



# Posterior Reversible Encephalopathy Syndrome

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## Abstract

**Purpose of Review** This review provides an updated discussion on the clinical presentation, diagnosis and radiographic features, mechanisms, associations and epidemiology, treatment, and prognosis of posterior reversible encephalopathy syndrome (PRES). Headache is common in PRES, though headache associated with PRES was not identified as a separate entity in the 2018 International Classification of Headache Disorders. Here, we review the relevant literature and suggest criteria for consideration of its inclusion.

**Recent Findings** COVID-19 has been identified as a potential risk factor for PRES, with a prevalence of 1–4% in patients with SARS-CoV-2 infection undergoing neuroimaging, thus making a discussion of its identification and treatment particularly timely given the ongoing global pandemic at the time of this writing.

**Summary** PRES is a neuro-clinical syndrome with specific imaging findings. The clinical manifestations of PRES include headache, seizures, encephalopathy, visual disturbances, and focal neurologic deficits. Associations with PRES include renal failure, preeclampsia and eclampsia, autoimmune conditions, and immunosuppression. PRES is theorized to be a syndrome of disordered autoregulation and endothelial dysfunction resulting in preferential hyperperfusion of the posterior circulation. Treatment typically focuses on treating the underlying cause and removal of the offending agents.

**Keywords** Reversible posterior encephalopathy syndrome · Immunosuppressive drugs · Vasogenic edema · Hypertensive encephalopathy · Headache

## Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological entity that was first described in 1996 in a series of fifteen patients with acute neurological symptoms including headache, seizures, visual disturbances, and other focal neurological deficits [1]. Though it was initially described as a reversible posterior leukoencephalopathy syndrome, PRES has since been the name most commonly applied to this entity. Here, we discuss the clinical presentation, diagnosis and radiographic features, mechanisms, associations and epidemiology, treatments, and prognosis of PRES. In addition, we propose criteria for a PRES-associated

headache syndrome for consideration by the International Classification of Headache Disorders [2].

## Clinical Presentation

PRES is associated with a wide array of clinical presentations including headaches, focal neurological deficits, seizures, visual disturbances, and encephalopathy. The severity and acuity of clinical symptoms vary, although typically occur with rapid onset.

## Headache

PRES-associated headache was first characterized by Hinchey et al. as sudden in onset, with or without associated neurologic deficits or seizures. It is typically described as constant and dull, at times intractable, and has been reported in 50% of patients [3, 4]. A subset of patients, however, describe a “thunderclap headache” as a harbinger of associated reversible cerebral vasoconstriction syndrome (RCVS) [5]. Headache in conjunction with PRES-associated disease states has been

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reported. Postpartum headache has been described as a recurrent syndrome associated with PRES. [6] In one prospective study of eclampsia patients, the presence of headache predicted abnormal imaging, with 95.6% of those with headache having abnormal imaging as compared to 12.5% of those without headache [7]. The most common characterizations of these eclampsia-associated headaches were throbbing or pounding pain (53%) and pressure like (40%). Of note, abnormal imaging findings in this study were not limited to PRES, but 16 of the 40 patients in the study had FLAIR abnormalities, a hallmark feature of the syndrome. One study demonstrated 58% prevalence of headache in preeclampsia/eclampsia patients with PRES. [8] Headache attributed to arterial hypertension is yet another syndrome associated with PRES and presents as severe in onset in conjunction with notably high blood pressures [9]. Prior reports have described headache in patients with PRES receiving associated medications; however, these patients are usually hypertensive at time of diagnosis [10, 11].

### Seizures

Seizures are common in PRES, seen in up to 81% of patients [4] and most often manifesting as generalized tonic-clonic episodes [12] with a propensity for recurrence. In a retrospective review of 49 patients with PRES, (17.6%) had recurrent generalized tonic-clonic seizures [13]. The semiology of PRES-associated seizures varies, however, and also includes convulsive status epilepticus (SE), complex partial seizures, and nonconvulsive SE. SE has been observed in up to 17% of patients with PRES in a larger case series [5]. It occasionally represents symptomatic onset of PRES, as seen in a series of 10 patients with the majority exhibiting focal-onset complex partial SE as the initial presenting complaint [14]. In another study of 11 pediatric patients with PRES undergoing stem cell transplantation, there was a high rate of SE with 12 episodes of SE in 10 patients, 8 cases of convulsive SE and 4 cases of nonconvulsive SE [15]. Seizures, when present, tend to occur early after disease onset in PRES. In a study of 38 patients with PRES and seizures, 100% had clinical seizures the first day after diagnosis, with no subsequent seizures [13]. Occipital lobe involvement has been identified as a significant predictor of the occurrence of seizures. On multivariate analysis in one study, occipital lobe involvement alone was significantly associated with the occurrence of PRES-related seizure development (OR: 9.63,  $p = 0.02$ ) [16]. In one prospective study of 40 women with eclampsia, which is defined by the presence of seizures, of the 22 women with MR imaging of the brain, all had T2 abnormalities including 11 with high parietal and 8 with occipital pole abnormalities [7].

### Encephalopathy

PRES can present with encephalopathy and, in one study, was the presenting complaint in 28% of patients [17]. Encephalopathy is present in most cases with a variable severity and can range from mild confusion to disordered consciousness [18••]. Practically, since seizures are so common in PRES, encephalopathy may also be associated with an ictal or postictal state.

### Visual Disturbances

Visual disturbances are common in PRES and were seen in 39% of patients in one study [19]. The symptoms can present as cortical blindness, various types of visual field deficits, visual neglect, hallucinations, and blurred vision. Ocular examination in patients with PRES is often unrevealing, although may reveal papilledema on fundoscopic examination along with nonspecific hemorrhages and exudates [20]. In one study of patients with PRES, visual complaints included bilateral vision loss in the majority of patients (64%), diplopia in 27%, and unilateral vision loss, color desaturation, and pain with extraocular movements each individually found in 9% of patients. Of note, of those patients with ocular complaints, 100% had a history of hypertension [21]. Visual symptoms have been theorized to occur with higher frequency with certain associations of PRES. A retrospective review observed that visual disturbances such as cortical blindness, blurred vision, and hemianopia are more common in eclampsia-related PRES. [8]

Visual recovery appears to be favorable in PRES. In a review of PRES in systemic lupus erythematosus (SLE), visual impairment was found in 15 of 26 episodes, with 87% of patients completely recovering their vision [22]. In two case reports of PRES and associated visual loss, follow-up results of visual field examination and peripapillary retinal nerve fiber lining were normal [23].

### Focal Neurologic Deficits

Focal neurologic deficits are varied and correlate with location of edema. In the literature, focal neurological symptoms have been reported in 10–15% of patients with PRES. [17] In one review of 71 patients with PRES, focal deficits were characterized as hemiparesis in 8.5%, followed by hemiplegia and speaking difficulty each in 4.2% of patients [18••].

### Diagnosis and Radiographic Features

The diagnosis of PRES is typically made with magnetic resonance imaging (MRI) of the brain. Imaging characteristically shows focal regions of symmetric hyperintensities on T2-weighted studies most commonly in the parietal and occipital

lobes, followed by the frontal lobes and the cerebellum. In a large cohort study by Bartynski et al., some degree of involvement of the parieto-occipital regions was seen in 98% of cases. In their review, imaging findings also included a holohemispheric watershed pattern with involvement of the frontal lobes in 22.8% of patients as well as a superior frontal sulcus watershed pattern in 27.2% of patients [24]. Apart from the aforementioned patterns, the less common but well-described additional regions of involvement may include the midbrain, pons, medulla, and basal ganglia. PRES has rarely been associated with spinal cord involvement [25]. PRES is also associated with hemorrhage, including small volume hemorrhage, subarachnoid hemorrhage, and hematomas, seen in 15.1% of cases in one study. Not surprisingly, there was a higher frequency of hemorrhage in those patients on therapeutic anticoagulation or undergoing bone marrow transplant [26]. Susceptibility weighted images (SWI) have also been utilized to assess for the presence of hemorrhage, seen in 64.5% of patients in another review [27]. Abnormal apparent diffusion coefficient is seen in approximately 20% of cases [28•] and has been associated with poor outcomes.

Vasculopathy is a common finding in patients with PRES. Angiography, if performed, can show evidence of constriction of the blood vessels, which suggests a possible overlap with reversible cerebral vasoconstriction syndrome (RCVS). Conversely, typical PRES imaging findings have been reported in 17–38% patients with RCVS [29].

In a series of 99 cases with PRES, 38% of patients had extensive vasogenic edema, 21% had brainstem edema, and 37% had evidence of intracranial hemorrhage—all classified as advanced radiologic PRES. Of the 94 cases with available MRIs, 16% had restricted diffusion on T2, also considered an advanced radiologic sign of PRES. Extensive vasogenic edema and the presence of hemorrhage were both associated with a low modified Rankin Scale (mRS) score at discharge ( $p = 0.047$  and  $0.021$ , respectively). The presence of diffusion restriction also showed a trend towards association with poor mRS at discharge ( $p = 0.074$ ). Overall, the presence of advanced radiologic PRES was associated with both poor discharge disposition ( $p = 0.021$ ) and poor mRS at discharge ( $p = 0.008$ ) [30].

## Mechanisms

PRES is a disorder of dysregulated perfusion, leading to usually reversible vasogenic edema. There are several theories as to why the cerebrovasculature becomes dysregulated in PRES. There is no single mechanism that explains the development of PRES in all cases, and multiple nonexclusive mechanisms likely contribute.

In cases where hypertension is a key feature, hyperperfusion is thought to play a critical role. In response to fluctuations in systemic blood pressure, cerebrovascular

autoregulation preserves cerebral blood flow, leading to vasodilation during systemic hypotension and vasoconstriction during systemic hypertension. Rapid development of hypertension can exceed the capacity of cerebral blood flow autoregulation leading to hyperperfusion. Consistent with the clinical and radiographic features of the disease, posterior brain regions are thought to be more vulnerable to hyperperfusion because there is less sympathetic innervation to the posterior circulation, potentially through reduced opposition to parasympathetic reflex vasodilation. Whether the systemic blood pressures seen in patients with PRES can truly overwhelm autoregulatory mechanisms has been questioned [18••]. Among patients who have PRES and hypertension, less than 50% have a mean arterial pressure (MAP) above the upper limit of cerebral blood flow autoregulation derived from physiological studies,  $MAP > 140$ – $150$  [31]. However, there may be individual and circumstantial variability. For example, arterial hypertension, acute fluctuations in blood pressure, and autonomic activity can all shift autoregulatory thresholds. Autoregulatory curves may also be shifted in pregnancy, making it a particularly vulnerable time for PRES despite only modest elevations in blood pressure.

On a mechanistic level, blood-brain barrier breakdown can result from hyperperfusion and increased cerebral perfusion pressure leading to extravasation of plasma and macromolecules into the interstitial space through tight junction proteins [32]. Other mechanisms also contribute to the loss of the integrity of the vascular endothelium, which can lead to vasoconstriction in and of itself. The release of vasoactive substances including nitric oxide, thromboxane A<sub>2</sub>, or endothelin-1 from the vascular endothelium contributes to cerebral autoregulation [33]. Thromboxane A<sub>2</sub> and endothelin-1 can mediate cerebral vasospasm and lead to blood pressure elevations. It has further been proposed that hypertension may also result from hyperperfusion caused by endothelial dysfunction or another systemic process. However, as development of hypertension usually precedes development of symptoms, this does not provide a unifying explanation. Indeed, hyperperfusion due to hypertension cannot explain the development of PRES in the 15–20% of patients who have normotension or hypotension [32].

Endothelial damage is also implicated in PRES. Vascular integrity is normally preserved by inter-endothelial adhesion molecules, and circulating toxins can trigger vascular leakage and edema. In immune disorders and other systemic disorders, release of cytokines including tumor necrosis factor alpha (TNF $\alpha$ ), interleukin-1 (IL1), and interferon gamma (IFN $\gamma$ ) activates the secretion of vasoactive factors from endothelial cells that increase vascular permeability leading to interstitial edema. The release of these cytokines can also influence downstream gene expression cascades. TNF $\alpha$  and IL1 induce the expression of adhesion molecules, including intracellular adhesion molecule 1 (ICAM-1), vascular cell adhesion protein

1 (VCAM-1), and E-selectin, that interact with circulating leukocytes and lead to endothelial activation [34]. Similarly, in infection, polymorphonuclear leukocytes are activated, marginate to the vessel wall, adhere to the vascular endothelium, and increase vascular permeability. TNF $\alpha$  also induces the expression of vascular endothelial growth factor (VEGF), which is thought to independently increase vascular permeability [33]. Elevated levels of VEGF have been implicated in a number of disease states associated with PRES, most notably SLE. Kuryliszyn-Moskal et al. showed that patients with SLE have significantly higher levels of VEGF than healthy controls ( $p < 0.05$ ) [35]. In addition, in patients with SLE and PRES, brain biopsies were performed that showed evidence of endothelial activation and subsequent VEGF expression, suggesting a possible relationship between PRES and VEGF levels [36]. Hypoxia has also been associated with the development of PRES. Release of endothelial factors in response to hypoxia promotes angiogenesis (including VEGF) and this breakdown of the blood-brain barrier has been postulated to contribute to vasogenic edema.

Taken together, and depending on the clinical situation, all these mechanisms may contribute to the development of PRES pathophysiology (Fig. 1).

## Epidemiology and Associations

PRES is seen in all age groups with a range from 4 to 90 years [37] and a mean age of 45 [4]. In adults, there is a female predominance of cases even after exclusion of patients with eclampsia [17]. The prevalence in the pediatric population has not been well established, although a prior study of 2588 admissions to a pediatric critical care unit reported a rate of 0.4% [38]. Another study of 825 pediatric hospitalizations for PRES-associated conditions such as bone marrow transplant, hypertension, and connective tissue disorders found the rate of PRES to be 0.04% [39].

## Renal Injury/Failure

Many studies suggest renal injury is the strongest predictor of the development of PRES—up to 55% of cases are associated with renal failure [17, 18•, 40]. In a retrospective study of 63 SLE patients, renal failure was the only independent predictor of the development of PRES. [40] Similarly, a case series involving thrombotic thrombocytopenic purpura (TTP) and PRES revealed glomerular filtration rate to be the only laboratory value with a significant association with the presence of PRES on brain MRI [41]. The mechanisms tying kidney injury to PRES have yet to be fully elucidated but may involve disruption in the renin-angiotensin-aldosterone system (RAAS). Another theory suggests that upregulation and accumulation of vasopressin in kidney failure may play a role in

arteriole vasoconstriction and failure of autoregulation in PRES. [42]

## COVID-19

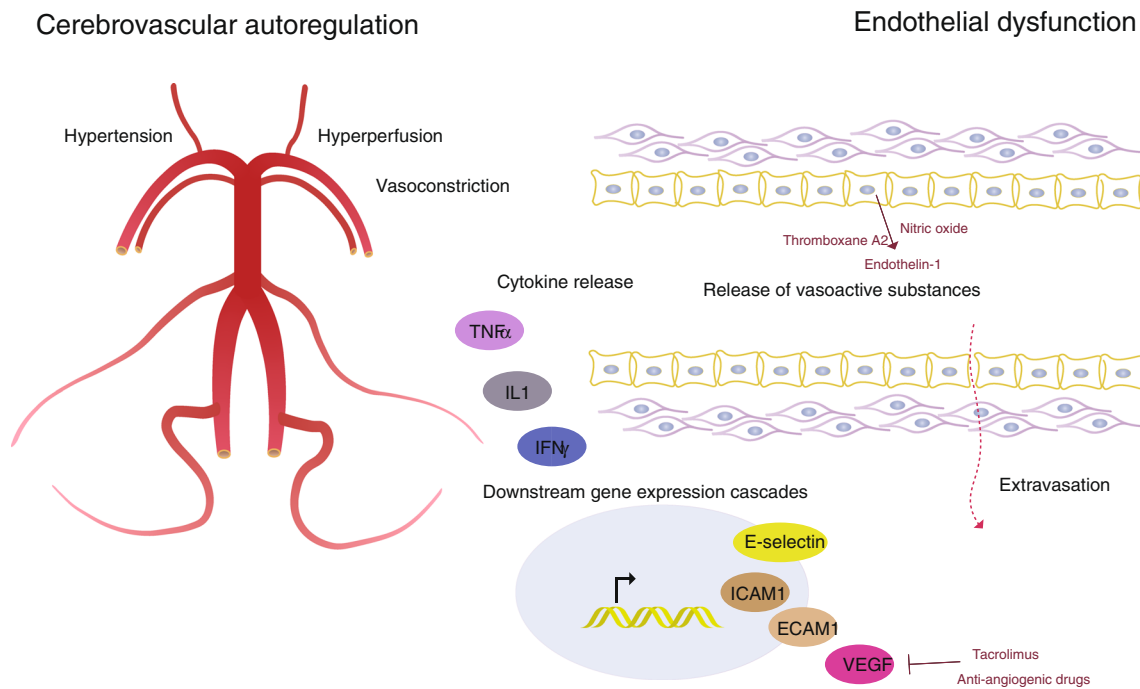
The combination of disordered cerebrovascular autoregulation, acute renal failure, acute hypertension, hypoxia, inflammation, and endothelial injury can characterize SARS-CoV-2 infection and its sequelae. Coincidence of PRES and COVID-19 disease has been reported, making recognition and diagnosis of PRES particularly timely. Along with the common use of immunomodulatory medications, these associated characteristics make this pandemic disease a perfect storm for the development of PRES. [43, 44] A larger study of 278 patients with confirmed COVID-19 undergoing imaging demonstrated a 1.1% prevalence of PRES. MRI as an imaging modality had a higher yield in detecting cases, demonstrating a 3.9% prevalence of PRES. [45]

## Preeclampsia/Eclampsia

The obstetric complications of preeclampsia and eclampsia are closely linked with PRES. In one study, 97.9% of patients with eclampsia had confirmed PRES on imaging [46], suggesting that the disease entities are essentially one and the same, with the eclampsia diagnosis existing long before imaging modalities were available. Widespread endothelial dysfunction in combination with abrupt elevations in blood pressure is thought to be the key features that drive PRES in preeclampsia and eclampsia [47]. In women with preeclampsia or eclampsia, those with PRES also have a higher prevalence of thrombocytopenia and proteinuria as compared to those without PRES. [48] However, PRES associated with these etiologies appears to have some key differences compared to PRES attributed to other etiologies. One study showed that patients with PRES associated with these conditions have a significantly higher prevalence of headaches (58% vs. 18%) and lower incidence of altered mental status (12.5% vs. 45%) as compared to patients with PRES associated with non-obstetric conditions [8]. Additionally, this study found that in this population, imaging showed less involvement of T2 hyperintensities in the thalamus, midbrain, and pons; lower incidence of hemorrhage and diffusion restriction; as well as less severe edema when compared to those patients with PRES associated with other etiologies. However, other studies have not found such differences in imaging findings [49, 50].

## Autoimmune Conditions and Hemoglobinopathies

Almost half of PRES patients have an associated autoimmune condition, including SLE, TTP, Crohn's disease, and scleroderma, among others [18••]. However, it is difficult to



**Fig. 1** Mechanisms contributing to the development of PRES. Disordered cerebrovascular autoregulation in hypertension can lead to hyperperfusion. Blood-brain barrier breakdown results from increased cerebral perfusion pressure leading to extravasation of plasma and macromolecules into the interstitial space through tight junction proteins.

Release of cytokines activates the secretion of vasoactive factors from endothelial cells that increase vascular permeability leading to interstitial edema. Release of these cytokines can also influence downstream gene expression cascades

determine if the root of the association is the autoimmune disease itself or rather the high incidence of renal injury as well as the immunosuppressive medications frequently used in these conditions. PRES has also been reported in a series of patients with neuromyelitis optica, and it has been postulated that disordered fluid shifts play a role in pathogenesis in these patients with abnormal function of aquaporin 4 [51]. Both solid organ and stem cell transplant patients have high incidence of PRES, with incidence in solid organ transplantation varying from 0.4 and 6% [52] and in hematopoietic stem cell transplantation between 1.1 and 22% [53–55]. Graft-versus-host disease associated with transplant also appears to increase risk for PRES. [55] PRES has been reported in individuals with sickle cell disease (SCD), typically in those with acute chest syndrome as well as post stem cell transplant patients on calcineurin inhibitors. In the pediatric population, PRES has been seen in children independently of acute chest syndrome. In a retrospective review of MRI findings in 80 children with SCD, 8 patients had radiologic and clinical characteristics consistent with PRES. [39] It is not clear whether PRES is independently associated with SCD or whether the underlying vasculopathy, hypertension, and endothelial damage contribute [56].

**Immunosuppression and Other Associated Medications**

Classically, the immunosuppressive medications highly associated with PRES are the calcineurin inhibitors tacrolimus and

cyclosporine, though this may be via induction of hypertension and/or impaired autoregulation as blood levels do not seem to correlate with incidence [18•, 42]. Steroids have both been implicated in the improvement of PRES-associated vasogenic edema and in the development of PRES itself [57]. Tocilizumab has also been reported in association with PRES. [57, 58] Hydroxychloroquine has also been implicated in PRES, though it is unclear if this is an independent risk factor or simply associated via its common use as a treatment for SLE [17, 59, 60]. Finally, several VEGF antagonists have been associated with PRES—bevacizumab, sunitinib, and sorafenib [18•, 61].

**Treatment and Prognosis**

There are no clinical trials to date regarding the treatment of PRES. Withdrawal or management of the offending trigger such as hypertension, impaired renal function, or immunosuppressive therapies appears to improve outcomes. Systemic blood pressure abnormalities, if untreated, can lead to development or exacerbation of cerebral edema. Correspondingly, aggressive blood pressure management in cases of hypertension-induced PRES has been shown to reduce associated morbidity [62]. In cases of pregnancy-associated PRES, management includes expeditious delivery of the infant. In pregnant women with PRES and preeclampsia, magnesium sulfate is indicated to prevent seizures [5].

In cases of calcineurin inhibitor-associated PRES, a common strategy is the replacement of the offending calcineurin inhibitor with other immunosuppressive agents (43.7% in one study). Other strategies include replacement with another calcineurin inhibitor (26.8%); replacement with sirolimus, everolimus, mycophenolate mofetil, or hydrocortisone (16.9%); or lowering the dose of the offending agent (22.5%). In only 9.9% of cases, discontinuation of the agent with no replacement was pursued [63]. Other studies suggest that continuation of the same calcineurin inhibitor or changing to alternative calcineurin inhibitors is well tolerated. In one study of patients with hematologic disorders, the majority of patients (77%) tolerated continuation or alternative calcineurin inhibitor therapy. An additional 11% tolerated conversion from a calcineurin inhibitor to sirolimus, with only 8% of patients experiencing recurrent PRES with continuation of calcineurin or sirolimus therapy [64].

Steroid therapy has not been shown to play a role in the routine treatment of PRES-associated vasogenic edema. In a study of 99 cases of PRES, corticosteroid therapy frequently preceded the onset of PRES and was not significantly associated with the extent of vasogenic edema, suggesting that it does not lessen edema and may in fact contribute to the development of PRES. [56]

Treatment of malignant complications of PRES is also paramount, such as IV anticonvulsants in status epilepticus and aggressive management of hemorrhagic PRES and increased intracranial pressure. Management of PRES often requires an ICU setting; in one study, 70% of patients with PRES required ICU care for PRES-associated complications including status epilepticus [65]. The optimal agent and length of treatment in PRES-associated seizures, however, remains controversial [66].

Prognosis is generally favorable and the majority of patients make a full recovery, though some diagnostic criteria require clinical and radiographic resolution [18••] which does not include the entire spectrum of the disease. When reversibility is not mandated, complete recovery is reported in 75–90% of cases, and most patients will recover within a week, though in some patients, recovery occurs over a longer interval and neurological sequelae have been reported in 10–20% of patients [9]. PRES can also be quite severe, and mortality has been reported in 3–6% of cases [67]. Etiology of severe neurologic injury and death include intracranial hemorrhage, edema in the posterior fossa leading to hydrocephalus or brainstem compression, or increased intracranial pressure. The underlying cause of PRES, time to treatment, and underlying imaging characteristics have all been shown to contribute to prognosis [4, 68]. As previously mentioned, a retrospective review of 99 cases with PRES showed that the presence of advanced radiologic PRES was associated with both an unfavorable discharge disposition and poor mRS at discharge [30].

**Table 1** Proposed diagnostic criteria: headache attributed to posterior reversible encephalopathy syndrome (PRES)

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- Any new headache fulfilling the following criteria and continuous for  $\geq$  72 h without treatment or continuous for  $<$ 72 h with treatment
1. Posterior reversible encephalopathy syndrome has been diagnosed
  2. Evidence of causation demonstrated by either or both of the following:
    - a. Headache has developed in close temporal relation to other symptoms and/or clinical signs of PRES, or has led to the diagnosis of PRES
    - b. Headache has significantly improved in parallel with stabilization or improvement of other symptoms or clinical or radiological signs of PRES
  3. Not better accounted for by another ICHD-3 diagnosis
- 

Headache attributed to reversible cerebral vasoconstriction syndrome (ICHD-3 code 6.7.3) and headache attributed to arterial hypertension (ICHD-3 code 10.3) can also be diagnosed

### Proposed New Criteria for PRES-Associated Headache

While some cases of PRES are likely captured under ICHD-3 “10.3.3. Headache attributed to hypertensive encephalopathy,” hypertensive encephalopathy and PRES are not equivalent diagnoses. About 30% of PRES cases are associated with normal or only mildly elevated blood pressure values [69, 70]. Many of these PRES cases end up being attributed to other known associations including immunosuppressive and cytotoxic medications, sepsis, autoimmune disorders, and renal failure [70]. Also, while the majority of patients with hypertensive encephalopathy will have altered mental status, this is not so with a significant portion of PRES cases [71]. In particular, PRES cases associated with preeclampsia and eclampsia have lower incidence of altered mental status and higher incidence of headache compared to PRES cases associated with other causes [8]. While some cases of PRES-associated headache may be captured under ICHD-3 10.3.4-Headache attributed to preeclampsia or eclampsia, these are again overwhelmingly entwined with hypertension [8]. As the ICHD-3 currently stands, there is still a significant diagnostic gap for headache that is associated with PRES but not associated with either hypertensive encephalopathy or preeclampsia/eclampsia.

### Conclusions

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological syndrome with a complex clinical presentation. Early recognition of classic radiographic features is vital to prompt recognition and treatment, as the symptoms are relatively nonspecific and the differential diagnosis is broad.

Fifty percent of patients will present with nonspecific headache as previously discussed. To date, headache secondary to

PRES is not listed as a distinct entity in the ICHD-3, though related conditions are including headache attributed to arterial hypertension and headache attributed to preeclampsia or eclampsia. We propose that PRES-associated headache should be its own unique diagnosis in the ICHD-3 under “6.7: Headache attributed to other acute intracranial arterial disorder” as seen in Table 1.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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