

Natural history of cows' milk allergy in children: immunological outcome over 2 years

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Summary

In this investigation 98 children (median age 24 months) with cows' milk allergy (CMA) were studied over a median period of 2 years to see whether acquisition of clinical tolerance to cows' milk was associated with the changes in levels of IgG and IgE anti-cows' milk antibodies, and skin test reactivity to a cows' milk extract. Two groups of CMA patients were examined. The first were IgE sensitized and responded rapidly to small volumes of cows' milk with urticaria, and/or exacerbations of eczema, and/or wheeze, and/or vomiting ($n=69$). The second, a late reacting group ($n=29$) demonstrated coughing, diarrhoea, eczematoid rashes, and/or a combination of these which developed more than 20 hr after commencing normal volumes of cows' milk. Significant immunological changes were confined to the 69 IgE sensitized immediate-reacting-group of patients. Of these, there were 15 children who achieved clinical tolerance to cows' milk and they showed a significant fall in the levels of skin test reactivity to cows' milk over the study period ($P<0.01$). In addition, these 15 children had lower serum IgE antibodies to cows' milk proteins both at the outset and the final follow-up compared with the 54 patients whose CMA persisted. No consistent change in the IgG antibody responses to cows' milk proteins was seen in either group of patients over the study period. The findings suggest patients with immediate type hypersensitivity to cows' milk proteins whose disease persists for more than 2 years have a more severe dysregulation of IgE synthesis to cows' milk proteins from the outset. The role of humoral immune mechanisms in the pathogenesis of late reacting CMA remains unclear.

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Introduction

Cows' milk allergy, defined as an adverse clinical response to cows' milk protein, affects between 2 and 7.5% of infants [1-3]. Studies from this laboratory of infants and young children with challenge-proven CMA identified three groups of patients and described their immunological features [4,5]. In Group 1, immediate reactors, urticaria and/or eczematous eruptions, and/or features of anaphylaxis developed within an hour of ingestion of small volumes of cows' milk; patients had elevated IgE anti-cows' milk antibody levels. In Group 2, intermediate reactors, vomiting and diarrhoea developed after ingesting modest amounts of cows' milk 1 to 20 hr after commencing challenge; IgE anti-cows' milk antibody

levels were not elevated. The patients in Group 3, late reactors, developed eczematous, and/or gastrointestinal and/or bronchitic symptoms after ingesting substantial volumes of cows' milk more than 20 hr after commencing challenge. The patients with eczematous eruptions in Group 3 also showed elevated IgE milk specific antibody levels. In all three patient groups, IgG anti-cows' milk antibody levels were low, a phenomenon we attributed to dietary milk exclusion [5]. As a group the late reactors demonstrated heightened T-cell reactivity to milk proteins reflected by enhanced leucocyte migration inhibition factor (LIF) production on exposure to cows' milk proteins *in vitro* [6].

In a previous preliminary investigation, the clinical and immunological outcome of children in each of the patient groups was examined [7,8]. One unexpected finding from that investigation was that, as a population, the patients

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when his eczematous patients developed clinical tolerance to foods but he defined SPT positivity as any test exceeding a 3 mm weal [18]. We measured SPT to WCME in relation to histamine because of the known effect of age on skin test reactivity in infants [10], and followed the method of Aas and Belin [11]. The difference in results between ourselves and Sampson may be accounted for by the different methods of assessing skin test reactivity.

We used an SPT $\geq +4$ as diagnostic of CMA based on the results of our previous investigations [9] in which all children with this level of SPT had CMA demonstrated on formal cows' milk challenge. Sampson [19], and Businco [20] have been unable to confirm our findings. While the level of skin reactivity to cows' milk proteins assigned significance by Businco is unclear [20], Sampson [19] followed the recommendation of Bock *et al.* [21] and used a 3 mm weal to WCME to predict outcome of cows' milk challenge. In the current investigation patients in whom the diagnosis of CMA was based on SPT $\geq +4$ had a weal SPT to WCME more than twice the 3.0 mm level, i.e. 8.0 mm median weal at initial assessment, and 9.0 mm weal at the final assessment. These levels of SPT to WCME were similar to those in our initial study [9].

Despite the presence of atopic clinical features in our Group 3 patients, the incidence and level of IgE hypersensitivity to cows' milk proteins reflected by SPTs and circulating IgE antibodies to cows' milk were low throughout the study. There was no significant difference in either of these IgE related parameters over the study period irrespective of whether or not cows' milk tolerance was achieved. Our previous investigations of this group of patients suggested they demonstrate heightened T-cell reactivity to milk proteins reflected by enhanced LIF production on exposure to cows' milk proteins *in vitro* [6]. The importance of IgE type hypersensitivity mechanisms in this group of patients is unclear.

The immunological findings of the study may be of some value in predicting clinical outcome for Group 1 patients. For example CMA persisted beyond 2 years in 87% of patients with an initial anti-cows' milk IgE antibody level exceeding 6 PRU/ml in 85% of patients with SPT $\geq +4$, and in 92% of patients in which both these parameters were elevated. Conversely neither the SPT, nor the IgE anti-cows' milk antibody levels, nor a combination of both these proved useful in predicting remission. Furthermore no association between IgG levels to cows' milk proteins or clinical status initially or at final assessment could be demonstrated for any of immediate or late reacting CMA patient groups. This, together with our previous studies, suggests that circulating IgG antibodies to cows' milk proteins as measured by ELISA do not have a major role in the pathogenesis of CMA [12].

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