Hyperammonemic Encephalopathy with Triphasic Waves: A Case

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Hyperammonemic Encephalopathy with Triphasic Waves: A Case

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Abstract

The exact mechanism with which hepatic encephalopathy results in impaired brain function is not known. Current theories suggest neurotransmitter abnormalities resulting from the accumulation of ammonia and other toxins, which leads to increased neural inhibition. We herein report a 56-year-old female patient with multiple comorbidities, who suffered from Non-Alcoholic Steatohepatitis and was hospitalized frequently for acute hepatic encephalopathy. She presented with altered mental and elevated ammonia levels. EEG depicted triphasic waves that are commonplace in hepatic encephalopathy and other metabolic encephalopathies. With each admission, her medication regimen was adjusted, but the patient continued to have rapid deterioration of her condition. The objective of this case report is to assess the need for further research into the disease modality and for potentially updating therapeutic options for hepatic encephalopathy. Appropriate patient care will need further research, which is important in the management of hepatic encephalopathy.

In April 2019, she presented to the hospital for the first time with complaints of altered mental status with an elevated ammonia level of 75. Stroke was ruled out at the time of arrival to the emergency room. The patient was being followed by a gastroenterologist and a hepatologist and was taking lactulose once a day. After further investigation, she was found to have cirrhosis, esophageal varices, portosystemic shunting, ascites, and anemia. She was started on antibiotics, proton pump inhibitor, lactulose, and iron supplementation. She was discharged in a stable condition with a plan to be seen in the hepatology clinic for further investigation.

The patient presented back to the hospital about a month later with a hemoglobin of 6, a 35.8 lbs gain since December, abdominal pain, +1 generalized edema in the lower extremities, melena, and confusion. On physical exam, the patient was noted to be in acute distress, with a heart rate of 120, blood pressure of 90/50, respirations of 24, and oxygen saturation of 94% on room air. Her abdomen was noted to be obese, tympanic with no rebound or guarding. Her peripheral pulses were strong, and her pedal pulses were 2+ bilaterally. Her abdomen was noted to be tender all over without rebound or guarding. Her liver was noted to be 6 cm below the right costal margin, and her spleen was palpable. Her blood work revealed a hemoglobin of 6, a white blood cell count of 11,000, with a platelet count of 116,000. Her liver function tests were significant for an international normalized ratio of 2.1, an aspartate aminotransferase of 296, and a alanine transaminase of 159. Her ammonia level was 50, and her lactate level was 4.4. Her creatinine level was normal at 0.7. Her urine toxicology screen was negative. Her insulin level was 8.9, her cortisol level was 5.6, and her thyroid stimulating hormone level was 3.4. Her urine protein was 4+.

The patient was diagnosed with cirrhosis, esophageal varices, portal hypertension, and esophageal varices. She was started on oxygen, lactulose, and iron supplementation. She was discharged on a home regimen of lactulose and rifaximin.

In May 2019, she was readmitted to the hospital with complaints of altered mental status with an elevated ammonia level of 75. She was started on antibiotics, proton pump inhibitor, lactulose, and iron supplementation. She was discharged in a stable condition with a plan to be seen in the hepatology clinic for further investigation.

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Discussion

Regardless of ongoing research, the true nature of hepatic encephalopathy is not completely understood. One idea is that the ammonia causes the astrocytes to swell in acute liver failure. This elevation also alters neurotransmission of GABA and leads to an accumulation of glycine in the brain, thus leading to a cascade of effects such as spatial memory dysfunction and motor and cognitive impairment. 1 2 Electroencephalography (EEG) can often show triphasic waves (TWs). Triphasic waves have been defined as periods of high-positive amplitude waves, which are then followed by smaller, negative waves with lower amplitude. TWs are believed to be a cause of dysrhythmia, sleep disturbance, and cognitive dysfunction. New treatment options have recently been explored, such as, ammonia lowering therapies, which may help to reduce the risk of ammonia-induced encephalopathy.1 2

Our patient was managed in the outpatient setting using typical medications such as antidepressants, sleep aid, and lactulose. Another option that could have been beneficial for our patient to use is flumazenil. Flumazenil is a benzodiazepine receptor antagonist that blocks the GABA-receptor complex, preventing inhibition in the mechanism of hepatic encephalopathy.4 New treatment options have recently been explored, such as, ammonia lowering agents like Citrulline Phenylalanine, which acts as an ammonia binder. Scolarich Carbon (AST-120), which lowers oxidative stress and edema in the brain, and probiotics or fecal microbial transplant. 5 Another drug used to treat hyperammonemia is sodium benzoate and phenylacetate with glycine to create hippurate, and this is then eliminated via the urine without going through the urea cycle.6

Patient care needs to be what drives patient treatment. New modalities, guidelines, and protocols need to be defined, studied, and then we'll see best practices. This disease process was identified in the 1950s, but the regulated treatment of hyperammonemic encephalopathy has lagged.

Conclusion

Hyperammonemic encephalopathy when having triphasic waves is no longer the pathognomonic identifier once thought, but is now a purely known association; the why some encephalopathies have the triphasic diagnosis is still unknown. More research into this thought process is needed to be more research conducted on treatment modalities of hyperammonemic encephalopathy as currently, there is no true consensus on the standard of care. There are however guidelines, and found within them are blanket statements that also acknowledge their weaknesses and the need for more data. However, the rarity of these diseases has resulted in mostly low evidence level for the statements made here, which corresponds to inferences derived from more analytical studies, such as case reports or case series or from expert opinion. Therefore, the recommendations contained herein should not be considered infallible or absolute.9

We do agree with this study that patients at risk of hyperammonemia need to be identified, due to prognosis if this patient population is not identified at an early enough point in the course of this disease process. Our patient would have had fewer complications if an accepted protocol for identifying and managing encephalopathy to be implemented early enough. If such a system were in place, more patients would be treated in a timely manner with a decrease in morbidity and mortality. Furthermore, as new treatments are being developed and tested, the care for patients needs to be current and be a reflection of new accepted care guidelines. There needs to be more categorization and grading when thinking of how to treat a patient with hepatic encephalopathy.

References

1 Taoro-Gonzalez, L. (2018) Hyperammonemia alters membrane expression of GluA1 and GluA2 subunits of AMPA receptors in hippocampus by enhancing activation of the IL-1 receptor: underlying mechanisms;  National Library of Medicine, National Institutes of Health. [online] Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6042798/
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Case Report Continued

Three days later, Ms. R was brought back to the emergency department from her physician’s office for altered mental status. Her hemoglobin was 50.5, and platelets were 20. However, her ammonia level was 95. CT scan of the abdomen and pelvis was consistent with the above ultrasound findings. Her ammonia level was 50, and her lactate level was 4.4. Her creatinine level was normal at 0.7. Her urine toxicology screen was negative. Her insulin level was 8.9, her cortisol level was 5.6, and her thyroid stimulating hormone level was 3.4. Her urine protein was 4+. The patient was placed on NPO for fear of aspiration, and a nasogastric tube was inserted. She was started on gentle hydration, and lactulose was given every hour until bowel movements. Her mental improvement significantly after 24 hours, and her ammonia level decreased to 64. It was noted in the patient's chart that she did not eat all of her dextrose after her last bowel movement and had gained almost 20 lbs by the next morning. In June 2019, she was transferred to the hospital from another hospital for ICU bed due to altered mental status. Astasias was present on examination and an urinalysis was done. Her ammonia level was 10. In the 200s with a baseline in the 60s. Neurology and Gastroenterology were consulted on this admission. On neurologic exam, she was noted to have normal neurologic exam with no focal neurologic deficits. Her ammonia level was decreased to 82, but her responsiveness remained the same. After several days of stable treatment, she was noted to have a normal ammonia level of 10 and was discharged home with follow up on her previous regimen of lactulose and rifaximin.

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