

Nonconvulsive Status Epilepticus in Hepatic Encephalopathy

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We discuss a case of a 64-year-old male with a history of liver failure presenting with altered mental status, initially diagnosed with hepatic encephalopathy but ultimately diagnosed with nonconvulsive status epilepticus (NCSE) by electroencephalogram (EEG). NCSE is a difficult diagnosis to make, given no clear consensus on diagnostic criteria. Especially in the intensive care unit setting of persistent altered mental status with no clear etiology, NCSE must be considered in the differential diagnosis, as the consequences of delayed diagnosis and treatment can be substantial. EEG can be useful in the evaluation of patients with hepatic encephalopathy who have persistently altered levels of consciousness despite optimal medical management. [West J Emerg Med. 2011;12(4):372–374.]

INTRODUCTION

Hepatic encephalopathy is a well-recognized and commonly diagnosed syndrome that has been researched and discussed for many years. Typically, hepatic encephalopathy is associated with advanced chronic liver disease and its clinical manifestations range from sleep disturbance to confusion or coma.¹ In rare cases, hepatic encephalopathy presents with overt seizure activity.²

Similarly, status epilepticus (SE) is a commonly diagnosed condition. While the dramatic tonic clonic features of SE are easily recognized, nonconvulsive status epilepticus (NCSE), a type of SE, tends to be underrecognized because of its inherent lack of discrete clinical signs.^{3–5} While a few case reports have been published describing patients with hepatic encephalopathy presenting in SE, here we describe the case of a patient presenting with hepatic encephalopathy and ultimately diagnosed with NCSE.

CASE REPORT

A 64-year-old man with a history of hypertension, chronic kidney disease, and liver failure secondary to hepatitis C, with status post liver transplant 13 years priorly, was brought in by ambulance to the emergency department for acutely altered mental status. The patient had been in his usual state of health, until he told his family 3 hours before that he “felt sick.” The family incidentally found him on the floor, confused and lethargic, and immediately called the ambulance.

Upon arrival, the patient had a temperature of 96.4°F;

pulse, 117 beats per minute; blood pressure, 151/93 mmHg; respiratory rate, 22 breaths per minute; and oxygen saturation of 100% on nonrebreather. The patient was known to have a history of recurrent episodes of hepatic encephalopathy, and his last episode of hepatic encephalopathy was in the prior 3 months, which was treated and controlled with lactulose. The patient’s family stated that the patient had run out of lactulose 4 days before presentation. Other than lactulose, the patient was compliant with all of his home medications, including amlodipine, bupropion, cyclosporine, hydrocodone, lasix, methocarbamol, and ramipril. The patient had no known history of seizure, recent illness, brain trauma, or recent surgical procedures.

Physical examination showed a male in no acute distress with a Glasgow Coma Scale of 12 (eyes, 4; verbal, 3; motor, 5). There were no signs of trauma found on his body. His pupils were equally round and reactive to light, and his neck was supple and soft with a cervical collar in place. Cardiopulmonary examination was unremarkable except for tachycardia. Abdominal examination was unremarkable. Because he was not following commands, the neurologic examination was limited. However, the patient was able to move all extremities equally and pulses were distally equal to all extremities. There was no posturing or clonus noted, and Babinski was downgoing in both feet.

Fingerstick glucose level was 210 mg/dL and bedside hemoglobin level was 13.1 g/dL. Noncontrast head and cervical spine computed tomography revealed no acute

pathologic lesion. Chest radiography also showed no acute pathologic lesion. Laboratory tests showed white blood cell counts of 5.5 K/mm^3 with 60% neutrophils, hematocrit of 36.5%, and platelets of 115 K/mm^3 . Electrolyte and liver function results were as follows: sodium, 141 mmol/L; potassium, 3.5 mmol/L; chloride, 104 mmol/L; bicarbonate, 22 mmol/L; calcium, 9.3 mg/dL; blood urea nitrogen, 71 mmol/L; creatinine, 1.9 mg/dL; total bilirubin, 2.1 mg/dL; aspartate aminotransferase, 128 U/L; alanine aminotransferase, 124 U/L; alkaline phosphatase, 231 U/L; albumin, 4.0 g/dL; lipase, 30 U/L; prothrombin time, 14.5 seconds; INR, 1.09; and ammonia, $501 \mu\text{mol/L}$ (reference range, 15–55 $\mu\text{mol/L}$). Toxicology serum screen results were negative for acetaminophen, salicylate, and ethanol. Urine toxicology screen results were positive only for opiates. Venous blood gas was pH 7.44.

Owing to the patient's obtunded condition and inability to protect his airway, the patient was electively intubated and given midazolam drip for sedation. The patient was admitted to the intensive care unit (ICU) for monitoring with a presumed diagnosis of hepatic encephalopathy. While administration of empiric antibiotics was started in the emergency department, it was discontinued after an infectious etiology was deemed unlikely and culture results were negative. Results of a magnetic resonance imaging brain scan were also negative, including no evidence of infarct.

During the ICU stay, the patient was readministered lactulose, and ammonia levels decreased to $117 \mu\text{mol/L}$ by hospital day 2 and to $78 \mu\text{mol/L}$ by hospital day 4. Despite discontinuation of sedation, the patient remained unresponsive. A neurologist was consulted and a bedside electroencephalogram (EEG) revealed findings consistent with status epilepticus. However, the patient had no clinical manifestations of status epilepticus, leading to a diagnosis of nonconvulsive status epilepticus. A phenytoin load was immediately administered, while a midazolam infusion was restarted, ultimately leading to EEG resolution of the status epilepticus. The patient did not immediately improve neurologically during the hospitalization stay and was ultimately transferred to another facility for continued treatment and rehabilitation.

DISCUSSION

Nonconvulsive status epilepticus has long been an underdiagnosed condition for a variety of reasons. Owing to its pleomorphic clinical presentation and its ultimate reliance on EEG for definitive diagnosis, NCSE has often been overlooked by physicians. Additionally, NCSE has undergone several changes in definition, reflecting our relative lack of understanding and the complexity of this disease process. In 2004, the Epilepsy Research Foundation consensus workshop defined NCSE as "a term used to denote a range of conditions in which electrographic seizure activity is prolonged and results in nonconvulsive clinical symptoms."⁶ Diagnostic criteria for NCSE continue to be debated. The clinical presentation of

NCSE varies greatly, from subtle behavioral changes to persistent confusional state to coma.³ EEG diagnostic criteria have also been the subject of vigorous debate.⁶ While the diagnostic criteria continue to be contested, many agree that NCSE is an underdiagnosed entity. A recent study of 236 comatose patients, with no overt clinical seizure activity and receiving EEG, found that 8% of those patients met the criteria for NCSE.⁷ Nonconvulsive status epilepticus itself encompasses several different subtypes, including but not limited to, absence status epilepticus, simple partial status epilepticus, complex partial status epilepticus, and nonconvulsive status epilepticus in coma.⁴

This particular case highlights the difficulty in diagnosing NCSE, especially in the setting of a seemingly obvious etiology for altered mental status, namely, hepatic encephalopathy. Although case reports have documented patients with hepatic encephalopathy presenting with generalized convulsive SE,^{8,9} a literature search at the time of this publication has revealed no published cases of NCSE in the setting of hepatic encephalopathy.

The pathophysiology underlying the development of seizures in the setting of hepatic encephalopathy remains unknown. Various metabolic factors are most likely involved, including short chain fatty acids, mercaptans, phenols, and false neurotransmitters.¹⁰ Hyperammonemia is likely a contributing factor, as triphasic waves and epileptiform abnormalities on EEG is a well-documented finding in hepatic encephalopathy and hyperammonemia.^{2,11,12} The association between hyperammonemia and seizures has further been highlighted by Velioglu et al,¹³ who discussed the case of a patient with no underlying hepatobiliary conditions who developed NCSE secondary to valproic acid-induced hyperammonemia.

There are other precipitant events or conditions in the setting of hepatobiliary disease that may contribute to the development of seizures. These include metabolic derangement from large-volume paracentesis or from acute decompensation of liver failure, and complications from recent liver transplant or from transjugular intrahepatic portal systemic shunt placement. Particularly in the unique setting of liver transplant, Wszolek et al¹⁴ reported in a retrospective chart review that 29% of 69 liver transplant patients had epileptiform abnormalities seen on EEG and ultimately died. The authors concluded that EEG epileptiform abnormalities after liver transplant, were "associated with serious, often irreversible, brain damage."

In this particular case, there were no overt precipitating factors leading to the patient's ultimate diagnosis of NCSE, other than noncompliance with medication. Unfortunately, the patient was presumably in NCSE for a significant period of time before the diagnosis was made. While morbidity and mortality remain high in patients with severe hepatic encephalopathy, this case highlights the reality of NCSE underlying hepatic encephalopathy and the importance and

utility of EEGs in evaluating for NCSE in a patient whose condition is otherwise not evaluable.

KEY POINTS

Nonconvulsive status epilepticus encompasses a wide range of diagnoses with no clear consensus on diagnostic criteria.

Nonconvulsive status epilepticus is a difficult diagnosis to make and requires a high index of suspicion.

Especially in the ICU setting of unresolving altered mental status with no clear etiology, NCSE must be considered in the differential diagnosis, as the consequences of delayed diagnosis and treatment can be substantial.

Emergent EEG can be useful in the evaluation of patients with hepatic encephalopathy who have alterations in levels of consciousness.

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