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ORIGINAL ARTICLE

Establishing a cut-off for the serum levels of specific IgE to milk and its components for cow's milk allergy: Results from a specific population☆

A.P. Castro[a,*], A.C. Pastorino[a], A.K.F. Gushken[a], C.M. Kokron[b], U.D. Filho[a], C.M.A. Jacob[a]

[a] *Department of Pediatrics, Faculty of Medicine, University of Sao Paulo, Brazil*
[b] *Division of Clinical Immunology and Allergy, University of São Paulo School, Brazil*

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Abstract
Background: Cow's milk allergy diagnosis many times requires double-blind placebo-controlled food challenge (DBPCFC), which presents high accuracy but involves risks, specifically in infants and anaphylactic patients. The identification of the cut-off values for specific IgE to milk or its components would contribute to cow's milk allergy (CMA) diagnosis. The aim of this study was to compare discriminating concentration of a cow's milk specific IgE and its fractions (α-lactoalbumin, β-lactoglobulin, casein) in children for the CMA diagnosis.
Methods: this study included 123 patients (M:F = 1.3:1) median age at diagnosis = 1.91 years, (3.5 m to 13.21 y) with CMA diagnosis via DBPCFC ($n = 26$), proven anaphylaxis due to cow's milk ($n = 46$) or a suggestive clinical history associated with a positive skin prick test ($n = 51$) and open oral food challenge. The control group included 61 patients (1 male:1.1 female) ages ranging from 0.66 to 16.7 years (median = 6.83 years). Receiver operator characteristics (ROC) curves were constructed to determine the best cut-offs that guarantees high specificity (>95%) for cow's milk and its components.
Results: considering 98% specificity, cut-off points were: 3.06 kU/L for cow's milk, 2.06 kU/L for α-lactalbumin, 1.85 kU/L for β-lactoglobulin and 1.47 kU/L for casein. The best ROC curve (area under the curve = 0.929) was obtained evaluating cow's milk.
Conclusion: this study showed that the cut-off point detected for whole cow's milk revealed a better discriminatory capacity for CMA diagnosis without the necessity of the milk components testing.
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☆ Part of these results were a poster presentation at 29 European Academy of Allergy and Clinical Immunology, http://www.postersessiononline.com/173580348_eu/congresos/29EAACI/aula/-P_1084_29EAACI.pdf.

* Corresponding author.
E-mail addresses: moschione@uol.com.br (A.P. Castro), acpastorino@uol.com.br (A.C. Pastorino), agushken@uol.com.br (A.K.F. Gushken), cmkokron@usp.br (C.M. Kokron), udoria@hotmail.com (U.D. Filho), miuki55@uol.com.br (C.M.A. Jacob).

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The prevalence of food allergy (FA) varies from 6% to 8% in children, and it is currently increasing in many countries.[1] Among all food allergens, cow's milk is one of the most common and often the first food introduced in the infant diet, even during breastfeeding. Cow's milk allergy (CMA) affects approximately 2.5% of children and may occur early in life, even during the neonatal period.[2] Clinical findings of CMA include a large spectrum of clinical manifestations including anaphylaxis, which can be life-threatening.[3]

The diagnosis of an Immunoglobulin E (IgE)-mediated FA depends on the clinical history and specific IgE detection through skin prick test or laboratory evaluation, including the investigation for the specific IgE (sIgE) of the triggering food and the double-blinded, placebo-controlled food challenge (DBPCFC). Although the DBPCFC is still considered the gold standard for FA diagnosis, it involves risks, demands adequate local conditions and is expensive.[4,5] Consequently, it is necessary to develop other laboratory tools with adequate accuracy and feasibility.

Several studies have been developed with the aim of determining the serum level cut-off of specific IgE for CMA diagnosis.[4–8] It was observed that this determinant concentration depends on the characteristics of the evaluated populations. Most of the studies included patients with atopic dermatitis, who usually present with high IgE serum levels that may interfere with the cut-off values.[4–8] Moreover, there are few studies that evaluated milk components as a tool in cow's milk allergy diagnosis.[6] The aim of this study was to establish a cut-off for the serum levels of specific IgE to milk and its components for CMA IgE-mediated diagnosis from a Brazilian food allergy reference centre. The hypothesis is that the local cut-offs in our population may have different characteristics than those previously evaluated in other populations.

Methods

Study population

This was a retrospective study evaluating 184 consecutive children and adolescents referred to a food allergy centre in Brazil for evaluation of suspected IgE-mediated food hypersensitivity, in a four-year period from March 2004 to March 2009. Inclusion criteria for CMA diagnosis were: (1) children who had a suggestive history of allergy to cow's milk and a positive DBPCFC for cow's milk; (2) children with at least one episode of anaphylaxis triggered by milk in the previous year and positive skin prick test (SPT); and (3) children with a suggestive CMA history associated with a positive SPT and positive open food challenge. Positive open challenge was defined as a known and confirmed ingestion of milk followed by immediate IgE-mediated symptoms.[3] The criteria adopted for anaphylaxis were defined by the ''Second symposium on the definition and management of anaphylaxis''.[9] Exclusion criteria were: children with previous CMA history but already tolerant, without symptoms after milk ingestion, or a dosage of serum-specific IgE to cow's milk one year after the last report of symptoms. All children were submitted to sIgE detection to milk and individual components.

From 184 children (1.2M:1F), 123 had a confirmed diagnosis of cow's milk allergy: 51 through a positive open food challenge, 46 with confirmed anaphylaxis to cow's milk, and 26 had positive DBPCFC. Sixty-one had negative challenges to milk (open challenge) and were considered the control group.

Diagnosis

SPTs were performed with glycerinated food extract to whole milk, α-lactalbumin, β-lactoglobulin and casein, a positive control (histamine 1%), a diluent as the negative control (IPI ASAC Brasil, ASAC Pharma – Alicante, Spain) and with a drop with fresh cow's milk (prick to prick). A wheal 3 mm larger than the negative control was considered positive.[10] The DBPCFCs were performed according to Williams and Bock[11] and modified for the use at Allergy and Immunology Paediatric Unit.[12] Patients were referred to the outpatient clinic for testing after six hours of fasting, and they received fixed volumes of 60 ml at each intake at intervals of 15–30 min to a total of 360 ml. During the period of cow's milk administration, increasing doses of milk were administered (5, 10, 15, 20, 25 and 25 ml) after being added to a vehicle (soy formula) to complete the total volume of 60 ml. Low lactose cow's milk was used to exclude clinical manifestations due to lactose intolerance. The test was considered positive when IgE-mediated reactions occurred up to two hours after the ending of the test.[12] After the test, the family was instructed to record any symptoms that the child may have during the following week. Serum samples from all patients and the control group individuals were collected during regular visits and analysed for specific IgE for cow's milk, α-lactalbumin, β-lactoglobulin and casein (ImmunoCAP – by Thermo Fisher Scientific Inc., USA) according to the manufacturer's instructions.[13] The age of the patients at blood collection varied from 0.3 to 13.21 years (median = 1.9 years), and the ages of the control group patients ranged from 0.6 to 16.7 years (median = 6.83 years).

The study received approval from the Department of Paediatrics and Clinical Hospital from University of Sao Paulo Institutional Review Board. Informed consent forms are routinely obtained to challenge test.

Data analysis

The cut-off levels of specific IgE for cow's milk and its components were determined by an analysis with the ROC curve. The analysis was performed using Med Calc 10 1.2.0 (MedCalc Software, Mariakerke, Belgium). The area under the curve (AUC) was calculated to quantify the test accuracy and was considered adequate when greater than 0.8.[14] The cut-off was considered adequate if the specific IgE cut-off levels presented specificity $\geq$ 95% and a positive likelihood ratio $\geq$ 10 (LR).[15] GraphPad Instat 3 (GraphPad Software Inc., CA 92037, USA) was used to calculate medians.

Results

The study included 123 children with confirmed CMA. Of these, 41.4% had a suggestive history and a positive oral food challenge, 37.4% had anaphylaxis and 21.2% had a positive DBPCFC. Only 21.1% of the patients were submitted to DBPCFC and the main reasons for this were: previous

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