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ORIGINAL ARTICLE

Baked milk tolerant patient: Is there any special feature?

C.P.G. Barbosa[a,*], A.P.M. Castro[a], G.H. Yonamine[b], A.K.F. Gushken[a], C.M.L. Beck[a], P.R.C. Macedo[a], M.B. Dorna[a], C.J.N. Santos[a], A.C. Pastorino[a], C.M.A. Jacob[a]

[a] *Allergy and Immunology Unit, Department of Pediatrics, Instituto da Criança, Hospital das Clínicas da Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil*
[b] *Division of Nutrition, Instituto da Criança, Hospital das Clínicas da Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil*

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Abstract
Background: Determining whether patients with cow's milk allergy (CMA) can tolerate foods produced with baked milk could provide a better quality of life, a better prognosis, and an option for desensitization.
Objectives: The aim of this study was to identify which patients over four years of age with persistent CMA could tolerate baked milk, to compare the clinical and laboratory characteristics of reactive and non-reactive groups and to describe their clinical evolution.
Materials and methods: A cross-sectional study was conducted (January/13 to November/14) that included all the patients followed at a food allergy center who met the inclusion criteria. The patients underwent an oral food challenge (OFC) with a muffin (2.8 g of cow's milk protein). To exclude cow's milk (CM) tolerance, the patients were subsequently challenged with unheated CM.
Results: Thirty patients met all the inclusion criteria. Fourteen patients (46.7%) were considered non-reactive to baked milk and reactive to unheated CM. When the groups that were reactive and non-reactive to baked milk were compared, no statistically significant differences in clinical features were found. The prick test for α-lactalbumin ($p = 0.01$) and casein ($p = 0.004$) and the serum specific IgE for casein ($p = 0.05$) presented statistical differences. After one year, none of the patients who were reactive to baked milk were ingesting CM, while 28% of the tolerant patients were consuming fresh CM ($p = 0.037$).
Conclusions: Baked milk can be tolerated by patients with CMA, especially those with lower levels of casein and α-lactalbumin. This option can improve quality of life and accelerate tolerance.

* Corresponding author.
E-mail address: claudiaplech@yahoo.com.br (C.P.G. Barbosa).

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Introduction

Cow's milk allergy (CMA) is the most common childhood food allergy, with a prevalence of 2–3% in children.[1,2] This disorder presents a risk of severe reaction and even potentially fatal outcomes. The natural history of CMA has been described as presenting a good prognosis, with most children becoming tolerant to cow's milk (CM) spontaneously at an early age: 80% are tolerant at three years of age.[3] However, in recent years, less optimistic results have been found, showing only a 19% tolerance at four years of age.[4]

The traditional treatment for CMA is restricting the intake of CM and its products, although doing so leaves these patients unprotected when they come into contact with small amounts of the antigen.[5–8] Currently, there is evidence that the ingestion of small amounts of milk could induce desensitization or tolerance.[9–12]

Recent studies have described that an oral food challenge (OFC) using baked milk can define two phenotypes of patients with CMA: those who are reactive to baked milk products and those who are non-reactive. These studies reported a 65–83% tolerance of heated milk,[13–16] which indicates a better prognosis in terms of earlier tolerance of CM and a better quality of life. Subsequent studies have suggested that baked milk could be an option for desensitization which is easy to perform and has a low number of adverse effects.[17–20] When exposed to high temperatures, CM antigens can lose their allergenic potential (in the case of conformational epitopes, such as β-lactoglobulin) or retain it (in the case of linear epitopes, especially casein).[21–24]

To identify whether a patient with CMA can tolerate a product containing baked milk, an OFC with baked milk is recommended because to date, clinical and laboratory data have been poorly able to make the distinction between baked milk tolerance and non-tolerance. The main objectives of this study were to identify patients over four years of age with persistent CMA who could tolerate the ingestion of baked milk, to compare the clinical and laboratory characteristics of those who are reactive to baked milk and those who are non-reactive, and to describe the clinical evolution after one year of consuming baked milk products.

This paper reports the Brazilian statistics regarding baked milk tolerance, a topic on which there are no published data for Latin America. It followed a careful methodological design that included a blinded researcher, collected data simultaneously with the OFC, and chose inclusion criteria that ensured a homogeneous sample. It utilizes an easily made baked milk recipe with a high CM protein concentration, thus facilitating patient compliance. The ability to identify a patient as baked-milk tolerant can lead to a significant improvement in quality of life, a better prognosis, and the possibility of desensitization. Finally, finding a clinical or laboratory marker for baked milk tolerance would make it possible to evaluate which patients can undergo an OFC with less risk.

Materials and methods

A cross-sectional study was conducted between January/13 and November/14. The sample was selected from patients who attended a tertiary food allergy center (Allergy & Immunology Unit, Department of Pediatrics, Instituto da Criança – HCFMUSP – São Paulo), met the inclusion criteria and agreed to carry out the OFC. The protocol was approved by the Ethical Committee from the Hospital das Clínicas, School of Medicine, Universidade de São Paulo.

The eligibility criteria included individuals between 4 and 18 years of age who had a diagnosis of IgE-mediated CMA based on[1]: a clinical history consistent with IgE-mediated manifestations up to two hours after exposure to CM[2]; a positive specific IgE to CM and/or fractions (serum IgE $\geq$ 0.35 kUA/L or prick test $\geq$3 mm); and[3] a clinical response to double-blind, placebo-controlled food challenges (DBPCFC) for milk upon diagnosis of CMA, except those with a history of anaphylaxis. All patients or guardians signed an informed consent form after they were notified about the study, including the possibility of severe reactions.

The exclusion criteria included pregnancy, acute infectious disease, chronic disease treated with immunosuppressive drugs, uncontrolled asthma, atopic dermatitis, eosinophilic oesophagitis, any allergic reaction in the past year to baked milk products, allergy to other ingredients used in the preparation, and a negative OFC with unheated cow's milk. All of the patients had a history of ingestion of soybeans, wheat and egg without any reaction.

The baked milk product was prepared by the Nutrition Division a day before each test. Each muffin contained 2.8 g of CM protein (corresponding to 100 mL) and was submitted to oven heating at 350 °F for 30 min according to references in the literature[13] adapted for Brazilian cooking (Fig. 1).

The selected patients were admitted to a hospital and provided venous access and monitoring under medical supervision. Each patient received a quarter of the muffin every 15 min, with clinical assessment (patient complaints, physical examination, monitoring vital signs, oxygen saturation, blood pressure and peak flow) prior to each dose; observation was maintained for two hours after the challenge. The challenge was discontinued at the first sign of an objective reaction, and the patient was properly assisted and medicated whenever necessary. The patients were defined as non-reactive to baked CM if they did not present any allergic reaction after ingesting an entire muffin. Patients who had no history of reaction to fresh CM in the past year were submitted to a challenge with unheated CM (300 mL, corresponding to 10 g of protein) to assess whether they would be considered reactive to CM.[25,26] The researcher who conducted the OFC did not have access to the patients' recent laboratory data at the time of testing.

The following clinical features were obtained before the test: gender, history of previous anaphylaxis, reports for the milk trace intake, reports of allergic reactions to CM in the past year, history of anaphylaxis in the past year, rhinitis, asthma, history of other allergies, and the family history of rhinitis, asthma and other allergies. The following laboratory tests were conducted simultaneous to the OFC: eosinophil blood count, total IgE, and serum specific IgE (ImmunoCAP®) to CM, α-lactalbumin, β-lactoglobulin and casein. Prick tests were also performed for CM, α-lactalbumin, β-lactoglobulin and casein according to the modified Pepys technique. The positive criterion was wheal larger than 3 mm compared with the negative control. For the comparative analysis, we used the mean of the two perpendicular diameters.[27]

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