

CAMEL MILK: A POSSIBLE ALTERNATIVE FOR CHILDREN WITH COW'S MILK ALLERGY ?

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ABSTRACT

BACKGROUND: Cow's milk protein allergy (CwMPA) is the most common food allergy during early childhood and its therapy is elimination of cow's milk proteins (CwMP) from the diet and introduction of alternative formulas. Evidence about clinical use of camel's milk (CM) in CwMPA in children is scarce. **OBJECTIVES:** The aim of this study was to determine the entity of cross-sensitization between CM and CwM in children with CwMPA. **METHODS:** This prospective study was performed in children affected by CwMPA. We evaluated Skin prick tests (SPT) for CwM, CwMP (alpha-lactalbumin-ALA, beta-lactoglobulin-BLG and casein-CAS) and CM and serum levels of CwM, ALA, BLG, CAS-sIgE. **RESULTS:** 67 children with CwMPA were included in this study: Twenty-one resulted SPT+ to CM. Mean wheal diameters towards raw CwM, ALA, BLG and CAS resulted significantly larger in the CM SPT+group than in the CM SPT-group (p-value <0.02). Likewise, mean IgE titers against CwM, ALA and CAS were significantly higher in the CM SPT+group than in the CM SPT-group (p-value < 0.01). The mean wheal diameter towards raw CwM was significantly larger than that towards CM (p<0.0001). **CONCLUSIONS:** In summary, this study confirms the presence of cross-sensitization between CwM and CM that remains, however, lower if compared to other mammalian milks. Small wheals at the SPT towards CwM antigens together with low IgE titers against them could work as predictors in selecting patients that are expected to have negative CM SPT and then could be fed with CM with lower risks of allergic reactions.

INTRODUCTION

Cow's milk protein allergy (CwMPA) is the most common food allergy during infancy and early childhood [1]. Current treatment for this condition implies a total elimination of cow's milk protein (CwMP) from the diet and introduction of alternative formulas [1-5]. However the low organoleptic acceptance of the industrial formulas, such as extensively hydrolysed or amino-acid formulas, greatly limits the use of these products, as does adherence. Several studies have evaluated the clinical use of animal non-bovine milk as an alternative including that of sheep, goat, donkey, mare, and buffalo [6-10]. However several authors have demonstrated how children with CwMPA can remain also intolerant to milk proteins of other species for the presence of an immunological cross-reaction with their counterparts present in cow's milk (CwM) [11]. Among mammals whose milk has been proposed as an alternative in allergic subjects, there is also the camel [12-17].

Medical literature on clinical use of camel's milk (CM) in CwMPA in children is scarce and the studies published had very small sample size and some criticisms.

So the aim of this study was to determine the entity of cross-sensitization between CM and CwM in children with demonstrated CwMPA.

MATERIALS AND METHODS

This prospective cohort study was performed from 2015 to 2016 on 67 children aged 1–192 months who were referred to the Allergy–Immunology Clinic at Regina Margherita Childrens' Hospital of Turin, Magna Graecia University of Catanzaro Department of Pediatrics and Bolognini-Seriato Hospital of Bergamo, affected by CwMPA. The inclusion criteria required clinical history suggestive of CwMPA (presence of respiratory, cutaneous, gastrointestinal or nasal symptoms associated with intake of CwMP) with one or more elevated CwM protein–specific IgEs and positive skin-prick test (SPT) to CwM proteins. Oral

double-blind placebo-controlled food challenge test was performed in selected children in order to confirm the diagnosis. Exclusion criteria were use of β -blockers or immunosuppressive drugs, severe cardiovascular diseases, renal diseases, debilitating diseases (e.g., terminal malignancy), marasmic kwashiorkor, respiratory diseases, severe skin diseases that preclude skin testing, persistent daily need for oral antihistamines and allergies from other food sources.

All participants/legal guardians gave written informed consent after receiving full explanation of the procedure given individually before testing.

We evaluated CM sensitization by using SPT with powdered CM imported from The Netherlands (Kamelenmelkerij Smits).

SPTs were performed following the “Updated Practice Parameter of Allergy Diagnostic Testing” [18]. Tests were performed on the volar surface of the forearm with homogenized CwM, CwM specific antigens (α -lactoalbumin, β -lactoglobulin, caseins) and CM rehydrated with saline (ratio CM 20 gr to 200 ml of saline), using a sterile lancet (Stallergen, Paris, France). A 50% glycerin/saline solution and HCl histamine solution at 10 mg/mL were used as negative and positive controls, respectively. SPTs were read after 15–20 minutes, and tests were considered positive if the mean diameter of wheal was at least 3 mm to the samples and greater than the negative control. CwM-specific IgEs were also measured by RIDA Allergy-Screen Panel 3 test kit (R-Biopharm AG, Darmstadt, Germany).

The data were analyzed using the Statistical Packages for Social Sciences (SPSS, Inc., Chicago, IL). Frequency distributions were obtained. Student’s t-test was used to ascertain the significance of differences between mean values of two continuous variables; Chi-square analysis and Fisher’s exact test (two tailed) were performed to test for differences in proportions of categorical variables between two or more groups. The level of $p < 0.05$ was considered as the cutoff value for significance.

RESULTS

A total of 67 children (52 boys and 15 girls) were included in this study. Their median age was 61,4 (range 1-192) months. Boys outnumbered girls by a ratio of 3,5:1.

All patients were SPT+ to CwM and 19 had also a history of anaphylaxis to CwM and/or other alimentary antigens. Twenty-one out of 67 patients (31,3%) resulted SPT+ and 46 out of 67 patients (68,7%) were SPT- to CM.

There were no significant differences between CM SPT+ and SPT- children in terms of age ($p=0,23$), sex ($p=0,76$) and reported history of anaphylaxis ($p=0,23$).

Mean wheal diameters towards raw CwM, α -lactoalbumin, β -lactoglobulin and caseins resulted significantly larger in the CM SPT+ group than in the CM SPT- group (p-value of 0.026, 0.002, 0.001, 0.013 respectively). The mean IgE titers against raw CwM, α -lactoalbumin and caseins were significantly higher in the CM SPT+ group than in the CM SPT- group (p-value of 0.013, 0.007 and 0.005 respectively); instead the β -lactoglobulin IgE mean titer did not reach statistical significance between the two groups (p-value of 0.08). (Figure 1 and Figure 2).

When we compared the extent of the cutaneous reaction in response to raw CwM and CM in CM SPT+ patients. Mean wheal diameter towards raw CwM was significantly larger than that towards CM (mean 10.15 vs 5.2 millimeters, $p<0.0001$).

DISCUSSION

The prevalence of CwMPA is a significant public health issue; in fact it has increased over the last decades and the whose treatment implies the total exclusion of the intake of this protein [1]. The clinical use of milk originating from other mammalian has been proposed; however their protein sequences have been found sometimes to be homologous to that of CwM, which is why their use is not recommended in CwMPA patients [1,2]. So the homology between

different mammalian milk proteins and CwM proteins has been the major focus of many studies. Based on structural similarities, the highest homology, in percentage, is noted between CwM proteins and those of Bovidae (i.e., water buffalo, 96.1%), lower with that of Camelidae (the one humped camel Arabian camel, *Camelus dromedaries*, 60%), and least with human milk (58.4%) [7,14,19].

From a nutritional point of view, although with large seasonal variations, it contains approximately 3-3.9% of proteins, 1.2-6.4% of polyunsaturated fats and 4.4-4.9% of lactose. [20]. About protein components, the important data is that camel milk presents low quantities of β casein (Bos d8) and no β lactoglobulins (Bos d5) [17]. Compared to cow's milk, camel's milk contains fewer short chains of fatty acids and low carotene content. The average content of unsaturated fatty acids is around 43%, especially essential fatty acids, a further characteristic that makes it similar to the human one. Similarly to human milk the LC contains a good concentration of antimicrobial factors with bactericidal and fungicidal action such as immunoglobulins and lactoferrin, scarcely present in cow's milk [21]. Minerals and vitamins are comparable to cow milk.

The most recent medical literature reveals that cross-sensitization between CwM and CM is the least among animal milks. Restani et al. revealed that monoclonal antibodies specific for CwM proteins reacted with milk proteins of sheep, goats, buffalos, and others, but not those of the camel [7].

A study by El-Agamy et al. [14] revealed that when applying CM protein-specific antisera in immunoblotting analysis, there was no immunologic cross-sensitization between CM and CwM proteins. Furthermore, they obtained similar results when they tested sera from 40 CwMPA children, 6 months to 8 years old, for the specificity of their IgEs to CM. Authors attributed this no reactivity to dissimilarities between CwM proteins and CM epitopes. However it was an in vitro study and lacked clinical confirmation by SPT or oral challenge.

In children with suspected food allergy, SPT is very useful because it can help to detect an IgE-mediated sensitization to foods and predict the risk of immediate reactions after their ingestion [22].

Among the clinical studies Shabo et al. [12] recommended the use of the CM for children with CwMPA but, their study small sample (eight children), the demographic characteristics, type and severity of allergic disease, and the absence of any diagnostic allergic test (food allergen-specific IgE or SPT), made that data be rather anecdotal.

In a study by Katz et al. [13] there were no data on two-thirds (16 of 24 subjects) of subjects regarding CM SPT status. Of the remaining eight patients, only two (25%) had positive SPT to CM.

Ehlayel et al. showed that 80% of their CWMA children were CM SPT- and they have been safely given CM without any reaction. Furthermore they did not find any statistically significant difference in CwM specific IgE titers between the two groups (CM SPT+ and CM SPT-) [15]. The most recent study of Rodriguex et al, in 15 patients with CwMPA, diagnosed with double-blind, placebo-controlled food challenges (DBPCFCs), showed that CM is safe and tolerable on patients above one year of age with CwMPA [16]. Throughout the literature data, we found only one reported case where a patient with CwMPA suffered from anaphylaxis with CM [21].

Our clinical study reveals low cross-allergenicity (31,3%) between CM and CwM proteins on the basis of the SPT, confirming low cross-sensitization of the *in vitro* studies [7,11]. Furthermore differences between CM SPT+ and SPT- groups resulted statistically significant for both the mean wheal diameters of each antigen tested and their mean specific IgE titers, except for the β -lactoglobulin IgE titer. This is reasonable considering the complete absence of the β -lactoglobulin in the CM.

According to our results larger wheals at the SPT and higher IgE titers against CwM antigens

(except for the β -lactoglobulin) could predict cross-sensitization and, consequently, patients SPT positivity to CM.

Additionally, patients with CwMPA who cross-reacted to CM showed a milder positivity to CM than CwM at the SPT. This result let us hypothesize a higher tolerance and lower antigenic power of CM, even in patients with CWMA and cross-sensitization to CM.

The strength of our study is that it is a cohort, prospective, clinical study on a relatively medium-sized sample. However, it has some limitations: subjects with negative SPT to CM were not fed with it to clinically confirm their lack of reactivity, those with positive SPT to CM were not evaluated by a formal, supervised, titrated, oral challenge test (e.g., DBPCCFCs). It also did not have any in vitro part to define the similar and/or dissimilar parts of the CwM and CM proteins using the sera of our subjects.

CONCLUSIONS

In summary, this study confirms the presence of cross-sensitization between CwM and CM that remains, however, lower if compared to other mammalian milks.

For these reasons CM could be a possible substitute of CwM in children with CwMPA. Small wheals at the SPT towards CwM antigens together with low IgE titers against them could work as predictors in selecting patients that are expected to have negative CM SPT and then could be fed with CM with lower risks of allergic reactions.

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LEGEND FIGURE

Figure 1: Mean wheal diameters in the two groups

Figure 2: Mean IgE Titers in the two groups