

Cow's milk allergy and eczema: patterns of the antibody response to cow's milk in allergic skin disease

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Summary

The pattern of the humoral-immune response to cow's milk was examined in children with eczema and in children who had acute urticarial and/or angioedematous reactions to cow's milk. Each patient group was compared to a group of age-matched controls.

Whereas the eczematous patients had significantly elevated IgG, IgA and IgE milk-antibodies, patients, allergic to cow's milk, had elevated IgE milk-antibodies. These differences in the pattern of antibody response to cow's milk suggests that these two patient groups constitute separate allergic populations, and that different pathogenic mechanisms may be operative in these two skin diseases associated with elevated levels of IgE antibodies to cow's milk.

Introduction

Raised levels of milk-specific IgE antibodies are often demonstrable in children with milk allergy (Fällström, Ahlstedt & Hanson, 1978; Dannaeus & Johansson, 1979; Hill *et al.*, 1979), although recent studies have reported similarly raised levels in atopic children who appeared to tolerate milk proteins (Foucard, 1973; Dannaeus *et al.*, 1977; Hill *et al.*, 1979; Turner *et al.*, 1980). Non-IgE antibodies to cow's milk have been demonstrated in healthy and atopic children, without symptoms of milk allergy (Kletter *et al.*, 1971; Foucard, 1973; Dannaeus *et al.*, 1977). These observations question the relevance of milk antibodies in the pathogenesis of allergic diseases.

Although the presence of these antibodies may not be of diagnostic value, we were interested in examining the possibility that the pattern of the humoral response to cow's milk may differ in patients with different allergic skin-diseases. We compared the humoral immune response to cow's milk of children who had acute urticarial and/or angioedematous reactions to cow's milk, with that of eczematous children who had no apparent clinical changes following ingestion of cow's milk.

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Patients

Cow's milk allergy (CMA)

From a group of sixty children with confirmed CMA, fourteen infants, who developed acute angioedema and/or urticaria within 20 min of challenge with cow's milk, were selected. The diagnosis of CMA had been made according to the protocol previously described (Hill *et al.*, 1979). These children were breast-fed for between 3 and 12 months and developed acute skin-eruptions after ingesting small volumes of cow's milk.

Eczema

The serum of twelve children with severe, generalized eczema were analysed. These children were older than the CMA patients (Table 1). They were tolerating normal volumes of milk, without obvious adverse effects. Four of the children had a history of allergy to egg.

Controls

Single serum samples from twenty-nine children made up the control population. Thirteen of these were drawn from a community survey of healthy children and were age-matched for the eczema patients. The remaining sixteen samples came from children hospitalized for various medical and surgical conditions, unrelated to CMA. These sixteen were age-matched for the CMA patients; no details of their previous history were available.

Materials and methods

Serum immunoglobulins

Total IgG, IgA and IgM were measured using a Technicon autoanalyser fluoronephelometer and these were expressed as percentile values for age (Shelton *et al.*, 1974). Total IgE was measured in iu/ml using the Phadebas IgE PRIST Kit (Pharmacia Diagnostics, Uppsala, Sweden).

Milk-specific antibodies

Milk-specific IgG, IgA and IgM antibodies were measured using an enzyme-linked immunosorbent assay (ELISA) developed in our laboratory. The details of this technique have been described elsewhere (Firer, Hosking & Hill, 1981a). The milk antibody measurements were expressed as milk antibody units (MAU) by comparison with a high-titred laboratory standard.

Table 1. Age distribution of patients and controls

Group	<i>n</i>	Mean age (years)
CMA patients	14	0.93 (range 0.5–2.3)
CMA controls	16	1.35 (range 0.5–7.5)
Eczema patients	12	5.9 (range 2.0–11)
Eczema controls	13	5.11 (range 2.4–12)

Milk-specific IgE antibodies were measured with the Phadebas RAST kit and the absolute ct/min of isotope-bound allergen-specific IgE measured, to allow comparison of specific IgE in controls and patients. The RAST scoring-scale was not used.

Statistical analysis

The Mann-Whitney U-test was used throughout to assess differences in immunoglobulin and antibody levels between the groups. The null hypothesis was rejected when $P < 0.05$

Results

Total immunoglobulins

There were no differences in total serum IgG, IgA or IgM between the two patient groups and their respective control populations. Total serum IgE was significantly

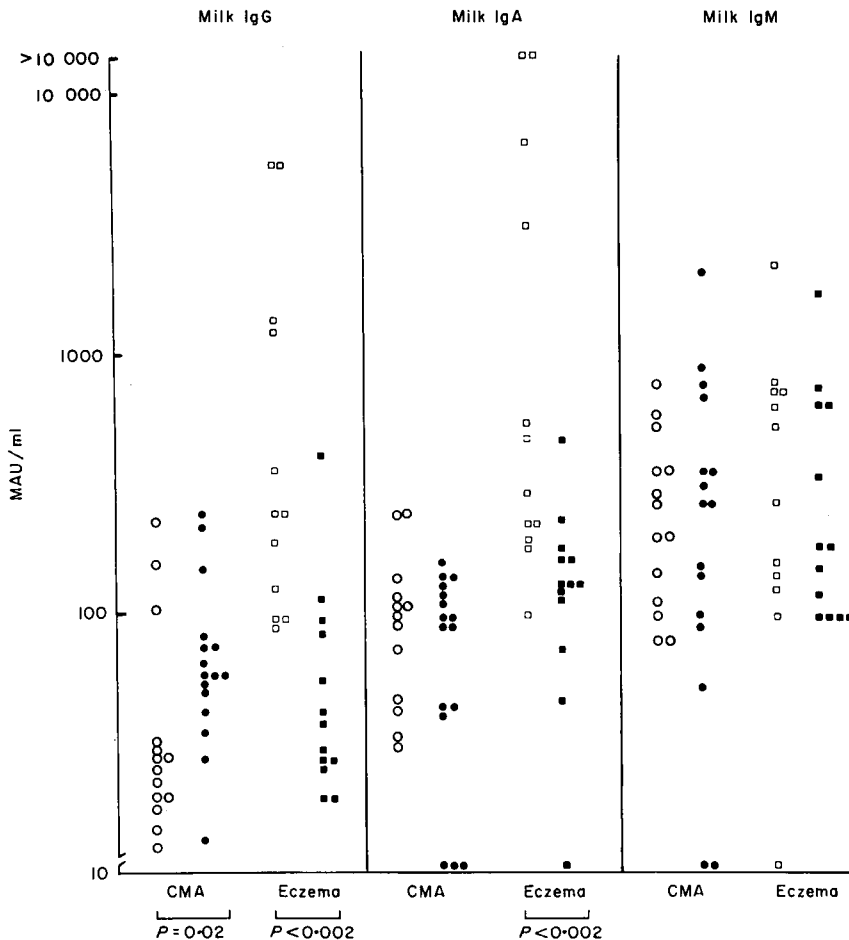


Fig. 1. Cow's milk-specific IgG, IgA and IgM antibodies in patients and controls measured by ELISA and expressed as milk antibody units (MAU) per ml. Significant differences between patient groups and their control group are indicated. O, CMA patients; ●, controls; □, eczema patients; ■, controls.

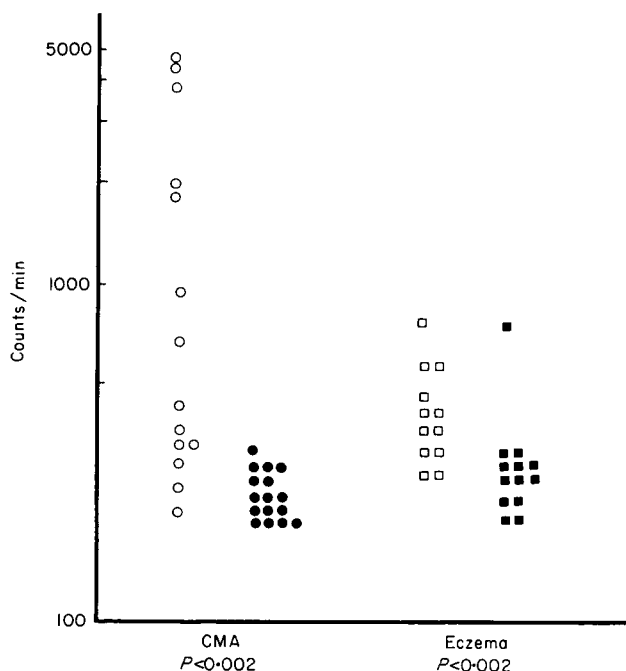


Fig. 2. Cow's milk-specific IgE antibodies in patients and controls measured by RAST and expressed as ct/min. Both CMA and eczema patients have significantly higher IgE milk-antibodies than their respective control groups. O, CMA patients; ●, controls; □, eczema patients; ■, controls.

higher both in the eczema group, compared to their controls ($P < 0.001$), and in the CMA group, compared to their controls ($P < 0.001$).

Milk-specific antibodies

There was no difference in IgM milk-antibodies between the two patient groups and their control populations. IgA milk antibody levels were significantly higher in eczematous patients than their controls ($P < 0.002$), but there was no difference between the CMA patients and their controls.

Milk-specific IgG and IgE levels were significantly different between the patient groups and their respective control populations (Figs 1 and 2). Patients, allergic to cow's milk, had significantly lower IgG and higher IgE milk-specific antibodies than their controls ($P = 0.02$ and $P < 0.002$ respectively; see Figs 1 and 2). Compared to their control group, eczema patients had significantly higher IgG and IgE milk-antibodies ($P < 0.002$ and $P < 0.002$).

Discussion

The results showed that the humoral immune response to cow's milk differed between the two patient groups and the control populations. Whereas the eczematous patients had significantly elevated IgG, IgA and IgE milk-antibodies, CMA patients had elevated IgE milk-antibodies, but significantly lower levels of IgG milk-antibodies.

Despite the association of IgE milk-antibodies with both CMA and eczema, observed in this study, the pattern of response of antibody of other immunoglobulin

classes to cow's milk raises the possibility that these two patient groups constitute separate allergic populations. There is evidence that eczematous patients show enhanced gut permeability (Jackson *et al.*, 1981), absorb more antigen and have decreased clearance rates of milk antigens following ingestion (Paganelli *et al.*, 1979) than non-atopic patients. Such chronic antigenic exposure may account for the elevated IgE, IgG and IgA, but not for normal IgM milk-antibody levels seen in our eczema patients. Whether these immunological phenomena might operate in response to other allergens remains to be studied, but we, and others, have recently described elevated IgE-antibodies to multiple dietary-antigens in children with eczema (Hill *et al.* 1981). In contrast, whereas the CMA patients also had elevated levels of IgE milk-antibodies compared to their controls, they had significantly lower levels of IgG milk-antibodies. Although these decreased levels of IgG milk-antibodies may simply reflect restricted milk intake, an alternative explanation for these findings would be that the small volumes of milk ingested by these patients facilitates an IgE, but not IgG milk-antibody response as we have recently reported (Firer *et al.* 1981b).

These observations suggest that different pathogenic mechanisms may be operative in these two skin diseases associated with elevated levels of IgE antibodies to cow's milk. One possible explanation, for the acute urticarial skin-responses seen in CMA patients, is that the absorbed cow's milk antigen triggers mast cell degranulation. Whether this response can be regulated by stimulation of effective blocking IgG-antibodies remains to be studied, but there is some evidence to support this concept in patients with bee venom anaphylaxis, who respond to immunotherapy (Lessof, Sobotka & Lichtenstein, 1977). Conversely, the skin lesions of eczema may be of different aetiology, being the result of chronic antigen-exposure to milk and other dietary antigens, leading to the formation of immune complexes which may become deposited in the skin and small vessels, causing a local inflammatory response (Cochrane & Weigle, 1958). However, although fragments of IgG, IgM and complement have been identified by immunofluorescence in eczematous skin-lesions (Ring *et al.*, 1978; Hodgkinson, Everall & Smith, 1977), intact dietary-antigens have yet to be identified in eczematous skin-lesions.

Our results support previous studies, which have shown elevated levels of IgE milk-antibodies in both CMA patients with skin diseases and in patients with eczema, thus questioning the relevance of these antibodies in the pathogenesis of these two diseases. Furthermore, the different patterns of non-IgE antibody responses to cow's milk, observed in this study, suggest that different immune mechanisms are involved in the pathogenesis of these two diseases.

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