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# Posterior Reversible Encephalopathy Syndrome

Courtney M. Schusse
*Barrow Neurological Institute*, courtney.schusse@dignityhealth.org

Alicia L. Peterson

Jason P. Caplan

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Review Article

# Posterior Reversible Encephalopathy Syndrome

Courtney M. Schusse, M.D., Alicia L. Peterson, M.D., Jason P. Caplan, M.D.

**Background:** *The presentation of posterior reversible encephalopathy syndrome (PRES) features neuropsychiatric symptoms in the context of predominantly white matter cerebral edema in the setting of a diverse variety of underlying clinical entities.* **Objective:** *To illustrate the presentation and diagnostic strategy for this under-recognized condition.* **Method:** *We present two cases of PRES and review the available literature.* **Results:** *PRES may be due to a number of underlying conditions, but typically presents with symptoms consistent with delirium.* **Conclusions:** *Psychiatrist practicing in the general hospital should be aware of the presentation and appropriate work-up of PRES to forestall serious potential sequelae.*

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Posterior reversible encephalopathy syndrome (PRES) is a condition that may present with a variety of neuropsychiatric signs and symptoms and is characterized by a pattern of abnormalities on brain imaging studies. PRES has occurred in the context of a spectrum of underlying clinical entities that affect blood pressure and permeability of the cerebral vasculature. Psychiatrists practicing in the general hospital setting should be aware of this phenomenon and the importance of differentiating it from other causes of delirium. Here, we present the cases of two patients who presented with PRES and review the current literature on pathophysiology, diagnosis, and treatment.

## Case 1

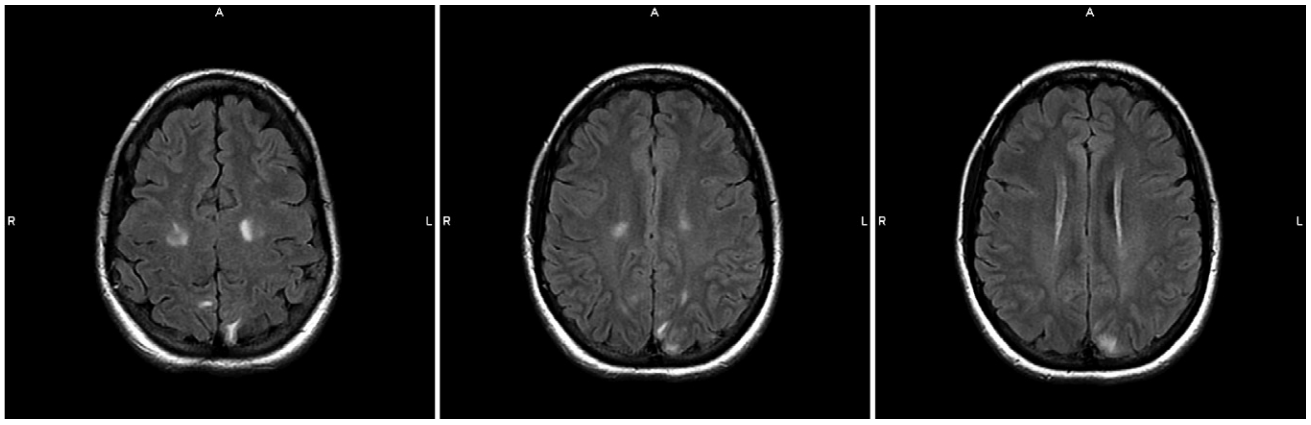
Ms. A, a 22-year-old woman with no significant past medical history, was brought to our hospital by ambulance at 28 weeks of pregnancy after she was found at home by her mother with generalized tonic-clonic seizure activity. En route to the hospital, blood pressure was found to be elevated to 176/106 mmHg (range: 148–176/98–106 mmHg). She had one additional seizure in the emergency room, and was obtunded on exam; initial treatment consisted of intravenous magnesium, blood pressure control with labetalol and, ultimately, delivery of her infant by emergency cesarean section. Magnetic resonance imaging (MRI) of her brain was obtained, which showed patchy T2 hyperintense white matter lesions consistent with a diagnosis of PRES secondary to eclampsia (Figure 1). An EEG was obtained on the day of admission, showing a predominant mixture of alpha and beta, but with theta and delta frequencies as well. There was only a brief period of wakefulness, and Ms. A was described as being "stuporous" by the technician performing the test. Postoperatively, Ms. A remained somewhat lethargic, but was arousable and oriented. She had no additional seizures in the hospital. MRI at 6-month follow-up showed resolution of the lesions (Figure 2) and her blood pressure was normal (122/79 mmHg).

## Case 2

Ms. B, a 55-year-old woman with a history of hypertension and both chronic back and abdominal pain, presented to our hospital with sudden onset of confusion,

Received November 27, 2012; revised January 23, 2013; accepted January 24, 2013. From the Department of Neurology, Barrow Neurological Institute at St. Joseph's Hospital and Medical Center, Phoenix, AZ (CMS); Department of Emergency Medicine, Maricopa Medical Center, Phoenix, AZ (ALP); Department of Psychiatry, Creighton University School of Medicine at St. Joseph's Hospital and Medical Center, Phoenix, AZ (JPC). Send correspondence and reprint requests to Jason P. Caplan, M.D., Department of Psychiatry, Creighton University School of Medicine at St. Joseph's Hospital and Medical Center, 350 W. Thomas Rd., Phoenix, AZ 85013; e-mail: jason.caplan@chw.edu

**FIGURE 1. MRI Brain Axial Fluid Attenuation Recovery (FLAIR) Images Showing White Matter Lesions in the Bifrontal, Biparietal and Left Occipital Lobes.**




lethargy, and elevated blood pressure to 183/78 mmHg. She was admitted to the intensive care unit and continued to exhibit fluctuating attention, consistent with delirium. MRI of the brain revealed diffuse patchy, subcortical white matter T2 and fluid attenuated inversion recovery (FLAIR) hyperintensities, consistent with PRES secondary to hypertensive emergency (Figure 3). An EEG was obtained, showing theta activity, admixed with polymorphic delta and frontal intermittent rhythmic delta activity (FIRDA) consistent with delirium. Ms. B's mental status slowly improved over the course of her 4 days in the hospital, returning to her baseline of function prior to discharge. Repeat MRI 4 months after discharge demonstrated resolution of the lesions (Figure 4). At that time, Ms. B was alert and oriented, with normal blood pressure (114/67 mmHg).

## DISCUSSION

In the cases of PRES described above, Ms. A developed generalized tonic-clonic seizures, and thus was immediately recognized as requiring medical attention; however, the more common and insidious scenario is that of Ms. B, in which a patient presents with confusion or delirium as the chief clinical symptom. The original nomenclature of reversible posterior leukoencephalopathy syndrome (abbreviated RPLE or RPLS), first described in 1996 by Hinchey et al,[1] has fallen out of use in favor of PRES, since lesions are not always confined to white matter. This designation too, may ultimately prove to be a misnomer, as this syndrome has been increasingly recognized in other regions of the brain and in some cases is not entirely reversible.

**FIGURE 2. 6 Month Follow Up: MRI Brain Axial FLAIR Images Showing Complete Resolution of Lesions.**

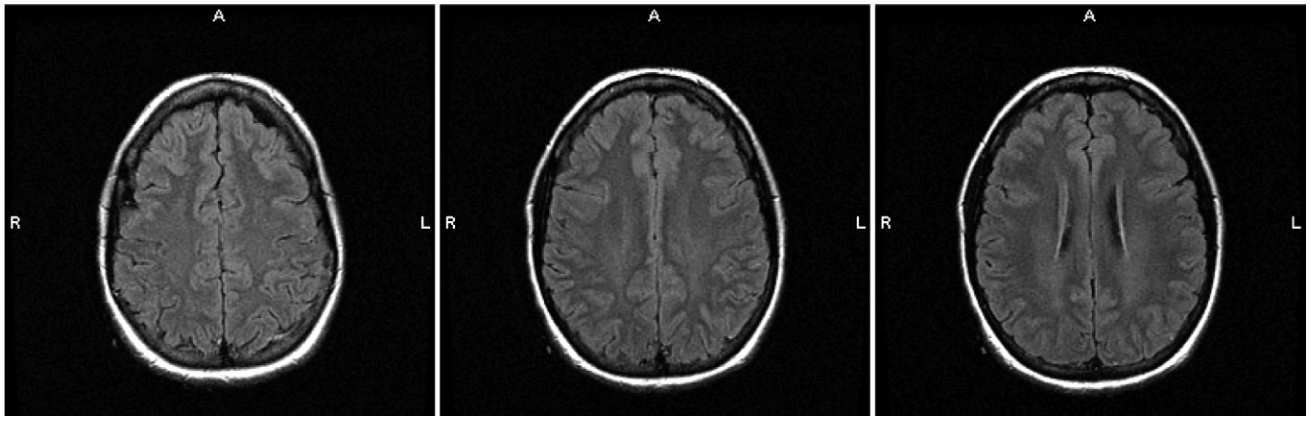
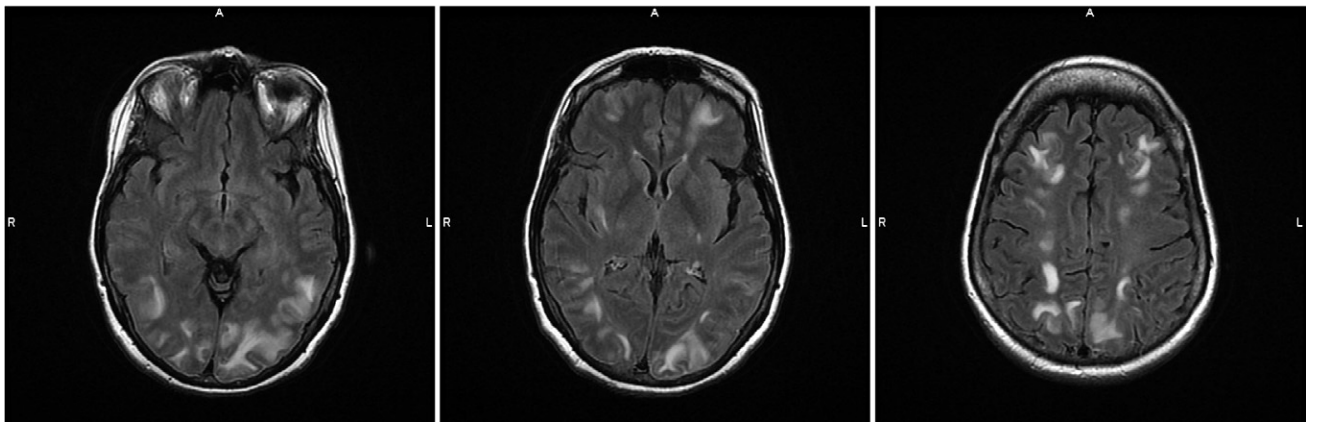


**FIGURE 3. Initial MRI Brain Axial FLAIR With Extensive Subcortical White Matter Lesions Involving all Lobes Bilaterally, as well as the Right Cerebellum (Not Pictured). Note that all Lesions Spare the Gray Matter of the Cortex.**



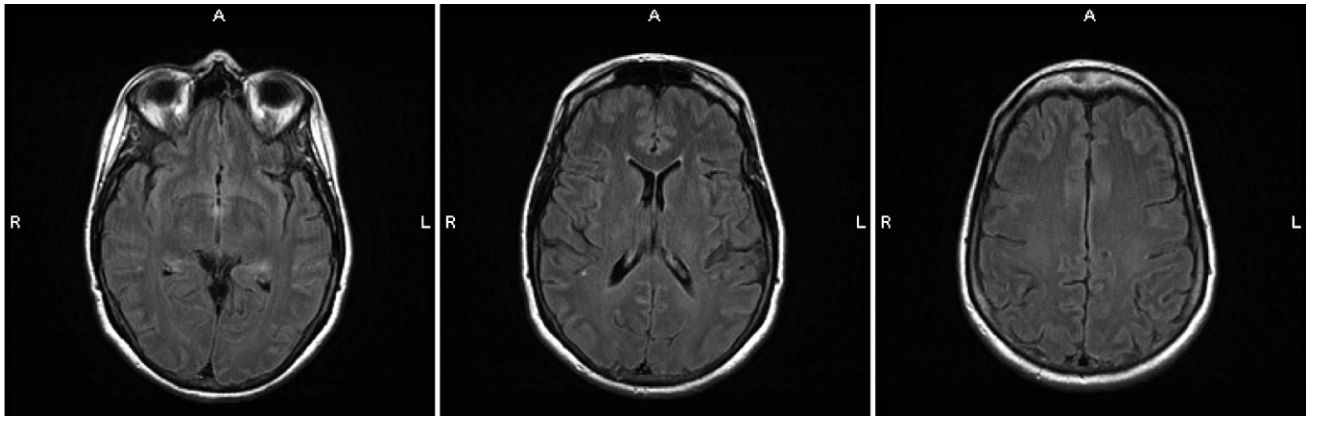

The syndrome was originally recognized in the setting of severe hypertension, eclampsia, or with the use of cyclosporine or other immunosuppressants; however, the underlying mechanism is still a subject of some controversy.[1,2] Classically, MRI of the brain (PRES is less easily recognized on computed tomography [CT]) will typically demonstrate symmetric, posterior occipital/parietal/temporal predominantly white matter edema, although a number of cases with atypical locations or asymmetric lesions have been reported.[1–3] Reports of frontal lesions have become increasingly common, and lesions consistent with PRES have also been found in occurring in the brainstem and basal ganglia.[2]

Clinically, the presentation may be nonspecific, but altered mentation is a nearly universal symptom, ranging from confusion and lethargy to stupor.[4,5] Seizures, headaches, and visual disturbances (including formed visual hallucinations and visual field cuts) are also common. Diagnosis of PRES is confirmed by MRI showing the characteristic edema. With aggressive and appropriate treatment, patients with PRES are likely to completely recover, and imaging changes are expected to resolve. If PRES is not aggressively and expediently managed, more deleterious outcomes are possible, with reports of progression to ischemia, frank infarction, and occasionally death.[6–8]

## Epidemiology

By its nature as a radiographic diagnosis, PRES is not isolated to one clinical entity or diagnosis. It is most commonly reported in cases of hypertensive encephalopathy. Reports to date indicate no clear male/female predominance; however, by virtue of gender-specific condi-

**FIGURE 4. 4 Month Follow Up: MRI Brain Axial FLAIR Images Showing Complete Resolution of Lesions. The Patient Does have a Few Areas of Non-specific White Matter Changes, Consistent With Chronic Small Vessel Disease, Likely Related to Her Underlying Hypertension.**



tions that can result in hypertensive encephalopathy (i.e., eclampsia), females tend to predominate in most case series. Patients with renal failure and those taking immunosuppressant or cytotoxic medications (especially calcineurin inhibitors) are especially susceptible.[2,4] Conditions with metabolic imbalances or fluid overload may predispose to PRES via blood pressure lability and elevation.[1]

In one large retrospective case series, males and females were represented almost equally (53% women, 47% males). Hypertension was overwhelmingly the most common risk factor, present in 68% of cases.[4] The average age was 45 years, with younger patients mostly representing cases of calcinuerin inhibitor (e.g., tacrolimus, cyclosporine) use.[4]

## Pathophysiology

The precise mechanism of PRES remains obscure. Although a few hypotheses have been cited, controversy still abounds. While a detailed evaluation of the proposed mechanisms is beyond the scope of this review, a brief description of the prevailing hypotheses is warranted. There are two major theories espoused in the literature: (1) sudden hypertension leads to failure of autoregulation followed by vasodilation and edema; and (2) vasoconstriction leading to ischemia and ultimately edema.[1,9–11]

## Failure of Autoregulation

Cerebral autoregulation is a function of the normal brain vasculature that compensates for fluctuations in blood pressure (either increased or decreased) in order to maintain stable blood flow to the brain.[10] Under normal conditions, within a range of blood pressures, vasodilation (in response to low blood pressure), and vasoconstriction (in response to high blood pressure) act to maintain constant cerebral circulation.[4,10,11] In the setting of severe hypertension, autoregulation fails and arterioles dilate, leading to transudation of fluid, injury to capillaries, hyperperfusion and, ultimately, vasogenic edema.[1,10] This theory would seem to be supported by the increase of water diffusion seen with the typical imaging lesions of PRES.[11] Though no large clinical series exist, the autoregulatory hypothesis has been supported by data from animal model studies and from isolated clinical cases where PRES lesions were studied with single-photon emission CT.[4] It is not entirely clear why PRES favors the posterior regions of the brain, but it has been postulated that the relative paucity of sympathetic innervation in the posterior circulation leads to greater inability to withstand perturbations of the cerebral autoregulatory mechanism.[11]

## Vasoconstriction

Vasoconstriction as a mechanism for PRES was the initial theory proposed based upon numerous underlying conditions where the characteristic lesions were known to occur, including pre-eclampsia and chemotherapy.[1,10] These pathophysiologic mechanisms are better understood, allowing for extrapolation to the hypothesis that PRES represents a cascade of events caused by endothelial dysfunction. Cyclosporine, for example, exerts a direct toxic effect on vascular endothelium, affecting the blood brain barrier and prompting endothelial cells to release endothelin—a potent vasoconstrictor.[1] Moreover, in pre-eclampsia, the inciting event is widely considered to be endothelial activation and injury, and the diffuse activation of endothelium leads to systemic vasoconstriction.[10] Of note, PRES has been shown to develop in patients with only mild elevation in blood pressure or in those who are normotensive,[4,10] adding credence to the idea that hypertension is not the inciting cause. In the vast majority of patients who develop PRES, regardless of the systemic process (e.g., chemotherapy-induced hypertension, eclampsia), the underlying biology is similar—endothelial dysfunction with systemic vasoconstriction, and hypoperfusion.[1,10] Sustained hypoperfusion leads to vasogenic edema through a complex mechanism of up-regulation of factors affecting vascular permeability.[10]

## Imaging

As the name PRES suggests, CT or MRI of the brain typically reveals focal edema of the white matter, especially the parieto-occipital regions.[1,4] However, PRES is not entirely a posterior phenomenon, as other regions including the frontal lobes (one series reported involvement in nearly 80% of their cases),[12] temporal-occipital junction, and cerebellum can also be involved.[2] There have been rare cases of PRES involving the brainstem.[12] In the occipital lobes, the paramedian and calcarine regions are usually spared, aiding in the differentiation from bilateral posterior cerebral artery infarction.[1] Lesions are typically bilateral, fairly symmetrical, and mostly involve white matter,[1,11] but there have been atypical cases of unilateral lesions, hemorrhage, or gray matter involvement, although these are rare.[1,4]

MRI studies are most useful diagnostic tests, with lesions most conspicuous with FLAIR imaging, especially

**TABLE 1. Differential of Magnetic Resonance Imaging (MRI) T2 White Matter Hyperintense Lesions**

Neoplasm
- glioma, lymphoma, gliomatosis cerebri, metastasis

Vascular
- PRES, AVM, vasculitis, amyloid angiopathy

Infection
- JC virus (PML), VZV, HIV

Demyelination
- MS, ADEM, leukodystrophy, Balos concentric sclerosis, Marburg

Trauma
- axonal injury

Inflammatory
- sarcoid, Behcet, Sjogren, SLE

Misc.
- Toxic (radiation, drugs), genetic syndromes (Myotonic dystrophy)

in cases of more subtle lesions that may be missed on the low resolution of CT.[4] Diffusion weighted imaging (DWI), with supplemental apparent diffusion coefficient (ADC) map images also aid in distinguishing the vasogenic edema of PRES (bright on both DWI and ADC), vs. cytotoxic edema associated with ischemic infarcts (bright on DWI, dark on ADC).[2,4] Table 1 summarizes the differential diagnosis of white matter T2 hyperintense lesions. There have been, however, some reports of foci of irreversible ischemia associated with PRES in addition to the traditional reversible vasogenic edema.[4]

## Laboratory Data

Given the wide range of systemic and metabolic conditions that predispose to PRES, there is no specific laboratory test available. Studies of pre-eclampsia/eclampsia demonstrate that there is often evidence of endothelial injury based upon findings of platelet consumption and the presence of schistocytes.[2] Similar laboratory findings have been noted in cases of PRES associated with sepsis and shock.[2]

## Clinical Presentation

Table 2 details some of the more common conditions that predispose to the development of PRES. The most common clinical symptoms and signs are detailed in Table 3. The onset of symptoms is usually subacute, with alterations in mentation developing over several days, but may be recognized more acutely if the patient has seizures.[1,5] In about 70% of patients, moderate or severe hypertension may be seen.[2] Seizures may be present at onset, but can also develop later in the course. Seizures may have focal onset, but generalized tonic-clonic activity is most often reported, with multiple seizures being more common than single events.[2,5] Patients invariably exhibit alterations in consciousness, with most presenting with lethargy and somnolence, though restlessness, agitation, and frank delirium are also common.[2] Stupor and coma may develop, but most patients remain at least somewhat responsive to stimuli.[2] Memory is usually impaired to some degree. Visual abnormalities are also frequently noted with patients reporting blurred vision or exhibiting visual neglect and cortical blindness.[2,5]

A clinically important differential diagnosis of PRES is that of progressive multifocal leukodystrophy (PML). In both cases, patients may present with neuropsychiatric symptoms, but in the case of PML, the onset is usually insidious and presents with motor signs and dementia rather than delirium.

## Electroencephalography

While generalized slowing on EEG has been noted as the hallmark of delirium, the EEG findings in PRES are usually nonspecifically abnormal. In one series of 17 patients, 13 patients showed diffuse theta and delta slowing, with two patients with periodic lateralized epileptiform discharges (PLEDs);[13] another series of 28 patients showed 22 patients with slowing on EEG, three patients with focal sharp waves and three which were normal.[14] A

**TABLE 2. Conditions Predisposing to Posterior Reversible Encephalopathy Syndrome (PRES)**

Pre-eclampsia/eclampsia

Post-transplantation
- allogenic-bone marrow transplantation
- solid organ transplantation

Immune suppression/chemotherapy
- Cyclosporine
- Tacrolimus
- Cisplatin*
- Avastin*
- Cytarabine*

Infection/sepsis/shock

Autoimmune disease
- SLE
- Wegener's granulomatosus
- Polyarteritis nodosa

Miscellaneous(reported associations)
- Hypomagnesemia
- Dialysis
- Hypercalcemia

* Reported associations.

**TABLE 3. Case Series of PRES and Their Presenting Signs and Symptoms**

| | Hinchey (1996)[1] *n* = 15 | Bartynski (2006)[8] *n* = 25 | Lee (2008)[4] *n* = 38 | Fugate (2010)[17] *n* = 113 | McKinney (2007)[12] *n* =7 6 |
|---|---|---|---|---|---|
| Symptom | | | | | |
| Confusion | 73% (11) | 40% (10) | 92% (35) | 28% (32) | 13% (10) |
| Headache | 53% (8) | 28% (7) | 53% (20) | 26% (29) | 4% (3) |
| Vision abnormalities (e.g., loss, hemianopsia, cortical blindness | 67% (10) | 20% (5) | 39% (15) | 20% (23) | 4% (3) |
| Seizures | 73% (11) | 64% (16)[c]<br>36% (9)[a] | 87% (33)[b] | 74% (84) | 76% (58) |

[a] Patients who presented with seizures initially.
[b] Focal onset in 10 patients.
[c] Patients that ultimately had seizure during course of acute illness.

small series in children showed continuous focal rhythmic slowing in the area of involvement, some with spike and wave discharges.[15] In all cases, the EEG abnormalities resolved as the clinical manifestations improved.[13–15]

## Pathologic Findings

Though it can be fatal, most cases of PRES do not lead to death; therefore, histopathologic evaluation of PRES is uncommon and, if obtained, may only represent an advanced course of the process. Cases of biopsy or autopsy during the acute phases have demonstrated vasogenic edema in the regions of DWI changes on MRI.[2] There are also activated or reactive astrocytes, macrophages, and lymphocytes, often without any inflammation, ischemia, or clear neuronal injury or vascular wall damage.[2,9]

In cases of PRES after cardiac transplantation, brain biopsy has shown similar findings of endothelial activation, diffuse vasogenic edema, reactive astrocytes, and reactive microglia.[16] Nonselective T cell trafficking with both helper (CD4) and cytotoxic (CD8) subtypes has been demonstrated but, interestingly, no B cell involvement, macrophages, or lymphocyte accumulation.[16]

Autopsy studies late in the process demonstrate some demyelination, ischemia, neuronal damage, necrosis, and hemorrhage in the involved white matter as well as the cortex.[2]

## Treatment

As with other causes of delirium, definitive treatment of PRES is aimed at identifying and ameliorating the underlying cause. Correction of systolic blood pressure is necessary to prevent worsening of the cerebral edema, though caution must be exercised in certain groups, such as pregnant women, where rapid decreases in blood pressure may lead to compromised placental flow.[5]

Though no consensus exists, several sources recommend the institution of antiepileptic therapy. Selection of therapy clearly depends upon a number of factors, including pregnancy and concern for status epilepticus. Magnesium sulfate is considered the drug of choice for treatment in pregnancy.[5] At this time, no data exist on the recommended duration of antiepileptic drug therapy.

The prognosis in the majority of patients with PRES is favorable as most cases do completely resolve as the name suggests. Some cases involve frank ischemia, with progression to infarction often correlated to the extent of T2 and DWI abnormalities on imaging.[17] The occurrence of hemorrhage has been found to be higher in patients with PRES who had undergone allogenic bone marrow transplant.[18]

## CONCLUSION

PRES has been recognized since 1996 as a distinct syndrome. Though it occurs in patients with a variety of complex systemic and metabolic conditions, the neuroimaging findings are characteristic of the condition. The specific pathogenesis remains unclear, and further research on this condition is needed. Nonetheless, it is clear that misdiagnosis or delay in treatment may result in permanent neurologic injury or even death.

Given the nonspecific constellation of symptoms associated with PRES, it is likely an under-recognized cause of neuropsychiatric symptoms in the acute hospital setting. Currently, there is little mention of this condition in the psychiatric literature, but because of the overlap of symptomatology that includes delirium and may potentially

mimic primary psychiatric illness, it is important that psychiatrists practicing in the general hospital setting are familiar with this syndrome in order to aid in timely diagnosis and appropriate treatment.

*Disclosure: J.P.C. is a member of the speakers' bureau for, has consulted to, and owns stock in Avanir Pharmaceuticals. C.M.S. and A.L.P. have nothing to disclose.*

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