Case Report

# Hyperglycemia Followed by an Abrupt Decrease of Blood Glucose Is a Rare Cause of Posterior Reversible Encephalopathy Syndrome (PRES)

Liza Garabet Diramerian, MD,[1] Nabila Ashraf, MD,[1] Admir Syla, MD,[1] Armen Malkhasian, MD,[1] Jason Madey, MD[1]

Author affiliations are listed at the end of this article.

Correspondence to:
Liza Garabet Diramerian, MD
907 Camelot Drive, Apt 17
Salem, VA, 24153
(liza_diramerian@yahoo.com)

## Abstract

### Introduction
Posterior Reversible Encephalopathic Syndrome (PRES) is a clinical syndrome of headache, confusion or decreased level of consciousness, visual changes, seizures and focal neurologic signs associated with characteristic neuroimaging findings of posterior cerebral white matter edema. In most cases, PRES is precipitated by sudden increase in blood pressure; however, in the case presented here, the etiology was different as it was secondary to extreme changes in glucose levels.

### Case Presentation
A 49-year-old female with a past medical history of hypertension and diabetes mellitus, type 2 was brought to the emergency room with a chief complaint of visual changes for 1 hour in duration. She described that the visual changes, like blurred vision in both eyes, happened after an abrupt decrease of blood glucose (BG) from 700 to 75 mg/dl. This abrupt drop in BG led to PRES in this patient, which is an uncommon presentation. Magnetic resonance imaging (MRI) of the brain was obtained, which was consistent with demyelinating lesions present in bilateral occipital lobes, suggestive of PRES. Fortunately, the patient's symptoms improved after avoidance of further abrupt fluctuations in BG. PRES commonly resolves within days if diagnosed and treated early. Prompt management can reduce morbidity and mortality.

### Conclusion
A diagnosis of PRES can be difficult, especially if it was caused by rare etiology. In this case we highlight the cause and explain the hypothesis behind it.

### Keywords
hyperglycemia; posterior leukoencephalopathy syndrome; hypertensive encephalopathy; magnetic resonance imaging; diagnostic imaging; diabetes mellitus type 2/complications; endothelial dysfunction

## Introduction
Posterior reversible encephalopathy syndrome (PRES) was first described in 1996 by Hinchey et al. This condition has been previously known by various names including reversible posterior leukoencephalopathy syndrome, reversible posterior cerebral edema syndrome and reversible occipital parietal encephalopathy.[1] PRES is a clinical-radiological diagnosis characterized by varying neurological manifestations including headache, vision changes, confusion, focal neurological deficits and seizure with classic brain magnetic resonance imaging (MRI) consistent with edema of the white matter of the bilateral posterior cerebral hemispheres, mostly in the parieto-occipital lobes. The most common entities associated with PRES include uncontrolled hypertension, pre-eclampsia/eclampsia, cancer chemotherapy, renal insufficiency, autoimmune disease, systematic lupus erythematosus (SLE), immunosuppression therapy and sepsis. More than 70% of patients with PRES are

hypertensive, though a significant proportion have normal or only mildly raised blood pressure (BP).[2-6]

The case presented is unique as PRES was precipitated by an episode of hyperglycemia followed by rapid drop of blood glucose (BG). A proposed mechanism for this very rare and unusual etiology is considered in the discussion.

## Case Presentation

A 49-year-old female with hypertension and diabetes mellitus, type 2 presented to the emergency department complaining of sudden, painless, non-traumatic vision changes in both eyes along with some flashes. Her symptoms began on the same morning after a rapid correction of BG by insulin administration. She stated that her BG readings were always within an acceptable range, except the night before presentation when she noticed that her BG was 900 mg/dl due to being out of insulin for about 2 days. Her high BG reading led to administration of both short and long acting insulin. Repeated BG was 500 mg/dl at bedtime, around 10:00 PM. The following morning at 7:00 AM she woke up with BG of 700 mg/dl without any symptoms. At that point she increased her short acting insulin dose to 25 units instead of 5 units (5 times her normal dose), which caused an abrupt drop of BG to 75 mg/dl one and a half hours after insulin administration. Shortly after that she started having blurred vision that caused her to present to the emergency department.

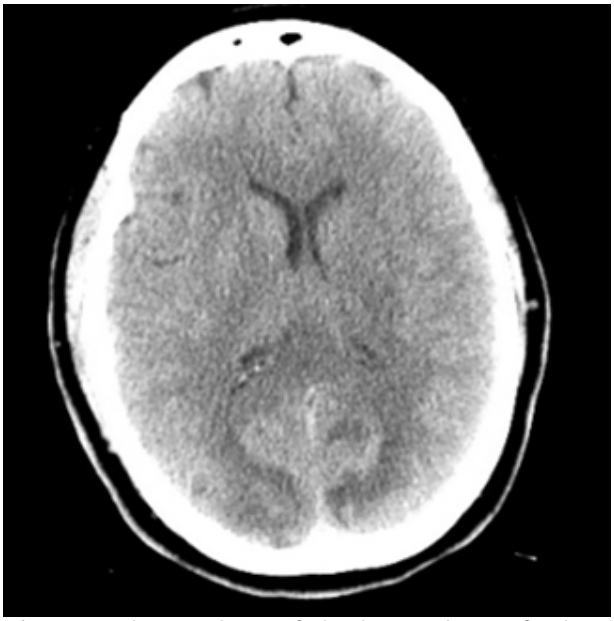

**Figure 1.** The axial CT of the brain shows fairly symmetric subcortical hypodensity involving a posterior predominant pattern highly suspicious for PRES.

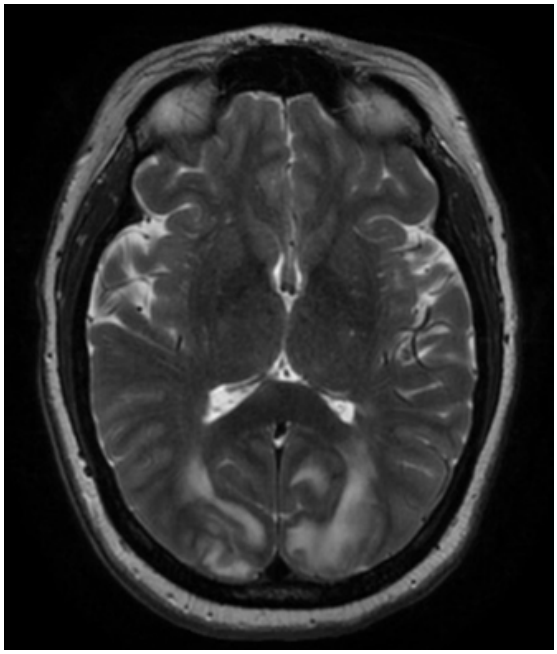

**Figure 2.** The MRI of the brain with axial T2 shows fairly symmetric subcortical area in a posterior predominant pattern including parietal lobes.

On arrival to the emergency department, her BP was 135/85, which was consistent with her typical BP at home. On neurological exam she was alert and oriented with normal speech. Visual acuity was 20/40 and visual field testing, performed clinically by counting the metric digit in all fields, and her examination showed that she had bi-temporal vision loss. The rest of the clinical exam was unremarkable including normal pupillary and corneal reflexes, no motor or sensory deficits, normal gait, cranial nerves II-XII intact and no meningeal irritation signs. During hospitalization, her BG readings were 85-120 mg/dl, hemoglobin A1C (HbA1c) was 5.6%, and both liver and kidney function were normal. On admission, computerized tomography (CT) of the brain (**Figure 1**) was obtained and showed bilateral, fairly symmetric subcortical hypodensities involving parietal and occipital lobes suspicious for PRES. Brain MRI Axial T2 with and without contrast (**Figure 2**) showed fairly symmetric subcortical hyperintensities in the parietal and occipital lobes. Brain MRI T2 fluid-attenuated inversion recovery (FLAIR) with and without contrast

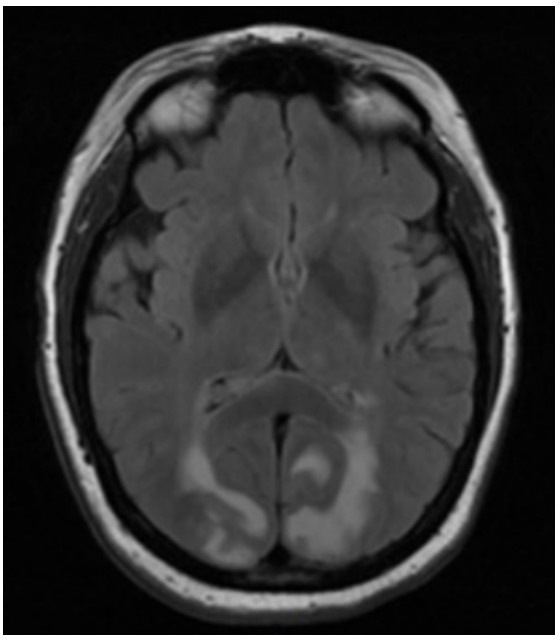

**Figure 3.** The T2 FLAIR of the brain shows fairly symmetric subcortical area in a posterior predominant pattern including parietal lobes.

(**Figure 3**) showed fairly symmetric subcortical hyperintensities in the parietal and occipital lobes, while diffusion-weighted imaging (DWI) of the brain (**Figure 4**) appeared to show clear restricted diffusion. Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) were negative. Lumbar puncture was performed and did not reveal any signs of infection, elevation in immunoglobulin G (IgG) index or oligoclonal bands. Her clinical symptoms and brain MRI findings suggested the possibility of PRES. The patient's vision gradually improved during the hospitalization as her BG levels were controlled, and BG was completely back to normal by the next day when she was discharged home.

It is important to differentiate PRES from other diseases. Differential diagnoses are osmotic demyelination syndrome (ODS), as an initial presentation of hyperosmolar hyperglycemia state, and cerebral venous thrombosis (CVT). ODS in the setting of hyperosmolar hyperglycemia state usually presents as altered mental status, dyspnea, dysarthria and dysphagia, which all occur 5 to 7 days after the rapid correction of severe hyponatremia,[7,8,9] while in PRES the presentation will be within hours. The other differential diagnosis is CVT. The clinical presentation of CVT is highly variable but often presents with headache, confusion and seizures. Usually it occurs in the setting of hereditary or acquired thrombophilia. Brain MRI in CVT usually presents with focal or multifocal areas of edema and venous infarction that are usually distinguishable from PRES.

## Discussion

PRES is usually diagnosed by clinical features and radiographic imaging such as a brain MRI. Clinical features may vary and include headache, altered mental status, visual disturbance and seizures.[10] PRES is most commonly caused by the sudden elevation of BP. Other causes include, but are not limited to, renal insufficiency, autoimmune disease, systemic lupus erythematosus, immunosuppression therapy and sepsis.[2,11,12] PRES is a reversible syndrome if it is diagnosed early and treated promptly.

The pathogenesis behind PRES remains unclear. However, we believe that PRES is caused by a failure of cerebral autoregulation, which usually occurs after a sudden rise of BP, and/or endothelial dysfunction of the blood-brain barrier (BBB) that can play a role in the pathogenesis by breaking down the BBB, which allows for hematogenous products to diffuse slowly over time into the brain cells, resulting in areas of edema.[13-15] Sudden increase in BP will lead to hyperperfusion of the brain, consequently causing extravasation of fluid and blood into the brain parenchyma.[16]

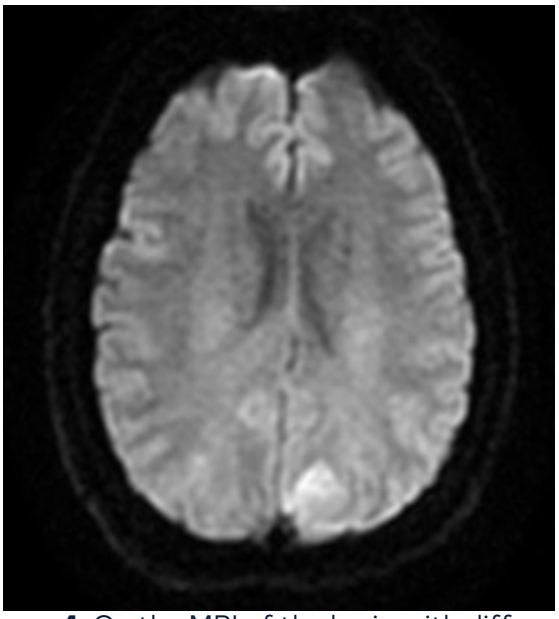

**Figure 4.** On the MRI of the brain with diffusion-weighted imaging (DWI) there is clear restricted diffusion.

The etiology of PRES in this case was unusual as it was likely caused by high BG followed by an abrupt drop in BG.[17] The underlying pathogenesis of PRES in hyperglycemia in the absence of ketoacidosis and other metabolic disorders is not fully understood. However, it is thought to be caused by endothelial dysfunction caused by excessive circulating inflammatory cytokines.[18] Hyperglycemia is associated with increased pro-inflammatory cytokines including interleukin 6 and tumor necrosis factor (TNF) alpha, which has been shown to regulate vascular endothelial growth factor (VEGF). VEGF will lead to increased vascular permeability and eventually vasogenic edema.[19] Vasogenic edema is an extracellular accumulation of fluid resulting from the disruption of the BBB and extravasation of serum protein.[20] The excessive extracellular accumulation of fluid leads to an increase of brain volume and intracerebral pressure. There has been one case report of PRES caused by hyperglycemia without any metabolic derangement, and the patient presented with reversible blindness.[17] The patient was a 28-year-old non-pregnant female with type 1 diabetes mellitus on basal bolus insulin, who presented with headache and blurred vision for 2 hours, after missing doses of insulin in the previous 2 days. On physical exam her BP was normal. Her BG was high with no ketone in the urine. She was managed for hyperglycemia and her vision recovered in 5 days.[17]

In our patient we hypothesize that the sudden drop in BG may also have precipitated PRES. We believe this is due to the sudden change in osmolality resulting in transient osmotic gradient between plasma and neuroglial cells. This gradient will result in a fluid shift into neurons and cause cerebral edema. PRES is likely more evident in the posterior brain region due to diminished sympathetic innervation of the vertebro-vascular system.[21,22]

As primary care physicians and hospitalists, it is important to identify complications such as PRES, which are reversible and associated with excellent prognosis if diagnosed early and treated promptly. Early diagnosis and treatment of the inciting cause are imperative to reduce the neurological sequalae, morbidity and mortality.

## Conclusion

PRES most often occurs in the setting of hypertensive crisis, pre-eclampsia or with cytotoxic immunosuppressive therapy. However, in our case, PRES was secondary to blood glucose fluctuations. After an extensive workup, we can conclude that this patient's symptoms, imaging findings and cerebrospinal fluid testing are consistent with PRES and that stabilizing the patient's BG level helped to resolve the symptoms. Therefore, early diagnosis is a crucial point in the case of PRES.

### Conflicts of Interest

The authors declare they have no conflicts of interest.

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### Author Affiliations

1. Department of Internal Medicine, LewisGale Medical Center, Salem, VA

## References

1. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. *AJNR Am J Neuroradiol*. 2008;29(6):1036-1042. https://doi.org/10.3174/ajnr.a0928
2. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med*. 1996; 334(8):494–500. https://doi.org/10.1056/nejm199602223340803
3. Fugate JE, Claassen DO, Cloft HJ, Kallmes DF, Kozak OS, Rabinstein AA. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. *Mayo Clin Proc*. 2010;85(5):427–32. https://doi.org/10.4065/mcp.2009.0590
4. Gokce M, Dogan E, Nacitarhan S, Demirpolat G. Posterior reversible encephalopathy syndrome caused by hypertensive encephalopathy and acute uremia. *Neurocrit Care*. 2006;4(2):133–6. https://doi.org/10.1385/ncc:4:2:133

5. Onder AM, Lopez R, Teomete U, Francoeur D, Bhatia R, Knowbi O. Posterior reversible encephalopathy syndrome in the pediatric renal population. *Pediatr Nephrol*. 2007;22(11):1921–9. https://doi.org/10.1007/s00467-007-0578-z
6. Ergün T, Lakadamyali H, Yilmaz A. Recurrent posterior reversible encephalopathy syndrome in a hypertensive patient with end-stage renal disease. *Diagn Interv Radiol*. 2008;14(4):182–5.
7. Mortiz ML, Ayus JC. The pathophysiology and treatment of hyponatremic encephalopathy: an update. *Nephrol Dial Transplant*. 2003;18(12):2486-2491. https://doi.org/10.1093/ndt/gfg394
8. Karp BI, Laureno R. Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia. *Medicine (Baltimore)*. 1993;72(6):359-373.
9. Pearce JMS. Central pontine myelinolysis. *Eur Neurol*. 2009;61(1):59-62. https://doi.org/10.1159/000175124
10. Stott VL, Hurrell MA, Anderson TJ. Reversible Posterior leukoencephalopathy syndrome. *Intern Med J*. 2005;35(2):83-90. https://doi.org/10.1111/j.1445-5994.2004.00750.x
11. Bartynski WS, Boardman JF, Zeigler ZR, Shadduck RK, Lister J. Posterior reversible encephalopathy syndrome in infection, sepsis, and shock. *AJNR Am J Neuroradiol*. 2006;27(10):2179-2190.
12. Ishikura K, Ikeda M, Hamasaki Y, et al. Nephrotic state as a risk for developing posterior reversible encephalopathy syndrome in pediatric patients with nephrotic syndrome. *Nephrol Dial Transplant*. 2008;23(8):2531-2536. https://doi.org/10.1093/ndt/gfn013
13. Lee SW, Lee SJ. Central-variant posterior reversible encephalopathy syndrome with albuminocytologic dissociation. *Case Rep Neurol*. 2018;10(1):29-33. https://doi.org/10.1159/000486444
14. Srinivasan KG, Balasubramanian P, Mayilvaganan KR, Kannan UN, Bilal M. Central variant of posterior reversible encephalopathy syndrome – a rare case report. *J Clin Diagn Res*. 2017;11(4):TD01-TD2. https://doi.org/10.7860/jcdr/2017/23269.9682
15. Ocek L, Sener U, Demirtas BS, Ozcelik MM, Oztekin O, Zorlu Y. Central-variant posterior reversible encephalopathy due to sulfasalazine: A case report. *Med Princ Pract*. 2015;24(6):578-580. https://doi.org/10.1159/000437386
16. Strandgaard S, Paulson OB. Cerebral autoregulation. *Stroke*. 1984;15(3):413-416. https://doi.org/10.1161/01.str.15.3.413
17. Dev N, Kumar R, Kumar P, Kumawat A. Hyperglycemia-induced posterior reversible encephalopathy syndrome: A rare cause of reversible blindness. *J Family Med Prim Care*. 2019;8(10):3431-3433. https://doi.org/10.4103/jfmpc.jfmpc_695_19
18. Muir A. Cerebral edema in diabetic ketoacidosis. *J Clin Endocrinol Metab*. 2000;85(2):509-513. https://doi.org/10.1210/jcem.85.2.6406-6
19. Kawaguchi M, Ogata H, Iwasaki K, et al. A case of type 1 diabetes with consciousness disturbance and defect of vision succeeding to hyperglycemia, yielding a diagnosis of posterior reversible encephalopathy syndrome (PRES). *J Jpn Diabetes Soc*. 2012;55(2):129–135.
20. Michinaga S, Koyama Y. Pathogenesis of Brain Edema and Investigation into Anti-Edema Drugs. *Int J Mol Sci*. 2015;16(5):9949-9975. https://doi.org/10.3390/ijms16059949
21. Trinh-Trang-Tan MM, Cartron JP, Bankir L. Molecular basis for the dialysis disequilibrium syndrome: altered aquaporin and urea transporter expression in the brain. *Nephrol Dial Transplant*. 2005;20(9):1984-8. https://doi.org/10.1093/ndt/gfh877
22. Sengupta P, Biswas S. Dialysis disequilibrium leading to posterior reversible encephalopathy syndrome in chronic renal failure. *CEN Case Rep*. 2016;5(2):154-157. https://doi.org/10.1007/s13730-016-0215-4