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Krystyna Mowszet[A–D], Krzysztof Matusiewicz[A–D], Barbara Iwańczak[A, D–F]

Value of the Atopy Patch Test in the Diagnosis of Food Allergy in Children with Gastrointestinal Symptoms

Department of Pediatrics, Gastroenterology and Nutrition, Wroclaw Medical University, Poland

A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. In recent years, food allergy, especially in the child population, has become an increasing problem in developed societies. In the youngest children, it is a frequent cause of gastrointestinal disorders. The atopy patch test, applied from several years in clinical practice, is one of the methods used in allergology.
Objectives. The objective of the work was an assessment of the diagnostic value of the atopy patch test in the diagnosis of allergy to cow's milk protein and to wheat proteins in children with gastrointestinal symptoms.
Material and Methods. The study was comprised of 61 children (37 boys and 24 girls, aged 3 to 36 months, average age 13.5 months). Their medical history might have indicated a connection between the symptoms and ingested food. In all the children, an atopy patch test and a skin prick test with native food allergens were carried out. Table 1 presents the characteristics of the studied patients. Diagnosis of allergy to cow's milk protein and to wheat was verified in the open food challenge.
Results. Sensitivity of APT for milk was 21%, specificity – 91%, PPV – 80%, NPV – 39% and for wheat – 67%, 100%, 100% and 77%, respectively (Table 4). For the skin prick test, sensitivity, specificity, PPV and NPV were 13%, 96%, 83% and 39% for milk and 22%, 80%, 50% and 53% for wheat.
Conclusions. APT demonstrates high sensitivity and high specificity in the diagnosis of allergy to wheat in children with gastrointestinal symptoms. The sensitivity of ATP in the detection of allergy to cow's milk in children with gastrointestinal symptoms was low and therefore the diagnosis should be verified by challenge tests (**Adv Clin Exp Med 2014, 23, 3, 403–409**).

Key words: food allergy, gastrointestinal symptoms, atopy patch test, children.

In recent years, food allergy, especially in the child population, has become an increasing problem in developed societies [1–4]. In the youngest children, it is a frequent cause of gastrointestinal sickness. Clinical symptoms are engendered by an inappropriate immunologic response to proteins present in food. 90% of the cases are instigated by antigens of cow's milk, hen eggs, soy, wheat, peanut tree nuts, fish and shellfish [5]. Reactions of hypersensitivity may appear directly after the consumption of allergic food and as such they represent an IgE-dependent reaction (type I Gell-Coombs reaction) or may appear several hours afterwards and are late reactions of a cellular type (type IV Gell-Coombs reaction). According to the current classifications of adverse reactions to food, allergic reactions are divided into three groups: IgE-dependent, IgE-independent and mixed [6–8]. Along with recognition of the pathological mechanisms of the allergy, a connection of the IgE-independent reaction with food-induced colitis and proctitis, enterocolitis, enteropathy, gastro-esophageal reflux, chronic constipation, infant colic, eosinophilic esopahgitis, gastritis and enterocolitis is also emphasized [9–13]. Atopy patch tests, applied for several years in clinical practice, are one of the methods used in allergology. For a long time, based on the pioneer studies on atopy patch tests, it has been thought that the positive result of the test is caused by a skin reaction to pollen allergens

in patients with atopic dermatitis and only recently has it been recognized that food allergens have also dominated works in the literature for a long time on atopic patch tests in patients with atopic dermatitis [6–8]. The early opinion that a skin patch test is an eczematous reaction in patients with eczema and that the result of that test in patients without atopic dermatitis may only be negative has not been confirmed [20]. In recent years, a greater attention has begun to be paid to the IgE--independent mechanism, since it has turned out to be very frequent and even predominant in the case of symptoms in the gastrointestinal system. Based on meticulous studies, it has been found that the symptoms of the alimentary tract are evoked by an IgE-independent mechanism with an inappropriate response of T regulatory lymphocytes. In this situation, an increased production of IgE antibodies is absent and mastocytes linked to these antibodies are not abundant in the skin, therefore, commonly-used skin prick tests are negative and specific IgE antibodies in the blood are not detected. Contrary to the skin prick test, the atopy patch test with food allergens, introduced recently to clinical practice, may detect IgE-independent reactions and may be a good method in the diagnosis of late allergic reactions [16–18].

A number of papers dealing with the utility of the food atopy patch test in food allergy in infants and children with atopic dermatitis has been published [16–20] but only a few have estimated the utility of these test in children with gastrointestinal symptoms [23–27]. The continuous search for new methods with high specificity and sensitivity is aimed at the introduction of necessary elimination diets but also at the avoidance of unnecessarily wide restrictive diets.

Objective of the Work

The objective of the work was the assessment of the diagnostic value of atopy patch tests in the diagnosis of allergy to cow's milk protein and to wheat in children with gastrointestinal symptoms.

Material and Methods

The study comprised 61 children (37 boys and 24 girls, aged 3 to 36 months, average age 13.5 months) who were hospitalized in the Clinic of Gastroenterology and Nutrition in Wrocław in the years 2010–2011 due to gastroenterological symptoms such as regurgitation, vomiting, diarrhea, abdominal pain, lower abdominal tract bleeding, constipation, failure to thrive and malnutrition.

Table 1. Characteristics of studied children

Number of children: boys girls	61 37 (60.6%) 24 (39.4%)
Age	3–36 months (average 13.5 months)
Family allergy history	11 (18.0%)
Breast feeding	0–18 months (average 5.4 months)
Gluten introduction	6–12 months (average 7.5 months)
Beginning of clinical symptoms	1–21 months (average 5.9 months)

A medical history of those patients might have indicated the connection of these symptoms with ingested food. Children with atopic dermatitis and alimentary tract infection were excluded from the study; and in children on gluten containing diet celiac disease was excluded (negative anti-tissue transglutainase and/or anti-endomysium antibodies). In all children, atopy patch tests and a skin prick test with native food allergens were performed. Since milk and wheat belong to the most frequent food allergens, a food challenge with milk was performed in all 61 children from the study group and, independently, in 19 of them, a food challenge with wheat. Table 1 presents the characteristics of the studied patients. A diagnosis of allergy to cow's milk protein and to wheat was verified in an open food challenge.

Atopy Patch Test

Atopy patch tests were applied to the skin of the child's back by using standard aluminum cups of an internal diameter of 8 mm on adhesive tape (Finn Cahmber Epitest Ltd., Finland). Native foods were put into the chamber: 3.2% cow's milk and wheat suspended in physiologic salt at a concentration of 1 g per 10 mL. Microcellulose served as a negative control. After 20 min, the sites of the test application were checked for immediate reactions. The results of the test were red after 48-h occlusion: preliminary result – 15 min after occlusion removal and final result – 72 h after application of the test. According to the common rules of APT reading [28–29], a lack of skin reaction (0) and only redness (–) were treated as a negative result. Redness and infiltration (+), redness, infiltration and papules (++), redness, infiltration and numerous confluent papules and vesicles (+++) were treated as a positive result [29].

Skin Prick Test

A skin prick test with native foods was performed with 3.2% cow's milk and wheat flour suspended in a concentration of 1 g in 10 mL of saline. A drop of prepared allergen was applied to the skin of the inner side of the forearm. Codeine 9% solution was a positive control and physiologic saline – a negative control. The results were read after 15 min. A blister with a diameter equal to or greater than 3 mm was treated as a positive result.

Food Challenge

Due to the young children's age, the food challenge was performed using the open method after at least 4 weeks of an elimination diet. According to the method recommended by EAACI, the dose of the challenging allergen was increased every 30 min. The challenge was done after a labial test. The initial dose of milk was 0.1 mL and the increments were a doubling of the previous dose every 30 min until the top dose was reached or an allergic reaction appeared. The initial dose of wheat was 100 mg and the incremental scheme was similar. The reaction was regarded as a positive when the adverse symptoms appeared not later than two hours after the last dose of allergen. The patient was followed for 48 h in the clinic and, after that, at home under the supervision of a physician. Either an early or late reaction was regarded as positive.

Statistical Analysis

In the statistical analysis, sensitivity, specificity and positive and negative predictive values were calculated. For the calculation of sensitivity, specificity and positive (PPV) and negative (NPV) predictive values, SPSS v. 8.0 software was used.

Results

From the 61 children in whom the provocation challenge was performed, in 39 (64%) an allergy to cow's milk protein was confirmed: in two of them an early reaction was observed (vomiting, skin rush), with late reactions in the remaining. 19 children underwent elimination and a provocation challenge with wheat. In nine of them (47%), hypersensitivity to gluten with late gastrointestinal symptoms was confirmed and in only one an early reaction was also observed (lids edema). An analysis of gastrointestinal symptoms is presented in Table 2.

Table 3 presents the results of skin prick tests (SPT) and atopy patch tests (APT) in the analyzed patients. A positive APT result for cow's milk was obtained in 10 children and in 8 of them, the food allergy was confirmed by a challenge test with milk. Positive SPT results were observed in only five children with a confirmed allergy to cow's milk protein. Positive results of APT for wheat flour were observed in 6 children and only in children with a confirmed allergy. SPT with wheat flour was positive in four children.

Table 2. Clinical symptoms in children with confirmed food allergy to cow's milk and/or gluten

Symptom	Allergy to cow's milk Total 39 children		Allergy to gluten Total 22 children	
	number	(%)	number	(%)
Failure to thrive	10	25.6	6	27.3
Chronic diarrhea	5	12.3	5	22.7
Recurrent diarrhea	5	12.3	4	18.2
Bloody stools	9	23.0	1	4.6
Perineal pathology	6	15.3	1	4.6
Regurgitations or vomiting	13	33.3	0	0
Bloody vomiting	2	5.1	0	0
Colic, abdominalgia	10	25.6	0	0
Constipation	2	5.1	2	9.1
Low body mass	13	33.3	8	36.6

Table 3. Results of skin prick test and atopy patch tests in children with positive and negative result of food challenge for milk and wheat

	Positive challenge for milk (39 children)				Negative challenge for milk (22 children)			
Test	**SPT**		**APT**		**SPT**		**APT**	
Result	+	–	+	–	+	–	+	–
Number	5	34	8	31	1	21	2	20
Rate (%)	12.8	87.2	20.5	79.5	4.5	95.5	9.1	90.9
	Positive challenge for wheat (9 children)				**Negative challenge for wheat (10 children)**			
Test	**SPT**		**APT**		**SPT**		**APT**	
Result	+	–	+	–	+	–	+	–
Number	2	7	6	3	2	8	0	10
Rate (%)	22.2	77.8	66.7	33.3	20.0	80.0	0	100.0

Table 4. Utility of atopy patch tests and skin trick tests in diagnosis of food allergy in children with gastrointestinal symptoms

Allergen	**Milk**		**Gluten**	
Kind of test	APT	SPT	APT	SPT
Sensitivity	21	13	67	22
Specificity (%)	91	96	100	80
Negative predictive value (%)	80	83	100	50
Positive predictive value (%)	39	39	77	53

The sensitivity of APT for milk was 21%, specificity – 91%, PPV – 80%, NPV – 39% and for wheat – 67%, 100%, 100% and 77%, respectively (Table 4). For the skin prick test, sensitivity, specificity, PPV and NPV were 13%, 96%, 83% and 39% for milk and 22%, 80%, 50% and 53% for wheat, respectively.

Discussion

Gastrointestinal symptoms suggesting food allergy such as vomiting, regurgitation, diarrhea and failure to thrive may rapidly lead to malnutrition and therefore to severe symptoms of allergy. In our material, malnutrition was observed in more than 50% of children (body mass below 3rd percentile). In our other study [30], in which the causes of malnutrition in children younger than three years, hospitalized in the gastroenterology unit, were evaluated, we observed that the most frequent reason for malnutrition was untreated, both diagnosed and undiagnosed food allergy. Besides malnutrition, the most frequent symptoms in the studied group of children were failure to thrive or even anorexia, colic/anxiety, diarrhea, regurgitation and vomiting. The prompt establishment of a diagnosis and identification of sensitizing food requires proper diagnostic methods with high sensitivity and specificity. The atopy patch test is a relatively new diagnostic method used in allergology [14, 15]. Most of the studies on the atopy patch test estimated their utility in diagnosis of allergy to milk, egg, soy and wheat in atopic dermatitis [16–22]. Only scarce studies evaluated the utility of APT in allergy with gastrointestinal symptoms [23–26, 29].

In our work we tried to determine the utility of APT in the diagnosis of allergy to cow's milk and wheat in children with symptoms from the gastrointestinal tract. In our study, the sensitivity of the test (milk 91%, wheat 100%) and its positive predictive value (milk 80%, wheat 100%) were high, and for wheat, the specificity and negative predictive values were also high (67% and 77%, respectively). All the parameters of APT were better than those of SPT, which might confirm that for the symptoms of allergy to cow's milk and to wheat, in most cases an IgE-independent mechanism might be responsible. In the case of cow's milk, low sensitivity (21%) and low negative predictive value (39%) indicate that the negative result of the test does not

allow excluding the allergy and that an elimination and provocation challenge are indispensable. Contrarily, a high specificity and positive predictive value might make it possible to omit a provocation challenge for both allergens, milk and wheat, since the risk of allergy in that case is very high.

Darsow et al. [31], in a multicenter study on a large group of patients with atopic dermatitis, obtained high specificity of APT for wheat (91%) but low sensitivity (30%). Similarly, a high sensitivity of APT in patients with atopic dermatitis was obtained by Tesse et al. [32] and the specificity of the test was also high (100% and 95%, respectively). In Polish literature, the first studies on the utility of APT in the diagnosis of allergy in children were from a Białystok center [17]. In the study, comprising 27 children younger than three years with symptoms from the skin and alimentary tract which indicated food allergy, the sensitivity and specificity of APT were 82% and 69%, respectively. In comparison to SPT and a specific IgE atopy patch test, they demonstrated significantly higher specificity which allowed for detection of allergy in children with late symptoms after milk consumption who had negative results of a skin prick test. Subsequent research of these authors demonstrated higher sensitivity and specificity of APT in the diagnosis of allergy in children with atopic dermatitis in comparison to IgE-dependent tests (the skin prick test, specific IgE) not only for cow's milk protein but also for cereals and soy protein [33]. The usefulness of APT in children with suspicion of milk allergy and atopic dermatitis has been studied by Krogulska et al. [34]. The above-mentioned authors obtained high specificity and high positive predictive value (87.5% and 87.4%, respectively), however, the sensitivity and negative predictive value were lower (54.5% and 58.5%, respectively). Specificity and positive predictive value are higher than sensitivity and negative predictive value in most studies, which could indicate that APT in patients with atopic dermatitis is more useful for confirmation of allergy than for exclusion of it both for cow's milk and wheat, which is similar to the results obtained in our work, but conducted in patients with symptoms from the gastrointestinal tract.

The number of studies evaluating APT in patients with gastrointestinal symptoms of allergy is significantly smaller. Canani et al. [26] studied children with gastrointestinal symptoms and used patch tests with both native allergens and commercial tests with milk and wheat. Besides unequivocally better results with native allergens than with commercial tests, the specificity of the test was also better than its sensitivity for both allergens, however, the small sample size with wheat did not allow for strong conclusions. Cudowska et al. [22] conducted studies on APT in patients with gastrointestinal symptoms after milk consumption and obtained similar sensitivity, specificity and positive predictive values (77%, 73 % and 71%, respectively) but a low negative predictive value (21%), which would confirm the better utility of APT for confirmation of allergy in this group of patients than for exclusion of it. It seems that apparent differences in sensitivity and specificity may result from the amount of the extract in chambers, and the kind of solution – physiologic saline, water and a concentration of allergen. The use of native allergens seems to be more effective than the use of commercial tests. The use of aluminum chambers of 12 mm diameter seems to be more effective than the use of smaller chambers but there is a lack of unanimous recommendations.

Reading of the reaction results after 72 h also has its significance in the estimation of sensitivity and specificity of APT. Heine et al. [27] demonstrated that the highest concordance of APT with the results of the challenge for cow's milk, wheat flour, hens' egg and soy was observed with the presence of infiltration and of seven or more papules in the place of occlusion on the skin. Also, in children with gastrointestinal symptoms of allergy, Canani et al. [29] demonstrated a higher specificity and positive predictive value of the patch test when the edema/infiltration and papules were present concomitantly. The above results may serve as a standard for the reading of APT results.

In spite of the progress of the studies on allergic mechanisms leading to particular gastrointestinal symptoms and the efforts to standardize atopic patch tests in all recommendations and standards elaborated by expert panels [1, 2, 8, 24, 36, 37], a positive result of the test with a particular allergen is treated as the detection of a potential candidate which is responsible for clinical symptoms of allergy, however, a conclusive diagnosis is made only after provocation challenge.

Based on our work, it seems that the provocation challenge is more necessary in the case of a negative result of the test.

The authors concluded that APTs demonstrate high sensitivity and high specificity in the diagnosis of allergy to wheat in children with gastrointestinal symptoms. The sensitivity of ATP in the detection of allergy to cow's milk in children with gastrointestinal symptoms was small and therefore the diagnosis should be verified by challenge tests. The results of our work suggest that APTs are more useful in the confirmation of allergy to milk and wheat than in the exclusion of such allergy.

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Address for corresponcence:

Krzysztof Matusiewicz
Department of Pediatrics, Gastroenterology and Nutrition
Wroclaw Medical University
M. Curie-Skłodowskiej 50/52
50-369 Wrocław
Poland
Tel.: +48 71 77 03 057
e-mail: vermer@poczta.onet.pl

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