

EDITORIAL

Persistent allergy to cow's milk: of greater a clinical concern than other food allergies

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The prevalence of cow's milk protein (CMP) allergy (CMPA) in children is estimated to be around 2% in Europe and elsewhere (1), although more recent data are lacking. CMPA is common in childhood but resolves by school age (2). A proportion of children retain their allergy: under 10% beyond age 10 yr in unselected birth cohorts (2), although persistent CMPA is seen in up to half of children attending specialist allergy clinics. (3)

Given the tendency toward natural resolution, CMP may be seen as a relatively minor cause of food allergy in the wider population. Other allergens, such as peanut and tree nuts, have been reported as carrying a greater risk to health (4). This, however, may not be true: in our tertiary center in London, the majority of recent severe anaphylactic reactions have been triggered by exposure to CMP in teenagers with CMPA. This observation is consistent with data from the largest registry of fatal anaphylaxis, based in the UK, in which CMP was as common a trigger of fatal food-induced anaphylaxis in children as peanut and tree nuts combined, accounting for 31% of cases in children under 16. (5) In terms of propensity toward severe allergic reactions in teenagers, CMP may therefore be considered to be a more 'dangerous' allergen than most.

The mainstay of management remains dietary avoidance combined with provision of rescue medication and an appropriate, individualized management plan. However, accidental exposures are common. Cross-contamination of pre-packed foods with CMP is even more common than for peanut; this is mostly due to the technical challenge of avoiding cross-contamination of chocolate with residual CMP from milk chocolate produced on the same machinery. (6) Indeed, Fleischer and colleagues recently reported results from a prospective study of allergic reactions in preschool children diagnosed with food allergies; CMP was by far the most common trigger, accounting for 42% of reactions, compared to egg (21%) and peanut (8%). (7) This is probably not surprising, given the ubiquitous role of mammalian milks within the human diet.

Recent guidance from Australia has suggested an action level of 0.1mg as a reference point for food allergen labeling, below which most individuals with CMPA are unlikely to react and therefore allergen advisory labels might not be required on packaging. (8) However, this level of allergen may be below the lower limit of detection of many commercially -available assays used to test for cross-contamination. Thus, use of an action level of this magnitude may be technically unfeasible in food production. An alternative strategy – maintaining a state of partial tolerance – may be useful in preventing allergic reactions to inadvertent exposure to CMP, thus reducing the risk of anaphylaxis.

A number of research centers are assessing the potential to hasten resolution of CMPA using desensitization protocols. Given the relative high frequency of recurrent anaphylaxis and fatal anaphylaxis in people with cow's milk allergy (5) attempts to induce a degree of desensitization are a high priority in those individuals whose allergy to CMP fails to resolve spontaneously. The two methods most commonly used are through the consumption of food products containing extensively heated CMP (9) and oral immunotherapy (10) (although other routes of immunotherapy are being trialed (11, 12)). Unfortunately, as demonstrated in a Cochrane review, these protocols frequently fail to achieve complete desensitization and long-term tolerance, with a significant rate of (often systemic) side effects. (10) A recent review concluded that most children undergoing immunotherapy to CMP experience side effects, although over 80% are able to complete the protocols. (13) However, severe reactions often occur and can be unpredictable, which limit its clinical application outside the research setting. Furthermore, a recent publication has cast doubt on the persistence of long-term tolerance: many subjects lost their level of tolerance over time, and under one-third of 32 patients who underwent desensitization were able to tolerate a portion of CMP without experiencing significant symptoms when reviewed at up to 5 yr later. (14)

In this issue, Dupont discusses issues surrounding re-introduction of CMP in children with CMPA, with regards to timing, location and in what form to test tolerance. (15) Clearly, this is important, given the need to re-assess tolerance not only in children with persistent CMPA but even in those who have completed a desensitization protocol. (14) Should attempts to re-introduce CMP be limited to testing for resolution of CMPA, or is there a role for re-introduction in terms of ongoing risk management?

Data from both USA and Australia demonstrate that around two-thirds of children with CMPA tolerate extensively heated CMP at oral food challenge, for example, in a cake. (16, 17) Presumably, this situation is analogous to children with egg allergy who tolerated extensively heated egg (thought to be due to factors including conformational changes of the allergenic epitopes through heating and matrix effects). (18) The same group presented data which suggest that consumption of extensively heated CMP in individuals with CMPA may hasten the resolution of the allergy (9) although this has not been tested in a double-blind placebo-controlled manner for pragmatic reasons.

Anaphylaxis to extensively heated CMP was common in those failing the food challenge. In the US study, 35% of reactors experienced anaphylaxis (16) while 27% had anaphylaxis in the Australian cohort (17) a rate almost double that seen in egg-allergic children who are unable to tolerate

extensively heated egg. (18) While tolerance to extensively heated CMP does not imply tolerance to low amounts of native CMP, the US study reported that lack of tolerance to extensively heated CMP was also associated with a more severe allergic phenotype (16). This raises the possibility that in addition to the benefits of incorporating baked CMP into the diet, determining tolerance to extensively heated CMP may help with risk stratification.

Unfortunately, while children with higher degrees of sensitization (skin prick test wheals, serum-specific IgE levels (19, 20)) are more likely to have persistent CMPA and less likely to tolerate extensively heated CMP (21), this is of little use in clinical practice as these tests lack high specificity and sensitivity. Therefore, the only means of testing tolerance to CMP (in any form) is through supervised challenge. Dupont's review is therefore a timely summary of the issues concerned.

A number of points are worth emphasis. Reactions to CMP can be severe (5), even to extensively heated CMP (16, 17). Initial re-introduction must therefore be done under medical supervision in a medical environment experienced in the management of anaphylaxis. In a child with partial tolerance to CMP, caution must be exercised before recommending a family to increase the amount of CMP given to a child with CMPA at home. On the basis of experience from trials of immunotherapy, one might consider that in most cases, up-dosing should take place in an environment equipped to manage a reaction, as these can be unpredictable. (13) The vast

majority of children with CMPA do not tolerate other mammalian milks (as reviewed in (22)), and while it is interesting that oral immunotherapy to CMPA can increase tolerance to milk protein from other animals (23) it is unclear whether this is clinically advantageous.

In the meantime, more research is needed to determine whether lack of tolerance to heated or fermented CMP is associated with a more severe allergic phenotype. Desensitization protocols should be adapted to look at partial long-term tolerance as a primary outcome, to reduce the risks associated with inadvertent exposure to CMP in those with persistent CMPA. Data exist to demonstrate that oral immunotherapy to CMP induces similar immunologic changes as those seen with the development of natural tolerance (24). Given that similar changes are seen with the dietary introduction of extensively heated CMP, perhaps partial desensitization results in similar immune changes that may, over a longer time period, hasten resolution and reduce the risk of severe or even fatal allergic reaction with inadvertent exposures.

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