

EDITORIAL

Cross-reactivity between milk proteins of different animals

Cow's milk allergy/intolerance (CMA/I) is the most common cause of clinically important adverse food reactions in infants and children during the first 2 years of life. Its frequency is obviously linked to the high cow's milk (CM) consumption during infancy and early childhood which makes CM the most important source of food allergens during these stages. Thus, a percentage of children varying between 0.3 and 7.5% of the general population has been reported suffering from CMA/I and needs to follow a CM-free diet [1–5]. Furthermore, whereas some studies evidenced that CMA/I symptoms tend to regress within 3 years [6–8], more recent prospective studies have revealed that a considerable percentage of patients (30–40%) remain symptomatic beyond 4 years of age [9,10]. This is also our experience in the paediatric gastroenterology unit of Palermo.

Another point which could contribute to increase the number of subjects who need elimination diets is the possibility that some of the patients with CMA/I persisting beyond the first few years of age might not be recognized because the clinical symptoms of CMA/I change over time and there is a more prolonged delay between CM ingestion and manifestation of symptoms [11]. All these considerations underline that the number of children who need a CM-free diet during their lives is very great, and an alternative 'milk source' must be used.

Although the efficacy and the tolerance of the L-amino acid-based infant formulas in patients with CMA/I or multiple food allergy have been clearly demonstrated [12,13], we feel that the use of a natural milk, during the CM-free diet period, should be encouraged because of its better palatability and its 'hormonal peptides' which stimulate the functional recovery and development of the intestine. In this respect, goat and/or sheep's milk are often used instead of CM in CMA/I patients, but due to immunological cross-reactivities between proteins from cow, sheep and goat's milk, the use of sheep or goat's milk is controversial [14,15]. In fact, immunological cross-reactivity between milk proteins of different animals can be fundamental in determining multiple food allergy, a clinical condition which is difficult to treat, especially in infancy [16]. As several proteins are contained in milk, each of these could be responsible for a cross-reaction between milks of different origin; in infants and small children a whey protein, β -lactoglobulin, is probably the major milk allergen [17], but in adults the predominant allergen is considered to be casein.

Thus, in the evaluation of cross-reactivity between milk

proteins of different animals, a study of casein is important because it represents 80% of the total bovine milk protein [18]. The analysis of the amino acid sequence of α_1 and α_2 caseins from cow, goat and sheep's milk evidences a 87–98% identity of amino acids [19]; this large identity facilitates immunological cross-reactivity. Moreover, cow casein structure is relatively simple and this may also explain the cross-reactivity with caseins of other mammals. Furthermore, as it withstands heating at high temperatures for prolonged periods [20], its immunogenicity is well present both in the whole milk and in cheese products.

The cross-reactivity between cow, goat and sheep's casein can give IgE-mediated clinical reactions both in children [14] and in adults [21]; these patients can present all the typical IgE-mediated symptoms including asthma, atopic dermatitis, angioedema, rhinitis, urticaria and anaphylactic shock. The severity of these reactions could advise against recommending sheep and goat's milk as a substitute for CM in the nutrition of CMA/I patients. However, this cross-reactivity and the consequent clinical reactions are not always present.

In this issue of the Journal, Umpierrez and colleagues [22] report on a child who had allergic reactions after eating goat's cheese and after touching goat and sheep's cheese, but not after consuming CM dairy products; *in vivo* (skin prick tests) and *in vitro* (IgE ELISA against the caseins from goats and sheep) tests confirmed that this child suffered from urticaria and wheezing due to IgE-mediated reactions. The authors were also able to demonstrate that goat's casein was the main allergen causing sensitization in goat's milk; however, it is of interest that the results of ELISA inhibition showed that goat and sheep's casein had a very high degree of cross-reactivity, but also cow's casein produced a 50% inhibition of ELISA activity to goat's milk; nevertheless, this child never showed any clinical reaction to CM, and skin prick-by-prick test with whole cow's milk and its casein elicited no reaction.

To our knowledge, there is only one other report in the literature of two cases of sheep and goat's milk allergy without associated clinical reactions to CM [23]; in this report two young male adult patients were described who had cutaneous, conjunctival and respiratory symptoms after eating all kinds of cheeses made from sheep or goat's milk. These two patients, however, had at least two laboratory characteristics that differed from those of the child described by Umpierrez *et al.* In one of these patients, in fact, RAST cross-inhibition study showed a high cross-reactivity between goat and sheep's casein (a 50% inhibition

was obtained at concentrations of 2–6 µg/mL both in homologous systems — goat–goat and sheep–sheep — and for sheep–goat systems), whereas a concentration of cow's casein 2000 times higher failed to produce any significant inhibition of the positive RAST response to sheep or goat's casein; the second patient showed the characteristic of a very low IgE antibody level to goat casein (0.35 PRU/mL) with a concomitant strong positive skin test response [23]. Thus, the laboratory data characteristics of the child described by Umpierrez and coworkers [22] and of the patients previously described [23] are worth considering: whereas in both reports ELISA-inhibition tests confirmed the very high cross-reactivity between goat and sheep's casein (well justified by the 97.4% identity of the amino acid sequence [19]), in the case reported by Umpierrez *et al.* there was also the evidence of a 'laboratory cross-reactivity' with cow's casein which, however, had no clinical correlative, as the patient was tolerant to CM. Moreover, the second patient described by Wuthrich and colleagues [23] had no 'laboratory evidence' of IgE-mediated hypersensitivity to goat casein but showed generalized urticaria, swelling of the eyelids and dyspnea within 30 min of eating goat's milk. All these findings once again confirm that the diagnosis of food allergy/intolerance must be based exclusively on clinical reaction to food ingestion and that despite many claims for effective *in vitro* diagnostic tests, the precise diagnosis of food intolerance relies on clinical methods.

However, the quoted reports [22,23] confirm the usefulness of the skin prick tests in predicting immediate allergic reactions to food ingestion; but in this respect, we must recall cases of immediate reactions to rice ingestion with severe clinical symptoms (shock) without positivity of prick tests to rice [24]. Furthermore, many atopic patients had IgE antibodies, often in high titre, to substances that they tolerated well.

The cross-reaction between milk proteins of different animals merits at least two further considerations. First, not all the 'alternative milks' used instead of CM in CMA/I patients cause frequent clinical reactions. We have a long experience in the use of ass' milk, in patients with CMA/I and/or multiple food allergy [25] and have recently reviewed our case histories: whereas 70–90% of CMA/I patients also showed intolerance to goat and sheep's milk, only 10% had concomitant intolerance to ass' milk. This different frequency may derive from a lower cross-reactivity between ass' milk proteins and CM proteins than between goat's/sheep's milk proteins and CM proteins.

Second, it has been hypothesized the possibility of cross-reactivity between bovine serum albumin, another protein contained in CM, and animal epithelia, dander or saliva containing serum albumin, also introduced through exposure by inhalation [26]; in fact, allergic cross-reactions

between serum and epithelium proteins from various animals have been documented [27,28].

In conclusion, the paper by Umpierrez and colleagues [22] add to our knowledge on milk protein cross-reactivity, but it is clearly evident that many factors determining the clinical immunological reaction and cross-reactivity to foods still remain to be understood. Among these, the organ distribution of mast-cells has been suggested [29], but it is an aspect little considered by allergists. Another interesting aspect is the way of allergen introduction; in fact, there is a reported decrease in tissue sensitivity for allergens in the order: skin–nasal–oral–gastrointestinal [30]; it is possible that protective factors in the intestinal mucosa could be responsible for the absence of any reaction after oral intake, despite strong IgE sensitization.

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