Arginine Deficiency-Induced Hyperammonemia in a Home Total Parenteral Nutrition–Dependent Patient: A Case Report

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ABSTRACT. Background: Patients with short bowel syndrome and renal dysfunction with TPN dependence are at high risk for developing hyperammonemia if the TPN does not contain sufficient quantities of arginine. Providing proper nutrition support is essential in the management of these patients. Methods: We report on a patient with short bowel syndrome, TPN dependence, and normal renal function who developed hyperammonemic encephalopathy due to inadvertent lack of arginine in his TPN. Results: The patient was successfully treated with hemodialysis and an IV arginine infusion to resolve the hyperammonemia. His home TPN was also adjusted such that arginine was added to his subsequent solutions. Conclusions: Our patient underscores the importance of adequate and sustained arginine supplementation to avoid hyperammonemia in TPN dependent patients with short bowel syndrome. (Journal of Parenteral and Enteral Nutrition 25:286–288, 2001)

It is essential to maintain nutritional status and avoid fluid and electrolyte abnormalities in patients with short bowel syndrome (SBS) who are dependent on total parenteral nutrition (TPN). Hyperammonemia has been reported in patients with short bowel syndrome and renal dysfunction while receiving TPN. The effectiveness of arginine supplementation in the treatment of hyperammonemia caused by inborn errors of metabolism or dietary arginine deficiency has been documented in the literature.[1,2] We report on a TPN-dependent patient whose hyperammonemia was successfully treated with arginine. Our patient underscores the importance of including arginine in a patient's daily TPN to avoid hyperammonemia.

CASE REPORT

A 19-year-old male was transferred to Children's Hospital of Michigan after he was found unarousable on the day of admission. He was obtunded and unresponsive. His past medical history was significant for autism (his baseline mental status consisted of being active but nonverbal), short bowel syndrome, TPN dependence, and multiple central venous line infections. The patient had been receiving TPN since December 1996 after resection of his small intestine from the ligament of Treitz to the ileocecal valve and partial colon. His resection was a result of a malrotation and midgut volvulus. We started caring for him for 1 year before the first episode of acute encephalopathy. Upon transfer to our care he had a baseline weight of 31 kg and had gained 5 kg over the course of the year. Before admission he tolerated only small amounts of oral intake, which included half-strength Ensure, 3 cans/d. Previous attempts to increase his oral intake had led to excessive diarrhea, requiring this patient to remain TPN-dependent. His home TPN prescription was for approximately 1500 kcal/d. Higher caloric intake from his home TPN regimen had been attempted in the past, but resulted in hepatic dysfunction.

Before admission the patient was under foster care. Based on information from the foster mother and the home visiting nurse, it appeared the patient was compliant with the prescribed regimen. The patient's medications included cholestyramine, 0.5 g given 3 times/d; Actigall, 250 mg given every day; Immodium, 1 mg given 2 times/d. He was taking these medications for more than 1 year before this admission.

On admission the patient had normal renal and liver function and was afebrile. The cerebrospinal fluid and blood cultures, urine drug screen, serum lead level, and head computerized axial tomography (CAT) scan showed no abnormalities. However, his plasma ammonia concentration was 375 μmol/L (normal: 9–33 umol/L). Blood gas analysis showed respiratory alkalosis with pH 7.63; pCO_2, 17 Torr; HCO_3, 17 mmol/L; and pO_2, 96%. Two hours later the ammonia concentration was measured as 344 μmol/L. The etiology of his hyperammonemic encephalopathy and coma was unknown. Hemodialysis was initiated on day 1 of admission until the ammonia concentration decreased

TABLE I
Summary of patient's plasma amino acid assay in relation to his presentation with hyperammonemia

Normal Range	First Admission			Second Admission		
	Day 1*	Day 2+	Day 3‡	Day 1‡	Day 3‡	Day 9§
Glutamine (42–760)	1371	482	758	571	640	682
Ornithine (26–195)	17	106	124	130	110	51
Citrulline (16–55)	Trace	Trace	Trace	Trace	Trace	Trace
Arginine (21–157)	Trace	102	195	212	153	Trace

All values used in assay measured in μmol/L.
*Prior to administration of the arginine infusion but during hemodialysis
+Post hemodialysis and during arginine infusion
‡Post arginine infusion
§Levels taken as an outpatient

from 344 μmol/L to 78 μmol/L in 4 hours. A plasma aminogram taken during hemodialysis revealed glutamine, 1370 μmol/L (normal: 42–760 μmol/L); ornithine, 17 μmol/L (normal: 26–195 umol/L); citrulline, trace (normal: 16–55 μmol/L); and arginine, trace (normal: 21–157 μmol/L). We considered that the patient may have a urea cycle enzyme deficiency.

On day 2 of admission and 5 hours postdialysis, the ammonia concentration was measured as 51 μmol/L. The patient was started on intravenous (IV) arginine hydrochloride 4.6 g (0.14 g/kg) over 90 minutes (3.1 g/h), followed by a continuous infusion of arginine at 1.9 mL/h (10% arginine hydrochloride).[3] Ammonia levels were within normal range 7 hours after having started the arginine infusion and the patient's mental status returned to baseline. Subsequent ammonia levels during this hospital admission remained within normal limits. On day 2 of admission after hemodialysis was completed and arginine initiated, the patient was resumed on his home TPN regimen of 1680 mL to infuse over 15 hours with amino acids 50 g/d (1.4 g/kg per day), final concentration of dextrose 17.5%, and 20% lipids (42 g/d). Total nonprotein calories derived from the TPN were 1420 kcal at 39 kcal/kg per day (weight = 36.3 kg). The arginine infusion was continued for 5 days and discontinued on day 7 of admission. A follow-up plasma aminogram, taken on day 10 of admission after the arginine infusion was discontinued, revealed glutamine, 758 μmol/L; ornithine, 124 μmol/L; citrulline, trace; and arginine, 195 μmol/L. The patient was discharged on day 10 of admission with an ammonia level of 18 μmol/L and continued on the same home TPN regimen before admission.

In <24 hours, the patient was readmitted to Children's Hospital of Michigan with mental status changes and a plasma ammonia concentration of 513 μmol/L. This time, the patient was treated with an IV arginine infusion. The ammonia level decreased from 513 μmol/L to 23 μmol/L within approximately 4 hours and the patient's mental status returned to baseline. A plasma aminogram, taken postarginine infusion, revealed glutamine, 571 μmol/L; ornithine, 130 μmol/L; citrulline, trace; and arginine, 212 μmol/L. During the course of his second admission, amino acid analysis of the patient's home TPN solution showed it had not contained arginine, thus causing the patient to become hyperammonemic and leading to his last 2 admissions. The patient's TPN prescription included 50 g/d of amino acids. The home infusion company made the TPN from individual amino acid powders but failed to add arginine in the solution. After this incident, the situation with his home TPN solutions was rectified and the patient has had normal ammonia levels and normal plasma amino acid levels on subsequent assays.

DISCUSSION

In patients with short bowel syndrome, especially those with greater than 100 cm resected, the body lacks the ability to absorb sufficient quantities of calories and nutrients.[4] This group of patients is at risk for significant nutritional and metabolic abnormalities. One such metabolic abnormality is D-lactic acidosis, which can result in mental status changes such as confusion, lethargy, aggressive behavior, and visual changes. Several cases have been reported in the literature of patients with SBS who developed D-lactic acidosis as a result of the fermentation of oral carbohydrates by the colonic bacterial overgrowth.[5–8] Although our patient had SBS, he did not have significant oral carbohydrate intake to result in D-lactic acidosis.

Another cause of encephalopathy that is potentially fatal is hyperammonemia. Recent literature reports hyperammonemia occurring in patients with SBS combined with chronic renal failure while receiving TPN supplementation with only essential amino acids (EAA).[1,2] Signs and symptoms of hyperammonemia can include any or all of the following: episodic irritability, lethargy, vomiting, ataxia, coma, mental retardation, and a disturbance of consciousness.[9] Ammonia is a byproduct of protein degradation and is toxic at high levels. Ornithine, citrulline, and arginine are nonessential amino acids that are involved in the Krebs urea cycle which converts ammonia into nontoxic urea.[10–12] The upper small intestine plays a major role in the Krebs urea cycle by providing citrulline to the liver and kidneys. The kidneys, in turn, make arginine from citrulline, which is transported to the rest of the body for protein synthesis and also serves as an intermediate for the urea cycle in the liver. Ornithine, which is a precursor to citrulline, is synthesized from glutamate in the small intestine exclusively.[1,10,11] For this, glutamate is first converted to pyrolline-5-carboxylate by the enzyme pyrolline-5-carboxylate synthase present only in the small intestine.[1] Pyrolline-5-car-

boxylate is then converted to ornithine by ornithine aminotransferase,[4] another enzyme present in the small intestine. Ornithine is then used for synthesis of citrulline, which is transported to the kidney for arginine synthesis. Patients with short bowel syndrome and chronic renal failure would have little or no pyrroline-5-carboxylate synthase or ornithine aminotransferase enzyme activity leading to arginine deficiency, and, in turn, hyperammonemia.[1,4]

An earlier case report published by Heird et al[13] illustrated the successful use of arginine to reverse hyperammonemia, which developed in infants receiving IV nutritional supplementation. The publication suggested that the amino acid mixture FreAmine (McGaw, Irvine, CA) may have been deficient in arginine. Current premixed standard amino acid solutions contain adequate arginine. However, some home infusion companies may still be using individual amino acid powders to make up the solution.

Patients with short bowel syndrome but normal renal function have not been reported to have hyperammonemia, so whether this population is at risk is not known. Our SBS patient had normal renal and liver function, and developed hyperammonemia because his home TPN solutions were lacking arginine due to an inadvertent omission of it. This suggests that our patient could not synthesize enough arginine inspite of having normal renal function and therefore was dependent on arginine from the TPN. A short period of about 2 weeks of arginine omission was enough to produce serious hyperammonemic encephalopathy.

Although a nonessential amino acid, administration of arginine is essential in patients with short bowel syndrome dependent solely receiving TPN, because they may have an inadequate ability for the synthesis of intermediates of the urea cycle. Pharmacists need to take measures to ensure that TPNs are made correctly when a premixed standard amino acid solution is not used and realize the implications of inadvertently omitting amino acids from TPN solutions.

REFERENCES

1. Yamada E, Wakabayashi Y, Saito A, et al: Hyperammonemia caused by essential amino acid supplements in patient with short bowel. Lancet 341:1542–1543, 1993
2. Yokoyama K, Ogura Y, Kawabata M, et al: Hyperammonemia in a patient with short bowel syndrome and chronic renal failure. Nephron 72:693–695, 1996
3. Arginine Hydrochloride. IN American Hospital Formulary Service Drug Information. McEvoy GK (ed). American Society of Health-System Pharmacists, Inc., Bethesda, 1998, pp 2047–2049
4. Jeejeebhoy KN: Intestinal disorders: Short bowel syndrome. IN Modern Nutrition in Health and Disease, Shils ME, Olsen JA (eds). Lea & Febiger, Philadelphia, PA, 1994, pp 1036–1041
5. Halperin ML, Kamel K: D-lactic acidosis: Turning sugar into acids in the gastrointestinal tract. Kidney Internat 49:1–8, 1995
6. Wilmore DW, Byrne TA, Persinger RL: Short bowel syndrome: New therapeutic approaches. Curr Prob Surg 34:428–444, 1997
7. Thurn JR, Pierpont GL, Ludvigsen CW, et al: D-lactate encephalopathy. Am J Med 79:717–721, 1985
8. Uribarri J, Oh MS, Carroll HJ: D-Lactic acidosis. A review of clinical presentation, biochemical features, and pathophysiologic mechanisms. Med 77:73–82, 1998
9. Felig DM, Brusilow SW, Boyer JL: Hyperammonemic coma due to total parenteral nutrition in a woman with heterozygous ornithine transcarbamylase deficiency. Gastroenterology 109:282–284, 1995
10. Wakabayashi Y, Yamada E, Hasegawa T, et al: Enzymological evidence for the indispensibility of small intestine in the synthesis of arginine from glutamate. Arch Biochem Biophys 291:1–8, 1991
11. Windmueller HG, Spaeth AE: Source and fate of circulating citrulline. Am J Physiol 241:473–480, 1981
12. Matthews DE, Fong Y: Amino acid and protein metabolism. IN Clinical Nutrition Parenteral Nutrition, 2nd edition. Rombeau JL, Caldwell MD (eds). W.B. Sanders Company, Philadelphia, 1993, pp 75–112
13. Heird WC, Nicholson JF, Driscoll JM, et al: Hyperammonemia resulting from IV alimentation using a mixture of synthetic L-amino acids: A preliminary report. J Pediatr 81:162–165, 1972