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Human milk fortifier in preterm babies: source of cow's milk protein sensitization?

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Key words: cow's milk allergy; human milk fortifier; human milk supplements; premature infants.

We report the cases of three preterm infants who presented signs suggestive of sensitization to cow's milk protein after supplementation of their mother's milk with a human milk fortifier (Table 1).

Cow's milk protein allergy (CMA) affects 2–7% of the pediatric population and the incidence is increasing. Symptoms usually appear during the first months of life and occasionally in the neonatal period for term and preterm infants (1–3). When preterm babies are fed human milk (HM), it is recommended to add commercially available fortifiers to meet all specific nutritional needs. In North America, these fortifiers are

generally produced from cow's milk nonhydrolyzed proteins.

The relationship between the use of a human milk fortifier and the symptoms evocating cow's milk protein sensitization has not, to our knowledge, been previously reported despite its extensive use in neonatal units. The product contains: 'Nonfat milk, corn syrup solids, whey protein concentrate, and MCT oil (fractionated coconut or palm kernel oil)' as sources of proteins, fat, and carbohydrate (Abbott Laboratories Pediatric Nutritional Products Guide, DIR/98A08, 2008, Mississauga, Canada). The corn syrup solids are the sole source of carbohydrates and do not contain proteins (id). Casein represents 80% of milk protein and is the major allergen in CMA.

In the neonatal period, cases of CMA are increasingly recognized including in premature infants (1, 2). Precocious exposure to cow's milk proteins increases the risk of developing CMA (4). The immature intestine has an increased permeability, especially in preterm babies, as integrity of the intestinal epithelium is affected by multiple factors (feeding restrictions, ischemic injuries, and high production of free radicals). One can therefore postulate that premature infants are at increased risk of exposure to food allergens and development of food allergy (such as CMA).

The oral challenge to diagnose CMA carries risk of significant allergic reactions which prohibits its systematic use in newborns and even more so in premature infants. Therefore, the diagnosis of CMA in the neonatal period is essentially based on the clinical response to the elimination of the allergen from the diet. The eosinophil count is not currently considered to be a significant adjunct to diagnosis of food allergies in young children, although a relationship between increased serum concentrations of IL-5 and marked eosinophilia in an infant with CMA has been reported (5). Transient eosinophilia can be present in prematurely born infants during the first month of life, has been associated with inflammation states [infection, necrotizing enterocolitis (NEC)] and transfusions, and is often considered

nonspecific (6). In the presented cases, eosinophilia correlated with the clinical symptoms; whether eosinophilia could be an adjunct for the diagnosis of CMA in premature infants remains to be demonstrated.

Even though CMA is reported in exclusively breastfed infants (3), the concentration of cow's milk protein is several magnitudes less, which might explain the fact that the presented cases tolerated breast milk without modification of the mother's diet. We conclude that even if HM is the preferred alimentation for premature babies, added supplements might expose the susceptible infants to high concentrations of allergens, such as nonhydrolyzed cow's milk protein.

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Table 1. Description of reported cases

	Case 1	Case 2	Case 3
Gestational age (weeks and days)/ birth weight	28 ⁺⁶ /1145 g	27 ⁺⁰ /910 g	25 ⁺⁴ /710 g
Start of enteral feeds, with HM	Day 2	Day 2	Day 2
Human milk fortifier added	Day 10	Day 32	Day 20
Clinical manifestations			
Symptoms	Day 14: distended abdomen, grossly bloody stools	Day 41: grossly bloody stools.	After Day 20: developed persistent abdominal distension
Abdominal X-ray	Mild, diffuse, small bowel distension; no pneumatosis	Unremarkable	
Biology	Blood eosinophils 1800/mm ³ , 16% of WBC	Day 36: eosinophils 1400/mm ³ (8% WBC). Day 41: Eosinophils 2700/mm ³ (16% WBC)	Progressive eosinophilia up to 3300/mm ³ (24% WBC) on Day 35
Diagnosis	NEC Bell stage 1	NEC Bell stage 1 / suspicion CMA	Suspicion CMA
Treatment/evolution	NPO, iv ampicillin and gentamicin Day 16: enteral feed restarted with HM alone Day 25: eosinophils 600/mm ³ (4% WBC). Day 28: fortifier added again to HM	NPO, iv ampicillin and gentamicin. Day 44: enteral feed restarted with HM fortified with aminoacid formula (Neocate [®] ; Nutricia North America-Canada, St-Laurent, QC, Canada), without modification of maternal diet. Digestive symptoms did not recur Day 49: eosinophils 1600/mm ³ (8%) Day 79: eosinophils 384/mm ³ (4%)	Day 35: fortification of HM changed to Nutramigen [®] (Mead Johnson Nutrition, Montreal, QC, Canada) without modification of maternal diet. Abdominal distension resolved. Day 47: eosinophils 330/mm ³ (2% WBC)
Second acute episode			
Symptoms	Day 30, increased apnoeas and bradycardias, grossly bloody stools		
X-ray	Unremarkable		
Biology	Eosinophils 6900/mm ³ (40 % WBC)		
Diagnosis	Suspicion of CMA		
Treatment/ evolution	Day 34: enteral feed restarted with HM fortified with Nutramigen [®] , without modification of maternal diet. Digestive symptoms did not recur Day 42: eosinophils 1000/mm ³ (10% WBC)		
Diet upon discharge home	Day 51: HM only	Day 73: HM and Neocate [®]	Day 80: HM and Nutramigen [®]

HM, human milk (own mother); WBC, total white blood cell count; NEC, necrotizing enterocolitis; CMA, cow's milk allergy; NPO, no enteral feeding.

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