food allergy is high between 33% and 39%, especially in patients with severe AD [20, 24]. Similarly, in our study, food allergy was detected in 32% of AD patients. The percentage of food allergy was significantly higher in the moderate AD group (82.6%) than in the mild AD group (24%).

The OFC is recommended to avoid unnecessary food elimination and is the gold standard for diagnosing correct food allergy, particularly in food-sensitive AD patients [8]. Previous studies have showed that the rate of food sensitization in AD patients is high, but the rate of food allergy confirmed by OFC test is lower and food allergy is mostly found in severe AD patients [25, 26]. In a study of AD patients aged 6 months to 6 years, it has been shown that sensitization to food allergens is detected in approximately 53% of patients, and food allergy is confirmed in only 15% of these patients [27]. In our study, an oral food challenge test was made on forty patients with food sensitivity and all of them passed. Fleischer *et al* investigated 125 children aged 1-19 years and the outcome of oral food challenges in patients, they reported OFCs were helpful in food allergy diagnosis because most (89%) were negative [28]. Although most food-induced hypersensitivity reactions are thought to be food allergies, non-immunological food reactions are much more common. In a survey of children and adults in the UK, the prevalence of food allergy complaints was 20%, whereas a double-blind placebo-controlled provocation test showed that the actual prevalence was 2% [4]. In a study on infants with AD, serum eosinophil and serum total IgE levels were detected to be higher in the group with food sensitization and it was shown that elevations in serum eosinophil and serum total IgE levels were effective in predicting food sensitization in patients with severe AD [29] In another report, no difference was reported between food sensitization, serum eosinophil total and serum IgE levels [30] In our report, there was no difference between moderate-severe AD and mild AD subgroups in terms of eosinophil count and total IgE levels.

Foods that cause hypersensitivity reactions differ according to age and geography. Mavroudi *et al*. found that clinically active food allergies were recognized in 26.13% of children with AD and they reported that a total percentage of one in every four children, of children with AD were truly allergic to egg proteins and/or cow's milk [31]. In this study, we identified food allergy in only 26.7% of the patients referred with a prediagnosis of food allergy. No food allergy was found in any patient presenting with flushing. Cow's milk allergy was found in two patients and hen's egg allergy in two patients who presented with urticaria. The other patients consumed the food comfortably and had no complaints during follow-up. In our study, sensitivity to egg white/yolk, cow's milk, was found most frequently similar to other studies in the literature [20, 32]

Limitations

The main limitation of this retrospective study is that the study was conducted in a single center creating a limitation in terms of the generalizability of the re-

sults. However, in accordance with the aim of the study, the relationship between food sensitivity and skin manifestations commonly seen in daily life in infants was examined.

CONCLUSION

In conclusion, this study evaluated infants with cutaneous manifestations and suspected food allergies. We identified food allergy in approximately one out of every four patients presenting with suspected food allergy. Among these patients, 93% were diagnosed with AD. In particular, the elimination of essential nutrients from the diet negatively affects the quality of life of both infants and their parents. Correct evaluation of hypersensitivity reactions to foods is important to avoid unnecessary food elimination from infants' diets.

Ethics Statement

The study was initiated with the approval of the Ankara Ataturk Sanatorium Training and Research Hospital Ethics Committee (Date: 2024, Decision No: 189). This study was made in accordance with the declaration of Helsinki principles. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Authors' Contribution

Study Conception: HÜ; Study Design: HÜ; Supervision: HÜ; Funding: N/A; Materials: N/A; Data Collection and/or Processing: BA; Statistical Analysis and/or Data Interpretation: HÜ; Literature Review: BA, HÜ; Manuscript Preparation: HÜ and Critical Review: HÜ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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