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Comparison of diagnostic tests for suspected cow's milk allergy in children with atopic dermatitis

Cow's milk allergy in children with atopic dermatitis

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ABSTRACT

BACKGROUND: Atopic dermatitis (AD) is a chronic inflammatory skin disease. A third of pediatric AD patients have also food allergy. Although food challenge test is gold standard test for the diagnosis of food allergies, they should be administered by experienced physicians, considering that the test is time-consuming and carries some risks. Documentation of the efficacies of specific IgE(sIgE), skin prick test(SPT),and atopy patch test(APT) are important for determining the necessity of oral food challenge tests(OFC).

METHODS: Fifty-three AD patients with suspected cow's milk allergy(CMA) were included in our study. Diet-related questions were asked to the patients. Blood samples were taken for measurement of total blood count, total IgE, and milk sIgE. OFC, SPT, and APT were performed using pasteurized cow milk.

RESULTS: The mean age of the study population was 1.4 ± 0.8 years, and the male:female ratio was 1.12. Cow milk allergy was detected in 45.3% of the patients after OFC. A comparison between CMA(+) and CMA(-) patients revealed no significant difference in sIgE positivity ($p=0.940$), but there was a significant difference in SPT ($p=0.000$) and APT ($p=0.001$) positivity. When our study group was divided into immediate reaction, delayed onset reaction, and not reactive subgroups after OFC, efficacy of SPT was more prominent in immediate reaction subgroup while APT was more efficient in delayed reaction subgroup.

CONCLUSIONS: Our study showed that using SPT test with APT test in allergic reactions with IgE and other mechanisms such as AD will increase the diagnostic yield, thereby reducing the need for OFC.

Keywords: Atopic dermatitis; Atopy patch test; Cow's milk allergy; Oral food challenge

INTRODUCTION

Recently, there has been a serious increase in food allergy prevalence all over the world. Egg and cow's milk are the most common food allergens causing allergic reactions in infants.¹ Atopic dermatitis (AD) is a chronic inflammatory skin disease commonly seen with food allergies during the first year of life.² Food allergy is present in as much as 33% of patients with AD, being particularly common in moderate and severe AD.³

Food allergies are divided into two groups by their mechanism of development as early onset-type and late onset-type reaction. In AD, allergic reactions are classified as mixed type, which can develop via immunoglobulin E (IgE) and or non-IgE mediated mechanisms. A single diagnosis method may not be adequate to determine the etiology as IgE and or non-IgE mediated mechanisms are efficient together in atopic dermatitis pathophysiology. In early-onset type reactions, skin prick testing and specific IgE (sIgE) algorithms are well established; however, there are still unclarified areas in the diagnosis of late-type reactions.⁴ Atopy patch test (APT) can be used in the diagnosis of late-type reactive food allergies.^{1,5} Some studies have shown the efficacy of APT in the identification of late-onset reactions in AD patients with cow's milk allergy (CMA).^{6,7} The gold standard in the diagnosis of food allergies is double-blind placebo-controlled food challenge tests (DBPCFC), although it has also been reported that open food challenge (OFC) can be used in young children.⁸

In our study, the aim was to review the efficiency of skin prick test (SPT), APT, and sIgE tests in diagnosis of suspected CMA in comparison with food provocation tests in children with AD under two years of age and to determine the efficacy of APT in late-type reactive CMA patients.

MATERIALS/ PATIENTS AND METHOD

Children between 0-2 years of age who were diagnosed with AD and were examined in Pediatric Allergy Clinic (Adnan Menderes University, Faculty of Medicine Hospital, Aydın, Turkey) with suspected CMA between 2010 and 2012 were included in the study. Atopic dermatitis diagnosis was made using Hanifin-Rajka criteria.⁹ All families were informed about the study and their informed consent was taken. Patients with reported AD flare-ups and/or allergic reactions following the consumption of cow's milk and milk products were included in the study. The patients with previously diagnosed or suspected food allergies other than cow's milk were excluded. Demographic properties, complaints, family and personal history were recorded. Having at least one family member diagnosed with conditions like as asthma, allergic rhinitis and/or conjunctivitis, AD, food and drug allergies was considered as a positive family history for atopy. Nutritional history of the patients including the period of breast-feeding and the start of cow's milk and milk products consumption. Two ml of blood was obtained from all patients for measurement of total IgE and milk sIgE. SPT, APT, and OFC were performed using pasteurized cow's milk. Patients with positive OFC results were diagnosed with CMA. Proper treatment methods were planned according to patient's symptoms and results.

Total IgE and sIgE measurements: Total IgE was measured using Prestige-24i (Boeki, Tokyo, Japan) turbidimetric device using commercial IgE-turbilatex (Spinreact, Sant Esteve de Bas, Spain) lab kits. Cow's milk sIgE measurement was done using immunoblotting method (Allergy-screen, Mediwiss Analytic, Moers, Germany). Values of sIgE > 0.35 IU/ml were regarded as positive.^{10,11}

Skin Prick Test: Suitable treatments in AD patients with active skin reactions were planned.

In patients with receding lesions, antihistamines and systemic steroids were stopped according

to suggested time periods, as were topical steroids applied to the test area. In all patients, pasteurized cow's milk was used for prick-to-prick skin test. Histamine was used as positive and saline was used as negative control indicators. After a single drop of cow's milk on a subject's forearm area, epidermis was pierced using Stallerpoint® (Stallergenes, France). Reactions were reviewed after 15 minutes. The test was regarded as positive after which the mean diameter of the swollen area became more than 3 mm greater than the negative control diameter.^{12,13}

Atopy Patch Test: Haye's Test Chamber® (0540577, Netherlands) was used for atopy patch test. A drop of pasteurized cow's milk was administered into the test chamber and saline solution was used as negative control. The test area was then checked after 20 minutes for early reactions. Patch was worn on application area for 48 hours. The initial review was done 20 minutes after the patch removal. Patch test results were reviewed within 72 hours. Reactions were grouped according to results: -: negative; +/-: doubtful: erythema only; +, weak positive: erythema and slight infiltration; ++, strong positive: erythema, infiltration, papules; +++, very strong positive: erythema, infiltration, papules, vesicles. Irritant or doubtful reactions, including sharply demarcated confluent erythema, or reactions confined to margins without infiltration were not regarded as positive.¹⁴⁻¹⁶

Open Food Challenge: OFC was performed in all patients after obtaining the informed consent forms. The patients were given a cow's milk elimination diet for two weeks before the test. Vital findings (peak heart rate, respiration rate, arterial blood pressure, and systemic examinations) were recorded. The necessary medications (adrenaline, antihistamines, nebulized salbutamol, inhaled and systemic corticosteroids) and equipment (oxygen mask, nebulization and resuscitation set) were made ready at bedside for possible serious reactions that might develop during the test period. Provocation was done using pasteurized cow's milk.

Patients were administered with 0.1 ml, 0.3 ml, 0.5 ml, 1 ml, 3 ml, 5 ml, 10 ml, 20 ml, 50 ml

and 100 ml cow's milk in 15-minute periods. During the test, blood pressure, peak heart rate, respiration rate, itching, erythema, swelling, nausea, emesis, abdominal pain, sneezing, nose itching, nasal congestion, rhinorrhea and coughing were recorded after each dose. The test was finalized in case of any occurrence of skin symptom (rash, urticaria and angioedema), gastrointestinal symptoms (vomiting, proctocolitis, enterocolitis, diarrhea) and/or respiratory symptoms (bronchospasm, dyspnea) during the test.¹⁷ Patients were monitored for 24 hours after the test at the hospital. OFC negative patients were administered 200 ml/day cow's milk for a week and were reviewed thereafter. The test was considered positive in case severe itching and/or exacerbation of atopic dermatitis lesions in the monitoring process.

Early onset reaction was defined as a reaction that occurred within the first two hours; late onset reaction was defined as reacting reaction that occurred between two hours to a week. Non-reactive patients were considered as negative.⁴

Statistical Analysis: The study data were analyzed with SPSS 20.0 for Windows (SPSS Inc., Chicago, Illinois). The normal distributions of quantitative variables were checked with Kolmogorov-Smirnov test. Descriptive statics were expressed as frequency (%), mean±standard deviation, and median (minimum-maximum). The normally-distributed variables were compared between independent groups using Student's t-test whereas non-normally distributed variables were compared with Mann-Whitney U test. Chi-square test was used to analyze qualitative data. In order to measure the reliability of specific IgE, SPT and APT variables in CMA diagnosis, sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were calculated. P value of less than 0.05 was considered statistically significant.

RESULTS

Of 57 patients meeting the inclusion criteria, two patients were excluded due to egg allergy, one due to hazelnut allergy and one due to wheat allergy. Therefore, 53 patients were included in the study. Mean age of study group was 1.4 ± 0.8 years and the male:female ratio was 1.12. Table 1 shows the demographic properties, dietary history, atopy rates in families, clinical and laboratory results of the patients.

In the study population, sIgE was positive in 37.7% (n=20), SPT was positive in 18.9% (n=10) and APT was positive in 28.3% (n=15) of the patients. Table 2 shows the distribution of sIgE, SPT and APT positivity across the OFC subgroups (early onset reaction, late onset reaction, no reaction). Twenty-four of 53 patients (45.3%) had positive OFC results and were therefore diagnosed with CMA. CMA (+) and CMA (-) patients had no significant difference in sIgE results ($p=0.940$) whereas their SPT ($p=0.000$) and APT ($p=0.001$) values were significantly different. Comparison of sIgE, SPT and APT results of CMA (+) and CMA (-) subgroups were shown on Table 3. Among the CMA (+) patients, 15 patients (63%) had early onset and 9 (37%) patients had late onset reactions. When our study group was divided into three subgroups as early onset reaction, late onset, and no reaction, SPT was more effective in early onset type reaction subgroup while APT was more effective in late onset type reaction subgroup. Table 4 shows sIgE, SPT and APT results of early onset reaction, late onset reaction patients.

To identify early reactions in CMA diagnosed patients with OFC, SPT had a sensitivity of 67% and a specificity of 100%; APT had a sensitivity of 100% and a specificity of 86% for the identification of late onset reactions. Table 5 shows sensitivity, specificity, PPV and NPV values of sIgE, SPT, and APT.

DISCUSSION

Our study showed that in patients with mixed type allergic reactions such as AD, using SPT with APT might increase the diagnostic power, thereby reducing the need for OFC testing. Six patients were diagnosed by OFC with CMA and had only positive APT results. This showed that when OFC cannot be performed, a diagnostic work-up consisting of only sIgE and SPT may be insufficient for the diagnosis allergic diseases mediated by both IgE and non-IgE mechanisms, such as AD.

It has been reported that at least one of the three AD patients was allergic to food causing allergies during infancy or early childhood, and it has been indicated that the frequency of prevalence reached up to 93% in direct proportion to severity.¹⁸⁻²² In our study, 45.3% of AD patients with suspected CMA were diagnosed with CMA.

Oral food challenge test is the gold standard for the diagnosis of food allergy. Using more easily performed and more widely available techniques such as sIgE to diagnose food allergies with detected sensitivity might cause unnecessary food eliminations and therefore, nutritional disorders. Likewise, performing advanced diagnostic tests about the suspected food in our study avoided unnecessary elimination of cow's milk which is a very important food in infant's diet in more than half of our patients. However, there are difficulties to carry out them in the centers, having no suitable laboratory conditions, especially due to the reasons such as risks of anaphylactic shock and taking long time.

Therefore, it is important to define the efficacy and cut-off values of sIgE, SPT and APT in comparison with provocation test results, which is the gold diagnostic standard in such patients. In our study, OFC was considered as the standard and efficacy of other diagnostic tests were reviewed accordingly.

Especially in the events, having critical and heavy reactions with nutrients, OFC should be carried out in hospital and under supervisory. Following the blood pressure is recommended during OFC due to the fact that blood pressure decreases and there is one finding for anaphylaxis in some events.²³ In our study, the blood pressure of all events was monitored during OFC, and no decrease was determined on blood pressure. This result can be examined by that severe reaction, which could comply with anaphylaxis, was not seen in any our events of OFC positive.

There are various treatment approaches such as oral immunotherapy on the selected events within food allergy.^{24,25} Confirmation of the diagnosis by means of OFC and diagnosis methods, indicating early and late-onset reactions, is significant from the point of selecting patients suitable for oral immunotherapy.

Specific IgE is an important diagnostic test especially in IgE mediated immune reactions. Atopic dermatitis can cause an immune response with IgE and non-IgE mediated mechanisms. In late-onset reaction subgroup of OFC, the reactions are formed by non-IgE mediated mechanisms. In positive sIgE patients, some have only sensitivity and food allergies must be proved by using the provocation tests. In our study, there was no significant difference between CMA (+) and CMA (-) patients with respect to milk sIgE results. Only half of sIgE positive patients were diagnosed with CMA. This indicated that diagnosis of food allergies solely based on sIgE values can cause unnecessary eliminations or false negative results in allergic reactions mediated by non-IgE mechanisms such as AD.

Positive SPT results were shown to be the most suitable method in detection of early-onset reactions. No patients that showed late-onset reactions during OFC testing had a positive SPT result. In general, when SPT is compared to OFC, a positive test results suggests that 50% of the patients have a possible food allergy and negative test results exclude an IgE

mediated food allergy by 95%.⁴ NPV values were lower in our study than previously published studies⁶. This can be explained by the fact that some of our patients include patients with late-onset reaction and very young patients, which decrease the test sensitivity.²⁶ In OFC positive patients NPV for SPT was calculated as 67% and it increased to 88% in early-onset reaction patients, which supports our hypothesis.

Atopy patch test was found to be a reliable method in the diagnosis of cow's milk allergy in AD patients. In all nine patients with late-onset reactions during OFC and three patients in early-onset reactions during OFC had positive APT results. Atopy patch test's NPV value for late-onset reaction patients was 100% in OFC. Six patients also had accompanying sIgE and SPT positivity. These results have shown that cow's milk can cause allergic reactions with both IgE and non-IgE mediated mechanisms. Atopy patch test was found to be especially suitable for the diagnosis of late-onset reaction patients in OFC. In a similar manner, previously published studies have shown that APT is a useful method for diagnosing diseases mediated by cellular immunity, such as atopic dermatitis and allergic eosinophilic esophagitis.^{27,28} Similarly, it was found out that APT and PPD were 78-82% in the food-allergic patients, whom there were findings of gastrointestinal system.^{29,30,31} Roeter et al.,³² in a study on 98 children diagnosed with AD who had a mean age of 13 months, reported that PPV value of APT was 95%, and reviewing APT results with SPT or specific IgE increased PPV, therefore the review of APT with SPT or sIgE in AD patients might decrease the need for provocation tests. On the other hand, there are studies against the usage of APT for diagnosing AD. Mehl et al.⁷ reported in 437 AD patients with suspected food allergies (mean age 13 months) that PPV contribution was minimal when APT was reviewed together with SPT or sIgE results (0.5-14%). In an AD case series consisting of 135 patients under 3 years of age, Devillers et al.³³ reported, that APT did not cause an increase in sensitivity and PPV compared with standardized tests. As a result of study carried out by

Çaglayan Sozmen et al., it was mentioned that the sensitiveness, specificity and PPV of APT were low, and that APT had no additional contribution on diagnosis of food allergy. However, in this study, the difference may be caused by that a great majority of patients constituted events of early-onset reactions, and that APT was realized with commercial solutions.³⁴ Application and review methods of APT are not well standardized, therefore experienced and competent physicians must perform this test to differentiate allergic reactions from simple irritation reactions. Those limitations can cause misinterpretation of APT results. In order to overcome these limitations, developing standardized methods can be useful to increase the rate of correct diagnosis with the test.

In spite of the fact that it is seen as a bias, the strengths of our study are that a homogenous group was created by including patients, having atopic dermatitis and clinically CMA suspicion, and that our study group was constituted from the AD patients, whom early-type diagnostic test methods may be inadequate and there were diagnostic difficulties. This study has several limitations. The trial was conducted in children referred to a tertiary allergy clinic because of possible allergy. Therefore, our level of diagnosis may have been more than the normal population. The diagnosis was not based on double-blind placebo-controlled OFC that is the ‘gold standard’ for diagnosing food allergy. We choose to perform open OFC as it is commonly used in daily practice in childhood.

One early-onset reaction case in OFC had no positive diagnostic test result. This suggests that negative results of sIgE, SPT, and APT tests can be insufficient for ruling out food allergies and patients with suspected food allergies should have provocation tests to confirm the diagnosis.

CONCLUSIONS

Our study results demonstrated that in patients with mixed type allergic reactions such as AD, using SPT with APT might increase the diagnostic power, thereby reducing the need for OFC testing. However, in order to use APT as a routine test in the diagnosis of allergic reactions with non-IgE mediated mechanisms such as AD, further studies with a larger sample size are necessary; consequently standardization of testing and review of APT results are necessary for a correct diagnosis.

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Table 1. Main demographic and clinical characteristics of the study population

Table 2. Comparison of sIgE, SPT and APT positivities according to the OFC results

Table 3. Comparison of sIgE, SPT and APT positivities in CMA(+) and CMA(-) patients

Table 4. sIgE, SPT and APT positivities of the patients with early and late OFC reactions and negative OFC reactions

Table 5. Specificity, sensitivity, PPV and NPV values of sIgE, SPT and APT levels in early and late reactions

Table 1. Main demographic and clinical characteristics of the study population

Age(mean±SD)	1.4±0.8
Male/Female	28/25
Positive family history for atopic disorders, n (%)	40(75.5)
Total breastfeeding duration (months) (mean±SD)	11.1±6.5
Milk and milk products initiation time (months) mean(minimum-maximum)	4(1-7)
Beginning time symptoms of atopic dermatitis (months) mean(minimum-maximum)	4(1-7)
Only atopic dermatitis n (%)	33(62)
Atopic dermatitis and wheezy infant n(%)	20(38)
Eosinophils ratio (%)(mean±SD)	4.2±2.4
Total IgE (IU/L) mean(minimum-maximum)	46(0-890)

Table 2. Comparison of sIgE, SPT and APT positivities according to the OFC results.

	OFC RESULTS		
	Negative(n)	Early reaction(n)	Late reaction(n)
None	19	1	-
sIgE positivity	7	2	-
SPT positivity	-	4	-
APT positivity	2	-	6
sIgE+SPT positivity	-	5	-
sIgE+APT positivity	1	2	3
SPT+APT positivity	-	1	-

APT: atopy patch test, SPT: skin prick test, sIgE: specific IgE, OFC: oral food challenge

Table 3. Comparison of sIgE, SPT and APT positivities in CMA(+) and CMA (-) patients.

	CMA(+) (n=24)	CMA(-) (n=29)	p
sIgE n(%)			
positive	12(50)	8(27.6)	0.940
negative	12(50)	21(72.4)	
SPT n(%)			
positive	10(41.7)	0(0)	0.000*
negative	14(58.3)	29(100)	
APTn(%)			
positive	12(50)	3(10.3)	0.001*
negative	12(50)	26(89.7)	

APT: atopy patch test, CMA: cow's milk allergy, SPT: skin prick test, sIgE: specific IgE

*p<0.05

Table 4. sIgE, SPT and APT positivities of the patients with early and late OFC reactions

	Patients with early reaction (n=15)	Patients with late reaction (n=9)
sIgE, n(%)		
Positive	9(60)	3(33.3)
Negative	6(40)	6(66.7)
SPT, n(%)		
Positive	10(66.7)	0
Negative	5(33.3)	9(100)
APT, n(%)		
Positive	3(20)	9(100)
Negative	12(80)	0

APT: atopy patch test, SPT: skin prick test, sIgE: specific IgE, OFC: oral food challenge

Table 5. Specificity, sensitivity, PPV and NPV values of sIgE, SPT and APT levels in early and late reactions

	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)
Early and late reaction				
sIgE	60	64	50	72
SPT	42	100	100	67
APT	50	90	80	68
Early reaction				
sIgE	60	71	45	82
SPT	67	100	100	88
APT	20	68	20	68
Late Reaction				
sIgE	33	61	15	81
SPT	0	77	0	79
APT	100	86	60	100

APT: atopy patch test, SPT: skin prick test, sIgE: specific IgE, NPV: negative predictive value, PPV: positive predictive value