Original Article

Awareness or neglecting the diagnosis of cow milk protein allergy in the neonatal period

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Background and Objectives: Cow milk protein allergy (CMPA) can mimic surgical disease, gastroenteritis, sepsis, and necrotizing enterocolitis in the neonatal period. For this reason, we aimed to evaluate the clinical features, differential diagnosis, and treatment methods of neonates with CMPA. **Methods and Study Design:** The charts of twenty-six breastfed full-term and preterm newborns presenting with CMPA between October 2018 and February 2021 were retrospectively reviewed. The clinical symptoms, laboratory findings, and methods used in diagnosis and treatment were analyzed. **Results:** CMPA was diagnosed in preterm infants 50% (n=13) at the same rate as in full-term infants 50% (n=13) between 32 to 38 weeks corrected age (median 36 weeks). Among patients with CMPA, 69.2% (n=18) had blood in the stool at the onset. Cow's Milk-related Symptom Score score was found to be significantly higher prior to diagnosis vs. after treatment with the cow milk protein-free mom's milk diet [12(11-13) vs. 4(3-5), p<0.001]. Seventy-two hours after the commencement of the mothers' elimination diet, macroscopic blood in stool disappeared in all patients except one patient. Oral food challenge (OFC) for the diagnosis of CMPA was carried out on all (n=26) neonates. Eosinophilia was seen in 46.2% of patients (n=12). The methemoglobin concentration was 1.1 to 1.5% (median 1.3%). **Conclusions:** CMPA should be kept in mind for well-appearing preterm and full-term infants suspected of necrotizing enterocolitis and gastroenteritis, respectively, presenting with bloody stool and eosinophilia. The use of OFC can be implemented since neonates were very well monitored in the neonatal intensive care unit. Treatment is possible by continuing breastfeeding.

Key Words: cow's milk protein allergy, neonate, differential diagnosis, CoMiSS score, oral food challenge

INTRODUCTION

The prevalence of food allergy has increased over the last 20-30 years, affecting 6-8% of children worldwide.[1] Cow milk protein allergy (CMPA) is the most frequent food protein allergy in the first year of life. It accounts for roughly 2-3% of cases in well-conducted studies, followed by allergies to peanut (0.8%), soy (0.8%), egg (0.6%), and wheat (0.2%). The prevalence of CMPA in breastfed infants is 0.5%.[2] Prospective cohort studies conducted in Europe have reported the prevalence of CMPA in children to be between 1.9% to 4.9%.[3] Milk and egg allergies are widespread among children worldwide, including Asia; however, other food allergies, such as wheat or peanut, may vary depending on the area.[4] A regional birth cohort study conducted in Turkey shows that the incidence of food challenge-proven CMPA is 1.45% in children.[5] In China, the challenge-proven prevalence of CMPA has been reported to be 0.83-3.5% in 0 to 2-year-olds.[6]

Food allergies occur through immunoglobulin E (IgE) and non-IgE mediated mechanisms.[7] There is no specific and conclusive laboratory test. Therefore, diagnosis is based on clinical response to the removal of the allergen that leads to the resolution of symptoms, with recurrence of symptoms following food challenge. In an infant presenting with vomiting, bloody stool, and diarrhea who otherwise appears healthy, food protein-induced enterocolitis (FPIEC) brought about by cow milk protein (CMP) is the likely cause. As awareness of CMPA remains low, it may often be misdiagnosed as sepsis, gastrointestinal disorders, abdominal pathologies requiring surgery, or even necrotizing enterocolitis (NEC).[8] Due to the intestinal mucosal inflammation associated with increased permeability, misdiagnosing CMP in infants can lead to malnutrition, growth retardation, and iron deficiency anemia. Due to the activation of IgE memory and antigen-specific T lymphocytes, as well as the increased leakage of gut pathogens, CMPA may also be associated with allergic reactions and gastroenteropathies later in life. Human milk is the optimal nourishment for infant growth, neurodevelopment, and protection against infectious and de-

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generative disorders. Compared to formula feeding, breastfeeding has been found to be associated with higher Intelligence later in life.[9] In addition, misdiagnosis may result in the cessation of breastfeeding. Consequently, accurate diagnosis is crucial throughout the neonatal period.[10]

We report a multi-center study including full-term and preterm newborns with CMPA and how to overcome the difficulties in diagnosis.

METHODS

Study design and ethical considerations

This retrospective patient-chart review study was conducted at two tertiary healthcare institutions: Tekirdag Namık Kemal University and Balıkesir Ataturk City Hospital. Both institutes are perinatal referral centers in northwest Turkey and have a tertiary-level neonatal intensive care unit (NICU) with a total number of 40 incubators. The study was approved by Tekirdag Namık Kemal University Ethics Committee (04.13.2021, No: 2021.88.04.06). The medical files of 103 newborns postnatal age <28 days presented with vomiting, bloody stool, diarrhea, and abdominal colic were analyzed retrospectively (Figure 1). Infections, anal fissures, coagulation disorders, invagination/intussusception, volvulus, Hirschsprung's disease, necrotizing enterocolitis, Meckel's diverticulum, and ingested blood were all ruled out. The data of 26 term and preterm neonates pre-diagnosed as CMPA and whose mothers commenced on an elimination diet between October 2018 and March 2021 were included in the study.

Food protein-induced allergic proctocolitis definition

Herein, food protein-induced allergic proctocolitis (FPIAP) secondary to CMPA in breastfed infants was defined following criteria set out in the European Academy of Allergy and Clinical Immunology food allergy and anaphylaxis guideline and the expert panel report (Guidelines for the Diagnosis and Management of Food Allergy in the United States).[11,12]

Oral food challenge

Milk and dairy products were eliminated from the diet of breastfed infants whose clinical examination and evaluation results indicated CMPA. CMP-free diet mom's milk was recommended for infants showing clinical improvements within 72-96h of commencing the elimination diet. Oral food challenge (OFC) for the diagnosis of CMPA was carried out on neonates by reintroducing cow milk protein as a challenge to the maternal diet during hospitalization.[13,14]

Cow's milk on the mother of-related symptom score (CoMiSS)

In primary care practice, the CoMiss score has been shown to be a useful tool in evaluating the symptoms of CMPA. The total CoMiSS score ranged from 0 to 33, with increasing numbers indicating increased severity of symptoms (Table 1).[15]

Specific IgE and eosinophilia

Specific IgE concentrations were measured using the immune-CAP system (Phadia, Uppsala, Sweden) with 0.35kUa/L accepted as the cut-off value. Eosinophilia is defined in neonates as an eosinophil count exceeding 700 cells/mm^3. It is divided into three subclasses; mild (700-999 cells/mm^3), moderate (1,000-2999 cells/mm3), or severe (>3000 cells/ mm^3).[16]

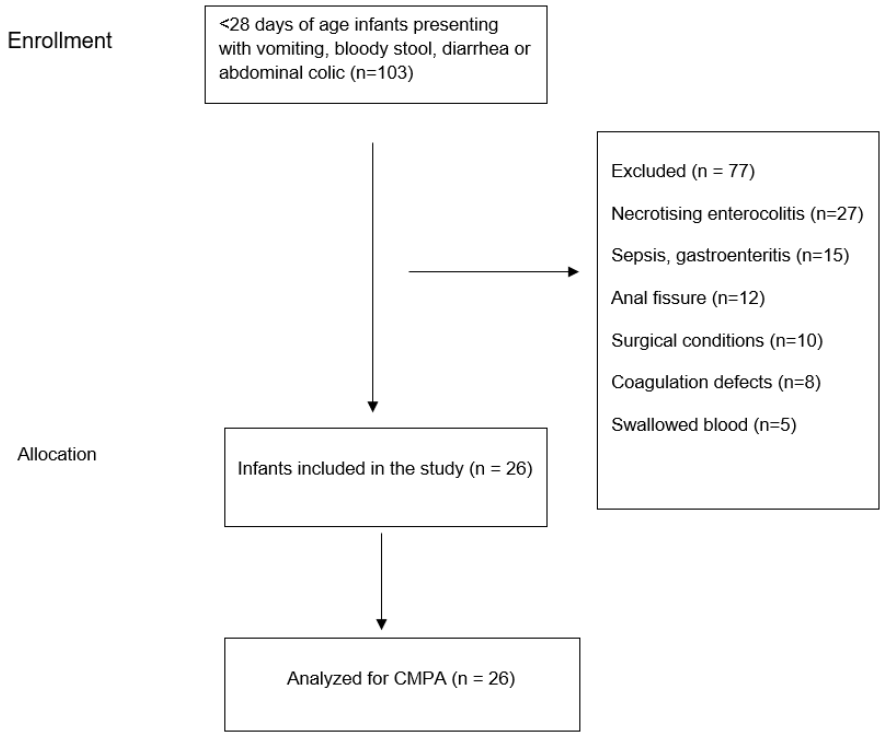

Figure 1. Flowchart for selection of eligible infants in the study

Table 1. The Cow's Milk-related Symptom Score (CoMiSS)

Symptom and score	Criteria
Crying	
0	≤1h/day
1	≤1-1.5h/day
2	1.5-2h/day
3	2-3h/day
4	3-4h/day
5	4-5h/day
6	≥5h/day
Regurgitation	
0	0-2 episodes/day
1	≥3-≥5 episodes of small volume
2	>5 episodes of>1 coffee spoon
3	>5 episodes of ±half of the feed in <half of the feeds
4	Continuous regurgitation of small volumes for >30 min after each feed
5	Regurgitation of half to complete volume of a feed in at least half of the feeds
6	Regurgitation of the complete feed after each feeding
Stools (Bristol Scale)	
4	Type 1 and 2 (hard stools)
0	Type 3 and 4 (normal stools)
2	Type 5 (soft stool)
4	Type 6 (liquid stool if unrelated to infection)
6	Type 7 (watery stools)
Respiratory symptoms	
0	No respiratory symptoms
1	Slight symptoms
2	Mild symptoms
3	Severe symptoms
Skin symptoms	
Atopic eczema	
Head-neck-trunk	
0	Absent
1	Mild
2	Moderate
3	Severe
Arms-legs-hands-feet	
0	Absent
1	Mild
2	Moderate
3	Severe
Urticaria	
0	No
6	Yes

Statistical analysis

Statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows, Version 24.0 Armonk NY: IBM Corp). Continuous variables were reported as mean ± standard deviation (SD) or median [interquartile range (IQR)] where applicable. The Shapiro-Wilks test was used to evaluate the distributional normality of continuous variables. The Student's unpaired t-test or the non-parametric Mann-Whitney test was utilized to compare continuous variables. Pearson's chi-square (χ^2) test or Fisher's exact test was used to compare categorical variables reported as n (%).

RESULTS

Cow milk protein allergy

Patient characteristics of 26 neonates are shown in Table 2. Commencement of rectal bleeding was observed between 32 and 38 weeks of corrected age (median 36 weeks). The birth weight of infants included in the study was 2.59±0.80kg. Diagnosis of CMPA was made in preterm infants (n=13, 50%) at the same rate as in full-term infants (n=13, 50%) in the NICU. Familial atopic diseases were present in 42.3% (n=11) of patients. The methemoglobin concentration was 1.1 to 1.5% (median 1.3%).

Symptoms of patients

Among patients with CMPA, the most common presenting symptom was blood in the stool (69.2%, n=18), followed by mucus in the stool (15.4%, n=4), vomiting (7.7%, n=2) and abdominal colic (3.8%, n=1).

The average age of symptom onset was 14±7.3 days of life. Symptom onset time was similar between preterm and term infants, 15.4±7 days vs. 12.6±8 days (p>0.05). Seventy-two hours after the commencement of the mothers' elimination diet, macroscopic blood in stool disappeared in all patients except one patient. At the same time, mild abdominal distension was the only physical examination abnormality observed in 30.8% (n=8) of patients.

CoMiSS score was found to be significantly higher prior to diagnosis vs. after treatment with the CMP-free mom's milk diet [12(11-13) vs. 4(3-5), p<0.001]. Due to

Table 2. Characteristics of participants

Characteristics	
Gestational age (weeks)†	36 (32-38)
Preterm population, n (%)	13 (50)
Birth weight (kg)	2.59±0.80
Gender (male), n (%)	12 (46.2)
Age of onset (days)	14±7.3
Symptoms at onset	
Blood in stool, n (%)	18 (69.2)
Mucus in stool, n (%)	4 (15.4)
Vomiting, n (%)	2 (7.7)
Abdominal colic, n (%)	1 (3.8)
Disappearance of blood in stool (hours) †	72 (24-96)
Physical examination	
Abdominal distension, n (%)	8 (30.8)
CoMiSS prior to diagnosis†	12 (11-13)
CoMiSS after treatment†	4 (3-5)
Laboratory results	
Methb % †	1.3 (1.1-1.5)
Eosinophil count, $10^3/\mu l$†	655 (177-977)
Eosinophil, % †	5.2 (1.5-7.8)
Eosinophilia, n (%)	12 (46.2)
Mild eosinophilia, n (%)	6 (23.1)
Moderate eosinophilia, n (%)	6 (23.1)
Severe eosinophilia, n (%)	None
Formula type after discharge, n (%)	
e-HF	11 (42.3)
AAF	5 (19.2)
Familial atopy, n (%)	11 (42.3)
Reevaluation by OFC in 6-12 months, n(%)	73.1 (19)
Recurrence of symptoms after OFC in 6-12 months , n(%)	57.7 (15)

CoMiSS; Cow's Milk-related Symptom Score; e-HF; Extensively hydrolysed formula; AAF; amino acid based; OFC, oral food challange.
†Data are presented as the median (IQR);

the presence of a familial history of atopy, the CoMiSS score was not found statistically significant prior to diagnosis and after treatment [13(11-15) vs. 12(10-13), p=0.314 and 4(3-6) vs. 4(3-5), p=0.459] respectively. However, when the CoMiss score was compared in patients replaced with amino acid-based formulas (AAF) with the extensively hydrolyzed formula (e-HF) replaced infants, it was found to be higher [17(15-18.5) vs. 12(11-13), p=0.002] in aa-based formula-fed infants.

OFC after discharge was performed in 73.1% (n=19) of patients, of whom 57.7% (n=15) had the recurrence of symptoms during the follow-up visits in 6 to 12 months (Table 2).

Offending foods

Of the 26 patients with CMPA, 24 were only breastfed, and the remaining 7.7% (n=2) were also breastfed with a bovine milk-based human milk fortifier. The e-HF was sufficient in 42.3% (n=11) of patients, while the remaining 19.2% (n=5) required aa-based formulas after discharge during the follow-up concurrently with breastfeeding.

SpIgE, eosinophil count

Sensitization to milk was investigated through spIgE concentrations in 76.9% (n=20) patients. No positive result was obtained. The eosinophil count was 177 to 977 (median 655), and the eosinophil % was 1.5 to 7.8 (median 5.2), respectively. Eosinophilia was observed in 46.2% (n=12) of patients. Of these, 23.1% (n=6) were classified as mild, and 23.1% (n=6) as moderate.

Endoscopy and histology

To exclude other pathologies, a colonoscopy was performed by a pediatric gastroenterologist on one patient whose rectal bleeding did not cease despite the mother's elimination diet. Colonoscopy in this patient revealed pancolitis (Figure 2).

DISCUSSION

Food allergies have increased dramatically in recent decades.[17] There is also an increase in the incidence of CMPA in the newborn population, including in premature

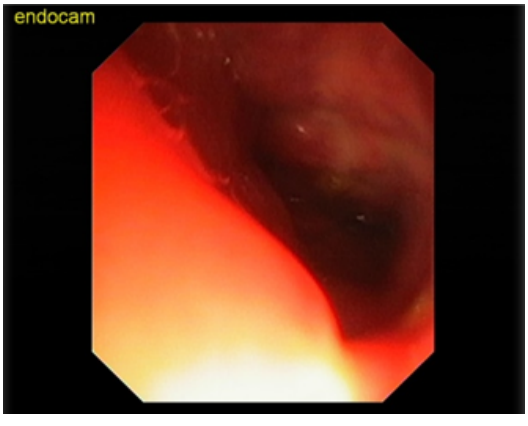

Figure 2. Endoscopic evaluation with pancolitis

infants.[18] In a Japanese multicentre trial, the prevalence of CMPA was reported as being 0.21% in neonates and 0.35% in very low birth weight preterm infants.[19] In the present study, half of our patients with CMPA were premature infants.

Sensitization and immune system reprogramming during in-utero development may be responsible for food allergies in neonates during the first postnatal days, even prior to allergen ingestion. The likelihood of developing CMPA is attributed to precocious exposure to CMPs conveyed via breast milk, which poses a challenge to newborns who are already sensitized.[20] However, Munblit et al. reported that an analysis of breastfeeding mothers consuming cow milk has low amounts of milk allergen to trigger an allergic reaction in infants with CMPA.[21] Multiple factors such as feeding restrictions and ischemic injury harm the developing intestinal epithelium of preterm infants, making them more susceptible to allergens.[11] On the other hand, it is hard for extremely preterm infants to develop a food allergy because food allergies require a Th-2 type immune response that can only occur with the maturation of the immune system at around 30-32 weeks of corrected gestational age.[22] Our study's youngest neonatal patient was at 30 weeks gestation when their first symptom occurred.

Dietary variables such as cooking methods, cultural preferences, allergen ingestion levels, and weaning patterns may influence the epidemiology of food allergies. This may explain disparities in the prevalence of food allergies between the East and West. Egg is the most allergenic food for Asian children, but peanuts in Asian cuisine are often cooked and fried, reducing their allergenicity relative to Western cuisine.[4] In addition, regional environmental factors such as solar radiation, humidity, and temperature may alter vitamin D status and eczema development, constituting a risk factor for food allergies. Low vitamin D levels in the serum have been linked to CMPA.[10] However, Vandenplas et al. reported insufficient data to advocate vitamin D supplementation for allergy prevention.[23] The Asian environment may have a preventive effect on the development of food allergies. In a cohort, birth in Asia and migration to Australia were found to be protective against nut allergy.[24]

A family history of atopy with a first-degree relative is an important risk factor for allergic manifestations in the offspring.[1] If one parent is allergic, their children have a 20-30% chance of developing allergies; if both parents are allergic, that risk climbs to 40-70%. Genetic risk factors play a role in the development of CMPA. Hou et al. found that the IL-10 rs1800896 gene polymorphism is related to CMPA in Chinese children with a parental allergy interaction.[25] In the present study, we also determined family-associated allergic disease 42.3% as a risk factor for CMPA.

Blood in stool is a serious symptom that necessitates further study and differential diagnosis. CMPA is considered the most common cause of bloody stools in infants. The differential diagnosis also includes NEC, gastroenteritis, and sepsis.[26]

Prematurity, low birth weight, and small for gestational age are the risk factors for NEC. The modified Bell's classification is widely used to classify suspected NEC.[27] NEC is a potentially morbid condition, while CMPA, on the other hand, is a self-limiting disease for infants. However, CMPA can mimic NEC with bloody stools and pneumatosis intestinalis.[28] Most infants with CMPA appear healthy despite having rectal bleeding, whether or not they have mucous stools or diarrhea.[29] In the present study, although they appeared well, the preterm population had initially presumed to have NEC due to the clinical and radiological findings. In NEC, decreased activity, repetitive vomiting, pallor, and watery or bloody diarrhea can also occur.[30] On physical examination, abdominal distension was most commonly observed in our patients. Kim et al.[31] reported that pneumatosis intestinalis was more commonly observed on abdominal ultrasonography, among preterm infants with FPIEC rather than NEC.

These patients did not have leukopenia or thrombocytopenia as expected in NEC but were observed to have increased eosinophilia.[32] Kimura et al.[33] reported an increase in eosinophil count in patients with FPIAP (median 9.0%) and in patients with FPIEC (7.5%). In the present study, eosinophilia was observed, with nearly half of the patients being mild and moderate. Accurate diagnosis and avoiding underdiagnosis are crucial for preventing dietary deficiencies and antibiotic exposure in preterm infants.[34] CMPA can also masquerade as a neonatal infection, especially diarrhea in full-term infants.[21]

CMPA can either be IgE-mediated or non-IgE mediated. Infants with non-Ig-E mediated CMP have more delayed-onset vomiting, again usually after the first exposure to milk, and may present with blood in stools (allergic proctocolitis) or with chronic cutaneous or gastrointestinal symptoms including diarrhea, failure to gain weight, crying, or vomiting.[21] Similarly, our patients presented a delayed onset with, in order of frequency, blood in stool, mucus in stool, vomiting, and colic with crying, suggestive of non-Ig-E mediated reaction, concomitant with no positive result of blood-specific IgE. Given those gastrointestinal manifestations such as FPIAP and FPIEC suggest non-Ig-E mediated types of CMPA, total IgE concentrations cannot be used for differential diagnosis. Nonetheless, specific IgE testing in serum may support the diagnosis in IgE-mediated instances (angioedema, wheezing, urticaria, immediate vomiting).[5]

Endoscopic examination to diagnose FPIAP is not recommended by guidelines.[8] However, an endoscopic examination may help to exclude other aetiologies in patients with severe symptoms who have not responded to an elimination diet. Despite the elimination of the offending food, recurrent bleeding was observed in one patient from our study that required endoscopic evaluation. In our group of patients, a colonoscopy was performed on one (3.8%) patient with symptoms refractory to the maternal elimination diet. Clinically, proctocolitis was suspected and confirmed by histologic examination.

Also, a symptom-based score CoMiSS has recently become an efficient and reliable tool for diagnosing CMPA. Vandenplas et al. reported that a CoMiSS score of more than 12 is likely to exist in 80% of patients with a positive challenge test. CoMiSS score can also contribute to the differential diagnosis of CMPA by improving symptoms.[35] It is also demonstrated in our study that the CoMiSS score of 12 has decreased to 4 by the elimination

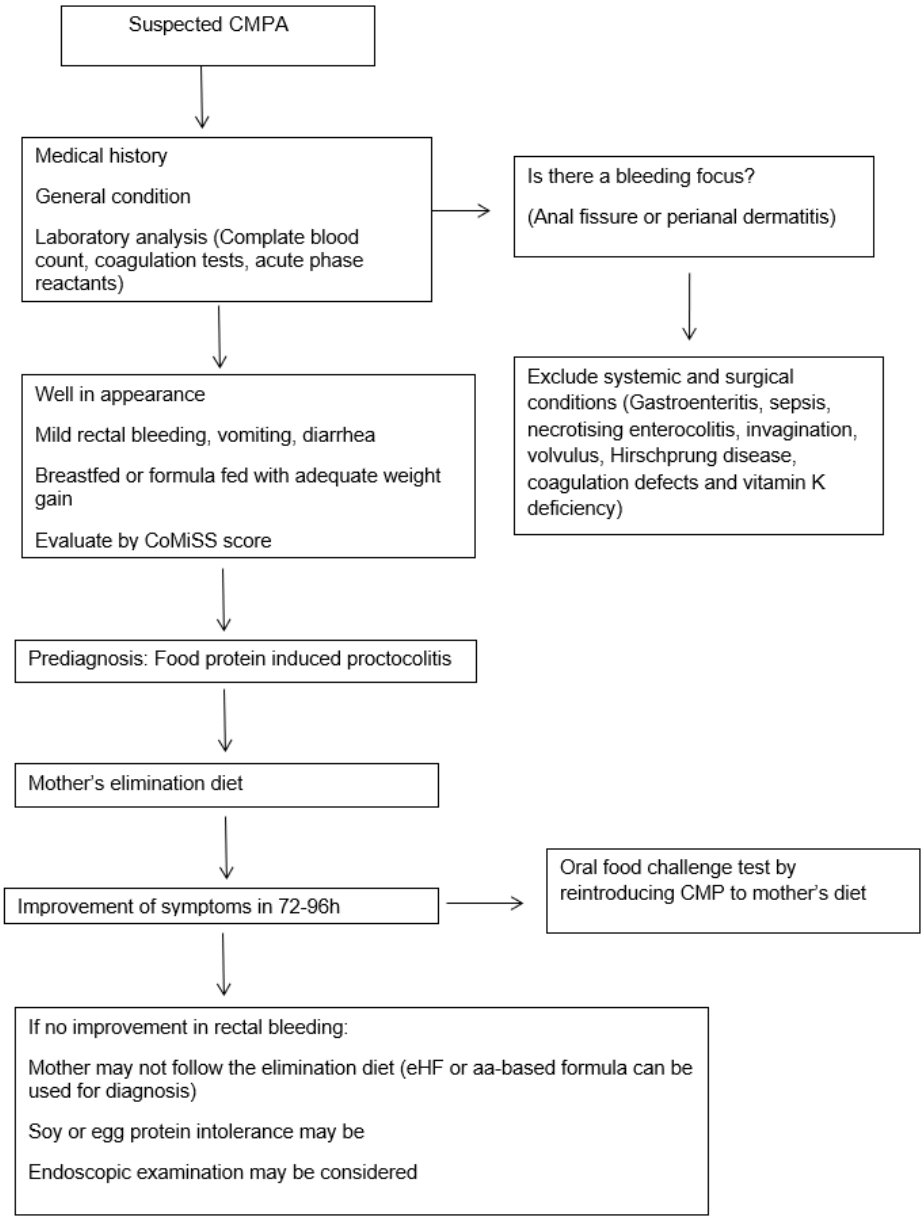

Figure 3. Conceptual approach diagram of cow milk protein allergy. eHF: extensively hydrolyzed formula.

diet. Infants respond to AAF rather than eHF, having a higher CoMiSS score. In the literature, the decrease in CoMiSS score with AAF was larger than with eHF in formula-fed infants.[36]

The clinical response to removing the allergen from the diet is used to diagnose CMPA in the neonatal phase and requires OFC after two to four weeks.[14] Some studies have reported OFC was not implemented in patients due to the risk of allergic reactions in the neonatal period.[36] Conversely, some studies reported the use of OFC through breastfeeding in the neonatal period.[37] In our study, we could perform the challenge since the patients were very well monitored in the NICU. In most cases, a positive OFC test is considered adequate evidence of CMPA to minimize false-positive differential diagnoses.[5,19] FPIEC resolves in most cases by 3-5 years of age, although the persistence of CMPA and soy FPIEC into adulthood has been reported.[38] In non-breastfed infants with CMPA, eHFs are usually the first option for nutrition. When we reevaluated the infants with OFC between 6-12 months, we found that 57.7% had a recurrence of symptoms. In infants reacting to eHFs, using AAF can be another choice. Breastfeeding mothers should also be educated on reading food labels to avoid dairy products and food containing casein, whey, lactalbumin, and albumin.[39]

Despite the potential severity of the reactions, the prognosis is favorable, with no fatal outcome observed in our patients. In our study, all patients with CMPA were discharged from the hospital, and the prolonged hospitalization period in preterm infants was related to preterm complications rather than CMPA.

A study reported that significantly higher methemoglobin concentrations were measured in newborns with FPIES.[40] Although two cases of FPIES with elevated methemoglobin concentrations have recently been reported, these results were inconsistent with our findings.[41] This may be explained by acute forms being observed in newborns and chronic forms in infants or the severity of the symptoms.

Our study has several limitations. Firstly, our study was designed as a retrospective chart review, and we could not perform follow-ups on all patients in our study group. Second, we could not assess the mother's vitamin D level during pregnancy and lactation.

Nevertheless, it is important to note that our study sheds light on the association of CMPA-related symptoms with eosinophilia in the neonatal period. The CoMiSS scoring system can be a useful tool in diagnosing and assessing clinical responses. OFC can be implemented for neonates who are very well monitored in NICU.

We would also like to emphasize that, in preterm and full-term infants, it is essential to consider NEC, sepsis, and gastroenteritis as differential diagnoses in CMPA, as breastfeeding can be continued in CMPA contrary to NEC and sepsis (Figure 3).

Conclusions

CMP-induced FPIAP can present in full-term and preterm neonates even if breastfed as early as the first days of life. CMPA should also be considered in the presence of bloody stools, particularly if the infant's general condition is good. CoMiSS score can be a non-invasive, rapid, and easy-to-use tool in diagnosis and follow-up. The use of OFC can be implemented since neonates are very well monitored in the NICU. Treatment is possible without discontinuing breastfeeding. Better diagnosis, treatment, and preventative measures can only be achieved with additional research.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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