HHS Public Access

Author manuscript

Am J Transplant. Author manuscript; available in PMC 2020 November 01.

Published in final edited form as:

Am J Transplant. 2019 November ; 19(11): 3197–3201. doi:10.1111/ajt.15545.

Non-cirrhotic hyperammonemia after deceased donor kidney transplantation: A case report

George Z. Li[#1], **Maria C. Tio**[#2], **Linda M. Pak**[1], **Joel Krier**[3], **Stefan G. Tullius**[1], **Leonardo V. Riella**[2], **Sayeed K. Malek**[1], **Andrew B. Stergachis**[3]

[1]Department of Surgery, Brigham and Women's Hospital, Boston, Massachusetts

[2]Department of Medicine, Renal Division, Brigham and Women's Hospital, Boston, Massachusetts

[3]Department of Medicine, Division of Genetics, Brigham and Women's Hospital, Boston, Massachusetts

[#] These authors contributed equally to this work.

Abstract

A 72 year-old woman with end stage kidney disease due to recurrent urinary tract infections and obstructive uropathy of a solitary kidney presented to our hospital for renal transplantation. She underwent successful transplantation of a deceased donor allograft, but developed acute mental status deterioration on the fifth postoperative day. Her serum ammonia was found to be markedly elevated to 447 μmol/L in the setting of normal hepatic function. She was treated with emergent dialysis and empiric antibiotics targeting urea-splitting organisms, and ultimately made a full neurologic recovery with stable renal allograft function. Non-cirrhotic hyperammonemia (NCH) is an exceedingly rare clinical entity but seems to have a predilection for patients who have undergone solid organ transplantation. This report emphasizes the importance of rapid diagnosis and initiation of treatment for NCH, which is associated with a high rate of mortality and irreversible neurological morbidity. We outline the successful workup and management approach for this patient.

Case Report

A 72 year-old woman with end stage kidney disease related to recurrent urinary tract infections, history of recurrent nephrolithiasis, and obstructive uropathy of a solitary kidney presented to our hospital for renal transplantation. Her past medical history was notable for a prior cerebrovascular accident without residual deficits, and oligometastatic colon cancer over thirty years ago, for which she underwent chemotherapy and extensive surgical resection, including a right colectomy, right nephrectomy, and partial hepatectomy. Subsequent to this surgery, she developed recurrent urinary tract infections and renal calculi requiring multiple procedural interventions. She had progressive deterioration of her

Correspondence Sayeed K. Malek, smalek@bwh.harvard.edu.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

remaining left kidney function and she eventually initiated hemodialysis 18 months prior to presentation. She had normal baseline functional status and was cleared by the transplantation committee at our institution to be listed as active on the United Network for Organ Sharing (UNOS) kidney waiting list. On the day of admission, a deceased donor organ with a kidney donor profile index (KDPI) of 85% had become available from a 55 year-old man with a 5 year history of hypertension who died of a hemorrhagic stroke. There was a 3 out of 6 human leukocyte antigen (HLA) mismatch between donor and recipient.

Pre-transplant work-up are as follows. Preoperative laboratory tests, including liver function tests, were normal with the exception of a creatinine of 4.7 mg/dL, blood urea nitrogen (BUN) of 15 mg/dL, and a urinalysis revealing a pH of 9, no nitrites, and 29 white blood cells per high-power field. The patient had no urinary tract infection-like symptoms, and on further review had had a urine pH of 9 for the previous 12 months. A urine culture drawn at the time of transplant grew >100,000 colony forming units of mixed flora bacteria. The organisms that have speciated for her recurrent urinary tract infections in the past included *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis,* and *Aerococcus urinae,* which was the last speciated organism two years prior to transplantation. An abdominal computed tomography (CT) a year before transplant revealed one nonobstructive left renal calculus measuring 1.5 cm in the lower pole of the left kidney. A 24-hour urine analysis done three years prior to transplantation revealed hypocalciuria (16 mg/day), hyperoxaluria (66 mg/day), and hypomagnesuria (9 mg/day). At that time, she had an increased risk of uric acid stone formation (super saturation of 1.16) with a urine volume of 1.41 L/day and a urine pH of 5.6. She had low super saturations for both calcium oxalate and calcium phosphate stones (3.01 and 0.05, respectively) at that time. No prior kidney stones had been analyzed for composition. A 24-hour urine analysis had not been obtained during the 12 months preceding her date of transplantation.

The patient underwent an uncomplicated transplantation of the deceased donor kidney. Total cold ischemia time was 23 hours. Induction immunosuppression included 20 mg of basiliximab (days 0 and 4) and maintenance immunosuppression with tacrolimus, mycophenolate sodium, and an early steroid taper. She was also started on prophylactic trimethoprim/sulfamethoxazole and valganciclovir. During her first four postoperative days, she had improving symptoms, normal mentation, and was starting to tolerate independent ambulation. However, she did exhibit delayed graft function which was managed medically without need for renal replacement therapy. On the morning of the fifth postoperative day, the patient began to experience significant nausea and emesis which escalated over the next three hours. In addition, she developed progressive confusion and was noted to have asterixis and uremic fetor, with a serum creatinine of 6.35 mg/dL (down from 7.1 mg/dL) and a BUN of 110 mg/dL despite improving urine output of over 1.5 liters in the preceding 2 days without need for diuretics. Urinalysis done on post-operative day 5 was remarkable for a pH of 5 with trace bacteria. A serum ammonia level was checked and was markedly elevated at 447 μmol/L (normal range 11– 60 μmol/L) (Figure 1A). She was emergently hemodialyzed for severe symptomatic hyperammonemia and during the treatment, she became progressively obtunded, necessitating intubation for airway protection. CT of the head was negative for signs of cerebral edema, cerebrovascular accident, or intracranial hemorrhage. After standard hemodialysis, continuous veno-venous hemofiltration (CVVH) was initiated

for ammonia clearance in addition to empiric doxycycline and levofloxacin given concern for urinary urease-producing bacterial infection. Plasma amino acids were sent prior to hemodialysis to a neighboring children's hospital to evaluate for a possible inborn error of metabolism, and she was empirically given a 2-hour intravenous (IV) bolus of nitrogen scavenger therapy (5.5 g/m^2 sodium benzoate/phenylacetate), in addition to IV arginine, IV levocarnitine, oral zinc, and oral carglumic acid. Protein intake was completely restricted on the first day and she was started on IV dextrose to help prevent catabolism. Plasma ammonia levels improved over the following 12 hours, obviating the need for additional nitrogen scavenger therapy while on CVVH.

Plasma amino acids returned later that evening with essentially normal ornithine and citrulline levels, mildly elevated glutamine levels and normal branched chain amino acid levels (Figure 1B), suggestive of relatively preserved ornithine transcarbamoylase and liver glutamine synthetase activity as well as a lack of severe protein malnutrition. Urine organic acids, orotic acid and amino acids returned over the next week and were largely normal (Figure 1B). Germline genetic testing of 58 genes associated with hereditary hyperammonemic syndromes did not demonstrate any pathogenic sequence variants, deletions or duplications. Zinc levels were mildly low at 0.62 mcg/mL (normal range 0.66–1.10 mcg/mL).

CVVH was discontinued on postoperative day 8, after which her ammonia levels stabilized. Her mental status improved, and she was extubated on postoperative day 9. She was discharged on postoperative day 20 to a rehabilitation facility with a stable creatinine of 2.28 mg/dL, BUN of 49 mg/dL, and with a mental status that was back to baseline. Subsequent urinalyses demonstrated consistent pH's of 5.0 for four months post-discharge.

Urine cultures and urine polymerase chain reaction (PCR) for *Ureaplasma* and *Mycoplasma* were sent after initiation of antibiotics and returned negative. Given her high urine pH and polymicrobial urine culture on admission, she was empirically treated with a full three-week course of ciprofloxacin and doxycycline for a presumptive urinary infection with a urease-producing organism.

Discussion

Adult-onset non-cirrhotic hyperammonemia (NCH) is a rare clinical condition that is distinct from hepatic encephalopathy. The condition is associated with a very high morbidity and mortality[1,2] and has been described in a variety of settings, including post-solid organ transplantations – most commonly post-lung transplantion,[3] but rarely in post-heart[4] or post-kidney transplantation.[5–8] Four prior case reports exist for post-kidney transplantation NCH, three of which were associated with patient mortality. One patient developed hyperammonemia to 146 μmol/L seven months post-kidney transplantation and this was attributed to *Mycobacterium genavense* infection. Despite treatment with antibiotics and maximal supportive therapy, she ultimately died of multiorgan failure.[7] Another patient presented nine days post-kidney transplantation with altered mental status, nausea, and emesis, and was found to have an ammonia level of 939 μmol/L. He was declared brain dead from cerebral edema and herniation despite initiation of continuous veno-venous

hemodiafiltration, and biochemical workup did not reveal a urea cycle defect.[6] A third patient presented four days post-kidney transplantation with altered mental status and seizures and on post-operative day nine was found to have an ammonia level of 368 μmol/L. Despite a lack of cirrhosis, he was treated only with lactulose and protein restriction, resulting in a continual rise in plasma ammonia levels to 628 μmol/L and subsequent brain herniation and death. Workup ultimately was notable for elevated orotic acid, so a urea cycle defect was suspected in this case.[5] Finally, a fourth patient developed ammonia levels higher than 286 μmol/L 26 days after renal transplantation, presumably from infection with an unidentified urease-producing organism. This patient was treated with arginine and continuous veno-venous hemodiafiltration and survived, making this the only other case known in the literature which was not associated with mortality.[8]

Within the lung transplantation literature, post-transplantation hyperammonemia is thought to result from a combination of immunosuppression-induced activation of urease-producing organisms such as ureaplasma[3,9] in addition to impaired hepatic glutamine synthetase activity as a result of hypoxic injury to zone three of the liver.[10] Outside of the transplantation literature, adult onset NCH has also been associated with: (1) infections with urease-producing organisms such as *Ureaplasma*, *Mycoplasma*, and *Proteus* species, which cleave urea to produce ammonia[11]; (2) drugs such as valproic acid[12]; (3) micronutrient deficiencies such as zinc[13] and (4) germline urea cycle disorders, which can rarely manifest for the first time in adulthood.[14]

Here we present a case report of NCH that was successfully managed in a 72 year-old woman who had undergone a deceased donor kidney transplantation. With this report, we hope to highlight several features that resulted in the successful clinical management of this patient, including: (1) the prompt recognition of hyperammonemia in the post-transplantation patient with altered mental status; (2) the prompt initiation of appropriate ammonia reducing therapies including renal replacement therapy; and (3) the multidisciplinary evaluation of the underlying etiology of hyperammonemia.

While uremia is often invoked as a cause of altered mentation post-kidney transplant in patients with delayed graft function, we emphasize that having a broad differential and work-up was key to this patient's diagnosis. Elevated BUN post-transplant may occur for multiple reasons including poor allograft function, use of high-dose steroids, hypovolemia and gastrointestinal bleeding. In addition, urea is also the end-product of ammonia metabolism, and therefore elevation of ammonia may lead to high BUN levels in patients with at least a partially working urea cycle. In this case, ammonia levels were checked within 3 hours of her presentation with nausea, emesis, and altered mental status. Immediate diagnosis and treatment are crucial to prevent the high mortality and devastating neurological consequences associated with the condition, and delayed diagnosis of NCH in the post-transplantation patient is routinely associated with a very high morbidity and mortality. As such, measuring serum ammonia levels should be routinely considered on all post-solid organ transplantation patients developing altered mental status.

Immediate treatment is critical. In our patient, renal replacement therapy for ammonia clearance was initiated within 1.5 hours of diagnosis, and the patient was subsequently

started on empiric antibiotics for urease-producing organisms, ammonia scavenger therapy, and urea cycle supportive therapies for inborn errors of metabolism. Ammonia levels above 200 μmol/L are associated with an increased risk for cerebral edema and herniation[14] and these levels can quickly rise in cases of NCH. Furthermore, serial neurological exams and frequent ammonia checks are important while ammonia levels remain elevated due to the risk of developing cerebral edema. Whereas cirrhotic hyperammonemia is usually managed with lactulose, it is important to note that treatment for NCH differs considerably and involves the timely and coordinated actions of a multidisciplinary team including genetics, nephrology, nutrition, and infectious diseases.

Finally, timely evaluation for causes of NCH is critical in terms of directing care in these cases. In this patient, plasma amino acids were run at a local children's hospital on the day of presentation, enabling rapid assessment for inborn errors of metabolism and subsequent refinement of her treatment and nutritional management. She was not on valproic acid at the time of presentation, but this should always be checked given the frequency of valproic acid induced NCH. Infectious workup for urease-producing organisms and genetic testing for germline disorders were sent as well.

Overall, the most likely cause of NCH in this patient was a urinary tract infection with a urease-producing organism that likely colonized the retained stone in her native kidney prior to transplantation, and subsequently led to an active infection upon initiation of immunosuppression. The change in her urine pH post-transplantation from 9 to 5 prior to any effective antibiotic treatment shows that the urine collected in her bladder was an admixture of alkaline from her native kidney and predominantly acid urine produced by her new allograft. The fact that the patient had extremely alkaline urine pre-transplantation, history of recurrent urinary tract infections some of which were urea-splitting organisms, and a retained renal pelvic calculus suspicious for a magnesium ammonium phosphate stone favor this diagnosis, as does the temporal relationship between her onset of symptoms and initiation of immunosuppression.

Conclusion

To the best of our knowledge, this is one of the only post-renal transplantation NCH cases reported in which the patient survived without neurologic sequelae. We argue that one must maintain a high index of suspicion for NCH in post-transplant patients with acute altered mental status, and that with the immediate initiation of treatments to clear ammonia and address possible underlying causes, outcomes can be improved for this condition.

Acknowledgments

A.B.S. was supported by NIH T32 grant GM007748. We thank Drs. Kris M. Mogensen, Roy WA. Peake and Hila Romi and the entire surgical ICU at Brigham and Women's Hospital for their care of this patient.

Abbreviations:

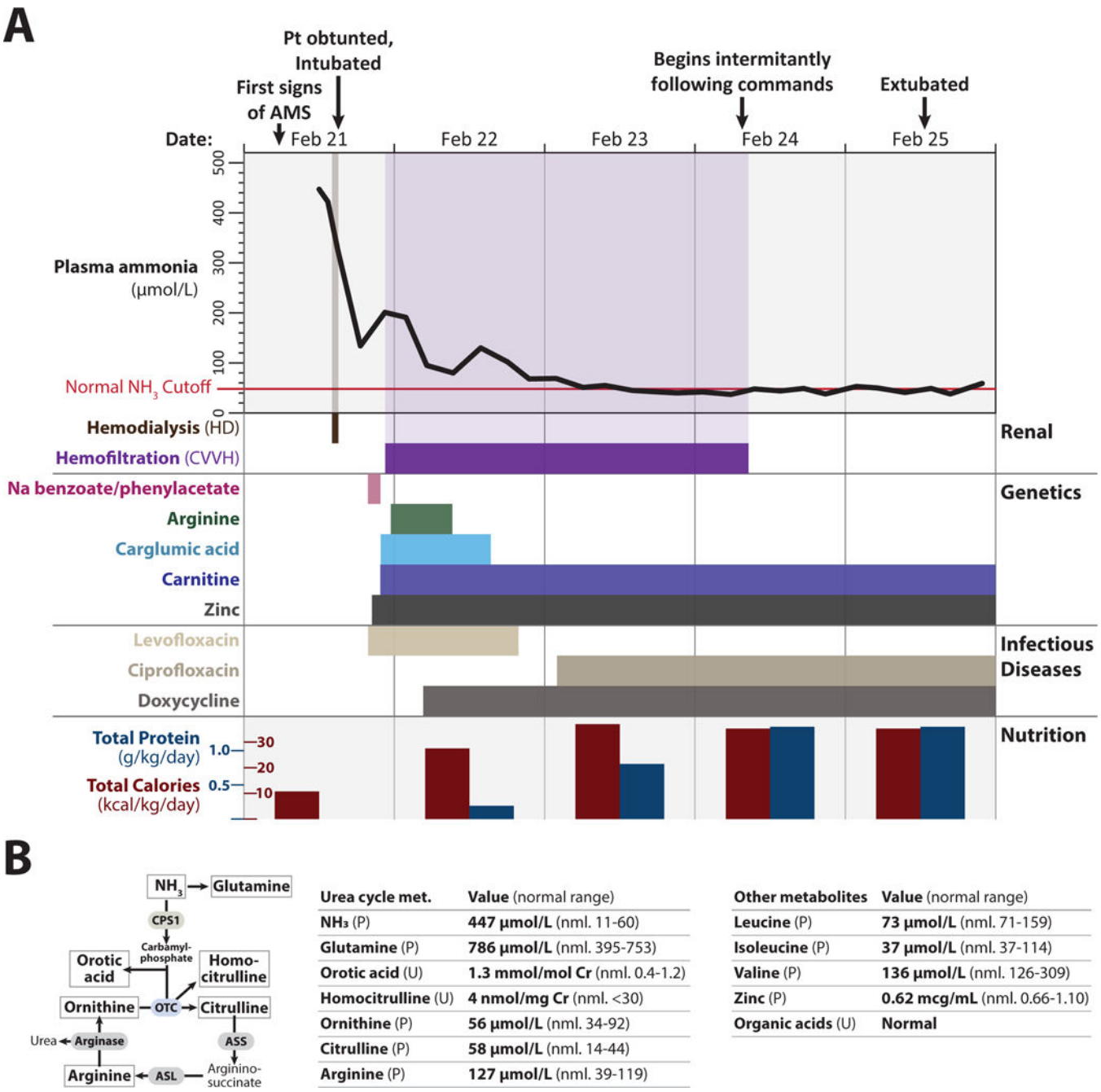
(UNOS)	United Network for Organ Sharing
(KDPI)	kidney donor profile index

(HLA)	human leukocyte antigen
(BUN)	blood urea nitrogen
(CVVH)	continuous veno-venous hemofiltration
(IV)	intravenous
(PCR)	polymerase chain reaction
(CPSI)	carbamyl phosphate synthetase I
(OTC)	ornithine transcarbamylase
(ICU)	intensive care unit
(CT)	computed tomography
(MRI)	magnetic resonance imaging

References

1. Davies SM, Szabo E, Wagner JE, Ramsay NK, Weisdorf DJ. Idiopathic hyperammonemia: a frequently lethal complication of bone marrow transplantation. Bone Marrow Transplant 1996;17:1119–25. [PubMed: 8807124]
2. Fenves AZ, Shchelochkov OA, Mehta A. Hyperammonemic syndrome after Roux-en-Y gastric bypass. Obesity (Silver Spring) 2015;23:746–9. [PubMed: 25754921]
3. Bharat A, Cunningham SA, Scott Budinger GR, et al. Disseminated Ureaplasma infection as a cause of fatal hyperammonemia in humans. Sci Transl Med 2015;7:284re3.
4. Yoshida EM, Ostrow DN, Erb SR, Fradet G. Hyperammonemia after heart-lung transplantation. Gastroenterology 1997;112:2162. [PubMed: 9178720]
5. Bezinover D, Douthitt L, McQuillan PM, et al. Fatal hyperammonemia after renal transplant due to late-onset urea cycle deficiency: a case report. Transplant Proc 2010;42:1982–5. [PubMed: 20620562]
6. Kiberenge RK, Lam H. Fatal hyperammonemia after repeat renal transplantation. J Clin Anesth 2015;27:164–7. [PubMed: 25573265]
7. Nurmohamed S, Weenink A, Moeniralam H, Visser C, Bemelman F. Hyperammonemia in generalized Mycobacterium genavense infection after renal transplantation. Am J Transplant 2007;7:722–3. [PubMed: 17250553]
8. Sayer J, Bhatti A, Jaques B, Nesbitt I. Hyperammonaemic coma post-renal transplantation. Clin Intens Care 2003;14:37–40.
9. Wang X, Karau MJ, Greenwood-Quaintance KE, et al. Ureaplasma urealyticum Causes Hyperammonemia in an Experimental Immunocompromised Murine Model. PLoS One 2016;11:e0161214.
10. Tuchman M, Lichtenstein GR, Rajagopal BS, et al. Hepatic glutamine synthetase deficiency in fatal hyperammonemia after lung transplantation. Ann Intern Med 1997;127:446–9. [PubMed: 9313001]
11. Albersen M, Joniau S, Van Poppel H, Cuyle PJ, Knockaert DC, Meersseman W. Urea-splitting urinary tract infection contributing to hyperammonemic encephalopathy. Nat Clin Pract Urol 2007;4:455–8. [PubMed: 17673917]
12. Zaret BS, Beckner RR, Marini AM, Wagle W, Passarelli C. Sodium valproate-induced hyperammonemia without clinical hepatic dysfunction. Neurology 1982;32:206–8. [PubMed: 6798491]
13. Prasad AS, Rabbani P, Abbasii A, Bowersox E, Fox MR. Experimental zinc deficiency in humans. Ann Intern Med 1978;89:483–90. [PubMed: 697227]

14. 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. [PubMed: 17538087]



Urea cycle met.	Value (normal range)
NH_3 (P)	**447 µmol/L** (nml. 11-60)
Glutamine (P)	**786 µmol/L** (nml. 395-753)
Orotic acid (U)	**1.3 mmol/mol Cr** (nml. 0.4-1.2)
Homocitrulline (U)	**4 nmol/mg Cr** (nml. <30)
Ornithine (P)	**56 µmol/L** (nml. 34-92)
Citrulline (P)	**58 µmol/L** (nml. 14-44)
Arginine (P)	**127 µmol/L** (nml. 39-119)

Other metabolites	Value (normal range)
Leucine (P)	**73 µmol/L** (nml. 71-159)
Isoleucine (P)	**37 µmol/L** (nml. 37-114)
Valine (P)	**136 µmol/L** (nml. 126-309)
Zinc (P)	**0.62 mcg/mL** (nml. 0.66-1.10)
Organic acids (U)	**Normal**

Figure 1. Clinical presentation, evolution and management of hyperammonemia in the case presented.

(A) Timeline of patient's post-operative course during the days surrounding her hyperammonemic crisis. The top of the graph is annotated with clinical events. Plasma ammonia is charted as a function of time. Below are rows indicating the duration of, from top to bottom: hemodialysis, continuous veno-venous hemofiltration, sodium benzoate/phenylacetate, arginine, carglumic acid, carnitine, zinc, and antibiotics. The bottom row indicates total amount of daily protein and caloric intake. (B) Urea cycle diagram including

metabolites in boxes that are were measured in this case. To the right are the values of different Plasma (P) and Urine (U) metabolites measured during this case.