Transient Organic Aciduria and Methemoglobinemia With Acute Gastroenteritis

Acute gastroenteritis remains a common medical problem in the pediatric population and diarrhea may be life threatening in the neonate. Organic aciduria has been observed in children with short bowel, malabsorption, and Hirschsprung's disease,[1-6] and methemoglobinemia has been observed in children with acute diarrheal disease.[7-15] The two infants described here, however, represent the initial report of concomitant transient organic aciduria and methemoglobinemia in patients with diarrhea. Awareness of the association of these findings will be valuable in directing the clinical evaluation of similar patients. Recognition that the organic aciduria may be transient in these patients will prevent the pediatrician from concluding that the child has a primary inborn error of metabolism and undertaking an inappropriate course of management.

CASE REPORTS

Patient 1

A 2-month old Latin American female infant (birth weight 2440 g), born of a 19-year-old primagravida after a normal pregnancy and vaginal delivery, had been well until age 5 weeks when she was admitted to the Texas Children's Hospital after 2 days of diarrhea, nonbilious vomiting, and refusing to feed. At age 2 weeks the neonate's formula had been changed empirically from Similac to Nursoy (Wyeth, Philadelphia, PA) because of constipation. The family history was significant for a maternal cousin with cystic fibrosis.

At the time of admission, the patient was lethargic, cyanotic, and 10% to 15% dehydrated. Her weight was 2.8 kg (below the third percentile). Her arterial blood pH was 7.13, and P_{CO_2} was 22 mm Hg with a P_{O_2} of 26 mm Hg while she was receiving 100% oxygen by face mask. The serum electrolyte levels were as follows: sodium 140, potassium 3.8, chloride 117, and bicarbonate 8 mEq/L. She was rehydrated with intravenous fluids, including sodium bicarbonate (1 mEq/kg), and serum electrolyte levels were normalized. The infant underwent endotracheal intubation for a brief period of ventilatory support. Blood, urine, and stool cultures were negative for bacterial pathogens; however, because no cerebrospinal fluid could be obtained, the infant was treated for 7 days with intravenous ampicillin and gentamicin. She continued to experience episodes of apnea and bradycardia with cyanosis. Subsequently, a sweat chloride evaluation yielded normal results and a barium swallow revealed gastroesophageal reflux, although results of an esophageal pH probe study were normal. The infant began a regimen of thickened feedings, positioning with head elevated at a 45° angle, and metoclopramide (Reglan, A.H. Robins, Richmond, VA). Urine and serum samples were obtained for evaluation of organic acids and amino acids, respectively. Because of adequate weight gain and clinical improvement while receiving Nursoy, the infant was discharged 15 days after admission.

Four days later, the results of the urine organic acid and serum amino acid evaluations became available. Abnormal urine metabolites included methylmalonic, ethylmalonic, and 3-hydroxypropionic acids. The serum amino acid levels were within normal limits. The infant returned the next day and appeared well. The urine organic acid evaluations were repeated and were essentially unchanged (Table).

The following day, the infant returned to the hospital after acute onset of vomiting. She had a mottled and cyanotic appearance. Her weight was 3.3 kg (below the fifth percentile), and her height was 52 cm (third percentile). While she was breathing room air, her arterial blood pH was 7.41 and P_{CO_2} was 23 mm Hg. Serum sodium level was 142 mEq/L, potassium 4.5 mEq/L, chloride 108 mEq/L, and bicarbonate 20 mEq/L, ammonia 32 μmol/L, blood urea nitrogen 3 mg/dL, creatinine 0.1 mg/dL, and glucose 66 mg/dL. Hemoglobin concentration was 10.2 g/dL, hematocrit 26%, white blood cell count $1.8 \times 10^4/\mu L$, and platelets 647 000/μL. Blood, cerebrospinal fluid, and urine cultures were negative for bacterial pathogens. The methemoglobin level was 8.7%. Intravenous methylene blue (1 mg/kg) was administered. Hemoglobin A and F levels were 64% and 36%, respectively. The serum carnitine levels were as follows: total, 26 nmol/mL (N 46 ± 10), free, 21 nmol/ml (N 37 ± 8.0); after an oral carnitine load (100 mg/kg), the urine acyl carnitine profile was reported to be normal (Dr Charles Roe, Duke University Medical Center).

Because of concern about potential organic acidemia, protein was restricted in the diet to 1.2 g/kg/day. The infant was treated empirically with hydroxycobalamine, 1 μg intramuscularly for 3 days. The methemoglobin level remained elevated at 6.7%. On the fourth day of hospitalization, she had increasingly loose stools with pH 4.5 to 5.0, reducing substances 1 to 3+, and positive guiac. Stool cultures for *Clostridium difficile* toxin and electron microscopic examination for viral particles were negative. The diarrhea began to resolve after oral administration of Pedialyte (Ross, Columbus, OH). Results of a subsequent urine organic acid analysis were normal (Table), and the methemoglobin level was 1.0%. The infant's diet was advanced to Pregestimil (Mead Johnson, Evansville, IN), and she was discharged on the 10th day of hospitalization on a regimen of Pregestimil, Polyvisol (Mead Johnson, Evansville, IN), and metoclopramide. Subsequent organic acid analyses at 12 and 14 weeks of age showed increased amounts of dicarboxylic acids typical

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TABLE. Urine Organic Acid Levels of Patients 1 and 2 at Various Ages*

Urine Organic Acids	Age (wks):	Patient 1							Patient 2		
		6 wk	7 wk	7.5 wk	12 wk	14 wk	20 wk	50 wk	4 wk	7 wk	12 wk
Lactic		++	+	+	0	0	+	tr	+	0	0
Methylmalonic		+	tr	0	0	0	0	0	+	0	0
Ethylmalonic		+	0	0	0	+	0	0	0	0	0
3-Hydroxypropionic		+	+	0	0	0	0	0	+	0	0
Adipic		+	0	+	+	+	+	0	+	0	0
Suberic		+	0	+	+	++	+	0	0	0	0
Sebacic		0	0	+	++	++	+	0	0	0	0

* Results are given semiquantitatively (0 to ++++); tr, trace.

of an infant fed a formula containing medium-chain triglycerides (Table). At age 5 months, while still on a diet of Pregestimil, she was growing well and weighed 6.15 kg (25th percentile). When examined at 11.5 months of age, her diet consisted of cow's milk and table foods. She weighed 9.68 kg (70th percentile). Her length was 77.6 cm (95th percentile), and her urine organic acid levels were normal (Table).

Patient 2

A 19-day-old black male neonate was admitted to Louisiana State University Medical Center after a 3-day history of vomiting and diarrhea. He was born at term to a gravida 2, para 2, 21-year-old mother and weighed 2.845 kg at birth. There was no family history of fetal wastage or severe illness in infancy. On admission, he weighed 2.46 kg and was severely dehydrated. His arterial pH was 7.27 and P_{CO_2} was 19 mm Hg. The serum electrolyte levels were as follows: sodium 134 mEq/L, potassium 5.1 mEq/L, chloride 114 mEq/L, and bicarbonate <5 mEq/L. His blood urea nitrogen level was 42 mg/dL, creatinine 1.6 mg/dL, and uric acid 20 mg/dL. The hemoglobin concentration was 11.5 g/dL, white blood cell count 4.2 $\times 10^4/\mu L$, and platelets 899 000/μL. Methemoglobin concentration was 20.2%. He was treated with intravenous fluids and began a regimen of half-strength Pregestimil. Twenty-four hours later the methemoglobin level was 3.6%. No viruses or pathogenic bacteria were cultured from stool, urine, blood, or cerebrospinal fluid. Urine organic acid analysis revealed the presence of methylmalonic and 3-hydroxypropionic acid. Serum amino acid levels were normal. Results of a test for glucose-6-phosphate dehydrogenase deficiency were negative.

The patient subsequently became acidotic again and required intravenous fluids. Protein was slowly increased from 0.5 g/kg when he began to tolerate formula feedings. For a period of 4 weeks, he was given supplemental sodium bicarbonate because of renal tubular dysfunction.

Serum protein levels fell markedly, reaching a nadir of 2.0 mg/dL, and intravenous albumin was given after increased oral protein intake proved to be ineffective. Levels of serum amino acids and urine organic acids were normal when the patient was on a diet of full-strength ProSobee (Mead Johnson, Evansville, IN). At 3 months of age, he was tolerating full strength ProSobee and weighed 4.92 kg (25th percentile).

DISCUSSION

The association of concomitant transient organic aciduria and methemoglobinemia during an acute diarrheal disease has not previously been reported. Although the presence of urinary lactic, ethylmalonic, methylmalonic, and 3-hydroxypropionic acids was not specific for any known enzyme deficiency in patient 1, the presence of methylmalonic and 3-hydroxypropionic acids in patient 2 suggested the possibility of an inborn error of metabolism. Several cases of transient D-lactic acidemia have been reported in adults with the short gut syndrome.[16,17] In three cases, abnormal gut flora were identified with enhanced metabolism of carbohydrate to D-lactic acid. Patients with short gut syndrome have been reported to exhibit a variety of organic acids in their urine, including metabolites observed in our two patients—specifically, lactic, methylmalonic, and 3-hydroxypropionic acids.[1-3,6] Abnormal urinary metabolites have also been observed in patients with malabsorption.[4,5] Recently, transient methylmalonic acidemia has been described in a 23-day-old infant being evaluated for apnea who was diagnosed with Hirschsprung's disease at 12 months of age.[6] There is strong evidence that the abnormal metabolites are by-products of bacterial metabolism in patients with underlying enteral disease[1-6] and gut flora may contribute to these metabolite concentrations even in patients with primary disorders of intermediary metabolism.[18]

More than 80 cases of nonhereditary transient methemoglobinemia in neonates and infants with a diarrheal illness and metabolic acidosis have been reported.[7-15] Several mechanisms have been proposed for this observation, including nitrite/nitrate ingestion, increased bacterial nitrite/nitrate production secondary to aberrations in normal bowel flora, or increased host nitrite/nitrate production by leukocytes after an inflammatory challenge (reviewed in Ref 19). Nitrate may be reduced to nitrite, and absorption of this ion leads to the reduction of hemoglobin to methemoglobin (reviewed in Ref 19).

Transient methemoglobinemia has been observed during a diarrheal illness without nitrite/nitrate ingestion.[20] The factors thought to predispose the infant rather than an adult or older child to clinically significant methemoglobinemia include a higher gastric pH level and subsequent bacterial colonization of the upper gastrointestinal tract, a lower activity of the nicotinamide adenine dinucleotide-dependent methemoglobin reductase, and a high proportion of fetal hemoglobin content during the newborn period (reviewed in Ref 11). Clinically, a methemoglobin value of less than 25% does not require therapeutic intervention.[21]

In a study of 11 patients with transient enteritis and methemoglobinemia,[7] at least 3 of these patients had no specific organic aciduria, although 1 had lactic aciduria. A large series of urine organic acid determinations performed at the Baylor College of Medicine for a variety of problems, including failure to thrive and diarrheal disease, have not revealed transient elevations in abnormal urine organic acids in other patients (W.O'B., Baylor College of Medicine, unpublished observations, 1989).

The organic aciduria in our patients may have resulted from increased rates of organic acid production from malabsorption, aberrant bacterial flora, and/or increased absorption of organic acids from the intraluminal contents due to damaged colonic mucosa. In addition, nitrites/nitrates have been shown to increase the rate of fatty acid oxidation in colonic mucosa,[22-24] possibly giving rise to abnormal metabolites. It is not clear whether concomitant methemoglobinemia and organic aciduria may be associated with a specific enteric pathogen or a more generalized physiologic process that has been previously unrecognized.

These patients illustrate that the organic aciduria associated with diarrhea and methemoglobinemia may be acquired and transient, and it may not represent a primary inborn error of metabolism. Recognition of this possibility will prevent incorrect diagnosis and inappropriate dietary manipulation in the patient with acute enteritis and organic aciduria.

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A Horrifying Television Commercial That Led to Constipation

I would like to call attention to an unusual event that led to constipation in a child I recently examined.

CASE REPORT

A 3-year-old boy who had been constipated for 6 weeks was brought to my office. He had previously moved his bowels approximately once a day and had been toilet trained for at least 6 months. However, the frequency of bowel movements had decreased to approximately every 4 days and his stools were usually hard. He had initially complained of anal discomfort and refused to move his bowels. Eventually, he began to move his bowels but only infrequently, while standing up, and while wearing a diaper. He adamantly refused to sit on the toilet and would ask for a diaper to be put on whenever he needed to move his bowels. He had been treated elsewhere, with transient improvement in his constipation.

Results of my examination of the boy were normal. A rectal examination showed no stool because he had recently moved his bowels. Treatment with a mineral oil preparation resulted in improvement in the character of his stools and the return of his regular, daily bowel movements. However, he persisted in moving his bowels only while standing up and wearing a diaper. His mother believed his refusal to use the toilet was uncharacteristic of her son. Furthermore, he refused to divulge his reason for not wanting to sit on the toilet. Finally, he gave in to his mother's constant asking and told her that he had seen a television commercial advertisement in which a toilet bowl was portrayed as turning into a monster, with the seat cover making a chomping movement. This image scared him from again sitting on the toilet; he feared that it "would get him." At present, efforts are directed at encouraging the patient, with much support and reassurances, to use the toilet. The family is having some success, although not consistently.

When the mother filed a complaint with the marketing director of the company that placed the advertisement, she learned that it was a modified version of a previous advertisement about which other viewers had complained. She was told that the advertisement was to be withdrawn 3 months later, when the contract expired.

COMMENTS

The circumstances in this case and the patient's communication of the reason for his constipation left no doubt that he had become constipated as a result of his inability to move his bowels regularly because of fear that harm would come to him if he sat on the toilet. Understandably, he needed to move his bowels eventually, but he was able to do so only while standing up and while using a diaper as a toilet replacement.

The importance of the history in arriving at the correct diagnosis for this child cannot be overemphasized. Without it, management might have been misdirected and the reason for the constipation never known.

This experience should alert us to be wary of allowing children to watch freely any television shows, even funny commercial advertisements. The advertisement described in this paper might have been funny to an adult, but it was certainly fearful and horrifying to a young child.

It may be difficult to control the shows and commercial advertisements that appear on television, but it is possible for physicians to make parents aware of the possible consequences[1,2] of not selectively regulating, according to age and maturity, the shows their children watch. Also, efforts toward making producers and markets aware of complaints about their shows may help minimize and curtail the showing of undesirable programs, as in this case.

Although there has been more concern about the relationship between television and aggressive behavior, we should not overlook the possibility of other psychological or behavioral problems arising from television viewing. The recommendation to obtain television-watching histories of patients

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