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COW'S MILK PROTEIN INTOLERANCE IN A YOUNG INFANT, CAN IT BE CURED

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ABSTRACT
Cow's milk protein allergy (CMPA) frequently occurs in the first year of life, with a prevalence of 23% in the infant population. Food protein-induced enterocolitis syndrome (FPIES) is a severe non-IgE (immunoglobin E) presentation—mediated food allergy, which CMPA frequently causes. FPIES is frequently misdiagnosed initially due to its non-specific symptoms and laboratory findings. We present a case of a three-month-old male infant with allergic colitis due to CMPA. The patient was initially diagnosed with infectious colitis, which was then found to be allergic. The patient also did not tolerate extensively hydrolyzed formula and needed amino acid formula. The patient was discharged home in a stable condition. This research implies an increase in awareness and health education among parents, especially those with young infants. The findings of this study can also have an impact on changes in healthcare services and encourage the development of substitute milk products more suitable for infants with cow's milk protein intolerance.

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INTRODUCTION

Cow's milk protein allergy (CMPA) is an adverse reaction to one or more milk proteins, typically caseins, α-lactalbumin, and β-lactoglobulin (Cubides-Munévar et al., 2020). CMPA frequently occurs in the first year of life, with a 2-3% prevalence in the infant population. The incidence then decreases to 1% in children aged six and above (Koletzko et al., 2013). CMPA can be classified as immunoglobulin E (IgE) – mediated and non-IgE-mediated (Cubides-Munévar et al., 2020). Many children and infants with CMPA do not have positive serum IgE levels. Food protein-induced enterocolitis syndrome (FPIES) is a severe presentation of non-IgE-mediated food allergy, which CMPA frequently causes. FPIES is frequently misdiagnosed initially due to its non-specific symptoms and laboratory findings (Michelet et al., 2017). We present a case of a three-month-old male infant who had allergic colitis due to CMPA, provided with an extensive review of critical clinical points in diagnosing FPIES.

A three-month-old male infant was brought to the emergency department at our hospital due to post-feeding vomitus and extensive diarrhea. The patient started showing symptoms of diarrhea at one month of age. During that time, the patient's mother had trouble breastfeeding. She gave the patient standard formula milk, widely available in supermarkets and kiosks. The symptoms were severe enough (the detailed history of the emergence of the symptoms was unable to be obtained due to the mother's inability to recall), which caused dehydration and weight loss, and the patient had to be admitted to NICU at our center from August 1st – 10th and put on mechanical ventilation. The patient was a second-born child, born via cesarean section with a gestational age of 42 weeks and a birth weight of 2300

grams. The patient was deemed normal and discharged home after three days postnatal. His mother had a history of asthma, but his father and sibling did not have any history of the disease.

During the first admission, the patient's abdomen was distended, and the characteristics of the diarrhea were very watery, greenish in color, and mixed with mucus, with no streaks of blood present. Colonin-loop examination revealed an extensively distended bowel (Figure 1). Megacolon was suspected initially, and the patient was referred to a tertiary center for adequate management. Colonoscopy was done and revealed signs of non-specific colitis (Figure 2). Suspicion of allergic colitis due to cowmilk protein allergy (CMPA) was made. After ten days of admission, the patient was referred back to extensively hydrolyzed formula.

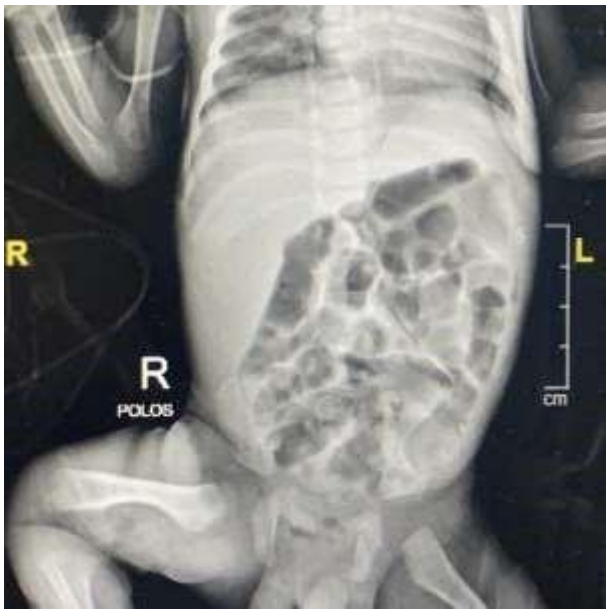

Figure 1. Colon-In Loop Examination Of The Patient Showing Extensively Distended Bowel

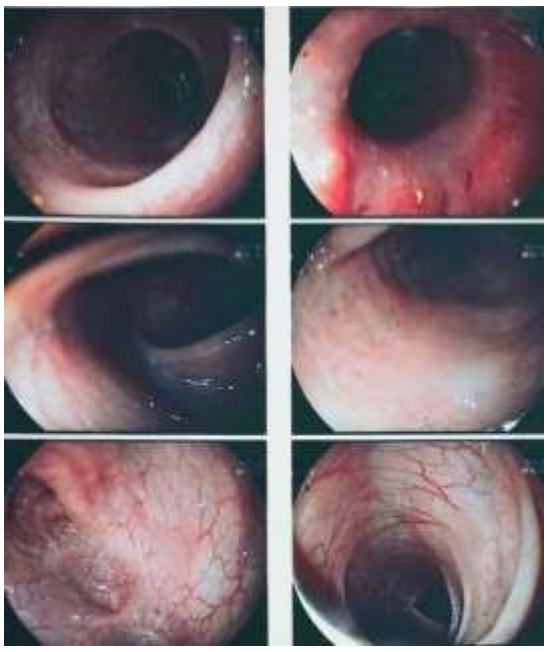

Figure 2. Colonoscopy examination of the patient showing non-specific signs of colitis

Symptoms started to show again when the patient was referred back to our center, with extensive diarrhea, which could happen thirty times daily. Diarrhea was accompanied by vomitus three times before the patient arrived in our emergency department. The characteristics of the diarrhea were yellowish white in color, semisolid, mixed with mucus, and no streaks of blood present. On physical examination, the patient appeared weak, with a GCS of 15, a heart rate of 141 beats per minute, a respiratory rate of 30 breaths per minute, and a body temperature of 36.5 C. Abdominal examination findings were within normal limits. Extremities were warm, with capillary refill time < 2 seconds. Laboratory examination results were as follows: Haemoglobin (Hb) 9.8 g/dL, leucocyte 14100 / µL, thrombocyte 492000 / µL, hematocrit 31.4%, sodium 129 mmol/L, potassium 5.7 mmol/L, calcium 1.42 mmol/L, and blood glucose 73 mg/dL. The initial diagnosis for the second admission was infectious diarrhea, anemia, hyponatremia, and dehydration. Therefore, the patient was given intravenous fluid, metronidazole 2x50 mg, hypertonic saline, and blood transfusions with premedications, prebiotics, and zinc supplementation. A stool culture was done, and the result was within normal limits. During the admission period, diarrhea could not resolve with antibiotics. Suspicion of extensive hydrolyzed formula intolerance was made. Therefore, the amino acid formula was given instead. The patient was discharged in a stable condition with a resolution of symptoms.

METHOD

When a patient's chart indicated any degree of autism, immediate action was taken to place the patient in the autism-type group for further follow-up, although it was not always a bad condition. Treatments were performed on average two to three times a week, and not all participants successfully completed the program. The treatment lasted four to eight weeks in patients without comorbid conditions. Patients with comorbidities first received appropriate therapies and then underwent treatment for autism. Mesenchymal stem cells (MSCUC) were delivered to patients, consistently monitored, and documented. The results were recorded, and appropriate actions were taken when necessary.

RESULT AND DISCUSSION

A reproducible adverse reaction to one or more milk proteins, typically caseins, α-lactalbumin, and β-lactoglobulin, is known as CMPA. CMPA is distinguished from other adverse reactions to cow's milk, like lactose intolerance, by the presence of an immunological mechanism (Cubides-Munévar et al., 2020). CMPA frequently occurs in the first year of life, with a 2-3% prevalence in the infant population. The incidence then decreases to 1% in children aged six and above (Koletzko et al., 2013).

CMPA is the most frequent food allergy presentation during the first year of life. CMPA can be classified as an immunoglobulin E (IgE) – mediated and non-IgE-mediated mechanism (Cubides-Munévar et al., 2020). Many children and infants with CMPA do not have positive serum IgE levels. An IgE-mediated response typically causes an acute reaction within two hours of ingesting an allergen. Non-IgE-mediated allergic reactions to foods, also known as cell-mediated reactions, are more prevalent and likely account for more than 40% of CMPA in infants and young children. Food allergy is now described in the form of syndromes, among which food protein-induced enterocolitis syndrome (FPIES) and food protein-induced allergic proctocolitis (FPIAP) (Aguirre et al., 2022) (Dupont, 2019). The main symptom of FPIAP is minor rectal bleeding in neonates, which was not seen in our patient; with this fact, FPIAP was excluded from our differential diagnosis (Turnbull et al., 2015).

The pathogenesis of non-IgE-mediated food allergies has yet to be clarified. The most studied allergy is FPIES, and multiple studies have indicated a crucial function for T-cells in releasing proinflammatory cytokines that may alter intestinal permeability (Sarinho & Lins, 2017). Risk factors

for developing FPIES include cesarean delivery, male gender, and FPIES to other food (particularly in older children). FPIES is associated with atopy, with 30 % of FPIES patients having a personal history of atopic disease, 40–80 % reporting a family history of atopic disease, and 20 % having a family history of food allergy (Nowak-Węgrzyn & Konstantinou, 2014). Recently, it has been proposed that the early introduction of soy or cow milk formula is a risk factor for FPIES (Michelet et al., 2017). The patient had a maternal history of asthma, which may have contributed to the development of his illness. In addition, breastfeeding was stopped early, which could be a risk factor.

CMPA is the most common cause of FPIES in infants, which triggers the development of the symptoms of allergic enteritis in 65-80% of cases. However, also egg, corn, soy, and wheat can be implicated (in 19%, 6%, and 3%, respectively) (Yang et al., 2015); (Nowak-Węgrzyn et al., 2017). FPIES caused by solid foods typically occur later, probably related to their introduction into the child's diet (Mennini et al., 2020).

The patient in our case was one-and-a-half months old when the symptoms first emerged. It is widely known that FPIES mainly occurs in infancy, typically before nine months of age, but may also occur in older children and adults (Sarinho & Lins, 2017). FPIES to cow's milk protein and soy commonly appear in the first 2-3 months of life (Michelet et al., 2017)(Mennini et al., 2020). The manifestation of FPIES is non-specific. However, it is essential to point out that there are no classic allergic symptoms from the skin (such as itching, urticaria, swelling) or respiratory tract (wheezing, cough, sneezing) in FPIES; if present, these points to IgE-mediated CMPA.

FPIES can present in acute, chronic, or acute-on-chronic forms. The diagnosis of acute FPIES requires that a patient meets the significant criteria: vomiting in the 1-4 h period after ingestion of the suspect food in the absence of classic IgE-mediated allergic skin or respiratory symptoms; and at least three minor criteria (Lemoine et al., 2022):

a. A second (or more) episode of repetitive vomiting after eating the same suspect food
b. An episode of repetitive vomiting 1-4 h after eating a different food
c. Extreme lethargy with any suspected reaction
d. Marked pallor with any suspected reaction
e. Need for emergency room visit with any suspected reaction
f. Need for intravenous fluid support with any suspected reaction
g. Diarrhea within 24h
h. Hypotension
i. Hypothermia

Our patient fulfilled the principal and three minor criteria: needing an emergency room visit, diarrhea, and lethargy. In young infants with a more severe phenotype (less than 30% are children older than one year), diarrhea may occur within 5–10 hours of intake (Dupont, 2019); (Sarinho & Lins, 2017). Infants less than two months of age are significantly more likely to manifest diarrhea. They may be accompanied by lethargy and dehydration, which both indicate a severe illness (Koletzko et al., 2013); (Dupont, 2019); (Nowak-Węgrzyn & Konstantinou, 2014). Older infants were likelier to present with vomiting alone (Nowak-Węgrzyn & Konstantinou, 2014). Symptoms normally go away after avoiding the offending food for a few days. However, they usually return within 1-3 hours of eating the offending food again (Nowak-Węgrzyn & Konstantinou, 2014). Chronic FPIES occurs when food is regularly consumed (Lemoine et al., 2022). The acute form of FPIES may happen as the initial manifestation, or it may happen when the food allergen is reintroduced after a time of exclusion, an acute episode happening during chronic FPIES (Sarinho & Lins, 2017).

The diagnosis of FPIES is based on clinical history, recognition of clinical symptoms, exclusion of other etiologies, and oral challenge test (OCT). Although the OCT is considered the gold standard

for diagnosing food allergies, most patients do not need confirmation, especially if they have a history of severe reactions and become asymptomatic after removing the suspected protein (Aguirre et al., 2022). Various non-specific markers can also be used (Aguirre et al., 2022). There are currently no radiographic or laboratory pathognomonic findings specific to FPIES. Barium enema or colon-in-loop examinations frequently shows a distended colon, which is also present in our case (Arunachalam & Mathai, 2013). Necrotizing enterocolitis can also present as necrotizing enterocolitis due to the presence of bowel dilatation. Thrombocytosis and an increased white blood count with a left shift are frequently observed, which were seen in our patient. The acute inflammatory response of the gastrointestinal tract, which results in the release of several cytokines and chemokines, is most likely the cause of the increase in peripheral neutrophils. A response to epinephrine produced by stress, which can move platelets from the spleen into the circulation, may be one explanation for acute thrombocytosis. Further research is necessary to determine if platelets and neutrophils may actively contribute to the pathogenesis of FPIES (Nowak-Węgrzyn et al., 2017).

Other diagnostic techniques include a skin prick test (SPT), where a positive result is defined as a wheal larger than 6 mm in children younger than two years of age, or a particular IgE blood test (value of 5 kilounits/ L or greater, for children younger than two years of age, is considered positive). ON THE OTHER HAND, the SPT test and serum IgE are typically not carried out until the child is about 1-2 years old since they can frequently result in a false-negative result in infancy (Helm, 2014). Although the majority of FPIES patients had undetectable serum IgE at the time of diagnosis, 18–30% of FPIES patients may eventually acquire IgE-mediated food sensitivity to the same food, with some displaying rapid symptoms of a conventional IgE-mediated food allergy. They are classified as atypical FPIES (Yang et al., 2015). Our patient was thought to have non-IgE mediated CMPA due to the existence of gastrointestinal-related symptoms without any other systems being affected. We could not, however, be entirely sure of the absence of IgE in our patient due to the existence of atypical FPIES. Due to a lack of financial resources, the IgE examination was not carried out. Occasionally, invasive tests like endoscopy with biopsy are required. In our patient, a colonoscopy was done due to suspicion of megacolon. Endoscopy in allergic enteritis typically reveals non-specific findings such as diffuse nodularity, ulceration, loss of vascular pattern, and localized erythema. It may, however, be normal (Mennini et al., 2020).

Numerous infectious diseases, additional food allergies, and intestinal obstruction are some differential diagnoses of FPIES. Infected colitis in infants can result from bacterial, viral, or parasitic agents and is a common cause of colitis in the pediatric population. The initial episodes of CMPA are frequently misdiagnosed as acute viral gastroenteritis or are evaluated for sepsis, especially if patients present with profound lethargy and hypotension and have an elevated white cell count with a left shift. This scenario did happen in our case. Acute onset of fever, nausea, cramps, or abdominal pain (severe irritability or fussiness in infants), several diarrheal stools in a day, and some cases, blood in the stool are common manifestations of infectious colitis. History and physical examination are frequently used to diagnose; however, stool cultures can also be performed to verify the diagnosis (Helm, 2014). Septic shock can also mimic FPIES due to leucocytosis and hypotension caused by dehydration. Negative findings of stool culture in our case further support the diagnosis of non-infectious etiology, which in our case is FPIES caused by CMPA.

The patient, in our case, had anemia. One of the CMPA complications is iron deficiency anemia (Lai & Yang, 2018). Anemia often results from delayed CMPA diagnosis that causes the disease to be prolonged and untreated. The mechanism of iron deficiency anemia could be gross or occult blood loss from the gastrointestinal tract and the possible effect of inhibiting non-heme iron absorption by calcium

and casein in cow's milk (Benz Jr, 2018). However, the patient in our case was only three months old. Therefore, the possibility of physiologic anemia in infancy could not be excluded.

Rapid intravenous hydration with 10–20 mL/kg of normal saline solution is the first-line treatment for acute diseases. In the event of severe reactions, a single dose of methylprednisolone (1 mg/kg, with a maximum of 60–80 mg may be administered, which is likely to minimize intestinal inflammation (Ren et al., 2022). Long-term management consists of strict dietary elimination of cow's milk protein products. 5,17,21

Formula feeding in children with CMPA should take into account several factors, including the likelihood of allergies, the formula's composition, cost, the child's tolerance, and clinical data demonstrating the efficacy of the formula (Ribeiro et al., 2018). For the treatment of FPIES, the official recommendations suggest a hypoallergenic formula (Nowak-Węgrzyn et al., 2017). The majority of children tolerate highly hydrolyzed formulas. However, 10-20% of them may require amino acid-based formula (Lai & Yang, 2018). AAFs are the only entirely nonallergenic formulas and can be helpful for patients who don't respond well to partially or extensively hydrolyzed formulas, which was the case in our patient. In addition, AAFs are also associated with better digestibility, therefore, provide higher concentrations of protein to support growth (Reynaldo & Hegar, 2014). Soy infant formula is a reasonable option. However, it is not advised to be used with CMPA in infants less than six months old (Ribeiro et al., 2018); (Turnbull et al., 2015); (Helm, 2014). However, a cautious introduction is advised due to the possibility of cross-reactivity between patients with CM- and soy-induced FPIES (Nowak-Węgrzyn et al., 2017).

Small amounts of cow's milk protein can be reintroduced into the diet between nine and twelve months of age or four to six months after milk products are removed from the diet. Beginning with modest doses of either hydrolyzed or cow's milk formula and increasing the amount each day, the reintroduction of the milk should take place gradually over the course of 3-5 days. Infants who have begun eating solids should first be exposed to foods that contain milk or a small number of milk products. The milk content of the foods should then be gradually increased. If symptoms return, the infant and mother must return to a restricted diet for four to six months (Helm, 2014).

Since FPIES caused by breast milk protein are uncommon, breastfeeding should be continued if possible (Lai & Yang, 2018). However, dairy products should be restricted in the maternal diet; 50% of FPIAP cases reported in the literature are exclusively breastfed infants (Mennini et al., 2020). The mother should receive counseling that covers alternative calcium sources and maintaining a balanced diet without milk products. The infant's symptoms should be improved in 2 - 4 weeks, but it may be noticeable as soon as 72 to 96 hours (Helm, 2014).

FPIES is a short illness (Aguirre et al., 2022). FPIES has a favorable prognosis if treatment begins in infancy (Dupont, 2019). By the age of 1one year, roughly 50% of children with CMPA will develop a tolerance to cow's milk protein, followed by about 75% by the age of three and about 90% by the age of six (Helm, 2014). According to the research, CM-induced FPIES was more likely to remain in children with atypical FPIES after age 3.

CONCLUSION

CMPA-induced allergic colitis is frequently misinterpreted as colitis caused by another, more prevalent etiology, like infectious colitis. When infants are given formula milk early and have persistent diarrhea, clinicians must have a high suspicion of CMPA. Even though the management remains similar, determining the presence of IgE can help anticipate how FPIES will progress. Early detection and treatment can lessen the financial burden of the condition and help prevent unwanted complications.

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