



Non-IgE-mediated Gastrointestinal Food Allergy in Children: Our Foods and Atopy Patch Test

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Abstract

Background: Food allergy (FA) is an increasing health problem in children. Previous studies have reported conflicting results about the diagnostic value of atopy patch test in food allergies. The aim of the present study was to investigate the accuracy of atopy patch test in identifying non-IgE-mediated gastrointestinal FA to pasteurized/homogenized cow's milk, heated raw cow's milk, white and yolk egg, soy, wheat, walnut, sesame, pistachio, almond, peanut, date and cumin which are popular food ingredients in southern Iran.

Methods: This study was performed on children with gastrointestinal allergic problems who were not improved after at least 4 weeks of cow's milk protein elimination. Atopy patch test (APT) was performed and the elimination diet was considered according to positive skin results and after resolving symptoms, introduction of each accused food was done sequentially.

Results: Fifty three children under 7 years old with mean age of 19.6 months underwent APT and the results were verified by open oral food challenge (OFC). Sensitivity in the range of 59%-95%, specificity of 80.7-92.8%, positive predictive values of 75-96.4% and negative predictive value of 23%-80.7% were calculated depending on the type of food. Compared to the heated raw cow's milk, the pasteurized/homogenized cow's milk reaction was significant.

Conclusion: APT can be included in the diagnostic workup of non-IgE-mediated GI allergy because it is safe and has great accuracy. However, several aspects require further investigation especially to enable the standardization of the technique. We should be aware of the allergenicity of our foods due to processing and geographic region.

Keywords: Allergy, Atopy patch test, Children, Gastrointestinal, Oral food challenge

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Introduction

Food allergy (FA) is an increasing health problem and affect 6% of children in the United States (1,2). Although more than 170 foods have been reported to cause IgE-mediated reactions, most prevalent studies have focused only on the most commonly used foods while little information is available regarding the prevalence of multiple food allergies (3). The majority of work is on reactions to cow's milk protein (CMP) or soy protein (4,5). Other food allergies begin to predominate in older children, including egg, fish, peanut, and wheat allergies (2,6). Type I (IgE-mediated) immediate hypersensitivity reactions to foods can be confirmed with skin prick test (SPT) and/or serum IgE testing (1-3). Non-IgE, cell-mediated food allergic disorders encompass food protein-induced enterocolitis syndrome (FPIES), food protein-induced enteropathy (FPE), food protein induced allergic proctocolitis (FPIAP) and Heiner's syndrome (pulmonary hemosiderosis) (2,4,5,7,8). For non-IgE mediated GI food allergy, diagnosis is based on history, clinical feature and the exclusion of other etiologies. In majority of patients,

specific IgE (sIgE) antibodies are undetectable and sIgE and SPT results allow for allergy persistence prediction while a negative test result does not exclude allergy (9,10). Indeed, for IgE-independent GI problems, the diagnosis is hampered by the lack of noninvasive confirmatory tests. Nevertheless, an oral food challenge (OFC) test is necessary in most cases to confirm an adverse food reaction and the gold standard is a double blind placebo controlled food challenge (DBPCFC) (1,2,8-11).

Atopy patch test (APT) was introduced as a diagnostic tool in the late nineteenth century. Since then, it has been improved considerably (12,13). The APT involves placement of allergens on the skin and evaluation of rash in the subsequent days after removal (14). The test is based on cutaneous T-cell mediated responses (15). A positive APT reaction correlates with a positive lymphocytes transformation test and allergen-specific Th₂ cells in the peripheral blood (16). Contrary to the SPT, the APT with food allergens may detect IgE-independent reactions and can be a good method in the diagnosis of late allergic reactions (17). Patch tests are used in the



diagnostic investigation of contact and atopic dermatitis worldwide. The investigators designed numerous studies dealing with APT methodology, interpretation, accuracy and indications in different allergic problems. The methodology is simple; however, it requires adequate training for the results to be correctly interpreted and used (18). DBPCFC is a time-consuming and costly procedure and requires onsite medical supervision and resuscitating medicines and devices on hand (17,19).

The aim of this study was to compare the APT with the OFC in children with non-IgE mediated GI food allergies. In addition to common food allergens, we considered popular foods in our geographic region.

Materials and Methods

This study was performed on children with GI problems who were referred to Pediatric GI Clinic of Afzalipoor Hospital, Kerman, Iran from March 2018 to June 2020. The children suspected of FPIPC, FPIES or FPE who were not improved after at least 4 weeks of cow's milk protein elimination were selected. The patients were evaluated by a pediatric gastroenterologist and allergist and those with other diagnoses rather than allergy were excluded from the study. The allergic patients were enrolled in this prospective trial and written informed consent was obtained from all participants.

After recording a questionnaire including demographic data, personal and family history, physical examination, previous medical prescriptions, laboratory results, endoscopic and pathologic findings and confirming the diagnosis, APT was performed with fresh foods. Multiple foods were selected including pasteurized/homogenized (P/H) milk (3.5% fat), heated raw cow's milk (strictly controlled raw cow's milk after 20 minutes of boiling), yolk and white eggs, almond, pistachio, walnut, soy, sesame, peanut, cumin and date (Figure 1). These foods were chosen because our province is a large producer of pistachio, date and cumin in Iran and these foods are used frequently in the people's diet. The APT interpretation was done based on International Contact Dermatitis Research Group (ICDRG). For the patients who had positive skin results equal, or more than +1, an elimination diet (mothers' elimination diet in breast feeders) according to APT results were applied for 2-4 weeks. After resolving symptoms, each accused food introduced for 1 week sequentially. Symptoms were closely monitored in hospital and at home by phone calls or visits during the challenges. If the symptom was substantially improved during the elimination period and reappeared after food introduction, this food was considered as a cause. Then APT results were compared with the results of elimination and challenge.

Statistical analysis was performed through SPSS, version 20 and P value < 0.05 was considered statistically significant and the Pearson correlation coefficient was



Figure 1. Prepared foods for APT test

used for assessing the correlation between variables.

Atopic patch test

Participants were instructed to withdraw previous prescriptions which included glucocorticoids, antihistamines and topical immunomodulators at least 5 days prior to the test. The 8mm Finn chambers on scanpors (SmartPractice, Phoenix, AZ, USA) used for different allergens. Fresh foods were distributed on the filter paper and covered with the Finn chambers. Heated raw cow's milk (strictly controlled cow's milk after 20 minutes of boiling) was used as H milk while pasteurized and homogenized (P/H) cow's milk was also tested. Whisked white and yolk egg were used separately. Native solid foods used in a powder form dissolved in isotonic saline (1 g of powder in 10 mL isotonic saline) and also fresh soft date was used. According to official consensus published by Turjanmaa et al, the application site was the upper back of patients (20). The results were obtained after occlusion time of 48 hours and reading at 72 hours according to the ICDRG. Result was considered positive if we observed erythema, infiltration, possibly papules (+) or erythema, infiltration, papules, vesicles (++) or intense erythema, infiltration and coalescing vesicles (+++) (21-23).

Oral food challenge

If the symptoms substantially improved or disappeared after 2-4 weeks on an elimination diet, an open challenge in hospital setting with safety facilities was performed. In case of CMP allergy (CMPA), a formula based on CMP in infancy and P/H and H milk after 9 to 12-month age was

considered. After physical examination of the undressed infant, with inspection of the skin, a drop of the formula/ milk was put on the child's lips. If no reaction occurred after 15 min, the formula/ milk was given orally and the dose was increased stepwise (0.5, 1.0, 3.0, 10, 30, 50 to 100 mL) every 30 minutes (10,24,25). Next, the child was observed for 2 hours and examined for cutaneous and respiratory reactions before going home. If no reaction occurred, the child received at least 250 ml of cow's milk-based formula or 50 ml of milk each day for the following week and the parents were told to observe the child for late reactions. Allergy was confirmed if symptoms of CMPA re-appeared and the infant maintained on an elimination diet. For children who did not develop symptoms during challenge and up to 1 week after the follow-up a negative challenge was assumed. A clinician advised parents to be attentive for delayed reactions which may evolve over several days following the challenge.

For other foods, allergen challenges were started with 0.2 g, 0.4 g and 0.6 g of the food per kilogram of the body weight (not exceeding a total dose of 10 gr of total food)

given in three incremental doses over 30 min. Parents were advised to give their child the food every day and the patient was followed for 1 week (26-30).

Results

Fifty-nine children from 1.5 months to 7 years old age were referred to our department because of FPIAP, FPE or FPIES and with no improvement after CMP elimination and in some cases soy and egg protein elimination. Five children were excluded owing to misdiagnosis and APT was performed for 54 patients. APT was negative for all of foods in a child who could not continue this trial as well. In whole, 24 male and 29 female participants continued the study. After elimination and resolution of the symptoms, 7 participants who were less than 9 months old refuse to take the challenge and this trial ended with 43 patients eventually (Figure 2).

The mean age of participants at the beginning of the study was 19.6 ± 18.2 months. The minimum age of the onset was 1.5 month and the maximum was 72 months. The mean age of symptoms onset was 9.1 ± 7.7 months.

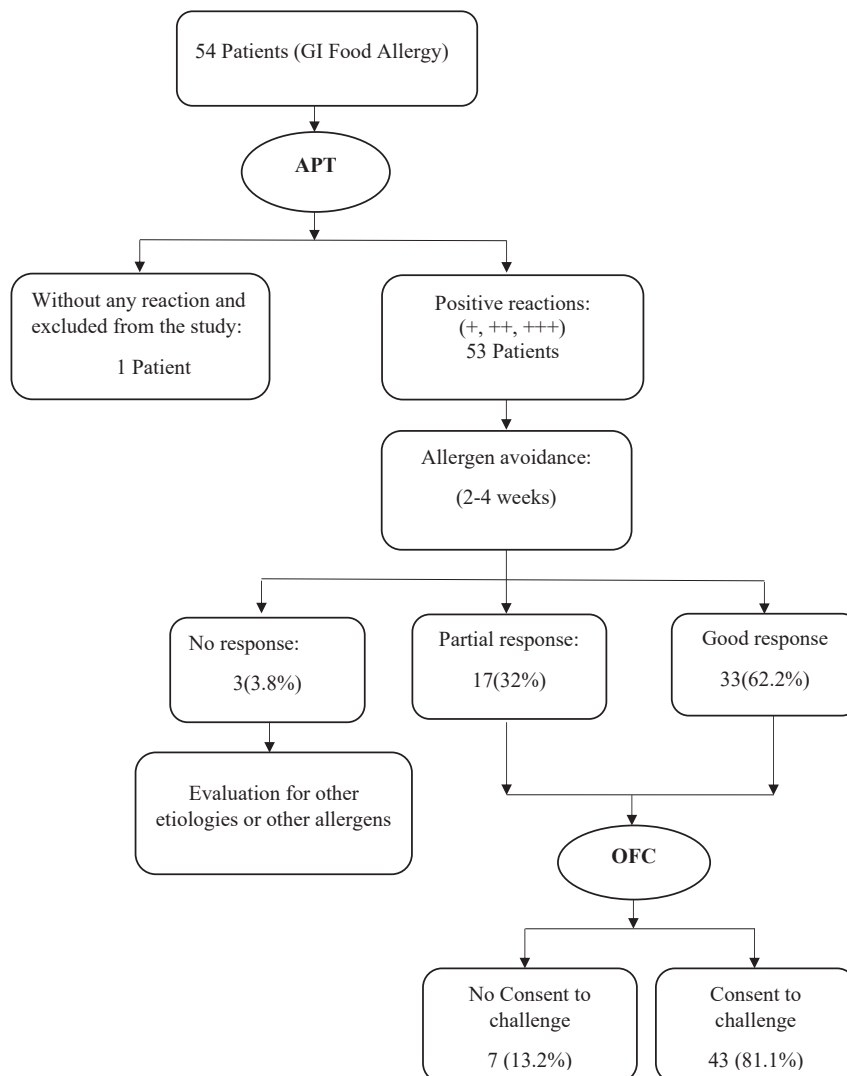


Figure 2. Study flowchart

The duration of symptoms at the time of the study was 14.6 ± 10 months. In terms of age, 54.7% of participants were under 1-year-old and 81.1% were under 3 years old.

The patients' symptoms were diarrhea either moderately loose stool or frank diarrhea (94.3%), growth failure (60.3%), tenesmus (52.8%), irritability (49%), vomiting (37.7%), hematochezia (19%), regurgitation (18.8%), atopic dermatitis (18.8%), asthma (18.8%) and allergic rhinitis (16.9%). Allergic problems in first-degree family members were allergic rhinitis in 43.3%, contact and atopic dermatitis in 24.5%, allergic GI problem in 18.8% and/or asthma in 15%. The allergic family member was mother in 25 children (47.1%), father in 14 ones (26.4%), and sibling in 11 ones (20.7%). All participants had history of food elimination diet before the trial; cow's milk protein in 53 (100%), egg in 24 (45.3%) and nuts in 10 (18.8%) cases.

The APT results of the study are shown in Table 1. P/H milk was the most common culprit in 44 patients (83%). There was no correlation between a specific symptom and APT intensity reactions. We did not find any correlation between a specific patient's symptom and mean numbers of allergens based on APT except for vomiting that had a noticeable correlation ($r=0.44$, $df=51$, P value: 0.003). Positive APT result for P/ H cow's milk were significantly more than that for boiled raw cow's milk ($r=0.46$, $df=51$, P value: 0.001) which was verified with OFC. Common allergens based on APT in different age ranges shows P/H milk, peanut, sesame, egg, fresh cow's milk, soy, almond, pistachio, cumin, walnut, wheat and dates were common in children younger than 3 years old age. Positivity of wheat, cumin and almond were substantially declined after 3 years old age.

Table 1. The result of atopy patch test

Allergens	+1 Number(%)	+2 Number(%)	+3 Number(%)	Total Number(%)
P/H milk	32(60.4)	12(22.6)		44(83)
Heated milk ^a	25(47.2)	9(17)	1(1.9)	35(66)
White egg	21(39.6)	15(28.3)		36(67.9)
Yolk egg	21(39.6)	6(11.3)		31(58.4)
Soy	22(41.5)	2(3.8)	2(3.8)	26(49)
Wheat	16(30.2)	12(22.6)		28(52.8)
Almond	25(47.2)	10(18.9)	3(5.7)	38(71.6)
Sesame	29(54.7)	9(17)	1(1.9)	39(73.5)
Peanut	27(50.9)	7(13.2)	1(1.9)	35(66)
Pistachio	25(47.2)	9(17%)	1(1.9)	35(66)
Walnut	15(28.3)	12(22.6)	6(11.3)	33(62.2)
Date	22(41.5)	5(9.4)		27(50.9)
Cumin	26(49.1)	6(11.3)		32(60.3)
N/S				IR: 12 (22.6)

P/H, Pasteurized /homogenized; N/S, Isotonic saline (Normal saline); IR, Irritant reaction

^a Heated cow milk (strictly controlled raw cow's milk after 20 minutes of boiling).

After 2-4 weeks of an elimination diet according to APT, response was recorded as no response in 3 (5.6%), partial response in 17 (32%), and good response in 33 (62.2%) cases. Open food challenge was performed in 43 patients who had partial or good response and 7 patients less than 9 months' age refused the challenge. The results of OFC in the patients are shown in Table 2. Sensitivity, specificity, positive and negative predictive value of APT compared to OFC, as a standard allergy test, is illustrated in Table 3. We found transient mild erythema in 25 patients which improved in one hour and did not find another complication.

Discussion

In the current trial, 53 children less than 7-year-old were evaluated and diagnosed as having GI food allergies. Cow's milk elimination in all patients had been started previously and with continuing the symptoms, multiple FA or other diagnoses had been considered and the patients had been referred to our department. The diagnosis of non-IgE-mediated FA is mainly clinical and is not always easy in contrast to IgE-mediated reactions (18,31). That was a reason of the relatively long mean duration of symptoms in the participants of the current study (14.6 months).

The prevalence of food hypersensitivities is greatest in the first few years of life (32). In this study, more than 50% of the children were infants and 81.1% had less than 3 years old and the mean age of the participants at the time of the study was 19.6 months which is consistent with the literature. In Meyer et al study on children with protein induced GI allergy, the median age of onset of symptoms of GI allergy was 5 months and the children on average were 63 months. In the mentioned study, participants were older than our patients because their tertiary center only accepted referrals from pediatricians

Table 2. The result of open food challenge

Allergens	Positive oral food challenge (Number)	Negative oral food challenge (Number)
P/H milk	35	3
Heated milk	27	2
White egg	30	3
Yolk egg	25	3
Sesame	30	5
Pistachio	24	5
Peanut	25	5
Wheat	20	8
Cumin	20	6
Walnut	20	7
Soy	20	2
Dates	20	5

P/H: Pasteurized /homogenized.

^a Heated cow milk (strictly controlled raw cow's milk after 20 minutes of boiling).

Table 3. Diagnostic efficacy of APT compared to OFC

Allergens	Sensitivity	Specificity	Positive predictive value	Negative predictive value
P/H milk	71	80	96.4	26.6
Heated milk ^a	65.5	92.8	95	56.5
Yolk egg	66.6	87.5	90	60.8
White egg	68.5	87.5	96	38.8
Soy	59	85.7	81.2	66.6
Wheat	66.6	92.8	95.2	56.5
Peanut	68.9	85.7	90.9	57.1
Walnut	73.6	80.7	91.3	80.7
Pistachio	81.4	87.5	91.6	71.6
Tree nut	75	86.6	91.3	65
Sesame	92	87.5	95.8	36.8
Cumin	44.4	85.7	94.1	23
Date	60	86.5	75	28

P/H: Pasteurized /homogenized.

^a Heated cow milk (strictly controlled raw cow's milk after 20 minutes of boiling).

(33). The delay in diagnosis is well recognized amongst specialists working with children with FA (33,34).

The risk of atopy increases if a parent or sibling has atopic diseases and is still higher if both parents are atopic (35, 36). In the current study, the allergic family member was mother in 47.1%, father in 26.4% and sibling in 20.7%. In the Meyer et al trial, the majority of children had an atopic family history (33). In our study, allergic problems in the first-degree family member include rhinitis in 43.3%, contact and atopic dermatitis in 24.5%, allergic GI problems in 18.8% and/or asthma in 15%. Meyer et al also found a significant association between having an atopic family history and the development of this type of GI food allergies which was not observed in our trial. In both Meyer et al and the current study, the history of allergy in mother was more than that in other family members. Koplin et al mentioned that defining "high risk" as two or more allergic family members may be more useful for identification of groups with a significantly increased risk of FA (37).

The most common symptoms in this trial were diarrhea, growth failure, irritability and vomiting which are consistent with previous studies (33). In terms of allergic symptoms, atopic dermatitis (18.8%), Asthma (18.8%) and allergic rhinitis (16.9%) were recorded in the participants of the current trial which were less frequent compared to the Meyer's retrospective study (33). In Caffarelli et al study focusing on children with atopic dermatitis, 42% of children with atopic dermatitis had GI symptoms (38). Therefore it is important that dermatologists, allergists, gastroenterologists and pulmonologists do not forget the overlapping symptoms and ideally run a multidisciplinary clinic (33,39).

In industry, fresh raw milk is centrifuged to produce skim milk. Raw milk is heated at 74°C for 15 seconds to produce pasteurized milk and homogenized milk is produced by passing pasteurized milk through homogenizer processing (40). Nowak-Wegrzyn and Fiocchi mentioned that the effect of the industrial process on the antigenic/allergenic properties of cow's milk proteins is minimal (41) but according to Feng et al significant changes to the properties of milk proteins occur as a consequence of heat treatment and homogenization (40). In the Australian study, groups of rats were immunized intraperitoneally with raw milk, skim milk, pasteurized milk or P/H milk and serum IgG antibodies directed against milk plasma proteins were assayed. Significantly higher concentrations of antibodies of all specificities were detected in the serum of animals immunized with P/H milk compared with animals immunized with raw or skim milk. Although care must be taken in extrapolating from the rodent IgG response after parenteral challenge to the human IgE response after milk ingestion, it is reasonable to consider that commercial processing may contribute to the propensity for cow's milk to induce allergic reaction in children (40). Investigators in the Netherlands found a direct link between one of the immunologically active whey proteins present in raw cow's milk and the suppression of allergic symptoms. Their study showed that the alkaline phosphatase is a promising raw milk component to be added to heat-treated milk (42). In another study by these researchers, mice sensitized to raw milk showed fewer acute allergic symptoms upon intradermal challenge than mice sensitized to processed milk. Moreover, allergen-specific IgE levels and Th2 cytokines were significantly lower in raw milk sensitized mice. In an oral provocation pilot, cow's milk allergic children tolerated raw milk (certified, strictly controlled) up to 50 mL, whereas they only tolerated 8.6 mL shop milk ($P=0.0078$) (43). In our trial, P/H cow's milk was the most common culprit according to APT; that is, 83% of patients had positive APT results for P/H and 66% for H milk with statistically significant difference and it was verified by the OFC (P value < 0.05). According to CDC, consumption of raw milk and products made from it can pose severe health risks including death due to harmful bacteria (44). Through elucidating the raw milk components responsible for the allergy-protective effects and understanding the underlying mechanisms, new dietary concepts aimed at safe allergy management could be developed (42,43).

In naming foods with a high allergenic potential to avoid, in most geographical regions, egg proteins are the most common cause of allergy after CMPA in infants and young children. Peanut allergy is more common in the US and Europe than in Asia (10,26). Europeans and Americans mostly eat roasted peanuts, whereas

Asians eat boiled and fried peanuts. Different processing methods may affect the sensitization of peanut products (45). From a biochemical perspective, thermal processing promotes conformational changes of food proteins and may further affect digestion and absorption of proteins or peptides by the intestinal epithelium. It has been shown that roasting and boiling processes increase or decrease the allergenicity of peanuts (46-48). In the present study, we selected a number of some popular foods which are used in our region for APT. In our geographical area, supplemental feeding usually starts with almond and rice. Furthermore, sesame (especially sesame oil), pistachio, walnut, cumin and date are local products and most consumed food ingredients in our diet. After analyzing the data, these foods were found as common culprits which had not been evaluated before (49-53). Although CMP was the most common cause of allergic reactions, other food products, especially nuts produced reactions and in more than 15 percent CMP did not play a role; therefore, clinicians should consider these possibilities.

According to the previous studies worked on APT in contact and atopic dermatitis, eosinophilic GI disease (EGID), FPIAP, FPIES, FPE and recently irritable bowel syndrome, the diagnostic role of APT can be different in each scenario (53-58). A diverse spectrum has been reported for the sensitivity, specificity and predictive values of APT in diagnosis of FA in atopic dermatitis and non-IgE mediated FA, depending on the study. Heine et al considered the number of papules, "Crescendo" phenomenon and induration with in Finn chamber margin or beyond it (15). Arshi et al interpreted APT test as positive if the reaction was equal or more than 2+ based on ICDRG (49). In Yang et al study, erythema and infiltration were not sufficiently indicative of a positive APT and the positive predictive value increased with the appearance of indurations and the number of papules and the true positive APT rate increased from score of + to ++++. The diagnostic accuracy of APT has been reported higher for fresh foods compared to frozen dried food extracts (24). In the present study, fresh foods were used and the APT was recorded as positive if skin results were equal or more than +1 based on the ICDRG. The sensitivity of 59%-95%, specificity of 80.7-92.8%, positive predictive value of 75-96.4% and negative predictive value of 23-80.7% were estimated depending on the type of food (Table 3). These results could reveal the effect of our family and country tradition on diet and FA in children. Moreover, the valuable diagnostic efficacy of APT in these GI problems and its role in avoiding OFC and limiting the complications due to under and over diagnosis of allergic GI problems were emphasized. A study, by Sirin Kose et al, aimed at determining the diagnostic efficacy of APT compared to OFC in patients with GI symptoms caused by cow's milk and hen's egg allergy. Patients with milk allergy APT had a specificity of 100%, sensitivity of 9.1%,

and in patients with egg allergy, a specificity of 78.6% and sensitivity of 77.0% were observed (60). In a meta-analysis on children with FA-related GI symptoms, the pooled sensitivity and specificity were 57.40% (95% CI 52.10%-62.50%) and 91.50% (95% CI 88.30%-94.10%), respectively (61).

Conclusion

In summary, FA is an important public health problem that affects children and its prevalence may be increasing. Food processing methods might have a role in this slope and we need more studies to understand this effect and find some techniques for reducing the allergenicity potential of our foods. Moreover, traditional and geographical diet can affect the FA. DBPCFC is the gold standard method for diagnosing non-IgE-mediated FA. However, due to the difficulty of their performance on routine clinic, there is a need for laboratory tools in order to minimize the frequency of DBPCFC. Our study showed that the APT represents a promising technique of diagnosing delayed-type GI allergic problems. However, the clinical relevance of positive APT reactions should be still proved by standardized outcome definitions.

Authors' Contribution

Data curation: Mahdiah Saviz.

Formal analysis: Maryam Ahmadipour.

Methodology: Nasrin Bazargan.

Project administration: Parvin Abbaslou.

Supervision: Nasrin Bazargan.

Writing—original draft: Mahdiah Saviz.

Writing—review & editing: Parvin Abbaslou.

Competing Interests

None.

Ethical Approval

This study was approved by the Ethics Committee of Kerman University of Medical Sciences (Ethics No. 1396.2121).

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