To the Editors-in-Chief:

On behalf of all the authors, I would like to request your consideration for publication of our manuscript titled “PRES in Alcoholic Hepatitis: Hepatic Encephalopathy a Common Theme ” for publication in *World Journal of Gastroenterology* as a case report. As PRES is an increasingly recognized finding on imaging and can be irreversible, it is imperative to report new associations to gain better understanding of the pathophysiology and causes of PRES.

We sincerely believe that the findings described in this research article will be of particular interest to the readers of *World Journal of Gastroenterology*.  This manuscript has not been published before and is not under consideration for publication elsewhere. None of the authors have submitted or published any related papers from this same study. All the authors have read the manuscript and have approved this submission. The authors report no conflicts of interest or financial interests.

Sincerely,

Elizabeth S. John, M.D.

Department of Internal Medicine

Rutgers Robert Wood Johnson Medical School

(P): 973 592 6116

Elizabethjohn17@gmail.com

Name of Journal: World Journal of Gastroenterology

Manuscript Type: Case Report

**PRES in Alcoholic Hepatitis: Hepatic Encephalopathy a Common Theme**

John ES et al. PRES and Hepatic Encephalopathy

Elizabeth S. John MD1, Ramy Sedhom MD1, Ishita Dalal MD1, Ranita Sharma MD1

1. Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Author Contributions: All authors took care of the patient medically, ESJ drafted the report, RS, ID, and RS made critical appraisals of the report.

Institutional Review Board Statement: not required as this was a case report

Informed Consent Statement: This was acquired from the patient.

Conflict of Interest Statement: None of the authors have any financial disclosures or conflicts of interest.

Correspondence to:

Elizabeth S. John, MD

1 Robert Wood Johnson Place

MEB 492

New Brunswick NJ 08901

Elizabethjohn17@gmail.com

973 592 6116

**ABSTRACT:** Posterior reversible encephalopathy syndrome (PRES) is a neuro-radiologic diagnosis that has become more widely recognized and reported over the past few decades. As such, there are a number of known risk factors that contribute to the development of this syndrome including volatile blood pressures, renal failure, cytotoxic drugs, autoimmune disorders, pre-eclampsia, and eclampsia. This report documents the first reported case of PRES in a patient with severe alcoholic hepatitis with hepatic encephalopathy and delves into a molecular pathophysiology of the syndrome.

**KEYWORDS:** PRES, alcoholic hepatitis, hepatic encephalopathy, seizure, headaches

**CORE TIPS:** PRES has been described in a number of settings, but not in the setting of severe alcoholic hepatitis, as is presented in this case report. There are clear molecular relationships between ammonia which is detoxified to glutamine in the brain causing astrocytic swelling and cerebral edema. This vasogenic edema is a pivotal component of PRES and accounts for one of the major hypotheses of the syndrome. Thus, though a clear connection between hyperammonemia and PRES has never been documented, there is a theoretical relationship.

**INTRODUCTION:** Posterior reversible encephalopathy syndrome (PRES) is a disorder characterized by various acute neurological symptoms and has been increasingly recognized over the past two decades due to advances in brain imaging. It is identified radiographically by subcortical vasogenic brain edema. PRES has been documented in patients with renal failure, labile blood pressure, cytotoxic drugs, autoimmune disorders, pre-eclampsia, and eclampsia(1). There has been one documented case of PRES in a patient with cirrhosis who presented with gastrointestinal bleeding, hypotension and hepatic encephalopathy (2). We present the first reported case of PRES in the setting of severe alcoholic hepatitis with hepatic encephalopathy and the absence of known predisposing factors described to date.

**CASE PRESENTATION:**

A 40-year-old female was readmitted to the hospital with a seizure following a 3-week admission for hepatic encephalopathy due to severe alcoholic hepatitis. The patient returned to the hospital in less than 24 hours of discharge following a witnessed tonic-clonic seizure at home. She had no prior history of seizures. She did not consume alcohol or non-prescription drugs between discharge and readmission. She reported compliance with prescribed medications at home.

During the preceding hospitalization, the patient presented with altered mental status, fever, jaundice, tender hepatomegaly, and a WBC count of 14.1 thousand/ul. Her discriminant Function was 99. Hepatic dysfunction characterized by an albumin of 3.0 g/dL, an INR of 2.36 and a bilirubin of 30.3 mg/dL was noted.  Her AST and ALT were 241 and 62 respectively. Clinical and radiographic features were suggestive of chronic liver disease, including encephalopathy, ascites, asterixis, spider angiomata, and esophageal varices without active GI bleeding were present. Her serum ascites albumin gradient was 3.8 gm/dL and confirmed portal hypertension. Due to persistent headaches despite a slow and steady improvement of the encephalopathy on lactulose and rifaximin, an MRI was obtained. Although a limited study, bilateral temporal parietal restriction was described, raising concern for PRES. There was no evidence of seizure activity on sixty-minute electroencephalography (EEG).Despite mild intermittent headaches, she remained stable without focal neurologic deficits, and was discharged home on the recommended steroid taper for alcoholic hepatitis, ciprofloxacin for spontaneous bacterial peritonitis prophylaxis, fluconazole for candidal esophagitis found on upper endoscopy, nadolol for Grade 1 esophageal nonbleeding varices, lactulose and rifaximin for hepatic encephalopathy, and spironolactone and furosemide for ascites.

The patient was readmitted in less than 24 hours following a witnessed tonic-clonic seizure. She was intubated for airway protection and rapidly extubated within 24 hours. Her admission vitals signs included a temperature of 97.2 F, pulse 95 beats/minute, respiratory rate of 8 breaths/minute and a blood pressure 114/78 mm Hg.  Off sedation, there were no focal neurologic findings. Labs were significant for a Hb 10.0 g/dL, INR 1.79, PT 19.4 sec, Creatinine 0.3 mg/dL, bicarbonate 15.5 mmol/L, anion gap 21 mEq/L, total bilirubin 10.8 mg/dL, and Direct Bilirubin 6.5 mg/dL, alkaline phosphatase 133 IU/L, ALT 54 IU/L, and AST 112 IU/L, all relatively unchanged from the her discharge labs. Urine drug screen was negative and alcohol level was undetectable.

A repeat MRI was performed. The high signal intensity in the subcortical and periventricular white matter of the bilateral temporal and parietal lobes on the FLAIR sequence of MRI was consistent with PRES (Figure 1). EEG showed high focal epileptogenic potential in the temporal-parietal area. Subsequent neurologic exam revealed right visual field deficits, and psychomotor retardation with subjective complaint of headaches, but no asterixis or other focal deficits. She was started on lacosamide for further seizure prevention and continued on lactulose and rifaximin. Fluconazole was switched to itraconazole to lower her seizure threshold. Prior to discharge, her neurologic deficits and headaches had completely resolved.

**DISCUSSION:**

PRES, first described in 1996 in the New England Journal of Medicine, is a clinic neuro-radiological diagnosis. While the pathogenesis of PRES is not fully understood, two prevailing hypotheses have been proposed, but neither has been fully validated thus far. The more popular theory purports that severe and rapidly developing hypertension can devastate auto-regulation resulting in hyperperfusion with endothelial injury/vasogenic edema (3). The posterior brain is more affected by hyperperfusion as minimal sympathetic innervation exists in the posterior fossa. The original hypothesis conversely suggests that hypoperfusion causes vasoconstriction resulting in brain ischemia and consequent vasogenic edema (3).

The increased intrahepatic resistance from cirrhosis causes portal hypertension, and is worsened by hepatic and non-hepatic endothelial dysfunction (4), a component found in the prevalent theory of PRES pathophysiology. Specifically, hypoactive endothelial cells decrease nitric oxide production that consequently initiates portal hypertension. This, in turn, results in endothelial dysfunction in the splanchnic and systemic, circulation (extrahepatic). There is a subsequent superfluous amount of vasodilators, resulting in vasodilation that further contributes to exacerbating the portal hypertension (4).

The pathophysiology of hepatic encephalopathy is not completely understood, but ammonia has been recognized as a pivotal player in the process. There are two forms of ammonia – ammonium (NH4+) and ammonia (NH3) – the latter of which is more predominant in alkalotic states, and described in approximately 70% of patients with decompensated liver disease (5) As the brain has no inherent cycle of urea metabolism, ammonia reaching the astrocytes are detoxified by glutamine synthetase in the presence of glutamate to form glutamine. Glutamate is a major transmitter involved in neuro-excitation in 80% of synapses. Glutamine over-production promotes swelling of astrocytes, which results in cerebral edema, resulting in intracranial pressure (6). In fact, using magnetic resonance diffusion tensor imaging, an increase in interstitial brain water in patients with cirrhosis and hepatic encephalopathy has been shown (7). This vasogenic edema is a culprit in both theories related to PRES pathophysiology. As evidenced, theoretically, portal hypertension and hepatic encephalopathy result in changes that are concurrent with the changes found in PRES. However, there is a dearth of literature regarding PRES and hepatic encephalopathy in the setting of portal hypertension irrespective of the underlying etiology.

Clinical manifestations of PRES have been variable. Most frequently it presents as various degrees of encephalopathy or seizures. It can also manifest as headaches, visual disturbances, other focal neurological deficits, or status epileptics (8). Symptoms are usually acute or subacute. As stated earlier, symptoms are most often seen in the setting of renal failure, labile blood pressures, autoimmune disorders, preeclampsia/eclampsia or cytotoxic or immunosuppressive drugs such as calcineurin inhibitors, cyclosporine, and cisplatin, but not steroids (8). The patient was on steroids, but there has been no defined relationship in the literature between the use of steroids and PRES. There have been sparse case reports of PRES occurring in patients with acute hepatic failure (9), and one in a cirrhotic patient (1) with hepatic encephalopathy. Our patient was hemodynamically stable and did not present with any of these known risk factors. Her ammonia level was significantly elevated despite lactulose and rifaximin therapy. The hyperammonemia could have been the triggering factor for developing PRES, while the fluconazole used to treat esophageal candidiasis likely lowered her seizure threshold, resulting in the witnessed tonic-clonic seizure.

Radiologic confirmation is an important component of diagnosis. Neuroradiologic images of PRES show characteristic white-gray matter edema predominantly involving the posterior region of the brain and best seen with brain MRI. Our patient had bilateral temporal and parietal lobe findings as seen in Figure 1, which are two common areas that are affected in PRES. It can also frequently be seen in parieto-occipital region, watershed regions, and frontal lobes.

Treatment of PRES has not been well studied; symptoms usually resolve once the underlying cause has been treated. Patients with seizures, such as our patient, should be placed on anti-epileptic medications. Once the underlying disorder has been treated, prognosis is usually favorable. Our case poses an interesting challenge because it introduces another potential etiology of PRES, which has not been studied in the past. Further research is needed to better understand the pathophysiology of PRES, a neurologic entity that can occur in many clinical conditions. Other possible etiologies, including exaggerated immune response or cytokine release may enhance systemic endothelial activation. This case adds to the literature of potential etiologies leading to PRES, an extremely rare clinical and radiologic diagnosis.

**CONCLUSION:**

This is the first reported case of acute alcoholic hepatitis with hepatic encephalopathy developing PRES in the absence of known risk factors such as hypotension, ischemia, and blood pressure fluctuations.

**REFERENCES:**

1. **Fugate JE**, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol. 2015; **14(9)**: 914-25.[PMID:26184985 DOI: [10.1016/S1474-4422(15)00111-8](http://dx.doi.org/10.1016/S1474-4422%2815%2900111-8)] \
2. **Chawla R**, Smith D, Marik PE. Near fatal posterior reversible encephalopathy syndrome complicating chronic liver failure and treated by induced hypothermia and dialysis: a case report. J Med Case Rep. 2009; **3**:6623. [PMID:19830117 DOI: [10.1186/1752-1947-3-6623](http://dx.doi.org/10.1186/1752-1947-3-6623)]
3. **Bartynski WS**, Boardman JF. Catheter angiography, MR angiography, and MR perfusion in posterior reversible encephalopathy syndrome. AJNR Am J Neuroradiol. 2008; 29(3): 447-55. [PMID:18079186 DOI:10.3174/ajnr.A0839]
4. **Iwakiri Y**, Groszmann RJ. Vascular endothelial dysfunction in cirrhosis. J Hepatol. 2007;46(5): 927-34. [PMID:17391799 DOI:[10.1016/j.jhep.2007.02.006]](http://dx.doi.org/10.1016/j.jhep.2007.02.006)
5. **Butterworth RF**. Pathogenesis of hepatic encephalopathy in cirrhosis: the concept of synergism revisited. Metab Brain Dis. 2015. [Epub ahead of print]. [PMID:26521983 DOI [10.1007/s11011-015-9746-1](http://dx.doi.org/10.1007/s11011-015-9746-1)].
6. **Lemberg A**, Fernandez MA. Hepatic encephalopathy, ammonia, glutamate, glutamine and oxidative stress. Ann Hepatol. 2009; 8(2):95-102. [PMID:19502650]
7. **Kale RA**, Gupta RK, Saraswat VA, et al. Demonstration of interstitial cerebral edema with diffusion tensor MR imaging in type C hepatic encephalopathy. Hepatology. 2006; 43(4): 698-706. [PMID:16557540 DOI: [10.1002/hep.21114]](http://dx.doi.org/10.1002/hep.21114)
8. **Servillo G**, Bifulco F, De Robertis E. Posterior reversible encephalopathy syndrome in intensive care medicine. Intensive Care Med. 2007; 33(2):230-6. [PMID:17119920 DOI: 10.1007/s00134-006-0459-0]
9. **Mettananda S**, Fernando AD, Ginige N. Posterior reversible encephalopathy syndrome in a survivor of valproate-induced acute liver failure: a case report. J Med Case Rep. 2013; 7:144. [PMID :23724918 DOI: [10.1186/1752-1947-7-144]](http://dx.doi.org/10.1186/1752-1947-7-144)

**FIGURE 1:**



Flair hyperintense signal axial view involving the cortex and subcortical white matter involving the parietal and temporal lobes, consistent with PRES.

**LIST OF ABBREVIATIONS:**

PRES: posterior reversible encephalopathy syndrome

EEG: electroencephalogram

ABG: arterial blood gas

NH4+: ammonium

NH3: ammonia

**ACKNOWLEDGEMENTS:** There were no other acknowledgements outside of the authors listed on the manuscript.