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Case report

Allergic enterocolitis in a preterm newborn

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Abstract

We report the case of an infant born at 28 weeks of gestation with a history of intestinal dysmotility over the first week of life, which was solved with the introduction of erythromycin. The infant was fed with breast milk and sporadic doses of special formula for preterm newborns. On the 17th day of life, post conceptional age of 30 weeks, she presented an episode of necrotizing enterocolitis treated with antibiotics. On the 45th day of life, post conceptional age of 34 weeks, the infant presented episodes of apnea, hemodynamic instability, abdominal distension, vomiting and mucous and bloody stools. Owing to the suspicion of a new episode of necrotizing enterocolitis, feeding was stopped and antibiotic therapy was started. Hypereosinophilia was detected in peripheral blood and tests were positive for specific IgE antibodies to cow's milk proteins. Antibiotics were stopped after negative sepsis workups and feeding with breastmilk and extensively hydrolyzed formula was resumed. The newborn presented with good tolerance.

Diagnosing allergy to cow's milk protein in a newborn infant requires a high degree of suspicion, as it presents with non-specific symptoms. In most cases it manifests as non-IgE-mediated proctocolitis and cases of enterocolitis with specific IgE antibodies to cow's milk proteins are rare. Some authors argue that the development of cow's milk protein allergy requires an immunological maturation level not present before a gestational age of 30-32 weeks. Therefore, in preterm newborns, there may be an asymptomatic period of life with subsequent development of an allergy. In the case described, the diagnosis of IgE-mediated cow's milk protein allergy was confirmed at 34 weeks of post conceptional age. However, the question remains whether the previous digestive symptoms were related to the allergy subsequently diagnosed.

Keywords

Allergy, cow's milk, IgE-mediated, enterocolitis, preterm newborn.

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Introduction

Food allergy is a major public health problem affecting individuals of all age groups. Cow's milk protein allergy (CMPA) is the most common food allergy in infants [1, 2], with a prevalence of 2% to 3% [1, 3]. It has been reported in a small series of hospitalized newborns (NBs) [4, 5], but its exact prevalence in this age group is unknown [4].

Most neonatal milk allergies are non-IgE-mediated and are classified according to symptoms into food protein-induced allergic proctocolitis (FPIAP), food protein-induced enterocolitis syndrome (FPIES) and food protein-induced enteropathy (FPE).

FPIES, FPIAP and FPE are part of a group of immune-mediated reactions to food that are thought to occur primarily via non-IgE-mediated pathways. All of them are typically infancy disorders characterized by gastrointestinal symptoms in the absence of respiratory and cutaneous findings seen in IgE-mediated food allergies. The most common triggers are cow's milk (CM) and soy, although a variety of other foods may also be triggers [6, 7].

FPIAP is a benign transient condition, which typically starts in the first few months of life, manifesting with blood-streaked and mucus stools in otherwise healthy appearing infants [6, 7].

FPE manifests with chronic diarrhea, malabsorption, vomiting and failure to thrive. In FPE, laboratory tests and endoscopy with biopsy are important to confirm the diagnosis and to distinguish this clinical condition from other causes of failure to thrive and diarrhea in infants [6].

FPIES represents the severe end of the spectrum of food protein-induced gastrointestinal diseases in infants. Symptoms usually start in early infancy, within one to four weeks following introduction of CM or soy protein. The usual presenting features are vomiting with lethargy and dehydration. Its onset may be either insidious with chronic exposure to the inciting food, or more acute, presenting 1-3 h after ingestion if exposure is intermittent [6, 7]. Though serum food-IgE testing and skin prick tests (SPT) are negative in the majority of FPIES cases, concomitant IgE sensitization to inciting foods is seen in up to 25% of FPIES patients and is referred to as atypical FPIES [6]. Laboratory studies reveal anemia, hypoalbuminemia and elevated white blood cell count with a left shift and eosinophilia in patients with chronic FPIES. Peripheral blood neutrophil counts are usually elevated in positive challenges (acute FPIES) peaking at 6 hours, and returning to baseline within 18-24 hours. Stool studies in symptomatic infants may reveal leukocytes, occult blood and eosinophils [6, 7].

CM-induced enterocolitis presenting in the neonate as early as the first week of life has been cited in some case reports [8-15] and surveys [16], in term and preterm NBs. In some of the reported cases the allergy is IgE-mediated [10, 11, 15, 16] and sometimes the symptoms start prior to any oral intake [12, 15, 16]. This very early form of allergic enterocolitis suggests intrauterine sensitization due to either CM antigen present in the amniotic fluid or antigen crossing the placenta to elicit an allergic response in the fetus.

Diagnosing CMPA in a NBs requires a high degree of suspicion as symptoms are nonspecific and common to other more frequent diseases, such as sepsis, necrotizing enterocolitis (NEC) and surgical conditions [2, 4].

CMPA is generally a benign condition, persisting in a minority of children. The prognosis depends on a positive screening for specific IgE at the time of diagnosis [1, 17-19]. A positive atopic family history, early respiratory or gastrointestinal symptoms as well as severe symptoms at diagnosis are also risk factors for allergy persistence [20].

Clinical case

A female preterm infant was delivered by normal labor at 28 weeks gestation with a birth weight of 1,030 g. The mother's prenatal screening serological tests were negative. The baby was admitted to the Neonatal Intensive Care Unit (NICU) and ventilatory support and antibiotics were started. Trophic feeds were given on the second day of life (DOL 2) with breast milk (BM). She developed a clinical picture suggestive of intestinal dysmotility which justified the introduction of erythromycin at the end of the first week of life. BM feedings were advanced with

sporadic intakes of special formula for preterm NBs after DOL 14.

On the DOL 17, post conceptional age of 30 weeks, the NB developed abdominal distension, mucus in stool, biliary vomiting and cardiorespiratory instability. Blood count was normal and maximum C-reactive protein was 14.16 mg/L; the abdominal X-ray showed diffusely dilated bowel loops and intestinal wall edema. The NB was made nil per os and parenteral nutrition and antibiotics were started. She was treated with amikacin and vancomycin for 14 days as *S. epidermidis* was isolated in blood culture. There was progressive improvement and oral feeding was restarted on the DOL 22, with BM and sporadic doses of special formula for preterm NBs, without complications.

On the DOL 45, post conceptional age of 34 weeks, she started new episodes of apnea, hemodynamic instability, abdominal distension, vomiting and bloody and mucous stools. Abdominal X-ray showed gaseous distension and intestinal wall edema without pneumomatosis. As a new episode of NEC was suspected, oral feeding was once again stopped and vancomycin, amikacin and metronidazole were started. These were suspended after septic screenings series and negative blood culture. The blood cell count revealed leukocytosis (25,120/μL) with hypereosinophilia (49% eosinophils – 12,310/μL, 17% neutrophils – 4,270/μL and 29% lymphocytes – 7,280/μL). Total IgE was 11 kU/L (UniCAP®).

The diagnosis of CMPA was considered at this point, and subsequently confirmed by positive tests for specific IgE antibodies to CM proteins (CMP) – IgE α-globulin 0.5 kUA/L and IgE β-globulin 3.13 kUA/L (UniCAP®). Specific IgE casein was negative – 0.17 kUA/L (UniCAP®).

Feeding was resumed with BM and alternatively with extensively hydrolyzed whey formula, without complications. The infant was discharged on the DOL 60, post conceptional age of 37 weeks, with a weight of 1,890 g and eosinophils had dropped to 2,550/μL. She was referred to Pediatric Gastroenterology consultation.

Discussion

Diagnosing CMPA in NBs can be difficult owing to its non-specific clinical picture [1, 4, 16] and the absence of confirmatory laboratory test for non-IgE-mediated food allergies [1]. The presence of eosinophilia in feces and peripheral blood is related to CMPA [21] so neonates with bloody stools and eosinophilia are more likely to have atopic enteropathy than NEC. However, eosinophilia lacks specificity and cannot exclude NEC from the differential diagnosis, therefore these patients should be managed aggressively until the diagnosis of NEC is firmly rejected. In their research, Christensen and colleagues [8] found that a large number of NBs with bloody stools and eosinophilia had a recent history of red blood cell transfusion. They realized that red blood cell transfusion is linked to the development of NEC and a poor prognosis. In non-IgE-mediated allergies, the improvement of symptoms after eviction of the allergen and a positive oral challenge test confirm the diagnosis [1, 4, 22]. Performing an oral food challenge (OFC) test in NBs is controversial, given the possibility of inducing severe symptoms [4, 16], which further hinder diagnosis.

In this case, the clinical manifestations without laboratory confirmation of infection and severe hypereosinophilia suggested the diagnosis. This was confirmed by positive testing for specific IgE antibodies to CM protein and supported by the favorable evolution following its restriction.

In a retrospective study [4], comparing the clinical characteristics of CMPA in preterm and full-term NBs, conducted in a neonatology unit, Yoshinori et al. concluded that although there are no differences between the two groups in the allergy symptoms presented, there is a significant difference in the average postnatal ages of symptom onset. In this study, all preterm NBs developed symptoms compatible with CMPA after 32 weeks of post conceptional age, the authors arguing that the development of CMPA requires an immunological maturation level present only at a gestational age of 30-32 weeks [4]. Therefore, in preterm NBs, there may be an asymptomatic period of life with subsequent development of an allergy. In the present case the diagnosis of IgE-mediated CMPA was confirmed at 34 weeks. The question remains if the previous digestive symptoms were already related to the undiagnosed allergy.

CMPA is less frequent in infants fed exclusively with BM [19]. In these, the symptoms are scarcer as concentration of CM proteins in BM is 100,000 times lower than in infant formulas [19]. In breastfed NBs with CMPA, it is recommended that the mother should avoid dairy products. Mothers who exclude dairy products should be evaluated for their own need for calcium and vitamin D supplementation [2]. They will require calcium

supplements during the milk-free diet (1,000 mg/day divided into several doses) [1, 20]. NBs not exclusively fed with BM should be fed with extensively hydrolyzed formula (EHF) to ensure adequate nutrition and help develop immunological tolerance [1, 19]. In this case, although the NB was essentially fed with BM, sporadic doses of formula adapted to preterm infants were introduced in the second week of life, which may have been responsible for development of the allergy and the severity of the symptoms presented. The symptoms subsided with the restriction of dairy products in the mother's diet and when BM was not available, the administration of EHF.

EHF is defined by the American Academy of Pediatrics, as a formula containing only peptides that have a molecular weight of < 3,000 Dalton [1], but in practice 95% of peptides in this milk have a molecular weight below 1,500 Dalton and < 0.5% of the remaining peptides above 6,000 Dalton [23]. Owing to its low allergenicity this is an ideal formula for children with CMPA [24]. This formula accelerates gastric emptying and gastrointestinal transit and promotes gastrointestinal hormone secretion, thus reducing the incidence of gastro-esophageal reflux and food intolerance in preterm NBs and promoting a faster achievement of full enteral nutrition [24]. There is no consensus on whether low-energy low-protein EHF can fulfil the high nutritional needs of preterm children in the feeding period, and there are few studies on whether feeding with extensively hydrolyzed milk protein formula in the early stage of life will have any impact on the future growth and development of preterm children. Yin et al., in a recent randomized controlled clinical study [24], confirm that feeding preterm children with EHF during the NICU stay is safe and effective and does not affect the normal growth and development of preterm children in the early stage of their lives. Whether the extra-uterine growth restriction, observed in this case, may be related to the use of EHF or just with postnatal complications that this child has undergone is questionable. There are no conclusive studies on EHF efficacy in preventing CMPA [25, 26].

Determining specific IgEs for CMP is essential, not only to confirm diagnosis of IgE-mediated allergy, but also to provide guidance on the prognosis. Positive screening for specific IgE to CMP is associated with increased risk of persistent allergy, severe reactions, multiple food allergies and sensitization to inhalant allergens in the future [1, 2, 17-19] Reassessments must be conducted often to check the induction of tolerance to CMP [1, 2] and avoid inappropriate or unnecessarily long dietary restrictions, which reduce the quality of life, affect the child's growth and entail unnecessary health costs [1]. Most of the current guidelines on the diagnosis and management of CMPA propose a revaluation every 6-12 months and reintroduction of CM after a negative OFC [1, 2]. The quantification of CM IgE and the SPT provide useful prognostic information in the course of CMPA, give information about when to perform an OFC and about the appropriate time for CM reintroduction [27]. Children who grow out of CM allergy become tolerant to milk in baked form before fresh milk, because baking reduces protein allergenicity. Moreover, the addition of baked milk to the diet may accelerate the development of tolerance, including to fresh milk. Thus, reintroduction of baked milk is attempted before reintroduction of fresh milk. Once tolerance is established a greater exposure through ingestion of less processed CM, limited by the individual's tolerance, might be encouraged [2, 28].

Conclusion

The authors intend to point out the non-specific clinical picture in NBs of CMPA, which requires a high degree of suspicion for a correct diagnosis, especially in preterm newborn infants, who can present with an initial asymptomatic period due to immunological immaturity with subsequent development of the allergy.

Owing to the difficulty in diagnosing this entity, especially in preterm NBs and, given the role of EHF in gastric emptying and gastrointestinal transit [24], the authors address the potential pertinence of supplementary formulas with these characteristics for preterm NBs in need of supplementary formula.

Declaration of interest

The Authors declare that there is no conflict of interest.

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