Challenge testing in children with allergy to cow's milk proteins

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SUMMARY

Objectives: to evaluate clinical response after challenge testing in infants with allergy to cow's milk proteins at diagnosis and again when these infants were aged 1 year old and had been fed an exclusion diet.

Material and methods: we performed a prospective study of 49 infants aged less than 6 months with a clinical history suggestive of cow's milk protein allergy, positive skin prick test and specific IgE for α-lactalbumin, β-lactoglobulin and casein. In all children challenge test with cow-milk adapted formula was carried out at diagnosis. The same procedures were repeated when the children were aged 1 year but challenge testing was repeated only in children with a negative skin prick test and specific IgE antibodies to cow's milk proteins.

Results: At diagnosis, challenge tests produced immediate hypersensitivity reactions in 94 % of infants. Late reactivity (i.e., more than 2 hours after challenge) was found in only 6 % of infants, all of whom presented dyspepsia. When the infants were aged 1 year, and after results of immunological study were negative, a further challenge test was performed in 24 (49 %) of lactating infants included in the study. Of these 24 infants, positive challenge was found in 5 (21 %). None of the infants presented immediate symptomatology (clinical features appeared 7 days after the reintroduction of cow's milk proteins).

Conclusions: Ninety-four percent of challenge tests performed at diagnosis provoked immediate reactions. The results of challenge tests after a negative skin prick test in children with normal concentrations of specific IgE were positive in 21 % infants, who presented late reactivity (a mean of 7 days after milk ingestion).

Key words: Cow's milk, alfalactalbumin, betalactoglobulin, casein, challenge test, children.

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INTRODUCTION

Allergic reactions to cow's milk proteins represents a significant problem in children in the first year of life. Currently, only studies including challenge tests (1-3) can be considered valid because diagnosis of allergy to cow's milk proteins implies a very restrictive diet for infants and children (3, 4).

We performed a prospective study of children diagnosed with allergy to cow's milk proteins. The aim of this study was to evaluate the different clinical reactions to challenge testing with cow's milk proteins at diagnosis and again after these infants had been fed an exclusion diet.

MATERIALS AND METHODS

Patients

Forty-nine consecutive infants aged less than 6 months old were included in the study. The infants had been referred to our allergy department with suspected allergy to cow's milk proteins and presented

clinical signs and symptoms suggestive of immediate hypersensitivity reactions.

Methods

Immediate hypersensitivity to cow's milk proteins was diagnosed using the following criteria: *a)* a clinical history suggestive of allergy to cow's milk proteins with development of acute symptoms in the first 2 hours after ingestion of adapted formula; *b)* the presence of specific IgE antibodies evaluated through a positive skin prick test to one or more related proteins (alpha-lactalbumin, beta-lactoglobulin and/or casein) and the presence of serum specific IgE antibodies to one of more of these proteins; *c)* a positive controlled challenge test.

Skin prick testing was performed following a standarized procedure (5), with α-lactalbumin or β-lactoglobulin extracts (5 mg/ml) and casein (10 mg/ml) (all from CBF Leti, Barcelona, Spain). A result was considered positive when the test produced a skin weal of 3 mm or more in diameter.

Specific IgE antibodies to α-lactalbumin, β-lactoglobulin and casein were determined using UniCAP® (Pharmacia & Upjohn, Pharmacia Diagnostics, Uppsala, Sweden). Determination was considered positive when concentrations were > 0.35 KUI/l.

After the infants had fasted for 4 hours and after registration of vital signs (blood pressure and heart rate, performed with a Dynamap(TM) XL, breathing rate and clinical status) open challenge was carried out (5, 6) by administering up to 20 ml of adapted cow's milk protein formula (Nidina 1®, Nestle, Spain). Vital signs were monitored every 30 minutes during the first hour after formula intake and again every hour for 3 hours after the last dose administered in the challenge test. The infants were monitored for 24 hours after the challenge test.

The same methodology was repeated when the infants were aged 1 year old but challenge test was performed only in infants in whom immunological study was negative.

RESULTS

At diagnosis, challenge testing provoked immediate reactions in 92% of the children studied. Symptoms found after the test were rush in 63%, vomiting in 43%, anaphylaxis in 10% and respiratory symptoms in 12%. Only 8% of the clinical reactions observed after challenge testing were late and all manifested as dyspepsia. Respiratory symptoms were never isolated and always appeared concomitantly. Some patients showed more than one symptom (table I).

All reactions after a positive challenge test were well controlled and in most cases the challenge was stopped. Some infants required treatment with oral antihistamine; all anaphylactic reactions required adrenaline treatment. Systemic corticoids were required in only 3 patients.

Clinical manifestations after challenge testing in patients at the age of 1 year with negative immunological reactions to cow's milk proteins [(skin prick test, radioallergosorbent test (RAST)] are presented in table II. Only five children (21%) presented positive reaction to challenge testing. Clinical manifestations never presented in the first 24 hours after the reintroduction of cow's milk protein to the diet. Two children showed clinical manifestations similar to those produced by the challenge test performed at diagnosis (table III).

DISCUSSION

We chose the open challenge test to study children with suspected allergy to Cow's milk protein (3, 6-8) because this test is accepted as a valid diagnostic procedure in such patients. Repetition of the challenge test after an exclusion diet is often the only means of confirming tolerance (4) because skin testing (and serum IgE) may remain positive for years after tolerance has been achieved.

Some authors (8, 9) have described the need to perform challenge tests in areas with resuscitation equipment. In our study, 10% of the patients required resuscitation, all of whom presented anaphylaxis.

After an exclusion diet, challenge testing (in the first 3 hours after milk ingestion) may fail to produce immediate hypersensitivity reactions (10) but manifestations may develop later. This reaction usually is IgE-dependent (rash, vomiting, etc.). In patients included in this study, 60% of positive reactions were of this kind. Whether these reactions are indeed late or whether they are a different type of immediate reaction is a matter of debate (11). In the present study, this type of reaction appeared in 21% of the children included.

CONCLUSIONS

Challenge testing for the diagnosis of hypersensitivity to cow's milk proteins produced immediate reactions in 92% of patients. Ten percent of these reactions manifested as anaphylaxis and required both resuscitation equipment and personnel trained in tre-

Table I

Clinical symptoms after challenge test at diagnosis

Patient number	Age of onset (mo)	Rush	Vomiting	Dyspepsia	Hypotension	Respiratory symptoms	Reaction
1	2 1/2	–	+	–	–	–	early
2	2	+	–	–	–	–	early
3	1	+	–	–	–	–	early
4	3 1/2	–	+	–	–	–	early
5	3 1/2	–	+	–	+	–	early
6	3	+	–	–	–	+	early
7	2 1/2	+	–	–	+	+	early
8	1 1/2	+	–	–	–	–	early
9	1	–	–	–	+	+	early
10	4	–	–	+	–	–	early
11	4 1/2	+	–	–	–	–	early
12	3 1/2	–	+	–	–	–	early
13	1 1/2	+	+	–	–	–	early
14	5 1/2	+	+	–	–	–	early
15	1	+	–	–	–	–	early
16	4 1/2	+	–	–	–	–	early
17	1 1/2	+	–	–	–	–	early
18	4	+	–	–	–	–	early
19	1	–	+	–	–	–	early
20	1	–	+	–	–	–	early
21	2 1/2	+	–	–	–	–	early
22	2 1/2	–	–	+	–	–	late
23	2	+	+	–	+	+	early
24	3	+	–	–	–	–	early
25	6	+	–	–	–	–	early
26	4	+	–	–	–	–	early
27	5	+	–	–	–	–	early
28	5 1/2	–	–	+	–	–	late
29	1 1/2	+	+	–	+	+	early
30	5 1/2	+	–	–	–	–	early
31	4 1/2	–	+	–	–	–	early
32	3 1/2	+	+	–	–	–	early
33	5 1/2	+	+	–	–	–	early
34	4 1/2	–	–	+	–	–	late
35	1	+	–	–	–	–	early
36	3 1/2	+	+	–	–	–	early
37	2	–	+	–	–	–	early
38	5 1/2	+	–	–	–	–	early
39	1 1/2	–	+	–	–	+	early
40	1/2	–	+	–	–	–	early
41	3	–	+	–	–	–	early
42	2	+	–	–	–	–	early
43	5 1/2	+	+	–	–	–	early
44	4 1/2	–	+	–	–	–	early
45	1	–	+	–	–	–	early
46	5	+	–	–	–	–	early
47	1 1/2	+	–	–	–	–	early
48	5	+	–	–	–	–	early
49	5 1/2	+	–	–	–	–	early

ating allergic reactions in patients admitted to day clinics.

Although not completely risk-free, diagnostic challenge tests are safe when performed under the conditions described. Challenge testing provoked no anaphylactic reactions in children who had followed a diet free of cow's milk proteins for 6 months and who had a negative skin prick test and negative IgE.

Table II

Clinical symptoms after challenge test the age of 1 year

Pacient number	Rush	Vomiting	Dyspepsia	Hypotension	Respiratory symptoms	Reaction	Other clinical symptoms
2	–	–	–	–	–		
3	–	–	–	–	–		
4	–	–	+	–	–	Late	
9	+	–	–	–	–	Late	
11	–	–	–	–	–		
16	–	–	–	–	–		
21	–	–	–	–	–		
23	–	–	–	–	–		
24	–	–	–	–	–		
25	–	–	–	–	–		
26	–	–	–	–	–		
27	–	–	–	–	–		
28	–	–	–	–	–		
29	–	–	–	–	–		
30	–	–	–	–	–		
31	–	+	–	–	–	Late	
33	–	–	–	–	–		
34	–	–	–	–	–		
35	–	–	–	–	–		
38	–	–	–	–	–		
43	–	–	–	–	–	Late	Atopic dermatitis
44	–	–	–	–	–		
46	–	–	–	–	–		
47	+	–	–	–	–	Late	

In these circumstances the challenge test may be performed in an out-patient clinic although the patient must be followed-up for the first 15 days after the reintroduction of milk into the diet. In a significant number of patients (21 %), reactions may appear a few days after cessation of exclusion diet.

RESUMEN

Objetivo: Evaluar la respuesta clínica tras la prueba de provocación, en niños con alergia a proteínas de leche de vaca, efectuada al diagnóstico y tras dieta exenta de proteínas de leche de vaca, al año de edad.

Material y métodos: Estudio prospectivo que incluye 49 niños, menores de seis meses de edad, con historia clínica sugestiva de alergia a proteínas de leche de vaca, prick e IgE específica positivos para α-lactoalbúmina, β-lactoglobulina y caseína a los que se les efectúa una prueba de provocación con leche de vaca adaptada en el momento del diagnóstico. Al año de edad se repite la misma metodología de estudio y se efectúa prueba de provocación sólo a los que presentan prick e IgE específica a proteínas de leche de vaca negativos en ese momento.

Table III

Clinical symptoms provoked by positive challenges performed at diagnosis and at 1 year

Pacient number	Challenge at the diagnosis	Challenge at one
4	Vomiting	Dyspepsia
9	Anaphylaxis	Rush
31	Vomiting	Vomiting
43	Rush + vomiting	Atopic dermatitis
47	Rush	Rush

Resultados: Al diagnóstico el 94 % de las provocaciones tuvieron una respuesta positiva inmediata, únicamente el 6 % presentaron una respuesta positiva tardía (más de dos horas después de la provocación) todas como dispepsia. Al año de edad y tras la negativización del estudio inmunológico se efectuó una nueva prueba de provocación a 24 (49 %) de los lactantes incluidos en el estudio y presentaron prueba de provocación positiva el 21 % de las efectuadas a esta edad (5 de 24), ninguna de ellas presentó sintomatología inmediata, la clínica apareció a los 7 días de estar tomando leche de vaca.

Conclusiones: La mayoría (94 %) de provocaciones al diagnóstico presentan una clínica inmediata. Las

provocaciones efectuadas tras la negativización de las pruebas de prick e IgE específica que fueron positivas (21 %), lo fueron todas tardíamente (media de 7 días tras la ingesta de leche).

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Palabras clave: Alergia a la leche de vaca. α-lactoalbúmina. β-lactoglobulina. Caseína. Prueba de provocación. Niños.

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