

Refractory Proctocolitis in the Exclusively Breast-Fed Infants

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Abstract: The aim of this review was to help general pediatricians and primary care physicians in diagnosing and managing cow's milk protein allergy in exclusively breast-fed infants.

Allergic proctocolitis is a cause of rectal bleeding in exclusively breast-fed infants aged from 1 to 6 months. It is due to cow's milk protein transferred *via* breast milk. Diagnosis is based on clinical features and recovery after dietetic therapy. Rectal bleeding generally resolves within 72-96 hours of cow's milk protein maternal avoidance. Most infants tolerate cow's milk by their first birthday.

Keywords: Allergic proctocolitis, α -S1-casein, β -lactoglobulin, blood streaked stool, breast-fed infants, cow's milk proteins, non-IgE mediated immunologic reactions.

INTRODUCTION

The incidence of adverse reactions to food proteins in the exclusively breast-fed infant is poorly defined. Approximately 0.5 to 1% of exclusively breast-fed infants developed allergic reactions to cow's milk proteins (CMP) excreted in the mother's milk. Breast-fed infants appear to have a lower incidence of allergic reactions to CMP than formula-fed infants. This may be attributable to the relatively low level of CMP excreted in human milk, immunomodulatory substances present in human milk and differences in the intestinal flora between breast-fed and formula-fed infants [1, 2].

CMP allergy results from an immunological reaction to one or more milk proteins. This immunological basis distinguishes CMP allergy from other adverse reactions to CMP such as lactose intolerance. CMP allergy may be immunoglobulin E (IgE) mediated, non-IgE mediated, or a combination of both. It is estimated that up to 50% of pediatric cow's milk allergy is non-IgE mediated. Non-IgE mediated immunologic reactions include proctocolitis, food protein-induced enterocolitis and enteropathy syndromes [3-6].

Allergic proctocolitis (APC) is characterized by inflammatory alterations of the colon and rectum, secondary to an immune reaction triggered by the ingestion of foreign proteins [7]. A number of food (cow's milk, soy, fish, egg, wheat, *etc.*) have been associated to allergic colitis. Cow's milk is implicated in almost all cases. Approximately 60% of all cases of APC are found in breast-fed children. CMP are excreted in breast milk after the ingestion of dairy products by the mother. Cow's milk contains more than twenty five different proteins, but only whey proteins α -lactalbumin,

β -lactoglobulin, bovine serum albumin, and lactoferrin, as well as the four caseins, have been identified as allergens [8]. The most allergenic protein is β -lactoglobulin. Sorva *et al.*, [9] showed that β -lactoglobulin in human milk may contribute, but does not alone explain, the development of CMA in breast-fed infants. The most relevant finding was the detection of the intact bovine α -S1-casein in both term and preterm colostrum. According to study results of Orru *et al.*, [10], bovine α -S1-casein is considered a major cow's milk allergen, is readily secreted in human milk, and so could be considered a possible cause of sensitization in exclusively breastfed infants. The rest of affected proteins correspond to infants fed formulas containing CMP or soy [7]. Odze *et al.*, reported that up to 30% of all patients are allergic to both proteins [11].

The risk factors for the development of APC are an immature immune system, altered intestinal permeability and other factors that activate focal immune function, such as genetic susceptibility in combination with particularly sensitizing foods (milk, egg, fish, nuts, soy) [7].

IMMUNE MECHANISMS

Food proteins carried *via* breast milk can sensitize exclusively breast-fed infant, and then trigger a T lymphocyte-mediated allergen-specific immune response [12]. Delayed-type hypersensitivity reaction has been proposed as a pathogenetic mechanism of APC by Dargent *et al.*, [13]. Wilson *et al.*, suggested that an allergic reaction in the first week of life could be due to an intra-uterine sensitization, secondary to transplacental antigen passage [14]. Bone *et al.*, suggested both intestinal immaturity and marked eosinophilic infiltration, which may significantly alter tight junctions, lead to increased intestinal permeability to food proteins [7]. Eosinophils may be directly responsible for tissue injury in allergic colitis because they can bind IgA, which are normally present in breast milk, and undergo degranulation. The immature immune system fails to prevent the infiltration

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of eosinophils, leading to destruction of epithelial cells, which are responsible for clinical features [15].

CLINICAL MANIFESTATION

APC is a begin disorders. The clinical picture (Box 1) develops in the first weeks or months of life (practically always within the first 6 months of life). The symptoms are gastrointestinal and comprise rectal bleeding. Hemorrhage can range from small spots of blood mixed with the stools to abundant bleeding. Bloody stools can increase gradually [7]. The infant appears well, (aside from the bloody diaper) in contrast to infants with enterocolitis. Growth and weight gain are normal. Anal fissures or perianal dermatitis are absent. The abdominal examination results are benign. Abdominal distension and emesis are not present [16]. The laboratory test results are normal in most infants. A fecal smear generally contains increased polymorphonuclear cells in the mucus layer [16]. Odze *et al.*, [11] reported that fecal smears are routinely negative for eosinophils. Mild peripheral eosinophilia was demonstrated, occasionally with mild hypoalbuminemia in the two prospective studies by Odze *et al.*, and Machida *et al.*, [11, 17]. Mild anaemia can develop in infants with continued bleeding [18, 19].

DIAGNOSIS

Diagnosis is usually made through clinical history, careful physical examination and response to an elimination diet. Rectal bleeding generally resolves within 72-96 hours of cow's milk protein maternal avoidance. Exclusion of infection, necrotizing enterocolitis, intussusceptions or anal fissure, is essential. Colonoscopy and biopsy are not routinely recommended. Endoscopic biopsies show superficial erosions, eosinophilic infiltration and frequent lymphoid nodular hyperplasia. There are no correlation of nature of feeding (breast vs. formula) with the gross endoscopic findings [3, 12, 16, 20].

Lucarelli *et al.*, reported a series of 14 exclusively breast fed infants with histologically documented APC and persistent bleeding refractory to maternal dietary restrictions. They suggested that atopy patch test (APT) might become a useful tool to identify subgroups of infants with multiple gastrointestinal food allergies involving a delayed immunogenic mechanism, with the aim to avoid unnecessary maternal dietary restrictions before discontinuing breast-feeding [12].

Box 1. Key feature of refractory allergic proctocolitis in breast-fed infants

Usually presents from 1 to 6 months of life

Rectal bleeding, blood-streaked stools in healthy-appearing infants

Diagnosis is via clinical history

Treatment is via protein elimination; resolution of symptoms in 72-96 h

Tolerance to allergen usually occurs by 1 year of life

Arvola *et al.*, showed a study in which 40 infants with visible rectal bleeding were evaluated by colonoscopy. Cow's milk allergy was determined to be the cause of the rectal bleeding for 18% of the study population [21].

Xanthakos *et al.*, confirmed allergic proctocolitis via endoscopy and biopsy in only 14 of 22 (64%) healthy infants with rectal bleeding [22].

Pumberger *et al.*, performed colonoscopy in 5 of 11 breast-fed infants with rectal bleeding, revealing benign eosinophilic proctocolitis. They suggested the algorithm of diagnosis and treatment of blood streaked stool in early infancy Fig. (1) [20].

Anverden-Hertzberg *et al.*, also confirmed allergic proctocolitis by rectosigmoidoscopic in nine exclusively breast-fed infants [23].

TREATMENT

Treatment consists of eliminating the suspect proteins from the diet. In breast-fed infants, elimination of the cow's milk from the mother's diet usually will lead to gradual resolution of symptoms. If the condition does not begin to subside within 72 to 96 hours, a hydrolyzed protein infant formula should be considered (in about 7% of cases), and if this does not improve the situation then an elemental amino acid-based formula is indicated (in 5% of cases) [3, 7, 12, 16, 20].

According to the recent guidelines [6] in case of APC the elimination diet for the mother should be continued for a minimum of at least 2 weeks, and up to 4 weeks, but if an infant has no cessation of rectal bleeding after 4 weeks of maternal cow's milk-free diet then infant has no cow's milk allergy. Although bleeding clears within days, the endoscopic and histologic healing can take several weeks. Rechallenge of the infant with the offending protein in the first 6 months usually provokes recurrence of bleeding within 72 hours. Lake reported a study of 21 infants who continued to have bleeding despite maternal dietary restrictions and those whose mothers decided not to stop breast-feeding. Six of these infants developed iron deficiency anemia, despite iron supplementation, but they gained weight and had normal development. These infants were able to tolerate a regular diet by their first birthday [16]. The persistence of rectal bleeding despite maternal dietary restrictions may be explained by the inability to remove all sources of allergen from the diet or by an allergen that has not been identified [3].

Proctocolitis is a self-limiting disease in which the infants by one year of age are able to tolerate a free diet, and the long-term prognosis is excellent [16]. Lake showed that all breast-fed infants with dietary protein eosinophilic proctitis tolerated a normal diet after 1 year of age [2]. Of the 35 infants with breast milk protein-induced proctitis that Lake has observed for more than 10 years, none has developed inflammatory bowel disease [16]. The same observation has been published by Hill *et al.*, [24].

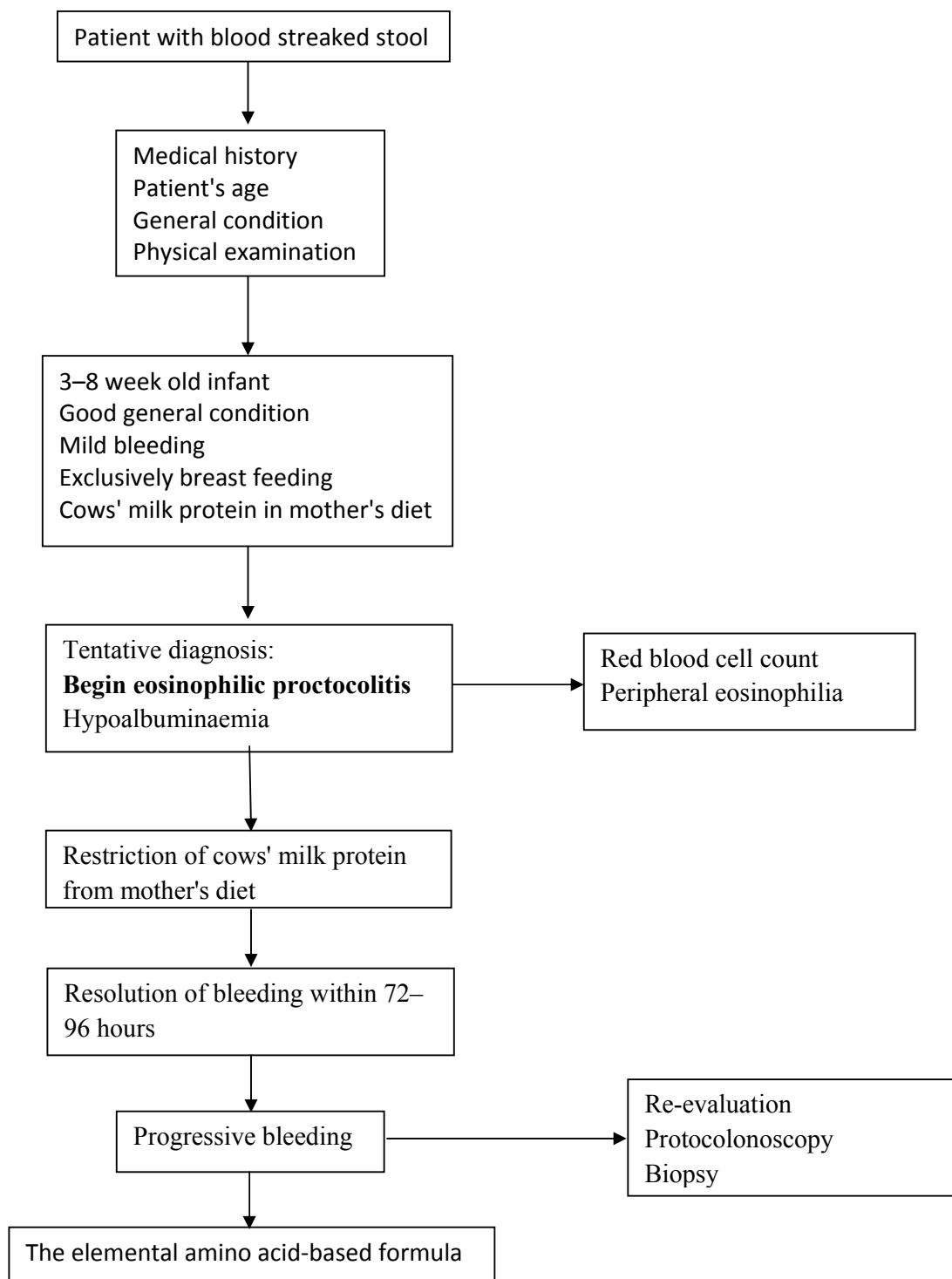


Fig. (1). The algorithm of diagnosis and treatment of blood streaked stool in early infancy.

CONCLUSION

APC is a begin disorders manifesting with blood-streaked stools in healthy-appearing infants who are breast-fed. Exclusion of cow's milk and dairy products from the diet of the mother is an effective therapeutic measure and breastfeeding should be maintained. It is important to point out that in the present experience, tolerance to cow's milk protein occurred by the age of 12 months.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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