Case Report

Hyperammonemic coma in a post-partum patient with undiagnosed urea cycle defect

Sananta Kumar Dash, Munish Chauhan, Vishakh Varma, Rakesh Sharma, Sudha Kansal, Rajesh Chawla

Abstract

Urea cycle disorders (UCD) are common during neonatal period, and it is rarely reported in adults. We are reporting a patient presenting with post-partum neuropsychiatric symptoms rapidly progressing to coma. Markedly raised serum ammonia level on presentation with an initial normal magnetic resonance imaging (MRI) of brain and normal liver function tests led to the suspicion of UCD, which was confirmed on the basis of urine orotic acid and elevated serum amino acid levels. We had to resort to hemodialysis to correct the hyperammonemic coma, which was unresponsive to conventional anti-ammonia measures. She exhibited remarkable improvement with a progressive decline in serum ammonia with repeated hemodialysis and made a full recovery. Timely diagnosis and early institution of hemodialysis in the setting of a poor neurological status maybe considered a suitable treatment option.

Keywords: Hyperammonemic coma, post-partum patient, urea cycle defect

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Introduction

Urea cycle disorders (UCD) are more common during the neonatal period. Late-onset urea cycle deficiencies are defined as those that have clinical onset after an age of 28 days.[1] This disorder occurs due to the deficiency of any of the following enzymes-ornithine transcarbamylase (OTC), carbamoyl-phosphate synthetase (CPSI), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), and (NAGS), which acts as a co-factor [Figure 1].[2] The suspicion for this disorder arises when patients have hyperammonemia without underlying hepatocellular dysfunction.

Case Report

A 33-year-old primigravida, four days post-cesarean section, was referred to us with 2 days history of altered sensorium progressing to coma. A pre-admission MRI brain with cerebral venography was unremarkable. The peripartum period was uneventful. She had past history of self-limiting episodes (3 in the last 5 years) of altered behavior and confusional state. In the intensive care unit (ICU), she was found to be in grade IV encephalopathy (Glagow Coma Scale (E1V1M2), pupils were bilateral mid dilated and reactive to light. Bilateral plantars were extensor, and deep tendon reflexes were absent. Neck rigidity was absent, and there was generalized hypotonia. She was hemodynamically stable. The trachea was intubated for airway protection. Her blood investigations showed a serum ammonia 286 mmol/L and serum urea of 13 mg/dL. Arterial blood gases showed well compensated respiratory alkalosis. Rest of the investigations including liver function tests and blood glucose levels were normal.

Plasma amino acid levels and urine orotic acid levels were sent. A protein-free nasogastric feed was started. Anti-ammonia measures were instituted in the form of lactulose (30 ml q4h) and tablet rifaximine (300 mg twice-daily) through nasogastric tube.

The next day, ammonia levels rose to 300 mmol/L, despite passage of good amount of loose stools. Decision of instituting hemodialysis was taken. On day 3, we received the report of amino acid levels with citrulline levels of

From:
Department of Critical Care Medicine, Indraprastha Apollo Hospital, New Delhi, India

Correspondence:
Dr. Sananta Kumar Dash, Department of critical Care Medicine, Medical ICU, First Floor, Indraprastha Apollo Hospital, New Delhi - 110 076, India.
E-mail: drsananta@yahoo.co.in

933 (normal <70) micromol/L, glycine 970 (normal <505) micromol/L and phenyalanine 181 (normal <120) micromol/L. Urinary orotic acid – result value 31.20, reference range in % 0.30, elevation factor 104.00. Ammonia levels after a second cycle of hemodialysis was 160 mmol/L.Serum ammonia level showed a progressive decline [Figure 2] over the next 3 days through 3 cycles of hemodialysis. She was extubated on day 5. Ammonia levels stayed below 50 mmol/L with no further dialysis required. She could be transferred out of ICU on day 7 and discharged on day 9 of hospitalization in a stable condition.

Discussion

In April 2000, research experts at the Urea Cycle Consensus Conference estimated the incidence of the disorders at 1 in 30,000 births.

These patients are either asymptomatic or have minor self-limiting neuropsychiatric symptoms. Symptoms may be triggered by illness or stress i.e., viral illnesses, childbirth, fasting, and use of valproic acid at almost any time of life, resulting in elevations of plasma ammonia concentration.[1] In patients with partial enzyme deficiencies, the first recognized clinical episode may be delayed for months or years.[3] Many of the adult onset UCDs leading to coma are precipitated in the peripartum period.[4]

The signs and symptoms during such episodes are vague and non-specific and usually include confusion, migraine headaches, loss of appetite, cyclical vomiting, lethargy, sleep disorders, delusions, hallucinations, psychosis, seizures, bizarre behavior, or psychomotor delay.[1,5] Deficiency of the fifth enzyme, arginase (ARG), results in a chronic debilitating disease affecting primarily the nervous system.[3]

This patient had history of self-limiting episodic confusion and abnormal behavior lasting only for few hours.

Hyperammonemia in the absence of hepatic dysfunction and a normal LFT should raise the suspicion for an UCD.[6,7] A low serum urea is an indirect evidence of an UCD.[6] An elevated serum ammonia levels with a low serum urea and a normal blood sugar, anion gap, and liver function test results raised strong suspicion for UCD in our case.

The first MRI brain of the patient done within 6 hours of coma was normal. Follow up MRI (48 hrs post-symptoms) exhibited diffusion restriction in bilateral perisylvian cortex [Figure 3], thalamus and cerebral cortices, sparing the occipital areas [Figure 4], suggestive of systemic metabolic or hypoxic insult. Her repeat MRI on 4th day showed restricted diffusion

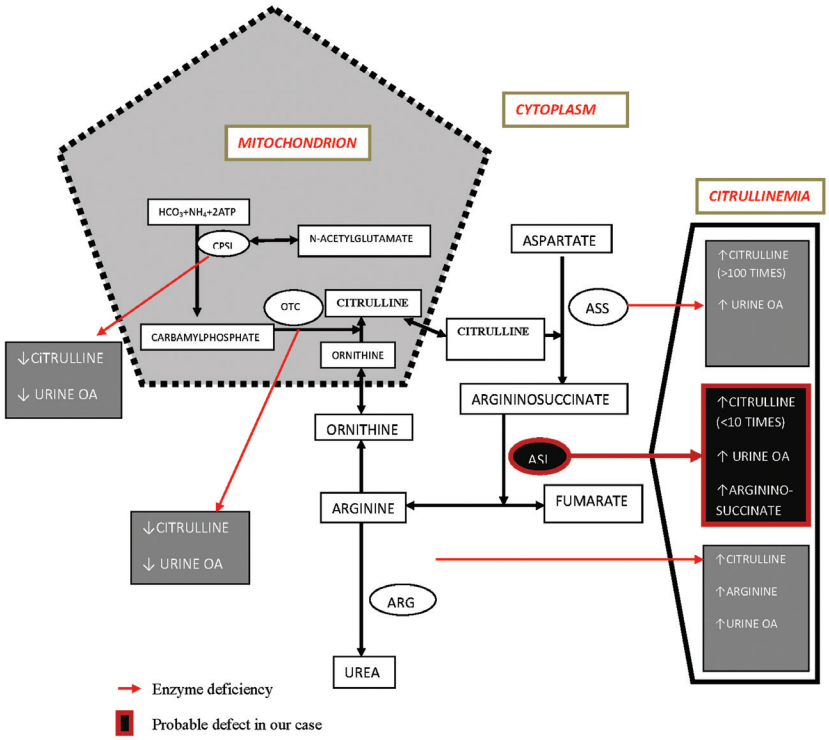

Figure 1: Urea cycle and diagnosis of probable argininosuccinate lyase deficiency in our case

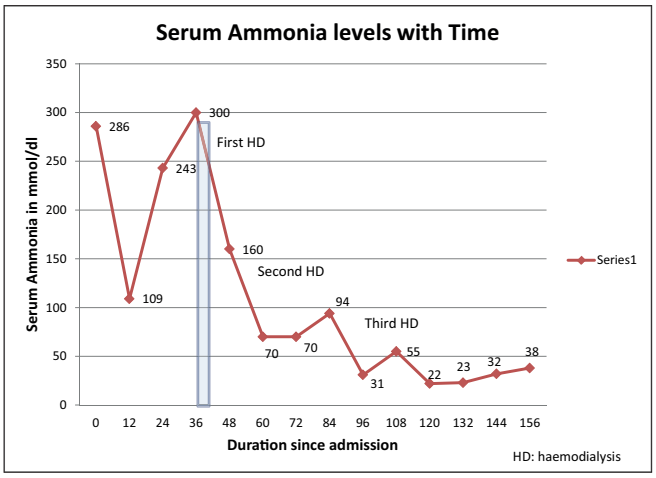

Figure 2: Serum ammonia levels in relation to hemodialysis

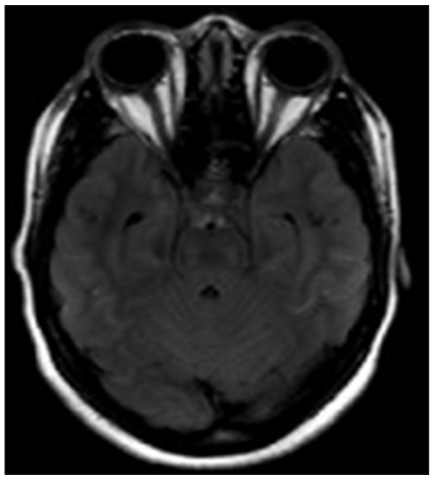

Figure 4: Bilateral temporal lobe flair hyperintensity with occipital sparing

in the splenium [Figure 5]. Extensive literature search yielded a few case reports revealing similar findings in hyperammonemia due to citrullinemia.[8,9]

Plasma citrulline is formed upstream to ASS enzyme action site; a decrease in plasma citrulline level distinguishes OTC and CPS1 from other enzyme defects (i.e., ASS, ASL, ARG). Laboratory values in our case showed a high plasma citrulline with a low plasma arginine. This ruled out the possibility of ARG enzyme defect, which presents as an increased plasma arginine [Figure 2].

This plasma quantitative amino acid analysis enabled us to narrow our possible diagnosis to ASS or ASL enzyme deficiency.

Urinary orotic acid is high in deficiency of OTC, ASS, and ASL deficiency. Deficiency of ornithine synthesis in intestinal cells of the newborn or of either argininosuccinate

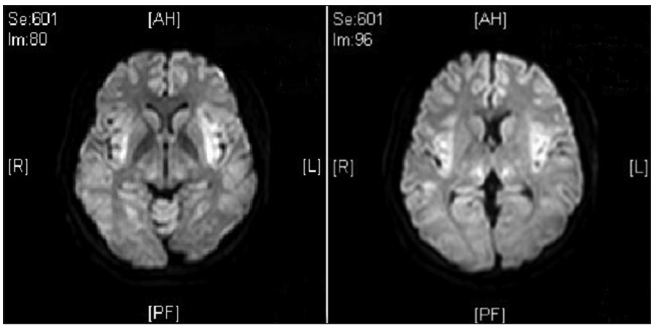

Figure 3: Diffusion restriction in peri-sylvian area and thalamic region bilaterally

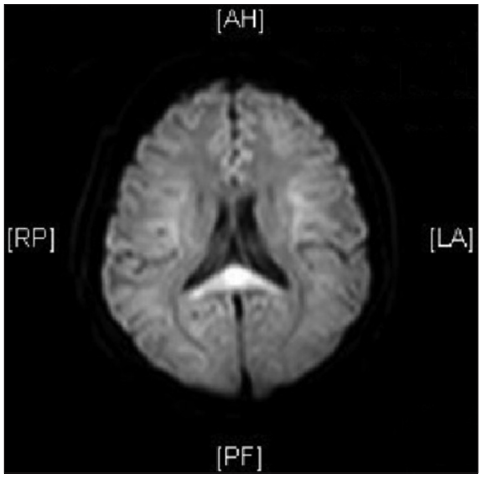

Figure 5: Diffusion weighted images showing bright areas in splenium

synthetase or argininosuccinate lyase in liver and kidney in the face of hyperammonemia can result in mild orotic aciduria together with a low rate of arginine synthesis.[10] Our patient presented with a high urinary orotic acid level, which is consistent with ASS or ASL deficiency.

The enzyme defect causing hypercitrullinemia can be detected by chromatographic pattern of aminoacids.[2] Hepatic biopsy can differentiate OTC, CPSI, and NAGS deficiency. Fibroblast and red cell enzyme assay differentiates ASS and ASL deficiency.

Treatment modalities found to be successful pertains to management of the acute phase and prevention of repeat episodes. In the acute phase, the mainstay of treatment involves rapid reduction in plasma ammonia level, dietary nitrogen restriction, and management of cerebral edema.

The treatment for hyperammonemia involves administering intravenous fluids, lactulose,[11] and rifaximine[12] to reduce the concentration of ammonia.

Restricting nitrogen in the diet is essential.[5] In older patients, alternative-pathway therapy i.e. sodium phenylacetate, sodium benzoate, and arginine therapy are the initial treatment options.[13] Hemodialysis can be successfully used for hyperammonemia not responsive to drug therapy[2] or when obtundation or coma persisted.[14] In a study, it was documented that dialysis was a more often used modality in neonates as compared to adults.[14] Conventional hemodialysis has the highest ammonium clearance rate, as compared with other methods such as peritoneal dialysis, exchange transfusion, and hemofiltration.[15] In our case, persistence of coma prompted us for early dialysis.

Conclusion

UCDs are uncommonly encountered in adults. A comprehensive family history, clinical presentation, plasma ammonia concentration, pH, CO2, anion gap, quantitative plasma amino acids analysis, and analysis of urine organic acids and urine orotic acid, and molecular genetic testing lead to near-confirmed diagnosis. Though alternative methods to hemodialysis are effective in correcting hyperammonemia, use of early hemodialysis is warranted in the setting of worsening coma. Hemodialysis for reducing serum ammonia level should be considered especially in patients with a poor neurological status.

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