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Safety and clinical predictors of reacting to extensively heated cow's milk challenge in cow's milk-allergic children

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ABSTRACT

Background: Many children with IgE-mediated allergy to cow's milk (CM) can tolerate CM in baked foods.
Objective: To define the clinical characteristics and severity of reactions to baked CM in children with CM allergy (CMA) at an oral food challenge (OFC).
Methods: Children with CMA presenting to a tertiary clinic from 2010 through 2013 with complete dietary CM avoidance were offered a baked CM OFC. Challenges were performed with incremental dosages to a total of 1 baked muffin.
Results: Seventy children with CMA underwent a baked CM OFC. Fifty-one children (73%) passed the OFC and successfully incorporated baked CM into their diet. Nineteen children (27%) reacted to their challenge. Of reactors, 4 (21%) developed anaphylaxis and required intramuscular adrenalin. Predictors of clinical reactivity to baked CM were asthma, asthma requiring preventer therapy, IgE-mediated clinical reactions to more than 3 food groups, and those with a history of CM anaphylaxis.
Conclusion: This study identified factors that were predictors of clinical reactivity to baked CM in this cohort of children with CMA. These risk factors do not represent contradictions to a baked CM challenge but may allow for risk stratification of challenges. Given the potential for anaphylaxis, an OFC to baked CM should be done under medical supervision in those children with CMA who have been strictly avoiding all CM.

Introduction

Food allergy has increased in prevalence over the past 2 to 3 decades, with a recent birth cohort reporting an incidence of more than 10% in Australian infants.[1] Until recently, most guidelines have recommended strict avoidance of the allergen, in all forms and amounts, from the diets of allergic children. This was done partly to decrease the risk of reaction but also because of the belief that accidental allergen exposure might delay the onset of tolerance.[2] Cow's milk allergy (CMA) is one of the most common food allergies in childhood, and dietary avoidance can be burdensome,[3,4] because of the ubiquitous nature of CM in Western diets.

Several groups have reported that many children with CMA can tolerate extensively heated CM (in baked products such as cakes and biscuits) in serving-size quantities.[5–8] The ability to incorporate extensively heated CM ("baked" CM) liberalizes the diet and may help to decrease anxiety over accidental ingestion. Regular ingestion of baked CM products also may accelerate acquisition of tolerance to CM and/or alter the natural history of the CMA.[9]

Tolerance to baked CM is usually demonstrated at a formal open food challenge (OFC) under medical supervision, given the potential for anaphylaxis.[7] Previous reported predictors of reaction to baked CM have included serum specific IgE (ssIgE) to heat-stable casein[6,8] and basophil reactivity.[10] These parameters do not always allow individual determination of risk. Children tolerant to baked CM are reported to have less severe reactions to follow-up whole CM challenge than those reacting to baked CM, suggesting that children with CMA who tolerate the baked CM may represent a different clinical phenotype from their counterparts with baked CMA.[7] It is unclear whether other clinical characteristics of children with CMA are helpful in predicting the outcome of a challenge to baked CM. Therefore, the authors sought to assess the safety of an OFC to baked CM in children with a high probability of clinical CMA and identify clinical factors that might predict reaction and anaphylaxis at an OFC.

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Table 1
Characteristics of children with a diagnosis of CMA and following strict dietary avoidance of CM

Characteristic	Negative OFC reaction: tolerates baked CM	Positive OFC reaction: all reactions	Relative risk (95% CI)	Positive OFC: anaphylaxis
Patients, n	51	19		4
Age at challenge (y), median (interquartile range)	4.5 (2.5–8)	7.3 (4.9–9.6)		5.2 (2.4–7)
SPT wheal (mm) to CM at OFC, median (interquartile range)	8 (7.0–10.0)	8.5 (7.5–10.0)		8.3 (7.3–8)
SPT wheal (mm) to muffin at OFC, median (interquartile range)	4.8 (3.0–7.0)	5.3 (4.9–7.3)		4.3 (3.0–5.5)
Sex, n (%)				
Male	30 (59)	11 (58)		3 (75)
Female	21 (41)	8 (42)		1 (25)
Other atopy, n (%)				
Asthma, n (%)	23 (45)	18 (95)[c]	12.7 (1.8–90.1)	4 (100)
Asthma, on preventer therapy, n (%)	12 (24)	13 (68)[b]	2.8 (1.3–6.0)	4 (100)
Eczema, n (%)	32 (63)	18 (95)		4 (100)
Food allergy to ≥3 allergen groups (MFA), n (%)	20 (39)	13 (68)[b]	2.4 (1.0–5.7)	4 (100)
Prior anaphylaxis to food other than CM (AnO), n (%)	6 (12)	6 (32)		3 (75)[a,b]
MFA + AnO, n (%)	4 (8)	6 (32)[b]	2.8 (1.4–4.5)	3 (75)
Previous reaction to CM, n (%)				
Anaphylaxis	14 (27)	10 (52)[b]	2.1 (1.0–4.5)	2 (50)
Nonanaphylactic reaction	36 (71)	8 (42)		2 (50)
No history of previous exposure to CM, n (%)	1 (2)	1 (5)		0
<12 mo since last clinical reaction to CM, n (%)	22 (43)	4 (21)		1 (25)

Abbreviations: AnO, anaphylaxis to food other than cow's milk; CI, confidence interval; CM, cow's milk; MFA, multiple food allergies; OFC, oral food challenge; SPT, skin prick test.
[a]Children reacting at the CM OFC without anaphylaxis compared with children reacting with anaphylaxis.
[b]$P < .05$.
[c]$P < .005$.

Methods

Children presenting to the authors' tertiary referral clinic with a clinical diagnosis of CMA and who were completely avoiding all forms of CM in their diet were offered an OFC to extensively heated CM in a muffin (baked CM) at the Children's Hospital at Westmead in Sydney, Australia. CMA in children was defined as a previous convincing clinical reaction to CM within the past 12 months (with evidence of current sensitization based on a positive skin prick test [SPT] reaction or ssIgE to CM) or a previous clinical reaction to CM more than 12 months previously and a current SPT reaction to CM with a wheal larger 7 mm in children older than 2 years or larger than 5 mm in those younger than 2 years or no history of exposure and a current SPT reaction to CM with a wheal larger than 7 mm in children older than 2 years or larger than 5 mm in those younger than 2 years. The exclusion criterion was a recent allergic reaction to baked CM within the past 6 months or refusal of consent; children with prior anaphylaxis to CM or baked CM were not excluded. Recruitment and challenges were conducted over a 3-year period from January 2010 until December 2013.

Children were assessed and examined before the challenge to ensure suitability and to confirm coexisting atopy (physician-diagnosed asthma and receiving preventer therapy, allergic rhinitis, and/or eczema). Allergy to foods other than CM was confirmed based on a history of clinical reaction with confirmatory positive testing (SPT or ssIgE) to the allergen implicated. SPT was performed on the day of the OFC according to standard guidelines using 10 mg/mL of histamine (Hollister Stier Laboratories, Spokane, Washington) as a positive control. SPT to muffin slurry was performed as previously reported.[11] A positive SPT reaction was defined as a wheal at least 3 mm larger than a saline control read at 15 minutes. The OFC to baked CM followed a national protocol using incremental doses of baked muffin.[12] A standard recipe was used for the muffin, baked at 180°C for 20 minutes, with 1 muffin containing 0.5 g of CM protein. The protocol used for the OFC was as follows: children were fed increments of the muffin, starting from 1/16 of a muffin, 1/8 of a muffin, 1/4 of a muffin, to 1/4 of a muffin and then the remainder at 20-minute intervals. The challenge was halted at the onset of objective clinical symptoms, in line with PRACTALL criteria.[13] Children were observed for another 2 hours after the last muffin dose. Anaphylaxis was defined according to World Allergy Organization criteria.[14] Children with reactions involving skin and/or gastrointestinal symptoms alone were classified as having mild to moderate reactions. Patients were instructed to avoid all baked CM for 48 hours to detect possible delayed symptoms and then to introduce baked CM (using a muffin containing a similar amount of CM) 2 to 3 times per week. Patients were followed up by telephone 1 week later to confirm ongoing tolerance.

Data analysis was performed using GraphPad Prism 6 (GraphPad Software, Inc, La Jolla, California). Statistical analysis was performed using nonparametric tests: SPT data were compared using the Mann-Whitney *U* test, and categorical data were analyzed using χ^2 test or the Fisher exact test where appropriate. A *P* value less than .05 was considered significant. The study was approved by the ethics committee at the Children's Hospital at Westmead. Written consent was obtained for all food challenges.

Results

Eighty-six children with a diagnosis of CMA and following strict dietary avoidance of CM were identified, and 70 met the inclusion criteria and were recruited to the study (median age 5.3 years; Table 1). Only 2 children were avoiding CM based on sensitization alone. Twenty-four children (34%) had a history of anaphylaxis to CM. Forty-one children (59%) had a diagnosis of asthma and 23 (33%) were using an asthma preventer. Twelve children (17%) had experienced anaphylaxis to CM and at least 1 other food. Thirty-three children (47%) had a clinical history of immediate IgE-mediated reactions to at least 2 other food groups, in addition to CM.

Challenge Outcome

Nineteen children (27%) reacted to their challenge (Table 1). Four children had anaphylaxis (Table 2). Fifty-eight percent of children with prior anaphylaxis to CM tolerated the baked CM. The size of the SPT wheal to CM or to muffin slurry was not predictive of outcome ($P > .05$; Table 1, Fig 1). An SPT wheal smaller than 7 mm in children with CMA older than 2 years did not predict tolerance to baked CM ($P = 1$). Children with a history of asthma ($P < .005$), using an asthma preventer ($P < .05$), a history of anaphylaxis to CM