Atopy patch test in the diagnosis of food allergy in children with atopic eczema dermatitis syndrome

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Abstract

Puropose: Food allergy has been demonstrated to play an important role in the pathogenesis of atopic eczema dermatitis syndrome (AEDS), affecting often atopic infants and young children. The most commonly offending foods are cow's milk, hen's egg, wheat and soy; implicating immediate (IgE-mediated) and late-phase (T-cells) immunological reactions in the pathogenesis of skin lesions. The diagnostic work-up of suspected immediate food reactions includes skin prick tests (SPT) and the measurement of food-specific antibodies (sIgE). The methodology of atopy patch test (APT) has been reported as a diagnostic tool with high predictive capacity for late-phase clinical reactions in children with atopic dermatitis. Although APT has been introduced into the diagnostic procedure for food allergy, its diagnostic accuracy remains still controversial; especially in older children. The aim of study was to evaluate the diagnostic accuracy of the atopy patch test in the detection of food allergy in correlation with SPT, sIgE and positive oral food challenge to milk, in children suffering from AEDS and to assess the sensitivity and specificity of this method in dependence on the age of investigated children.

Material and methods: 34 children (25 boys, 9 girls) aged 5 months-16 years with suspicion of milk-related AEDS were investigated. These patients were subdivided into 2 age groups: group A – 20 children (<3 years), group B – 14 children (>3 years). The diagnostic procedures as skin-prick tests and atopy patch test were performed. The specific IgE to cow's milk allergens were also measured. The open and blind diagnostic oral food challenge were performed to verify the results of tests. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive value of APT were calculated in both age groups.

Results: A positive challenge response to milk was found in 65.0% of investigated children in group A and in 35.7% in group B. No statistical differences in the prevalence of immediate ($p<0.1905$) and delayed-type ($p<0.409$) reactions has been found between age groups. Positive APT to milk were noticed in 55.0% of patients in group A and in 35.7% of children from group B, that has been in correlation with positive delayed-type reactions in oral food challenge in 72.7% and 80.0% in corresponding age groups. Polysensitization to other food allergens confirmed by SPT and/or sIgE was detected in 35.0% of patients younger than 3 years of age and in 50.0% of older children. The prevalence of positive APT to other foods (soy, rice, maize, cereals) was significantly higher ($p<0.0073$) in the polysensitized children from group A. Sensitivity of SPT/sIgE in children with immediate-type reactions to milk was 100%, specificity 94%. Sensitivity of APT to cow's milk in children with late-phase reactions was 80% in both age groups; specificity 70%/89% with comparable PPV in both groups (73%/80%). Parallel skin testing with combined patch test and evaluation of sIgE enhanced the value of sensitivity to 92% in the group A and specificity to 89% in the group B. For PPV corresponding figures were 85%/80%.

Conclusions: APT was found to be more sensitive and specific method than SPT/sIgE in diagnosing delayed food allergy in children with AEDS. No age correlation between positive results of APT and oral food challenge and higher specificity of APT in older children confirm its accuracy in diagnosing delayed cow's milk allergy in all age groups of children. Combined skin prick and patch testing significantly enhances identification of food allergy in children with AEDS. The outcome of the APT with food does not seem to be influenced by age of children, but because of its variability of sensitivity and specificity, a diagnosis of food allergy should be confirmed by oral food challenge.

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Abbreviations: AEDS – atopic eczema dermatitis syndrome; APT – atopy patch test; CI – confidence interval; DBPCFC – double blind placebo controlled food challenge; IgE – immunoglobulin E; LR – likelihood ratio; NPV – negative predictive value; PPV – positive predictive value; sIgE – specific IgE; SPT – skin-prick tests.

Introduction

Atopic eczema dermatitis syndrome (AEDS) is a form of multifactorial skin disease that generally begins in early infancy and is characterized by extreme pruritus, chronically relapsing course and distinctive morphology and distribution [1]. Frequently there is an association with increased IgE production (I, immediate type of allergic reaction by Gell-Coombs) as well as a local infiltration of T-cells and antigen-presenting cells (IV, cellular type of immunologic reaction) [2]. AEDS is also associated with some of environmental and genetic factors. In older children and adults, exacerbations of eczematous skin lesions have been described after contact with aeroallergens (e.g. house dust mite, pollen or animal dander) [3,4]. Atopic dermatitis is frequently associated with food allergy, but the role of foods in pathogenesis of skin lesions is not well known. A number of early reports suggested that food proteins could provoke eczematous skin rashes, what has been proved by observations performed in the group of cow's milk feeding infants in comparison to breast feeding children [2]. The number of children with AEDS and clinically relevant food allergy is reported to be around 40%. The most commonly offending foods in infants and young children are cow's milk, hen's egg, wheat and soy; in older children the most important role play cereals, citrus fruits, colorants and preservatives [5,6].

In patients with food hypersensitivity and skin lesions, the very small quantity needed for degranulation of IgE-sensitized mast cells probably reaches the tissues via the bloodstream, after entry into body through the mucous membrane of the mouth, stomach or proximal intestine. Antigen which induces local immune-complex reactions or T-cell mediated immunity probably reaches the gut lamina propria through the overlying surface epithelium [2]. After the antigen-specific hypersensitivity response starts, the cytokines and inflammatory mediators may develop a variety of allergic (IgE-mediated and T-cells-mediated) reactions. The eczematous skin lesions of atopic eczema are infiltrated by activated T-cells.

The diagnostic work-up of suspected IgE-mediated food allergy includes skin prick tests (SPT) and the measurement of food-specific IgE antibodies (sIgE) by means of serologic assays. The results of SPT were found to be indicative for early reactions to food challenges. No relationship has been established between reactivity in SPT and delayed-onset clinical reactions. To date, double-blind, placebo-controlled, food challenge (DBPCFC) remains the gold standard for diagnosing clinically relevant food allergy.

Recent clinical and immunologic features indicate that there are atopic patients with no discernible IgE-mediated reactivity, where no detectable IgE antibodies were indistinguishable [7]. During last years, it has been found that about half of children with food allergy have no food-specific IgE as measured by skin tests or sIgE. Some patients with late reactions to foods may when challenged develop immediate reactions [8].

In recent years, the atopy patch test (APT) has been established as a tool in the diagnostic work-up of food allergy in infants and children with AEDS and late phase clinical reactions [9,10]. Although patch testing for foodstuffs has been described by some authors as a method with high sensitivity and specificity to identify delayed hypersensitivity in small children, the others have concluded that the patch test does not be useful in the diagnosis of food allergy; especially in older children [11,12]. Most of data concern the ability of APT in diagnosing allergic sensitization in infants in the first 2 years of life [9,10].

The aim of study was to evaluate the diagnostic accuracy of APT in the detection of food allergy in correlation with SPT, sIgE and positive oral food challenge to milk, in children suffering from AEDS and to assess the sensitivity and specificity of this method in dependence on the age of investigated children. The diagnostic value of APT in diagnosing sensitization to other plant-derived and animal food allergens was also established.

Material and methods

Patients

The prospective, nonrandomized study were carried out on the group of 34 children (25 boys, 9 girls) aged 5 months-16 years, referred to the III Department of Paediatrics in Bialystok in the period from January 2003 to December 2004, for evaluation of atopic eczema dermatitis syndrome (AEDS) suspected of food hypersensitivity. These patients were subdivided into 2 age groups: group A – 20 children (<3 years), group B – 14 children (>3 years). Children with suspicion of milk-related skin symptoms were enrolled to the study according to the inclusion and exclusion criteria.

Inclusion criteria to both groups were: atopic dermatitis as defined by the criteria of Sampson for infants [13], modified from Hanifin and Rajka for children older than 1 years [14], history indicated the time correlation between milk and/or food ingestion and exacerbation of clinical skin symptoms. Exclusion criteria were: active AEDS with skin lesions on the back and forearms, actual and earlier treatment with antihistaminic and antiallergic drugs (in dependence of wash-out period for different types of antihistaminics), treatment with topical corticosteroids applied on the back and forearms (at least 48 hours before testing).

Severity of eczema was scored according to the SCORAD score, with assessment of topography items (affected skin area), intensity criteria (extent of erythema, edema, crusts, excoriations, lichenification and xerosis) and subjective parameters (extent of itch and loss of sleep) [15,16]. Population characteristics are presented in the *Tab. 1*.

Table 1. **Population characteristics**

	Group A (n=20)	**Group B** (n=14)	p
Age (months): Mean: (CI 95%)	5-36 17.1±10.18 (12.33-21.87)	62-192 104.21±43.37 (79.17-129.26)	ns
Boys n (%)	16 (80.0%)	9 (64.3%)	ns
Family history of food allergy n (%)	7 (35.0%)	4 (28.6%)	ns
Family history of atopy n (%)	9 (45.0%)	7 (50.0%)	ns
Breast feeding time Min-max (months): Mean: (CI 95%)	 0-7 3.9±2.17 (2.88-4.92)	 0-7 4.0±2.32 (2.66-5.34)	 ns
Onset of clinical symptoms Min-max (months): Mean: (CI 95%)	 1-12 2.85±2.58 (1.64-4.06)	 1-24 7.07±6.27 (3.45-10.69)	 <0.0069
Gastrointestinal symptoms n (%)	10 (50.0%)	7 (50.0%)	ns
Respiratory tract symptoms n (%)	9 (45.0%)	7 (50.0%)	ns
SCORAD index Min-max: Mean: (CI 95%)	 5-85 36.68±27.31 (23.52-49.85)	 15-57 25.71±17.05 (15.87-35.56)	 ns
Milk-free diet n (%)	15 (75.0%)	5 (35.7%)	ns

Skin prick test

The skin prick tests with cow's milk allergens were performed in all investigated children, by the same person on the volar side of the forearm in accordance with the instructions of the European Academy of Allergy and Clinical Immunology [17]. Milk powder containing 3% of fat was diluted in water (1 g/10 mL) to normal feed concentration. Whisked egg white and yolk was put directly on the skin in the form of a small drop. The SPT with other food allergens (soy, wheat, banana, orange, sesame, arachides, fish, beef, hen) were performed with the same procedure as cow's milk powder, to detect co-sensitization. In all patients, food allergens were tested in native form by means of a modified skin prick technique (prick by prick tests). To perform tests with aeroallergens (mites, tree, grass and weed pollen, dog and cat epithelia, wool, cotton) commercial extracts from Allergopharma Company were used. A 1 mm, single-peak lancet with shoulder was used, and negative (NaCl 0.9%) and positive (9% Codeine) was used as control. Reactions were read after 15 minutes by the author. The mean weal diameter was calculated and a reaction of at least 3 mm was considered as positive without reaction of negative control.

Atopy patch test

Atopy patch tests were applied on uninvolved skin of the child's back, according to the method described by Isolauri and Turjanmaa [18]. A "porridge" was made fresh every day with 0.2 ml isotonic saline and cow's milk powder (300 mg), egg white (40 mg), cereals – wheat, barley, oat, rye (200 mg), gliadin (200 mg), soy (200 mg), maize (200 mg), rice (200 mg). Approximately 20 mg of each porridge was put without filter paper into aluminium test cups on adhesive tape. We used 8 mm diameter aluminium cups for children younger than 3 years and 12 mm aluminium cups for children older than 3 years (Finn Chamber, Epitest Ltd., Finland). Microcrystalline cellulose was used as negative control. Application sites were checked after 20 minutes for immediate reactions. The occlusion time of patch test was 48 hours. The results were read for the first time 15 min after removal of the cups. If irritative redness was found in the test area, the results were read after 30 min. The second evaluation was done 72 hours after attaching the patch tests. Reactions were classified according to standards and considered as: 0 – negative – no reaction, either visible or palpable; + – redness – negative or doubtful reaction; ++ – redness and palpable infiltration with papules – positive reaction; +++ – redness, palpable infiltration with many papules and eczema – strong positive reaction. If the reaction was very intensive as: redness, edema, palpable infiltration and vesicles, the result was marked as ++++. Reactions 0 and + (redness without infiltration) were regarded negative, as redness alone can be the results of local irritation. All tests were prepared and applied by the same nurse and all reactions were classified by the author. The test material used was not standardized as such materials are not available.

Determination of total IgE and specific IgE antibodies

Serum samples (2 ml) were analyzed for concentration of total IgE and specific IgE antibodies to food allergens as: cow's milk, egg white, soy, wheat, maize, rice (Pharmacia Upjohn) with a fluoroimmunoenzymatic essay (UniCAP) according to the manufacture's instruction. The detection limit of the CAP system is 0.35 kU/L IgE; measurable specific IgE was defined as a positive test result if >0.7 kU/L.

Oral food challenge

Standardized oral challenge was performed according to Moneter-Vautrin guidelines [19], with the increasing amounts of the milk at 30 min intervals until intake appropriate for their

age was reached. A challenge was done in all children after 4 week on an elimination milk-free diet. Cow milk challenge was performed as the open challenge being a reliable method in infants and young children (<1 year) and as a blinded test in older children. The foodstuff was blinded in apple pulp or rice if no sensitization to these allergens was detected. Oral food challenges were preceded by labial food challenge. The same doses of milk formula were given in open and blinded challenges. The food challenge was performed in the period of no active AEDS (inclusion criteria was SCORAD index<20) and wash-out period of topical corticosteroids.

Immediate reactions were defined as reactions within 2 hours after the last dose of milk was administered. The challenge was started in the hospital when rising doses of the infant formula were given and continued after 24 hours of observation in the patient's home, where the parents recorded the symptoms of the child being with telephone contact with the author. The challenge was discontinued when a clinical reaction was noticed. If one of the following symptoms such as skin eruptions, pruritus, edema, utricaria, exacerbation of atopic skin lesions, vomiting, diarrhoea, irritability, rhinitis, wheezing, anaphylactic shock, was noticed, the challenge was regarded as positive. The evaluation of symptoms and decision to stop a challenge was made by the investigator. All children were examined once a week to verify reported symptoms and seen 1 month after the beginning of challenge to confirm the diagnosis.

Statistical analysis

Statistical analysis was performed by using SPSS for Windows software (version 8.0; PL). Two-by-two tables were used to calculate sensitivity, specifity, positive (PPV) and negative predictive value (NPV), likelihood ratio (LR) individually for SPT, sIgE for immediate-onset reactions in the group A (in the group B no positive immediate reactions) and for APT in patients with delayed-onset reactions in the group A and B. The analysis was performed for combined SPT, sIgE, APT for immediate and delayed reactions, in both group of children. The Mann-Whitney nonparametric test was used to compare the results of IgE serum concentration in children with/or without cow's milk allergy. The χ^2-test was used for group comparison. Data are presented as mean with ranges or 95% confidence interval (CI). Statistical significance was defined by a level of 0.05.

Results

Cow's milk oral food challenge

A positive challenge response to milk was found in 13/20 (65.0%) of investigated children in group A and in 5/14 (35.7%) in group B (*Tab. 2*). Of the positive reactions, 3/34 (8.8%) involved immediate-type reactions; in the other children, delayed-onset reactions appeared. All positive immediate-type reactions were noticed in the group A of children in the form of urticaria, pruritus and/or exacerbation of atopic dermatitis. Gastrointestinal symptoms (vomiting, diarrhea) occurred in one of patients. No anaphylactic shock was noticed.

In patients with delayed-onset reactions, the symptoms were confined to the skin (exacerbation of atopic dermatitis with pruritus) in 11/15 (73.3%) of children; to the respiratory tract (rhinitis, cough) in 3/15 (20.0%) of patients; to the gastrointestinal tract (vomiting, loss of appetite, irritability) in 4/15 (26.7%) of investigated children. All of mentioned symptoms were observed within 48 hours after the last dose of milk was administered.

Table 2. **Positive results to milk (SPT, sIgE, APT, oral food challenge) in children with AEDS**

	Group A (n=20)	Group B (n=14)	p
SPT n (%)	4 (20.0%)	0 (0.0%)	ns
sIgE n (%)	4 (20.0%)	0 (0.0%)	ns
APT n (%)	11 (55.0%)	5 (35.7%)	ns
Oral food challenge n (%)	13 (65.0%)	5 (35.7%)	
immediate-onset reactions	3/20 (15.0%)	0/14 (0.0%)	ns
delayed-onset reactions	10/20 (50.0%)	5/14 (35.7%)	ns

No statistical differences in the prevalence of immediate ($p<0.1905$) and delayed-type ($p<0.409$) reactions has been found between age groups.

Relationship between clinical response and skin test reactivity (SPT and APT) in children with AEDS and cow's milk allergy

Positive APT to milk were noticed in 11/20 (55.0%) of patients in group A and in 5/14 (35.7%) of children from group B, that has been in correlation with positive delayed-type reactions in oral food challenge in 8/11 (72.7%) and 4/5 (80.0%) of children in corresponding age groups. There was no correlation between positive APT and oral food challenge in 4/34 of children from both age groups. The percentage of false-positive results was 25% for both groups and was comparable (27.3% – group A, 20.0% – group B).

The prevalence of positive SPT and sIgE to milk was higher in the group A, but it was not statistically significant (for SPT and sIgE $p<0.1045$). The results correlated with elevated IgE serum concentration for separate patients. No statistical difference has been found between IgE concentration in both age group ($p<0.6242$). Mostly (75.0%), positive SPT to milk were associated with sIgE to milk.

3/4 (75%) of patients with positive SPT and/or sIgE developed immediate-onset reaction to milk in oral food challenge. The percentage of false-positive results was 25%. Coincidence of IgE-mediated allergy to milk with delayed- type of immunological reactions (IV type) was noticed only in the group A (*Tab. 2*).

No milk hypersensitivity was confirmed by parallel testing (SPT, sIgE, APT, oral food challenge) in 5/20 (25%) of children form group A and in 9/14 (64.3%) of children from group B. These results were in correlation with the percentage of children on the milk-free diet before being enrolled to the study (*Tab. 1*).

8 of children demonstrated positive SPT or APT to other foodstuffs; in 2 of them sensitization to aeroallergens was confirmed.

***Table 3*. Polysensitization to other food and inhalant allergens in children with AEDS**

	Group A (n=20)	Group B (n=14)	p
Food allergy n (%)	16 (80.0%)	9 (64.3%)	ns
Type I (SPT, sIgE)	7 (35.0%)	7 (50.0%)	ns
Type IV (APT)	9 (45.0%)	2 (14.3%)	0.0073
Inhalant allergy (SPT, sIgE) n (%)	3 (15.0%)	6 (42.9%)	0.0789

***Table 4*. Sensitivity, specificity, PPV, NPV, LR for SPT/sIgE in children with immediate-type reactions to milk and for APT in children with delayed-type reactions to milk**

	Group A (n=20)		Group B (n=14)
	SPT/sIgE	APT	APT
Sensitivity (%)	100	80	80
Specificity (%)	94	70	89
PPV (%)	75	73	80
NPV (%)	0	22	11
LR+	17.0	2.67	7.2
LR -	0.0	0.29	0.23

Food and inhalant allergy in SPT and APT

The clinical reaction to cow milk challenge was more frequently noticed in the multisensitized patients (69.2% in the group A and 80.0% in the group B).

Polysensitization to other food allergens confirmed by SPT and/or sIgE (immediate-type reaction) was detected in 7/20 (35.0%) of patients younger than 3 years of age and in 7/14 (50.0%) of older children (group B), but the difference was not statistically significant (*Tab. 3*). SPT were positive to hen's egg white, soy, citrus fruits. The prevalence of positive APT to other foods (soy, rice, maize, cereals) was significantly higher ($p<0.0073$) in the polysensitized children from group A; mostly to soy, cereals, maize, rice. This difference was significant only to cereals ($p<0.0096$) (*Tab. 4*). Although no statistical difference was stated between the prevalence of symptoms from respiratory and gastrointestinal tract in both age groups (*Tab. 1*), inhalant allergy was noticed more often in the group of older children, 42.9% vs 15.0% ($p<0.0789$) (*Tab. 3*).

Sensitivity and specifity of SPT/sIgE, APT in correlation to oral food challenge

Sensitivity of SPT/sIgE in children with immediate-type reactions to milk (group A) was 100%, specificity 94%. No positive immediate-onset reactions in the group B were noticed. Sensitivity of APT in children with late-phase reactions to cow's milk was 80% in both age groups; specificity 70% vs 89% with comparable PPV in both groups (73% vs 80%) (*Tab. 4*). Parallel skin testing with combined patch test and evaluation of sIgE enhanced the value of sensitivity to 92% in the group A and specificity to 89% in the group B. For PPV corresponding figures were 85%/80% (*Tab. 5*).

***Table 5*. The comparison of diagnostic value for combined skin prick and patch testing in correlation to oral food challenge tests (immediate- and delayed-onset reactions)**

	Group A (n=20)	Group B (n=14)
	SPT+sIgE+APT	SPT+sIgE+APT
Sensitivity (%)	92	80
Specificity (%)	71	89
PPV (%)	85	80
NPV (%)	17	11
LR+	3.23	7.2
LR -	0.11	0.23

Disscusion

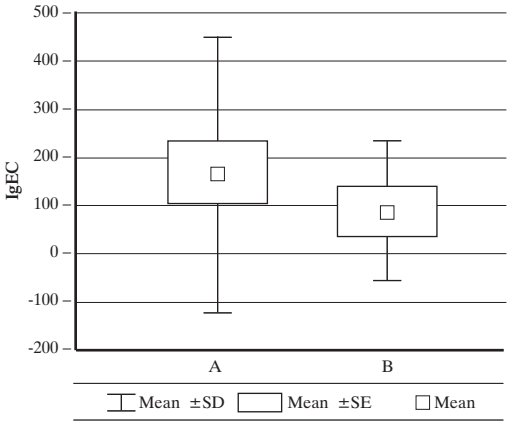
Current data indicate an obvious relation between food allergy and atopic eczema in infants. It has been demonstrated by double-blind placebo controlled food challenges (DBPCFC) that food can exacerbate skin rashes in infants and young children [2,5,6]. Most food allergies involve an IgE-mediated hypersensitivity reaction with positive skin prick test responses, however, no relationship has been established between reactivity in skin prick tests and delayed-onset clinical reactions [18,20]. Patients with atopic eczema who manifest delayed clinical reaction to food challenge have been show to have higher interleukin 2, interferon gamma and TNF-alfa, what confirm the role of lymphocytes T in pathogenesis of AEDS [2,20]. It has been shown that in certain patients with delayed-type reaction eczematous skin lesions can be induced by epicutaneous application of aeroallergens. This procedure was named the atopy patch test (APT).

Identification of offending allergens, food or inhalant, is very important in the management. Accurate and objective demonstration of a casual relationship between the dietary allergen and exacerbation of atopic dermatitis allows for the compliance of the family to the treatment, is the condition of growth in early life and is essential for avoidance of unnecessary elimination diets. Confirmation of the diagnosis and adequate management plays the role in the secondary prevention of multiple food allergies and bronchial asthma.

Other authors suggest that children in whom atopic dermatitis does not improve despite routine treatment with emollients and topical corticosteroids should be tested for allergy to foods, in particular cow's milk [2,5,6,18].

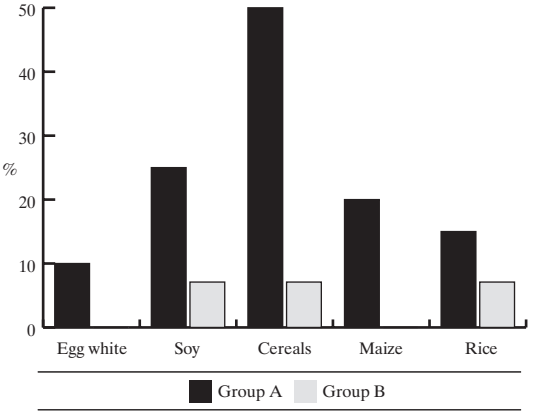
Population of children with AEDS and food hypersensitivity is diversified by age and offending foods. Milk, egg allergy is the most frequent cause of food-induced eczematous symptoms, affecting infants and young children with food hypersensitivity and AEDS. School children are more often polysensitized to soy, arachides, cereals, maize, what has been confirmed in our study. Although approximately 85.0% of patients with AEDS have elevated serum IgE levels, and about 85% of these have evidence of specific IgE antibodies to food and inhalant allergens, not always positive reactions are noticed in DBPCFC [2]. The elevated IgE serum concentration has been confirmed in

Figure 1. **Serum IgE concentration in investigated group of children**



	Group A (n=20)	Group B (n=14)	p
Serum IgE concentration			
Min-max	3-1089	4-575	
Elevated n (%)	10 (50.0%)	7 (50.0%)	ns
Mean (IU/ml)	167.5±282.93	91.57±142.36	
(CI 95%)	(35.08-299.92)	(9.37-173.77)	

Figure 2. **Sensitization to food allergens in APT in children with AEDS**



Foodstuff	Group A (n=20) n (%)	Group B (n=14) n (%)	p
Egg white	2 (10.0%)	0 (0.0%)	ns
Soy	5 (25.0%)	1 (7.1%)	ns
Cereals (barley, wheat, rye, oats)	10 (50.0%)	1 (7.1%)	p<0.0096
Maize	4 (20.0%)	0 (0.0%)	ns
Rice	3 (15.0%)	1 (7.1%)	ns

50.0% of investigated children and no difference between age groups has been noticed (*Fig. 1*). Only three of them presented positive immediate-onset reaction to milk in food challenge. Our results indicated, that as positive SPT/sIgE as immediate-onset reactions in food challenge were observed only in the group of younger children (<3 years). The prevalence of delayed-onset reactions were higher in older children, what was in correlation with positive results of APT. Cow's milk allergy was confirmed in 65.0% of children from group A and in 35.7% from group B, that has been in correlation with positive delayed-type reactions in oral food challenge in 72.7% and 80.0% in corresponding age groups. These results confirm diagnostic accuracy of APT for the diagnosis of food allergy with the elimination-challenge procedure as the most reliable method. Our and previous studies have also shown that immediate-type clinical reactions are more often associated with urticaria and skin prick test positivity and delayed reactions with atopic eczema and patch test positivity [21].

Because more of the current data concern diagnostic accuracy of APT in children less than 2 years [8-10,21], we wanted to assess in our study the relevance of patch testing in the detection of food allergy in older children.

According to recently studies and published data, we expected that the results would show significantly lower sensitivity, specificity and PPV. However, although there was a tendency toward these results, it did not reach statistical significance. Correlation of APT with clinical symptoms and in 80.0% with oral food challenge in the group of older children, indicate the diagnostic value of APT in all age groups. Calculation of PPV and sensitivity of APT showed comparable values in both age groups; specificity was higher in older children. Our observation is in accordance with previous studies by Perackis et al. performed in the group of 498 children in age from 3 to 148 months, indicating that the value of sensitivity, specificity, PPV and NPV concerning cow's milk, hen's egg and wheat does not seem to be influenced by age in infancy and childhood [22].

Our results of sensitivity (100.0%) and specificity (94%) for SPT/sIgE showed a high predictive capacity of these tests for children with immediate-type reactions in food challenge. In the recent study Niggemann and Roehr concluded that the combination of positive APT results and measurement of levels of specific IgE makes DBPCFC superfluous for suspected food allergy [9,23,24]. This and other studies have shown the correlation of SPT/sIgE with immediate-onset reactions and APT with delayed-onset reactions, what confirm the role of these methods in diagnosing of different type of food allergy [10,21,24]. The percentage of false-positive and false-negative results was comparable for SPT, sIgE and APT.

Although the history indicating the time correlation between milk ingestion and exacerbation of clinical skin symptoms, no milk hypersensitivity was confirmed by parallel testing (SPT, sIgE, APT, oral food challenge) in 5/20 (25%) of children form group A and in 9/14 (64.3%) of children from group B. It allows to state that the milk is the main, offending food allergen in infants, but not in older children.

In our study population, some patients were sensitized to soy and cereals and showed symptoms exacerbation after ingesting of foods containing these allergens. Polysensitization was significantly more frequent in children older than 3 years. The results of APT suggest the role of delayed-type reactions in wheat allergy and that sensitization to cereals appears to be more common than generally believed among infants with atopic eczema [25] (*Fig. 2*). Cereal allergy in infants may be the first sign of further pollen allergy and cross-reactivity in older

children. Positive results of APT to cereals should be verified by oral food challenge, but the inclusion criteria to this study was suspicion of cow's milk allergy, so we decided to perform the elimination-challenge procedure to cereals as the next step of diagnosing.

In this investigation, the prevalence of inhalant allergy was statistically higher in children older than 3 years, what confirm the role of aeroallergens in the pathogenesis of AEDS. It is also the risk factor for allergic rhinitis and bronchial asthma. Natural history of AEDS shows that about 80% of children with atopic dermatitis and food allergy will "lose" their clinical reactivity to milk over 1 to 3 years, developing multiple food allergies with allergic rhinitis and/or bronchial asthma [26]. It suggests that the successful management of AEDS and food allergy requires food allergens avoidance and the diagnostic procedures with other foodstuffs.

There are not a lot of study concerning the diagnostic value of combined skin prick and patch testing in correlation to oral food challenge. The findings of Isolauri, Turjanmaa and Majamaa et al. indicate that skin prick and patch testing significantly increases the chances of early detection of food allergy in infants [10,18,23,24]. But there are also the study concluding that the APT was of little value in diagnosing food allergy in small children. In the study of Vanto et al. who investigated 301 children with suspected cow's milk allergy, the PPV was 40% for APT in correlation to immediate-type reactions [12]. The explanation for the divergence and such a low predictive capacity of APT is that the investigations were carried out on the group of unselected children with skin, respiratory and digestive symptoms and that the figures concerned immediate-onset reactions but not delayed-onset reactions.

In our study, in combined skin and patch testing with evaluation of sIgE, the sensitivity was higher in children less than 3 years (92%), but specificity in children older than 3 years (89%). These results and high PPV confirm that APT might be performed in the diagnostic work-up of food allergy in children with atopic dermatitis up to 3 years of age with unimpaired accuracy.

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