Case Report

A novel cause of emergent hyperammonemia: *Cryptococcal* fungemia and meningitis

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A B S T R A C T

Among etiologies of hyperammonemic emergencies, infection must be considered in certain clinical contexts, particularly among immunocompromised individuals. Although *Cryptococcus neoformans* is known to be urease-producing, to our knowledge it has not previously been described as a cause of hyperammonemia in patients. We report an immunocompromised man with acute on chronic kidney disease with hyperammonemic crisis due to *Cryptococcal* meningitis and fungemia. It is important to be aware of *C. neoformans* as a possible cause of hyperammonemia.

1. Introduction

The differential diagnosis of hyperammonemic crisis is broad. Among etiologies of life-threatening elevations of plasma ammonia concentration, infectious causes are becoming better characterized. Urease-producing bacteria can precipitate emergent hyperammonemia, often due to urinary tract infections (UTI) in patients at increased risk of UTI due to anatomic anomalies [1]. Numerous bacteria have been implicated in infections causing elevated ammonia, including *Ureaplasma* infection, particularly in immunocompromised patients [2,3] and in individuals following lung transplantation [4,5]. In some clinical settings, infection with a urease-producing pathogen must be considered as a cause of hyperammonemia. *C. neoformans* is a fungal pathogen known to be urease-producing. It has been suggested that urease is important for the virulence of *Cryptococcus* [6–8].

Herein, we outline the first described case, to our knowledge, of hyperammonemia due to *C. neoformans* infection.

2. Case

A 59-year-old man with focal segmental glomerulosclerosis (baseline

serum creatinine of roughly 3.6 mg/dL) on long-standing immunosuppression presented to his local hospital with nausea, confusion, and poor oral intake. He became increasingly confused, was determined to be hyperammonemic with a peak plasma ammonia concentration of 676.8 μmol/L (reference range 15–45 μmol/L), and required continuous veno-venous hemofiltration (CVVH). He was transferred to the medical intensive care unit of a tertiary care center for hyperammonemic encephalopathy and acute on chronic kidney disease. He had no prior hyperammonemic episodes, no dietary aversions, no family history of genetic or metabolic disease, and was not given any medications known to induce hyperammonemia. There was no history of liver disease, vascular anomalies or portosystemic shunt, renal tubular acidosis, or organ transplantation which are known causes of hyperammonemia in certain settings. Aspartate transaminase, alanine transaminase, direct and total bilirubin, alkaline phosphatase, and coagulation studies were within the reference intervals.

He was placed on lactulose and rifaximin, but he required continued renal replacement therapy via CVVH to control hyperammonemia. During hospitalization, a percutaneous endoscopic gastrostomy tube was placed, and there was concern for melena and a decline in hemoglobin. Upper endoscopy and colonoscopy did not identify a source of

gastrointestinal bleeding, and bleeding resolved. The biochemical genetics service recommended dextrose-containing fluids and intralipids to promote anabolism given the possibility of an inherited metabolic disease as a cause of hyperammonemia. Levocarnitine was initiated until secondary carnitine deficiency was ruled out. An exhaustive search for inborn errors of metabolism was unrevealing. Initial plasma amino acids demonstrated glutamine of 443 μM (reference 205–756), citrulline 23 μM (reference 12–55), arginine 41 μM (reference 15–128), and ornithine 39 μM (reference 48–195). Urine orotic acid ranged from normal to slightly elevated at 6.8 mmol/mol Cr (reference 0.4–1.2) when he was critically ill with acute on chronic kidney disease. During this time, serum methylmalonic acid was also mildly elevated to as high as 1012 nmol/L (reference 0–378) in the setting of homocysteine 4.47 umol/L (reference 5.00–13.9). Plasma acylcarnitine analysis had nonspecific abnormalities including a low free carnitine and elevated C4OH consistent with ketosis in the setting of critical illness. Of note, there was not any elevation of propionylcarnitine. Analysis of the following genes did not report any sequence variants or deletions or duplications based on read depth analyses: *ARG1, ASL, ASS1, CPS1, NAGS, OTC, SLC25A13,* or *SLC25A15*. He developed apparent septic shock. Lumbar puncture revealed elevated opening pressure, and blood and cerebrospinal fluid cultures were positive for *C. neoformans*. Serum *Cryptococcal* antigen was 1:262,154 reflecting disseminated infection. He was managed with amphotericin B and flucytosine. Eventually, his hyperammonemia resolved, he no longer required CVVH, and his mental status returned to baseline.

A multidisciplinary team including infectious disease providers, biochemical geneticists, and intensivists effectively excluded known causes of hyperammonemic crisis except for infectious etiologies. When blood and cerebrospinal fluid cultures were positive for *C. neoformans*, it seemed likely that this pathogen, known to be urease-producing, was the cause of elevated ammonia concentration. Very strongly supporting infection as the cause of hyperammonemia, his ammonia in the setting of acute renal failure was only stabilized by CVVH. It did not normalize until the underlying infection was treated effectively, likely due to the fact that urea produced in the liver was not cleared due to renal failure, setting up a vicious cycle between the urease producing organism and his functional hepatic urea cycle.

3. Discussion

The differential diagnosis of hyperammonemia is broad. Numerous inborn metabolic disorders can result in hyperammonemia. Urea cycle disorders may lead to respiratory alkalosis and low blood urea nitrogen in the setting of hyperammonemic crises. Biochemical laboratory values including plasma amino acids and urine orotic acid can help localize the defect [9]. Pathway metabolites upstream of the defect may accumulate with concentrations significantly exceeding reference intervals while pathway metabolites distal of the defect may be low. For example, low plasma citrulline concentrations may suggest a proximal (mitochondrial) urea cycle disorder whereas elevated plasma citrulline concentrations may point toward a distal (cytosolic) urea cycle disorder [9]. Both biochemical laboratory tests and molecular testing are important parts of the diagnostic evaluation [10].

Additionally, other classes of inborn metabolic disorders may affect the urea cycle and lead to hyperammonemia. Disorders of fatty acid oxidation, characterized classically by hypoketotic hypoglycemia, may lead to hyperammonemia. This is thought to be related to decreased acetyl-CoA affecting available *N*-acetylglutamate [11], a molecule important for activation of carbamyl phosphate synthetase 1 [11]. Additionally, accumulated metabolites in some organic acidurias can inhibit the proximal urea cycle [12]. For instance, hyperammonemia has been described as part of the phenotypic spectrum in isovaleric acidemia, propionic acidemia, and methylmalonic acidemia [12]. Plasma acylcarnitine and urine organic acid profiles are informative in the consideration of disorders of fatty acid oxidation or organic acidurias.

Conditions that affect transport of intermediates in the urea cycle can lead to hyperammonemia such as citrin deficiency, hyperornithinemia-hyperammonemia-homocitrullinuria syndrome, and lysinuric protein intolerance [9]. Additional Mendelian disorders that cause hyperammonemia have been described. For instance, pyruvate carboxylase deficiency is associated with impairment of anaplerosis affecting reducing equivalent equilibrium and the malate/aspartate shuttle [13]. Given the effect on aspartate, plasma ammonia and citrulline may be elevated [13]. Hyperammonemia can clearly be seen in additional inborn metabolic disorders. Numerous hereditary conditions, most of which are treatable, can cause hyperammonemic crises. A broad differential diagnosis and systematic approach are essential, and involvement of a biochemical geneticist in the care of the patient can often inform the workup and management.

The spectrum of infectious causes of hyperammonemia is still being characterized but likewise appears broad. Numerous bacteria have been suggested to cause hyperammonemia. In a systematic review of hyperammonemia associated with either urinary tract infections or distal renal tubular acidosis by Clericetti et al., 31 individuals were described with urinary tract infection and acute hyperammonemia [1]. Of these 31 patients, 30 had an abnormal urinary tract, 19 with anatomic anomalies and 11 with functional anomalies. 28 patients had urea-splitting bacteria isolated (including *Proteus*, *Corynebacterium*, *Klebsiella*, *Enterobactericeae*, and *Enterococcus* species), and 3 of the 31 individuals did not have urine culture. Interestingly, in a paper describing 60 Japanese patients with acute pyelonephritis [14], ammonia concentrations were elevated in five individuals; however, they were noted to be infected with urease-negative bacteria (*Escherichia coli*, *Streptococcus*, *Staphylococcus epidermidis*). The authors suggest that increased intravesical pressure leads to absorption of urinary ammonia in the vesical venous plexus and ultimately hyperammonemia.

In addition to urinary tract infections, other infectious etiologies have been suggested to cause hyperammonemia, with reports mainly describing urease-producing pathogens. Hyperammonemia has been described in immunocompromised children with acute myeloid leukemia due to *Ureaplasma parvum* bacteremia [2,3]. *Ureaplasma* infection has also been reported to cause hyperammonemia in an individual following liver-kidney transplant [15]. Infective enterocolitis has been suggested as a cause of hyperammonemia, although no urease-producing bacteria were cultured in the patient [16].

Among other hypotheses, it has been postulated that infection may be the mechanism of hyperammonemia in lung transplant recipients. Although the prevalence of hyperammonemia following lung transplantation is still being characterized, prior estimates have suggested around 1% to 4.1% [17–19]. In a study of 145 individuals with orthotopic lung transplantation 6 developed hyperammonemia (approximately 4%), all in the 26 days following transplantation [17]. These individuals had a higher mortality rate 30 days following transplantation (67%) compared to individuals without hyperammonemia (17%) [17]. In one center's experience, 8 of 807 (roughly 1%) of lung transplant recipients had hyperammonemia with all 8 receiving hemodialysis, and 6 of 8 died [18]. There have been numerous hypotheses regarding the mechanism of hyperammonemia following lung transplantation including infection with urease-producing bacteria [19]. One group described systemic *Ureaplasma urealyticum* or *Ureaplasma parvum* infection in 6 of 6 transplant patients who developed hyperammonemia (1 individual also had *Mycoplasma hominis* infection) and in 0 of 20 lung transplant patients with normal ammonia concentrations [20]. One of several proposed mechanistic hypotheses has been that urease-producing bacteria of the genitourinary tract may lead to hyperammonemia following lung transplantation due to dissemination in an immunosuppressed state [19,20]. Additionally, hyperammonemia (of 80 μM) was reported in an individual following lung transplantation where the donor had bronchoalveolar lavage positive for *U. parvum* prior to the procedure [4]. The mechanism of hyperammonemia in lung transplant recipients is still being evaluated, but it may be due to an

infectious etiology in an immunocompromised host. Of note, a case in the literature acknowledged *Ureaplasma parvum* infection in a hyperammonemic individual following hematopoietic cell transplantation [21].

Briefly, in addition to inborn metabolic disorders, infectious etiologies, and lung transplantation, other causes of hyperammonemia have been well described. Liver failure is a very well-characterized cause of hyperammonemia [22]. Other described etiologies include medications (such as valproic acid and asparaginase), anatomic anomalies (portosystemic shunt), and transient hyperammonemia of the newborn, among other causes [23].

The spectrum of causes of hyperammonemia is broad. Although the species and pathophysiology are still being described, infectious etiologies of hyperammonemia are clearly an important, treatable consideration. To our knowledge, this is the first documented case of hyperammonemia due to disseminated *Cryptococcal* infection. Given acute on chronic kidney disease in this case, the ammonia could only be controlled by renal replacement therapy until the meningitis and fungemia were treated. In addition to this novel finding, we emphasize three learning points:

- Regardless of age and known medical history, plasma ammonia should be considered in the evaluation of individuals with inadequately explained encephalopathy.
- Biochemical geneticists have expertise in assessing inborn errors of metabolism and have a broad understanding of non-genetic causes of metabolic decompensation. Genetics evaluation can be extremely helpful early in the course of unexpected hyperammonemia.
- An infectious cause of hyperammonemia is an important part of the differential diagnosis, particularly in immunocompromised individuals.

Declaration of Competing Interest

No authors have a conflict of interest to disclose or funding source.

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