Beef allergy in children with cow's milk allergy; cow's milk allergy in children with beef allergy

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Objective: To review the literature on the prevalence of beef allergy in children allergic to cow's milk and to report a series of patients with beef allergy evaluated for cow's milk allergy.

Data Sources: A MEDLINE search for *cow's milk allergy* and *beef allergy* was conducted. Also included in this report is a clinical evaluation of both these entities in a population of children with atopic dermatitis.

Study Selection: Data from the literature were summarized. Recruited patients with beef allergy were evaluated on the basis of history, serology, skin prick tests, and double-blind, placebo-controlled food challenge (entry criterion), and presented between 1992 and 2000.

Results: In the literature, between 13 and 20% of children with cow's milk allergy also have beef allergy. In our personal series of patients, 28 children (18 boys and 10 girls) diagnosed with beef allergy underwent skin prick tests and double-blind, placebo-controlled food challenge, which showed that 26 (92.9%) were allergic to cow's milk. Two children nonallergic to cow's milk were the only ones who were not sensitized to bovine serum albumin.

Conclusions: Most children with beef allergy are also allergic to cow's milk and should avoid the consumption of dairy products. Sensitization to bovine serum albumin is a marker of cow's milk allergy in children with beef allergy. Elimination of beef from the diet of children with cow's milk allergy should be evaluated on an individual basis after diagnostic workup.

Ann Allergy Asthma Immunol 2002;89(Suppl):38–43.

INTRODUCTION

Proteins from milk, beef, and dairy products are staples of the western diet, but epidemiologic data have not addressed the prevalence of beef allergy (BA) relative to cow's milk allergy (CMA) or the possibility of an overlap of these two conditions. The prevalence of CMA ranges from 2 to 7.5% in pediatric studies,[1–3] and an incidence of CMA of approximately 0.3% after the third year of life has been reported.[4] Meat allergy is relatively frequent, and beef proteins are among the most common allergens involved in food hypersensitivities.[5–7] The prevalence of BA has been estimated to be between 3 and 6.5% among children with atopic dermatitis (AD),[6,8–10] and AD affects at least 5% of children.[11] Thus, BA may be present in 0.3% of the pediatric population. The known allergenic cross-reactivity of bovine serum albumin (BSA) and bovine γ-immunoglobulin (Ig), which are present in both milk and beef, has therefore been noted as a cause for concern.

BA IN CMA

The prevalence of BA in patients with CMA is difficult to infer from a review of the literature because samples are generally small and observations are heterogeneous (Table 1).[12–15] Further, the diagnostic workup of BA in children has not yet been standardized. In a 1986 study of 15 children with AD who were also allergic to cow's milk, only two patients (13.3%) tested positive on an oral challenge with beef.[13] In 1990, a frequency of 14.5% was reported for BA in a population of 96 children with CMA diagnosed on the basis of an open challenge with milk.[15] The diagnosis of BA was based on parental reports of the occurrence of an adverse reaction in a child within 1 hour after ingestion of beef during followup (or on at least two such occurrences more than 1 hour after the child ate beef). In 1997, 25 children were diagnosed with CMA during a double-blind, placebo-controlled food challenge (DBPCFC); although only five children responded to beef on a DBPCFC, beef sensitization was found in 21 patients by a skin prick test (SPT).[5] The beef challenge dose and the processing methods for the food preparation used as SPT material were not reported in this study, however. This discordance between DBPCFC and SPT results may reflect varied allergen concentrations and allergenicity in the test materials used, and industrial processing may reduce the allergenicity of beef proteins.[16] Such prevalence figures, independently, do not warrant a recommendation for withholding beef from the diet of all children with CMA. Multiple allergic reactions to foods are not always an expression of the cross-reactivity between food allergens, and proteins from closely related food classes do not invariably induce symptoms. Thus, many children with CMA are tolerant of beef, just as children allergic to peanut may tolerate soy[15,17] or carob.[18]

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Received for publication February 14, 2002.
Accepted for publication in revised form April 18, 2002.

Table 1. Reported Prevalence of BA in Children With CMA

Reference	No. with CMA	No. (%) with BA	Diagnostic method
Gerrard et al,[12] 1967	150	5 (3.3)	. . .
Sampson,[13] 1986	15	2 (13.3)	Oral challenge
Host & Halken,[14] 1990	21	5 (23.8)	. . .
Bishop et al,[15] 1990	96	14 (14.5)	Parents' report
Werfel et al,[5] 1997	25	5 (20)	DBPCFC
		21 (84)	SPT

CMA IN BA

In our search of the literature, we found only a single investigation of a series of children with BA evaluated for cow's milk tolerance.[5] Of the 11 children (median age, 4.3 years; range, 1.3 to 14 years) with AD and BA, 8 (72.7%) were found to respond to a challenge with cow's milk. We report here on a series of 28 consecutive beef-allergic children who underwent evaluation for their tolerance of cow's milk by DBPCFC.[19]

CURRENT CASES

Between 1992 and 2000, 28 children with AD (18 boys and 10 girls; median age, 2.54 years; range, 0.75 to 4.66 years) presenting at our institution were evaluated with BA. Diagnostic criteria included a history of asthma, rhinitis, urticaria, or lip edema (or a combination of these) within 30 minutes after ingestion of beef. Previous informed parental consent to research the allergic status of these children was on file, as was institutional ethics committee approval for the research and design of this study. The stated aim of the study was the evaluation of CMA status in a population of children with BA (sole entry criterion) at our institution.

METHODS

SPTs were performed with commercial beef extracts solubilized in glycerol 50% at 1 mg/mL concentration (Bayer, Spokane, WA) and BSA (Sigma Chemicals, Rome, Italy). Fresh raw beef obtained locally was also used in fresh food SPTs. SPTs were performed with whole milk and casein extracts (both from Bayer) solubilized in glycerol 50% at 1 mg/mL concentrations. Pasteurized fresh milk was similarly used for SPTs. Histamine phosphate (10 mg/mL) in 50% glycerosaline and glycerosaline alone were used as positive and negative controls, respectively. All children underwent SPTs with the principal food allergens, including egg white, egg yolk, wheat, rice, peanut, soy, tomato, and codfish. The children were also tested with commercial reagents for lamb, pork, chicken, turkey, and rabbit (Bayer), as well as with a panel of aeroallergens including grass, *Parietaria officinalis*, *Dermatophagoides farinae* and *D. pteronyssinus*, cat dander, dog dander, and *Alternaria tenuis* (Bencard, London, UK).

A wheal diameter >3 mm[20] was the cutoff point for positivity on SPTs. Cutoff points of 1.8 kU/L for beef[21] and 5.8 kU/L for cow's milk[22] were selected. Beef- and whole milk-specific IgE determinations were performed on stored serum samples from the patients with use of CAP technology (Pharmacia, Uppsala, Sweden). A DBPCFC with beef was conducted as described elsewhere,[6] and a food-challenge symptom score was used, with interpretation based on the method of Bock et al.[23] Raw beef muscle (180 g) was administered in four doubling doses, and turkey was used as placebo. The beef had been steamed for 20 minutes at 100° C and then minced to form four 1-cm-thick patties. When compatible with the patient's history, DBPCFC with cow's milk formula (180 g in four doubling doses at 30-minute intervals, with pear juice used as placebo after a negative SPT) was performed, and doses eliciting an immediate reaction were noted. The physician responsible for the DBPCFC was blinded as to the sequence of doses which was decided by an independent operator.

Correlations and their significance within a 95% confidence interval were calculated using Pearson's correlation coefficient to evaluate the relationships between BA, age at diagnosis, and onset of tolerance. The strength of the relationships (expressed as r^2) was interpreted on the basis of Colton's rule.[24]

Clinical Characteristics

The clinical characteristics of the patients at diagnosis of AD are reported in Table 2. Of the 28 children, 6 had had respiratory allergic disease, 8 had one family member with allergic disease, 7 had two family members with allergic disease (both parents or one parent and one sibling), 3 had three family members with such a history, and 10 had no family history of allergic disease. Seven patients were sensitized to inhalant allergens, and 24 showed sensitization to nonbovine food allergens. The most frequent nonbovine food sensitizer was lamb (18 cases), followed by pork, egg, wheat, codfish, chicken, and peanut. The patients underwent followup until tolerance of bovine proteins was attained, and the duration of adverse reactions to bovine proteins (ARBPs) was reported. All these children were under followup surveillance for the tolerance of beef; one was lost during followup when he was tolerant of beef but not yet tolerant of cow's milk.

RESULTS

All except two of the study patients tested positive to BSA (Table 3). Of the 28 children, 26 (92.9%) were sensitized to cow's milk on both commercial SPTs and fresh food SPTs. Ten patients (35.7%) had positive results of SPTs to casein. No child younger than 2 years was sensitive to casein, although all children in this age-group tested positive to commercial whole milk extracts and fresh whole milk. Of the serum samples studied by radioallergosorbent tests, 26 reacted to beef and 23 to cow's milk. All children (except the two with BA not sensitized by BSA) were classified as allergic to cow's milk during 20 DBPCFCs, and six patients with a history of anaphylaxis in response to cow's milk were considered as having positive challenges.

Age at diagnosis of BA correlated significantly with casein sensitization ($r^2 = 0.57$; $P < 0.001$). No correlation was

Table 2. Clinical History and Sensitization to Nonbovine Allergens in 28 Children With AD*

Sex	Age (yr)	Age (yr) at onset of AD	Concomitant allergic diseases	Family history	SPT with aeroallergens	SPT with food allergens†
M	2.58	0.25	AR	2P + 1S	Grass	EW, EY, W, L, PK, PN
M	1.25	0.41	. . .	None	None	EW, EY, L, PK, C
F	1.41	0.75	ACM	None	None	L, PK, CF
M	3.16	0.16	ACM, A, AR	2P	DF, DP, cat	L
F	1.00	0.33	. . .	None	None	L
M	4.33	0.75	ACM, A	2P	DF, DP	EW, EY, CF
M	2.00	0.75	. . .	1S	None	None
F	3.00	0.58	A	None	DF, DP	L, PK, C, T
M	3.33	0.33	ACM	2P + 1S	None	L, PK, W, PN
M	2.25	0.41	. . .	1P	None	L, EW, EY
F	3.00	0.25	ACM	None	None	L, R, PK, C
M	2.50	0.33	. . .	1P + 1S	None	L, PK, W
M	1.25	0.83	. . .	1P	None	L, W
M	2.83	1.08	. . .	None	None	L
F	1.58	0.58	. . .	1P + 1S	None	L, PK, CF
F	4.66	0.66	. . .	None	DF, DP	None
F	2.91	0.16	ACM, A	2P	Cat	L, PK
F	2.00	0.41	. . .	1P + 1S	None	W
M	3.83	0.75	. . .	1P	None	PN
M	3.83	0.91	. . .	None	None	L
M	3.16	0.50	. . .	None	None	Not done
M	1.75	0.66	. . .	1P	None	EW, EY
F	2.83	0.75	A, AR	1P + 1S	Grass, cat	CF
M	2.58	1.25	. . .	None	None	None
M	1.66	0.91	. . .	2P + 1S	None	L
M	0.75	0.41	. . .	1S	None	L, PK
F	1.58	0.83	. . .	1P	None	L
M	1.66	0.83	. . .	1P	None	EW

* A, asthma; ACM, anaphylactic response to cow's milk; AR, allergic rhinitis; DF, *Dermatophagoides farinae*; DP, *D. pteronyssinus*; P, parent; S, sibling.

† C, chicken; CF, codfish; EW, egg white; EY, egg yolk; L, lamb; PK, pork; PN, peanut; R, rabbit; T, turkey; W, wheat.

found between the dose of beef and cow's milk necessary to elicit a response at DBPCFC and any other clinical characteristic (wheal diameter on SPTs with bovine proteins, level of specific IgE to beef and cow's milk, or duration of the disease). At followup, three children are still reacting to beef at 4.5, 7.75, and 7.91 years after diagnosis of BA. The median duration of the condition was 3 years (standard error, 0.25; range, 0.83 to 4.83).[25] The following correlations were found significant with the duration of BA: levels of specific IgE to beef ($r^2 = 0.52$; $P < 0.001$) and reaction at lower doses of beef at first DBPCFC ($r^2 = 0.45$; $P < 0.001$). The relationships between wheal diameter with fresh beef and high total IgE ($r^2 = 0.28$; $P = 0.003$) were also significant but exhibited little correlation ($r^2 = 0.17$; $P = 0.027$) with the duration of disease.

DISCUSSION

Infants and children with BA in our series had a high rate of clinical reactivity to cow's milk, with a prevalence in excess of the previously published 72.7% estimate.[5] The 92.9% CMA prevalence we found may reflect the fact that our patients were younger at the time of diagnosis (median age, 2.54 vs 4.3 years). Only two of our patients with BA were not sensitized by BSA. We hypothesize that these patients may have reacted to other beef proteins (for example, actin, myosin, and myoglobin), as their positive radioallergosorbent test with beef and negative BSA skin sensitization suggest. No evidence indicates that they had been sensitized to BSA, but because they were older (4.66 and 3.83 years), they may have developed BSA tolerance. These same children were the only patients without a reaction to cow's milk challenge. Unusually for children with ARBP, lower sensitivity to casein was found (35.7%) than in previously described series (range, 43 to 80%).[26] In this sample, no child younger than 24 months was sensitized to casein (Table 3). In older children, however, the prevalence of sensitization (62.5%) was well within the reported range for casein.

As suggested in the literature, clinical sensitization to casein may be a marker of ongoing milk allergy.[27] That children with BA may have a lesser frequency of sensitization to casein may therefore translate into a more favorable prognosis for CMA. Cow's milk tolerance was established by the

Table 3. Characteristics and Clinical Outcomes of 28 Study Patients*

Sex	Age (yr)	FU (yr)	C beef	F beef	BSA	C CM	C cas	F CM	RAST beef	RAST CM	Beef dose	CM dose	Tol beef	Tol CM
M	2.58	8.25	4	5	6	7	1	8	9.29	28.93	12	36	3.00	3.50
M	1.25	8.16	3	4	4	5	0	4	2.70	9.76	84	12	1.41	1.58
F	1.41	8.08	3	6	7	4	0	7	2.22	4.33	36	†	3.00	3.33
M	3.16	8.00	4	4	6	6	5	10	4.61	13.09	36	†	4.25	4.50
F	1.00	8.00	4	5	6	4	2	6	2.35	4.78	84	12	2.16	2.50
M	4.33	7.91	4	5	5	6	5	8	7.80	16.16	12	†	7.91‡	7.91
M	2.00	7.91	4	4	5	4	1	5	2.22	10.77	84	12	1.58	1.33
F	3.00	7.83	5	5	4	4	3	4	1.24	12.19	36	36	2.50	2.25
M	3.33	7.75	6	6	5	6	5	8	10.0	30.09	12	†	7.75‡	7.75
M	2.25	5.00	4	5	6	5	2	7	9.25	27.45	12	12	4.83	5.00
F	3.00	5.00	5	4	6	6	3	8	4.90	20.62	12	†	4.83	5.00
M	2.50	5.00	5	6	4	6	2	10	9.00	21.24	36	36	4.50	4.75
M	1.25	4.75	3	3	3	4	0	6	3.06	12.58	180	36	1.00	1.25
M	2.83	4.66	3	5	5	5	3	6	2.93	17.20	36	12	2.83	3.00
F	1.58	4.50	4	4	8	6	1	5	2.19	6.61	12	12	2.16	2.58
F	4.66	4.50	4	7	0	0	0	1	2.98	0.05	36	180§	4.50‡	0
F	2.91	4.25	5	6	6	7	3	6	3.85	12.18	12	†	3.83	4.00
F	2.00	4.25	4	6	5	5	1	9	6.36	15.10	36	12	3.58	3.83
M	3.83	4.25	5	5	1	0	0	0	3.86	0.21	36	180§	3.75	0
M	3.83	4.00	3	5	6	5	4	5	2.15	16.19	36	36	3.66	3.83
M	3.16	4.00	5	5	5	6	4	7	4.55	17.99	12	12	3.58	3.75
M	1.75	3.91	5	6	4	5	0	7	4.78	11.73	36	12	3.16	3.41
F	2.83	3.75	5	5	4	6	4	7	3.76	9.65	36	12	3.08	3.41
M	2.58	3.00	2	6	5	3	2	5	1.75	6.74	180	12	1.41	1.50
M	1.66	2.75	2	5	6	3	0	5	2.64	8.98	84	36	1.75	1.91
M	0.75	2.00	3	4	4	3	0	4	2.16	8.52	84	36	0.83	0.83
F	1.58	1.50	4	5	4	5	0	5	1.99	10.62	180	12	1.00	1.25
M	1.66	1.50	4	3	5	5	1	4	2.72	4.49	84	36	1.16	1.00

* Column heading explanations: Age, age at diagnosis of beef allergy; FU, followup (in years); C beef, SPT with commercial beef extract (wheal diameter in mm); F beef, SPT with fresh beef (wheal diameter in mm); BSA, SPT with bovine serum albumin extract (wheal diameter in mm); C CM, SPT with commercial cow's milk extract (wheal diameter in mm); C cas, SPT with commercial casein extract (wheal diameter in mm); F CM, SPT with pasteurized whole cow's milk (wheal diameter in mm); RAST beef, beef IgE determination by radioallergosorbent test (kU/L); RAST CM, cow's milk IgE determination by radioallergosorbent test (kU/L); Beef dose, beef challenge dose eliciting symptoms (in g); CM dose, cow's milk dose eliciting symptoms (in g); Tol beef, time between diagnosis and tolerance of beef (in years); Tol CM, time between diagnosis and tolerance of cow's milk (in years).

† Challenge with cow's milk not done because of history of anaphylaxis.

‡ Ongoing BA.

§ Children tolerating the maximal dose administered.

third year of life in up to 85% of one population of milk-allergic children,[28] and in this series, 24 of 26 children with CMA (92.3%) similarly achieved tolerance by the age of 2.7 years on average.

A thorough diagnostic workup—based, when clinically possible, on DBPCFC—should be performed in all cases to minimize the need for stringent dietary restrictions. The evaluation of tolerance becomes crucial when children have both BA and CMA, and prolongation of restricted diets should be avoided as much as possible. In children with multiple food allergies, immunologic tolerance should be temporally redefined, inasmuch as reduced sensitization to IgE-inducing proteins develops at different times for milk and beef. Because BSA is the sensitizing agent of BA, tolerance of beef may correspond to tolerance of BSA during infancy and early childhood. We were unable to demonstrate this relationship within the present experimental framework. Most toddlers ultimately "outgrow" their cow's milk hyperreactive phase, but there is such an evident link between sensitization to BSA and BA that it is difficult to imagine a similar sequence in CMA, when multiple proteins are involved. Thus, tolerance of beef may be achieved earlier than tolerance of cow's milk, as indicated by the 26 children with CMA in the current series. Of the 26 patients with CMA, 20 (76.9%) reached tolerance of milk after beef had been reintroduced into their diet without untoward effects. In three children, tolerance of milk and beef became established at the same time, whereas in another three patients, the later onset of tolerance of beef was only apparent and evaluated at differently timed challenges.

In the current series, the onset of tolerance of beef was reached after a median duration of 3 years. For this reason, we propose the scheduling of provocation tests for the reintroduction of beef into the diet at yearly intervals. On the basis of our data, indices of a more favorable prognosis

toward the induction of tolerance include reactions to high doses at diagnostic challenge (>48 g), low beef-specific IgE levels, and smaller wheal diameter induced by SPT with beef.

Although no consensus exists about the actual requirements for dietary meat (as opposed to proteins), parents are often worried that their children may not receive an adequate supply from special diets that restrict beef and dairy products. This restriction poses specific problems for children in the various phases of allergic diseases discussed here. Potential cross-reactivity with other meats excludes the possibility of blanket recommendations for beef substitutes, and a case-by-case evaluation of alternative protein sources must be part of the followup. Turkey or more exotic alternatives have been proposed, but some patients may be affected by cross-reacting antigenic proteins,[16] as our cases demonstrate. Research into temperature ranges and preparation that might achieve the same effect by denaturing BSA seems more practical in a clinical setting. Commercial treatment may technologically inactivate BSA[29] and may also support the introduction of processed beef (and other meats) into the diet after clinical evaluation.

CONCLUSION

CMA and BA are not the same thing. In evaluation of nutrition, access to other protein sources must be consistently monitored in the case of patients with ARBP. In patients with CMA, the low prevalence of BA (13% to 20%) does not support the exclusion of beef from the diet except in selected cases. Beef has a high protein content, and nothing warrants its wholesale elimination from the diet of children who may have prolonged protein restrictions if also affected by multiple food allergies. These principles are not applicable to children with BA. Younger patients allergic to beef almost always fare better by avoiding cow's milk proteins, but restricting milk products from the diet of these children must be critically considered. Cross-reactivity between proteins that are phylogenetically similar (and to BSA in particular) suggests caution (and the possibility of negative diagnostic challenges) in planning an alternative diet, such as one based on turkey or lamb. Followup studies continue to investigate whether avoidance of cow's milk proteins offers children with ARBP protection against the onset of other atopic manifestations.

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