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CASE REPORT



Hyperammonemic encephalopathy in an adenocarcinoma patient managed with carglumic acid

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ABSTRACT

Hyperammonemic encephalopathy (HE) is a rare complication of malignancy and chemotherapy. Although the cause of HE is unclear, a functional arginine deficiency secondary to increased catabolism has been suggested as a possible mechanism. Either that deficiency or an undetermined metabolite could lead to inhibition of *N*-acetylglutamate synthase (NAGS), a urea cycle enzyme, resulting in hyperammonemia.

We present a case of chemotherapy-induced HE in a patient with no underlying primary urea cycle disorder. The patient had a successful trial of carglumic acid (a synthetic analog of the product of NAGS), which suggests that, at least in some cases, HE can be treated by overcoming proximal inhibition of the urea cycle. Further, our case is the first in the literature to exclude genetic defects and disorders of the proximal urea cycle, suggesting that hyperammonemia in these patients is probably secondary to chemotherapy.

KEY WORDS

Carglumic acid, idiopathic hyperammonemic encephalopathy, hyperammonemia, carbamoyl phosphate synthase, chemotherapy, drug toxicity, *N*-acetylglutamate

1. INTRODUCTION

Ammonia is a waste product of protein catabolism and is usually detoxified in the urea cycle (Figure 1). High levels of ammonia can lead to neurologic complications, including irreversible brain damage and death. Toxins, liver failure, and inborn errors of metabolism (especially urea cycle disorders) have all traditionally been associated with hyperammonemia. Idiopathic hyperammonemic encephalopathy (HE) has been recognized as a rare complication of malignancy and might be associated with malignancy itself or with chemotherapy[2–7].

The cause of HE is unclear. In cases of chemotherapy-induced HE, suggested mechanisms include a catabolic state induced by chemotherapeutic agents that overwhelms the capacity of the urea cycle; intrahepatic shunting that bypasses the liver; or tumour replacement of normal liver cells, leading to decreased expression of the ornithine transcarbamylase (*OTC*) gene and insufficient OTC enzyme production[3,5,8,9]. Reports in which HE has been treated with L-arginine suggest the possibility of a functional arginine deficiency secondary to chemotherapy-induced catabolism.

Arginine has multiple metabolic fates: not only does it serve as a precursor for synthesis of proteins, nitric oxide, creatine, polyamines, agmatine, and urea, but it is also an activator of *N*-acetylglutamate synthase (NAGS), an enzyme that catalyzes the synthesis of *N*-acetylglutamate (NAG)[10]. *N*-Acetylglutamate activates carbamoyl phosphate synthase 1 (CPS1), the rate-limiting step in the urea cycle. Genetic metabolic deficiencies in either of the foregoing enzymes leads to severe hyperammonemia in the newborn period[5]. Hyperammonemic encephalopathy can manifest with acute neurologic deterioration, and the clinical presentation can be similar to that seen in patients with genetic mutations in the urea cycle enzymes causing activation of NAGS and CPS1, and OTC deficiency, thus suggesting a proximal block in the urea cycle[3,5,9].

To date, treatment for HE has consisted of standard therapy for hyperammonemia secondary to urea cycle decompensation. The primary objective of standard therapy is to remove ammonia through salvage pathways. The typical approach includes high-rate glucose infusion (to reverse catabolism), hemodialysis to directly remove ammonia, limitations on ammonia sources through dietary protein restriction, and use of ammonia scavengers[2,3,5,11–13]. The combination of scavenger medications is often called the "urea cycle cocktail." Treatment carries with it a high fluid load and a combination of medications that can cause not only gastrointestinal upset, but also electrolyte imbalances such as hypernatremia and

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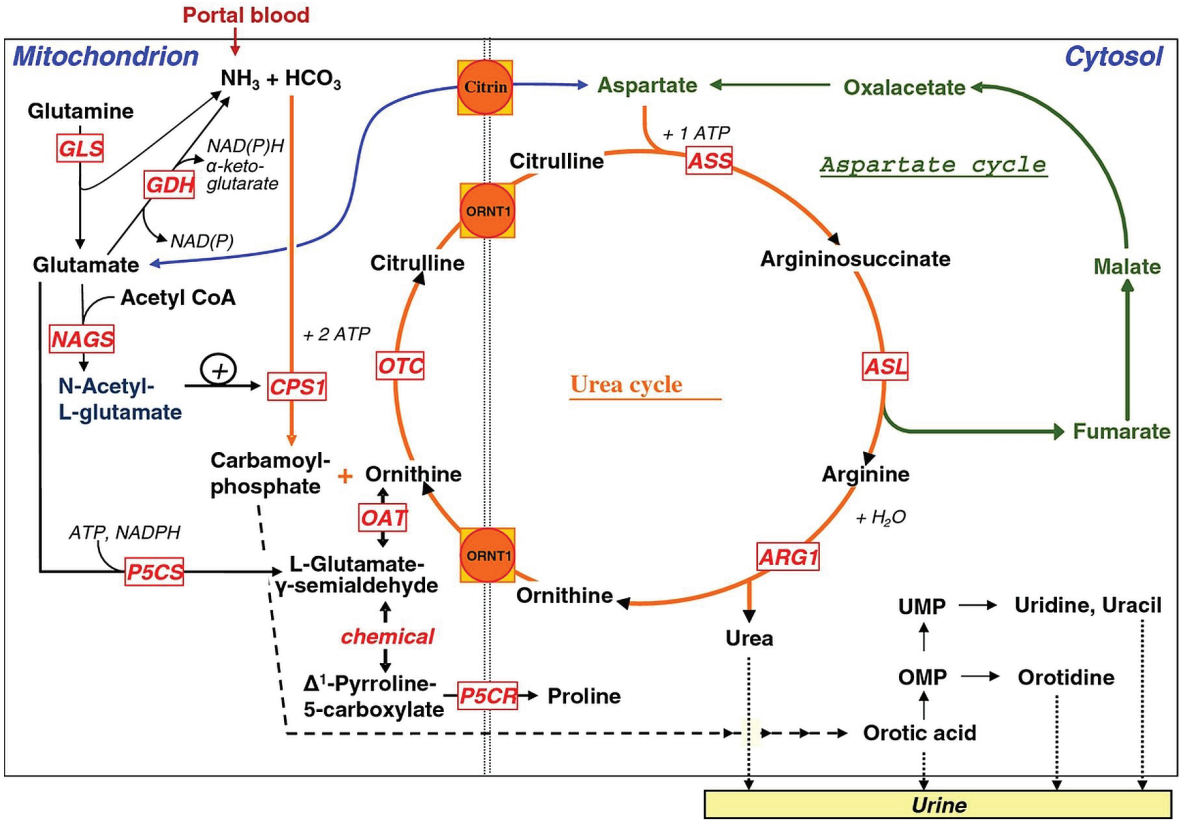


FIGURE 1 *The urea cycle, showing the importance of* N*-acetylglutamate synthase (NAGS), carbamoyl phosphate synthase 1 (CPS1), and ornithine transcarbamylase (OTC). GLS = glutaminase; GDH = glutamate dehydrogenase; NAD(P)H = nicotinamide adenine dinucleotide (phosphate); ASS = argininosuccinate synthetase; ASL = argininosuccinate lyase; ARG1 = arginase 1; ORNT1 = ornithine transporter; OAT = ornithine aminotransferase; P5CS = Δ^1-pyrroline-5-carboxylate synthetase; P5CR = pyrroline-5-carboxylate reductase; UMP = uridine monophosphate; OMP = orotidine monophosphate. Reprinted with permission from Haberle* et al.*, 2012*[1].

hyperchloremic metabolic acidosis. Although this approach is the standard in children with a primary urea cycle disorder, its role in a secondary deficiency has not been well studied.

While never previously used to treat HE, carglumic acid [CA (Carbaglu: Orphan Europe, Paris, France)] has been used in the treatment of hyperammonemia resulting from NAGS or CPS1 deficiency. Carglumic acid is a synthetic analog of NAG. By eliminating the need to synthesize NAG, CA is thus an obvious treatment for NAGS deficiency or for any other cause of NAGS inhibition[14–16].

Here, we present the case of a patient with chemotherapy-induced HE treated with a successful trial of CA. Further, our case is the first reported of chemotherapy-induced HE in which the investigations almost completely excluded a primary disorder of the urea cycle, thus indicating that the hyperammonemia was the result of a secondary urea cycle dysfunction.

2. CASE DESCRIPTION

The patient, a 24-year-old man, was being treated for a poorly differentiated carcinoma of the gastric fundus, with hepatoid features and bulky metastases to liver and peritoneum. He developed delirium after treatment with cisplatinum, epirubicin, and capecitabine chemotherapy.

The patient's plasma ammonia was elevated at 192 μmol/L (reference value: 12–47 μmol/L)[17]. His hyperammonemia was not controlled with oral lactulose, dietary protein restriction, and intermittent hemodialysis for 4 days; it increased steadily to 409 μmol/L with obtundation. The Metabolics service was consulted on the suspicion that a primary urea cycle disorder had been unmasked by the effects of the chemotherapy.

A high dextrose infusion (10 mg/kg/min) and an intravenous cocktail of nitrogen scavengers (sodium phenylacetate, sodium benzoate) with arginine were started. The patient's ammonia returned to 146 μmol/L the next day, and the delirium resolved.

An initial review of the patient's plasma amino acid profile showed a nonspecific pattern including low citrulline, ornithine, and arginine, and no significant elevation of urine orotic acid. The foregoing pattern can be seen in either NAGS or CPS1 deficiency; it would be unusual for OTC deficiency. We therefore

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used CA monotherapy at 150 mg/kg daily as ongoing treatment for the patient's hyperammonemia.

The patient was able to maintain an ammonia level between 70 μmol/L and 80 μmol/L and normal mental function while on a diet with unrestricted protein. The patient was discharged from hospital on CA.

After discharge, testing—including *NAGS* gene sequencing of exons 1–7 (Weber J, Prevention Genetics, Marshfield, WI, U.S.A.), *CPS1* sequencing of exons 1–38 and deletion/amplification testing by array comparative genomic hybridization (Weber J, Prevention Genetics), and OTC multiplex ligation-dependent probe amplification (Parboosingh J, Molecular Diagnostic Laboratory, Calgary, AB)—revealed no causative mutations. The combination of biochemical and molecular results almost completely excluded an inborn error of metabolism in any of the relevant enzymes. Because the patient did not have a primary urea cycle disorder, we were no longer able to use CA because that drug is not labelled for use in secondary hyperammonemia.

A little more than 1 week after his last dose of CA, the patient was readmitted with delirium and hyperammonemia (355 μmol/L). Given that he had previously stated that he would like comfort measures only should the hyperammonemia reoccur, no further active treatments were given, and he died 6 days later. Autopsy showed hepatic steatosis and liver metastases, but no features suggestive of liver failure or cirrhosis that would have been a consideration for organ dysfunction as the cause of his hyperammonemia.

3. DISCUSSION

Chemotherapy-induced HE is a rare complication that can begin after initiation of treatment in patients with normal liver function. Patients with defects such as citrullinemia and OTC deficiency can have characteristic biochemical findings, but NAGS and CPS1 deficiency require DNA testing for diagnosis. Molecular and biochemical testing was chosen over liver enzyme testing, because the former approach is preferred in testing for NAGS and for CPS1 and OTC deficiency, all of which can result in false negative results on liver biopsy because of heterogeneous liver expression[18–20]. This practice accords with recent guidelines[1]. Furthermore, given the presence of adenocarcinoma in the liver, a delay of more than 24 hours between time of death and autopsy would confound liver enzymology. The patient had a coagulopathy and could not have tolerated liver biopsy to test for urea cycle enzymes while living.

This case is the first in which specific testing has almost entirely excluded a primary defect of the urea cycle. We therefore hypothesize that a secondary inhibition of the urea cycle occurs in patients undergoing certain forms of chemotherapy[3,5].

Previous reports of HE resolution with arginine treatment suggested that a functional arginine deficiency was possibly caused by an increased ammonia load secondary to chemotherapy-induced catabolism[5]. Monotherapy with L-arginine would be insufficient to control ammonia in the presence of NAGS or a CPS1 deficiency.

Carglumic acid has previously been used in both inborn errors of metabolism and acquired conditions associated with CPS1 inhibition. Such conditions have included NAGS deficiency and CPS1 deficiency, together with certain organic acidemias in which byproducts cause NAGS inhibition[14]. Further, valproic acid has been found to decrease production of NAG by direct inhibition of NAGS and an accumulation of propionate; a response to CA therapy is seen as well[15,16]. In our patient, CA normalized ammonia levels, and we observed rebound hyperammonemia when the CA was stopped.

With CA controlling his hyperammonemia, our patient was able to regain a near-normal quality of life, allowing the family much needed time and the patient the ability to make his own decisions about ongoing care. We were restricted in the ongoing use of CA for off-label indications such as secondary hyperammonemia, but the patient felt that, given his poor prognosis because of the underlying cancer, he would not want to be restarted on treatment for hyperammonemia should it reoccur.

Our patient's case suggests an expanded role for CA in cases of secondary hyperammonemia. Our centre has also observed CA to be efficacious in controlling plasma ammonia while awaiting the diagnostic studies that ultimately ruled out inherited urea cycle deficiencies in cases of methylmalonic acidemia, herpes hepatitis, and gastrointestinal bleeding (Khan A. Unpublished observations). Those cases all suggest the need to consider policies of drug availability and of flexibility in indications for drug use when clinical care is an issue.

No medication being taken by our patient has previously been associated with HE, although 5-fluorouracil (5FU) has been implicated in some cases. However, capecitabine (an oral pro-drug of 5FU) has previously been associated with lack of hyperammonemia in a patient who had previously experienced HE while taking 5FU[21]. Thus, to avoid delayed treatment, it is important to consider HE in any patient on chemotherapy who presents with confusion, agitation, or a decreased level of consciousness.

4. SUMMARY

Chemotherapy-induced HE continues to be a rare and often misdiagnosed disorder of unclear causation. Based on cases such as ours, it appears that HE can be caused by an acquired inhibition of proximal urea cycle enzymes. For such patients, we have found CA to be an effective oral treatment that, compared with

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more traditional intravenous therapies, can allow for better quality of life. More work is needed to understand the heterogeneity of HE. Further discussion about the expanded use of CA might be warranted.

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6. CONFLICT OF INTEREST DISCLOSURES

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7. REFERENCES

1. Haberle J, Boddaert N, Burlina A, *et al.* Suggested guidelines for the diagnosis and management of urea cycle disorders. *Orphanet J Rare Dis* 2012;7:32.
2. Nott L, Price TJ, Pittman K, Patterson K, Fletcher J. Hyperammonemia encephalopathy: an important cause of neurological deterioration following chemotherapy. *Leuk Lymphoma* 2007;48:1702–11.
3. Chan JS, Harding CO, Blanke CD. Postchemotherapy hyperammonemic encephalopathy emulating ornithine transcarbamoylase (OTC) deficiency. *South Med J* 2008;101:543–5.
4. Chang YY, Lin JK, Jiang JK. Oxaliplatin-related hyperammonaemic encephalopathy in a patient with colon cancer. *Colorectal Dis* 2012;14:e821.
5. Winter SS, Rose E, Katz R. Hyperammonemia after chemotherapy in an adolescent with hepatocellular carcinoma. *J Pediatr Gastroenterol Nutr* 1997;25:537–40.
6. Espinos J, Rifon J, Perez–Calvo J, Nieto Y. Idiopathic hyperammonemia following high-dose chemotherapy. *Bone Marrow Transplant* 2006;37:899.
7. Willson KJ, Nott LM, Broadbridge VT, Price T. Hepatic encephalopathy associated with cancer or anticancer therapy. *Gastrointest Cancer Res* 2013;6:11–16.
8. Sethi S, Tageja N, Singh J, *et al.* Hyperammonemic encephalopathy: a rare presentation of fibrolamellar hepatocellular carcinoma. *Am J Med Sci* 2009;338:522–4.
9. Jeffers LJ, Dubow RA, Zieve L, *et al.* Hepatic encephalopathy and orotic aciduria associated with hepatocellular carcinoma in a noncirrhotic liver. *Hepatology* 1988;8:78–81.
10. Morris SJ Jr. Arginine metabolism: boundaries of our knowledge. *J Nutr* 2007;137(suppl 2):1602S–9S.
11. Mitchell RB, Wagner JE, Karp JE, *et al.* Syndrome of idiopathic hyperammonemia after high-dose chemotherapy: review of nine cases. *Am J Med* 1988;85:662–7.
12. Turken O, Basekim C, Haholu A, *et al.* Hyperammonemic encephalopathy in a patient with primary hepatic neuroendocrine carcinoma. *Med Oncol* 2009;26:309–13.
13. Kikuta S, Asakage T, Nakao K, Sugasawa M, Kubota A. The aggravating factors of hyperammonemia related to 5-fluorouracil infusion—a report of two cases. *Auris Nasus Larynx* 2008;35:295–9.
14. Daniotti M, la Marca G, Fiorini P, Filippi L. New developments in the treatment of hyperammonemia: emerging use of carglumic acid. *Int J Gen Med* 2011;4:21–8.
15. Haberle J. Role of carglumic acid in the treatment of acute hyperammonemia due to *N*-acetylglutamate synthase deficiency. *Ther Clin Risk Manag* 2011;7:27–32.
16. Segura–Bruna N, Rodriguez–Campello A, Puente V, Roquer J. Valproate-induced hyperammonemic encephalopathy. *Acta Neurol Scand* 2006;114:1–7.
17. Enns GM, Berry SA, Berry GT, Rhead WJ, Brusilow SW, Hamosh A. Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. *N Engl J Med* 2007;356:2282–92.
18. Heckmann MI, Wermuth B, Häberle J, Koch HG, Gortner L, Kreuder JG. Misleading diagnosis of partial *N*-acetylglutamate synthase deficiency based on enzyme measurement corrected by mutation analysis. *Acta Paediatr* 2005;94:121–4.
19. Gebhardt RI, Lindros K, Lamers WH, Moorman AF. Hepatocellular heterogeneity in ammonia metabolism: demonstration of limited colocalization of carbamoylphosphate synthetase and glutamine synthetase. *Eur J Cell Biol* 1991;56:464–7.
20. Mukhtar A, Dabbous H, El Sayed R, *et al.* A novel mutation of the ornithine transcarbamylase gene leading to fatal hyperammonemia in a liver transplant recipient. *Am J Transplant* 2013;13:1084–7.
21. Advani PP, Fakih MG. 5-FU–induced hyperammonemic encephalopathy in a case of metastatic rectal adenocarcinoid successfully rechallenged with the fluoropyrimidine analog, capecitabine. *Anticancer Res* 2011;31:335–8.

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