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Neonatal metabolic acidosis caused by food protein-induced enterocolitis syndrome: a case report

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ABSTRACT

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE mediated allergic reaction with gastrointestinal symptoms, such as vomiting and diarrhea. FPIES diagnosis is based on clinical criteria and on a food challenge test. It is an unknown disease in neonatal units due to its nonspecific symptoms in newborn infants. An elevated methemoglobin level is a simple way to approach diagnosis.

Here we describe a clinical case of a newborn admitted to the emergency department because of dehydration, lethargy, vomiting, diarrhea, severe metabolic acidosis, and a high methemoglobin level. Clinical improvement and complete recovery was achieved after initiation of elemental formula. The diagnostic suspicion was confirmed after a positive challenge test.

Key words: *enterocolitis, food hypersensitivity, immunoglobulin E, methemoglobin, newborn.*

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INTRODUCTION

Food protein-induced enterocolitis syndrome (FPIES) is a rare and potentially severe non-IgE mediated food hypersensitivity disorder. The clinical manifestation begins in infancy with digestive symptoms (vomiting, diarrhea, irritability) while respiratory and skin manifestations are absent.[1] In acute forms, the onset of symptoms is 1-3 hours after the ingestion of food, and vomiting and dehydration predominate. The chronic forms have been described with intermittent vomiting, diarrhea, weight loss, and failure to thrive.[1]

The usual age of onset is in the first month of life, although it might occur in newborn infants and also, a likely sensitization in the fetal period is suggested.[2,3] Although the prevalence of FPIES has not been well established, some series, such as the one from Israel, estimate that 0.34% of cases are caused by hypersensitivity to cow's milk.[4] The role of methemoglobin as a marker of intestinal damage in severe FPIES has been described.[5,6]

The objective of the article is to describe the case of a newborn infant with dehydration, lethargy, vomiting, diarrhea, failure of thrive, and severe metabolic acidosis after the initiation of feeding with adapted formula. The characteristic finding was methemoglobinemia.

The parent´s consent has been obtained for the publication of this article.

CASE REPORT

Our case was a full-term newborn infant with an adequate weight for gestational age (41^{+4} weeks/3380 g) taken to the emergency department at 24 days of life with vomiting, diarrhea, and weight loss of 4.7% since birth. Regarding the family history, the infant's mother suffered from manic episodes, but did not need to take medications during her pregnancy and there was consanguinity in the maternal branch.

The delivery was by elective C-section. The Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. The physical examination was normal. He was discharged on the third day; the neonatal screening was normal. He was exclusively breastfed up to 15 days of age when formula feeding was initiated due to maternal hospitalization (psychiatric reasons). After the initiation of formula feeding, projectile vomiting after feedings and diarrhea with 8–10 bowel movements per day were observed. When admitted to the emergency department, he weighed 3180 g and was hemodynamically stable, dehydrated, pale, irritable, with depressed anterior fontanelle, poor peripheral perfusion, and a lethargic appearance. His abdomen was soft and depressible, without masses or organ enlargement. Skin and respiratory symptoms were absent, and the examination of the rest of the systems and organs was normal.

Table 1 shows the laboratory findings upon admission to the Neonatal Unit. The rapid test for rotavirus and adenovirus antigens in stools was negative; the abdominal ultrasound was normal; and hypertrophic pyloric stenosis was ruled out. Intravenous fluid replacement therapy (dextrose solution and 10 mEq of sodium bicarbonate) was started, and the patient was admitted to the

Table 1. Patient's laboratory tests upon admission to the Neonatal Unit

Blood tests	
Blood count	Hemoglobin 16.2 g/dL Hematocrit 50.8% Leukocytes 13.64 10^9/L Neutrophils 6.2 10^9/L Lymphocytes 5.0 10^9/L
C-reactive protein	CRP 10.3 mg/L
Venous blood gases	pH 7.21 pCO_2 25.5 mmHg HCO_3 13 mmol/L BE -15.7 Lactic acid 1.4 mg/dL Methemoglobin 2.7%
Ionogram	Na 153 mmol/L K 4 mmol/L Cl 136 mmol/L Ca 1.46 mmol/L
Liver function tests	ALT 25 U/L AST 34 U/L Total proteins 7 g/dL Albumin 3 g/dL
Renal function tests	Urea 22 mg/dL Creatinine 0.24 mg/dL
Phosphocalcic metabolism	Total calcium 10 mg/dL Calcium correction for albumin 10.9 mg/dL Phosphorus 5 mg/dL 25-hydroxy-vitamin D 24.7 ng/mL
Urine tests	
pH 5	
Density 1030	
Anion gap -70.6	

CRP: C-reactive protein; pCO_2: partial pressure of carbon dioxide; HOC_3: bicarbonate; BE: base excess; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Neonatal Unit for the management of moderate to severe dehydration and fluid and electrolyte imbalance.

Metabolic acidosis of gastrointestinal origin (development of clinical manifestations after starting infant formula feeding) and methemoglobinemia (observed in blood gas monitoring) led to the suspicion of chronic FPIES, which was managed together with the Department of Pediatric Gastroenterology. After 12 hours of total fasting, vomiting and diarrhea resolved, while methemoglobinemia persisted (2.9%). Afterwards, the administration of hydrolyzed formula was resumed, and symptoms and metabolic acidosis recurred, so the patient was fasted for another 12 hours. Finally, feeding was restarted with elemental formula (Neocate®). With the change of the feeding formula, symptoms rapidly improved, weight was gained (300 g increase in 4 days), lab tests were back to normal, and methemoglobin levels decreased (1.4%), which resulted in the discontinuation of the intravenous fluid replacement therapy after 48 hours (*Table 2*).

Follow-up was conducted by the Department of Pediatric Gastroenterology, where adequate tolerance and weight gain with the elemental feeding formula was observed. At 45 days of life, a challenge test with infant formula (30 mL) was performed in the Pediatric Day Hospital. At the time of intake, the patient developed clinical (vomiting) and analytical (methemoglobin 1.8%) signs and symptoms of acute FPIES as a result of cow's milk protein hypersensitivity.

DISCUSSION

FPIES was first described by Powell in 1986.[7] The most frequent allergen in our environment is cow's milk protein, followed by fish and cereals.[8] In a Spanish multicenter study, the mean age at diagnosis of FPIES caused by cow's milk was 5 months, with a diagnostic delay of 4–6 months. Most patients suffer 2 or 3 episodes before diagnosis.[8]

FPIES diagnosis is based on clinical manifestations, which may be nonspecific and usually present with vomiting and/or diarrhea

Table 2. Patient´s clinical and laboratory course in our clinical case

	24 dol	25 dol	25 dol	26 dol	27 dol	45 dol
Hours elapsed since admission	**Hospital admission**					**Pediatric Day Hospital**
	0	**10**	**30**	**42**	**72**	
Status	Emergency	Start of intravenous fluid replacement therapy	Intravenous fluid replacement therapy + sodium bicarbonate bolus (1 mEq/kg)	After total fasting and start of elemental feeding formula	After vomiting resolution	Challenge test
Clínical manifestations	Pallor, lethargy, vomiting, diarrhea			Good skin color, good oral tolerance		Vomiting and irritability
pH	7.21	7.27	7.32	7.40	7.45	7.39
HCO_3- (mmol/L)	13	14	16.6	21.5	22.3	25.6
pCO_2 (mmHg)	25.5	20	27.8	32.5	28.7	42.4
BE (mmol/L)	-15.7	-14.5	-9.6	-3.4	-2.5	0.5
Láctic (mmol/L)	1.4	2.6	5.5*	3.2	5.8*	1.5
Methemoglobin (%)	2.7	2.9	2.9	1.4	1.6	1.8
Na^+ (mmol/L)	153	152	141	140	141	135
K^+ (mmol/L)	4	6.5*	5.1*	4	8.9*	5
Ca^{++} (mmol/L)	1.47	1.67	1.31	1.25	1.25	1.41
Cl^- (mmol/L)	136	135	118	115	114	104
Glucose (mg/dl)	76	97	80	91	83	68

dol: days of life; HCO_3: bicarbonate; pCO_2: partial pressure of carbon dioxide; BE: base excess.
*Parameter possibly altered due to difficult blood collection.

associated with lethargy, irritability, and pallor that develop 1 to 3 hours after allergen exposure. Neonatal clinical symptoms are similar to those already described, but newborn infants may also present with hematochezia or severe metabolic acidosis simulating inborn errors of metabolism.[2,3] Cases of neonatal FPIES have been described in which symptoms develop after the first ingestion of formula[9] or breast milk;[2] sensitization to the allergen may have occurred in the fetal period through transplacental passage of allergenic proteins.[2,9] In the differential diagnosis of neonatal-onset FPIES, it is critical to consider sepsis, hypertrophic pyloric stenosis, necrotizing enterocolitis or inborn errors of metabolism (*Table 3*).[1]

FPIES diagnosis is based on clinical criteria.[1] Skin allergy tests and food-specific IgE determination are usually negative. There is no specific laboratory test to detect FPIES; several tests have been described that can guide to the diagnosis, such as the presence of eosinophils in stool samples (detection of Charcot-Leyden crystals) or the lymphocyte stimulation test (increase of casein and beta-lactoglobulin levels).[10] However; these tests are not available in all hospitals. In neonatal units, the detection of methemoglobinemia in blood gas testing can be considered as a marker of severe FPIES. Decreased catalase activity during periods of acute intestinal inflammation leads to increased intestinal nitrites causing increased heme oxidation and consequently methemoglobinemia.[5,6] In a recent Japanese study, a methemoglobin cut-off level of 1% is necessary to diagnose FPIES (sensitivity 72.7% and specificity 97.1%) compared to other gastrointestinal conditions.[5] In our case, the clinical history was compatible with FPIES and the increase of methemoglobin levels up to 2.9% led us to suspect this disease. After initiation of hydrolyzed formula (fractionated milk proteins), metabolic acidosis improved, but methemoglobin levels remained unchanged and symptoms persisted. Following the change to elemental formula (with amino acids), symptoms disappeared and methemoglobin levels went back to normal (*Figure 1*). Other analytical abnormalities mainly associated with chronic FPIES have been described, such as anemia, hypoalbuminemia, leukocytosis with left shift, thrombocytosis, and eosinophilia.[1]

Although not necessary in patients with a high clinical suspected likelihood of FPIES, the established diagnosis of the chronic form consists in performing a challenge test with the suspected allergen when symptoms of acute FPIES start. It is advisable that the challenge test is performed at a hospital, with a peripheral venous access, because serious symptoms may develop subsequent to the challenge.[1] In our case, the challenge test was performed at 45 days of life and the clinical and analytical signs confirmed the diagnosis.

In most of the series described, patients with FPIES resulting from hypersensitivity to cow's milk have good tolerance to hydrolyzed milk; however, in cases of severe FPIES, it is necessary to frequently use elemental formulas.[1]

Definitive tolerance to cow's milk protein usually occurs around 24 months of age,[1,11] although the study from Israel reports a tolerance of 50% at 1 year of age.[4]

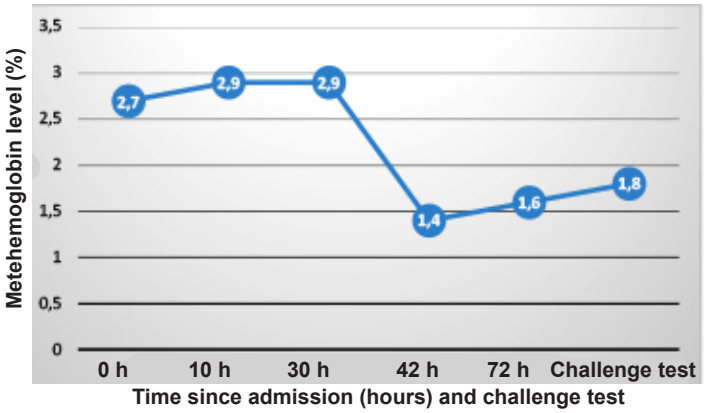
In conclusion, FPIES is an underdiagnosed and potentially serious disease, especially in the neonatal period, when the clinical signs and symptoms are nonspecific. In case of vomiting, diarrhea, and symptoms of lethargy or irritability, it is critical to ask about the infant's and mother's types of feeding. Several tests have been described to aid in the diagnosis, including an increase in methemoglobin levels. An accurate diagnosis is based on clinical criteria and a challenge test.[1]

Table 3. Differential diagnosis of FPIES

• Viral or bacterial gastroenteritis
• Sepsis
• Necrotizing enterocolitis
• Anaphylaxis
• Eating disorders
• Inborn errors of metabolism
• Lactose intolerance
• Cyclic vomiting
• Hirschsprung's disease
• Gastroesophageal reflux disease
• Eosinophilic gastroenteropathies
• Celiac disease
• Immune-mediated enteropathies
• Obstructive problems
• Clotting defects
• Alpha-1-antitrypsin deficiency
• Primary immunedeficiencies

FPIES: food protein-induced enterocolitis syndrome.

Figure 1. Methemoglobin level (%) is shown upon admission of the patient to the Neonatal Unit, as well as in the challenge test performed at the Pediatric Day Hospital. A decrease in methemoglobin level is observed 42 hours after admission, consistent with the fasting period and the start of elemental formula administration



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