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Induced proctocolitis – oral food challenge should be done to confirm the diagnosis of cow's milk allergy in neonates?

Camila Paula Munhoz **AGUIRRE**, Príscila da Silva Pereira **VASCONCELOS**, Jamil Pedro de Siqueira **CALDAS**, Elizete Aparecida **LOMAZI** and Maria Angela **BELLOMO-BRANDÃO**

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ABSTRACT – Background – Suspicion of food protein-induced proctocolitis based on empirical understanding of rectal bleeding can lead to misdiagnosis. **Objective –** to verify clinical and evaluative characteristics of patients who presented neonatal rectal bleeding and were on a restricted cow's milk diet. **Methods –** A cross-sectional retrospective study included patients followed up in a tertiary care center, who presented rectal bleeding in the neonatal period. The analyzed data included gender, gestational age, type of delivery, use of antibiotics during the last trimester of pregnancy, use of parenteral nutrition before the first manifestation, use of mechanical ventilation, initial clinical manifestations associated with rectal bleeding, diet before the first manifestation, period of elimination diet, oral food challenge (OFC) results and symptoms presented in cases of positive OFC. Fisher's exact test and Mann-Whitney test were used to analyze the data. The level of significance was set to 5%. **Results –** Forty-two patients were selected: 30 preterm infants, 34 cesarean deliveries, 10 exclusively breastfed patients before rectal bleeding. Median age at OFC was 6.3 months old. Median of length of the elimination period before OFC was 5.9 months. OFC was negative in 33/42 (79%) patients and positive in 9/42 (21%). There was no association between OFC results and the evaluated data. The main symptom observed in patients with positive OFC was blood in stools. **Conclusion –** OFC was negative in most cases of suspected cow's milk allergy due to rectal bleeding in neonates, most of them with a history of prematurity.

Keywords – Neonate; rectal bleeding; cow's milk allergy; allergic proctocolitis; oral food challenge.

INTRODUCTION

Allergic proctocolitis due to cow's milk allergy (CMA) is only one of the possible diagnoses in the presence of blood in stools in neonates[1]. Bleeding can occur in severe diseases, such as idiopathic neonatal transient colitis[2], Hirschsprung's disease[3] and necrotizing enterocolitis related to changes in the intestinal microbiota due to the significant growth of *Escherichia coli*[4], intussusception[5], Meckel's diverticulum[6], drug gastritis[7], necrotizing enterocolitis[8] and related nosological entities[9], infectious colitis[9], lymphoid nodular hyperplasia, vitamin K deficiency[10], anal fissure and evacuation of swallowed blood[11].

CMA is the main cause of food allergy in infants and children younger than 3 years old. Peak incidence occurs in the first year of life, with prevalence of 2 to 3% in the pediatric population[12]. CMA is an abnormal clinical response, of immunological pathophysiology, after the ingestion of one or more cow's milk proteins, which may be IgE-mediated or non-IgE-mediated[12]. The clinical manifestations can considerably vary and include a wide range of symptoms, such as anaphylactic shock, atopic dermatitis, irritability, poor weight gain and rectal bleeding[12,13]. For non-IgE-mediated manifestations, such as allergic proctocolitis, the diagnostic method is elimination of cow's milk protein from the infant's diet or from the maternal diet while breastfeeding and subsequent challenge with the suspected protein. This test is called oral food challenge (OFC) and despite all scientific advances, it remains the most reliable method for diagnosing or to verify tolerance to cow's milk allergy[13-15].

Few studies have used OFC, considered a gold standard of diagnosis, to confirm CMA[16]. Most frequency estimates are based on the diagnosis by self-perception, which can considerably overestimate the actual frequency of CMA[17,18]. A European study[19] carried out in infants with rectal bleeding, demonstrated that 3/20 (15%) of patients showed positive OFC. Another American study[20] diagnosed CMA using OFC in only 7 (18%) of 40 cases with rectal bleeding. Finally, a Korean study[21] with 16 neonates with rectal bleeding without other associated symptoms diagnosed CMA using OFC in only 2/16 (12%).

Some factors may be associated with CMA, such as gestational age[22-25], the use of antibiotics in the third trimester of pregnancy[22,24,25], type of diet (exclusive breastfeeding, mixed feeding or formula feeding from the start[22,24,25] and the type of delivery[22-26]. Although it hasn't been proved yet, other factors may also have an influence on CMA, such as mechanical ventilation[23,27,28] and parenteral nutrition[27,28], as they may alter intestinal microbiota composition (dysbiosis) and may be associated with the development of food allergy.

Due to the wide range of diagnoses for rectal bleeding in neonates, OFC is necessary to determine the diagnosis of CMA in infants[29,30].

This study aimed to verify the clinical and evaluative character-

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Universidade Estadual de Campinas, Faculdade de Ciências Médicas, Departamento de Pediatria, Campinas, SP, Brasil.
Corresponding author: Maria Ângela Bellomo-Brandao. E-mail: angbell@unicamp.br

istics and the frequency of cow's milk allergy after an elimination diet period using OFC in neonates with suspicion of food protein-induced proctocolitis (FPIPC) and to evaluate variables that may be associated with the diagnosis of CMA in neonatal rectal bleeding.

METHODS

This is a cross-sectional retrospective study. The data were obtained from medical records of patients assisted at a tertiary hospital and of patients admitted to neonatal intensive care unit (ICU), with a diagnostic hypothesis of due to rectal bleeding and who underwent OFC.

The data were collected from August 2017 to December 2019. This study was approved by the local Research Ethics Committee N. 3.008.074.

Inclusion criteria: 1. Presence of isolated rectal bleeding in neonatal period (first 28 days of life), defined as the presence of blood in stools, visible in small to moderate amounts. CMA was the main diagnostic suspicion, after excluding other diagnoses for more severe diseases, such as sepsis and necrotizing enterocolitis. 2. Elimination of cow's milk and dairy products from the infant's diet or maternal diet while breastfeeding showing improvement of symptoms and disappearance of the blood in stools.

Patients were excluded if they showed rectal bleeding as well as symptoms suggestive of IgE-mediated CMA, such as: urticaria, dermatitis, papules, angioedema, hyperemia, pruritus (cutaneous, labial, oropharyngeal, nasal or ocular), runny nose, sneezing, coughing, and wheezing.

OFC is performed at the neonatal ICU in patients who are hospitalized due to complications related to prematurity. In outpatient referrals for CMA and on a restrictive diet, our OFC is performed in a room prepared for such procedure at the Pediatric outpatient clinic, both used the same protocol for OFC.

OFC is carried out under medical supervision according to the following protocol adapted from Vandenplas et al.[29]:

- Drop formula based on intact cow's milk protein on the patient's lips.
- If the patient remains asymptomatic after 15 min, formula based on intact cow's milk protein is administered orally and the dose is gradually increased (0.5, 1, 3, 10, 30, 50 to 100 mL) every 30 min.
- Observe the infant for 2 more hours and administer the last dose.

After performing the test, if no symptoms are identified until the end of the observation period, the infant is discharged. A telephone number is provided for contact with the follow-up team and the patient returns after 7 days to be evaluated for late symptoms[29].

- Positive test: immediate signs and symptoms; increased intensity and/or prolonged maintenance of subjective symptoms, late symptoms reported by caregivers.
- Negative test: absence of immediate and late symptoms.

The following variables were obtained:

- Gender.
- Type of delivery.
- Gestational age: term (greater than or equal to 37 weeks) and preterm (less than 37 weeks).
- Type of feeding when symptoms appeared: breast milk, formula based on intact cow's milk protein, mixed feeding (breast milk and formula based on intact cow's milk protein).
- Initial clinical manifestations associated with rectal bleeding: diarrhea, vomiting, abdominal distention and restlessness.
- Length of the elimination diet period before OFC.
- Formula used during the elimination diet.
- Maternal use of antibiotics in the last trimester of pregnancy.
- Use of parenteral nutrition before the first manifestation.
- Use of mechanical ventilation.
- OFC result.
- Symptoms/signals presented in positive OFC tests.

The Fisher's exact test was used to evaluate the relation between variables: gender, gestational age, type of diet before the first manifestation, type of delivery, use of antibiotics during the last trimester of pregnancy, use of parenteral nutrition, and use of mechanical ventilation. The Mann-Whitney test was used to evaluate the length of the elimination period before OFC, between positive and negative OFC results. The level of significance was set to 5% for this study.

RESULTS

Forty-two patients were selected. OFC was performed at neonatal ICU in patients, who were hospitalized due to complications related to prematurity (16 cases). OFC was performed at pediatric outpatient clinic in 26 outpatients referred for on a restrictive diet, with diagnostic of CMA.

Median age at OFC was 6.3 months old and mean was 7 months old (1.5–18 months old). Median and mean of length of the elimination period before OFC was 5.9 months. The length of the elimination period varied between 2 weeks and 18 months. In seven patients, the length of the elimination diet period was between 2–4 weeks, in two patients the symptoms showed up again.

Clinical characteristics: gender, gestational age, initial clinical manifestations (diarrhea, vomiting, abdominal distention, and restlessness), type of diet before rectal bleeding, use of antibiotics in the last trimester of pregnancy, type of delivery, use of mechanical ventilation, use of parenteral nutrition and length of the elimination period before OFC, are shown in TABLE 1.

Regarding formula during the elimination diet: 20/42 patients used extensively hydrolyzed formula; 16/42 patients used amino acid formula; 5/42 patients were exclusively breastfed with the mother on a milk and dairy elimination diet; and 1/42 patient used soy formula.

OFC was negative in 33/42 (79%) patients and positive in 9/42 (21%) patients. TABLE 2 shows clinical characteristics, and symptoms presented in the nine positive OFC. The most frequent symptom was bloody in stools (n=5). No child needed intervention since the symptoms were mild.

Gender, use of antibiotics in the last trimester of pregnancy, use of mechanical ventilation and use of parenteral nutrition were not correlated with the OFC results, as well as gestational age (TABLE 3). About type of delivery all nine positive OFC were caesarean deliveries.

Length of the diet elimination period was not correlated with the result of OFC (P=0.09).

DISCUSSION

In our study, OFC was negative in most patients referred for FPIPC. In clinical practice, FPIPC is diagnosed when patients respond positively to the diet elimination of a suspected triggering, in this case, cow's milk protein[31]. Most patients were preterm newborns and delivered by cesarean section. Only 10/42

TABLE 1. Clinical characteristics and frequency in patients with neonatal rectal bleeding suspected cow's milk allergy.

Gender	
Male	21 (50%)
Female	21 (50%)
Gestational age[a]	
Term	12 (28%)
Preterm	30 (72%)
Initial clinical manifestations	
Diarrhea	3 (7%)
Vomiting	2 (5%)
Abdominal distension	3 (7%)
Restlessness	2 (5%)
Diet before rectal bleeding	
Exclusive breastfeeding	10 (23%)
Breastfeeding plus formula based on intact cow's milk protein	20 (48%)
Formula based on intact cow's milk protein	12 (29%)
Use of antibiotics in the last trimester of pregnancy	
Yes	10 (24%)
No	32 (76%)
Type of delivery	
Cesarean section	34 (81%)
Vaginal birth	8 (19%)
Use of mechanical ventilation	
Yes	27 (64%)
No	15 (36%)
Use of parenteral nutrition	
Yes	28 (66%)
No	14 (34%)

Classification of gestational age: term >37 weeks; preterm <37 weeks.

TABLE 3. Association between the oral food challenge test and the clinical characteristics of patients with suspected cow's milk allergy.

Gender	Oral food challenge test		*P**
	Positive (%)	Negative	
Female	4 (44%)	17	1
Male	5 (55%)	16	
Diet before rectal bleeding			
Exclusive breastfeeding	2 (22%)	8	1
Breastfeeding plus formula based on intact cow's milk protein	4 (44%)	16	
Formula based on intact cow's milk protein	3 (34%)	9	
Use of antibiotics in the last trimester of pregnancy			
Yes	2 (22%)	8	1
No	7 (78%)	25	
Use of mechanical ventilation			
Yes	6 (66%)	21	1
No	3 (34%)	12	
Use of parenteral nutrition			
Yes	6 (66%)	22	1
No	3 (34%)	11	
Gestational age[a]			
Term	5 (55%)	7	0.09
Preterm	4 (45%)	26	

**P*: Fisher's exact test. [a]Classification of gestational age: term >37 weeks; preterm <37 weeks.

TABLE 2. Clinical characteristics and symptoms presented in the nine positive OFC.

Patients	Gender	Gestational age	Length of the diet elimination period	Symptoms presented at OFC
1	Female	preterm	9 months	rash
2	Female	term	5 months and 15 days	vomiting
3	Male	term	27 days	Blood in stools
4	Male	term	39 days	blood in stools, restlessness, rash
5	Female	preterm	36 days	blood in stools
6	Male	preterm	9 months and 14 days	rash
7	Female	term	3 months and 10 days	non-bloody diarrhea
8	Male	term	1 month and 16 days	blood in stools, restlessness
9	Male	preterm	1 month and 12 days	blood in stools

OFC: oral food challenge.

patients were exclusively breastfed when CMA was suspected due to rectal bleeding. According to the literature, about half of cases of FPIPC in infants occur during exclusive breastfeeding[1]. However, the studies published on rectal bleeding in neonates[20-22] do not include samples with most preterm infants, as described in our study.

Recently published CMA guidelines[14,30] recommend an elimination period for diagnostic purposes for 2 to 4 weeks and OFC following improvement of symptoms. Among studies that also evaluated rectal bleeding and OFC, length of the elimination diet period varied between 2 to 9 weeks and 12–18% positive OFC[20-22]. Although our study included the largest number of neonates with rectal bleeding who underwent OFC tests[20-22], our sample consisted of infants referred already on an elimination diet with the diagnostic of CMA and neonates hospitalized for complications of prematurity, we did not control the time of the elimination diet before OFC, which implied maintaining an expensive diet in many patients who might not need this diet. It is a limitation of our study because it is not possible to say that the patients did not have CMA as a diagnosis, as these patients could have already developed tolerance.

Some caregivers may be reluctant to perform OFC, fearing that the baby will have severe symptoms, which we did not find in our study. An interesting fact is that, of the patients with positive OFC, two (oldests of OFC positive cases) had skin rash as the only manifestation which may suggest that the prolonged time of restriction of the cow's milk may have lost the tolerance window[32].

Extensively-hydrolyzed formulas have been prescribed for most cases and are the most globally indicated for mild and moderate cases of CMA[14]. Amino acid-based formulas were also widely used in our sample and its use was proposed as an initial screening evaluation for CMA[33]. This procedure is more related to an attempt to reduce health care costs than to a clinical indication, in mild and moderate cases of CMA.

Toro et al.[22] observed a statistically significant association between CMA and the use of antibiotics in the last trimester of pregnancy and the duration of breastfeeding, but not with gestational age and type of delivery. Tsaubori et al.[23], on the other hand, in a review article report that patients delivered by cesarean section, use of parenteral nutrition and the hospitalization of preterm newborns play a key role in developing altered microbiota (dysbiosis), which can be risk factors for CMA. In our study, none of these factors were associated with CMA.

In our study, OFC were conducted under medical supervision; however, in mild and moderate suspected cases of CMA, following the elimination diet and improvement of symptoms, the cow's milk and dairy products can be introduced in the maternal diet or in the child's diet at home with outpatient follow-up[13-15].

CONCLUSION

Our study shows the importance of performing OFC for FPIPC, to avoid an unnecessary restrictive diet, which affects the quality of life of the infant and family, as well as unnecessary costs for public health system.

Authors' contribution

To the research: Aguirre CPM, Lomazi EA, Bellomo-Brandão MA. conceived the project, wrote and critically reviewed the study; Aguirre CPM, Caldas JPS and Vasconcelos PSP collected participants data; Lomazi EA and Bellomo-Brandão MA accounted for supervision, performance and validation using reproducibility criteria; Aguirre CPM and Bellomo-Brandão MA analyzed an interpreted the data. All authors have read and approved the last version of the manuscript prior to submission.

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Camila Paula Munhoz Aguirre: 0000-0003-1712-7086.
Príscila da Silva Pereira Vasconcelos: 0000-00031964-1265.
Jamil Pedro de Siqueira Caldas: 0000-0001-5292-2320.
Elizete Aparecida Lomazi: 0000-0001-5504-4746.
Maria Angela Bellomo-Brandão: 0000-0002-1145-2606.

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RESUMO – **Contexto –** A suspeita de proctocolite induzida por proteína alimentar (PCIPA) com base na compreensão empírica de sangramento retal pode levar a diagnósticos equivocados. **Objetivo** – Verificar as características clínicas e evolutivas de pacientes que apresentavam sangramento retal neonatal e faziam uso de dieta restrita com leite de vaca. **Métodos –** Estudo transversal retrospectivo com pacientes acompanhados em um centro terciário, que apresentaram sangramento retal no período neonatal. Os dados analisados incluíram: sexo, idade gestacional, tipo de parto, uso de antibióticos no último trimestre da gravidez, uso de nutrição parenteral antes da primeira manifestação, uso de ventilação mecânica, manifestações clínicas iniciais associadas ao sangramento retal, dieta antes da primeira manifestação, período de dieta de eliminação, resultados do teste de provocação oral (TPO) e sintomas apresentados em casos de TPO positivo. O teste exato de Fisher e o teste de Mann-Whitney foram usados para analisar os dados. O nível de significância adotado foi de 5%. **Resultados –** Quarenta e dois pacientes foram selecionados: 30 prematuros, 34 partos cesáreos, 10 pacientes amamentadas exclusivamente antes do sangramento retal. A idade média na ocasião do TPO foi de 6,3 meses. A mediana da duração do período da dieta de eliminação antes do TPO foi de 5,9 meses. O TPO foi negativo em 33/42 (79%) pacientes e positivo em 9/42 (21%). Não houve associação entre os resultados do TPO e os dados avaliados. O principal sintoma observado em pacientes com TPO positivo foi sangue nas fezes. **Conclusão –** O TPO foi negativo na maioria dos casos de suspeita de alergia ao leite de vaca devido a sangramento retal em neonatos, a maioria deles com história de prematuridade.

Palavras-chave – Recém-nascido; sangramento retal; alergia ao leite de vaca; proctocolite alérgica; teste de provocação oral.

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