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Different clinical manifestation of cow's milk allergy in two preterm twins newborns

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Adverse reactions to cow's milk in the first year of life occur in 2–7%. There is an increase in the incidence of cow's milk protein allergy (CMA) in newborn population including premature infants. We report two cases of CMA in preterm twins. The first one developed recurrent episodes of proctocolitis and the second one two necrotizing enterocolitis (NEC) -like episodes. Our cases demonstrate different clinical presentations of the same disease and add to literature the peculiarity of the early onset, the recurrence of episodes of enterocolitis associated with increasing systemic eosinophilia and episodes clinically and radiologically mimicking NEC.

Keywords: allergic enterocolitis, allergic proctocolitis, cow's milk protein allergy, NEC, preterm

Introduction

Adverse reactions to cow's milk in the first year of life occur in 2–7% [1]. Symptoms often appear during the first months of life, with cutaneous, gastrointestinal and respiratory symptoms, even in exclusively breast-fed children [2,3]. There is an increase in the incidence of cow's milk protein allergy (CMA) in newborn population including premature infants [2]. We report two cases of CMA in preterm twins: the first one developed recurrent episodes of proctocolitis and the second one two necrotizing enterocolitis (NEC) -like episodes.

Case report

Two preterm female twins were born at $30th^{+5}$ week of gestation by caesarean section. The first born (FS) had a birth weight of 965 g and an Apgar score of 7^{I} and 9^{V}. The second born (AS) with a birth weight of 1340 g had an Apgar score of 8^{I} and 9^{V}. Both of them presented respiratory distress at birth and were treated with surfactant and then with nasal continuous positive airway pressure for about 3 days. They were fed with breast milk since the first day of life (DOL) and with fortified human milk since the 8th DOL. Both developed CMA with two different clinical presentation: the first one with recurrent episodes of proctocolitis and the second one with two NEC-like episodes.

The first twin FS, on DOL 10, presented lethargy, vomiting, abdominal fullness and massive bloody mucous stools. Blood cell count, C-reactive protein and abdominal X-ray were normal. Enteral feeding was stopped and in few days bleeding showed a gradual resolution. Breast milk feeding was restarted on day 21 and it was well tolerated. Radioallergosorbent test (RAST) analysis made on day 27 was negative. After 35 days from restarting enteral nutrition, bleeding reappeared. No changes occurred in clinical, laboratory and imaging findings except for eosinophils count (20.3%) and RAST positivity to β- and α-lactoglobulin. Enteral feeding was again stopped and the infant's symptoms settled. Few days later an amino acid-based milk, Neocate, was introduced with excellent results. FS showed good clinical conditions and she started to gain weight. The baby was discharged and 2 months follow-up reported good clinic condition and appropriate neurodevelopment outcome.

The second infant AF, on DOL 10, 2 days after human milk fortified introduction, developed abdominal fullness and positive fecal occult blood test. Abdominal X-ray was remarkable for the presence of nonspecific diffusely dilated bowel loops. On DOL 14, enteral feeding was stopped because of the onset of feeding intolerance, diffuse abdominal distension and pain, with pre-NEC signs at abdominal X-ray. Laboratory tests including total white cells count, blood and stool cultures were all in normal range. After elimination of enteral feeding, clinical condition improved, fecal occult blood test returned negative and enteral feeding with breast milk was resumed on DOL 20.

Seven days after resuming enteral feeding (DOL 27), the baby developed again abdominal distension, hypotonia, lethargia and episodes of bradycardia. Positive fecal occult blood test was found and abdominal X-ray showed diffuse pneumatosis. A repeated sepsis evaluation and the stool cultures were all negative. NEC diagnosis was made (stage 2A). The baby was managed medically with antibiotics, gastrointestinal decompression and parenteral nutrition. Clinical and radiological signs over the next several days, showed a normal abdominal X-ray on DOL 33. The WBC was showed marked eosinophilia (17.7% eosinophils). On suspicion of allergic enterocolitis, RAST analysis was performed showing a positivity to β-lactoglobulin (0.30 kUA/l; negative <0.1 kUA/l). After the resolution of this episode and considering the blood parameters, the baby was switched to amino acid-based milk formula (Neocate) like her sister. AF developed two clinical episodes of allergic enterocolitis mimicking NEC with definitive pneumatosis on abdominal X-ray. The baby was discharged with Neocate milk and 2 months follow-up reported good clinical condition, without gastrointestinal problems and appropriate neurodevelopment outcome.

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Discussion

Milk protein allergy is the most common food allergy in infants and young children [4]. Most infants with allergic proctocolitis show symptoms between 1 and 6 months of age and are predominantly term infants [5].

Cases of CMA are increasing in newborn population including premature infants [2]. The risk of developing CMA is due to precocious exposure to cows milk proteins and in many cases, to cow's milk proteins transferred via breast milk [4,6]. The immature intestine, especially in preterm babies, is exposed to multiple aggressive factors (such as feeding restrictions and ischemic injuries) that could damage intestinal epithelium and make it more vulnerable to allergenic agents. Allergic enterocolitis presenting as a recurrent NEC in preterm neonates was reported by Srinivasan et al. According to this report, we suppose that premature infants are at increased risk of exposure to food allergens and development of food allergy and that the early onset is secondary to intrauterine sensitization [7].

Most common symptoms of this disease include bloody stools (often mixed with mucus), abdominal distension (from flatus and third spacing) and irritability [7].

The diagnosis of CMA in the neonatal period is essentially based on the clinical response to the elimination of the allergen from the diet. Atopy patch test could help in detecting CMA with high specificity and poor sensitivity. Together with prick testing and serum specific IgE assay, a positive predictive value of about 95% can be obtained [8]. The oral challenge to diagnose CMA cannot be performed in premature infants and in neonatal age because of its risk of significant allergic reactions. Therefore, the eosinophils count is not currently considered to be a significant adjunct to diagnosis of food allergies in young children.

Our cases showed different clinical presentations of the same disease in two preterm twins newborns. The first twin presented an allergic proctocolitis (APC). The diagnosis of APC is commonly based on clinical features and on the response to maternal avoidance of the offending proteins. Endoscopical examination is helpful in refractory cases to exclude other causes, explaining symptom persistence, different from APC [4]. Symptoms such as rectal bleeding generally resolves within 72–96 hours of cow's milk protein maternal avoidance.

The second twin presented symptoms of allergic enterocolitis which is generally a benign condition; however, our case manifested episodes of clinical and radiological findings mimicking NEC. This condition observed in our twins is not well documented and does not seem to affect NEC clinical trials [9].

Cow's milk induced enterocolitis in preterm infants has rarely been reported in literature [5]. Similar symptoms are sometimes associated with the initial presentation of NEC in preterm neonates. In our cases, both infants were exposed to human milk fortifier some days before manifesting CMA.

Transient nonspecific eosinophilia, which can be present in prematurely born infants during the first month of life, has been associated with inflammation states (infection, NEC) and transfusions [10].

When eosinophilia is associated with clinical and radiological findings of NEC, even in breast-fed newborns, RAST analysis for cow's milk proteins should be performed to exclude allergic enterocolitis mimicking NEC. Our case adds to literature the peculiarity of the early onset of this disease and the recurrence of episodes of enterocolitis associated with increasing systemic eosinophilia.

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