Methemoglobinemia: Key in the Diagnosis of Food Protein-Induced Enterocolitis Syndrome by Cow’s Milk Protein in Infants

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Abstract

Background: Cow’s milk protein is the leading cause of food allergy in infants and children younger than 3 years. Food protein-induced enterocolitis syndrome is a non-IgE mediated cow’s milk protein allergy that presents with gastrointestinal manifestations and failure to thrive and could lead to severe dehydration and metabolic acidosis.

Case report: Here we report the case of a neonate with emesis, diarrhea and loss of weight, in which the finding of an increased methemoglobinemia was essential to suspect the final diagnosis: a food protein-induced enterocolitis syndrome by cow’s milk protein.

Conclusions: Endogenous acquired methemoglobinemia can occur in circumstances of colonic inflammation such as food protein-induced enterocolitis syndrome by cow’s milk protein. This entity is often misdiagnosed leading to severe dehydration and metabolic acidosis. Methemoglobinemia could help to guide the diagnosis and rapidly start with the exclusion diet.

Keywords: Cow’s Milk Protein; Allergy; Enterocolitis; Methemoglobinemia

Abbreviations

CMP: Cow’s Milk Protein; CMPA: Cow’s Milk Protein Allergy; FPIES: Food Protein-Induced Enterocolitis Syndrome; MetHb: Methemoglobin

Introduction

Food allergy is an increasing health concern. It is defined as an adverse health effect arising from a specific immune response that occurs reproducibly following exposure to a given food [1]. The immune reaction may be immunoglobulin (Ig)E mediated, non-IgE mediated, or mixed. Cow’s milk protein (CMP) is the leading cause of food allergy in infants and young children younger than 3 years [2,3].

Fifty percent of affected children have evidence of food-specific IgE antibody; however, skin prick tests and serum food-IgE levels correlate with response to elimination of diet poorly. Elemental diet based on the amino-acid formula leads to resolution of gastrointestinal eosinophilic inflammation typically within 6 weeks [4]. Gastrointestinal manifestations of non-IgE mediated cow’s milk protein allergy (CMPA) are nonspecific. In infants, history and physical manifestations may not distinguish between gastroesophageal reflux disease and CMPA. In a small group of older children, this entity may present also with dyspepsia or abdominal pain, and hence may be easily confused with functional gastrointestinal disorders or lactose intolerance [5]. Therefore, the challenge remains to make a correct diagnosis while minimizing the burden to patient family. Allergic proctocolitis is a benign disorder manifesting with blood-streaked stools in otherwise healthy appearing infants. Symptoms resolve within 48 - 72h following elimination of CMP. Most infants tolerate cow’s milk by their first
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birthday [6]. Allergic eosinophilic gastroenteritis affects infants as well as older children and adolescents. Abdominal pain, emesis, diarrhea, failure to thrive, or weight loss are the most common symptoms. A subset of patients may develop protein-losing enteropathy [7]. Food protein-induced enterocolitis syndrome (FPIES) presents in young formula-fed infants with chronic emesis, diarrhea, and failure to thrive. Reintroduction of cow’s milk following a period of avoidance could result in profuse, repetitive emesis within 2 - 3h following ingestion, and even in hypovolemic shock in up to 20% of accurate exposures. Therefore, attempts of re-introduction of milk must be done under physician supervision and with secure intravenous access [8].

A correct diagnosis allows the appropriate diet to be given to affected infants, thus supporting normal growth and development. While IgE mediated CMPA and allergic proctocolitis are easy to be recognized by medical team, FPIES is usually delayed in diagnosis leading to severe dehydration and malnourishment. Familiarization of different forms of presentation of CMPA would facilitate the rapid implementation of an elimination diet and, thus, the improvement of clinical symptoms.

Here we report the case of a neonate with FPIES in which the finding of a significant methemoglobinemia was key to achieve diagnosis. Acquired methemoglobinemia in infants has been observed mostly in association with diarrheal illnesses with shock and acidosis. There have been very few reports of methemoglobinemia associated with FPIES in infants.

Case Report

A 29-day-old Spanish male infant was referred to our Neonatal Unit with a history of poor weight gain associated with diarrhea. The baby was born at term by spontaneous vaginal delivery after an uneventful pregnancy. Anthropometry at birth was normal: weight: 3.04 kg; length: 50 cm; and head circumference: 35.5 cm. Apgar score was 9/10. He was fed with regular milk formula by mother’s decision. No remarkable familiar medical history was referred. The baby was described to be asymptomatic, but crying spells from the second week of life attributed to baby colics. At 22 days of age started with diarrhea. The number and volume of stools increased progressively up to a maximum of ten at day 25th, leading to weight loss. Those facts motivated the visit to the emergency department of his local hospital. Baby was admitted because of moderate dehydration (6% of weight loss) and hyperchloremic metabolic acidosis. Although i.v. fluids were started and even parenteral bicarbonate administered, this disorder persisted leading to the suspicion of a renal tubular acidosis and it was decided to be referred to our tertiary hospital for study.

At admission, his weight was 3.2 kg. Temperature, pulse, blood pressure, respiratory rate and oxygen saturation in room air were normal. The physical examination was only remarkable for mild signs of dehydration. His behavior was normal. Capillary blood gases showed: pH 7.27; pCO2 23.5 mmHg; HCO3 - 10.5 mEq/l; EB -14; GAP: 15.5; Cl-: 115 mEq/l. Thus, intravenous bicarbonate was prescribed for its correction and subsequent controls demonstrated a gradual improvement within the first 12 hours. Abdominal ultrasound showed normal structure and flow of both kidneys, but distended loops of small bowel and increased peristalsis. No polyuria was detected. Urine pH was 6 - 7. Due to gastrointestinal symptoms, feeding was reinitiated with a semi-elemental formula (Alfarè®). The acceptance was good and the diarrhea progressively remitted. After four days, the neonate was asymptomatic and discharged home with normal weight.

One day later, on day 33rd of life, presented to our emergency department because of discoloration and vomits after each feeding. The weight was 3.04 kg; temperature: 36.4°C; pulse: 140 bpm; blood pressure: 88/45 mmHg; respiratory rate: 50 - 55 bpm; oxygen saturation: 99%. The baby showed a pale, grayish discoloration; but good tone, activity, state of hydration and capillary refill. Abdominal examination was normal. No other physical signs were observed. His admission complete blood count (CBC) showed: white blood cells (WBC) 29.73/mcl; hemoglobin (Hb) 10.6 g/dl; and platelets 389/mcl. The differential was neutrophils (N) 16.03/mcl; lymphocytes (L) 10.8/mcl; monocytes (M) 2.5/mcl; and eosinophiles (E) 0.4/mcl. C-reactive protein, procalcitonine, serum electrolytes and creatinine were normal. Urea was increased for age: 30 mg/dl, in connection with dehydration. Capillary blood gases showed: pH 7.21; pCO2 35.7 mmHg; HCO3 - 13.6 mEq/l; EB -13; GAP 14.6; lactate 5.6 mmol/l; Cl 117 mEq/l. Urine pH was 5.5. The observation that the metabolic decompensation...
and gastrointestinal symptoms (repeated vomits) rapidly reappeared after the reintroduction of the regular formula after his discharge, supported the hypothesis that metabolic acidosis and previous gastrointestinal symptoms (crying spells, diarrhea and thus weight loss) might be secondary to a CMPA. Additionally, the capillary blood gases study with co-oximetry unveiled an increased methemoglobin (MetHb): 11.3%. Stool was negative for rotavirus, adenovirus, astrovirus, and bacterial growth for enteric pathogens. Urine culture and renal function were normal. A semi-elemental formula was reinitiated; therefore, the baby became less irritable, accepted the hydrolyzed formula with eagerness and remained relaxed after each feeding. The vomits subsided and the metabolic acidosis with high MetHb completely normalized in 8 hours, without any supply of bicarbonate or blue methylene. The patient gained weight: 360g in 5 days. The rapid and complete recovery after the initiation of the elimination diet supported the hypothesis of FPIES induced by CMP. Specific IgE to total milk formula, α-lactalbumin, β-lactoglobulin, seroalbumin and casein were negative; and total IgE 9.12 kU/l. Glucose-6-phosphate dehydrogenase (G6PD) and Hb electrophoresis studies were normal.

Discussion

FPIES is a symptom complex of severe vomiting and diarrhea caused by non-IgE-mediated allergy to CMP. Symptoms typically begin in the neonatal period in association with failure to thrive and may progress to metabolic acidosis and methemoglobinemia. MetHb, a form of hemoglobin that cannot bind oxygen, is synthesized when the deoxygenated heme is oxidized from the ferrous (Fe2+) to the ferric state (Fe3+). In this state the heme iron is unable to bind and transport oxygen. Oxidative forces continually form small amounts of methemoglobin that are rapidly reduced to the ferrous state by enzymes (primarily NADH-dependent cytochrome b5 methemoglobin reductase) present in the red blood cells. But in the erythrocytes of infants under 6 months of age this enzyme activity has been found to be only about 50% as active as adults [9].

Methemoglobinemia in early infancy can be congenital or acquired. Congenital methemoglobinemia is usually either due to hemoglobin M (HbM), which has a predisposition to stabilize heme iron in the ferric state, or due to congenital deficiency of the cytochrome b5 enzyme. Acquired methemoglobinemia occurs when the rate of heme iron oxidation to the ferric state is greater than the erythrocytes' capacity to reduce MetHb to deoxyhemoglobin. Exogenous causes include ingestion of oxidative substances such as nitrite from fertilizers contaminating well water and baby foods such as spinach, carrots, and beets that are rich in nitrates. It can also occur iatrogenically from diaper making ink, dyed blankets, chlorhexidine in disinfectants, silver nitrate, and inhaled nitric oxide and local anesthetics such as EMLA and benzocaine spray. Endogenous methemoglobinemia in early infancy probably occurs during conditions of colonic inflammation. In a normal population, the colonic anaerobic bacteria reduce the luminal nitrate to nitrite and subsequently to ammonia. The bacterial reductase enzymes bring this about. The nitrite is also taken up to the colonocytes where, with the help of catalase, it is oxidized to nitrate, which is then returned to the enteric anaerobes for reduction and energy production. This balance is disrupted by colonic mucosal inflammation (as in CMPA) when the bacterial nitrite reductase and possibly the colonic catalase are inhibited [10]. This leads to decreased production of ammonia by the bacteria and fewer nitrates by the colonocytes leading to accumulation of intracellular nitrite and eventually erythrocyte nitrite level. As the NAD-dependent cytochrome b5 methemoglobin reductase activity is reduced in young infants and with continuing inflammation MetHb accumulates.

The diagnosis of FPIES rests on clinical and challenge criteria. In practicality, many patients would not undergo a formal challenge as infants because the diagnosis becomes self-evident after elimination of the causal protein. Particular features do not satisfy the general description of infantile FPIES: reaction to foods other than cow’s milk or soy, onset of symptoms beyond 9 months of age, and development or presence of IgE antibody directed toward the causal protein [11]. Symptoms recur approximately 2 hours after reintroduction of the protein along with a coincident elevation of the peripheral blood polymorphonuclear leukocyte count. Most of infants do well consuming a casein hydrolysate formula; however, for the rare patients reactive to hydrolysate, an amino acid-based formula is appropriate [12]. Follow-up challenges should be performed at intervals to determine tolerance (approximately every 18 - 24 months, depending on the clinical severity). These challenges should be performed under a physician’s supervision with emergency medications immediately available, because dramatic reactions, including shock, can occur [13].
Endogenous methemoglobinemia in infants has been mostly reported in relation to diarrheal illnesses and acidosis [14]. There have been very few reports of methemoglobinemia in infants in conjunction with FPIE [15]. From the above information, we hypothesize that in early infancy certain conditions that lead to colonic inflammation, such as CMPA, may show methemoglobinemia. Methemoglobinemia may be key to achieve a correct and rapid diagnosis in FPIES by CMP in infants. Therefore, in such patients, the MetHb level should be checked and managed accordingly.

**Conflict of Interest**

The authors declare no financial interest or conflicts of interest.

**Bibliography**