Allergenicity of a whey hypoallergenic formula in genetically at risk babies: four case reports

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Abstract. – Background: Hydrolysate formulas (HF) have been developed with the goal of reducing the allergenicity of cow’s milk (CM) proteins, thus providing a suitable formula for feeding babies with CM allergy (CMA).

Objective: More recently, whey HFs have provoked 208 reactions in babies at high risk of atopy when given for CMA prevention.

Material and Methods: We report the clinical and immunologic findings of four babies apparently sensitized by a partially whey hydrolysate formula (PWHF) in the nursery. They were exclusively BM (breast milk)-fed by their mothers avoiding highly allergenic foods, but experienced anaphylaxis after a re-feeding with the PWHF.

Results: Sensitization to PWHF seems to have occurred in the first days of life. No baby suffered from allergic symptoms during BM-feeding.

Discussion: These case reports suggest that a PWHF may be allergenic not only in an already sensitized subject, but also sensitizing in a genetically predisposed baby being immunogenic in the IgE system. These data strongly indicate that maternal diets during BM-feeding, in two instances suggested by family doctors, are effective as a BM complement.

Key Words: Neonates, Infants, Atopy, Cow’s milk allergy, Partially whey hydrolysate formula, Anaphylaxis, Emergency department.

Introduction

Hydrolysate formulas (HFs) are obtained by changing the primary structure or the conformation of cow’s milk (CM) proteins by enzyme hydrolysis and heat treatment. Depending on the degree of hydrolysis, HFs can be extensively (EHF) or partially (PHF) hydrolyzed. HFs have a substantial amount of peptides with MW (molecular weight) higher than 5 kD, and even higher than 15 kD, carbohydrates, and a mixture of vegetable oils.

In total, we have recently reported 208 reactions to HFs. Notably, we first described 5 exclusively breast milk- (BM)-fed infants aged 3-8 months (median 5 months) with IgE-mediated cow’s milk allergy (CMA), who experienced anaphylactic reactions when first fed a small amount of a partially whey hydrolysate formula (PWHF). All infants had AD (atopic dermatitis) during BM feeding, positive SPTs and RAST to CM proteins and to the HF; total IgE levels ranged from 45 to 2,990 U/ml. Several additional reports have demonstrated that CM-based HFs can trigger allergic reactions in children with CMA.

Case Reports

The first case, a 3.5-month-old male baby, was born after a normal pregnancy and delivery. In the neonatal nursery he received a few feedings of a PWHF since he had a genetic risk of atopy, being his father allergic to grass pollen, and his mother and older sister to CM. Subsequently to his discharge, he was exclusively BM-fed and his mother completely avoided CM and dairy products for the prevention of CMA at her doctor advise. However, when the healthy baby was 4 months old and BM-feeding was terminated, feeding of the same PWHF was decided. During the first feeding, the infant elicited an anaphylactic shock. Instantly, he received epinephrine, diphenhydramine and hydrocortisone at the Emergency Department and the shock subsided within minutes. After 24 hours, when he still was in the hospital, under strict medical supervision and with emer-
emergency treatment at hand, a drop of the same PWHF was put upon the inner border of his lower lip. Immediately the boy developed lip swelling, generalized urticaria and difficulty in breathing, requiring prompt administration of epinephrine and diphenhydramine in the hospital emergency room.

The second case was a 3-month-old male baby who was born after a normal pregnancy and delivery. During his first three days of life because of a positive family history of atopy due to allergic asthma and rhinitis of his father and CMA of his sister, he received a few PWHF feeds. When discharged he was totally BM-fed and his mother completely avoided CM and dairy products for food allergy (FA) prophylaxis. When the baby was 4 months old and still wholly BM-fed, he received a feeding with the same PWHF. At once, he manifested a generalized urticarial rash, lip edema and anaphylactic shock. Admitted to the Emergency Department the boy was administered epinephrine, antihistamines and corticosteroids. The allergic symptoms abated within 2 hours.

The third case was a 4-month-old female infant, who was the product of an uneventful pregnancy and delivery. Because she was at high risk of atopy due to her father and paternal grandfathers with house-dust-mite (HDM) allergy, and a brother with CMA, a PWHF was given in the nursery. Thereafter, the baby was exclusively BM-fed and his mother totally avoided CM and dairy products during the period of lactation, for the prophylaxis of CMA. The baby was healthy until 2 months and 15 days when, within a few minutes after the ingestion of a few drops of the same PWHF, explosive vomiting, generalized urticaria-angioedema, wheezing and cyanosis occurred. The baby was taken to the Emergency Department where epinephrine, diphenhydramine and hydrocortisone were administered. All acute allergic symptoms disappeared within 2 hours.

The fourth case was a 5-month-old female infant, who was born after a normal pregnancy and delivery. As the previous reported three infants, she was genetically at risk of atopy (mother and maternal uncles with HDM allergy, and father with pollen allergy) a PWHF was given in the nursery. Later, the girl was exclusively BM-fed and her mother also totally avoided CM and dairy products during BM-feeding for atopy prevention as suggested by family doctor. The girl was healthy until 5 months when, after the feeding of a small quantity of the same PWHF, cyanosis, generalized urticaria, and wheezing developed. Happily enough, the father had some epinephrine for personal use, which was immediately injected to the baby. Subsequently, she was admitted at the Emergency Department where she received additional epinephrine, and also diphenhydramine and hydrocortisone were required. All acute allergic manifestations elapsed within 40 minutes.

After the severe anaphylactic episodes, the babies were referred for evaluation to our Division and were successfully fed a soy-protein-formula. Informed consent was obtained from parents of each child.

Methods

Skin prick tests (SPTs) were performed by the prick method on the volar surface of the forearm. The babies were tested with histamine hydrochloride (1 mg/ml) as a positive control and isotonic saline as a negative control. We continued with a battery of foods, such as: whole CM protein, casein, lactalbumin, and the PWHF in the recommended ready to eat concentration which was further diluted with water to one part per hundred (1:100). In addition a SPT with the BM of their own mother was done. The diagnostic extract of each individual allergen was placed on the volar surface of the forearm as drops through which the skin was superficially pricked with a straight pin. A new pin was used for each SPT and then discarded, and the drop of the extract was then wiped off about one minute after the prick. SPTs were read at 20 minutes and considered positive as follows:

+ when the wheal was the half of the histamine wheal;
++ when the wheal was equal to the histamine wheal;
+++ when the wheal was two-fold the histamine wheal;
++++ when the wheal was more than two-fold the histamine wheal.
We took for positive only children with a +++ or ++++ reaction, that is a wheal $\geq 3$ mm with an area $= 7$ mm$^2$ (cut-off). So we considered as positive only the children with a mean wheal diameter of 3 mm or larger than the negative (saline) control. A positive (histamine, 1:1000) control was performed to ensure the absence of any antihistamine drug interference$^{17}$.

**Results**

Physical examination of the infants at the age of 4-5 months revealed no abnormal findings; weight and height were both at the 50th percentile.

SPTs results.

There was a remarkable skin reactivity to casein (++++) and lactalbumin (+++), and a strongly positive SPT reaction to the 1:100 dilution of Nidina HA (++++). SPTs to BM were negative.

**Discussion**

The findings of this study show that four wholly BM-fed babies were urgently admitted to hospital emergency rooms having experienced anaphylaxis when fed a PWHF. The sensitization seems to have occurred in the very first days of life as a result of some feeds in the nurseries with the PWHF, which was given again at 2-5 months of life for CMA prophylaxis. While we cannot confirm that the babies were targets of pirate bottles, nor we analyzed BM samples for the presence of CM proteins, we emphasize that no mother consumed any CM and dairy products during BM-feeding, thus excluding a sensitization via BM. Although the babies were healthy during BM-feeding and did not show any symptom or sign suggestive of CMA, they presented with highly positive SPTs to the PWHF. A notable instance was the doctor interventions to suggest an atopy prophylaxis by feeding an HF, and the presence of epinephrine in one house.

We have investigated the immunogenicity in the IgE system of a PWHF, 400 ml daily of which were given to 39 mothers of HR babies during the lactation period, while 39 control mothers of HR babies consumed 400 ml daily of CM. Although there was no significant difference in both the incidence and prevalence of CM-induced AD and of CMA in the babies at 0.5 and 1 year of age, according to the mother’s diet, the number of babies with IgE antibodies to CM and with total IgE levels more than 2SD for normal values for age were significantly higher in the group of babies whose mothers received the HA formula ($p = 0.02$). We may speculate that when a mother drinks this product, a large amount of immunogenic peptides are easily absorbed through the intestinal mucosa, thus rapidly reaching the breast and then presented to the T and B cells of her baby$^{18}$.

Taken together, the cases presented in this study add to a meta-analysis of 70 diverse reactions to either extensively or partially WHFs in children aged one month-15 years, detailing one case of shock, ten of anaphylaxis, 13 systemic reactions, and two apparent life-threatening events$^{3}$, to a submitted paper with 41 more cases$^{19}$, and to two babies included in an allergy prevention$^{20}$. These data and the two case reports show that such PWHF seems to be more immunogenic in the IgE system than CM$^{20}$.

We stress the malpractice of giving CM feedings in the nursery to at risk neonates. Several studies have highlighted the sensitizing role of early exposure to CM formula$^{21-25}$. Høst et al$^{22}$ support this hypothesis, since they reported that only the 39 fully BM-fed babies who developed adverse reactions to CM, none of whom had symptoms at the first exposure to CM, received CM supplements in the nursery.

de Boissieu and Dupont have added nine more reactions to an extensively hydrolysate formula in infants aged 2.4 ± 0.8 months who all presented with digestive symptoms$^{13}$ and we have published 202 reactions to HF formulas, 70 of whom in PWHFs$^{3}$. A 12-month-old girl had SPT reactions to Profylac, Nutramigen, and Neocate, besides being positive in RAST to Nutramigen$^{26}$.

We conclude that such PWHF is very allergenic, especially for allergic children and high-risk babies. Moreover we suggest that double-blind placebo-controlled food challenges studies in larger cohorts of babies evaluated with well-defined and well-validated diagnostic methods should establish a more reliable prevalence of HF allergy$^{21,22}$. 

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References


