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Atopy Patch Test in the Diagnosis of Food Allergens in Infants with Allergic Proctocolitis Compared with Elimination/Introduction Challenge

Saba Arshi[1], Majid Khoshmirsafa[2], Maryam Khalife[3], Mohammad Nabavi[1], Mohammad Hasan Bemanian[1], Sima Shokri[1], Farhad Seif[2], Azizollah Yousefi[3], and Morteza Fallahpour[1]

[1] Department of Allergy, Rasool-E-Akram Hospital, Iran University of Medical Sciences, Tehran, Iran
[2] Department of Immunology, Medicine school, Iran University of Medical Sciences, Tehran, Iran
[3] Department of Pediatric, Rasool-E-Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Allergic proctocolitis is a cell-dependent food allergy that is present in both breast and formula-fed infants. The presence of blood with different amounts in the stool is the main manifestation of the disease. Different results have been published on the accuracy and specificity of the atopic patch test (APT). The purpose of this study was to evaluate the results of the APT and compare them with those obtained in the food elimination/introduction (E/I) challenge, as the gold standard of confirming the allergy.

Twenty-eight patients (18 boys, 10 girls, <1 year) with allergic proctocolitis were recruited in this study. The mean age of the disease onset and enrolling the study were 2.23±1.7 and 5.25±2.19 months, respectively. After performing APT with fresh foods, an E/I challenge was done in a patient with positive tests, and results were analyzed.

APT was positive in 14/28 (50%) individuals. The most common foods detected by APT in all of the individuals were: milk (10/28), rice (5/28), soy (4/28), and egg white (4/28), while in E/I challenge in the APT-positive individuals were: milk (8/10), rice (3/5), egg white (1/4), and soy (0/4). APT was positive in half of the infants<1 year with allergic proctocolitis and there was no significant correlation between the APT results and the E/I challenge test for all foods.

Comparing the results of APT and E/I challenge methods showed a convergence between the milk and rice sensitivity, thus we suppose APT to be a useful tool in identifying these two allergens in cell-mediated food allergies like allergic proctocolitis.

Keywords: Food hypersensitivity; Patch tests; Proctocolitis

INTRODUCTION

Allergic proctocolitis is one of the most common causes of bloody stool in healthy infants. Blood presence in the stool may range from only positive occult blood in the stool to exact obvious blood streaks

Corresponding Author: Morteza Fallahpour, MD; Department of Allergy, Rasool-E-Akram Hospital, Iran University of Medical Sciences, Tehran, Iran. Tel: (+98 911) 1264 497, Fax: (+98 21) 6649 3355, E-mail: fallahpour.m@iums.ac.ir, fallahpour.morteza@yahoo.com

accompanied by mucus.[1] Although the patients are healthy, the bloody stool is a diagnostic test to findvery horrific for parents.

Parental anxiety alongside the lack of a specific accused food will complicate the treatment. Three immunological mechanisms have been determined in food allergies: IgE-mediated, cell-mediated, and mixed IgE- and cell-mediated type. IgE-dependent reactions may present via various symptoms such as urticaria, itching, angioedema, and in severe cases can lead to anaphylaxis. Foods are one of the most common causes of anaphylaxis of all ages.[2] Despite these kinds of reactions, in proctocolitis the food antigens that are either indirectly transmitted through the mother's milk or directly by infant feeding are involved in the development of the disease via a pure cell-mediated mechanism. The nature of the reaction in this disease is delayed-type (hours or even days later), which makes it more difficult to rely on the patients' history to identify culprit food, because it may be a long gap between the food eaten and the symptoms.[3,4] Atopic patch test (APT) has been used in various studies in patients with food allergies and skin eczema to identify the accused food with a non-IgE-dependent mechanism. It is suggested that IgE-bearing Langerhans cells in addition to specific T cells influx into the site of exposure to the allergen can explain the underlying mechanism of APT in allergen detection in non-IgE-dependent disorders, but there are still many uncertainties.[5-7] Elimination/introduction (E/I) challenge is the gold standard method approved in these patients. [4]This study aimed to evaluate the results of APT in allergic proctocolitis in infants less than one year of age and compare the APT results with the E/I challenge.

MATERIALS AND METHODS

Patient Selection and Study Design

This study was performed on less than one-year-old patients with allergic proctocolitis who were referred to allergy, gastroenterology, and general pediatric clinics in Rasoul-E-Akram and Firoozabadi hospital, Tehran, Iran from September 2017 to June 2018. Diagnosis of allergic proctocolitis was confirmed by both pediatric gastroenterologist and allergist after excluding the differential diagnosis.[8] Individuals who did not have recurrent bloody stools after recruitment to the study or who had no visible blood in the stool (only occult blood in their stools), those with other diagnoses rather than allergic proctocolitis, and those whose parents did not adhere to dietary protocols were excluded from the study. Written informed consent was obtained from all participants and the protocol was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC.1397.202). After confirming the diagnosis, a questionnaire about, age of onset and feeding status was recorded. APT was done for all of the individuals and those who had positive skin test results equal, or more than 2+ were recalled and an E/I challenge was done based on the APT result. When more than one food was positive, all the accused foods were removed first, after 2-4 weeks if all symptoms resolved, food(s) were introduced (were added to the infant's or mother's diet (if breastfeeding) separately with a 10-day interval.[9] If symptoms disappeared with elimination and reappeared after introduction, that food was known as the culprit. Finally, APT results were compared with the results of the E/I challenge.

Atopic Patch Tests (APT)

APT was performed for all participants, the same fresh foods (cow's milk, egg yolk and white, peanuts, soybeans, rice, wheat, corn, sesame, and red meat) were placed on a filter paper disc (Chemo technique Finn chamber, Sweden) protected with petrolatum in 12 mm Finn chambers and one empty chamber filling with petrolatum only was also considered as a negative control. and covered with adhesive tape, and were removed after 48 h. The results were recorded 48h after the removal. The APT interpretation was done based on the International Contact Dermatitis Research Group (ICDRG) and a result was considered positive if we observed erythema, infiltration, possibly papules (+), or erythema, infiltration, papules, vesicles (++), and intense erythema, and infiltration and coalescing vesicles (+++).[10]

Statistical Analysis

Statistical analysis was performed with SPSS software, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The data were presented; using Prism software, version 8.01 (GraphPad, La Jolla, California). Results were expressed as frequency (number and percentage) and analyzed using a one-sample chi-square test. A value of $p<0.05$ was considered statistically significant.

RESULTS

Forty-six infants less than one year of age were referred with a probable diagnosis of allergic proctocolitis of whom 8 infants were excluded owing to misdiagnosis, and 10 patients did not adhere to the E/I protocol or did not come for follow-up. Overall, this study ended with 28 patients. The mean age of symptom onset was 2.23±1.7 months and the mean age of the participant at the time of the study was 5.25±2.19 months. Ten of them were girls and 18 were boys. The lowest age of onset was 16 days and the lowest age at the time of the study was 3 months. Feeding status at the time of presentation and participation in the study are shown in Table1.

The patch test was positive in 14 patients (50%) of which 6 (43%) patients were sensitized only to one food, 7 (50%) patients had shown two sensitizations, and one (7%) patient presented reactions to three foods. The frequency of allergens among positive patch tests was as follows; milk 10 (71.4%), Rice 5 (35.7%), white egg 4 (28.5%), soya 4 (28.5%). Furthermore, there was no positive reaction (0.0%) for corn, red meat, wheat, and sesame allergens in the skin patch test (Table 2 and Figure 1A). The successful rate of E/I challenge in positive skin patch test was 80% (8 of 10) for milk, 60% (3 of 5) for rice, and 25% for white egg (1 of 4), respectively (Table 2, Figure 1B).

Table 1. Feeding status of patients at the time of disease onset and participating in the study

Feeding status		At the time of Disease onset		At the time of Participating in the study	
		Number	%	Number	%
Feeding	Breast milk-fed	11	39.2	5	17.9
	Formula-fed	5	17.9	6	21.4
	Both breast and formula	12	42.9	17	60.7
	Supplementary feeding	6	21.4	18	64.3

Table 2. The result of the patch test and E/I challenge

Allergens	Patch test			E/I from Positive patch test		
	Number	%	*p*	Number	%	*p*
Milk	10	71.4	**<0.001**	8	80	**<0.001**
Rice	5	35.7	-	3	60	**<0.05**
White egg	4	28.5	-	1	25	-
Soya	4	28.5	-	0	0	-
Corn	0	0	-	-	-	-
Red meat	0	0	-	-	-	-
Wheat	0	0	-	-	-	-
Sesame	0	0	-	-	-	-

The results were analyzed by One sample chi-square. E/I; elimination/introduction

DISCUSSION

In the current study, 28 infants less than one year old were diagnosed with allergic proctocolitis underwent APT. Subsequently, patients with positive skin test results were selected to do the E/I challenge, which is the gold standard test for confirming the accused food. In this study, only 50% of contributors had positive APT. Interestingly, the APT result was not the same in all the foods, as milk, rice, soy, and egg white were the most common positives. It was negative in peanuts, wheat, corn, sesame, and red meat in our study which was in line with other studies. Pustišek showed that milk and soy are the most common[11] and Aslan et al. showed that milk is the culprit in 75% of infants while egg, nut, fish, and red meat were involved in the rest cases.[12] What we know about skin tests is that they only show sensitization, and that is why

finding relevancy should be taken into account for interpreting them correctly.[13] APT has long been used to identify allergens that are involved in causing disease by mechanisms other than IgE-dependent mechanisms A diverse spectrum has been reported in sensitivity, specificity, positive and negative predictive value of APT in diagnosis food allergy in atopic dermatitis and non-IgE mediated food allergy ranged from 40% to 91%.[14-16] One of the major challenges in APT seems to be the lack of standardization of this test.[17] On the other hand, all known allergy tests are only able to identify the probable allergen and whether the known substance is the main culprit is questionable.[13] Currently, the gold standard test for identifying a culprit food in allergic proctocolitis is the elimination and reintroduction test.[9] To the best of our knowledge, this study is the first research that compares APT test results in allergic proctocolitis with gold standard diagnostic test results, the positive findings in APT were confirmed in E/I tests in different values. The highest consistency was for milk and rice. It should be noted, however, that the main limitation of our study was the low sample size. Therefore, we recommend further studies in a larger sample size.

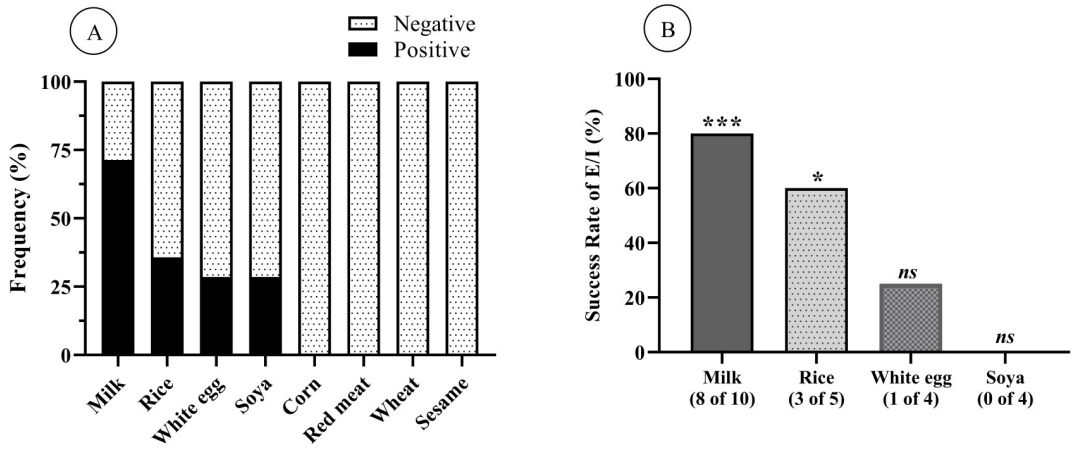

Figure 1. (A) The frequency of positive and negative patch tests based on different allergens in patients. (B) The success rate percentage of elimination/introduction (E/I) challenge in 10 patients with a positive milk patch test, 5 patients with positive rice patch test, 4 patients with a positive white egg patch test, and 4 patients with positive soya patch test. The success rate were analyzed by a one-sample chi-square test for each group of patch tests separately (not comparison among different patch tests). * $p<0.05$, ** $p<0.001$, ns: not significant.

In conclusion, we found that the atopic patch test is positive in half of the infants which is consistent with the published papers; however, the comparison of results with E/I challenge showed that APT is not consistent with E/I in soybean, corn, and egg white, but the correlation was found in milk and rice was 80 and 60 % respectively, so we suggest APT may be an effective assay with satisfying relevancy with the gold standard for detecting some of non-IgE mediated food allergen(s) in allergic proctocolitis.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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