

Is the Atopy Patch Test Reliable in the Evaluation of Food Allergy-Related Atopic Dermatitis?

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Keywords

Atopic dermatitis · Patch test · Food allergy

Abstract

Background: Aeroallergens and food allergens are found to be relevant in atopic dermatitis. The atopy patch test (APT) can help to detect food allergies in children with atopic dermatitis. This study evaluates if the APT is a valuable tool in the diagnostic workup of children with food allergy-related atopic dermatitis. **Methods:** 42 children between 6 months and 12 years of age were selected at the Mofid Children Hospital. Atopic dermatitis was diagnosed, and the severity of the disease was determined. At the test visit, the patients underwent a skin prick test (SPT), APT, and serum IgE level measurement for cow's milk, egg yolk, egg white, wheat, and soy. **Results:** We found a sensitivity of 91.7%, a specificity of 72.7%, a positive predictive value (PPV) of 88%, a negative predictive value (NPV) of 80%, and an accuracy of 85.7% for APT performed for cow's milk. APT performed for egg yolk had a sensitivity and a NPV of 100%, while the same parameters obtained with egg white were 84.2 and 75%, respec-

tively. The sensitivity, specificity, and NPV of the APT for wheat were 100, 75, and 100%, respectively. The sensitivity, PPV, and NPV of the APT for soy were 87.5, 70, and 87.5%, respectively. **Conclusions:** Our data demonstrate that the APT is a reliable diagnostic tool to evaluate suspected food allergy-related skin symptoms in childhood and infancy.

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Introduction

Atopic dermatitis is one of the most common allergic diseases with an estimated incidence of 10–30% in children [1]. It is a multifactorial disease caused by intrinsic abnormalities and extrinsic factors [2]. Among the relevant allergens mediating atopic dermatitis, aeroallergens and food allergens are the most important ones [3]. The

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role of food allergens in triggering inflammation and influencing the severity of atopic dermatitis is well documented [4]. However, the type of food inducing atopic dermatitis can vary with age [1]. In western countries, the most common food allergens in infants are cow's milk, egg, and peanut. In older children, wheat, fish, and tree nuts predominate. The diagnosis of food allergy is confirmed by clinical history taking, skin prick test (SPT), and measurement of specific IgE (sIgE) followed by an elimination diet and/or oral food challenge. However, diagnosing patients with the non-IgE (cell-mediated) or mixed (IgE and cell-mediated) forms of food allergy remains challenging. In many studies, the atopy patch test (APT) has been evaluated as an additional tool in the diagnostic workup of food allergy in late-positive clinical reactions in children with atopic dermatitis. Any food can be assessed by this method, and cow's milk, egg, and soy have been studied most extensively [5]. The earliest description of patch testing in eczema was in 1937 by Rosenthal, and the first controlled trial was provided by Mitchell in 1982. APT with food allergens was introduced in clinical use in 1996 by the group of Isolauri in Finland [3].

This study is designed to investigate whether APT with food allergens could increase the identification of food allergies in children with atopic dermatitis, especially in cases suspicious of food allergies without predictive sIgE levels or positive SPT. Therefore, a positive APT may act as a simple method for the identification of the offending allergen as the cause of skin involvements. It would not only help to avoid unnecessary prescription of strong topical corticosteroids in refractory cases, but also help to prevent extensive restrictive and unnecessary diets which are the consequences of the clinicians' misjudgment and can be harmful for the child's health and growth. To our knowledge, this is the first study conducted in our country on children suffering from food allergy-related atopic dermatitis in which the obtained results are confirmed with oral food challenge. Besides, APT is not used as a useful diagnostic tool in the diagnosis of this condition, and it can be used to prevent unnecessary extensive diet eliminations which are prescribed unreasonably and may cause nutritional problems in growing children.

Materials and Methods

Forty-two children aged between 6 months and 12 years were selected and followed at the Allergy Clinic of the Mofid Children Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Atopic dermatitis was diagnosed according to the criteria of Hanifin and Rajka [6]. The SCORAD (Score of Atopic Dermatitis) index was used for the patients to determine the severity of the disease, and patients were classified into mild, moderate, and severe groups. Their parents accepted and signed an informed consent form.

At the test visit, total serum IgE levels were measured, and the patients underwent SPT and APT with 5 major allergens (cow's milk, egg yolk and white, wheat, and soy). SPT was performed by using the extracts produced by the Stallergen Company (Paris, France). APT was performed with puree freshly made for every patient with 1 g of the above-mentioned food allergens, passed through a sieve or blender, and diluted in 10 mL of distilled water. Of each solution, 1–2 drops were put on filter paper and applied to the unaffected skin of the child's back with 12-mm aluminum cups of an adhesive tape (Finn chamber, Epitest Ltd, Finland). Normal saline was used as a negative control. The APT occlusion time was 48 h. Application sites were checked after 48 h [7]. Reactions were classified according to standards and considered as: 0/ negative (no reaction, either visible or palpable), 1+ (palpable erythema; weak reaction), 2+ (strong, infiltrate with numerous papules and vesicles present; strong reaction), and 3+ (coalescing vesicles, bulla or ulceration; extreme reaction) [3, 7]. One person prepared all tests, and the author classified all the reactions. However, the test material was not standardized. Reactions 0 and 1+ were excluded.

All the patients with 2+ and 3+ reactions were first treated with the application of local emollient and steroid therapy.

In the cases without optimal improvement or those who experienced a relapse after stopping the above-mentioned local treatment, a 2-week avoidance diet was recommended according to the positive results of the SPT (wheat >2 mm) and serum sIgE (which was divided into 4 levels [0: <0.35 IU/mL, 1+: 0.35–0.70 IU/mL, 2+: 0.70–3.5 IU/mL, 3+: 3.5–17.5 IU/mL, and 4+: ≥17.5 IU/mL]). The patients were reevaluated after this period of avoidance. If there was any improvement, the allergens were again introduced into the diet one by one every 2 weeks, and the patients were observed for reappearing cutaneous manifestations. At the next stage, the food allergens with the positive patch test results (indicating a reaction >+) were eliminated from the diet. In those cases with a complete improvement, the results were confirmed with an oral food challenge. The improvement was defined as any decrease in the estimated severity of the SCORAD indexes, from severe to mild, or from moderate to the complete resolution of the cutaneous manifestations after 2 weeks of strict avoidance. This challenge was performed as introducing soy, egg yolk, egg white, wheat, and cow's milk one by one, respectively, only in the case of positive patch test results with a 2-week interval. In those cases with multiple positive allergens, we also considered a 2-week gap between the introduction of the 2 consecutive allergens to obviate the effect of the previous allergen on the following. Patients were carefully observed, and any cutaneous, respiratory, and gastrointestinal manifestations were recorded. Subsequently, strict avoidance was again recommended according to the observed adverse events. If no clinical manifestations were observed in the next 2 weeks, the next allergen in the order of the above-mentioned list was introduced and evaluated. Finally, the collected data from oral food challenges were compared with the results of serum sIgE measurements, SPTs, and patch tests. Statistical analysis was performed by using SPSS version 19 for Win-

Table 1. The results of in vitro and in vivo tests for 5 major allergens

	Milk		Egg yolk		Egg white		Wheat		Soy	
	–	+	–	+	–	+	–	+	–	+
sIgE, %	41.4	58.6	89.7	10.3	82.8	17.2	60.7	39.3	89.3	10.7
SPT, %	52.4	47.6	70	30	55	45	70	30	75	25
APT, %	28.6	71.4	8.1	91.9	33.3	66.7	51.4	48.6	48.5	51.5
Food challenge, %	30.8	69.2	30.8	62.9	48.7	51.3	81.8	18.2	57.1	42.9

APT, atopic patch test; sIgE, specific IgE; SPT, skin prick test.

Table 2. A summary of the sensitivity, specificity, negative (NPV) and positive predictive value (PPV), and accuracy in the atopic patch test (APT), skin prick test (SPT), and serum IgE for 5 major allergens

	Cow's milk			Egg yolk			Egg white			Wheat			Soy		
	APT	SPT	IgE	APT	SPT	IgE	APT	SPT	IgE	APT	SPT	IgE	APT	SPT	IgE
Sensitivity, %	91.7	63.6	68.4	100	44.4	15.4	84.2	63.6	25	100	100	0	87.5	50	28.6
Specificity, %	72.7	62.5	50	18.8	80	93.3	56.3	87.5	86.3	75	63.6	46.7	70	85.7	88.3
PPV, %	88	70	76.5	61	66.7	66.7	69.6	87.5	60	50	20	0	70	66.7	66.7
NPV, %	80	55.6	40	100	61.5	56	75	63.5	59.1	100	100	77.8	87.5	75	61.8
Accuracy, %	85.7	63.1	62.9	64.8	63.1	57.1	80	73	59.2	80	66	41.1	77.7	72	62.5
Correlation coefficient	0.66	0.25	0.17	0.2	0.24	0.09	0.41	0.48	0.12	0.54	0.22	0.23	0.56	0.37	0.18
<i>p</i> value	0.00	>0.25	>0.05	0.03	>0.05	>0.05	0.01	0.02	>0.05	0.006	>0.05	>0.05	0.01	>0.05	>0.05

dows. The test outcomes were analyzed both individually and combined, with a focus on the combination of tests.

This study was approved by the Ethics Committee of the Mo-fid Children Hospital, Shahid Beheshti University of Medical Sciences.

Results

This study was performed in a population of 42 children (18 girls and 24 boys) aged 6 months to 12 years (mean: 19.4 months; median: 13 months); 32 of them (76.2%) had a positive family history for allergy. All the available diagnostic tools (SPT, APT, sIgE, and oral food challenge) have been included for each patient in this study. The results of the IgE measurement, SPT, APT, and food challenge for 5 major food allergens (cow's milk, egg yolk and white, wheat, and soy) are summarized in Table 1. Surprisingly, there were more positive APT results confirmed by food challenge for the 5 major allergens tested than by the other 2 tests (SPT and IgE measurement).

The sensitivity, specificity, positive (PPV) and negative predictive value (NPV), and accuracy of APT, SPT, and serum IgE for the 5 major allergens, including cow's milk, egg yolk and white, wheat, and soy, are compared and summarized in Table 2.

The combination results of SPT and APT for cow's milk demonstrated a significant increase in specificity and PPV. While other parameters were not significantly affected (Fig. 1), the sensitivity, NPV, and accuracy of patch testing for the 5 major allergens studied were higher for APT than SPT in this study. The combination of sIgE plus APT increased the specificity, PPV, NPV, and the accuracy of diagnosis of cow's milk allergy (Fig. 1).

APT alone had an acceptable sensitivity, specificity, PPV, NPV, and accuracy, equal to SPT, sIgE, and even the combination of them, in the diagnosis of allergy to egg yolk and white. However, APT in combination with neither SPT nor sIgE did have a significant influence on diagnostic parameters of patients with allergy to egg yolk and white.

In patients allergic to wheat, the combination of SPT and APT was more significant for PPV, accuracy, and

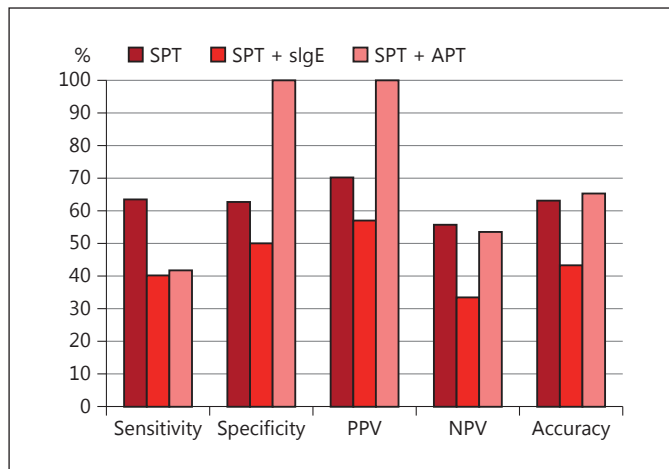


Fig. 1. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the skin prick test (SPT) alone and in combination with specific IgE (sIgE) and the atopy patch test (APT) for cow's milk.

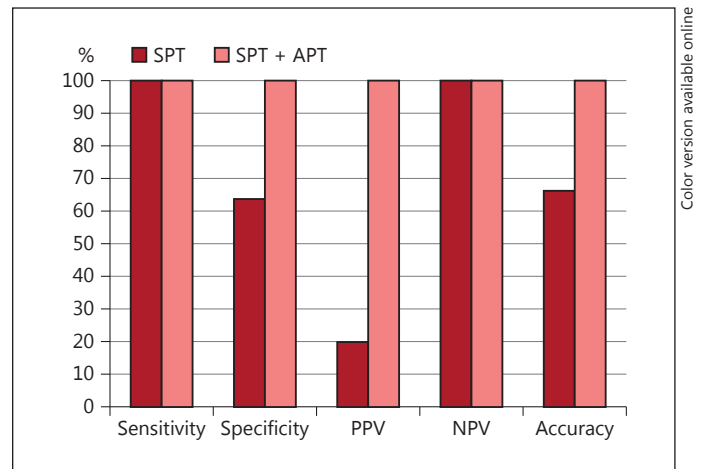


Fig. 2. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the skin prick test (SPT) alone and in combination with the atopy patch test (APT) for wheat.

specificity than SPT alone. The results of SPT and sIgE were never positive concomitantly, and APT had a greater specificity, accuracy, and PPV than SPT for wheat (Fig. 2).

In patients allergic to soy, we did not find APT or its combination with any other diagnostic tools to significantly influence the sensitivity, specificity, PPV, NPV, and accuracy of the diagnosis of soy allergy.

Subsequently, we evaluated the effect of age on the results of APT; therefore, the children were divided into 2 age groups (children ≤ 1 and > 1 year). The obtained data indicated that the age of the patients did not influence the APT results except for egg white (all the parameters were significantly higher in children < 1 year).

Discussion

Food allergy is an important contributing factor in the pathogenesis of atopic dermatitis. History, sIgE, and SPT are almost only used to identify type I (IgE-mediated) reactions. However, despite some limitations to its use, the gold standard for food allergy is still the double-blind, placebo-controlled, oral food challenge [8].

The important role that APT can play in identifying the causative allergens in atopic dermatitis is based on the pathophysiological mechanism of atopic dermatitis in which immediate IgE-mediated mechanisms concurrently exist with T-cell-induced delayed hypersensitivity.

APT seems to reproduce the pathophysiological events of atopic dermatitis, which is characterized by inflammatory dendritic epidermal cells and a TH2 cytokine pattern in the first 24 h of the test with a shift to a TH1 pattern after 48 h [3].

In this study, we tried to determine if APT could act as a valid diagnostic tool in delayed hypersensitivity reactions, which are still a challenge in many cases. We expected more positive results by APT for the 5 mentioned allergens than with the other tests because of the predominantly cell-mediated type (delayed-type hypersensitivity) of food allergies.

In this study, 71.4% of cases were positive for cow's milk by APT, which was comparable with the results published by Cudowska and Kaczmarek [4] in 2005, in which patients were evaluated in 2 age groups: < 3 and > 3 years (72.7 and 80%, respectively). In another study performed by the same authors later in 2010, a sensitivity of 77%, specificity of 73%, and PPV of 71% was reported for cow's milk allergy assessed by APT [9].

In 2002, Strömberg [10] compared APT sensitivity for cow's milk, eggs, and wheat, which were 60, 71, and 90%, respectively, and the same parameters were 41, 60, and 13%, respectively, for SPT. The specificity for both tests was $> 90\%$ regarding the same mentioned allergens.

In another study, conducted in 2007 in Italy by Canani et al. [11], sensitivity, specificity, PPV, and NPV were 64.5, 98.5, 95.2, and 67.6% for cow's milk and 95.8, 100, 100, and 75% for egg, respectively, by APT. In another

study, Lipozencic and Wolf [12] proposed that patch testing was more sensitive than SPT in the diagnosis of food allergy in young children with atopic dermatitis, particularly for cereals. This was confirmed in our study in which the sensitivity, NPV, and accuracy of patch testing for the 5 allergens tested were higher than SPT values.

In this study, APT was proven to be a helpful diagnostic tool, but its predictive capacities varied according to allergens. However, it should be considered that positive APT results, similar to positive SPT results, indicate only sensitization to food allergens and should be verified by oral food challenge [4].

By combining the results of both APT and SPT in allergic patients in the study by Cudowska and Kaczmariski [4], specificity and PPV were increased, while sensitivity was decreased and NPV remained the same.

Comparing our results, we found out that our and their results were the same. The APT-sIgE combination for cow's milk also heightened the validity of specificity and the PPV from 50 and 78 to 100%, respectively ($p < 0.05$). NPV and accuracy were also increased but to a lesser extent. In fact, the APT-SPT combination increased the diagnostic power significantly in both the study by Cudowska and Kaczmariski [4] and in our study.

In 2 recent studies, positive APT results were analyzed in association with sIgE and SPT and increased the PPV in 1 study and improved sensitivity and specificity for all the allergens in the other [13, 14]. According to our data in patients of the APT-SPT-sIgE combination, the need for performing oral food challenge was decreased in children with atopic dermatitis.

The results of APT-SPT as well as APT-sIgE for other allergens (egg yolk and white, wheat, and soy) did not have any significant advantage regarding the interpretation of variables, except for wheat, in which the APT-SPT combination showed a significant improvement in nearly all of the parameters ($p < 0.05$). Analysis of the sIgE/APT results also increased specificity, NPV, and accuracy of the tests.

A surprising result while evaluating the SPT-sIgE combination for wheat was that SPT and sIgE were never concomitantly positive in our patients.

The influence of age on APT results in terms of sensitivity remains controversial in this study. No significant difference is reported in some studies, while others showed that the frequency of positive APT results was lower in children > 2 years [15]. In 2014, APT was considered as a suitable method for the diagnosis of atopic dermatitis in food-allergic Chinese children aged < 2 years in a study by Yang et al. [16].

Cudowska and Kaczmariski [4] could not find an age correlation between positive APT results and oral food challenge, but they concluded that the higher APT specificity in children confirms its accuracy in diagnosing delayed cow's milk allergy in children. Mehl et al. [16] reported increased APT sensitivity for cow's milk with increasing age and a specificity of 100% in children 3–6 years of age. This was not confirmed in our study.

In conclusion, our findings indicate that APT results for food allergens seem not to be influenced by age in infancy and childhood. Therefore, it can be performed on children of any age with unimpaired accuracy.

Finally, we evaluated the effect of the severity of atopic dermatitis on APT results.

The SCORAD index did not correlate with the grade of the APT test reaction for cow's milk in our study. In patients with milder forms of dermatitis, APT specificity was decreased, but other parameters increased with increasing disease severity.

According to the above data, none of the available diagnostic tests prove or disprove that the child suffers from food protein allergy, but patch tests may contribute to the diagnosis of food allergy, even when SPT and RAST (radioallergosorbent test to detect sIgE antibodies) are negative. APT was the best single predictive test for milk, egg, and soy in our study, and the combination of a positive APT with a positive SPT increased the PPV to 100% for some major food allergens.

Conclusion

Our data demonstrate that although APT results for all 5 major allergens were not consistent among our patients, the APT is a reliable and safe diagnostic tool to evaluate suspected food allergy-related skin symptoms in infancy and childhood. The APT may identify patients with food allergies with negative sIgE. A positive response to the APT is associated with a delayed-type reaction to foods. When used in parallel with SPT, it increases the detection rate. Our findings could act in support of the idea to add the APT to the standard allergy workup in children with atopic dermatitis and suspected food allergy.

Our key aim in this study was not to conclude that the APT – either alone or in combination with other diagnostic tools – could make double-blind, placebo-controlled food challenges superfluous for suspected food allergies in patients with atopic dermatitis, but it can prevent unnecessary restrictive diets which may be the consequence of misjudging by clinical assessments alone.

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Disclosure Statement

The authors declare no conflict of interest.

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