

quire hospitalization, and who have a history of asthma or allergy in the immediate family) who may have a greater risk for developing asthma. As a result, additional studies to examine the prevalence of IgE antibodies to foods in such children may be needed. Among toddlers seen because of wheezing in our study, tests for IgE antibodies to both foods and inhalants improved the assessment of atopy compared with tests for inhalants alone. After the age of 4 years, however, most of the allergen-specific IgE antibody responses among wheezing children were to aeroallergens, and it is not clear that routine tests for food sensitization will enhance their evaluation.

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Allergy to cheese produced from sheep's and goat's milk but not to cheese produced from cow's milk

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Most adult patients with cow's milk allergy (CMA) are sensitized to cow's milk casein, as can be demonstrated by specific IgE determination

with the Pharmacia RAST or CAP system (Pharmacia, Uppsala, Sweden), and they do not tolerate sheep's or goat's milk or cheese made from sheep's or goat's milk because of the existence of cross-sensitivities among the different caseins (α , β , γ , κ)

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Abbreviations used

BC:	Bovine casein
CMA:	Cow's milk allergy
GC:	Goat casein
PRU:	Phadebas RAST units
SC:	Sheep casein
SPT:	Skin prick test
SST:	Skin scratch test

with a molecular weight between 11,500 and 24,000 d.^{1,2} Cross-reactivity with cow's milk caseins was also demonstrated with mare's milk in patients with CMA and atopic dermatitis who experienced severe clinical symptoms after using ointments that contain mare's milk.³ We report on two young adult male patients who had allergic reactions after eating cheese made from sheep's or goat's milk but not after consuming other dairy products, including cheese produced from cow's milk. The Greek name *feta* is used in our countries for all kinds of cheeses made from sheep's milk.

CASE REPORTS

Case 1

A 15-year-old Turkish boy with moderate atopic dermatitis and hay fever since childhood experienced (in the last 2 years) recurrent episodes of acute rhinoconjunctivitis, redness, and angioedema of the face (without gastrointestinal symptoms or dyspnea), which occurred 15 to 30 minutes after eating feta or other dishes containing cheese made from sheep's or goat's milk. He had no problems when drinking cow's milk or eating cheese made from it. Skin prick tests (SPTs) were performed with commercial extracts in glycerol (Alyostal; Stallergenes Laboratories, Fresnès, France) of routine inhalants and foodstuffs, including whole unpasteurized cow's milk, goat's milk, cow's milk casein, and α -lactalbumin. Skin scratch tests (SSTs) were also performed with native feta and other kinds of cheese placed on a fresh scratch in the skin. The results were graded from 0 to 3+ in relation to a negative control (saline solution) and a positive control (histamine hydrochloride, 0.1 mg/ml). Results were strongly positive with feta, whereas results were negative with cow's milk and Gruyère cheese, which is made from cow's milk. Results of SSTs with the same feta in three nonatopic control subjects were negative.

Case 2

A 25-year-old Italian patient without obvious atopic disease, according to the anamnesis, noted the appearance of generalized urticaria, swelling of the eyelids, and dyspnea 30 minutes after eating different kinds of cheeses made from sheep's or goat's milk, whereas he

had no problems when eating cheese made from cow's milk. According to the case history, the results of the SSTs with different brands of cheese were only strongly positive with the ones made from sheep's or goat's milk.

METHODS

Specific IgE antibodies to "whole cow's milk" (f2), α -lactalbumin (f76), β -lactoglobulin (f77), and cow's milk casein (f78) were determined by Immuno CAP fluoroenzymimmunoassay (Pharmacia Diagnostics) according to the manufacturer's recommendations. The results were expressed in kilounits per liter. Disks prepared with feta, sheep casein (SC [5 μ g/disk, Sigma]), and goat casein (GC [5 μ g/disk, Sigma]) were used to measure IgE antibodies⁴ with Phadebas RAST (Pharmacia Diagnostics), and the results were expressed in Phadebas RAST units (PRU) per milliliter. For determination of allergenic cross-reactivity, RAST inhibition was performed with bovine casein (BC; Pentex, Miles Laboratories, Kankakee, Ill.), SC, and GC in decreasing concentrations from 10 mg/ml to 300 pg/ml. The concentration producing 50% inhibition as compared with a saline control was calculated.

RESULTS

The skin test and RAST responses to different cow's milk proteins and SC and GC of the two patients are listed in Table I. Patient 1 also had positive responses to SC (9.8 PRU/ml) and GC (7.6 PRU/ml) as determined by RAST but had negative responses to cheese produced from cow's milk and to cow's milk proteins. RAST inhibition was performed with serum from patient 1 and from a patient with cheese allergy (no. 6) who was sensitized to BC (18.7 kU/L), SC (17.5 PRU/ml), and GC (13 PRU/ml). BC at a concentration of 1 to 10 μ g/ml produced a 50% inhibition of RAST response to BC for patient 6, and a similar figure was found for solutions of SC and GC. A RAST cross-inhibition study with serum of patient 1 produced a different result. In homologous systems (goat-goat and sheep-sheep) a 50% inhibition was obtained at concentrations of 2 to 6 μ g/ml, and similar data were found for sheep-goat systems, whereas a concentration of BC 2000 times higher failed to produce any significant inhibition of the positive RAST response to SC or GC.

DISCUSSION

The major cow's milk antigens, which have the ability to bind IgE antibodies from sera of atopic individuals and the capacity to activate mediator-releasing cells, are the whey proteins α -lactalbumin, β -lactoglobulin, bovine serum albumin, and the caseins. According to our experience¹ and the data shown in Table I, the predominant

TABLE I. Clinical and allergologic data of 10 patients with cheese allergy

Patient No.	Sex	Birthdate (yr)	Previous atopies	Age (yr) at diagnosis	Symptoms	SST Feta	SPT					RAST (CAP) (kU/L)					RAST (PRU/ml)	
							RIN	CM	GM	BC	LA	CM	LA	LG	BC	FC	SC	GC
1	M	1975	AD, HF	15	AE, RC	+++	+	0	+	0	0	0	0	0	0	13.8	9.8	7.6
2	M	1968	0	25	U, AE, A	+++	+	0	+	0	0	0	0	0	0	0.5	0.35	0.35
3	F	1959	A	38	A, R		+	+	+	+	+	1.5	0	1.5			1.0	0.8
4	F	1951	HF, PA	39	A, R, AE		+	+	+	+	0	2.7	0	0	2.4		3.2	2.0
5	F	1964	0	28	EIFA, R, A, U, AE, GI		+	0	0	++	0	1.3	0	0	1.2		0.6	0.6
6	F	1938	0	53	R, U, AS		0	++	+	++	0	16.0	0	0	18.7		17.5	13
7	F	1942	0	50	U, AE, A		0	+	0	+	+	11.0	0	0	10.1		8.9	10.2
8	F	1961	0	30	R, AE, A		0	+	0	+	+	3.0	0	0	4.2		0.9	1.6
9	F	1948	0	44	E, R, A, GI		0	+	+	+++	0	13.7	0	0	14.3		14.1	16.4
10	F	1967	0	26	R, U, A, GI		0	++	++	++		2.3	0	0	2.1		1.6	2

Patients 1 and 2 had symptoms only after eating cheese made from sheep's or goat's milk and not after eating cheese made from cow's milk, whereas patients 3 to 10 had symptoms after eating all cheeses and, in general, in response to all dairy products.

A, asthma; AD, atopic dermatitis; AE, angioedema; AS, anaphylactic shock; E, erythema; EIFA, exercise-induced food anaphylaxis; GI, gastrointestinal symptoms; HF, hay fever; R, rhinitis; RC, rhinoconjunctivitis; U, urticaria; PA, pollen asthma; 0, not known, negative; RIN, routine inhalant allergens; CM, cow's milk; GM, goat's milk; LA, α -lactalbumin; LG, β -lactoglobulin; FC, feta cheese.

Grading of SPT reactions: + wheal 3 to 5 mm; ++ wheal 5 to 10 mm; +++ wheal 10 to 15 mm by negative glycerol control.

allergen in adults with IgE-mediated allergy to cow's milk is casein. Infants and small children are generally allergic to the species-specific and heat-unstable whey protein β -lactoglobulin.⁵ The reason that the sensitization pattern of adults with CMA differs from that of infants is probably a decreased consumption of whole milk but a comparable high intake of casein-enriched cheese products in adulthood. Thus β -lactoglobulin is the most acid-stable whey protein, will not be coagulated at the stomach pH, and can pass the mucosa even under physiologic conditions. Caseins represent 80% of mass in milk; they possess ordered structure to a relatively low extent, which explains the cross-reactivity with caseins of other mammals; and they resist heating at very high temperatures for prolonged periods.⁶ Whey proteins are naturally separated from the casein fraction during traditional cheese making. So far, patients 3 to 10 had symptoms after eating all kinds of cheeses, and all demonstrated IgE antibodies to BC, SC, and GC. The two patients in our case studies are unique because they are able to tolerate cheese made from cow's milk, although they react to cheese made from sheep's and goat's milk. Accordingly, all results of SPTs and RASTs with cow's milk antigens were negative, whereas results of SSTs and RASTs with feta were positive. Because of the unquestionable case history of recurrent acute anaphylactoid reactions always

occurring immediately after eating cheese made from sheep's or goat's milk, complete disappearance of symptoms after dietary elimination of cheese made from sheep's or goat's milk, the strong positive SST response to feta, and the positive SPT response to GM, the diagnosis was obvious. Therefore the patients and the parents of the boy refused oral challenges. In vitro experiments demonstrated that the IgE antibodies of patient 1 did not show any detectable reaction with BC and that a concentration of BC more than 2000 times higher than SC or GC did not produce any measurable inhibition of the positive RAST response to SC and GC. Thus the IgE response of patient 1 is very specific. In patient 2 the IgE antibody level to GC is very low, but it is well known that the RAST only measures the circulating IgE antibodies and results can be negative also in the presence of strong positive skin test responses, which indicate an allergen-induced histamine release from the cutaneous mast cells. A toxic reaction caused by vasoactive amines in feta could be excluded by means of negative SST results in control subjects.

In conclusion, this report is, to our knowledge, the first that documents the existence of allergy to SC and GC in the absence of CMA and demonstrates that in some atopic individuals a clinically significant IgE-mediated allergy to sheep's and goat's milk products may develop.

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