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Idiopathic Hyperammonemia and Rituximab Therapy

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Idiopathic Hyperammonemia and Rituximab Therapy

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.

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, HYPERAMMONEMIA or hepatic dysfunction. By day 10 of her Liver function tests abnormal or No evidence tigmata of chronic liver disease liver disease hospitalization, her serum ammonia gradually Consider alternate diagnosis e.g. Cirrhosis increased to levels >1000 with rapidly Possible Hepatic Infection w/urease-Hyperalimentation worsening and recurrent encephalopathy. Errors of Metabolism Recent surgery (e.g.) Medications (e.g.) Encephalopathy Lung Transplant producing bacteria Valproic Acid Bariatric Surgery Chemotherapy Hyperammonemia reached a level as high as Ureterosigmoidoscopy Normal pH or Alkalosis 1370 and was refractory to renal replacement Organic Acidemia; Normoglycemia Hypoglycemia Pyruvate Metabolism therapy. The patient increasingly became Measure plasma amino acids hemodynamically unstable with eventual Fatty Acid Oxidation Defects expiration within 48 hrs. Further investigation \uparrow citrulline and \downarrow or no ↑ citrulline and ↓or no citrulline arginosuccinic acid arginosuccinic acid of serum amino acid levels suggested no Carbamoyl Phosphate Synthetase I (CPS I Citrullinemia Arginosuccinic or Ornithine Transcarbamoylase Deficiency enzymatic deficiencies to diagnose urea cycle Aciduria Measure Orotic Acid disorders. An autopsy was declined by family members. **OTC Deficiency CPS I Deficiency**

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INTRODUCTION

CASE PRESENTATION

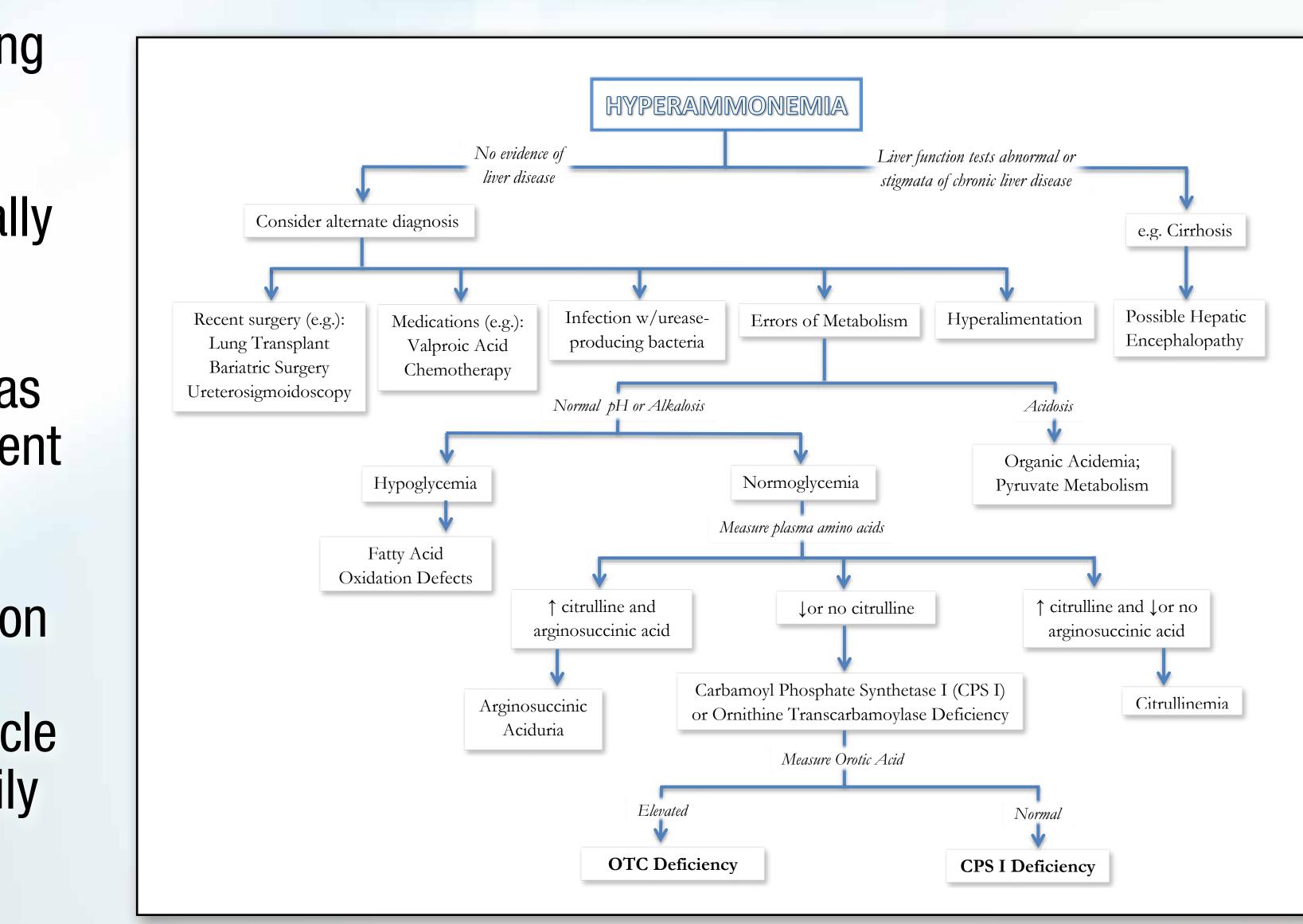


Figure 1. Algorithm for diagnosis of hyperammonemia in an adult aptient.

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.

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DISCUSSION

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