Idiopathic Hyperammonemia and Rituximab Therapy

Samer Bolis DO
Lehigh Valley Health Network, Samer.Bolis@lvhn.org

Daniel Schwed-Lustgarten
Lehigh Valley Health Network, Daniel.Schwed@lvhn.org

James Ross MD, FACP
Lehigh Valley Health Network, James.Ross@lvhn.org

Published In/Presented At

Bolis, S. Schwed, D. Ross, J. (2016, Oct). *Idiopathic Hyperammonemia and Rituximab Therapy*. Poster Presented at: ACP Regional, Danville, PA.

Idiopathic Hyperammonemia and Rituximab Therapy

Samer Bolis DO, Daniel E. Schwed, MD and James M. Ross, MD
Lehigh Valley Health Network, Allentown, Pennsylvania

INTRODUCTION

Hyperammonemia is most commonly encountered as a complication of hepatic dysfunction. As ammonia levels acutely rise, neurons suffer oxidative and mechanical stress due to increased intracellular osmolarity. There is no numeric cutoff to predict clinical impairment, but high enough concentrations can lead to coma and even death. Recognition and management of non-hepatic hyperammonemia in adult patients is a great challenge as such cases are not often encountered, tend to be persistent, with rapid progression to a poor prognosis.

CASE PRESENTATION

A 69 year-old female with no known history of inborn errors of metabolism or hepatic dysfunction presented with acute encephalopathy and was noted to be hyperammonemic (Serum ammonia of 860). She was treated with Rituximab (a monoclonal antibody against CD20) approximately 6 weeks prior for a cryoglobulinemic vasculitis and polyarticular inflammatory arthritis. She was initially managed with lactulose and rifaxamin, demonstrating improvement in mental status with decreased yet fluctuating ammonia levels (Approximately 150). Work up yielded no obvious explanation for the high ammonia levels. There were no signs of gastrointestinal hemorrhage, infection with urease-producing bacteria, seizures, intoxication of any sort, or hepatic dysfunction. By day 10 of her hospitalization, her serum ammonia gradually increased to levels >1000 with rapidly worsening and recurrent encephalopathy. Hyperammonemia reached a level as high as 1370 and was refractory to renal replacement therapy. The patient increasingly became hemodynamically unstable with eventual expiration within 48 hrs. Further investigation of serum amino acid levels suggested no enzymatic deficiencies to diagnose urea cycle disorders. An autopsy was declined by family members.

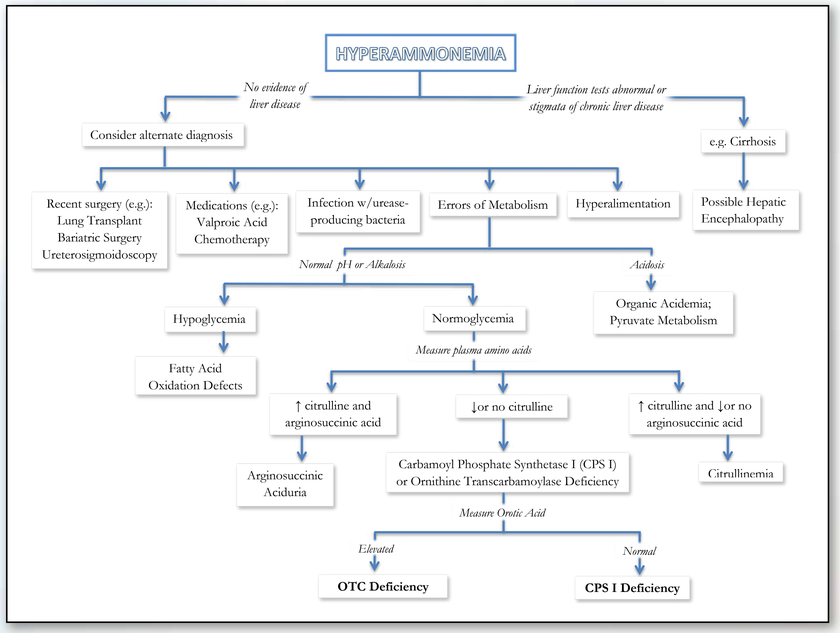

Figure 1. Algorithm for diagnosis of hyperammonemia in an adult aptient.

DISCUSSION

Several medications i.e., Valproic acid, are known for their potential to disrupt the hepatic urea cycle, causing mild elevations in serum ammonia. Several reports have observed hyperammonemia with levels comparable to our patient's following high-dose chemotherapy. While Rituximab is implicated in multiple cases, it has never been documented as being the sole culprit in patients with hyperammonemic encephalopathy. Given its prolonged half-life, we suspect that Rituximab contributed to our patient's hyperammonemia, making this case iatrogenic in nature. The fact that the patient was not encephalopathic until serum ammonia reached levels >800, suggests that this was a chronic process rather than an acute hyperammonemia. In this case, when a CD 19 count was checked, it was found to be <1, indicating that Rituximab was still active. Proposed mechanisms suggest that Rituxumab may unmask mild or compensated urea cycle deficits. For instance, orthinthine transcarbamylase deficiency is X-linked and only 10 percent of female carriers become symptomatic, sometimes late in life. Despite the non-specific findings on serum amino acid analysis, enzymatic deficiencies of hepatic urea cycle cannot be ruled out. The diagnosis of inborn errors of metabolism is difficult to make in the setting of an acute illness and often cannot be confirmed for days or sometimes months after the initial presentation.

References:

1. Labuzetta JN, Yao JZ, Bourque DL, Zivin J. Adult nonhepatic hyperammonemia: a case report and differential diagnosis. *Am J Med.* 2010;123(10):885-91.
2. Acharya G, Mehra S, Patel R, Frunza-stefan S, Kaur H. Fatal Nonhepatic Hyperammonemia in ICU Setting: A Rare but Serious Complication following Bariatric Surgery. *Case Rep Crit Care.* 2016;2016:8531591.
3. Espinós J, Rifón J, Pérez-calvo J, Nieto Y. Idiopathic hyperammonemia following high-dose chemotherapy. *Bone Marrow Transplant.* 2006;37(9):899.
4. Jones JD, Hamilton BJ, Rigby WF. Rituximab mediates loss of CD19 on B cells in the absence of cell death. *Arthritis Rheum.* 2012; 64(10):3111-8.
5. Nott L, Price TJ, Pittman K, Patterson K, Young R, Fletcher J. Hyperammonaemic encephalopathy associated with rituximab-containing chemotherapy. *Intern Med J.* 2008;38(10):800-3.