

[REVIEW ARTICLE]

Posterior Reversible Encephalopathy Syndrome: A Review of the Literature

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Abstract:

Posterior reversible encephalopathy syndrome (PRES) is a group of clinical syndromes typically characterized by bilateral reversible vasogenic edema of the subcortical white matter in the parieto-occipital region on neuroimaging that causes a wide variety of acute or subacute neurological symptoms, including headache, mental status alteration, seizures, and visual dysfunction. PRES is classically suspected in patients with severe hypertension, renal failure, autoimmune disorders, eclampsia, or immunosuppressant medications. Frequent neurological evaluations and neuroimaging examinations by computed tomography or magnetic resonance imaging are required for both the diagnosis and assessment of the condition. Early detection of the disease is key for a rapid recovery and good prognosis.

Key words: posterior reversible encephalopathy syndrome, bilateral reversible vasogenic edema, neurological symptoms, reversible cerebral vasoconstriction syndrome

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Overview of PRES

This topical review aims to provide a brief overview of posterior reversible encephalopathy syndrome (PRES) and to describe the recent findings and future perspectives.

PRES is a clinical and radiological syndrome that was initially described in 1996, in a case series by Hinchey et al. (1). It is sometimes referred to as reversible posterior cerebral edema syndrome, posterior leukoencephalopathy syndrome, hyperperfusion encephalopathy, or brain capillary leak syndrome. The name 'reversible' derives from the fact that both neurological and neuroimaging findings spontaneously recover within a few hours or 7-8 days (1-5) after the initiation of treatment.

Previous studies retrospectively investigated the clinical and radiographic manifestations of PRES (2, 4, 5). The symptoms of PRES are diverse and include headache, altered mental status, blurred vision, and seizures (4). Epidemiological data suggested that all age groups can suffer from PRES and that women are more prone to suffer from

PRES than men (5, 6). Pediatric inpatients accounted for 825 cases and 0.04% of all hospitalizations in the Kid's Inpatient Database in the United States in 2016, and the mortality rate was 3.2% (6). Uniform and validated diagnostic criteria for PRES have not been established because of its rarity (2, 3, 7-9). Even studies focusing on PRES have differed in their diagnostic criteria, which led Fischer and Schmutzhard (9) to warn about the interpretation of epidemiological data related to PRES.

Etiology and Epidemiology

Classically, two main theories for the pathogenesis of PRES have been proposed. The first is severe hypertension that leads to disruption of the brain autoregulation system, consequently resulting in endothelial edema or injury (1, 7-9).

PRES is frequently found in patients with reversible cerebral vasoconstriction syndrome (RCVS), characterized by segmental vasoconstriction and vasodilation in small cerebral vessels arising from cerebral vascular tone dysregula-

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Table 1. Risk Factors for Posterior Reversible Encephalopathy Syndrome.

Hypertension
Renal disease
Immunosuppressive state
Chemotherapy/chemoradiotherapy
Autoimmune disorders
(Pre) eclampsia
Infection/sepsis
Steroids
Dialysis
Transfusion
Endocrine and metabolic disorders
Surgery
Anemia (Sickle cell anemia)
Hypomagnesemia

tion (10). The abrupt blood pressure surge associated with RCVS may play a pivotal role in the pathogenesis of PRES in these patients (10). This theory is supported by the fact that hypertensive crisis leads to PRES. The second is endothelial dysfunction caused by circulating endogenous or exogenous toxins (8). This hypothesis provides a plausible reason why patients with preeclampsia/eclampsia, sepsis, immunosuppressant medications, and cytotoxic drugs have a higher probability of developing PRES (9). However, neither of these theories can completely explain the etiology or pathology of PRES, and thus the mechanisms remain controversial (2, 3, 8).

Risk Factors

PRES is associated with several risk factors (5, 6, 11) (Table 1). Abrupt elevation of blood pressure is the most commonly described risk factor in previous studies (2, 4, 5, 11-13). However, PRES should still be suspected in patients without hypertension because one quarter of patients with PRES have normal blood pressure (8). Certain types of diseases, drugs, and clinical conditions that cause fluctuations of blood pressure can also be regarded as risk factors, including dysautonomia, subarachnoid hemorrhage, discontinuation of antihypertensive drugs, and initiation of chemotherapy (12, 14, 15). Endocrine disorders such as pheochromocytoma, ganglioneuroma, and primary aldosteronism can cause secondary hypertensive encephalopathy that leads to PRES (12, 14). In addition, hypercalcemia associated with elevated serum parathyroid hormone-related peptide can cause PRES (16).

Renal failure leads to secondary hypertension and electrolyte imbalance, and is commonly described as a risk factor for PRES, possibly accounting for more than half of PRES cases (2, 4, 5, 12). However, because renal failure usually accompanies all risk factors for PRES, including hypertension and drug-induced endothelial dysfunction, it remains unknown whether renal failure itself is an independent risk

factor for PRES (2, 9).

Among the risk factors, immune system activation/disruption has recently been considered a critical initial step in the pathogenesis of PRES and plays a pivotal role in the development of the disease (17, 18). Immunosuppressant or cytotoxic drugs, such as cyclosporin A, tacrolimus/FK-506, methotrexate, sirolimus, lenvatinib, bevacizumab, carboplatin, and paclitaxel, are also significant predisposing factors (5, 12, 19-22). Nearly half of patients with PRES have a clinical history involving an autoimmune disorder (2, 17). Systemic lupus erythematosus is the autoimmune disease most frequently associated with PRES. Infection or septic shock can induce a cytokine storm, consequently leading to immune system activation, endothelial cell activation, endothelial injury, vascular instability, and systemic/organ hypoperfusion in addition to procoagulant and metabolic effects (17).

Given that preeclampsia and eclampsia are highlighted as immunological disorders, seizures diagnosed as PRES during the maternal period are not rare (2). The incidence of preeclampsia or eclampsia accompanied by PRES is quite common (23), and PRES with preeclampsia or eclampsia is not associated with a poor prognosis (24).

The trends in risk factors between adults and children (< 20 years of age) are different, with hypertension ranked first among the adult risk factors and renal disease ranked first among the pediatric risk factors.

Clinical Manifestations

The clinical manifestations of PRES are characterized by the acute or subacute onset of non-specific neurological symptoms, with varying frequencies among studies. A recent study on 556 cases in the PubMed, EMBASE, and Web of Science databases (5) indicated that the most common symptom is headache (50.6%; 282/556), followed by altered mental status (43.7%; 243/556), seizures (41.9%; 233/556), visual disturbance (34.9%; 194/556), nausea/vomiting (23.4%; 130/556), and focal neurological deficits (18.2%; 101/556). These symptoms can develop within several hours or days and cease within several days or weeks with a reduction of blood pressure and retraction of the causative drugs.

Fugate and Rabinstein (2) warned that presence of status epilepticus may be an initial sign of PRES and recommended that clinicians should obtain an electroencephalogram (EEG) when they suspect a PRES case, even though prevalence of status epilepticus is low in patients with PRES.

Recurrence

One crucial aspect of PRES is that recurrent episodes are sometimes documented. Sweany et al. (25) reported that 3.8% (3/78) of PRES patients with risk factors had experienced recurrence. They also suggested that infectious or in-

flammatory events in patients with recurrent PRES could trigger neurotoxicity and the development of PRES.

Laboratory Findings

Patients with PRES show several serological abnormalities. Previous reports described that serum lactate dehydrogenase (LDH) levels are elevated in PRES patients with malignancy or eclampsia/preeclampsia, which may be derived from endothelial disturbance (12, 26, 27), while low serum albumin levels can accelerate the development of edematous lesions (12, 28, 29). Electrolyte imbalances like hypomagnesemia or elevated creatinine and liver function parameters are listed as diagnostic findings (9). The C-reactive protein (CRP) level is also elevated and was identified as a risk factor for an adverse outcome (24). In addition, data obtained from a lumbar puncture can reveal an elevated albumin level in the cerebrospinal fluid (12, 30, 31).

EEG is useful to exclude non-convulsive status epilepticus (12). However, the sensitivity and specificity are not good, because various EEG patterns have been reported. In other words, there are no specific EEG waves that can characterize PRES.

However, as mentioned above, these laboratory findings are not components for the diagnosis of PRES, and further studies on laboratory data should be undertaken to achieve a better understanding of its pathophysiology.

Neuroimaging Examinations

Even though there are no established diagnostic criteria for PRES, neuroimaging examinations, such as contrast computed tomography (CT) and magnetic resonance imaging (MRI), especially T2-weighted and fluid-attenuated inversion recovery sequences, are essential for its diagnosis (1, 4, 5, 7, 32). Brain MRI characteristically reveals vasogenic edema in patients with PRES (Figure A-E) (13). Quantification of the apparent diffusion coefficient can generally be useful to differentiate vasogenic edema from cytotoxic edema. Figure 1B and 1C show a lesion with high signal intensity on diffusion-weighted images and a high apparent diffusion coefficient, consistent with the high water mobility associated with vasogenic edema. The most common neuroimaging finding is a bilateral edematous focal region in the brain hemisphere (1, 4, 5, 7). The parietal and occipital lobes are most commonly affected, followed by the frontal lobes, the inferior temporal-occipital junction, the cerebellum, and the spinal cord (5, 33, 34). Despite the fact that these radiologic abnormalities usually resolve within weeks, the neuroimaging findings are not necessarily correlated with the clinical manifestations in patients (5, 35) even after complete resolution.

Diagnosis

It is difficult and complex to diagnose PRES in patients

due to the lack of validated diagnostic criteria for PRES. A diagnosis of PRES is usually made when patients have neurological symptoms, radiographic abnormalities, and risk factors (2, 12). However, the diagnosis must be made after the probabilities of other neurologic disorders have been excluded.

Fugate and Rabinstein (2) proposed an algorithm for the diagnosis of PRES: acute onset of neurological disorder, neuroimaging abnormalities, and reversible clinical-radiological symptoms. Zou et al. (36) discussed the utility of the PRES early warning scoring (PEWS) system, which includes risk factors (underlying disease, hypertension, infection, drug toxicity), clinical features (high cranial pressure, visual symptoms, seizure, consciousness disturbance), and EEG features (slow wave discharges, epileptiform discharges). According to the PEWS system, a patient with a score of more than 10 points is likely to have PRES.

Malignant PRES is defined as follows: radiological findings consistent with PRES, Glasgow Coma Scale score of less than 8, and clinical decline despite standard elevated intracranial pressure management (37).

Differential Diagnoses

The differential diagnoses for PRES are shown in Table 2. Because acute or subacute non-specific neurological symptoms appear in PRES, the differential diagnoses for PRES vary among studies (2, 11). Faille et al. (11) retrospectively examined the medical records of 220 patients with suspected PRES and found that the most frequent differential diagnoses were primary or secondary headache, followed by toxic-metabolic encephalopathy.

Eclampsia and preeclampsia associated with PRES are quite common (38). In addition, preeclampsia is sometimes confused with HELLP syndrome (a syndrome during pregnancy characterized by hemolysis, elevated liver enzymes, and low platelet count). HELLP syndrome is a serious condition that can manifest during any period of pregnancy (38, 39).

The etiology of RCVS overlaps with that of PRES because cerebral vascular tone dysregulation can lead to both of these syndromes (10, 40). RCVS also shares some clinical manifestations with PRES, including visual symptoms, seizures, and MRI abnormalities. However, RCVS is characterized by recurrent thunderclap headache that occurs during the postpartum period or while taking adrenergic or serotonergic drugs in more than half of all cases (41). Clinicians should perform vascular imaging examinations, such as CT angiography, magnetic resonance angiography, or transcranial Doppler ultrasonography when RCVS is suspected. Early and timely neuroimaging makes the diagnosis of PRES easier for physicians, while the misinterpretation of neuroimaging findings can lead to the suspicion of other diseases, such as cerebral infarction, paraneoplastic demyelinating disorder, or acute disseminated encephalomyelitis (14).

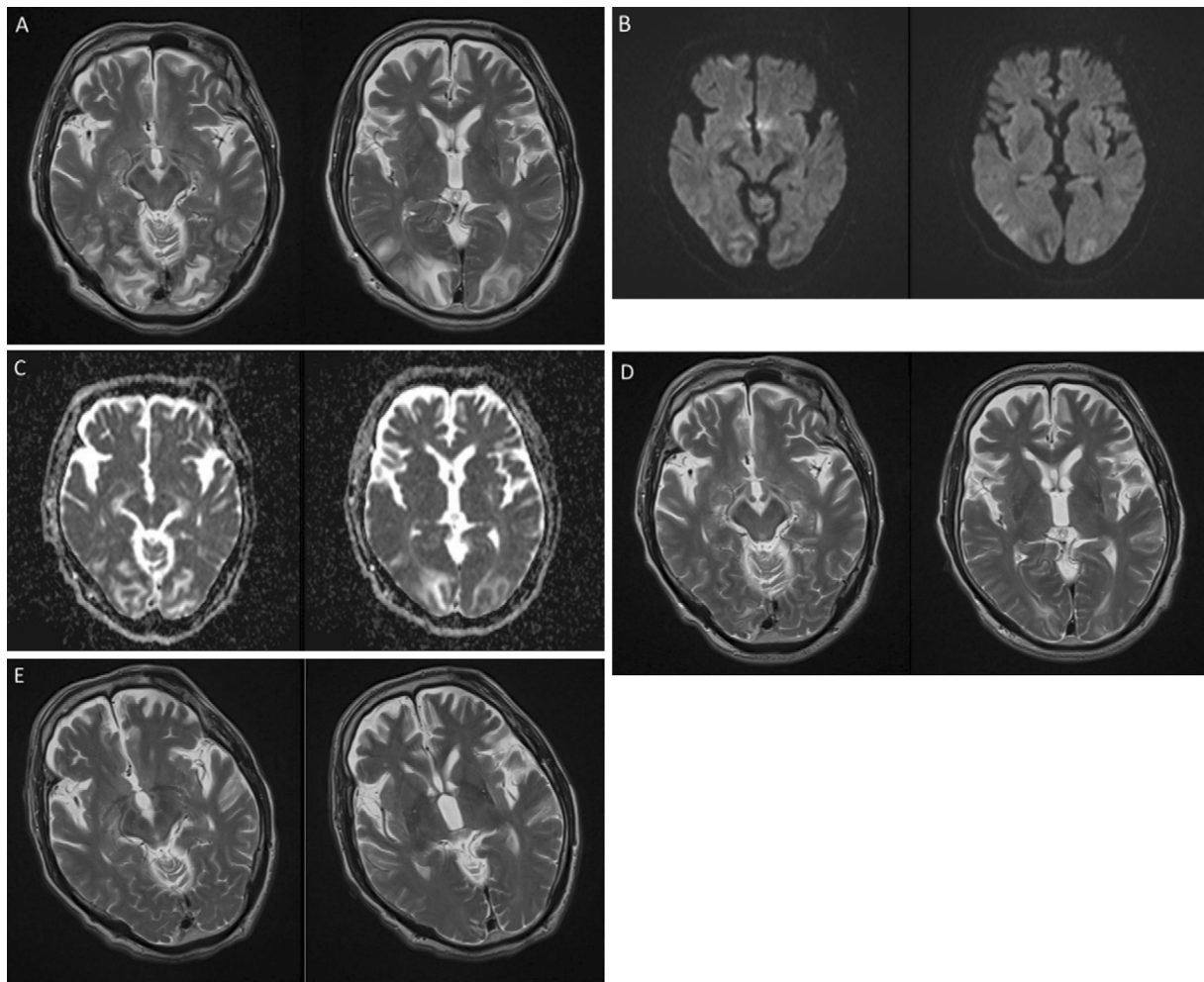


Figure. Brain magnetic resonance imaging (MRI) on the day of onset of posterior reversible encephalopathy syndrome. (A) T2-weighted image showing hyperintensity in the cortical and subcortical bilateral occipital-temporal lobes. (B, C) Diffusion-weighted image and apparent diffusion coefficient map demonstrating vasogenic edema. (D) T2-weighted brain MRI after 15 days, showing remarkable reduction in high signal intensity, and (E) MRI after 92 days, showing the complete resolution of abnormalities. A-E and its figure legend were reprinted from reference #13 with permission from Internal Medicine.

Treatment

There have been no randomized controlled trials on the management and treatment of PRES, because of its rarity and rapid manifestation. The primary objective in the treatment of PRES is to address the underlying cause, including blood pressure reduction, antiepileptics, or sedation, stopping or switching drugs, correction of electrolyte disturbances with hydration, and prompt delivery in pregnant women. In cases with acute hypertension, the patients should undergo gradual blood pressure reduction because the immediate normalization of blood pressure can lead to cerebral, coronary, and renal ischemia (42). Antiseizure drugs are frequently used, yet the drugs should be chosen in consideration of the patient's renal clearance and side effects. In pregnant women, magnesium sulfate is suitable for treating preeclampsia or eclampsia (37). It is crucial for cli-

nicians to frequently obtain neuroimaging data, not only for the assessment of the intervention but also for consideration of other causes. Although approximately 70% of patients with PRES require intensive care unit (ICU) care, most patients recover within 2 weeks (43).

In PRES cases with malignancy (36), ICU care is necessary. These patients require aggressive supportive clinical intervention (12), such as mechanical ventilation, transfusion of blood products for the reversal of coagulopathy, steroids for autoimmune disorders, intracranial pressure monitoring, cerebrospinal fluid drainage, and craniectomy.

Prognosis

It was reported that the prognosis in most PRES cases is reversible and favorable (12, 24, 35, 44, 45). However, the term 'reversible' is not always appropriate, because cases of irreversible PRES have also been reported (37, 46). Recur-

Table 2. Differential Diagnoses for Posterior Reversible Encephalopathy Syndrome.

Common
Primary or secondary headache
Cerebrovascular disease
ADEM
Toxic-metabolic encephalopathy
Eclampsia (during pregnancy)
RCVS
Less common
Status epilepticus
Malignancy (lymphoma, gliomatosis cerebri, metastatic disease)
Infectious, paraneoplastic, or autoimmune encephalitis
HELLP syndrome
Radiation necrosis
Osmotic demyelination syndrome
CADASIL
MELAS

ADEM: acute disseminated encephalomyelitis, RCVS: reversible cerebral vasoconstriction syndrome, HELLP syndrome: a syndrome during pregnancy characterized by hemolysis, elevated liver enzymes, and low platelet count, CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, MELAS: mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes

rent episodes are seen when patients have risk factors, such as sickle cell crisis, autoimmune conditions, hypertensive crisis, renal failure, and multiorgan failure (25, 35, 47). Legriell et al. (45) evaluated 70 cases of severe PRES, and reported that 11 patients (16%) died, 26 (37%) had marked functional impairments, and 33 (56%) had a good recovery. Patients with PRES and coexisting intracranial hemorrhage or cytotoxic edema have a worse prognosis (24, 44). Poor prognostic factors include autoimmune disease, infection, moderate or severe edema, mental alteration, altered coagulation, CRP elevation, high serum creatinine, uric acid, and LDH levels, and highest glycemia on day 1 (24). Meanwhile, preeclampsia or eclampsia are not related to a poor prognosis; rather, they are associated with a better outcome (24).

Recent Findings

Recent studies have suggested that arginine vasopressin hypersecretion leads to PRES. The arginine vasopressin receptor V1a is activated, resulting in cerebral vasoconstriction that induces endothelial dysfunction and cerebral ischemia (48). In addition, advances in imaging techniques, such as magnetic resonance spectroscopy or positron emission tomography, enable neuroimaging examinations to add more information (49). Other techniques, such as susceptibility-weighted imaging, improve the detection of hemorrhage, which is a predisposing factor for the prognosis. CT or MRI perfusion, as well as single-photon emission CT, are more useful to understand the cause of PRES. Marrone et al. (50) reported that restricted diffusion-weighted imaging is associ-

ated with high mortality in PRES patients.

Fang et al. (51) hypothesized that PRES in preeclampsia/eclampsia cases has a strong connection with hypomagnesemia. This hypothesis provides a logical background for why magnesium sulfate should be supplied for patients with (pre)eclampsia-related PRES.

Future Perspectives

PRES is a rare condition that is usually reversible, but which can result in persistent neurological deficits or death. The most problematic point when encountering PRES is that no diagnostic criteria or algorithms have been officially established. Use of the PEWS system or neuroimaging techniques can be helpful for the diagnosis of PRES. The contradictions in the etiology should be resolved, as a better understanding of the etiology may lead to more effective treatment. The next steps should be the establishment of validated diagnostic criteria for PRES, and the establishment of a case registration system that includes detailed clinical information and neuroimaging findings, with a view to achieving a good prognosis.

Conclusion

Although the etiology and pathology concerning the development of PRES remain uncertain, patients with PRES usually have a good prognosis. Early detection and interventions, such as treatment of hypertension or withdrawal of cytotoxic drugs are the key to achieving a favorable clinical outcome. Because there are no diagnostic criteria, frequent neuroimaging examinations combined with careful monitoring to distinguish PRES from other differential diagnoses can provide clues for the diagnosis.

The authors state that they have no Conflict of Interest (COI).

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