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ORIGINAL ARTICLE

Evaluation of Skin Prick Test and Specific Immunoglobulin E for Diagnosis of Infants with Cow's Milk Protein Allergy

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ABSTRACT

Background: Cow's Milk protein allergy (CMA) is a common finding in infants and young children (2-3%). Its diagnosis is a multifaceted aspect including medical history, clinical examination, diagnostic elimination diets, oral challenge tests (OCT), skin prick tests (SPTs) and specific immunoglobulin E (sIgE) measurements. We aimed to assess the value of SPT and sIgE for diagnosis of infants with CMA in routine clinical practice.

Methods: This cross-sectional study included 102 infants with suspected CMA. They were subjected to OCT, SPT with pasteurized cow's milk and measurement of serum sIgE for cow's milk by immunoblot technique.

Results: Seventy-two infants (70.59%) showed positive allergic reactions with OCT. Comparing SPT to OCT, sensitivity was 75%, specificity was 68.7%, predictive value for negative (PVN) was 59% and predictive value for positive (PVP) was 93.1%. Comparing sIgE to OCT, sensitivity was 68.1%, specificity was 96.7%, PVN was 69% and PVP was 98%. Comparing both SPT and sIgE together to OCT, sensitivity was 62.5%, specificity was 96.6%, PVN was 51.8% and PVP was 97.8%.

Conclusions: For clinical practice, our findings suggest that correlation between SPT and sIgE is significant regarding CMA diagnosis. Therefore, these tests can be used together for diagnosis of CMA. However, still some cases can be only diagnosed with positive OCT with non-detectable sensitization. Therefore, a detailed history is a major factor in assessing CMA. In addition, definition of new optimal cut-offs for sIgE and SPT to cow's milk can improve the accuracy of these tests, hoping to avoid unnecessary and potentially dangerous OTC.

Keywords: Skin prick test; Specific IgE; Cow's milk allergy.

INTRODUCTION

Cow's Milk protein allergy (CMA) is a reproducible, adverse, immune-mediated reaction to one or more milk proteins [1,2]. According to the underlying immune mechanism and timing of symptoms, CMA can be classified into immediate Immunoglobulin E (IgE)-mediated CMA and delayed non-IgE mediated CMA. However, mixed-IgE and non-IgE CMA can occur [3].CMA usually presents within early infancy (first 6 months of life). Most of the cases have a symptom or more related to the gastrointestinal tract, the skin, the respiratory tract and/or the cardiovascular system. The allergic manifestations are typically mild to moderate, however, severe complications in the form of anaphylaxis can ensue in (1–2 %) of the cases [4,5]. CMA is a common finding in infants and young children. Its prevalence is about 2 to 3%, and so it is considered the most prevalent cause of food allergy in children [6- 7]. CMA can be misdiagnosed in many cases. It is essential to realize that precise diagnosis of CMA is a multifaceted aspect that includes a comprehensive medical history and clinical examination, diagnostic elimination diets and oral challenge tests, skin prick tests (SPTs) and specific IgE (sIgE) measurements [4,5,8].A double-blind, placebo-controlled food challenge (DBPCFC) test is known to be the gold standard for food allergy diagnosis [9]. However, it has its disadvantages; first, it is time-consuming, and costy, secondly it requires a suitable physical structure and a multidisciplinary team. Moreover, there is still a risk of life-threatening allergic reaction in the patient. This raised the need for a simpler method of diagnosis [10].In-vivo SPT and in-vitro sIgE for

cow's milk are scientifically valid tests to evaluate IgE sensitization. However, they usually lack standardization and reproducibility. It is worth mentioning that sensitization indicates the production of serum- sIgE to allergens and not the development of clinical symptoms of an allergic reaction upon allergen exposure. Therefore, these tests independently cannot always reliably diagnose food allergy [11]. This study aimed to assess the value of SPT and sIg E for the diagnosis of Egyptian infants with CMA in routine clinical practice.

METHODS

This cross-sectional study was performed during the period from April 2019 to September 2019 in the Pediatrics Department of Zagazig University Hospitals. The study included 102 patients with suspected CMA. Inclusion criteria were male and female infants aged up to 24 months with any manifestations suggesting allergy in the skin (urticaria, atopic dermatitis, and angioedema), respiratory tract (rhinorrhoea, wheezing and coughing), gastrointestinal tract (dysphagia, regurgitation, colic, constipation, vomiting and diarrhea ± blood loss), and/or anaphylaxis and shock following consumption of cow's milk. Infants with known chronic diseases, malabsorption syndromes, inflammatory bowel diseases, lactose intolerance, and/or intestinal congenital anomalies were excluded from the study.A written informed consent was signed by the infants' guardians to participate in the study. Approval for performing the study was obtained from the Pediatrics and Medical Microbiology and Immunology Departments, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval. The study was performed in accordance with the Declaration of Helniski [12].

All infants were subjected to detailed history taking include age, sex, history of any diseases, family history for allergy and presence of allergic manifestations with the introduction of cow's milk. A full general examination was performed including measurement of the body weight and length to assess growth status. Laboratory investigations performed included a Complete Blood Picture (CBC) with differentiation of WBCs, total protein and albumin levels, stool analysis and occult blood in stool.

As previously described [9], oral food challenges were administered to all eligible patients in the form of the DBPCFC to confirm the diagnosis of CMA. All patients remained for, at least, 2 hours under observation after the last milk dose intake, before being discharged. If a clinical reaction appeared, the challenge was discontinued, and treatment was provided, and the test was considered positive. Special investigations to assess sensitization to CMP were performed in the form of SPT and measurement of sIgE. SPT was performed for all patients using fresh pasteurized cow's milk. Histamine dihydrochloride was used as positive control while saline solutions were used as negative control. The diameters of the wheal reactions were determined after 15-20 minutes. All tests with a wheal diameter of > 3 mm elicited by cow's milk and valid controls were considered positive. Specific IgE for CMP was measured by Immune blot assay (Allergy Screen test, UK) Allergy Screen Panel 1 (MEDIWISS Analytic GmbH, Hanover, Germany) according to the manufacturer's instructions. The result was stated in KU/L.

STATISTICAL ANALYSIS

The collected data were coded, entered, presented, and analyzed by computer using a database software program, Statistical Package for Social Science (SPSS) version 20. Qualitative data were represented as frequencies and percentages. Quantitative data were expressed as the mean ± SD & median (IQR), and qualitative data were expressed as absolute frequencies (number) & relative frequencies (percentage). Independent samples Student's t-test was used to compare between the two groups of normally distributed variables, while Mann Whitney U test was used for non-normally distributed variables. Spearman's rank correlation coefficient was calculated to assess the relationship between various study variables, (+) sign indicates direct correlation & (-) sign indicates inverse correlation; values near 1 indicate a strong correlation and values near 0 indicate a weak correlation. The results were considered statistically significant and highly statistically significant when the significant probability (P value) was **< 0.05*** and **<0.001**** respectively. Sensitivity, specificity, predictive value for positive (PVP), predictive value for negative (PVN), and accuracy were calculated at 95% CI to measure the validity.

RESULTS

This study included 102 infants suspected to have CMA. (**Table 1)** showed that (53.9 %) of them were male with a mean age of 7.86±2.8 months and a mean weight of 6.2±1.56 kg. The entire studied group (n = 102) was subjected to DBPCFC test with cow's milk, SPT and measurement of serum sIgE to cow's milk. Regarding Oral challenge test, a total of 72 infants (70.59%) showed positive allergic reactions to oral intake of cow's milk, while 30 infants (29.41%) showed no reaction. Comparing both groups (positive challenge test and negative challenge test) regarding their age, sex and body weight, they were matched for age and sex with p value (0.08 and 0.098, respectively, but those with a positive challenge test had

significantly lower body weight (5.99±1.14) kg vs. (6.73±2.22) kg for the challenge test negative group with (*P* value = 0.028). As shown in **(Table 2)**, there was a highly statistically significant difference between allergic and non-allergic groups regarding levels of sIgE and the wheel diameter, with the allergic group had higher sIgE levels and larger wheel diameter in SPT (*P* value <0.001). As shown in **(Figure 1.a)**, the ROC curve for the ratio of sensitivity and specificity of the wheal diameter of SPT compared to the OCT (gold standard) results was highly significant, with AUC of 0.868, CI of (0.8-0.935), and *P* 0.001. **(Table 3)** described the performance accuracy of wheal diameter in SPT compared to the OCT (gold standard) results. When the 3-mm value was established as a cut-off for positivity, the sensitivity was 75%, the specificity was 68.7%, the PVN was 59%, and the PVP was 93.1%. However, based on Youden's index, which is the suggested measure for establishing an optimal cut-off point, the optimal wheal diameter for the diagnosis of CMA is 3.75 mm, while that obtained with maximum specificity (specificity = 100% and PVP = 100%) was 4.75 mm. The ROC curve for the ratio between sensitivity and specificity of sIgE measures compared to the OCT (gold standard) results was highly significant, as shown in (**Figure 1.b)**, where AUC was 0.923, CI was (0.872-0.974) and (*P* <0.001). **(Table 4)** described the performance accuracy of sIgE compared to the OCT (gold standard) results, When the value of 0.35 kU/L was established as the cut-off point for test positivity, the sensitivity was 68.1%, the specificity was 96.7%, the PVN was 69%, and the PVP was 98%. Using Youden's index, the serum sIgE concentration considered optimal for the diagnosis of CMA was also 0.35 kU/L, while that obtained with the maximum specificity measure was 0.45 kU/L. When the SPT wheel size and serum sIgE levels for cow's milk in the allergic group were compared, there was a highly significant correlation with a *P* value of <0.001, as shown in **(Figure 2).**The performance accuracy of both serum sIgE and wheal diameter in SPT together compared to the OCT (gold standard) results was shown in **(Table 5).** The sensitivity was 62.5%, the specificity was 96.6%, the PVN was 51.8% and the PVP was 97.8%.

Table 1: Demographic characteristics of the studied group (n=102).

Characteristics	Value	
Age (month):		
Mean± SD	7.86±2.8	
(Minimum-maximum)	(1.3-18)	
Weight (kg):		
Mean± SD	6.2±1.56	
(Minimum-maximum)	(2.7-11)	
Sex: No (%)		
Male	55	53.9
Female	47	46.1

Table 2: Comparing wheal diameters measurements in skin prick test and serum level of specific Ig E between allergic and non-allergic groups.

Items	Allergic	Non allergic	Test*	P value
S IgE (kAU/L)				
Mean± SD	0.50± 0.21	0.29 ± 0.06		
Median (IQR)	0.55 (0.34-0.62)	0.33 (0.23-0.34)	-6.82	<0.001**
Wheel diameter (mm)				
Mean± SD	6.29±3.58	2.12±0.96		
Median (IQR)	6 (2.9-9)	2.2 (1.22-2.62)	-5.38	<0.001**

* Mann Whitney U test

Table 3: Sensitivity (S), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) for wheal diameters of SPT compared to oral challenge test as a gold standard

Wheel diameter	Value
Cut-off (Skin index) **3mm**	
Sensitivity	75.0
Specificity	86.7
PVP	93.1

Wheel diameter	Value
PVN	59.0
Cut-off (Youden index) 3.75mm	
Sensitivity	69.4
Specificity	93.3
PVP	96.1
PVN	56.0
Cut-off of max Specificity 4.75mm	
Sensitivity	55.6
Specificity	100
PVP	100
PVN	48.8

Table 4: Sensitivity (S), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) for sIgE levels compared to oral challenge test as a gold standard

Specific IgE	Value
Cut-off (Youden index) 0.35 ku/l	
Sensitivity	68.1
Specificity	96.7
PVP	98.0
NPV	69.0
Cut-off of max Specificity 0.45ku/l	
Sensitivity	51.4
Specificity	100
PVP	97.3
NPV	46.1

Table 5: Sensitivity (S), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) for combined positive SIgE and SPT compared to oral challenge test as a gold standard

Item	Value
Sensitivity	62.5
Specificity	96.6
PVP	97.8
NPV	51.8

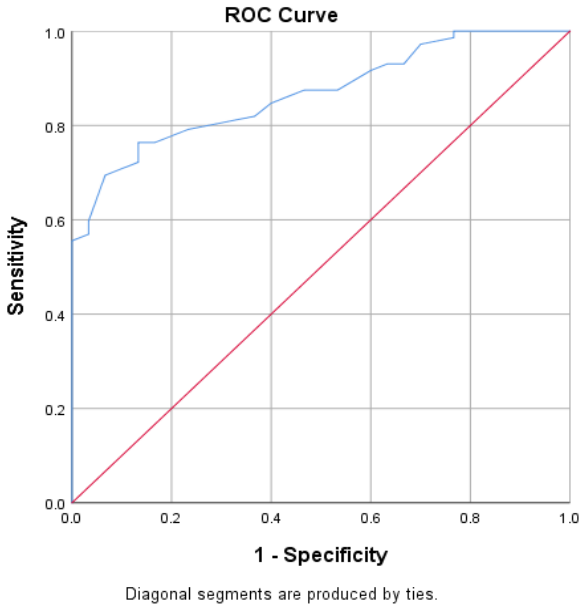

Figure 1a: ROC curves illustrating optimum cut-off of wheal diameter [AUC 0.868], CI (0.8-0.935), (p<0.001). (ROC: Receiver operating characteristics Curve, AUC: area under the curve, CI: confidence interval)

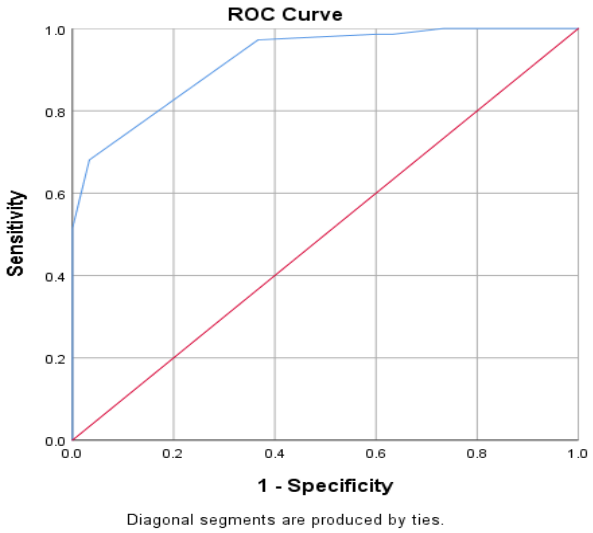

Figure 1b: ROC curve revealing optimum cut-off of sIgE levels [AUC 0.923], CI (0.872-0.974), (p<0.001). (ROC: Receiver operating characteristics Curve, AUC: area under the curve, CI: confidence interval)

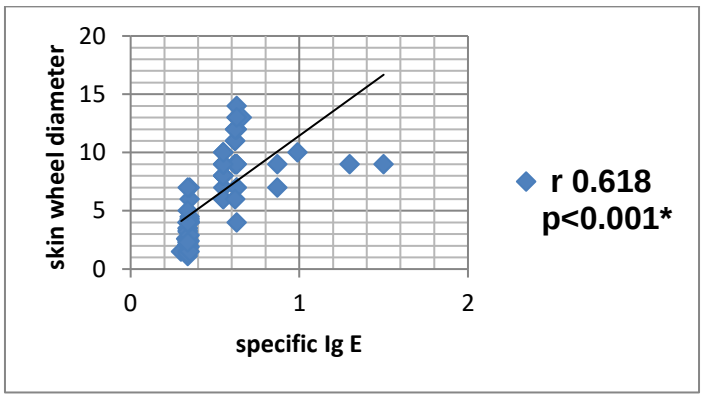

Figure 2: Correlation between wheel size of skin prick test (in mm) and specific serum IgE levels (in kAU/L) for cow's milk in the allergic group

DISCUSSION

Cow's milk is usually the earliest food presented into an infant's diet and consequently is one of the first and most prevalent causes of food allergy in early childhood [13]. A timely and confirmed diagnosis of CMA is essential to start the proper diet replacement when needed or otherwise avoid unrequired diet restrictions [14]. Several methods have been used to diagnose CMA. However, the food challenge is still the only definitive way to establish or rule out food allergy [15].Our study included 102 infants suspected of having CMA according to their history and clinical examination. On performing oral challenge tests, only 72 infants (70.59%) developed allergic reactions and were confirmed as CMA. The prevalence of CMA varies widely among different studies (from 41 up to 79%) [16-27] due to different selection criteria of the studied children regarding their age and clinical presentation, in addition to, different protocols used to perform the OCT. Food challenge tests are time-consuming, expensive and not free of undesirable effects and so, there is a great demand for more simple diagnostic procedures [10]. In vivo SPT and in vitro serum sIgE detection for CMP can be used to assess IgE sensitization by detecting the presence of sIgE antibodies (tissue-bound and circulating IgE antibodies, respectively). However, these tests cannot always accurately diagnose food allergy without relevant history or positive food challenge test [4, 5, 8]. In our study, we investigated the accuracy of SPT mean wheal diameter and sIgE serum levels for the diagnosis of CMA in Egyptian infants. We found a high statistically significant variance between allergic and non-allergic infants regarding the wheel diameter and the levels of sIgE and with the allergic group having a larger wheel diameter (6.29±3.58 vs 2.12±0.96) mm and higher sIgE levels (0.50±0.21 vs 0.29±0.06) KUA/L (*P* value <0.001 for both) as shown in **(Table 2)**. Similarly, previous studies have reported significant differences between allergic and non-allergic patients regarding the results of SPT and sIgE serum levels [19,24,27] SPT is a simple in vivo technique to assess the existence of IgE sensitization. When a specific allergen is brought through a lancet into the skin of allergic patients,

dermal mast cells degranulate due to the crosslinking of allergen-sIgE attached to their membrane receptors. These mast cells can attach individual allergen sIgE molecules for over one year. Degranulation results in the immediate release of histamine and other mediators, producing a skin response, in the form of a wheal and erythema that can be measured in order to evaluate the degree of skin reactivity [11].

In our study, SPT was performed using fresh pasteurized cow's milk. It was favored over commercial extracts for testing because it has been shown to result in significantly larger wheal diameters and to have higher sensitivity when used for skin [16]. Using the previously defined 3 mm cut-off value for positivity of SPT wheal diameter, the sensitivity was 75%, the specificity was 68.7%, the NPV was 59% and the PPV was 93.1%. Previous studies have reported sensitivities 61-94%, specificities 62-78%, NPV 67-98% and PPV 48-76% [16,18,19,21,22]. This variability in the accuracy of SPT results could be related to different populations included in the studies and different sources of cow's milk used for testing.

We tried to define new optimal cut-offs by Youden's index and the maximum specificity criterion. Using Youden's index, it was found to be 3.75 mm, which was comparable to those reported before by Franco et al. (3.5 mm) [24] and Neves et al. (4.5 mm) [27]. However, for the maximum specificity, the cut-off was 4.75 mm which was comparable to those reported by Franco et al. [24] (5 mm) and Sporik et al. (6 mm) [17] but smaller than those reported by other authors (8-13.8 mm) [16, 19, 21-23, 26, 27]. This variability may be related to the age of the study population, as it has been reported that younger children show smaller wheal diameter in SPT with fresh milk [17, 26].

SPTs are well-tolerated, easy, reproducible, biologically relevant, cost- and time-effective, and very sensitive. However, they are not standardized, subjective, affected by the administration of anti-histaminic drugs and not without risk of anaphylaxis and death (<0.02%). Most of these back draws are avoided by in vitro detection of serum sIgE for CMP [12].

In our study, the detection of serum sIgE was performed by immunoblot assay. Using 0.35 kU/L as the cut-off point for test positivity as described by the kit manufacturer, the sensitivity was 68.1%, the specificity was 96.7%, the NPV was 69% and the PPV was 98%. Previous studies have reported sensitivities 67-78%, specificities 39-56%, NPV 43-81% and PPV 58-63% [18-20, 24, 25]. According to Youden's index criterion, the optimal cut-off point was 0.35 kU/L (the same cut-off described by the kit manufacturer) while the cut-off of maximum specificity was 0.45 kU/L **(Table 3)**. A wide range of cut-offs has been suggested by previous studies ranging from 3 up to 88 kU/L [18-20, 22, 24, 25, 27]. The variability of results may be related to differences between reagents and producers of the tests. Our study showed a highly significant correlation between SPT wheel size (in mm) and serum sIgE levels (in kU/L) for cow's milk ($p < 0.001$), as shown in figure 2. However, on comparing the accuracy of SPT weal diameter and sIgE serum level measurement for diagnosis of CMA, the results were comparable with SPT being more sensitive (75% vs 68.1%), while sIgE being more specific (96.6% vs 86.7%). So, the best accuracy was when using both tests together for the diagnosis (sensitivity 62.5% and specificity 96.6%) as shown in **(Table 5)**. SPT represents the overall response according to the levels of histamine and other mediators (e.g., prostaglandin, leukotrienes, and platelet-activating factor) released from mast cells activated by the interaction between allergen and sIgE antibodies on the cell surface. Therefore, it has been suggested that SPT should not be interchangeably used with sIgE because circulating IgE is not equivalent to cell bound histamine-releasing active mediators [28]. However, serum sIgE measurement is more quantitative compared to SPT beside being safer, not affected by drug intake or skin hyper-reactivity (dermatographism) [11].

CONCLUSION

For clinical practice, our findings suggest that the correlation between both SPT and sIgE is significant regarding CMA diagnosis. Therefore, these tests can be used together for the diagnosis of CMA. However, still some cases can be only diagnosed with positive oral food challenge with non-detectable sensitization. Therefore, a detailed history is a major factor in assessing the CMA. In addition, the definition of new optimal cut-offs for sIgE and SPT to cow's milk can improve the accuracy of these tests, hoping to avoid unnecessary and potentially dangerous oral food challenge tests.

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