

Systemic Reactions to Skin Prick Test with Food Allergens in Children

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What is already known on this topic?

- Skin prick tests (SPTs) are performed to identify the responsible food allergens when suspecting a type I food allergy. These tests offer rapid results and are generally considered safe. There are limited studies evaluating the development of systemic reactions (SRs) associated with skin tests for allergens.

What this study adds on this topic?

- This study specifically investigated the development of SRs resulting from SPTs with food allergens in children. The prevalence of both SRs and anaphylaxis resulting from SPTs with food allergens was found to be low. When conducting prick-to-prick tests with food and assessing patients with food-induced anaphylaxis indications, it is important to keep in mind the possibility of developing SRs.

ABSTRACT

Objective: Although skin prick tests (SPTs) are generally considered safe, limited studies have specifically evaluated reactions related to SPTs with all allergens. In contrast to these studies, our aim is to exclusively evaluate systemic reaction (SR) occurrences with food allergens during SPTs in children.

Materials and Methods: All patients who underwent skin prick and/or prick-to-prick (PtoP) tests with food allergens at our clinic between January 2010 and January 2020 were included in the study. The occurrence of SR during SPTs was evaluated based on patient records.

Results: The study included 1852 patients, with 57% males and a median age of 31 months (1-210). Skin tests were most commonly conducted for the indication of atopic dermatitis (29.3%). During the study, 11.2% had repeat SPTs for tolerance and a new allergy diagnosis. No local reactions or SRs occurred during SPTs. Among those with PtoP tests, 3 patients (0.16%) experienced SRs—1 had anaphylaxis (0.05%), the rest had angioedema. Legumes and sea bass caused these reactions. In patients with severe index reactions and those who underwent PtoP testing, SR development was significantly higher ($P < .001$ for both), and anaphylaxis occurrence was significantly higher among those undergoing PtoP testing compared to prick testing alone ($P = .03$).

Conclusion: The prevalence of both SR and anaphylaxis due to SPT with food allergens was found to be quite low in children. However, it is important to consider the possibility of SR development before conducting SPT with food allergens, especially in patients who will undergo the PtoP test and those with severe index reactions.

Keywords: Children, food allergens, prick-to-prick test, skin prick test, systemic reactions

INTRODUCTION

Allergy skin tests, which consist of prick tests and intradermal tests, are performed to identify the responsible allergens when type I hypersensitivity is suspected and give results in a short time.¹ Skin prick tests (SPTs) can be performed with standardized extracts available for many allergens, such as aeroallergens, venoms, and drugs. In cases where there is no standardized extract for food, fresh forms of food can be tested using the prick-to-prick (PtoP) technique.^{1,2}

Although SPTs are generally considered safe, limited studies have assessed the development of reactions associated with skin testing.³⁻⁸ These limited studies have evaluated the development of reactions for a wide range of allergens, including drugs, venom, aeroallergens, and foods. Furthermore, some studies have examined reactions in patients who underwent both prick tests and intradermal tests.^{4,5,7} It is worth noting that in nearly all of these studies, both pediatric and adult patients have been evaluated together.⁵⁻⁷

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We aimed to evaluate the prevalence of systemic reactions (SRs) and the characteristics of these reactions in children who undergo skin testing, specifically with food allergens.

MATERIALS AND METHODS

Study Population

Patients were included in the study who were aged 0–18 years and underwent skin prick and/or PtoP tests with food allergens in the Gazi University Pediatric Allergy Clinic between January 2010 and January 2020. The patients' medical records were retrospectively reviewed.

We collected demographic data, which included the patient's age, gender, and the presence of comorbid allergic diseases (including atopic dermatitis and whether there were active lesions during the test). The recorded information encompassed the indication for conducting skin tests with food allergen(s), the testing method (prick and/or prick-to-prick), the specific food allergen(s) tested, and details about retesting with the same or different food allergen(s). All the results of the conducted tests, the presence or absence of any reactions during the tests, and if a reaction occurred, details about the nature of the reaction and the treatment administered were obtained from the patient's medical records. Additionally, it was documented whether simultaneous SPTs were conducted with other allergens (aeroallergen, venom, drug), and if so, which allergen(s) were tested simultaneously.

Skin Test Procedure

In our clinic, SPTs are performed by 2 trained testing nurses. The prick test is performed by placing a small drop of each allergen extract and control solution on the volar surface of the patient's forearm (or on the back for children <5 years old). The drops are placed at least 2 cm apart. Then, the single-head metal lancet tip is gently lifted upward to elevate a small portion of the epidermis without inducing bleeding. Separate lancets are used for each test. Histamine phosphate (10 mg/mL, ALK-Abello) was used for the positive control, and physiological saline (0.9% NaCl) was used for the negative control. Allergen extracts of ALK-Abello (Pharm. Madrid) were used for SPT.

When stable test extracts cannot be obtained or are difficult to obtain for certain foods, such as vegetables and fruits, we use the PtoP technique for testing. In our clinic, especially for patients suspected of having oral allergy syndrome, we perform the PtoP test using the relevant fresh form of the vegetable and/or fruit. For dry foods, such as nuts, cereals, or legumes, we pestled them in saline and used the PtoP technique.² In the PtoP test, we first prick the food with a lancet and then use the same lancet to prick the epidermis.

Evaluation of Skin Test Result

All prick/PtoP test results, including the results of histamine and negative control tests, are read 15 minutes following application. The extracts are gently wiped away with a paper tissue just before reading the tests. The longest diameter of the formed induration and the diameter perpendicular to it were measured and recorded in millimeters (mm), with a positive result considered when the induration diameter is ≥ 3 mm.

Evaluation of Reactions with Food Allergens

During or within the 2-hour period following the test, any reactions that occurred were categorized as local reactions or SRs. A local reaction was considered as pain, tenderness, itching, and redness in the test area. In the case of SRs, objective findings included generalized itching, flushing, urticaria, angioedema, redness outside the test area, cough, wheezing, itching-watering-redness of the eyes, runny nose, nasal itching, congestion, sneezing, vomiting, hypotension, tachycardia, and desaturation. In addition to the objective findings, subjective symptoms such as nausea, abdominal pain, shortness of breath, feeling of pressure in the chest, choking sensation, dizziness, and anxiety were also considered. If the SR met the criteria for anaphylaxis based on these objective and subjective findings, a diagnosis of anaphylaxis was made, and its severity was classified according to Brown's classification.^{9,10}

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences Statistics software, version 22.0 (IBM Inc, Armonk, NY, USA) computer program. Categorical variables were given as numbers and percentages, continuous variables were presented as median depending on its distribution. The normality of continuous variables was assessed using visual methods, including histogram plots. Following this assessment, the continuous variables did not follow a normal distribution and were, therefore, presented in terms of median values (minimum–maximum) in the results. When more than 20% of the expected frequencies in the contingency table cells were less than 5, violating the conditions for the chi-square tests, the Fisher's exact test was utilized. A P -value < .05 was considered statistically significant.

Ethics Committee Approval

This study was approved by the Ethics Committee of Gazi University (Approval Number: 131/2022). Verbal informed consent was obtained from the patients who agreed to take part in the study.

RESULTS

Demographics

A total of 1852 patients were included in the study, 57% of whom were male, with a median age of 31 months (1–210 months). The

Table 1. Characteristics of Patients who Underwent Skin Test with Food Allergens

	n	%
Female	794	43
Patients who underwent prick test only	1645	88.8
Patients who underwent prick-to-prick test only	53	2.8
Patients who underwent simultaneous prick and prick-to-prick tests	154	8.3
Patients who underwent prick test with concomitant aeroallergens	1105	59.6
Patients who underwent prick test with concomitant drug and/or vaccine	28	1.5
Personal history of atopic diseases		
Atopic dermatitis	182	9.8
Allergic rhinitis	120	6.5
Asthma	96	5.1

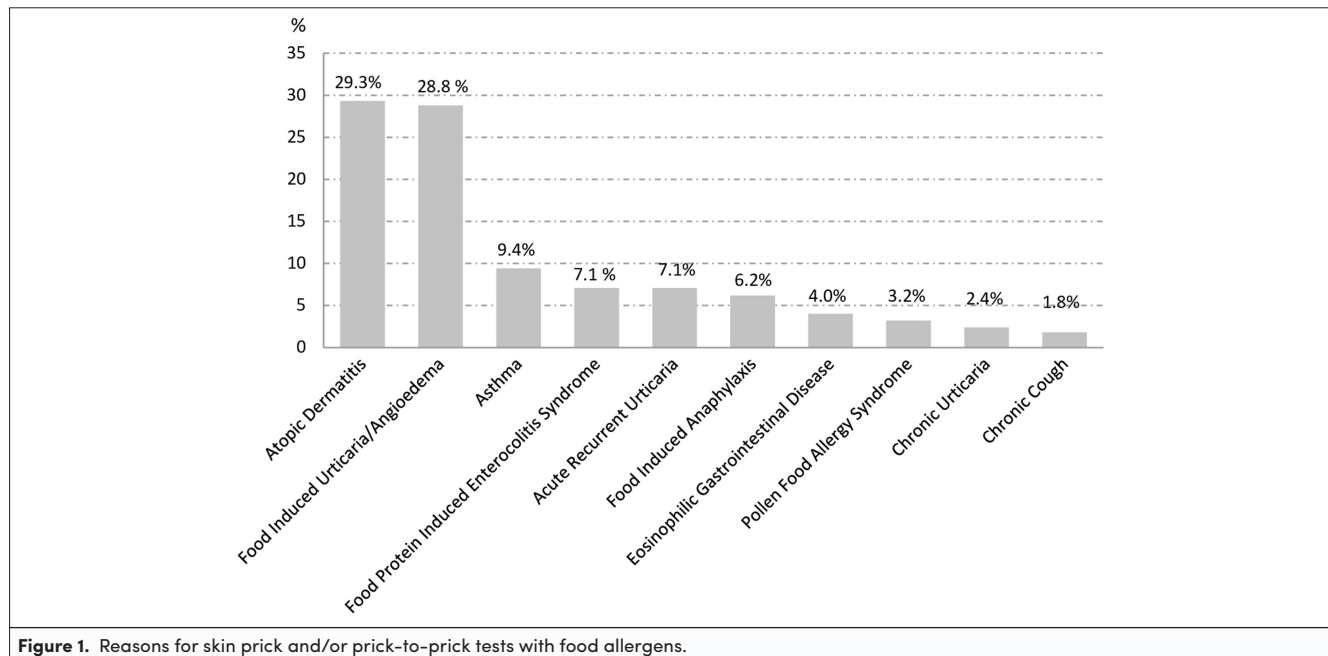


Figure 1. Reasons for skin prick and/or prick-to-prick tests with food allergens.

characteristics of patients who underwent skin tests with food allergens are shown in Table 1. Skin tests with food allergens were most frequently performed for atopic dermatitis (AD) (29.3%). Among these patients, 31.6% ($n = 172$) had active AD lesions at the time of testing. The reasons for performing skin tests with food allergens are presented in Figure 1.

During follow-up, 11.2% of patients underwent retesting using the same or different food allergens. Retesting was performed most frequently with the evaluation of the development of tolerance and a new diagnosis of type I food allergy (74.1% and 23.9%, respectively).

Among the 1775 patients for whom we obtained skin test results, a positive test result for at least 1 food allergen was found in 29.1% of the patients ($n = 518$).

Number of Tests and Application Method

During the study, a total of 9557 tests were performed using food allergens ($n = 8703$ for the prick test and $n = 854$ for the PtoP test). Patients who underwent SPT only were tested with a median of 3 (1-33) food allergens, while patients who underwent PtoP test only were tested with a median of 1 food (1-21). In total, 1 patient underwent testing for up to 42 food allergens, which included both prick and PtoP tests.

Systemic Reactions

In patients undergoing SPTs neither local reactions nor systemic reactions were observed. However, in three patients who underwent PtoP tests with foods, SRs were observed. In these cases, the PtoP test was indicated due to food-induced anaphylaxis. Among the reactions during the test, 1 was anaphylaxis, while the other 2 cases involved angioedema. The triggers were legumes for 2 patients and sea bass for the third. The characteristics of these 3 patients are detailed in Table 2. In case 2, anaphylaxis occurred 15 minutes after the simultaneous application of 9 different legumes before the PtoP tests were read. In the other 2 cases, SR developed at the fifth and tenth minutes of the test, respectively.

Systemic Reaction and Anaphylaxis Rate

The rate of SR development per patient was 0.16%, and the rate of anaphylaxis due to skin testing with food allergens was 0.05%. When considering only patients with positive skin test results, the rate of SR was 0.57% per patient, and the rate of anaphylaxis was 0.19%.

Patients with and without SRs and anaphylaxis were compared based on the index reaction (anaphylaxis or not), PtoP testing method, single food allergen testing, positive test for a single food allergen, and whether they were tested for at least 1 legume (Table 3). In patients with an index reaction of anaphylaxis and those who underwent PtoP testing, the development of SRs was significantly higher ($P < .001$ for both). The occurrence of anaphylaxis was significantly higher only in those who underwent PtoP testing compared to those who underwent prick testing alone ($P < .05$). In the others, however, there was no significant difference in terms of both SR and anaphylaxis ($P > .05$ for each) (Table 3).

DISCUSSION

In our study, SR development due to a skin test with only food allergens was evaluated in a single center over a 10-year period. While studies assessing SR development through food allergen skin tests reported rates ranging widely from 0.02% to 0.52%, our study showed a low SR rate (0.16%).⁴⁻⁸ The rate of anaphylaxis due to tests with food allergens was also quite low (0.05%), and it was found to be similar to the literature.⁵ However, in contrast to other studies, when we analyze these rates among patients with positive tests for food or food extracts, both the SR and anaphylaxis rates were approximately 3.5 times higher, falling within a range similar to the literature (0.57% and 0.19%, respectively).

We reviewed other studies assessing the development of SR through SPT, and the study conducted by Devenney et al is the only one that exclusively evaluated SR development related to food allergens.⁴⁻⁸ Notably, this study showed

Table 2. Characteristics of Patients who Developed Systemic Reaction due to Prick-to-Prick Test with Food Allergens

	Case 1	Case 2	Case 3
Age at development of systemic reactions (months)	48	114	54
Indication for test	Mild anaphylaxis with sea bass	Moderate anaphylaxis with red lentil and pea	Severe anaphylaxis with red lentil and chickpea, Urticaria with pea
Presence of comorbid allergic disease	No	No	Asthma Allergic rhinitis Atopic dermatitis
Application inducing systemic reactions	First	Second	Second
Foods tested at the time of systemic reactions (induration diameter, mm)	Sea bass (30 × 20)	Pea (18 × 10), red lentil (14 × 8), green lentil (20 × 10), chickpea (15 × 7), kidney bean (10 × 6), white bean (10 × 7), fresh bean (4 × 3), peanut (5 × 5), soy (4 × 3)	Red lentil (15 × 15), chickpea (8 × 8), pea (7 × 7)
Signs and symptoms of systemic reactions	Flushing on the face and neck, angioedema on the eyelids and lips	Moderate anaphylaxis Consecutive cough, wheezing, generalized redness and itching in the body	Angioedema on the eyelids
Treatment	Antihistamine (oral)	Adrenaline (IM), nasal oxygen, antihistamine (IV), systemic steroid (IM), inhaled bronchodilator	Antihistamine (oral)

the highest rate (0.52%) of SR development during food skin testing. In this study, only the PtoP test was performed simultaneously with multiple foods. Additionally, a double-test was performed for each allergen in the same session, leading to SR development in 6 patients, all of whom were younger than 6 months old. The patients' young age was cited as the reason for the SR development, and it was also observed that each of these patients had varying degrees of active eczema.⁵ Therefore, the presence of active eczema, in addition to simultaneous testing with more than 1 food, double-testing for a single food, and conducting the PtoP method, may have also contributed by increasing the allergen load. In our study, the majority of patients who underwent SPT with food consisted of those with an AD indication. One-third of these patients also had an active lesion at the time of testing. However, only 1 of the 3 patients who developed SR had concomitant AD and was in remission. Since SPTs were not applied to areas with active lesions in our clinic, we think that SR did not develop in any of our patients with active AD.

Norrman and Fälth-Magnusson⁴ investigated adverse reaction prevalence and risk factors during SPTs. Like our study, it focused on pediatric patients and extended to aeroallergens, drugs, latex, and food allergens. Using the PtoP method for food tests, the study found 6 cases of generalized allergic reactions (GAR) among 5918 SPT patients, at a 0.12% rate. The risk factors for GAR development were identified as young age (<1 year) and the presence of active eczema.⁴ We also collected extensive data from patient files that we believed might be potential risk factors. In our study, the development of both SR and anaphylaxis was significantly higher only in those who underwent PtoP testing for foods compared to those who underwent prick testing alone. However, due to the rarity of SR and anaphylaxis cases, we were unable to ascertain the risk factors and calculate odds ratios. Consequently, we cannot provide commentary on whether PtoP testing is an independent risk factor or not.

In Sellaturay et al's⁶ study, SR frequency and clinic during 6 years of SPTs were assessed. Among around 31000 patients receiving prick and PtoP tests, 24 cases of SR (0.07%) emerged,

Table 3. Comparison of Characteristics Between Patients Developing Systemic Reaction and Anaphylaxis During Skin Testing and Those Who Do Not

	Systemic Reaction Development		Anaphylaxis Development	
	n (%)	P*	n (%)	P*
Patients with anaphylactic index reactions, n = 116	3 (2.58)	<.001	1 (0.86)	.063
Patients with non-anaphylactic index reaction, n = 1736	0 (0)		0 (0)	
Patients who underwent only prick-to-prick tests, n = 53	3 (5.6)	<.001	1 (1.88)	.031
Patients who underwent only skin prick tests, n = 1645	0 (0)		0 (0)	
Patients who were tested with atleast 1 legume allergens, n = 464	2 (0.43)	.157	1 (0.2)	.251
Patients who were tested with non-legume food allergens, n = 1388	1 (0.07)		0 (0)	
Patients who were tested with a single food allergen, n = 127	1 (0.78)	.192	0 (0)	1
Patients who were tested with multiple food allergens, n = 1725	2 (0.11)		1 (0.05)	
Patients with a positive single food allergen test, n = 224	1 (0.44)	1	0 (0)	1
Patients with positive tests for multiple food allergens, n = 294	2 (0.68)		1 (0.34)	

*Fisher's exact tests. *P* < .05 values were significant and indicated in bold.

ranging in age from 0.5 to 56 years. While the SR rate appears low compared to our study, it's uncertain which allergens were used for SPT in non-SR patients or how many were children. Nonetheless, two-thirds of those with SRs had food as the responsible allergen, with peanut (in 7 patients) being the most common trigger. Other foods included walnut, brazil nut (in 2 patients), pistachio, broad bean, soybean, pea+chickpea, spinach, and cow's milk. Considering that peanuts are from the legume family, it can be said that legumes were the responsible food in two-thirds of the patients who reported SR with food in this study.^{6,11} However, this has been explained by the gradual increase in peanut allergies. In our study, legumes other than peanut were responsible for 2 of the 3 patients who developed SR. Both of our patients have consumed peanuts without any problems. However, in Turkey, legume allergies other than peanuts seem more frequent without accompanying peanut allergies due to geographical and cultural differences in consumption.¹² This may be the difference in the result of this study related to this issue. On the other hand, we believe that conducting multiple tests of cross-reactive legumes in our patients might have increased the allergen load.¹³ Although it's common to perform all SPT together, in cases requiring more tests, awareness of cross-sensitization patterns is crucial. In such situations, performing SPT in multiple sessions is highly recommended.^{3,14} Additionally, when separate PtoP tests were conducted for each legume during their follow-up period, no systemic reaction was observed.

Furthermore, this study aimed to elucidate potential risk factors for the development of SR. They reported that, except for 1 patient who developed SR, the index reactions of the remaining patients were at stage 2 and above. Index reactions occurred with trace amounts of allergen exposure in one-quarter of the cases. Half of the patients had asthma, with 2 of them having uncontrolled asthma during the test. Severe index reactions and a wide SPT response (>8 mm) have been reported to be associated with SR development.⁶ If we examine our patients based on these parameters, in support of the study by Sellaturay et al,⁶ we can conclude that all 3 experienced a severe index reaction. The induration diameters of the responsible foods were ≥ 8 mm in all cases, except for the pea-related induration diameter in the third patient. Furthermore, when comparing patients tested for the food-induced anaphylaxis indication to those tested for other indications in terms of SR development, a significant difference was observed.

Swender et al⁵ evaluated adrenaline administration rates during 13 years of prick and intradermal tests using an electronic database. Among 28907 SPT patients, 6 (including 3 children) received adrenaline during testing. All 6 patients shared the characteristic of undergoing SPTs with multiple food allergens (ranging from 11 to 71 each) at the time of SR development; all but 1 had a history of anaphylaxis. Multiple SPT administrations may have triggered SR by increasing the allergen load in these patients.^{3,13} Moreover, the fact that the index reaction is anaphylaxis could indicate that SR may develop even with minimal exposure to allergens. The testing indication for all 3 of our patients with SR development was mild to severe food-induced anaphylaxis. Consequently, in cases where the index reaction to food is severe, it might be more prudent to

consider examining specific Immunoglobulin E (IgE) for the relevant food before conducting a prick test to confirm the diagnosis.^{1,15} Unfortunately, specific IgE measurements could not be conducted at our hospital during the study period. If we could have conducted these tests before SPT, our SR rate could have been lower. On the other hand, SPT results sometimes become clearly positive before the usual waiting time of 15 minutes. Terminating the test prematurely in these situations could also be a way to decrease SRs.

When examining case reports documenting the development of SRs caused by skin tests involving food allergens, a total of 16 patients have been presented across 10 separate reports.^{14,16-24} One of them (case-2) had been previously reported by us. Among the 9 case reports excluding this instance, only 3 of them concerned pediatric patients.^{14,20} Interestingly, 6 of these 16 patients were tested with fish for the indication of urticaria/anaphylaxis. It is seen that the PtoP method was used in the tests performed with fish in most of the patients, as in our first case. It is understood that all but 1 patient was tested simultaneously with more than 1 fish allergens.^{14,16,18,20,24} In our first case, the PtoP test was only performed with sea bass, and test-related angioedema was developed. We believe that this patient was very sensitive, and it's possible that we unintentionally administered a large amount of sea bass allergen during the PtoP test.

We believe that the major strength of our study lies in its exclusive focus on SR development due to SPT with food allergens, while many studies have included non-food allergens. Another strength is that our study exclusively included pediatric patients, whereas several studies assessed both pediatric and adult patients together.

The limitations of our study include its descriptive cross-sectional design and the inability to evaluate independent risk factors and odds ratios for the development of SR and anaphylaxis due to the small number of patients who experienced such reactions. A multicenter and prospective study may help guide the identification of risk factors. Another limitation is our inability to perform specific IgE assessments before SPT in patients with severe index reactions. Furthermore, we have shared our local data, which could also be considered a limitation. Considering that food allergies can develop with different foods based on countries' dietary habits, the foods triggering reactions in skin tests might vary. In addition, although AD was the most common indication for SPT in our study, complete data on the severity of AD could not be obtained from our file records.

In conclusion, SRs associated with skin tests for food allergens are quite rare in children. Nonetheless, when conducting PtoP tests with food and testing patients with severe index reactions, keeping in mind the possibility of developing SRs would be beneficial. All skin tests should always be performed by trained personnel, ensuring that all precautions are taken for anaphylaxis management.

Ethics Committee Approval: This study was approved by Ethics Committee of Gazi University (Approval No: 131, Date: 2022).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

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