Posterior Reversible Encephalopathy Syndrome

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Abstract:
Introduction - Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiologic entity occurring in varied clinical setting and characterized by headaches, confusion, visual disturbances, seizures, and posterior transient changes on neuroimaging. The radiological features are often reported as demyelination which confounds the diagnosis.

Observations - Of the 14 patients included for the study, 13 (93 percent) were females. The common symptom being Headache in 13 (93 percent), Seizure in 10 (71 percent), Visual disturbance in 7 (50 percent), altered sensorium in 7 (50 percent) and hypertension in 11 (78 percent). On MRI the sites involved were Occipital 13 (92 percent), Parietal 9 (64 percent), frontal 4 (28 percent), temporal 2 (14 percent), deep nuclei 2 (14 percent), cerebellum 1 (7 percent) and brain stem 1 (7 percent). The symptoms were reversible in 12 (86 percent) patients, the remaining 2 (14 percent) had complications of PRES with 1 (7 percent) having right occipital infarct and 1 (7 percent) right parietal hemorrhagic transformation.

Discussion - Acute rise in blood pressure is one of the factors in the pathogenesis of PRES, degree of raise in blood pressure doesn’t correlate with the clinical severity or radiological manifestations. Pathophysiology of PRES remains controversial with two main hypotheses contradicting each other. One being impaired cerebral autoregulation leading to increased cerebral blood flow (CBF) as noticed in severe hypertension, whereas the other postulate is endothelial dysfunction with cerebral hypoperfusion as in cases with normal blood pressure or on cytotoxic therapy. The common final outcome in both is alteration in cerebral perfusion with blood brain barrier dysfunction causing vasogenic cerebral edema. The common etiology of PRES in this study was eclampsia, autoimmune disease, renal disease and other causes.

Conclusion - PRES can manifest with atypical features like normal blood pressure, presence of MRI evidence of infarct or hemorrhage. Clinical suspicion in appropriate setting will lead to early diagnosis and appropriate therapeutic intervention. Reversibility of
the clinical and radiological abnormalities is contingent on early treatment. On the contrary when unrecognized, conversion to irreversible cytotoxic edema may occur.

**Keyword**: Encephalopathy, Eclampsia, Hypertension, PRES, atypical PRES

**Introduction**: Acute neurological manifestations may be due to various causes. Among them reversible conditions like Posterior reversible encephalopathy syndrome (PRES) requires prompt identification and early intervention to ensure reversibility.

The term describes a potentially reversible imaging appearance and symptomatology that is shared by a diverse array of causes, including hypertension, eclampsia and preeclampsia, systemic lupus erythematosus, various causes of renal failure and use of immunosuppressive drugs etc. (1–10). Given the multitude of potential offending conditions, some authors suggest that rather than concentrating on new causes of PRES, the focus should be on atypical and potentially misleading imaging findings and common pathophysiology (11). The mechanism is not entirely understood but is thought to be related to a hyperperfusion state, with blood–brain barrier breakthrough, extravasation of fluid potentially containing blood or macromolecules, and resulting cortical or subcortical edema (12–14). Alternatively, others have proposed that vasospasm may precipitate the reversible edema, leading to cytotoxic edema if left untreated [15, 16]. The typical imaging findings of PRES are most apparent as hyperintensity on FLAIR images in the Parietooccipital and Posterior frontal cortical and subcortical white matter; less commonly, the brainstem, basal ganglia, and cerebellum are involved (8, 9). Atypical Imaging appearances include contrast enhancement, haemorrhage, and restricted diffusion on MRI (1–7, 10).

**Materials and Methods**: Retrospective analysis of clinical, radiological and response to treatment of 14 patients of PRES at Government Stanley hospital, Chennai.

**Results**: 13 (93%) females and 1 (7%) male. Of them 6 (42%) patients were pregnancy associated PRES and rest 8 (58%) were due to non pregnancy related etiology. In the non pregnancy associated PRES there were 7 (88%) females and 1 (12%) male patients. Among them the most common symptom was Headache in 13 (93%), only 1 patient did not have headache. All 6 pregnancy associated PRES were preceded by headache by 2 hours to 14 days prior to diagnosis. Among the others with PRES headache preceded 1 to 14 days prior to diagnosis. Seizure is the other most common symptomatology of PRES with 10 (71%) of 14 patients, of them 4 (67%) of 6 patients with pregnancy associated PRES and 6 (75%) of 8 patients with non pregnancy related PRES. Visual disturbance was present in symptom in 7 (50%) of 14 patients in 3 (50%) of 6 patients in pregnancy associated PRES and 4 (50%) of 8 patients in non pregnancy associated PRES. The common visual disturbance was, transient blurring, transient blindness and transient hemi-field deficit. One patient had persistent left hemianopia – secondary to infarct in right occipital lobe secondary to PRES. In addition to the above symptoms there is variable degree and duration of altered sensorium in these patients. Mostly which is reversible unless there is a secondary complication of PRES like infarcts, hemorrhage or rarely herniation. On examination hypertension was detected in 11 (78%) of 14 patients. Among them 4 (67%) of 6
patients with pregnancy associated PRES and 7 (88%) of 8 patients with non pregnancy associated PRES. In the patients with pregnancy, 3 had transient rise in blood pressure which normalized following delivery. In patients without pregnancy Hypertension was transient in 2 patients (25%) they were diagnosed to have transient hypertension in post infectious glomerulonephritis and transient hypertension in the setting of GBS. the patient with GBS had acute kidney injury - the cause of transient HTN was suspected to be probably due to acute kidney injury or probably due to dysautonomia in GBS. Among patients who had persistent hypertension, 3 had primary hypertension, 2 had autoimmune disorders like - takayasus arteritis and polyarteritis nodosa. One patient with SLE and PRES did not have documented hypertension, though this patient had reversible nephritis, it was hypothesized that the patient probably would have had an undocumented transient rise in blood pressure prior to seeking medical attention. Among the radiological findings. All patients had radiological findings consistent with PRES. 5 (35%) of 14 patients had grey matter involvement, all of them with grey matter involvement were in the non pregnancy associated PRES. The common site of involvement in decreasing order of involvement was Occipital 13 (92%) > Parietal 9 (64%) >frontal 4 (28%) >temporal 2(14%) > deep nuclei 2(14%) > cerebellum 1(7%) = brain stem 1(7%). Among the radiological pattern of involvement, the MRI findings were present in asymmetrical pattern in 10 (71%) compared to 4 (29%) with symmetrical pattern, of the 10 patients with asymmetrical involvement almost 7 (70%) had bilateral involvement with involvement of one side more than the other and 3 (30 %) had unilateral MRI changes. The classical finding of MRI in PRES patients was facilitated diffusion on diffusion image (normal on diffusion and bright on ADC) Though PRES was previously perceived as completely reversible, later studies have contradicted the same. In this patient group 2(14%) patients had complications of PRES with 1 (7%) having a unilateral occipital infarct clinically had a residual deficit in the form of left hemianopia and 1 (7%) had a parietal hemorrhagic transformation with clinically residual left hemiparesis. These patients had radiological correlate with the presence of diffusion restriction (diffusion bright and ADC dark) on diffusion imaging and blooming on GRE sequence. Among the etiology of PRES - pregnancy complication in 6 (43%), autoimmune disease in 4 (29%), primary hypertension in 3 (21%) and renal parenchyma disease in 1(7%). One patient had SLE and nephritis, in this patient the etiology of PRES could not be attributed to one specific reason however it was hypothesized it could be due to transient nephritis, however for statistical purpose this patient was included in the autoimmune group and not under renal parenchyma disease. In patients with pregnancy associated PRES, all were primigravida in the age group of 19 to 24 years. Among the 6 patients in total, 2 (33.3%) had pre eclampsia, 2(33.3%) had antipartum eclampsia and 2(33.3%) had post partum eclampsia.

**Discussion:**
Posterior reversible encephalopathy syndrome is a clinico-radiological syndrome characterized by seizures, impaired consciousness, visual disturbance, hypertension, seizures, nausea, vomiting and focal neurological signs and transient changes in neuroimaging in varying combination. In this study normal blood pressure in 23% of patients which is slightly more than seen with previous studies.
(20%) conducted by Hinchey et al (2). This highlights the importance of suspecting PRES even in the absence of Hypertension in appropriate clinical setting. Acute hypertensive emergency or high mean blood pressure is often observed was not significantly associated with the intensity of the clinical severity or radiological manifestations of PRES (23). The common site of involvement in decreasing order of involvement was Occipital 13 (92%) > Parietal 9 (64%) > frontal 4 (28%) > temporal 2 (14%) > deep nuclei 2 (14%) > cerebellum 1 (7%) > brain stem 1 (7%) was consistent with that noted in other studies. However asymmetry was noted in 71% of our patients MRI in contrast to predominant symmetrical involvement as reported in study (76%) by Hinchey et al (2) this variation could again be explained by the early case detection and MRI evaluation in our study which have picked the lesion at the early asymmetrical stage compared to later symmetrical pattern. Based on the finding that 43% of PRES are pregnancy associated as noted in this study, pregnant women having headache and one of the following - blurred vision, seizure or hypertension, should be considered to be having probably PRES and MRI brain should be done to look for MRI features and appropriate measures to treat the etiology of PRES. The complication rate noted in this study was 14%, which is less with that noted in study, 17% for hemorrhage and 17% for cytotoxic edema as reported by Alexander M. McKinney et al (1) this difference could be because of early suspicion (with in 4 to 36 hours of headache onset or seizure) and identification leading on to early therapeutic intervention to control blood pressure or remove the offending cause for PRES in our study. This syndrome is predominately reversible but however if the inciting etiology and hypertension are not controlled at the earliest, can lead to permanent neurological damage characterized by increased DWI signal and decreased ADC (17) and even death in up to 15% (18,19). Pathophysiology of PRES in patients with hypertension: The preferential distribution of white matter lesions in posterior brain regions is not well understood. Topographic variation in the cerebrovascular sympathetic innervation may be important. The blood vessels of the pia are supplied by sympathetic nerves from the superior cervical sympathetic ganglion. The density of sympathetic innervation is maximal in the internal carotid and anterior cerebral territories. It decreases posteriorly and is the least in the basilar artery and its branches. Importantly, the superficial vessels over the cortical surface respond to changes in blood pressure and function as a pressure equalization reservoir. Conversely, the penetrating vessels (medullary arteries), which arise from the superficial arteries, supply deep gray and white matter and receive scarce adrenergic innervation. Local metabolic products such as lactic acid and carbon dioxide affect the size and permeability of these perforating arteries. Sympathetic mediated vasoconstriction may be more effective in protecting the perforating small arterioles in the anterior circulation from over perfusion in acute hypertension (20). In a study conducted by Kazuma Nogawa et al., (21) MRI with contrast may show characteristic findings of sulcal hyperintensity and leptomeningeal enhancement in early preeclampsia that could precede the more classic clinical presentation.
, such as hypertension, proteinuria, brain edema, or seizure. Brain edema develops only secondary to elevated blood pressure. Limits of cerebral autoregulation pass beyond the normal levels of blood pressure and vasogenic edema occurs in posterior circulation areas, especially in the occipital lobes and watershed zones, which are relatively sparsely innervated by sympathetic nerves. Anterior watershed zones have been demonstrated to be rich in sympathetic innervation as compared to posterior circulation areas (22).

Pathophysiology of PRES in patients without hypertension:

Patients with normal to low blood pressure readings lesions predominantly occur secondary to endothelial injury; blood pressure elevations do not play a major role in pathogenesis. As a result of a failure of the blood-brain barrier, fluid leaks into the interstitium due to endothelial and causes interstitial edema (24). Distribution of lesions similar to one with hypertension occurs in the patients with PRES with outhypertension. However in a study by Steinborn M (24) et al., noted Symmetrical basal ganglion involvement is typical in these cases; thalamus, cerebellum, and brain stem involvement follow this. Occipital lobe and watershed zone involvement is not as prominent as they are in PRES cases with hypertension (24).

Pathophysiology of Complications of PRES: Cerebral Ischemia, Cerebral Haemorrhage and Cerebral herniation:

Ischemia following vasogenic edema may involve conversion to cytotoxic edema and may result from longer exposure to the initial source of injury. However the distinction between vasogenic and cytotoxic edema may be somewhat artificial, as both forms of edema probably co-exist in many conditions. Cytotoxic edema is defined as a pre-morbid cellular process characterized by induction of swelling of all cellular elements of the brain (neurons, glia, astrocytes, and endothelial cells). The swelling is indirectly related to ATP depletion with the failure of the ATP-dependent Na+/K+ channel and diffusion of extracellular water according to the osmotic gradient into the intracellular sector. Cells in both the white and the gray matter are affected, and swelling is more severe in the astrocytes than in the neurons. Compensatory mechanisms induce calcium overload and activation of proteases (cathepsin B, calpain, serine proteases), nucleases, and phospholipases (cytotoxic Ca2+- dependent phospholipase A2), leading to necrosis and apoptosis. These phenomena are potentiated by mitochondrial damage related to ATP depletion. Bleeding related to reperfusion injury is another potential complication of blood-brain-barrier dysfunction and cerebraledema. Oxidative stress with overproduction of reactive oxygen species (ROS) and oxidative damage to lipid membranes in the blood-brain-barrier causes vessels within ischemic foci to leak or rupture. Leukocyte trafficking with endothelial cell adhesion and activation leads to proteolysis of catenin, a component of the endothelial cell-cell junction. The resulting damage to microvascular endothelial cells causes edema and bleeding. Proteolysis by matrix metalloproteinases and proteases secreted by activated leukocytes may cause Mechanism of hemorrhage is presumed to arise from the phenomenon of breakthrough perfusion, in which the maximally constricted end arteries cannot further respond to hyperperfusion; this failed autoregulation leads to macromolecule extravasation and possibly hemorrhage into the cortex or subarachnoid space (1).
bleeding after reperfusion injury [1,25,26,27,28]. Cerebral herniation: Posterior edema, particularly when located in the cerebellum and brainstem, may cause transtentorial cerebral herniation (20). There have been various description of the the pattern of involvement of brain in PRES, although the pattern of involvement does not correlate with the outcome. In our study too the radiological pattern was consistent with the study of Legriel et al (20).

The radiological patterns of PRES (20)

1 Holohemispheric watershed pattern (Fig 1): A swath of confluent vasogenic edema extends through the frontal, parietal, and occipital lobes. Involvement of the temporal lobes is less marked. This topography matches the watershed zone between the anterior and posterior cerebral arteries, on the one hand, and the middle cerebral artery, on the other.

2) Superior frontal sulcus pattern (Fig 2): Patchy edema predominates in the frontal lobes along the superior frontal sulci. The parietal and occipital lobes are variably involved.

3) Dominant parietal-occipital pattern (Fig 3): In this pattern previously thought to be typical of PRES, the posterior part of the parietal and occipital lobes is predominantly involved. The edema varies in severity from mild to extensive.

4) Partial or asymmetric expression of the primary patterns (Fig 4): The above described 3 patterns are the primary patterns which are usually symmetrical, however in the 4th pattern of involvement, there is asymmetric expression of the above described pattern, usually with predominant one side involvement.

5) Deep grey matter involvement (Fig 5): Edema predominates in the deep grey matter nuclei - basal ganglia, thalamus and caudate are variably involved.

6) PRES with haemorrhagic transformation (Fig 6): Hemorrhage seen with in areas of vasogenic edema is a complication of uncontrolled PRES.

7) PRES with infarct / diffusion restriction: Transformation of vasogenic edema to cytotoxic edema & infarction is another complication of uncontrolled PRES
Fig 1: Holohemispheric watershed pattern
Fig 2: Superior frontal sulcus pattern
Fig 3: Parietal-occipital pattern
Fig 4: Asymmetric primary pattern
Fig 5: Deep grey matter involvement
Fig 6: PRES with hemorrhagic transformation

Recurrent PRES
Recurrent PRES has been anecdotally reported in severe hypertension and after allo-BMT. In a recent reported series, recurrent PRES was noted in 3 (3.8%) of 78 patients and was associated with sickle-cell disease with infection, allo-BMT with infection, or atypical autoimmune disease and possible viral infection. Recurrent eclampsia is well recognized with a reported incidence of 2% of live births. Management of PRES General measures - Patients with PRES require the symptomatic measures usually taken in the ICU. Although most patients have stable hemodynamics, catecholamines are required occasionally. The need for upper airway protection should be evaluated continuously in patients with marked consciousness impairment or seizure activity. If endotracheal intubation is performed, rapid-sequence induction with etomidate and succinylcholine can be used, provided there is no evidence of hyperkalemia. Propofol or thiopental are also good choices, since they have anticonvulsant effects. Neuromuscular blocking agents may transiently mask seizures. Hypoglycemia should be looked for routinely and corrected. If glucose is given, 100 mg of thiamine should be administered concomitantly, most notably when there is evidence of vitamin B1 deficiency. Patients should be routinely evaluated for hyperthermia and metabolic disturbances, in particular hypomagnesemia, which require prompt correction.

Seizure control - Antiepileptic treatment, appropriate for the electrical and clinical pattern in
the patient, should be initiated on an emergency basis and according to current guidelines. Patients with persistent seizure activity at ICU admission should be given intravenous benzodiazepines (lorazepam 4mg or diazepam 10 mg) either before ICU admission or in the ICU. The dose can be repeated up to three times if necessary. Patients with continuing seizure activity despite intravenous benzodiazepines should receive standard complementary intravenous anticonvulsant drugs (phenytoin 18 mg/kg, or equivalent dose of fosphenytoin, phenobarbital 10 to 15 mg/kg). Patients with refractory status epilepticus need midazolam, propofol, or thiopental in titrated doses until remission of the clinical seizure activity. When the EEG reveals electrical status epilepticus, these anesthetic drugs are given in titrated doses to induce EEG burst suppression then as a continuous infusion for at least 12 hours. Long term Antiepileptic medications are rarely required. If there is no preexisting seizure disorder AED can be withdrawn after the acute event is under control.

Control of hypertensive emergency - is an important part of the symptomatic management, if there is documented hypertension. The aim is not to normalize the blood pressure but rather to decrease the MAP by 20–25% within the first 2 hours and to bring the blood pressure down to 160/100 mmHg within the first 6 hours. More rapid blood pressure reduction is not recommended since it can aggravate the cerebral perfusion pressure alterations and promote ischemia. Intravenous antihypertensive drugs are necessary. Appropriate choices include labetolol, nicardipine, or fenoldopam. Correction of the underlying cause of PRES - An early etiologic diagnosis allows prompt correction of the cause of PRES. Patients may require blood pressure control, withdrawal of cancer chemotherapy or immunosuppressive agents, Cesarean section, dialysis, or other interventions. Prompt correction of the cause is crucial to decrease the risk of ischemia or bleeding and therefore to avoid permanent disability or death.

Conclusion:
PRES can manifest with atypical features like normal blood pressure, presence of MRI evidence of infarct or hemorrhage. A high index of clinical suspicion in appropriate setting will lead to early diagnosis and appropriate therapeutic intervention for better prognosis. Aetiology of the PRES if not associated with pregnancy should include search for renal disease, autoimmune disease and toxic agents. Reversibility of the clinical and radiological abnormalities is contingent on the prompt control of blood pressure and/or treatment of the offending cause. On the contrary when unrecognized, conversion to irreversible cytotoxic edema may occur occur and sometimes may lead to development of haemorrhage or herniation.

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