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CASE REPORT

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Coexisting posterior reversible encephalopathy syndrome and ischemic hepatopathy: A case report

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is acute neurologic symptoms with specific radiologic findings. This unique case shows coexisting PRES with acute liver injury, which could suggest common pathophysiologic process.

KEYWORDS

encephalopathy, hepatitis, hypertension

1 | INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES), first described in 1996 by Hinchey and colleagues, is a syndrome that pairs acute clinical neurologic symptoms with characteristic radiologic findings.[1] The magnetic resonance imaging (MRI) of affected patients often shows characteristic posterior, parieto-occipital white matter vasogenic edema. The pathophysiology is uncertain and resulting edema is hypothesized to be either related to endothelial dysfunction causing leakage or disrupted autoregulation of cerebral blood flow causing hyperperfusion.[2] PRES is truly an incompletely understood syndrome with heterogeneous etiologies including renal failure, hypertension, cytotoxic drugs, autoimmune disorders, preeclampsia/eclampsia, infection, transplantation, and chemotherapeutic agents.

While PRES is associated with multiple etiologies, acute arterial hypertension accompanies PRES in up to 70% of cases and its treatment can result in clinical and radiologic resolution.[3] In the case to be reviewed, our patient demonstrated fluctuations in blood pressure (BP) and neurologic symptoms, which align with the development of PRES. However, our patient also showed concurrent evidence of acute hepatic insult, also known as "shock liver." Review of current literature fails to find association between labile hypertension, isolated hepatic ischemia, and PRES. We present a unique case of PRES and associated ischemic hepatopathy in the setting of arterial hypertension with no identifiable triggers. This association raises

the potential for a common pathophysiologic process affecting both the brain and liver.

2 | CASE REPORT

A 54-year-old female patient with a history of alcohol abuse, intravenous drug use, depression, and hypertension (not on pharmacotherapy) and no known history of seizure, presented to the emergency department with an episode of seizure. In the morning, the patient complained to a family member of nausea and vision changes and then was found unresponsive and emergency medical services responded. En route to hospital, the patient had a witnessed generalized tonic-clonic seizure and was postictal on arrival. Vital signs were remarkable for BP of 170/103 mmHg and heart rate of 104 beats per minute, other vital signs were normal. Upon outpatient chart review, the patient's BP has been persistently elevated at 150–180 s/80–90 s mmHg without proper measures of intervention.

Laboratory tests showed marked transaminitis of aspartate aminotransferase (AST) level of 5359 IU/L and alanine aminotransferase (ALT) level of 2359 IU/L. Total bilirubin was 3.0 mg/dl. Alkaline phosphatase level was normal at 81 IU/L. Of note, the patient's baseline liver function has been normal. Serum lactate level was increased at 18.1 mmol/L with venous blood pH of 7.11 and increased anion gap at 31 mmol/L. WBC was elevated at 17,800/ul. Urine drug screen was negative, and serum alcohol level was undetectable. Electrocardiogram demonstrated sinus tachycardia without signs of acute ischemia. Chest x-ray showed no acute cardiopulmonary disease. Computed tomography (CT) scan of the head without contrast showed small left parietal scalp swelling which suggested possible hematoma without evidence of underlying fracture. Right upper quadrant abdominal ultrasound showed normal liver and gallbladder without biliary ductal dilatation. Lumbar puncture was unremarkable without evidence of central nervous system infection. The patient was admitted to the general medical unit for further evaluation and management. Initial differential included alcohol withdrawal, hepatic encephalopathy, infection, or posterior reversible encephalopathy syndrome.

On hospital day 1, the patient's mentation returned to baseline. Serum lactate and pH improved at 5.5 mmol/L and 7.44, respectively. Patient was placed on the alcohol withdrawal management protocol per the institution's policy but did not show any signs of alcohol withdrawal throughout the 6-day admission. Lactated ringers intravenous fluid was maintained. Serum AST and ALT level began to trend down. Further hepatic laboratory workup showed markedly increased ferritin level of 16,368.3 ng/ml, increased serum iron level of 289 μg/dl, and increased transferrin saturation of 98%. Viral hepatitis markers (hepatitis A/B/C, cytomegalovirus, and Epstein-Barr virus) were negative. Studies for hemochromatosis, Wilson's disease, and autoimmune hepatitis were also negative. Specialty teams of neurology and hepatology were consulted. Neurology recommended magnetic resonance imaging (MRI) of the brain. Ischemic hepatopathy secondary to seizure activity was the suggested diagnosis per hepatology team. MRI of the brain (Figure 1) completed on hospital day 2 revealed bilateral cortical and subcortical areas of T1 hypo-intensity and T2 hyper-intensities with involvement of bilateral cerebellum and posterior parietal regions. There was no evidence of hemorrhage, abnormal enhancement, or restricted diffusion. These findings were consistent with PRES. Neurology recommended strict BP control with no need for further measures such as anti-epileptic medications. Hepatology recommended monitoring with trending liver function tests. No further

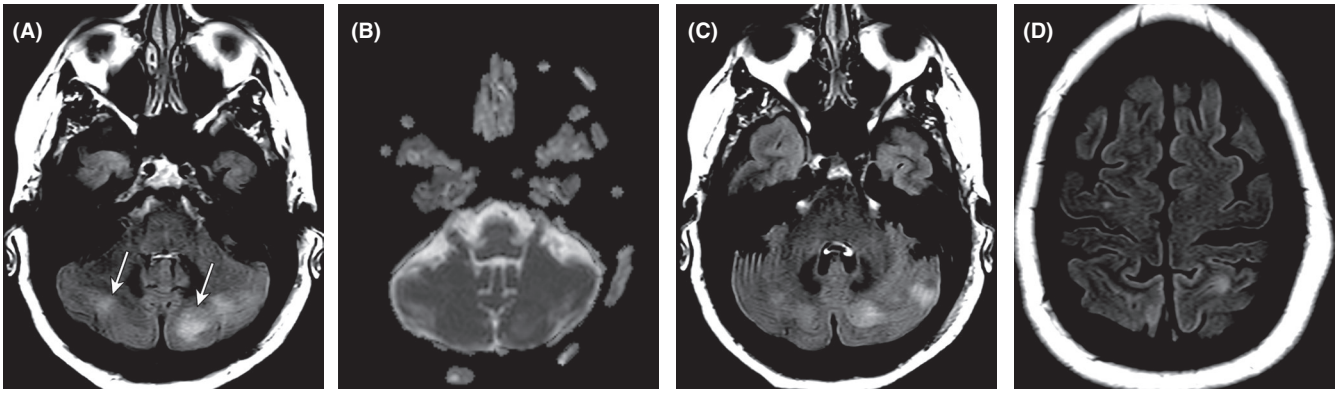

FIGURE 1 Magnetic resonance imaging of the brain. (A) Subcortical areas of white matter involvement with increased fluid-attenuated inversion recovery (FLAIR) signal (arrows) in bilateral cerebellar cortex. (B and C) Corresponding diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) demonstrating no restricted diffusion with no contrast enhancement. (D) Few areas of edema involving bilateral subcortical white matter in parietal lobes with worse involvement in the cerebellum

workup such as hepatitis D serology, hepatitis E serology, or hepatic vascular imaging (to rule out thrombosis) was advised given that the liver enzymes started and continued to improve with BP control.

On hospital day 2, patient's BP became increasingly difficult to control. Amlodipine was initiated and up-titrated to 10 mg daily. On hospital day 3, the patient began experiencing intermittent episodes of spikes in BP to >200 mmHg systolic and >100 mmHg diastolic, and complained of headaches with a normal physical and neurological examination. The elevated BPs were treated with intravenous labetalol. On hospital day 3, oral labetalol 100 mg twice daily was initiated. The patient continued to have elevated BP along with complaints of numbness and tingling in her scalp and face. The neurological examination was consistently normal and symptoms improved after intravenous labetalol. The medical team continued to up-titrate oral labetalol.

At time of discharge on hospital day 6, the BP was well-controlled on oral labetalol 200 mg in the morning, 100 mg in the afternoon, and 200 mg in the evening along with oral amlodipine 10 mg once daily. Patient's BP at discharge was 118/68 mmHg and heart rate of 70 beats per minute. The patient no longer experienced episodes of headaches, numbness, or tingling. AST, ALT, and total bilirubin were 42 IU/L, 236 IU/L, and 1.1 mg/dl, respectively. Serum ferritin level had decreased to 1001.4 ng/ml. The patient continues to follow-up with her outpatient primary care provider. Follow-up laboratory findings 6 weeks after the hospital discharge showed AST, ALT, total bilirubin, and serum ferritin level of 16 IU/L, 16 IU/L, 0.3 mg/dl, and 158.4 ng/ml, respectively. BP continues to be well-maintained with the range of 100–120/60–70 mmHg.

3 | DISCUSSION

In this report, we discussed the novel co-occurrence of PRES and hepatic ischemia in a middle-aged woman with labile BPs. On review of available research, this association has not previously been reported. Prior singular case reports have shown the development of PRES in a patient with cirrhosis with gastrointestinal bleeding, hypotension, and hepatic encephalopathy[4] and a patient with alcoholic hepatitis and hepatic encephalopathy.[5] However, in our patient, neither there was no history of long-standing liver dysfunction or hepatitis nor was their evidence of hepatic encephalopathy or hyperammonemia. Rather, this patient demonstrated acute onset and resolution of both PRES and liver insult (elevated AST and ALT) with BP control.

Our patient met clinical criteria for diagnosis of PRES with seizure and vision changes on presentation and with radiological findings on MRI-bilateral subcortical vasogenic edema predominantly affecting the gray and white matter of the posterior regions of the cerebral hemispheres.[6] Interestingly, the involvement of cerebellum was much more obvious compared with minimal involvement of bilateral parietal regions in our case. This can be seen in PRES but it is an atypical appearance as the parieto-occipital lobes are particularly vulnerable due to sparse sympathetic innervation of the posterior circulation resulting in less protection against the effects of severe systemic hypertension.[7,8] Anticipated neurologic signs and symptoms of PRES include the sub/acute presentation of headache, seizures, visual disturbance, and other focal neurological deficits.[1] PRES is known to be associated with various factors such as hypertensive encephalopathy, renal failure, preeclampsia, eclampsia, exposure to immunosuppressive or cytotoxic agents, and autoimmune disorders.[6] Our patient had hypertension but no other comorbidities or metabolic disorders known to be associated with increased likelihood of development of PRES.

The pathogenesis of PRES is still not completely understood but among several proposed theories there are two main hypotheses. The first is the "vasogenic theory" that labile BPs exceed the limit of cerebral autoregulation leading to hyperperfusion and endothelial injury causing breakdown of the blood brain barrier and eventually vasogenic edema.[2] However, while PRES is often associated with high BP particularly in those with hypertension, renal disease, and autoimmune disorders,[2] studies have shown that up to 30% of patient who develop PRES are normotensive or only have mildly elevated BPs.[9] Therefore, an alternate or additional mechanism was searched for. The second major hypothesis is known as the "neuropeptide theory," which proposes that endogenous or exogenous cytotoxins trigger endothelial dysfunction. This dysfunction can trigger the release of potent vasoconstrictors causing vasospasm, ischemia, and edema.[6]

A recently published theory proposed by Largeau et al.[10] suggests that arginine vasopressin (AVP) hypersecretion plays a key role. They hypothesize that the activation of vasopressin receptors leads to cerebral vasoconstriction, causing endothelial dysfunction and cerebral ischemia. We know vasopressin treatment is used in cases of hypotensive shock due to its vasoconstrictive properties. Interestingly, AVP is also elevated in women with preeclampsia and infusion of this hormone in mice models has been sufficient to induce clinical features of preeclampsia.[11] Furthermore, evidence supports a positive relationship of copeptin levels, AVP precursor, and increased BP.[12]

In addition to PRES, our patient developed ischemic hepatopathy. This syndrome, also known as "shock liver" or hypoxic hepatitis, is characterized by rapid

and transient increases in either AST or ALT often in the setting of cardiac, circulatory, or respiratory failure. It produces a primary hepatocellular pattern of injury, without evidence of cholestasis and exclusion of other sources of hepatocellular injury.[13] The pathogenesis of ischemic hepatopathy is multifactorial and poorly understood. The liver has a dual blood supply from cardiac output via the hepatic artery and the portal venous system. Ischemic hepatopathy is thought to occur by a "two-hit mechanism. "The first is due to a low-flow state, typically from right-sided heart failure leading to elevated hepatic pressures. In this state, the liver is at increased risk for ischemic injury. The second hit occurs with an episode of acute hypoperfusion due to cardiac, circulatory, or respiratory failure that lead to systemic hypotension and hypoxia of hepatic cells. There is a dramatic rise in serum aminotransferase levels between 25 and 250 times the upper limit of normal.[14] Despite elevations in AST and ALT, minimal to mild elevations of the serum bilirubin, alkaline phosphatase levels, and prothrombin time are expected. Worsening to acute liver failure with evidence of impaired metabolic function is possible, but often with resolution of the underlying hemodynamic disturbance liver abnormalities will normalize. This was observed in our case patient, who had steady down-trending of liver enzymes and acute phase reactants with BP control. Even though our case did not show a clear picture of the "two-hit mechanism" given the absence of systemic hypotension, it is possible that acute elevation of BP in the setting of chronic uncontrolled hypertension could have caused acute elevation of hepatic pressure secondary to elevated intra-cardiac pressure.

While PRES due to other causes is frequently accompanied by hypertension, high BP alone is not associated with ischemic hepatopathy. It is unclear why the liver enzymes in our case were extremely, but transiently elevated at presentation. It could potentially be explained by hepatic tissue hypoperfusion secondary to severe vomiting and the seizure activity evidenced by initial high serum lactate level. Acetaminophen-induced hepatic injury could have been potential cause given that the patient had been taking hydrocodone-acetaminophen for chronic pain. However, authors believe that it is less likely given that the liver enzymes continued to improve with optimized BP control even with continued administration of hydrocodone-acetaminophen as needed for pain while inpatient and after hospital discharge.

On the contrary, our case report can also highlight co-occurrence of PRES and hepatic dysfunction from a possibly shared trigger. While the pathophysiologic mechanisms underlying PRES are multiple, the concept that they could simultaneously act on another organ system such as liver is plausible, though not previously described. Evidences suggest that PRES is strongly associated with preeclampsia and eclampsia with possible shared pathophysiology.[15,16] It is well-established that preeclampsia and eclampsia can lead to end-organ injury including hepatic dysfunction, mainly via endothelial dysfunction triggered by vasoactive substance release.[17] Therefore, it can be inferred that PRES and hepatic dysfunction could potentially share the same pathophysiologic trigger, and our case could suggest non-obstetric manifestation of PRES and hepatic dysfunction similar to preeclampsia and eclampsia. Identifying further cases demonstrating neurologic and other organ system involvement may contribute to more fully understanding the disputed pathophysiology of this syndrome.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

AUTHOR CONTRIBUTIONS

Mercy A. Adetoye and Meredith G. Baumgartner contributed equally to this work as first authors. MAA, MGB, and BP provided direct patient care and conceived of the study. KR provided the radiologic interpretation of magnetic resonance imaging. MAA and MGB drafted the manuscript. KR added radiologic input and provided figure images. BP directed, supervised, revised, and edited the manuscript.

ETHICAL APPROVAL

A written informed consent was obtained directly from the patient regarding the publication of this case report and the use of radiologic imaging.

DATA AVAILABILITY STATEMENT

The data for this study will be available online once it is published.

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REFERENCES

1. Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med*. 1996;334(8):494-500.

2. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. *J Neurol*. 2017;264(8):1608-1616.
3. McKinney AM, Short J, Truwit CL, et al. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. *Am J Roentgenol*. 2007;189(4):904-912.
4. 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.
5. John ES, Sedhom R, Dalal I, Sharma R. Posterior reversible encephalopathy syndrome in alcoholic hepatitis: hepatic encephalopathy a common theme. *World J Gastroenterol*. 2017;23(2):373-376.
6. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. *Am J Neuroradiol*. 2008;29(6):1036-1042.
7. Ollivier M, Bertrand A, Clarençon F, et al. Neuroimaging features in posterior reversible encephalopathy syndrome: a pictorial review. *J Neurol Sci*. 2017;373:188-200.
8. Shankar J, Banfield J. Posterior reversible encephalopathy syndrome: a review. *Can Assoc Radiol J*. 2017;68(2):147-153.
9. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurol*. 2015;14(9):914-925.
10. Largeau B, Le Tilly O, Sautenet B, et al. Arginine vasopressin and posterior reversible encephalopathy syndrome pathophysiology: the missing link? *Mol Neurobiol*. 2019;56(10):6792-6806.
11. Sandgren JA, Deng G, Linggonegoro DW, et al. Arginine vasopressin infusion is sufficient to model clinical features of preeclampsia in mice. *JCI Insight*. 2018;3(19):e99403.
12. Afsar B. Pathophysiology of copeptin in kidney disease and hypertension. *Clin Hypertens*. 2017;23:13.
13. Lightsey JM, Rockey DC. Current concepts in ischemic hepatitis. *Curr Opin Gastroenterol*. 2017;33(3):158-163.
14. Giallourakis CC, Rosenberg PM, Friedman LS. The liver in heart failure. *Clin Liver Dis*. 2002;6(4):947-967.
15. Brewer J, Owens MY, Wallace K, et al. Posterior reversible encephalopathy syndrome in 46 of 47 patients with eclampsia. *Am J Obstet Gynecol*. 2013;208(6):468.e1-468.e6.
16. Postma IR, Slager S, Kremer HPH, de Groot JC, Zeeman GG. Long-term consequences of the posterior reversible encephalopathy syndrome in eclampsia and preeclampsia: a review of the obstetric and nonobstetric literature. *Obstet Gynecol Surv*. 2014;69(5):287-300.
17. Armaly Z, Jadaon JE, Jabbour A, Abassi ZA. Preeclampsia: novel mechanisms and potential therapeutic approaches. *Front Physiol*. 2018;9:973.

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