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Oral food challenge in children with contact urticaria in reaction to cow's milk

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Abstract

Objective: To evaluate the relationship between the occurrence of contact urticaria in reaction to cow's milk in infants and the diagnosis of cow's milk allergy (CMA) established by supervised oral food challenge.

Methods: In this cross-sectional study, we identified 184 children who had undergone 221 oral food challenge (OFC) at a CMA reference center between July 2015 and August 2019. Of these, 23 (12.5%) had a history of contact urticaria to cow's milk and underwent a total of 30 OFC. Baked cow's milk OFC were excluded, and 21 children were included in the study. All data from clinical history and allergy tests (serum-specific IgE dosages and skin prick test [SPT] with reconstituted cow's milk formula) were recorded on standardized forms. The challenge was conducted with reconstituted cow's milk formula in increasing volumes every 15-20 min.

Results: 24 OFC were performed; 13/24 (54.2%) for diagnostic purpose and 11/24 (45.8%) to evaluate cow's milk tolerance. Allergy tests were positive in 14 patients (87.5%). Positive oral challenge outcomes were identified in 7/24. One patient had a late flare of atopic dermatitis and five children presented with immediate urticaria (two generalized urticaria and three perioral urticaria). The median papule diameter was 6.5 mm in patients with a positive OFC and 3.75 mm in the negative group ($P = 0.02$).

Conclusion: The occurrence of contact urticaria might be the only manifestation among infants sensitized to cow's milk with tolerance to oral ingestion. Reactions due to oral challenge were related to a larger wheal diameter on the SPT.

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Introduction

The prevalence of food allergy has increased markedly in the last decades, and is currently reported to occur at rates ranging from 1 to 10% in distinct studies.^{1,2} This substantial variation in prevalence rates is due to differences between populations and diagnostic methods across studies.^{3,4} The prevalence of food allergy may be overestimated based on skin allergy tests or measurement of serum-specific IgE antibodies because sensitization may occur in the absence of food allergy.^{5,7}

Oral food challenges (OFC) are recognized as the gold standard diagnostic method to confirm the occurrence of food allergy, although they are still underused in clinical practice and are only performed at a few reference centers worldwide.⁸⁻¹¹ The risks involved in an OFC and the possibility of severe reactions have led physicians and patients to avoid this test. A clinical history of hives associated with positive skin allergy tests or measurement of food-specific antibodies has been accepted as a sign of food allergy in many studies.^{2,4,12}

According to Schichter-Konfino et al.,¹³ 44.9% of the children with IgE-mediated cow's milk allergy (CMA) had contact urticaria in reaction to cow's milk. However, these authors assumed the diagnosis of CMA without performing an OFC in 86.5% of their cohort. Niggemann et al.⁷ reviewed aspects of OFC outcomes and pointed out objective clinical signs that define a positive oral food challenge for diagnosis of food allergy, that include immediate manifestations on skin, gastrointestinal, respiratory, cardiovascular, or neurologic system due to ingestion of the culprit food. They suggested that the occurrence of contact urticaria or no persistence of urticaria after a few minutes of observation during OFC is not sufficient to define OFC as positive.^{7,8}

However, the occurrence of contact urticaria has been accepted as a manifestation of food allergy, and life-threatening reactions have been described in patients with contact urticaria after skin contact with the trigger food, and thereby physicians have deferred the challenge in this group. When a patient presents with urticaria or other immediate symptoms after ingestion of a culprit food, IgE antibodies may be involved in the physiopathology of the food allergy.^{9,12} Still, little is known about the relationship between the occurrence of contact urticaria in reaction to cow's milk in infants with sensitization to cow's milk and the diagnosis of CMA established by supervised OFC.

This cross-sectional study was carried out to evaluate the relevance of contact urticaria in reaction to cow's milk as a clinical sign of sensitization and diagnosis of CMA, as established by open OFC at a reference center.

Material and Methods

Population

The population consisted of all children (n = 184) with suspected CMA who underwent an OFC at the *Mãe Curitibana* Healthcare Unit, by the Program of Nutritional Care for People with Special Dietary Needs of the Municipal Health Office of Curitiba, in the state of Paraná (Brazil), a reference center for CMA, between July 2015 and August 2019.

Children under the age of 2 years who had suspected CMA and required special infant formulas supplied by the public healthcare system were referred to this outpatient setting for confirmation of the CMA diagnosis and adequate treatment. Inclusion criteria were history of contact urticaria in reaction to cow's milk who underwent OFC with reconstituted cow's milk formula and whose parents reported developing hives upon skin contact with cow's milk, as the main symptom of CMA. Exclusion criteria included OFC performed only with baked or fermented cow's milk food or alternative therapeutic formulas.

Study sample

Among the 221 OFC suspected of having CMA, 30 OFC were performed in 23 children (12.5%) with a history of contact urticaria to cow's milk. 6/30 OFC were performed with baked cow's milk food or therapeutic formula and were excluded. Notably, some children had undergone more than one OFC during the study period. The final analysis included 21 infants who had undergone 24 cow's milk OFC.

Clinical history, age at symptom onset, information about breastfeeding and maternal dietary restrictions, time since the previous manifestation, results from allergy tests (serum IgE antibodies or skin prick testing [SPT]), physical examination obtained before and during the OFC, and OFC-related volumes, time intervals, occurrence of reactions, and requirement for rescue treatment (if needed) were obtained from data recorded on standardized OFC forms collected in a cross-sectional study.

Patients with suspected IgE-mediated food allergy underwent SPT at the outpatient reference center when needed. The SPT were conducted using reconstituted infant cow's milk-based formula and were performed on the patients' volar forearm surface using disposable plastic devices (ALKO; FDA Allergenic, Rio de Janeiro, Brazil). Wheals with an average diameter of 3 mm greater than a negative control (0.9% saline solution) were defined as a positive test. In some patients, serum IgE antibodies specific to cow's milk and their molecular components (casein, alpha-lactalbumin, and beta-lactoglobulin) were considered positive when > 0.35 IU/L.

Oral food challenges

Open OFC protocol was performed using reconstituted infant formula offered increasingly every 15-20 min: 0.1, 0.3, 1, 3, 10, 30, and 90 mL.^{6,11} All OFC were followed by 2 h of observation in which both health team and caregivers knew which formula was offered on a non-blinded oral challenge manner. Special care was taken to avoid cow's milk spillage on the skin during the OFC in the selected patients with contact urticaria to prevent the occurrence of hives that would mask an episode of urticaria triggered by oral food allergy. All infants were reviewed for late reactions from Week 1 until 2 months later.

The protocol of this study was approved by the Human Research Ethics Committee of the Health Sciences Center of the Federal University of Paraná (approval number CAAE 15103119.0.0000.0096). The results are reported following

the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.¹⁴

Statistical analyses

All data was analyzed with descriptive and inferential statistics. Measures of central tendency and dispersion were expressed as mean and standard deviation (SD) for continuous variables with symmetric distribution, measured by Shapiro-Wilk test, and as median and interquartile range (IQR) for those with asymmetric distribution. Categorical variables were expressed as absolute and relative frequency.

The Mann-Whitney test was used for those with asymmetric distribution, and Fisher's exact tests were applied to estimate differences between categorical variables. All statistical analyses were carried out using the software Statistica 4.0 (StatSoft Power Solutions, Inc., Palo Alto, California, USA). P values < 0.05 were considered significant.

Results

The study included 21 children (11M/10F) with a median age of 15 months (interquartile range [IQR] = 10-19 months) and a median age at the contact urticaria occurrence of 4.0 months (IQR = 3-6 months), see Table 1.

Regarding the infants' dietary history, five mothers (23.8%) had been advised to refrain from consuming cow's milk before their infants' first outpatient visit, after which cow's milk was reintroduced to the maternal diet without triggering allergic manifestations in the infants. In 13 (61.9%) cases, the infants' formulas were replaced by soy-based (n = 7) or hydrolyzed cow's milk (n = 6) formula. Eight infants (38.1%) reached the age of 6 months with exclusive breastfeeding even after the reaction, and 14 (66.7%) were breastfed until the time of the first OFC (Table 1).

Referred clinical manifestations included atopic dermatitis (AD)-associated disease in three (14.3%), angioedema and/or rhinitis (9.5%), generalized urticaria (9.5%), one AD acute exacerbation, and gastrointestinal symptoms (33.3%), see Table 1.

A diagnostic OFC was performed within ≤ 6 months from the first episode of contact urticaria in 14 infants (82.4%), of whom 10 underwent OFC in less than 8 weeks from the admission to the unit care. Only four children had OFC performed within 8 weeks from the first reaction, as recommended for diagnosis of food allergy (Table 1).

Positive allergy tests were seen in 14 cases (87.5%). SPT was positive in 13 (61.9%), and cow's milk serum-specific IgE antibodies were positive in 5 (23.8%). The median wheal diameter was 5 mm (IQR = 3.8-6 mm), and the median level of cow's milk-specific IgE antibodies was 5.05 kU/L (IQR = 2.88-6.53 kU/L), see Table 1.

Twenty-four OFC were performed; 13/24 (54.2%) for diagnostic purpose and 11/24 (45.8%) to assess cow's milk tolerance. Three children were submitted to more than one OFC in the study period. The cumulative dose was 94 mL (IQR = 76.5-124.5), and the eliciting dose was 49.2 mL (IQR = 42.1-73.6). OFC was positive in seven (29.2%), see Table 2.

Table 1 Characteristics of the infants presenting with contact urticaria in reaction to cow's milk.

Characteristics	Median (IQR)/n (%)
Gender (M/F)	11 / 10
Age (months)	15 (10-19)
Age of onset of symptoms (months)	4 (3-6)
Age at first OFC (months)	13 (10-19)
Exclusively breastfed (up to six months)	8 (38.1%)
Continued breastfeeding until OFC	14 (66.7%)
Maternal elimination diet on admission	5 (23.8%)
Substitute formula use (or consumption)	13 (61.9%)
Soy based formula	7 (53.8%)
Hydrolyzed formula	6 (46.2%)
Baked milk consumption before OFC	10 (47.6%)
AD associated	3 (14.3%)
Other manifestations on clinical history	
Angioedema and/or rhinitis	2 (9.5%)
Generalized urticaria	2 (9.5%)
AD exacerbation	1 (4.8%)
Gastrointestinal symptoms	7 (33.3%)
Positive allergy tests	14 (82.4%)
Prick to prick	13 (61.9%)
Positive (> 3mm)	5 (3.8-6)
Specific IgE	5 (23.8%)
Positive (> 0.35kU/L)	5.05 (2.88-6.53)

AD: Atopic dermatitis; F: Female; IQR: Interquartile range; M: Male; OFC: Oral food challenge.

Six infants had the procedure interrupted due to the development of an immediate positive OFC, and one developed a late flare of atopic dermatitis after 2 days. Five children presented with immediate urticaria; among these, two had generalized urticaria, and three had just perioral urticaria including areas of the chin and ears. Three had emesis (Table 3). The reactions presented by these infants were similar to what they had reported.

None of them required drug treatment, and the symptoms improved in less than 1 h. The occurrence of an immediate positive OFC was related to a larger wheal diameter on the SPT, as the median wheal diameter was 6.5 mm (IQR = 5.50-9.50 mm) in the group with a positive response and 3.75 mm (IQR = 3-5) in the group with a negative response (P = 0.02).

Discussion

The development of contact urticaria in reaction to cow's milk during childhood may be a clinical feature of a systemic oral food allergy. In this study, not all infants with contact urticaria to cow's milk had CMA through OFC, indicating that many infants may present a cow's milk skin allergy while tolerating the ingestion of cow's milk. Although there were limitations about the time until first OFC has been identified, because only four individuals had performed OFC less than 8 weeks as recommended.

Table 2 Characteristics of OFC among infants presenting with contact urticaria in reaction to cow's milk.

Characteristics	Median (IQR)/n (%)
OFC indication	
Diagnostic OFC	13 (54.2%)
Acquisition of tolerance	11 (45.8%)
Time of follow-up until diagnostic OFC (weeks)	4 (3-8)
Reason in when to perform Diagnostic OFC	13
Contact urticaria as main symptom	7 (53.8%)
Prolonged time since first symptom	3 (23.1%)
Never ingested cow's milk	2 (15.4%)
Accidental ingestion of cow's milk	1 (7.7%)
Reason for Tolerance OFC	11
Isolated contact urticaria in accidental contact	6 (54.5%)
Prolonged time since the last allergic manifestation	3 (27.3%)
Prick test diameter or IgE levels decrease	3 (27.3%)
Accidental ingestion of cow's milk	1 (4.2%)
Cumulative dose (mL)	94 (76.5-124.5)
Eliciting dose (mL)	49.2 (42.1-73.6)
Positive OFC	7 (29.2%)

n = 24.

OFC: Oral food challenge.

Delayed diagnosis has been reported as a major concern from parents leading with a food allergic child.^{15,16}

Many children with contact urticaria in reaction to cow's milk may have a positive allergy skin test or high levels of IgE specific to cow's milk, described as an immunological food-induced contact urticaria.¹⁷ Even though the percentage of sensitization in the analyzed cohort was high (87.5%), only 33.3% presented manifestations to OFC.

Levels of food-specific IgE are likely to predict a positive response to the OFC. A systematic review from 31 studies analyzing the cutoff values for skin or serum allergic tests found that children younger than 2 years of age with IgE antibodies specific to cow's milk ≥ 5 kU/L or SPT wheal size ≥ 8 mm have a higher risk of a positive response to the OFC and should not undergo the test.^{18,19} Previous studies have shown that a wheal size < 5 mm in the SPT to cow's milk has a negative predictive value of around 100% for a positive response to the OFC.^{17,20,21} Although, it has been suggested that an SPT wheal diameter < 6 mm is likely associated with a negative response to the OFC, while wheals larger than that are probably associated with a positive response to this test.²² This finding was corroborated in the present study, in which a median wheal diameter of 6.5 mm in the SPT was found in the positive OFC group, larger than the median of 3.75 mm diameter found in the group with a negative response to the OFC.

The SPT with natural food is a pivotal tool in diagnosing food allergy, as it is easy, cost-effective and fast to perform, providing a pretest risk before the OFC.¹⁷ In this

Table 3 Clinical manifestations due to OFC.

Characteristics	n / Median (IQR)
Immediate reactions	6
Time to symptom onset (min)	82 (64-90)
Urticaria	5
Contact or perioral urticaria	3
Generalized urticaria	2
Emesis	3
Delayed reactions	1
Time to symptom onset (days)	2
Atopic dermatitis	1
Prick to prick	4
Positive (> 3 mm)	6.5 (5.8-8.3)
Specific IgE	1
Positive (> 0.35)	6.4

n = 7.

OFC: Oral food challenge.

study, positive SPT with reconstituted cow's milk-based formula overestimated the CMA diagnosis in children aged less than 2 years when they are supposed to have less sensitization.¹⁷ Respecting the observed SPT cutoffs, even in infants, is useful to prevent severe reactions during the OFC. Still, the OFC remains the only method to safely exclude the diagnosis of food allergy and assess the development of tolerance among patients with food allergy.

Open OFC may yield false-positive results, especially in those cases with values critically near the threshold in allergy tests obtained immediately before the OFC. In some cases, the occurrence of contact urticaria may be overvalued by the healthcare team, resulting in premature interruption of the OFC. To prevent false-positive results in the OFC, hives arising during the OFC must be observed in terms of extension and persistence. A modified score proposed by Bock et al.²³ has helped identify symptoms and signs during the OFC that should be considered a true response to this test.

Given the high rate of allergic sensitization in our sample, we postulate that contact urticaria may be as an isolated clinical manifestation of a skin CMA or may be present before the occurrence of a systemic CMA. Although this hypothesis has little support in the literature, sensitized infants have a high risk of becoming allergic to a food when this specific food is excluded from the diet.²⁴⁻²⁶

According to the "skin-gut dual allergen exposure" hypothesis, postponing the introduction of potentially allergenic foods during complementary feeding could increase the odds of an infant developing food allergy, as it delays the development of intestinal tolerance through skin exposure to these foods (cutaneous sensitization route).^{27,28}

Notably, all breastfed infants in this study continued breastfeeding without maternal dietary restriction.²⁹ Breastfeeding protects the infant against allergic diseases and should be encouraged to continue beyond the infant's second year of life to prevent and treat CMAs.³⁰

We conclude that in sensitized infants whose clinical history of allergic reaction to cow's milk was restricted to contact urticaria or perioral urticaria, it is essential

to perform a supervised OFC without delay to assess the infant's tolerance to this allergen.

Conclusion

Contact urticaria may be the only manifestation of sensitization to cow's milk in infants. The oral food challenge was helpful in determining the diagnosis of cow's milk allergy in these infants and allowed those without this allergy to be introduced to cow's milk in the diet. Such unnecessary restrictions may impair quality of life of the children and their parents, induce improper nutrition or child's nutrition and growth, cause social restrictions, and elevate health-care costs to families and public health system with therapeutic formulas.

In infants sensitized to cow's milk, whose clinical history indicates reactions restricted to contact or perioral urticaria, it is essential to perform a supervised oral food challenge without delay to assess the infant's tolerance to this allergen. The cutoff values previously found of wheal diameter on prick test with fresh milk or reconstituted cow's milk formula may help to establish the probability of positive outcome in the OFC. Larger studies are needed to confirm these cutoffs in Brazilian children allergic to cow's milk.

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