Online Case Report

Further Concerns About Glutamine: A Case Report on Hyperammonemic Encephalopathy

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Objective: We report a case of a woman with hyperammonemic encephalopathy following glutamine supplementation.
Design: Case report.
Interventions: Plasma amino acid analysis suggestive of a urea cycle defect and initiation of a treatment with lactulose and the two ammonia scavenger drugs sodium benzoate and phenylacetate. Together with a restricted protein intake ammonia and glutamine plasma levels decreased with subsequent improvement of the neurological status.
Measurements and Main Results: Massive catabolism and exogenous glutamine administration may have contributed to hyperammonemia and hyperglutaminemia in this patient.
Conclusion: This case adds further concerns regarding glutamine administration to critically ill patients and implies the importance of monitoring ammonia and glutamine serum levels in such patients. (*Crit Care Med* 2015; 43:e458–e460)
Key Words: ammonia; encephalopathy; glutamine

Glutamine is rapidly depleted in hypercatabolic conditions, and supplementation in critically ill patients has been advocated (1). But some investigators report an increased mortality among critically ill patients receiving glutamine in addition to enteral feeding (2, 3). Its role in the pathogenesis of ammonia-induced encephalopathy has been widely recognized (4). We present the case of a patient with metabolic encephalopathy following glutamine supplementation whose mental status was more closely related to plasma levels of glutamine than ammonia.

CASE REPORT

A 52-year-old woman was transferred to our department because of cerebral edema. One year after pancreaticoduodenectomy due to suspected duodenal gastrinoma with secondary total pancreatectomy because of anastomosis leakage, adhesiolysis was performed because of mechanical partial intestinal obstruction. The postoperative course was complicated by abdominal wound healing disorder requiring multiple surgical revisions of the laparotomy wound. After a more extended debridement, septic shock with coagulopathy developed and was followed by altered mental status and myoclonus. Brain CT showed diffuse cerebral edema and blood tests a hyperammonemia (271 µmol/L; reference value, 11–48 µmol/L). The patient was then referred to our hospital for further diagnosis and treatment. Since the primary operations, the patient lost around 30 kg of her body weight. For the last 3 days prior to referral, enteral glutamine supplementation (30 g each day) had been given. The total daily nitrogen intake during these 3 days of glutamine supplementation was 13 g, 17 g, and 21 g, respectively.

At admission, the patient was comatose (Glasgow Coma Scale 3) with otherwise normal vital signs. Laboratory tests showed increased total and direct bilirubin (107 µmol/L and 70.6 µmol/L, respectively; reference values, < 17 µmol/L and < 5 µmol/L, respectively) with otherwise irrelevant alteration of liver and coagulation tests. Blood gas analysis: pH, 7.48; base excess, –3.8 mmol/L; lactate, 2.3 mmol/L. Urinary analysis was negative for ketones and orotaciduria. Doppler ultrasound confirmed normal liver perfusion. Brain MRI and electroencephalography suggested metabolic encephalopathy. To rule out a blind-loop syndrome, gastroscopy was performed. Upon finding of *Enterobacter cloacae* in jejunal biopsy, antibiotic therapy

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TABLE 1. Patient Values of Different Amino Acids at Hospital Admission With Reference Range and *z* Score

Amino Acids	Patient Value (μmol/L)	Reference Range (μmol/L)	*z* Score
Alanine	1,870	200–550	17.09
Arginine	142	25–125	2.68
Asparagine	482	30–90	28.13
Aspartic acid	45	3–15	12
Citrulline	46	< 60	1.07
Cystine	39	20–85	−0.83
Glutamic acid	100	10–120	1.27
Glutamine	7,142	300–900	43.61
Glycine	1,316	120–400	15.09
Histidine	397	60–120	20.47
Isoleucine	63	45–115	−0.97
Leucine	128	70–200	−0.22
Lysine	746	125–250	17.87
Methionine	23	10–40	−0.27
Ornithine	215	30–100	8.57
Phenylalanine	78	30–85	1.49
Proline	1,436	100–380	17.09
Serine	418	60–170	11.02
Taurine	74	35–250	−1.27
Threonine	341	65–220	5.12
Tryptophan	6	30–90	−3.6
Tyrosine	64	40–100	−0.4
Valine	166	150–350	−1.68

The *z* score describes the number of SDS an observation is above or below the mean.

with doxycycline was initiated. Plasma amino acid analysis showed a marked elevation of glutamine, alanine, asparagine, lysine, proline, and glycine (**Table 1**) and low to normal levels of most essential amino acids. The massively increased glutamine, alanine, and asparagine pointed toward a urea cycle defect and therefore a protein restriction and a treatment with lactulose and the two ammonia scavenger drugs sodium benzoate and phenylacetate was begun. The protein and nitrogen intake was stopped the first 2 days in our department and then a carefully monitored protein intake was begun. The patient received 4 g of nitrogen on day 3 and 6 g of nitrogen on day 4 and day 5 in our ICU. Under these measures, ammonia and glutamine plasma levels decreased with consequent improvement of neurologic status. Enzymatic analysis of transjugular liver biopsy found a 50% reduction of carbamoylphosphate synthase (CPS) activity.

After increasing protein intake, a decreased level of consciousness, hemiparesis, and nonconvulsive status epilepticus occurred. This clinical deterioration was paralleled by a rebound increase in plasma glutamine (2,230 μmol/L), but not ammonia levels (22 μmol/L) (**Fig. 1**). Sodium benzoate was again administered and protein intake restricted, with prompt decrease of glutamine levels and neurologic improvement.

Seven weeks later, the patient was discharged without relevant neuropsychologic deficits.

DISCUSSION

Hyperammonemia is well known as a cause of encephalopathy. Risk factors include hepatic dysfunction, enteral bacterial overgrowth, and a variety of metabolic conditions, such as hereditary urea cycle defects, organic acidemias, carnitine deficiency, and fatty acid oxidation defects (5). Among iatrogenic causes, parenteral nutrition, intrahepatic portosystemic shunts, and adverse drug reactions are the most prominent.

In our patient, no obvious cause of the hyperammonemia could be identified. Liver failure was excluded, even though there was some degree of liver dysfunction and cholestasis. The latter cannot, however, account for the observed biochemistry. Blind-loop syndrome seemed unlikely, as the rebound decline in vigilance occurred after successful bacterial eradication. A paraneoplastic phenomenon was deemed improbable, as postoperative histologic examination failed to demonstrate the suspected gastrinoma. No drugs that have been associated with hyperammonemia could be identified. The patient did not have the biochemical signs or any risk factor for Reye syndrome, rare among adults.

The extent of glutamine, alanine, and asparagine elevation was suggestive of a urea cycle defect. On the other hand, normal citrulline and arginine as well as undetectable argininosuccinate and orotate in urine did not point to a specific defect. This profile is, however, compatible with CPS deficiency. The observed reduced CPS activity could point toward a mild or secondary CPS deficiency, but sequencing of the corresponding gene failed to reveal any mutation. Alternatively, CPS could have been down-regulated after total pancreatectomy.

Deficiency of *N*-acetylglutamate synthase (NAGS), the obligate activator of CPS, is clinically and biochemically indistinguishable from the latter. Molecular analysis of NAGS gene did not show any mutation although mild defects cannot be excluded. Therefore, NAGS deficiency cannot be completely ruled out as some patients have been shown to have reduced hepatic enzyme activity despite failure to detect gene mutations (6).

Hyperammonemia was accompanied by a disproportionately high increase in the ammonia-buffering amino acid glutamine. Interestingly, clinical deterioration was more

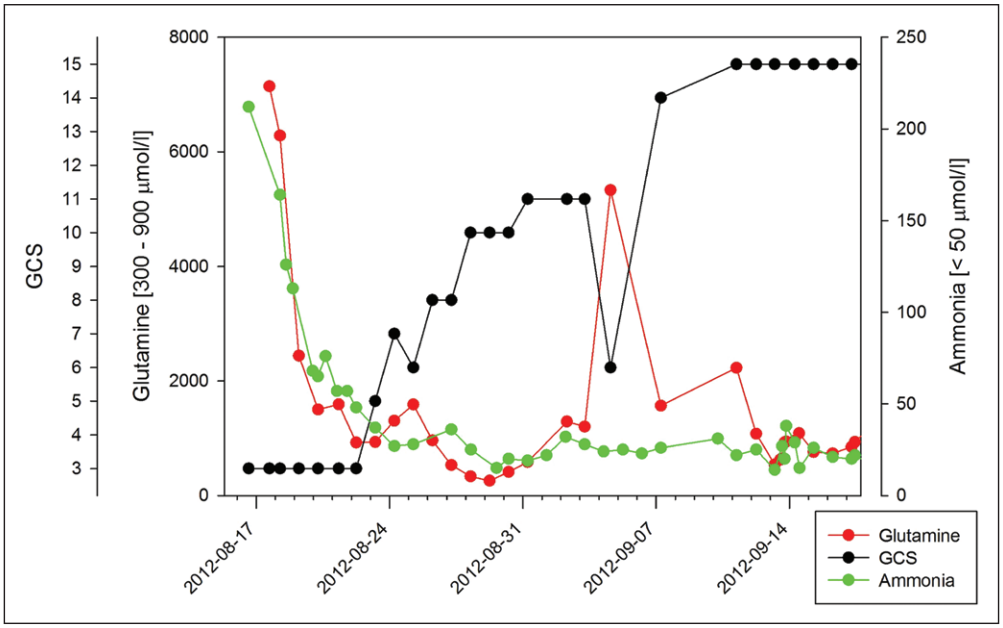

Figure 1. Plasma glutamine and ammonia levels in correlation with the Glasgow Coma Scale (GCS) during the patient hospitalization. Reference ranges are indicated in square brackets.

closely related to rising plasma levels of glutamine than ammonia. Excess of glutamine accumulating in the brain leads to impairment of mitochondrial function in astrocytes and by this means mediates neurotoxicity (7). The precise mechanisms are still debated. Our patient received enteral glutamine supplementation as she was treated for abdominal sepsis in another hospital before referral. The combination of mild hepatic dysfunction, malnutrition, catabolic muscle wasting, and intra-abdominal infection has been reported to contribute to idiopathic hyperammonemia (8). Our patient had been subjected to total pancreatectomy. This condition could have caused a further hormonal-metabolic imbalance (aglucagonemia and consecutive relative hypoinsulinism) which in turn may have led to inhibition or down-regulation of urea cycle enzymes, increasing the risk of developing toxic glutamine levels. The reason for the striking and recurrent glutamine elevation remains obscure. In animals, repressed urea cycle enzyme synthesis is seen following malnutrition (9), as are changes in hepatic glutamine synthetase activity, possibly representing an attempt to survive with hyperammonemia (10). Such a reactive alteration of glutamine metabolism, counteracting reduced CPS activity after a prolonged catabolic state, might have been present in our patient as she was severely malnourished after a prolonged and complicated postoperative course accompanied by intestinal malabsorption after the primary operations. Under such circumstances, exogenous glutamine administration can cause metabolic decompensation.

In summary, catabolism, reduced CPS activity, and exogenous glutamine administration could have contributed to hyperammonemia and hyperglutaminemia in this patient. This case adds further concerns regarding glutamine administration to critically ill patients and implies the importance of monitoring ammonia and glutamine serum levels in such patients.

REFERENCES

1. Singer P, Berger MM, Van den Berghe G, et al: ESPEN Guidelines on Parenteral Nutrition: Intensive care. *Clin Nutr* 2009; 28:387–400
2. Heyland D, Muscedere J, Wischmeyer PE, et al; Canadian Critical Care Trials Group: A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med* 2013; 368:1489–1497
3. van Zanten AR, Sztark F, Kaisers UX, et al: High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: A randomized clinical trial. *JAMA* 2014; 312:514–524
4. Desjardins P, Du T, Jiang W, et al: Pathogenesis of hepatic encephalopathy and brain edema in acute liver failure: Role of glutamine redefined. *Neurochem Int* 2012; 60:690–696
5. Auron A, Brophy PD: Hyperammonemia in review: Pathophysiology, diagnosis, and treatment. *Pediatr Nephrol* 2012; 27:207–222
6. Vockley J, Vockley CM, Lin SP, et al: Normal N-acetylglutamate concentration measured in liver from a new patient with N-acetylglutamate synthetase deficiency: Physiologic and biochemical implications. *Biochem Med Metab Biol* 1992; 47:38–46
7. Albrecht J, Zielińska M, Norenberg MD: Glutamine as a mediator of ammonia neurotoxicity: A critical appraisal. *Biochem Pharmacol* 2010; 80:1303–1308
8. Navaneethan U, Venkatesh PG: Idiopathic hyperammonemia in a patient with total pancreatectomy and islet cell transplantation. *JOP* 2010; 11:620–624
9. Aperia A, Broberger O, Larsson A, et al: Studies of renal urea cycle enzymes. I. Renal concentrating ability and urea cycle enzymes in the rat during protein deprivation. *Scand J Clin Lab Invest* 1979; 39:329–336
10. Skarpetas A, Mawal Y, Qureshi IA: Developmental study of hepatic glutamine synthetase in a mouse model of congenital hyperammonemia. *Biochem Mol Biol Int* 1997; 43:133–139