

Case Report of Methemoglobinemia in Two Patients with Food Protein-Induced Enterocolitis

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Introduction

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 food protein-induced enterocolitis. We report two such cases.

Patient 1

A 32-day-old African-American male infant presented to our emergency department (ED) with a history of poor weight gain associated with vomiting and blood-stained stools. He was born by spontaneous vaginal delivery to a G5P5 lady at 38 weeks after an uneventful pregnancy. He weighed

2.64 kg at birth. He was discharged to home with Isomil (Ross) at 48 hours, as there was a family history of cow's milk protein intolerance. At 5 days of age he started to spit up and it worsened by 2 weeks of age. He also had diarrhea with specks of blood in the stool. He was therefore started on Alimentum (Ross), and the symptoms persisted and by 3 weeks of age he started to have about 10 stools per day. At this stage his pediatrician changed his milk to Nutramigen (Mead Johnson), and in spite of this the symptoms have persisted. His mother brought him to our hospital for second opinion. Apart from the family history of cow's milk protein intolerance, the father and a sibling of the patient had asthma.

At admission he weighed 2.9 kg. His temperature was 37.1°C, pulse rate 150/min, respiratory

rate 44/min, and oxygen saturation was 100% in room air. The physical examination was only remarkable for a scrawny infant with signs of dehydration. After a fluid bolus and septic workup with blood and urine culture he was started on intravenous ampicillin and cefotaxime. His admission complete blood count (CBC) showed white blood cells (WBC) 31.6, hemoglobin (Hb) 10.9, and platelets 951. The differential was neutrophils (N) 45%, lymphocytes (L) 35%, and monocytes (M) 19%. Serum electrolytes were normal except for bicarbonate, which was 14 mEq/L and a serum lactate level of 4 mmol/L. The formula was changed to Neocate (SHS International) on the next day. Although there was some improvement with spit-ups and weight gain, the symptoms grossly persisted. An upper gastrointestinal and follow-through study on the 6th day of admission was reported to be normal. In view of the persistence of the spit-ups and increased lactate at admission, a metabolic consult was obtained. An arterial blood gas (ABG) study with co-oximetry showed a pH 7.396, base deficit -5, lactate of 2.7 mmol/L, and methemoglobin (MetHb) of 22.1%. In view of high MetHb and lactate he was treated with Methylene blue IV at

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a dose of 2 mg/kg. Prior to Methylene blue therapy, glucose-6-phosphate dehydrogenase (G6PD) and Hb electrophoresis were sent and both were reported to be normal for age. MetHb level dropped to 2.2% after treatment with Methylene blue. Stool was negative for rotavirus, clostridium difficile toxins, and bacterial growth for enteric pathogens. The stool was hemocult negative at discharge. With a negative culture report the antibiotics were stopped after 48 hours. The patient had gained 460 g in 9 days and had stopped vomiting. He was discharged with Neocate, Pepcid, and vitamin C. On phone inquiry at 1 year of age he was reported to be thriving well.

Patient 2

A 5-week-old African-American female infant was admitted to the intensive care unit (ICU) with dehydration and shock after a history of persistent vomiting and loose stools for 4 weeks. She was born to a G1P1 lady, at term, by emergency cesarean section for fetal distress due to cord around the neck. She weighed 3.15 kg at birth. The infant had no immediate problems and was started on Similac (Ross). As she started to have spit-ups, the formula was changed to Isomil (Ross) on day 4 of life. At 3 weeks the patient started to have loose stools, initially 5 to 7/day and later going up to 20/day. There was also gross blood seen in the stool. As the vomiting and loose stools persisted, her pediatrician had changed the Isomil to ProSobee (Mead Johnson). By the next day the patient became lethargic and the fluid intake started to drop. Her pediatrician referred her to a local emergency room (ER) where she was found to have a

weak cry, poor capillary refill, and dry mucosa. Her vitals were heart rate (HR) 172/min, respiratory rate (RR) 44/min, temperature 36.8°C, and pulse ox 97%. CBC, blood culture, and urine culture were drawn and IV fluid bolus was given. The patient was then transferred to our ICU.

On admission the patient was still sleepy and lethargic but arousable. She had a pale gray look, appeared dehydrated and capillary refill was poor. She weighed 3.4 kg. Her physical examination was otherwise significant for a distended but soft, nontender abdomen with normal bowel sounds. ABG drawn at admission showed pH 7.19, base deficit -12, lactate 1.4 mmol/L, and MetHb 14%. CBC was significant for WBC 23.1 and platelet of 562. Blood biochemistry showed serum bicarbonate of 5 mEq/L. Intravenous fluid bolus was given and maintenance fluid with bicarbonate was started. Ampicillin, cefotaxime, and metronidazole were started. As the MetHb level was not too high no specific treatment was started. Antibiotics were discontinued in 2 days as the cultures were reported to have no growth. Stool was negative for rotavirus, clostridium difficile toxins, and bacterial growth for enteric pathogens. Her formula was changed from ProSobee to Neocate. The vomiting and diarrhea stopped within 3 days. But the stool was still hemocult positive at discharge. She was discharged home on the 6th day. She gained 580 g during the 6 days in hospital. The gastroenterology and allergy team has since followed her up. After 1 year of age she was tried on dairy products, but developed diarrhea in 1 week. At 17 months she is still taking Neocate 1+ and continues to be on a dairy- and soy-free diet.

Discussion

Methemoglobin, a form of hemoglobin that cannot bind oxygen, is formed when the deoxygenated heme is oxidized from the ferrous (Fe^{2+}) to the ferric state (Fe^{3+}). In this state the heme iron is unable to bind and transport oxygen. Naturally occurring 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 young infants this enzyme activity has been found to be only about 50% as active as in adults.¹ By 6 months of age this enzyme activity should reach adult levels.

Methemoglobinemia in early infancy can be congenital or acquired. Congenital methemoglobinemia is usually either due to hemoglobin M (HbM), which has a predilection to stabilize heme iron in the ferric state, or due to congenital deficiency of the cytochrome b5 enzyme. In infancy 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. It can be due to exogenous or endogenous cause. Exogenous causes include ingestion of oxidative substances such as nitrite from fertilizers contaminating well water and prepared baby foods such as spinach, carrots, and beets that are rich in nitrites. It can also occur iatrogenically from diaper marking 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 in 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 (Figure 1). This balance is disrupted by colonic mucosal inflammation (as in cow milk or soy protein intolerance) when the bacterial nitrite reductase and possibly the colonic catalase are inhibited.² 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 NADH-dependent cytochrome b5 methemoglobin reductase activity is reduced in young infants and with continuing inflammation methemoglobin accumulates.

Endogenous methemoglobinemia in infants has been mostly reported in relation to diarrheal illnesses and acidosis.³⁻⁵ There have been very few reports of methemoglobinemia in infants in conjunction with food protein-induced enterocolitis⁶⁻⁹ of which only Murray and Christie's series had patients with soy protein intolerance. Both our patients started to have symptoms of enterocolitis while they were receiving a soy formula (Isomil), but the symptoms persisted even when they switched to a protein hydrolysate formula (Alimentum, Pregestimil, and Nutramigen). In Murray and Christie's series the patients described tolerated a hy-

drolysate formula, whereas the symptoms in the patient reported by Sicherer⁷ improved after starting a soy formula. The two patients described here recovered only after introduction of Neocate, an amino acid-based formula.

We conclude that endogenous methemoglobinemia in young infants can occur as a complication of inflammation caused by food protein intolerance. Although protein hydrolysate formulae have been used successfully to treat this condition we recommend that using an amino acid formula like Neocate will be the definite way to treat these infants. From the above information we hypothesize that in early infancy any condition that leads to colonic inflammation can lead to methemoglobinemia. Therefore, in such patients, the MetHb level should be checked and managed accordingly.

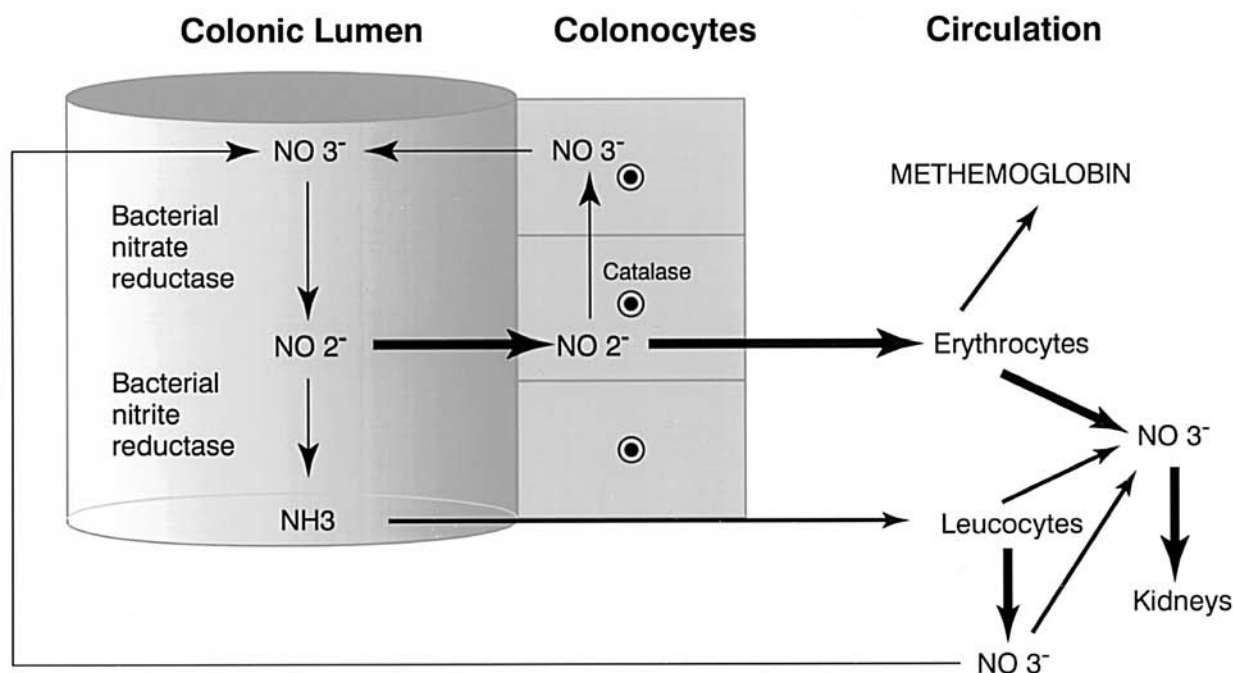


Figure 1. Mechanism of methemoglobin production under conditions of colonic inflammation. (From Roediger WEW, Radcliffe BC. Role of nitrate and nitrite as a veclox couple in the rat colon: implications for diarrhea conditions. *Gastroenterology*. 1988;94:915-922.)

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