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Milk Causes a Rapid Urticarial Reaction on the Skin of Children with Atopic Dermatitis and Milk Allergy

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Salo OP, Mäkinen-Kiljunen S, Juntunen K. Milk causes a rapid urticarial reaction on the skin of children with atopic dermatitis and milk allergy. Acta Derm Venereol (Stockh) 1986; 66: 438–442.

Open skin challenge test with whole milk and its large and small molecular fractions was performed on intact skin of children with atopic dermatitis and suspicion of milk allergy. Of the 51 children challenged with milk 35 reacted within minutes with contact urticaria. The large molecular (m.w.>10000 d) fraction gave an urticarial reaction as often as whole milk, whereas the small molecular fraction gave only a few positive reactions. These were obviously caused by alpha-lactalbumin which was present only in small amounts in the small molecular fraction. These findings indicate that immediate contact allergy to relevant food allergens can be very common in children with atopic dermatitis and that the large molecular antigens readily penetrate children's skin. *Key words: Milk allergy; Contact urticaria; Allergens.* (Received September 10, 1985.)

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The penetration of different chemicals into human skin has been widely studied. Most of the studies have concerned substances with relatively low molecular weight such as steroids and other drugs used for the treatment of skin diseases or substances capable of causing contact dermatitis.

Contact urticaria can be induced on human skin either by immunological or non-immunological mechanisms. Non-immunological contact urticaria is often caused by small molecular weight substances such as benzoic, cinnamic and sorbic acids. The testing of these substances is often performed using a modified chamber test method for patch testing. On the other hand, open test can also be used (1). In both tests the optimum time of recording the results is from 10 to 40 min after application of the test substance. In the adult neither stripping nor scratching the skin enhances the reaction.

Immunological contact urticaria has been described as caused by a wide variety of substances ranging in molecular weight from small such as ethanol (2) to proteins in food industry. Most of the reported instances are rare individual cases but also groups of patients, e.g. among those working with foods (3) or experimental animals (4) have been reported.

In this paper we report the occurrence of contact urticarial reactions to milk and its fractions in children with atopic dermatitis and milk allergy.

PATIENTS AND METHODS

Fifty-one patients hospitalized at the Department of Allergic Diseases, Helsinki, because of atopic dermatitis and anamnestic and clinical suspicion of milk allergy were included. Thirty-two of the patients were males and 19 were females. The age of the patients varied between 5 months and 7 years 2 months with a mean of 1 year and 10 months. The onset of dermatitis had occurred in the mean at 4.2 months of age with a range from birth to 2 years 8 months. Atopic diseases were present in the immediate family in 84 % of the patients and 37 % of them had either asthma or allergic rhinitis or both in addition to dermatitis.

The patients were skin prick tested with the common food allergens including fish, egg, milk, wheat using allergens supplied by Allergologisk Laboratorium, Copenhagen, Denmark. RAST tests using reagents obtained from Pharmacia, Uppsala, Sweden, were performed with the same allergens. The antigens were used in a concentration of 1 HEP (5) with 1 mg/ml histamine chloride as a positive control and the allergen diluent as a negative control. A wheal at least the size of that caused by histamine was considered as a positive result. Before the open cutaneous or peroral challenge test all the patients were on a milk-free diet.

Open skin test

The open cutaneous test was performed with pasteurized milk and milk divided into two fractions. The test was always performed on intact skin either on the arm or on the breast. A drop of milk and its fractions were applied on the skin and the resultant reaction was followed for 30 min. Development of wheal(s) on the test site was considered as a positive result.

Fractionation of milk

Milk was fractionated into two fractions according to the molecular weight. The "micro" fraction was obtained by filtrating pasteurized milk through Amicon ultrafilter at 4°C (filter: YM10, MW cutoff 10000 d). The "macro" fraction was obtained by 48 hour dialysis of 100 ml of milk at 4°C against 4×2 liters of 0.9 % NaCl through Thomas 3787-D22 (MW cutoff 12 000 d).

Analysis of the milk fractions

Protein elctrophoresis of the fractions was performed according to a modified Lowry's method (6, 7). Total allergenic activity was measured with RAST inhibition according to Yman (8) using Pharmacia milk RAST discs. Crossed immunoelectrophoresis (CIE), crossed-line immunoelectrophoresis (CLIE) and crossed radioimmunoelectrophoresis (CRIE) and rocket immunoelectrophoresis were performed according to Løwenstein (9) using rabbit antisera against cow's milk whey proteins (Behringwerke) and alpha-lactalbumin (Sigma) as a standard. The human IgE used in CRIE was a pool of 20 sera positive (RAST score 3–4) in milk RAST. Fuji RXOG X-ray film and Trimax 4/8 intensifying screen were used in autoradiography. The exposure time varied from 5 to 15 days.

RESULTS

The RAST and skin tests performed on the patients are presented in Table I. The majority of the patients were sensitive to milk and egg as revealed by both skin tests and RAST. About one third of the patients were sensitive to fish and wheat allergens.

Open skin test with pasteurized milk was performed on all 51 patients. A positive result with an urticarial reaction was obtained in 35 of them. The whealing appeared from two to ten minutes from the application of milk on the intact skin. There was a significant correlation between the open skin test result and family atopy, skin prick and RAST tests

(Table II). On the other hand, no correlation was found between the open skin test result and the length of breast feeding or other atopic symptoms.

The skin reactions obtained with the ultrafiltrated milk fractions are presented in Table III. Of the 18 patients tested 16 reacted to the large molecular fraction and 4 of them also to the small molecular fraction. All the patients who reacted to the fractions had also reacted to whole milk. Of two patients with a negative skin prick test to milk antigen both reacted

Table I. *Skin and RAST test results in patients with atopic dermatitis*

	Skin test		RAST	
Antigen	No. pos	No. tested	No. pos.	No. tested
Milk	34	51	39	50
Egg	36	49	37	45
Fish	16	46	10	40
Wheat	18	47	27	45

Table II. *Open skin challenge with pasteurized milk in patients with atopic dermatitis and suspected milk allergy*

	Milk challenge		
	Positive	Negative	*p*
Family atopy			
Positive	34	31	<0.05
Negative	1	3	
Breast feeding			
<=3 mo	10	9	NS
3–6 mo	23	6	
Asthma and/or rhinitis			
Present	15	4	NS
Not present	20	12	
Milk prick test			
Positive	30	4	<0.001
Negative	3	12	
Milk RAST test			
Positive	33	6	<0.001
Negative	2	9	

Table III. *Results of open skin tests with whole milk and its fractions* (limit mol. w. 10000 d)

	Whole milk	
	Positive	Negative
Small mol. fraction		
Positive	4	0
Negative	13	1
Large mol. fraction		
Positive	16	0
Negative	1	1

in open test to large molecular and one to the small molecular fraction. The two patients giving a negative reaction to the large molecular fraction had a weak positive reaction (1 to 2) in the milk RAST test. The reactions obtained with the fractions were obtained within the same time limits as those obtained with whole milk.

Analysis of the milk fractions

The total protein contents of the large and small molecular milk fractions were 27 and 0.11 g/l, respectively. The corresponding concentrations of alpha-lactalbumin were 2 and 0.03 g/l. Total allergenic activity measured by RAST inhibition was more than 500 times greater in the large molecular than in the small molecular fraction. CLIE analysis of the proteins in the fractions revealed one common component which was identified as alpha-lactabumin. On the basis of CRIE this was the only allergen present in the small molecular fraction.

DISCUSSION

Skin is considered as an organ protecting man from outer influences. It is, however, readily penetrated by various chemical substances such as drugs and many contact allergens. Some of the contact allergens causing symptoms on the skin are large molecular substances such as proteins. These do often cause contact urticarial reactions especially in persons working in food industry (3). Atopic dermatitis in infants is often caused or aggravated by peroral or topical contact with food components. One of the most common causes of atopic skin symptoms in young children is cow's milk. The patients in the present series were selected on the basis of clinical suspicion of milk allergy. In skin prick test they reacted as often to milk and egg antigens. In the open skin test application of a drop of milk on intact skin caused within minutes an urticarial reaction in the majority of the patients. The reaction was obtained with greater frequency with the milk fraction containing the large molecular components of milk than with the fraction containing the small molecular components. This is in good accordance with the fact that the majority of the allergenicity of milk is formed by beta-lactoglobulin. The fraction with the small molecular components contained only one obvious allergen—alpha-lactalbumin, which was present in the small molecular fraction only in small amounts.

The rapid onset of the clinical reaction was typical of the open skin test. According to Lahti (1) the onset of the clinical reaction in non-immunologic contact urticaria caused by benzoic and cinnamic acids is optimally read 40 min after application of the substance on the skin. This difference in the time schedule indicates that either protein allergens in milk penetrate the skin faster than the smaller molecular substances used by Lahti or immunologic and the non-immunologic irritants differ from each other either in their capability to cause mediator release from mast cells or in the mediators on which the whealing reaction is based.

The present findings indicate that the skin of a child with atopic dermatitis is readily penetrated by relevant protein antigens. This penetration can be used as a clinical test for protein allergy in these children. The antigens of cow's milk capable of causing clinical symptoms in children on intact skin are substances with molecular weight $>10\,000$ dalton.

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Reticular Erythematous Mucinosis Syndrome in a Patient with Polyarthritis

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A patient with seronegative oligoarthritis who developed the reticular erythematous mucinosis (REM) syndrome is described. This syndrome is considered to be a dermatological entity unrelated to systemic disorders. Aggravation of the rash by exposure to sunlight and a good response to anti-malarial agents suggest a relationship with rheumatological disorders, e.g. rheumatoid arthritis and systemic lupus erythematosus. Dermatologists consulted by a patient with the REM syndrome should be aware of the possibility of an associated rheumatological disease. (Received January 15, 1986.)

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The reticular erythematous mucinosis (REM) syndrome is a relatively new dermatological entity characterized by a net-like, reddish blue, somewhat infiltrated rash on the chest, upper back, neck, or abdomen (1). Microscopical examination of biopsy specimens shows a perivascular lymphocytic infiltrate and characteristic dermal deposits staining non-metachromatically with Alcian blue (1). At present about 50 cases of REM syndrome can be found in the literature (2). This disease is not known to be related to systemic disorders. However, the aggravation of the rash by exposure to sunlight (1, 3) as also seen in lupus erythematosus, and the response to treatment with antimalarial agents (1, 3) as seen in rheumatoid arthritis and cutaneous features of lupus erythematosus, suggest a relationship with rheumatological disorders.

The following report of a patient with seronegative oligoarthritis who developed a REM syndrome supports this hypothesis.

CASE REPORT

A previously healthy 36-year-old Caucasian man came to our out-patient clinic in December 1984 because some of his joints were painful and tender. Two and a half months earlier after an attack of "flu", he had developed these symptoms in the left mandibular joint, metatarsophalangeal joints II,