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Open challenge for the diagnosis of cow's milk protein allergy

Fernanda Ferreira Correa,[1] Mário César Vieira,[2] Danielle Reis Yamamoto,[2] Patrícia da Graça Leite Speridião,[3] Mauro Batista de Morais[4]

Abstract

Objective: To report the results of open challenge tests performed in children fed with cow's milk-free diet.

Description: Cross-sectional study evaluating cow's milk open challenge performed under supervision in a hospital setting during 2.5 hours and ambulatory follow-up for 30 days when no immediate reaction occurred. One hundred and twenty-one patients were included, with ages between 4 and 95 months. Cow's milk open challenge tests were positive in 28 patients (23.1%). A clinical manifestation of cow's milk allergy different from the one presented at diagnosis occurred in 12 (24.9%) patients with positive challenge. Positive challenge was more frequent (p = 0.042) in patients fed with extensively hydrolyzed formulae or amino acid-based formulae (30.3%) when compared to those fed with other exclusion diets (14.5%).

Conclusion: Open challenge allowed the interruption of exclusion diet in a significant proportion of the patients.

J Pediatr (Rio J). 2010;86(2):163-166: Milk allergy/diagnosis, milk protein, cow's milk, diagnosis, immunologic tolerance.

Introduction

The most frequent food allergy in infants is cow's milk protein allergy,[1-4] which may lead to gastrointestinal or cutaneous manifestations. The challenge test is of great importance for the diagnostic approach of infants with suspected cow's milk allergy or those receiving cow's milk elimination diet for the identification of tolerance development.[1-5] There are three types of challenge tests: double-blind, single-blind, and open. For infants, an age group in which late reactions mediated by cells are predominant, the European Society of Pediatric Gastroenterology and Nutrition recommends that open challenge is appropriate.[6] A recent review recommends that the open challenge is appropriate also for children younger than 3 years old with IgE mediated reactions.[7] It must be highlighted that the challenge test must not be undertaken when previous clinical manifestations were severe and death risk may exist, as for instance, in face of previous anaphylactic reaction.

The objective of this brief communication is to report the results of an open challenge protocol performed in two Brazilian pediatric gastroenterology services in children fed with cow's milk-free diet.

Methods

In this cross-sectional study the results of the first cow's milk open challenge conducted in 121 patients of the pediatric gastroenterology outpatient clinic of Universidade Federal de São Paulo (UNIFESP) São Paulo, Brazil, and Hospital Pequeno Príncipe, Curitiba, Brazil, were included. Data collection was performed from June, 2006 to October, 2008. Of the 136 challenge tests performed, 121 (89.0%) tests containing all the necessary patient information were included in the study. Demographic data and clinical manifestations that motivated the diagnostic hypothesis of cow's milk allergy were collected.

1. Nutricionista, Disciplina de Gastroenterologia Pediátrica, Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil.
2. Mestre. Centro de Gastroenterologia Pediátrica, Hospital Pequeno Príncipe, Curitiba, PR, Brazil.
3. Doutora, Curso de Nutrição, UNIFESP, Santos, SP, Brazil.
4. Livre-docente, Disciplina de Gastroenterologia Pediátrica, UNIFESP, São Paulo, SP, Brazil.

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The open challenges followed the same protocol in both clinics.[1-5] Tests were performed in the morning, with patients fasting, under the supervision of a pediatric gastroenterologist and a nutritionist. Before the initiation of the procedure, physical examination with special attention to skin evaluation, pulmonary auscultation, and abdominal evaluation was performed. Children who were not suitable to undergo the test due to any sign or symptom that could confound test interpretation, remained on an elimination diet until their complete recovery when a new challenge was scheduled. The test was initiated in the hospital or clinic where appropriate emergency equipment for resuscitation was available. Intravenous access was not obtained in any patient before the administration of cow's milk. The follow-up period lasted for 30 days after the open challenge test performed for 2.5 hours in the hospital or outpatient clinic. Initially, a cow's milk-embedded gauze was placed in contact with perioral region and lips. After 30 minutes, 10 mL of whole cow's milk or infant formula were administered with an incremental scheme doubling the dose every 20-30 minutes for 2.5 hours. At 150 minutes, the first phase of the challenge test was finalized at the health care facilities. The test was interrupted and considered positive when one or more of the following reactions suggestive of the cow's milk protein allergy occurred: vomiting, diarrhea, blood in stools, erythematous skin rash or urticaria, rhinoconjunctivitis, and wheezing. Patients who did not present reactions suggesting cow's milk protein allergy were discharged home where normal volumes of milk were administered. This second phase of the test (follow-up period) lasted for 30 days, with the recommendation that the patients consumed cow's milk and food containing cow's milk regularly. At the end of this period, patients were evaluated to detect if clinical manifestations had occurred on a cow's milk containing diet.

When parents did not return with the patients at the end of 30-day period, a telephone interview was conducted. At the end of this period, if the patient remained asymptomatic, the challenge test was considered negative.

The project was approved by the Research Ethics Committee (UNIFESP), and a written informed consent was obtained from all parents or guardians.

Results

Of the 121 patients on a cow's milk elimination diet, 69 (57.0%) were boys. At the time of the challenge, the age ranged from 4 to 95 months (mean 16.9±11.9 months). Clinical manifestations at the initiation of the elimination diet included diarrhea (28.6%), vomiting or regurgitation (27.9%), blood in stools (23.5%), irritability (16.9%), colic or abdominal pain (13.2%), atopic dermatitis (11.0%), urticaria-like manifestations (9.5%), constipation (8.1%), wheezing (6.6%), bloody diarrhea (5.8%), abdominal distention (4.4%), allergic edema of face or ears (2.9%), hematemesis (2.2%), otitis (2.2%), and rhinitis (0.7%). Of the 121 patients, 20 (14.5%) had already had a positive challenge before being referred to the specialty clinics. The duration of the elimination diet was less than 12 weeks in 31 (25.6%) patients; between 12 and 23 weeks in 28 (23.1%); between 24 and 47 weeks in 42 (34.7%); and more than 48 weeks in 20 (16.5%).

The challenge was positive in 28 (23.1%) patients, with the manifestations appearing in the first 4 hours in 14 of them; in up to 24 hours in seven; and in three of them, in more than 24 hours. Table 1 shows the clinical manifestations at diagnosis and during challenge. No patients presented with severe manifestations, like anaphylactic shock. Clinical manifestations of cow's milk allergy different from those presented at the time of diagnostic suspicion occurred in 12 (42.9%) of the 28 patients with a positive test (Table 1). Table 2 shows the association between the positive challenge tests and different variables. A higher frequency of positive tests in children who were being fed with protein hydrolysates or amino acid formulae was observed in comparison with those fed with soy formulae or without cow's milk substitutes.

Discussion

The approach of the child with cow's milk protein allergy includes clinical response during elimination diet and confirmation of diagnosis through the challenge test after approximately 6 to 8 weeks. If the diagnosis is confirmed, it is recommended to repeat the challenge test every 6 to 12 months until immunologic tolerance is developed.[1-5]

One of the important findings in this study was that the challenge test was negative in 93 (76.8%) of the 121 patients studied. In those cases it was possible to stop cow's milk elimination diet. This approach led to an important cost reduction with the substitutive diet, especially with the use of extensively hydrolysed or amino acid-based and yet, the reduction of nutritional risks to which the patient undergoing exclusion diets is subjected.[8,9] Another point that must be highlighted is the importance of a careful follow-up of patients with a negative challenge, considering that subclinical manifestations may occur[10,11]

In 42.9% (12/28) of the positive challenges, clinical manifestations different from those that motivated the diagnostic suspicion of cow's milk allergy occurred. In the 1960s, Goldman et al., in their classic article,[12] stated that the reappearance of the same clinical manifestations in three consecutive tests was required for the diagnosis of food allergy to be confirmed. Currently, one positive challenge test may be accepted as a diagnostic criterion.[1-5] However, even if over time clinical manifestations of allergy may change, the possibility of part of these positive results being secondary to other clinical disorders must be considered.

Table 1 - Gender, age and clinical manifestations at diagnostic suspicion of cow's milk allergy and at open challenge

Gender	Age (months)	Initial clinical manifestation	Manifestation in challenge	Same type of manifestation at onset	Time elapsed for the reaction (hours)
F	16	Vomiting	Vomiting	Yes	< 4
M	34	Diarrhea, abdominal distension, allergic edema of face and ears	Urticaria	Yes	< 4
M	11	Urticaria, vomiting	Lower lip edema and perioral hyperemia	Yes	< 4
M	31	Constipation, blood in stools	Blood in stools	Yes	< 4
M	13	Diarrhea and vomiting	Nausea	No	< 4
M	28	Diarrhea and vomiting	Diarrhea, vomiting, and abdominal pain	Yes	9
M	31	Constipation, blood in stools	Blood in stools	Yes	< 4
M	14	Wheezing, diarrhea	Wheezing	Yes	48
M	7	Dyspnea and urticaria	Urticaria	Yes	< 4
M	20	Diarrhea	Urticaria	No	< 4
M	15	Wheezing, failure-to-thrive, vomiting	Wheezing	Yes	< 4
M	14	Urticaria	Urticaria	Yes	< 4
M	5	Bloody diarrhea, irritability	Urticaria	No	
M	4	Constipation, failure-to-thrive	Vomiting, cough, flatulence	No	< 4
M	5	Abdominal pain, irritability	Intense colic	Yes	< 4
F	9	Bloody diarrhea	Vomiting	No	< 4
F	24	Diarrhea	Vomiting	No	< 4
F	12	failure-to-thrive, urticaria	Wheezing, ocular edema, and itching	Yes	
M	15	Abdominal pain, blood in stools, vomiting	Diarrhea	No	48
F	7	failure-to-thrive, diarrhea	Diarrhea and vomiting	Yes	48
M	12	Diarrhea, abdominal pain	Diarrhea	Yes	24
F	5	Bloody diarrhea, abdominal pain	Bloody diarrhea	Yes	24
M	12	Vomiting	Diarrhea and vomiting	Yes	24
M	15	Wheezing, blood in stools	Diarrhea	No	24
F	12	Abdominal distension, blood in stools	Diarrhea and vomiting	No	48
M	19	Anorexia, poor weight gain, irritability	Urticaria	No	24
F	12	Anorexia, poor weight gain	Irritability, colic	No	24
F	12	Bloody diarrhea and vomiting	Wheezing, urticaria, poor weight gain	No	

M = male; F = female.
Manifestation at challenge considered different from the initial clinical presentation = 12/28 (42.9%).

Furthermore, the physician must be alert to possible incorrect information provided by the family. Food allergy may be simulated in the Munchausen syndrome by proxy.[13,14] In face of a non-characteristic or unexpected positive result, it is advisable to repeat the challenge test in a short time interval. On the other hand, when the test is negative, the possibility of the development of tolerance, few weeks after the onset of the elimination diet, must be considered.

One aspect that must be highlighted is the period of time during which the patients remained under elimination diet: 20 patients were under elimination diet for 48 weeks (approximately 11 months), and 42, between 24 to 48 weeks. In this context, it must be considered that in a great proportion of patients studied the challenge test was performed to confirm the development of tolerance and not actually to confirm the diagnosis of cow's milk allergy. Many patients were referred to the specialty clinics in order to have the open challenge performed. Another aspect that explains the long period on an elimination diet is the fact that part of the patients presented a history of recent adverse reactions after the intake, inadvertent or not, of cow's milk protein. In this context, during the follow-up

Table 2 - Assessment of the association of positive challenge test and certain variables

	Cow's milk challenge		
	Positive, n (%)	**Negative**	**p***
Gender			
Male	19 (27.5)	50	
Female	9 (17.3)	43	0.188
Age			
≥ 12 months	20 (21.5)	73	
< 12 months	8 (28.5)	20	0.793
Initial clinical manifestation†			
Gastrointestinal	24 (21.8)	86	
Skin	6 (24.0)	19	
Respiratory	2 (28.6)	5	0.901
Duration of cow's milk protein elimination diet			
≤ 12 weeks	4 (12.9)	27	
13-24 weeks	9 (32.1)	19	
25-47 weeks	8 (19.0)	34	
≥ 48 weeks	7 (35.0)	13	0.166
Type of cow's milk substitute			
Soy extract or formula	5 (11.9)	37	
Protein hydrolysate	18 (34.6)	34	
Amino acid- based formula	2 (14.3)	12	
No formula	3 (23.1)	10	0.058

* Chi-square test with Mantel-Haenszel correlation.
† Each patient could present more than one type of clinical manifestation by the time of admission.
Chi-square test with Mantel-Haenszel correlation - protein hydrolysate + amino acid-based formula (30.3%) vs. soy + no formula (14.5%) – p = 0.042.

of patients undergoing elimination diet, it is important to identify if cow's milk protein is effectively being excluded from the diet.

In conclusion, no severe reactions during challenge tests were observed, once a history of an anaphylactic reaction was considered a contraindication for the test. In patients with positive challenge presenting with manifestations which were different from those at diagnosis the possibility of a false positive result must be considered, and the diagnosis must be reevaluated. On the other hand, a great proportion of patients were able to stop the elimination diet, reinforcing the importance of cow's milk open challenge in the follow-up of these cases.

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Correspondence:
Mauro Batista de Morais
Rua Pedro de Toledo, 441
CEP 04039-031 - São Paulo, SP - Brazil
E-mail: mbmorais@osite.com.br