
Evaluation of the utility of atopy patch testing, skin prick testing, and total and specific IgE assays in the diagnosis of cow's milk allergy

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Background: Information on the utility of atopy patch testing (APT) in the diagnosis of food allergy is derived from studies of children with atopic dermatitis.

Objective: To evaluate the usefulness of APT in the diagnosis of cow's milk allergy (CMA) and to determine interleukin 4 and interferon- γ production by peripheral blood mononuclear cells.

Methods: Thirty-seven children (median age, 11 months) with suspected CMA who had a variety of symptoms that involved many organ systems were evaluated using double-blind placebo-controlled food challenges (DBPCFCs), and the performances of milk specific IgE, skin prick testing (SPT), and APT were determined. To search for a possible relationship between the diagnostic tests and the T_H1/T_H2 immune response, we measured interferon- γ and interleukin 4 levels in the supernatants of peripheral blood mononuclear cell cultures.

Results: Seventeen children with positive DBPCFC results and 6 with a history of anaphylaxis were diagnosed as having CMA. The combined use of APT and SPT had a sensitivity of 100% and a negative predictive value of 100% but a specificity of 50% and a positive predictive value of 76%. The addition of milk specific IgE assays to APT and SPT did not improve these values. Pattern of cytokine secretion was not associated with APT positivity or a specific response to DBPCFC.

Conclusions: Atopy patch testing may be a useful adjunct to SPT in excluding CMA in children who have allergic manifestations other than atopic dermatitis. However, DBPCFCs are still necessary in the presence of positive test results.

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INTRODUCTION

Cow's milk is a major cause of food allergy in childhood.¹ Laboratory workup of food allergy involves determination of food specific IgE levels by skin prick tests (SPTs) or serologic assays. Skin prick testing has a negative predictive value (NPV) of 95% but a positive predictive value (PPV) of 50%,^{2,3} which makes SPTs useful for excluding food allergy but much less so for reaching a definitive diagnosis. In addition, SPTs may not be helpful for diagnosing non-IgE-mediated or delayed-type food allergy.^{4,5} Therefore, double-blind placebo-controlled food challenges (DBPCFCs) are still the "gold standard" for the diagnosis of food allergy.

However, DBPCFCs are not easy to perform. They require a long period of observation, may involve a risk of anaphylaxis, and are costly and time-consuming. It has also been suggested that with non-IgE-mediated disorders, challenges to new foods often need to be a few days apart.⁶ Furthermore, in cases in which the patient's symptoms are largely subjective, confirmation of a positive response may require more than 1 crossover trial with consistent results.⁶

Atopy patch testing (APT) was recently introduced as a new diagnostic tool for food allergy.^{5,7–14} Clinical studies have generally included patients with atopic dermatitis associated with food allergy with or without the involvement of other systems, and the results have been conflicting.^{7,10–13} In addition, the question of whether APT identifies a subset of individuals with a distinctive clinical presentation or a distinctive immune response remains unanswered. It has been proposed that an early reaction to APT may represent a T_H2 -type immune response, whereas in the late reaction the immune response shifts to the T_H1 profile.¹⁵ Recent studies¹⁶ support the hypothesis that IgE has a key role in the delayed reactions produced by APT.

The primary aim of this study was to evaluate the usefulness of APT in the diagnosis of cow's milk allergy (CMA). We also wanted to determine whether the combined use of available methods would abolish the need for cumbersome DBPCFCs in children with CMA. For this purpose, we calculated the performances of various tests, including their sensitivity, specificity, PPV, and NPV. To investigate whether the response to APT is associated with a specific T_H1/T_H2 response, we determined interleukin 4 (IL-4) and interferon- γ (IFN- γ) production by peripheral blood mononuclear cells (PBMCs) with or without stimulation by cow's milk antigen.

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MATERIALS AND METHODS

Patients

Thirty-seven consecutive children aged 1.5 to 84 months (median age, 11 months) who were referred to the Allergy and Asthma Unit at Hacettepe Children's Hospital participated in this study. Children were referred on the basis of suspected CMA by the examining physician from the Outpatient Department at Hacettepe Children's Hospital, a tertiary care medical center with referrals from across the country. Children with systemic diseases, including active tuberculosis, autoimmune diseases, immune deficiency, chronic inflammatory diseases, and malignancy, were excluded from the study. The most common symptom for referral was urticaria, followed by wheezing, vomiting, cough, angioedema, eczema, erythema, colicky abdominal pain, and cyanosis. The families of all the children provided written informed consent.

Study Design

Children suspected of having CMA were challenged in a double-blind and placebo-controlled manner. The SPTs and APTs were performed during the elimination period before the DBPCFC. Blood was sampled immediately before the commencement of the challenge for determining levels of total IgE and specific IgE to cow's milk and for cytokine studies. The physician responsible for the DBPCFC was blinded to the results of the APTs, SPTs, and specific IgE assays in serum.

Skin Prick Testing

The SPTs were performed on the upper back of all the children using a commercially available cow's milk allergen (ALK; Allergologisk Laboratorium A/S, Horsholm, Denmark) by the same nurse, and the results were evaluated by the same physician throughout the study. Wheal reactions 3 mm greater than the negative control were considered positive.

Atopy Patch Testing

The APTs were performed and evaluated by the same physician on the upper back of all the children (except 1 whose parents refused APT) as described previously.¹² Approximately 20 µg of cow's milk powder containing 35 g of protein per 100 g was mixed with saline solution, placed in aluminum test cups (Finn Chamber; Epitest Ltd Oy, Tuusula, Finland), and attached to the patient's back using Scanpor tape (CR Bard Inc, Murray Hill, NJ).⁸ The diameter of the chamber was 8 mm. The children were examined for an immediate reaction in 30 minutes, at which time the test was stopped in the case of a positive reaction. The patches were removed after 48 hours of occlusion, and the final reading was taken at 72 hours. Reactions were considered positive only if the erythema was accompanied by infiltration and papulation.⁸ The control cup readings were subtracted from the test cup readings to make the final evaluations.⁸ The reactions were graded as negative (0), doubtful (?+), or

positive (+ or ++), according to the criteria proposed by Vanto et al.⁸ In a negative reaction, there was no change in the skin. A doubtful reaction appeared as mild erythema with no induration. A positive reaction was indicated by redness with induration. If the palpable induration extended beyond the area covered by the cup and included vesicles, the reaction was defined as ++. Children and their families were requested to report any delayed skin reaction that was noticed after this point.

Determination of Total IgE and Cow's Milk Specific IgE Levels

Total IgE (Dr. Fooke Laboratorien GmbH, Neuss, Germany) and cow's milk specific IgE (ImmunoCAP; Pharmacia, Uppsala, Sweden) levels were determined according to the instructions of the manufacturers.

Double-Blind Placebo-Controlled Food Challenge

Cow's milk allergy was evaluated in all patients by means of a DBPCFC except in 6 patients with a history of anaphylactic reactions to cow's milk.¹⁷ The formula used during the elimination period was used as the placebo for challenge. The test formula comprised 10 g of cow's milk powder (containing 35% protein) in 100 mL of placebo formula. The DBPCFC comprised the following 3 phases.

Elimination. Milk products were eliminated from the diet for at least 2 weeks. Breastfed infants were placed on a whey-based, extensively hydrolyzed formula (Peptijunior; Nutricia, Cuijk, Holland), and the mothers were instructed to abstain from food containing cow's milk proteins during the elimination period.

Short-term challenge. The test or placebo formula was given in successively increasing doses (1, 5, 10, 20, 50, and 100 mL) at 20-minute intervals in the morning, followed by an observation period of at least 2 hours. Any reaction during this period was classified as an early reaction. The afternoon session consisted of administration of the alternative formula in the same manner as defined previously.¹⁸

Long-term challenge. To exclude the possibility of the early reaction, the child was kept under observation during the first 2 hours of milk intake. The test or placebo formula was given by the parent at home for 7 days (200–600 mL/d). If any symptoms occurred during this period, the parent contacted the responsible physician. On day 7, the children were examined and the parents were interviewed at the hospital. After a washout period of 7 days, when the infant was fed like in the elimination period, the alternative formula was given for 7 days as outlined previously. The hospital visit at the end of day 7 completed the study.

Eighteen children received short- and long-term challenges, and 13 received only short-term challenges. Children without any symptoms during the procedure were given cow's milk ad libitum. If no reaction ensued within 4 to 6 days, the challenge result was considered negative.

Cell Preparation and Culture and Cytokine Measurements

The PBMCs were isolated from heparinized venous blood by density-gradient centrifugation on Histopaque 1077 and cultured (1×10^6 cells/mL) in complete medium consisting of RPMI 1640 supplemented with penicillin (100 U/mL), streptomycin (100 μ g/mL), and 10% heat-inactivated fetal bovine serum (all from Sigma-Aldrich Corp, St Louis, MO) at 37°C in 5% carbon dioxide–humidified atmosphere in the presence or absence of cow's milk protein (1 mg/mL). Supernatants were collected at 24 hours for IL-4 and at 72 hours for IFN- γ and were stored at -80°C until analysis. The enzyme-linked immunosorbent assay kits used to detect IFN- γ (Quantikine) (sensitivity, <8 pg/mL) and IL-4 (Quantikine HS) (sensitivity, <0.13 pg/mL) were from R&D Systems (Wiesbaden, Germany).

Statistical Analysis

Comparisons between 2 groups were performed using the *t* test and the Mann-Whitney *U* test. Levels of IFN- γ before and after antigen stimulation were compared using the paired-samples *t* test after normalization of the data by natural log transformation. Levels of IFN- γ in the culture supernatants were compared using analysis of variance. The sensitivity, specificity, NPV, and PPV were calculated in reference to DBPCFCs. To calculate the sensitivity and specificity of diagnostic tests, we used fixed cutoff points (SPT, ≥ 3 mm; cow's milk IgE, ≥ 0.7 kU/L) and receiver operating characteristic (ROC) curves. The optimal decision point for milk specific IgE was calculated based on the constructed ROC curve.

RESULTS

Patients

All 37 patients who were originally recruited completed the study. Of these 37 patients, 13 had immediate and 4 had delayed-type CMA according to the results of the DBPCFCs (Fig 1). Six patients with a history of anaphylaxis were not challenged but were included in the group with immediate CMA, and all had positive SPT results and serum specific IgE measurements. The characteristics of the patients are given in Table 1. There were no differences between children who

showed an immediate reaction vs a late reaction or no reaction to DBPCFC with respect to duration of exclusive breastfeeding, total duration of breastfeeding, age at first cow's milk feeding, age at first symptoms, and family history of atopy (data not shown). As expected, there were more girls in the group that had a negative reaction to the challenge.^{19,20}

Outcomes of the DBPCFCs

A total of 62 challenges were performed on 31 patients. The results of the challenges are summarized in Figure 1. All patients with a positive DBPCFC result became symptom free after the elimination of milk products. Two patients with atopic dermatitis who showed a late skin response to placebo did not react with the test formula and were considered to have negative challenge results. In these patients, symptoms decreased but did not totally disappear after the elimination of milk products.

As expected, the cumulative amount of milk that started the symptoms was much smaller in the immediate-reaction group (median, 6 mL; interquartile range [IQR], 1–186 mL) than in the late-reaction group (median, 650 mL; IQR, 500–1,200 mL) ($P = .003$, by Mann-Whitney *U* test). Similarly, the reaction time after the first dose was much shorter in the immediate-reaction group (median, 0.5 hours; IQR, 0.28–1.07 hours) than in the late-reaction group (median, 60 hours; IQR, 30–120 hours) ($P = .004$, by Mann-Whitney *U* test). The symptoms that developed after DBPCFC are summarized in Table 2.

Results of the Diagnostic Tests

The results of the APTs, together with specific IgE and SPTs, are given in Table 3. None of the patients developed a positive reaction to the control cup (negative control). Of the 16 patients with CMA and a positive APT result, 14 were younger than 24 months. In 2 patients, large erythematous reactions were observed within 30 minutes of placement of the cup, and urticarial lesions were observed in the cup area. One patient who had a positive reaction (+) and 1 with a doubtful reaction at 48 hours had negative readings at 72 hours. Within 1 week of this final reading, 2 patients displayed redness and itching at the area of cup placement.

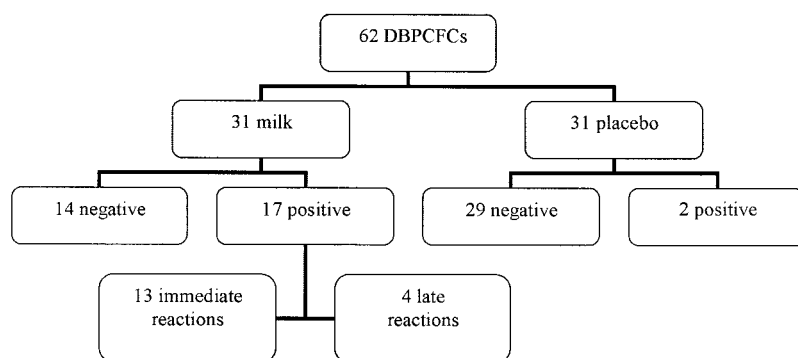


Figure 1. Results of the double-blind placebo-controlled food challenges (DBPCFCs).

Table 1. Characteristics of the Study Population According to the Results of the DBPCFC

	Patients with early reactions (n = 19)	Patients with late reactions (n = 4)	Patients with negative reactions (n = 14)	P value
Age, median (interquartile range), mo	12.0 (6.0-22.5)	19.5 (12.5-35.0)	8.8 (5.5-17.0)	>.05*
Sex, No.				
M	16	3	5	
F	3	1	9	<.05†
Total IgE, mean ± SEM, kU/L	176 ± 43	171 ± 88	42 ± 15	<.05‡
Milk specific IgE, median (interquartile range), kU/L	14.6 (1.3-57.8)	2.5 (0.3-5.1)	0 (0-0.6)	<.01§
Skin prick test results, No.				
Positive	19	2	7	
Negative	0	2	7	<.05†
Atopy patch test results, No.				
Positive	13	3	2	
Negative	5	1	12	<.05†

Abbreviation: DBPCFC, double-blind placebo-controlled food challenge.

*By 1-way analysis of variance.

†By χ^2 test.

‡P < .05, immediate vs negative reaction using the Tukey test.

§P < .05, immediate vs negative reaction using the Dunn method.

||One patient with a history of anaphylactic reaction refused atopy patch testing.

Table 2. Characteristics of the Immediate and Late Reactions After DBPCFC

	Immediate reactions, No. (%) (n = 13)	Late reactions, No. (%) (n = 4)
Urticaria	9 (69)	0
Erythema	6 (46)	1 (25)
Rhinoconjunctivitis	5 (38)	2 (50)
Vomiting	4 (31)	1 (25)
Per oral urticaria	4 (31)	0
Wheezing	3 (23)	2 (50)
Cough	3 (23)	2 (50)
Angioedema	2 (15)	0
Eczema flare	2 (15)	1 (25)

Abbreviation: DBPCFC, double-blind placebo-controlled food challenge.

Sensitivity, Specificity, PPV, and NPV of the Diagnostic Tests in the Diagnosis of CMA

The results of the calculations, using fixed cutoff points for milk specific IgE (≥ 0.7 kU/L), APT (+), and SPT (≥ 3 mm) are summarized in Tables 4 and 5. Because our study population may significantly differ from a "healthy" population with respect to the frequency and severity of CMA, we also used an ROC curve to determine the optimal decision point for milk specific IgE values (Fig 2). The PPVs and NPVs for newly determined cutoff values for milk specific IgE are given in Table 6. These values are also corrected for the prevalence observed in the healthy population (see the "Discussion" section).³ The sensitivity and specificity for different cutoff values of milk specific IgE calculated in reference to the results of the DBPCFCs are also summarized in Table 6.

Table 3. Results of the Diagnostic Methods Used in the Diagnosis of CMA

	APT results*			
	0	?+	+	++
CMA				
Immediate type	2	3	2	11
Delayed type	0	1	1	2
Negative	9	3	2	0
Milk specific IgE, kU/L				
≥ 0.7	3	3	2	11
<0.7	8	4	3	2
SPT, mm				
≥ 3	5	3	4	12
<3	6	4	1	1

Abbreviations: APT, atopy patch test; CMA, cow's milk allergy; SPT, skin prick testing.

*Data are given as number of patients.

Cytokine Production by PBMCs

The median IL-4 value before and after stimulation was 0 pg/mL. Levels of IFN- γ decreased in all groups after stimulation with milk allergen (Fig 3). However, because of the small number of individuals (n = 4), the difference did not reach significance in the late-reaction group. The IFN- γ production by unstimulated or milk-stimulated PBMCs failed to show any differences among the 3 groups (P > .05, by analysis of variance).

Comparison of Patients With Positive vs Negative APT Results

There was no significant difference in the total IgE level between children who had negative vs positive APT results.

Table 4. Performance of the Individual Tests Used in the Diagnosis of CMA Using Fixed Cutoff Points

	Cutoff point	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Milk specific IgE	≥ 0.7 kU/L	74	79	85	65
SPT	≥ 3 mm	91	50	75	78
APT	+	73	86	89	67
APT+SPT	≥ 1 positive	100	50	76	100
APT+SPT+milk specific IgE	≥ 1 positive	100	50	76	100

Abbreviations: APT, atopy patch testing; CMA, cow's milk allergy; NPV, negative predictive value; PPV, positive predictive value; SPT, skin prick testing.

Table 5. Performance of the Diagnostic Tests for Early and Late Reactions Using Fixed Cutoff Points

	Cutoff point	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Milk specific IgE	≥ 0.7 kU/L				
Immediate		79	79	83	73
Late		50	79	40	85
SPT	≥ 3 mm				
Immediate		100	50	73	100
Late		50	50	22	78
APT	+				
Immediate		72	86	87	71
Late		75	86	60	92

Abbreviations: APT, atopy patch testing; NPV, negative predictive value; PPV, positive predictive value; SPT, skin prick testing.

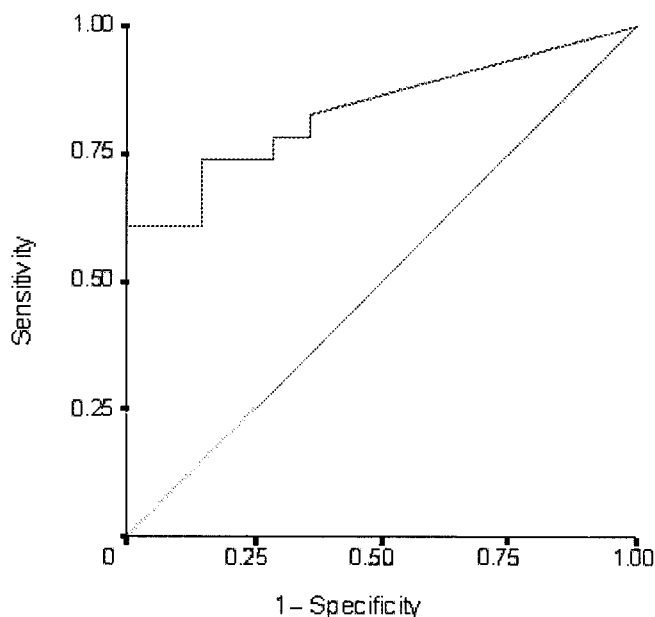


Figure 2. Receiver operating characteristic curve for milk specific IgE.

Children with positive APT results ($n = 18$) had significantly higher milk specific IgE levels (median, 10.2 kU/L; IQR, 0.6–39.9 kU/L) than those with negative APT results ($n = 18$) (median, 0.2 kU/L; IQR, 0.0–2.6 kU/L) ($P = .02$, by Mann Whitney U test). There was no difference between the 2 groups with respect to IFN- γ production before and after antigen stimulation.

DISCUSSION

The results of this study show that APT may be a useful adjunct in the diagnosis of CMA and that the combined use of simpler methods may negate the need for DBPCFCs. The combined use of APT and SPT has a sensitivity of 100% and an NPV of 100%, showing that false-negative results are extremely uncommon and that in the population studied, CMA can be excluded if both test results are negative. This observation is not in agreement with the results of Kekki et al,¹³ who reported that of 54 children with a positive response to milk challenge, 19 had negative APT and SPT results.

Because the specificity (50%) and the PPV (76%) are relatively low, false-positive results are common, and a positive result in either or both APT and SPT is not sufficient to confirm CMA. Therefore, DBPCFCs are still necessary to confirm or refute the diagnosis in the face of positive results. The addition of cow's milk specific IgE does not improve the performance of the diagnostic methods, making this test superfluous when SPT and APT can be performed.

Studies on the use of APT have generally investigated its usefulness in patients with atopic dermatitis.^{7,10–13,21} In fact, it was suggested that APT works only in patients with atopic dermatitis.^{7,12,22} Our study included patients with a variety of symptoms that involve different organ systems. Of the 16 patients with milk allergy with positive APT results, the reactions on presentation involved only the skin in 4 patients, the skin and the respiratory system in 3, the skin and the gastrointestinal system in 2, the gastrointestinal and respiratory systems in 2, the respiratory system in 1; and all 3 systems in 4. This suggests that APT may also be useful for

Table 6. Performance of Milk Specific IgE for Cutoff Points Based on the ROC Curve

Milk specific IgE	Cutoff point, kU/L	Sensitivity, %	Specificity, %	PPV, %*	NPV, %*	Corrected PPV, %†	Corrected NPV, %†
Screening	0.59	78	71	81	66	23	97
Optimal decision point	0.84	74	86	90	67	37	97
Confirmation	4.18	61	100	100	61	100	96

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

*Predictive values based on the present study population.

†Predictive values based on a “normalized” population (corrected for a cow’s milk allergy prevalence of 10%).

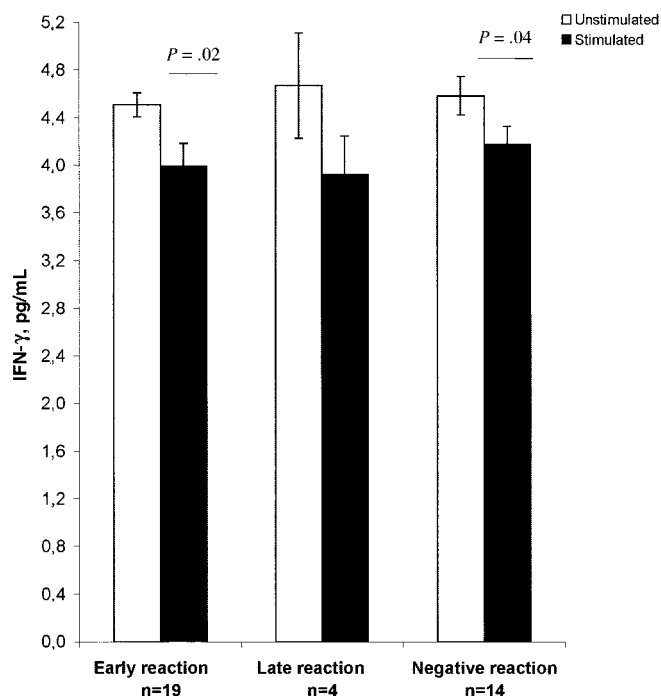


Figure 3. Mean interferon- γ (IFN- γ) production by unstimulated and milk antigen-stimulated peripheral blood mononuclear cells (natural log transformed). Error bars represent SEM.

infants who have allergic manifestations other than atopic dermatitis.

In accordance with other studies, we showed that APT has a better performance for late reactions than SPT or specific IgE (Table 5). Of the 4 patients who had a late reaction to DBPCFC, 2 had negative results and 2 positive results on SPTs with cow’s milk antigen. Because the NPV of the SPTs is generally known to be high,^{23–26} these 2 patients might have gone undiagnosed if APTs had not been performed. The few patients with late reactions might be due to the inclination of physicians to associate the early symptoms with CMA. If APT becomes part of the routine clinical evaluation of suspected CMA in the general pediatric practice, a lot of unnecessary procedures could be eliminated. It is possible that the value of APT can vary depending on the age of the patient, the offending allergen, and the organ system involved. Although our sample size does not allow analysis of each of

these factors separately, the results suggest that APTs are more likely to yield positive results in patients younger than 24 months. This observation is in agreement with previous findings that suggest that the prevalence of positive APT results is higher in younger children with CMA.²⁷

In this study, we observed significantly higher cow’s milk specific IgE levels in individuals with a positive response to APT and the higher performance of cow’s milk specific IgE in late reactions compared with SPTs. The association between specific IgE and APT was previously reported for inhalant allergens²⁸ but not for food. This may be because of the presence of Langerhans cells bearing specific IgE in the epidermis, as previously suggested.^{16,29} This observation requires further investigation.

The study population presenting to the tertiary care center is significantly different from a “healthy” population with respect to the prevalence and severity of CMA. Therefore, we also constructed an ROC curve to define different cutoff points for specific IgE in the study population. The cutoff values of milk specific IgE for a screening test and a confirmation test are 0.59 kU/L (NPV, 99%) and 4.18 kU/L (PPV, 100%), respectively. According to our results, if the concentration of milk specific IgE is 4.18 kU/L or greater, DB-PCFCs may be unnecessary in children presenting to a tertiary care center with suspected CMA.

An alternative way to establish an optimal cutoff value for a test is to determine the optimal decision point from an ROC curve, whereby equal weight is given to the sensitivity and specificity of the test. The optimal decision point for milk specific IgE was 0.84 kU/L, close to the fixed cutoff point we used in our calculations. These figures are strongly influenced by the prevalence of the condition.³ In our study, 23 of the 37 patients had CMA, thus producing a prevalence of 62%. In addition, the percentage of children with a history of anaphylaxis is exceptionally high (16%). These figures are high and do not reflect the general population presenting to a general health care facility for the evaluation of food allergy. To obtain corrected figures for PPV and NPV, we used a hypothetical prevalence rate of 10%, as previously suggested.³ Table 6 shows that the NPVs for milk specific IgE performed in the hypothetical, normalized population are excellent but that the PPVs are poor, even when the optimal cutoff point derived from the ROC curve is used. Similar to our actual study population, 100% predictive accuracy in this normalized population is also obtained at specific IgE levels

of 4.18 kU/L or greater. This observation suggests that children suspected of having CMA with a milk specific IgE level of 4.18 kU/L or greater can be diagnosed as having milk allergy without DBPCFC regardless of the selected population. In the population studied, this would eliminate the need for approximately 38% of the DBPCFCs performed. In a cohort study, Saarinen et al³⁰ showed that milk specific IgE levels of 3.5 kU/L or greater had a PPV of 94%, which is similar to the results of the present study.

We also attempted to define a relationship between the cytokine production by PBMCs and CMA. Similar to other studies,^{31,32} owing to the relatively young age of our study population, IL-4 had a median level of 0 pg/mL. Production of IFN- γ by PBMCs showed a decline after antigen stimulation compared with baseline in all 3 groups (Fig 3). The magnitude of the decline was not different among the 3 groups. Thus, IFN- γ production by PBMCs was not helpful in differentiating children with and without milk allergy, and neither was it useful for differentiating early and late reactions. There are conflicting reports regarding IFN- γ production by PBMCs in patients with food allergy. Hill et al³³ showed that IFN- γ production was lower in children with immediate reactions compared with those with late reactions or milk-tolerant children. Sutas et al,³² on the other hand, found that among patients with atopic dermatitis, the immediate-reacting but not the late-reacting patients produce IFN- γ in response to specific allergen stimulation. Taken together, IFN- γ production by PBMCs is unlikely to be clinically helpful or to define a subgroup with a distinct immune response.

One weakness of this study is the small number of patients, especially in the delayed-reaction group. This is probably because our study is not confined to children with a specific disease, such as atopic dermatitis, but includes children with a variety of symptoms. Although this may be a weakness of the study, we believe that this approach has also resulted in a better reflection of the patient profile at a tertiary care center.

In conclusion, the results of this study suggest that APT may be a useful supplement to the existing methods in evaluating children with suspected CMA and may make DBPCFC superfluous in some instances. Larger studies are needed to define the exact role of APT in children with CMA and with other food allergies.

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