Case Report
An Unusual Cause of Fatal Acute Hyperammonemic
Encephalopathy in a Non Cirrhotic Patient – Case Report

2015

An Unusual Cause of Fatal Acute Hyperammonemic Encephalopathy in a Non Cirrhotic Patient – Case Report

Cyriac Abby Philips[1], Amrish Sahney[2], Awinash Kumar[3], Chinmaya Bal[4]

ABSTRACT

Hyperammonemia can be secondary to hepatic or non hepatic and idiopathic causes. Among non hepatic or non cirrhotic causes of hyperammonemia, excess of ammonia production or decrease in ammonia excretion predominates to produce the clinical syndrome. Cirrhosis is the commonest cause of hyperammonemia in adults. In children, disorders of urea cycle need to be considered as a suspecting but rare cause. Here we present a middle aged non cirrhotic female patient who presented to us in a state of shock, in whom, severe septicemia with urea-splitting organisms along with sepsis related cardiogenic shock leading to ischemic hepatitis led to severe hyperammonemia eventually leading to brain stem herniation and immediate death.

Key words: adenocarcinoma, cerebral herniation, gall bladder, hyperammonemia, liver failure, non cirrhotic

[1,2,3] Senior Fellow, [4]Junior Fellow

Hepatology and Transplant Medicine, Institute of Liver and Biliary Sciences, New Delhi 110070, India.

Corresponding author mail: abbyphilips@gmail.com

INTRODUCTION

Ninety percent of adult hyperammonemia are secondary to severe acute or chronic liver disease. A very small subset of hyperammonemia cases are secondary to non hepatic causes of increased ammonia production or decreased ammonia elimination. [1] Hyperammonemic encephalopathy in the acute setting can lead to brain stem herniation that lead to imminent death. [2] Increased ammonia production can be secondary to aggressive plasma cell dyscrasias as these abnormal cells have been shown to produce excess of ammonia through enhanced amino acid metabolism. [3] Patients on intensive chemotherapy regimens also culminate hyperammonemic episodes. [4] Severe infections caused by urea splitting organisms lead to hyperammonemia.

Case Report
An Unusual Cause of Fatal Acute Hyperammonemic Encephalopathy in a Non Cirrhotic Patient – Case Report

2015

These include Proteus mirabilis, Eschrechia coli, Klebsiella pneumoniae and Providencia rettgeri. [5] Extreme protein overloading can also lead to hyperammonemia. [6] Certain disorders seen in childhood result in non hepatic hyperammonemic episodes. These include organic aciduria, dibasic aminoaciduria, urea-cycle disorders, fatty acid oxidation disorders and pyruvate metabolism disorders. [7] Congenital portosystemic shunts can also produce hyperammonemia as seen in Abernathy malformations. [8] Drugs like valproate, ribavirin and carbamazepine can cause non cirrhotic hyperammonemic encephalopathy. [9] Very rarely, hyperchloremic alkalosis resulting from ureterosigmoidostomy has also been reported to cause hyperammonemia related encephalopathy. Here we present a an interesting case, where in multiple factors for hyperammonemia coincide in a single patient, resulting in a severe hyperammonemic state, leading to encephalopathy and organic brain disease that ultimately resulted in death within a few hours.

CASE REPORT

A 48 year old lady, hailing from the district of Uttar Pradesh in India, was brought into the emergency department (ER) of our hospital in a state of shock. At presentation, she was found to have a very feeble pulse, bradycardia and unrecordable blood pressure. Fluid resuscitation was initiated and the patient was started on inotropic support, intubated and mechanically ventilated. She was then shifted to the intensive care unit for further evaluation after initial stabilization in the ER. Twenty days prior to this presentation, the patient had complained of progressive jaundice associated with mild to moderate right upper quadrant pain.

This was also associated with loss of appetite and nausea. Fifteen days prior to presentation in the ER, she had episodes of high grade fever with chills and rigors that lasted till one day before the presentation to our hospital. Eight days prior to the current presentation, she had complaints of a 'racing heart' with feeling of impending doom and chest discomfort, without cough or expectoration. Four days prior, she had complained of breathlessness intermittently and associated chest discomfort that worsened from the previous episode. Two days prior to this admission, she was seen by her local physician who diagnosed her to have

Case Report
An Unusual Cause of Fatal Acute Hyperammonemic Encephalopathy in a Non Cirrhotic Patient – Case Report

2015

obstructive jaundice and advised immediate hospitalization.

One day prior to this current presentation, she was admitted to a local hospital nearby her home, where they started her on IV fluids, nebulisation with beta blockers and broad spectrum antibiotics to combat infection secondary to obstructive jaundice. Her condition and sensorium worsened over time at the local hospital and she was then shifted to our hospital for further management. The patient was diagnosed to have adenocarcinoma of the gall bladder, incidentally, on histopathological study of gall bladder specimen which was resected in view of symptomatic gall stone disease 8 months prior to her initial jaundice presentation. Six months into follow up, she was found to have space occupying lesions of the liver which was proven by fine needle aspiration cytology to be that of metastatic adenocarcinoma.

She was then put on an intense regimen of chemo-radiation (cisplatin + capecitabine with 45 Gy radiation therapy in 25 fractions for 25 days) and had completed 6 cycles of the same, one month prior to this presentation. She has had no other co morbidities and did not take over the counter medications or any anti epileptic drugs. There is no history suggestive of complementary and alternative medication use and the patient did not have similar episodes or any illness pertaining to the liver in the past. On examination, the patient was sedated and on mechanical ventilation. Pallor and icterus were evident as was grade 1 clubbing.

The pupils were anisocoric (4mm left, 2 mm right) but reacting sluggishly to light. The bilateral deep tendon reflexes were diminished and the plantar response was mute in both lower limbs. The abdomen was tense and distended with audible bowel sounds. The liver was firm to touch, with normal borders and rounded margins and smooth surface and was enlarged 3 centimetres below the right costal margin. The spleen was not palpable and shifting dullness was absent. The cardiovascular, pulmonary and the musculoskeletal systemic examination was otherwise non contributory.

The haematological and biochemical investigations revealed the presence of anemia (9.9g/dL; normal 12-15), leukocytosis (32000 cells per cumm; normal 4000 to 10000), normal platelet

Case Report
An Unusual Cause of Fatal Acute Hyperammonemic
Encephalopathy in a Non Cirrhotic Patient – Case Report

2015

counts and a raised ESR (88mm; normal 0-8). The CRP was 118mg/L (normal less than 1) and the serum procalcitonin level was above 10 pg/mL (normal less than 0.5). The liver function tests revealed the presence of conjugated hyperbilirubinemia (total bilirubin 22.2 mg/dL, direct bilirubin 18.6 mg/dL), transaminitis that was 15-20 times raised from the baseline (AST – 8235 IU/L, ALT – 9832 IU/L), raised serum alkaline phosphatise and gamma glutamyl transpeptidase enzymes (234 and 767 IU/L respectively) hypoalbuminemia (albumin 1.8 g/dL, normal 3.5-5.5 g/dL) and a raised prothrombin time/INR (34.3/5.4). Her kidney function tests revealed the presence of raised blood urea nitrogen (266mg/dl) along with deranged creatinine values (3.6 mg/dl, normal <1.2 mg/dL) with electrolytes including calcium and magnesium being normal. The arterial blood gas analysis revealed the presence of severe lactic acidosis (8.8, normal less than 1 mmol/L) secondary to hypotensive shock she suffered in the ER. The arterial ammonia that was send from the ER was reported as 1777 mcg/dL (normal 10 to 60; Beckman Coulter Synchron CX5 system; spectrophotometric enzymatic timed endpoint method).

An abdominal ultrasonography imaging revealed the presence of an enlarged liver (span 14 cm) with multiple small hypo echoic lesions scattered throughout the parenchyma of both lobes, with maintained architecture and normal hepatic outlines. There was severe intrahepatic biliary radical dilatation, more on the left side than the right. A percutaneous transhepatic biliary drainage (PTBD) was attempted and jet black, sticky bile was aspirated. Following the procedure, the drain output was active and hemodynamic parameters started to show improvement. Further Neurological testing revealed a worsening in anisocoria which was associated with an increase in ventilatory support. In view of worsening Neurological condition, the patient was imaged with plain computed tomography of the brain at first, which scan revealed the presence of severe diffuse hypo-atenuation of the entire cerebral parenchyma with relative sparing of the cerebellum which was suggestive of gross cerebral edema. Subsequently an magnetic resonance imaging (MR) of the brain was undertaken along with diffusion weighted imaging which revealed evidence of diffuse marked cerebral edema as shown

Case Report
An Unusual Cause of Fatal Acute Hyperammonemic
Encephalopathy in a Non Cirrhotic Patient – Case Report

2015

by effacement of cerebral sulci and cisternal spaces with edematous gyri, chinked lateral ventricles and accentuation of gray white matter differentiation (Figures 1a, 1b, 1c, 1d) with attendant descending transtentorial herniation of midbrain and prominence of transcerebral and cortical veins in bilateral cerebral parenchyma (Figures 2a and 2b); there was also associated diffusion restriction in the bilateral insular cortex and with focal areas of diffusion restriction dispersed in the brain parenchyma. These features suggested the presence of severe hyperammonemic encephalopathy with the possibility of brain death.
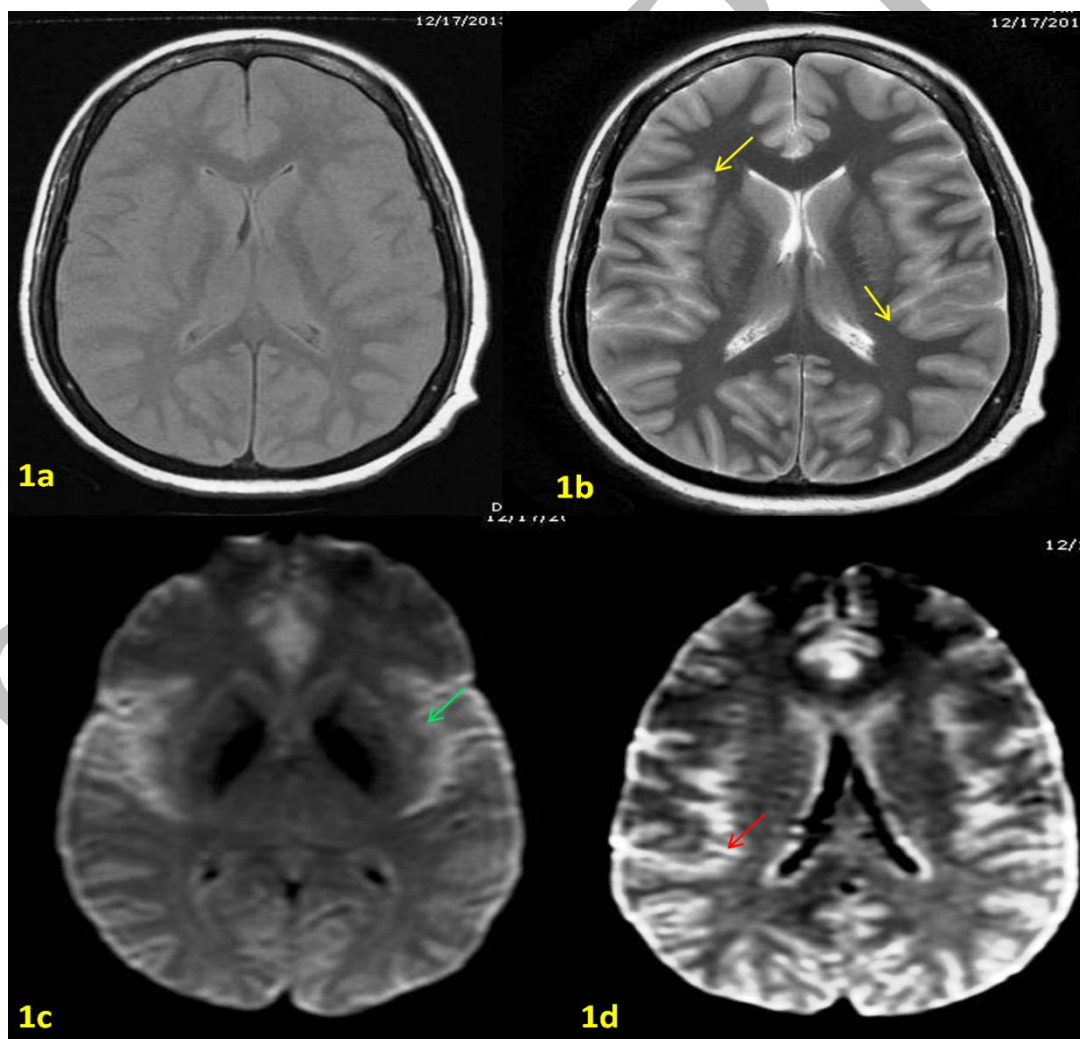

Figure (1a, 1b, 1c, 1d): Clockwise from Left: MRI imaging. 1a - T2W FLAIR revealing marked cerebral edema evidenced by effacement of cerebral sulci and cisternal spaces with

Case Report
An Unusual Cause of Fatal Acute Hyperammonemic
Encephalopathy in a Non Cirrhotic Patient – Case Report

2015

edematous gyri and chinked lateral ventricles; 1b – AXIAL T2WI showing accentuation of gray-white matter differentiation (yellow arrow); 1c and 1d – DWI showing features of diffusion restriction in focal areas of the parietal cortex (green arrows) and bilateral insular cortical areas (red arrows)
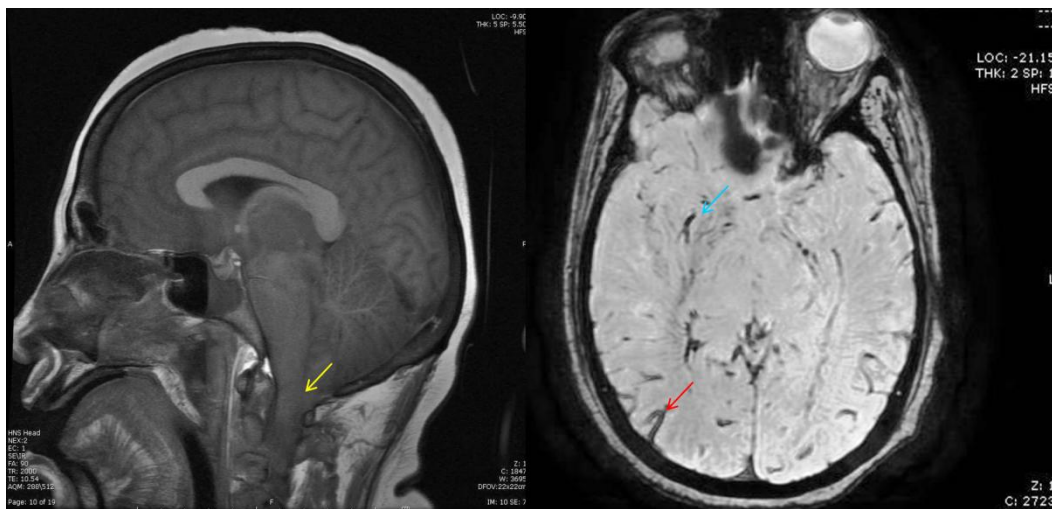

Figure 2a, 2b: From Left: 2a – Sagittal T1 FLAIR imaging revealing features of transtentorial herniation of midbrain (yellow arrow); 2b – Axial 3D SWI showing features of bilateral transcerebral (blue arrows) and cortical vein sign (red arrows)

Serial plasma ammonia samples were sent two hourly. Meanwhile the patient was started on broad spectrum antibiotics (carbapenems 1g Q8 hourly with Tigecycline 100mg Q 12 hourly), 3% normal saline infusion to combat the cerebral edema. Serial ammonia measurements revealed an increasing trend, with ammonia peaking up to 4200 mcg/dL 8 hours after initial presentation. Serial liver enzyme measurements also revealed peaking progressively increasing levels of transminases. The patient eventually developed refractory ventricular tachycardia on ventilator support which led to asystole. She could not be resuscitated and was declared dead 16 hours after presentation to the intensive care unit. Follow up of the blood and bile culture reports revealed heavy growth of Eschrechia coli and Klebsiella species. The final diagnosis at the time of declaration of

death was acute severe hyperammonemic encephalopathy secondary to severe septicaemia related to Eschrechia coli and Klebsiella infection with severe ischemic hepatitis leading to brain stem herniation and cardiorespiratory arrest.

DISCUSSION

Hepatic hyperammonemia usually occurs in the setting of underlying chronic liver disease and the diagnosis in such a situation is fairly uncomplicated. A number of non hepatic causes of hyperammonemia have been described that could be severe enough to cause coma and death. Even though these causes are rare, the diversity in etiology makes it challenging to diagnose. Some of these causes are reversible which makes it even more important to identify the etiology, for timely intervention. Endogenous and exogenous protein load undergoes transamination and deamidation in the liver through the urea cycle to produce urea that is excreted by the kidney. A rare cause of non hepatic hyperammonemia is urea cycle enzyme defects that are more commonly seen in children and very rarely in adults. [10]

Ornithine transcarbomoylase (OTC) deficiency is the commonest in this group and has a distuighised feature of having large amounts of orotic acid in the urine. There are many cases reported, of OTC deficiency occurring in older children and in adults, homozygous males and heterozygous females (who become symptomatic when diversion procedures are done on them for other reasons). [11] Congenital portosystemic shunts like those seen in Abernathy malformations or in cases of portal vein thrombosis secondary to infection in neonates leads to large load of ammonia been transferred into the systemic circulation that lead to acute hyperammonemic episodes. [12]

Hyperammonemia can also result when there is a metabolic derangement secondary to urinary diversion procedures like uretero-sigmoidostomy. The diversion retains its venous drainage and as a result, the colonic ammonia load enters the systemic circulation. [13] Severe hyperammonemia leads to increased intracranial tension, cerebral edema, herniation, coma and death. The ammonia levels do not always correlate with the clinical severity. Reliable methods of ammonia estimation include those of ion selective electrode system and an automated enzyme method (which was

Case Report
An Unusual Cause of Fatal Acute Hyperammonemic
Encephalopathy in a Non Cirrhotic Patient – Case Report

2015

used in our case). Rarer causes of acute hyperammonemia are seen with severe infections with urea splitting organisms like Proteus, Klebsiella and Providencia. [14]

In our case, the bile, blood and the tracheal aspirate had heavy growth of mixed E.coli and Klebsiella bacteria. Ischemic hepatitis as evidenced by highly raised enzymes in the presence of a preceding episode of severe hypotension characteristically can lead to acute hyperammonemia. In the current presentation, severe urea splitting organism related septicaemia along with shock liver produced very high values of plasma ammonia in the range of thousands that led to intense and severe cerebral edema with immediate brain stem herniation leading to death in a matter of time in the patient. Imaging findings in acute hyperammonemic encephalopathy may mimic that of hypoxic ischemic brain injury. In severe hyperammonemia, the computed tomography can reveal the presence of diffuse cerebral edema and in late stages, uncal herniation. Extensive signal intensity changes are seen on MR imaging and is associated with diffusion restriction.

The classical picture is that of bilateral involvement of the insular cortex and cingulate gyrus. [15, 16] Particularly, this picture is associated with relative sparing of peri-rolandic and occipital cortices. Rarer involvement pattern can be seen at regions of basal ganglia, brain stem and thalamus. Subcortical white matter involvement predominating over cortical involvement is more evident in hyperammonemia secondary to inborn errors of metabolism and valproate induced hyperammonemia. [17] More extensive and apparently uncommon area involvement is seen with higher levels and severity of hyperammonemia. Our case represents a unique amalgamation of many features, both etiological and radiological.

Firstly, the presence of two rare coincidental aetiologies that produced severe hyperammonemia is described. Secondly, the highest level of ammonia documented due to these aetiologies is presented and thirdly, multiple radiological evidences suggestive of hyperammonemia and hypoxic brain injury are also presented. The etiological diagnosis of acute severe hyperammonemic encephalopathy is not an easy one. But in the wake of early diagnosis and

Case Report
An Unusual Cause of Fatal Acute Hyperammonemic
Encephalopathy in a Non Cirrhotic Patient – Case Report

2015

recognition, better outcomes in affected patients are a possibility.

REFERENCES

1. Blom HJ, Ferenchi P, Grimm G, *et al*. The role of methanethiol in the pathogenesis of hepatic encephalopathy. Hepatology 1991;13:445–54.

2. Butterworth RF. Effects of hyperammonaemia on brain function. J Inherited Metab Dis 1998;21(suppl 1):6–20.

3. Thompson EN, Sherlock S. The aetiology of portal vein thrombosis with particular reference to the role of infection and exchange transfusion.Q J Med 1964; 33:465.

4. Hughes PJ, Kiely PDW, Davies PTG, *et al*. Hyperammonaemia—an important cause of encephalopathy: three case reports. Ann Clin Biochem 1993;30:225–7.

5. Kaveggia FF, Thompson JS, Schafer EC, *et al*. Hyperammonemic encephalopathy in urinary diversion with ureasplitting urinary tract infection. Arch Intern Med 1990;150: 2389–92.

6. Rowe PC, Newman SL, Brusilow SW. Natural history of symptomatic partial ornithine transcarbamylase deficiency. N Engl J Med 1986;314:541–7.

7. Yoshino M, Nishiyori J, Yamashita F, *et al*. Ornithine transcarbamylase deficiency in male adolescence and adulthood. Enzyme 1990;43:160–8.3

8. Morse SS, Taylor KJW, Strausse EB, *et al.* Congenital absence of the portal vein in auriculo-vertebral dysplasia (Goldenhar syndrome). Paediatr Radiol 1986;16;437.

9. Duarte J, Macias S, Coria F, *et al*. Valproate-induced coma: case report and literature review. Ann Pharmacother 1993;27:582–3.

10. Wilson BE, Hobbs WN, Newmark JJ, *et al*. Rapidly fatal hyperammonemic coma in adults—urea cycle enzyme deficiency. West J Med 1994;161:166–8.

11. Häberle J. Clinical practice: the management of hyperammonemia. Eur J Pediatr 2011; 170: 21-34

12. Laish I, Ben Ari Z. Noncirrhotic hyperammonaemic

Case Report
An Unusual Cause of Fatal Acute Hyperammonemic
Encephalopathy in a Non Cirrhotic Patient – Case Report

2015

encephalopathy. Liver Int 2011; 31: 1259-1270

13. Bjerring PN, Eefsen M, Hansen BA, Larsen FS. The brain in acute liver failure. A tourtous path from hyperammonemia to cerebral edema. Metab Brain Dis. 2009;24(1):5-14.

14. Chamuleau RA, Vogels BA. Hyperammonaemia without portal systemic shunting does not resemble hepatic encephalopathy. Adv Exp Med Biol 1997;420:173–83.

15. Capizzano AA, Sanchez A, Moritani T, Yager J. Hyperammonemic encephalopathy: Time course of MRI diffusion changes. Neurology. 2012;78(8):600-601.

16. McKinney AM, Lohman BD, Sarikaya B, et al. Acute hepatic encephalopathy: diffusion-weighted and fluid-attenuated inversion recovery findings, and correlation with plasma ammonia level and clinical outcome. AJNR Am J Neuroradiol. 2010; 31(8):1471-1479.

17. Bindu PS, Sinha S, Taly AB, Christopher R, Kovoor JM. Cranial MRI in acute hyperammonemic encephalopathy. Pediatr Neurol. 2009; 41(2):139-142.