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Hyperammonemic Encephalopathy with Triphasic Waves: A Case

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Hyperammonemic Encephalopathy with Triphasic Waves: A Case

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Abstract

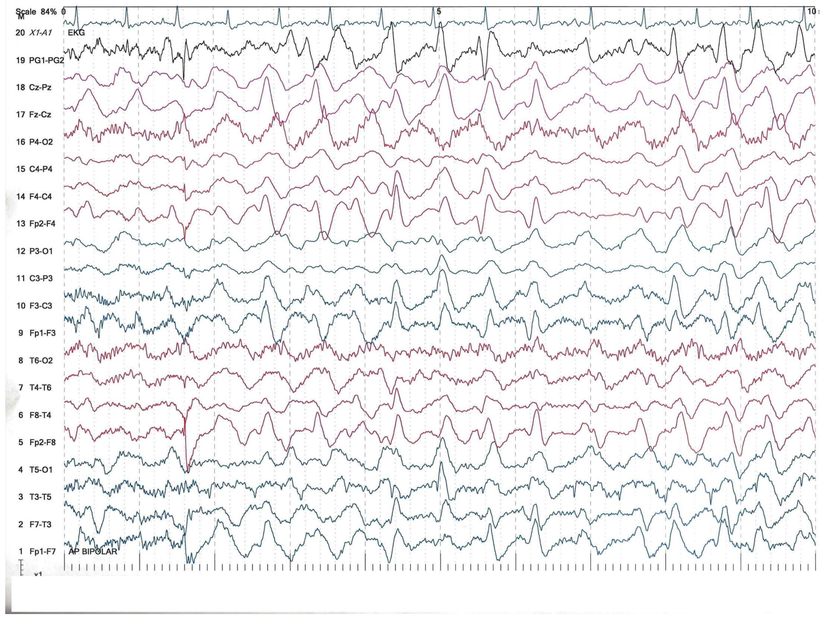
The exact mechanism with which hepatic encephalopathy results in impaired brain function is not known. Current theories suggest neurotransmitter abnormalities resulting from the accumulation of ammonia and other toxins, which leads to increased neural inhibition. We herein report a 56-year-old female patient with multiple comorbidities, who suffered from Non-Alcoholic Steatohepatitis and was hospitalized frequently for acute hepatic encephalopathy. She presented with altered mentation and elevated ammonia levels. EEG depicted triphasic waves that are commonplace in hepatic encephalopathy but are also seen in 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 require further research into the mechanism behind hepatic encephalopathy. With a better understanding of the disease, we will ultimately be able to identify, treat, and improve morbidity and mortality associated with hepatic encephalopathy

Case Report

The patient is a 56 y/o female with a past medical history of hypothyroidism, hypertension, sick sinus syndrome with pacemaker, coronary artery disease, depression, dyslipidemia, diabetes, and gastroesophageal reflux disease who presented multiple times to the emergency room with altered mental status between 2018 and 2019. In 2018, Ms. R was diagnosed with non-alcoholic steatohepatitis. She was never a drinker of any alcoholic beverages, and it is unclear how this diagnosis was made. An esophagogastroduodenoscopy was conducted in October of 2018 after complaints of anemia and gastrointestinal bleeding showing portal hypertensive gastropathy vs. gastric antral vascular ectasia. A biopsy was also performed, noting H. Pylori infection, which was treated. Follow up was recommended for further investigation for possible liver cirrhosis during that time. An ultrasound of the abdomen was completed in December of 2018, showing a small cirrhotic appearing liver with probable fibrofatty changes and mild splenomegaly with collateral vessels suggestive of portal hypertension. CT scan of the abdomen and pelvis was consistent with the above ultrasound findings.

In April 2019, she presented to the hospital for the first time with complaints of altered mental status with an elevated ammonia level of 79. 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, the patient was admitted for loose stools, weakness, hypernatremia, and presence of asterixis suggestive of acute hepatic encephalopathy. Her lactulose was increased to twice a day. Her ammonia level increased to 84 during admission; however, her symptoms improved, and she only complained of weakness. Her ammonia level continued to increase after several days, regardless of lactulose and gentle hydration to 553. Her hemoglobin was 10.5, hematocrit 30.3, and platelets 55. After a week, the ammonia level started to decrease, and her condition began to improve slowly. There were no clinical signs of spontaneous bacterial peritonitis or ascites during the visit, and the patient was discharged home with follow up with her hepatologist.

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, she complained of diffuse tenderness to palpation of the abdomen with hepatomegaly. Her wrists were swollen bilaterally with lower extremity edema and tenderness. Her ammonia level was 44; however, her hemoglobin was critically low, and platelets were 49. The patient was admitted to the hospital and transfused. During this admission, it was discussed with the patient, and a decision was made to be added to the liver transplant list. CT scan of the abdomen was completed showing small ascites, liver cirrhosis, and body wall anasarca. Her ammonia level remained stable, and her hemoglobin continued to improve. During this admission, she was a Child-Pugh class B. Her lactulose was increased to three times daily and was started on rifaximin by her hepatologist two weeks before admission to the hospital. She was also started on furosemide and spironolactone for continued diuresis. Her weight dropped 10 pounds after starting these medications. Her hemoglobin, ammonia levels, and condition continued to improve, and she was discharged home to her daughter's house.



EEG from actual patient, Ms. R, depicting triphasic waves

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 10.9, and platelets were 103; however, her ammonia level was 93. CT scan of the head was normal. During this presentation, Ms. R was described as "very lethargic and responding to only very simple commands." According to the family, she was able to perform ADLs after discharge until the morning of admission. She had been taking her lactulose and rifaximin as prescribed but had not had a bowel movement since her discharge. On physical exam, there were active bowel sounds appreciated in all four quadrants without shifting dullness. 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 mentation improved significantly after 24 hours, and her ammonia level decreased to 64. It was noted in the patient's chart that she did not fill all of her diuretics after her last discharge and had gained almost 20 lbs after her readmission. In June 2019, she was transferred to the hospital from another hospital for ICU bed due to altered mental status. Asterixis was present on examination and an unclear presence of seizures. Her ammonia level was in the 200s with a baseline in the 60s. Neurology and Gastroenterology were consulted on this admission. On neurologic exam, she was made no verbal attempts and did not follow verbal commands, her pupils responded to light. She had some rigidity and jerking movements in the upper and lower extremities. Her feet were in the decorticate position. Reflexes on the left were hyper reflexive and depressed on the right. There was a positive plantar reflex on the right. STAT CT and CTA of the head and neck were ordered, which were unremarkable. EEG was ordered and showed slow background in range of theta to a delta range with generalized slowing. No epileptiform activity was noted. These findings were consistent with generalized encephalopathy. After aggressive treatment, her ammonia level decreased to 82, but her responsiveness remained the same. After several days of unresponsiveness, Ms. R started to follow commands and verbally communicate. She complained of a headache and right-head pain. Her ammonia level was in the 40s, and she continued to receive aggressive treatment. At this point, she was oriented and able to follow commands correctly. She was stable and tolerating her treatment and transferred to step down. Palliative care was consulted for her rapid worsening in symptoms over the past several months, her current MELD score of 7, and not a current candidate for transplant per her recent visit with the transplant team. During this consult discussion, SSRIs were considered, optimize pain control, and continue with current treatment. Ms. R then underwent another EGD which showed a grade 1 esophageal varices and portal hypertensive gastropathy. There were no signs of active bleeding, and the patient was discharged home with outpatient follow up on her previous regimen of lactulose and rifaximin.

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 glutamate in the brain, thus leading to cerebral edema. This elevation can cause 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 non-epileptic electrographic transients that last high-positive amplitude waves, which are then followed by smaller, negative waves with lower amplitude. TWs are believed to be a cause of dysfunction in the thalamo-cortical circuit.3 Studies have been done to support the association between TWs and acute encephalopathy, as well as the circuit controlled by GABAnergic neurotransmitters.

TWs since being coined in the 1950s in association with hepatic encephalopathy have since been identified with other medical derangements such as structural, metabolic and toxic abnormalities. This paper finds our patient as having hyperammonemic encephalopathy with triphasic waves and hopes to add to the current data that this association between hyperammonemia and triphasic waves continues and needs further study.

Our patient was managed in the outpatient setting using typical medications such as antibiotics, low protein diet, and lactulose. Another option that could have been beneficial for our patient to use is flumazenil. Knowing that the hepatic encephalopathy can affect the GABA receptors, the role of flumazenil is believed to lower the activity of the GABA/benzodiazepine receptor complex, preventing inhibition in the mechanism of hepatic encephalopathy.4. New treatment options have recently been explored, such as, ammonia lowering agents like Ornithine Phenylacetate, which acts as an ammonia binder. Spherical Carbon (AST-120), which lowers oxidative stress and edema in the brain, and probiotics or fecal microbiota transplants. 5 Another drug used to treat hyperammonemia is sodium benzoate that causes a conjugation of benzoate with glycine to create hippourate, 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 derived, studied, and then set as 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 purely a known association; the why some encephalopathies have the triphasic distribution is poorly understood and will need further research on this characteristic. There also needs 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 none 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." 7

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 most likely would have had fewer complications if an accepted protocol for identifying and managing encephalopathy for an example modeled after code sepsis. 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 than categorization and grading when thinking of how totreat a patient with hepatic encephalopathy.

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