

Clinical and radiological spectrum of posterior reversible encephalopathy syndrome

Vikrant Kanagaraju¹, Divya Karuppanasamy², Maheshchander B¹, Devanand B¹

¹(Department of Radiodiagnosis, PSG Institute of Medical Sciences and Research, India)

²(Department of Ophthalmology, PSG Institute of Medical Sciences and Research, India)

Abstract:

Background and purpose: Posterior reversible encephalopathy syndrome (PRES) is characterized by headache, seizures, visual disturbances and altered mental status associated with typical neuroimaging findings of reversible vasogenic brain edema. The objectives of this study were to review the clinical and radiological findings of patients diagnosed with PRES.

Materials and methods: 31 patients with clinical and neuroimaging findings consistent with PRES were included in this retrospective study. Data on clinical presentation, peak blood pressures, risk factors precipitating PRES, location and severity of lesions on brain imaging, associated ischemia or hemorrhage were collected and analyzed.

Results: 24 patients (77.4%) were females and 7 (22.6%) were males. Mean age at presentation was 38±20 years. Hypertension was noted in 13 out of 31(42%) patients. Mean peak systolic and diastolic blood pressures were 136±23 and 88±13 mm of Hg respectively. The most common clinical presentation was seizures (74.2%), followed by headache (54.8%) and visual disturbances (41.9%). Eclampsia (17/31) was the most common precipitating factor identified. The parietooccipital lobes were the most commonly involved (96.8%) followed by the frontal lobes (32.2%) and the cerebellum (25.8%). 3 patients had associated acute focal ischemic lesions and 2 patients had intracranial hemorrhage. The severity of vasogenic edema in hypertensive patients was not significantly different from that of normotensives.

Conclusion: PRES has a wide clinical and radiologic spectrum and may also involve the anterior circulation structures. The severity of edema does not correlate with the blood pressure at toxicity.

Key words: Hypertensive encephalopathy, Leukoencephalopathy, Posterior reversible encephalopathy,

I. Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiologic entity characterized by headache, seizures, altered mental status and visual disturbances. Ever since its first description by Hinchey et al^[1], PRES has been reported to occur in diverse clinical scenarios like hypertension, eclampsia, post transplant status, cytotoxic medications, sepsis, auto immune diseases and multiple organ dysfunction.^[2,3] MR imaging is of great importance in the diagnosis of this clinically inhomogeneous syndrome, which typically shows bilateral signal-intensity alterations in cortical and subcortical regions of the posterior circulation, indicating vasogenic edema.^[4] The cause of neurotoxic syndrome and mechanism behind the PRES imaging appearance are still poorly defined. Impairment of cerebral autoregulation and endothelial dysfunction are the two most commonly proposed underlying mechanisms.^[5] Treatment of hypertension and withdrawal of causative agents are the mainstays of therapy in PRES.

The objectives of this study were to retrospectively review our series of patients with PRES for clinical associations and radiologic findings and compare with previous literature.

II. Materials and methods

This retrospective study was conducted from a tertiary health care centre in South India after approval from the local ethics committee. Magnetic resonance imaging (MRI) reports within the radiology information system database between December 2010 and December 2015 was searched for selection of patients retrospectively by using search terms such as “PRES”, “posterior reversible encephalopathy syndrome”, “reversible posterior leukoencephalopathy” and so forth.

Inclusion criteria were (1) Clinical history of acute neurologic change including headache, encephalopathy, seizure, visual disturbance or focal deficit and (2) Brain imaging features of otherwise unexplained focal or diffuse vasogenic edema consistent with PRES. Patients with edematous lesions in the brain secondary to ischemic, hemorrhagic, infectious, space occupying or inflammatory insult were excluded from the study. Hypertension was defined as a systolic blood pressure of 140 mm Hg or greater and/or a diastolic blood pressure of 90 mm Hg or greater.

The clinical inpatient and outpatient records of these patients were reviewed. Data on the age and gender of patients, peak systolic and diastolic blood pressure, clinical presentation, risk factors surrounding and leading up to the development of PRES, location of lesions on brain imaging, presence of associated ischemia or hemorrhage were collected and analyzed. The MR images were graded for extent and severity of cortex and white matter vasogenic edema, degree of confluence, mass effect and ventricular distortion on a scale from 1 to 5, developed by Bartynski et al.^[6] This was done independently by two radiologists blinded to patients' clinical profile. Differences in edema grade were agreed upon by consensus. Edema grade results for normotensives and hypertensives were separately averaged and compared.

III. Statistical analysis

Data are presented as mean and standard deviation or as frequency and percent. The software used for statistical analysis was SPSS version 19. Comparison between hypertensive and normotensive subsets was performed with student *t* test. A P value of less than 0.05 was considered to be statistically significant.

IV. Results

A total of 31 patients with PRES were included in this analysis. 24 patients (77.4%) were females and 7 (22.6%) were males. Mean age at presentation was 38±20 years (range-20-87 years). Hypertension was noted in 13 out of 31(42%) patients. Mean peak systolic and diastolic blood pressures were 136±23 and 88±13 mm of Hg respectively. The most common clinical presentation was seizures seen in 23 (74.2%) patients, followed by headache (54.8%, n=17) and visual disturbances (41.9%, n=13) in the form of cortical visual loss. 3 patients had presented with altered mental status and 2 patients had focal neurologic deficit in the form of weakness of limbs.

Among the predisposing risk factors eclampsia was the most common (17/31) followed by hypertension associated with chronic kidney disease (6/31). Other risk factors identified were sepsis, systemic lupus erythematosus, post liver transplantation state on tacrolimus therapy and Guillain-Barre syndrome. (Table 1)

The regions of brain most commonly involved (in order of frequency) were the parietooccipital, frontal lobes and the cerebellum. Less common areas of involvement included the temporal lobe, basal ganglia and the brainstem. (Table 2)

The MR images revealed hyperintensities on T2-weighted images and fluid attenuated inversion recovery (FLAIR) sequences in these regions. (Figures 1-5) Diffusion weighted imaging (DWI) showed high signal intensity with no areas of restricted diffusion while apparent diffusion coefficient (ADC) mapping did not show corresponding low signal intensity thus suggesting vasogenic edema. Of the cases studied, 25 patients had subcortical involvement while 10 had cortical involvement. 3 patients had associated acute focal ischemic lesions and 2 patients had intracranial hemorrhage.

The extent of vasogenic edema in patients with and without hypertension was compared and results summarized in Table 3. No statistically significant difference was noted in the severity of edema in both the groups (t=-0.361)

Follow up imaging revealed complete resolution of the abnormalities in 23 patients. In 6 patients repeat imaging was not performed but clinical recovery had been noted. 2 patients had died because of sepsis related complications.

V. Discussion

In this retrospective study of patients with PRES, we noted a female preponderance. PRES has been said to affect the young more frequently than the elderly and women more than the men. This can be due to the natural history of diseases that predispose people to PRES, many of which affect young women disproportionately, such as collagen vascular diseases or exclusively eclampsia.

In most patients of our series, the predisposing factors were those classically described namely eclampsia and hypertension. Although several theories have been proposed to explain the mechanism behind PRES, the most widely accepted theory states that sudden elevation of blood pressure causes failure of autoregulation in the cerebral blood vessels leading to hyperperfusion and breakdown of blood brain barrier which causes the fluid to leave the vessels and pass into the interstitial compartment.^[7] This hypothesis is further supported by the usual increase of water diffusion (higher ADC) seen in PRES.^[8] The posterior circulation is preferentially affected since it has less sympathetic innervation than the carotid circulation, thus rendering it less able to adjust to blood pressure fluctuations.^[9]

However this theory is not comprehensive because it does not explain the occurrence of PRES in normotensives and those with only mild blood pressure elevation as seen in our series where blood pressures were normal at toxicity in 58% of patients. Studies have shown that blood pressure is essentially normal at toxicity in 20-30% of patients who develop PRES.^[10, 11] Our observations could be because of predominance of patients with eclampsia (17/31) where endothelial dysfunction is the major triggering factor. The presence of

endothelial dysfunction decreases the threshold at which vasogenic edema occurs and also leads to systemic vasoconstriction, labile blood pressure and abnormal response to vasopressors. ^[12]

Endothelial dysfunction also leads to inflammatory cytokine production, activation of coagulation cascade and loss of fluid from the intravascular compartment. This explains the occurrence of PRES in conditions like sepsis and auto immune diseases like systemic lupus erythematosus. ^[5]

Regarding the clinical presentation, seizures was the presenting symptom in majority of the patients(74.2%), followed by headache (54.8%).We observed a higher prevalence of visual disturbances in our patients compared to studies elsewhere.^[6,13]This can be attributed to the fact that over half of our patients had eclampsia as the predisposing factor. We had earlier reported a higher prevalence of cortical visual loss in patients with late post partum eclampsia.^[14]Our observations are consistent with Liman et al who observed that visual disturbances are more common with eclampsia related PRES than PRES due to other etiologies. ^[15]They also noted major clinicroadiological differences between preeclampsia-eclampsia related PRES and patients with other PRES predisposing diseases. Preeclampsia-eclampsia related PRES was associated with less severe edematous lesions in the brain, lesser frequency of brainstem involvement or hemorrhage and better reversibility.

The parietooccipital regions were the most commonly involved (96.8%), followed by the frontal lobes (32.2%) and the cerebellum (25.8%).Our observations are in accordance with several other studies ^[6,13,16]thereby suggesting that PRES is not an entirely posterior phenomenon, but rather appears in a gradient- like fashion from posterior to anterior, presumably reflecting the gradient of sympathetic innervation.^[17] Thus the term “posterior” is controversial since vasogenic edema characteristic of PRES may also involve the anterior circulation structures like the frontal lobes. Involvement of cerebellum was noted in over a quarter of patients in our series. Fugate et al have noted a higher frequency of cerebellar involvement in patients with autoimmune disease and a higher frequency of cortical involvement in patients with sepsis or active infection. ^[13] However no such association was found in our series.

On comparing the edema grades for patients with and without hypertension, the difference between both groups was not significant .These observations are contrary to the findings of Bartynski et al who noted less vasogenic edema in severely hypertensive patients compared to normotensives in patients with PRES secondary to infection, sepsis and shock. ^[6] However their cohort of PRES patients had multiple other associated systemic risk factors. Also blood pressures can be labile and blood pressure at the time of MRI may not be necessarily representative of the initial insult since the findings on MRI may persist even days after the initial insult.

Out of the two patients who had associated hemorrhagic lesions, one had petechial hemorrhages in bilateral parietooccipital lobes and the other patient had subarachnoid hemorrhage. Frequency of intracranial hemorrhage associated with PRES has been reported to vary between 15% and 32%. ^[18, 19]Mechanisms postulated for the occurrence of hemorrhage in PRES include non aneurysmal subarachnoid (sulcal) hemorrhage due to rupture of pial blood vessels in the face of severe hypertension with impaired cerebral autoregulation and post ischemic reperfusion injury leading to multifocal brain hemorrhages. ^[20]

Radiologic and/ or clinical recovery was noted in most of our patients supporting the reversibility of this syndrome. However the disorder is not always benign and can be complicated by gliosis, infarction and hemorrhagic residua resulting in neurologic deficits, substantial morbidity and mortality. ^[21]

VI. Figures and tables

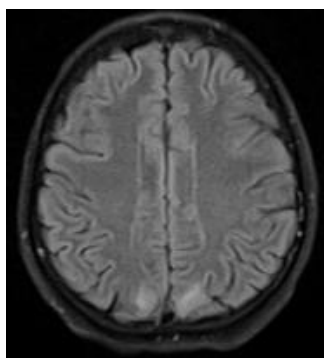


Fig 1: Axial MR imaging (FLAIR sequence) showing focal areas of vasogenic edema in bilateral occipital lobes consistent with grade 1 PRES.

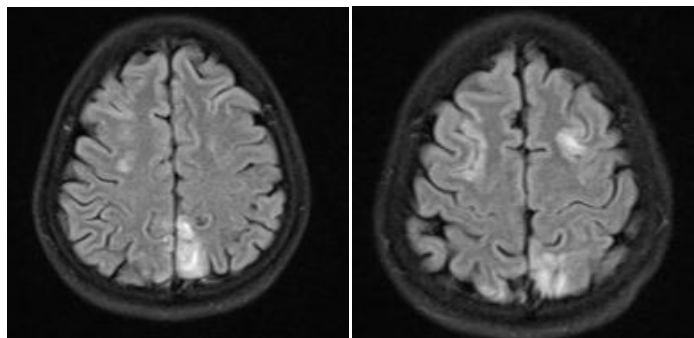


Fig 2 (A, B): Axial MR imaging (FLAIR sequence) showing vasogenic edema in bilateral frontal and parietal lobes with extension into the deep white matter judged grade 2 PRES.

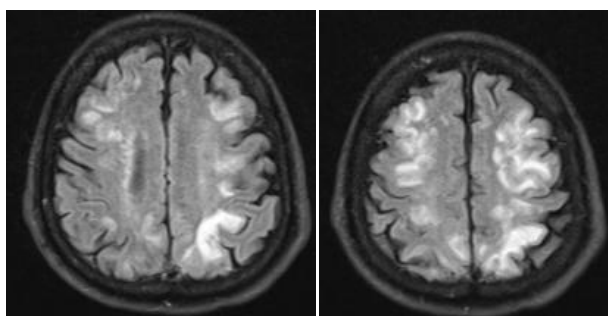


Fig 3 (A,B): Axial MR imaging (FLAIR sequence) showing vasogenic edema in bilateral fronto parietal lobes with extension to the ventricular surface and moderate local cortical mass effect suggesting grade 3 PRES.

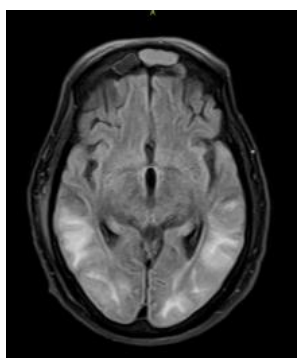


Fig 4: Axial MR imaging (FLAIR sequence) showing vasogenic edema in the temporal and occipital lobes bilaterally with substantial whitematter edema extending to the ventricular surface without ventricular distortion judged grade 4 PRES.

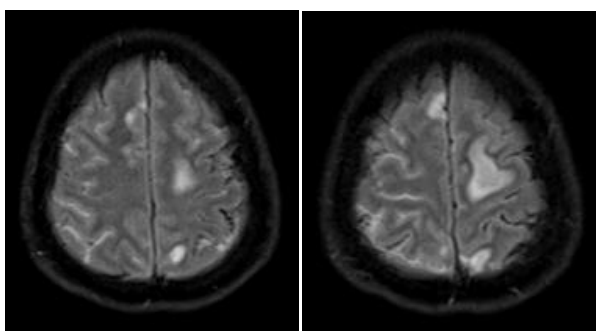


Fig 5 (A, B): Brain MR imaging (FLAIR sequence) demonstrates vasogenic edema in frontal and parietal lobes bilaterally with high signal intensity in the subarachnoid space suggesting subarachnoid hemorrhage

Table 1: Predisposing factors

	Number of patients (n=31)
Eclampsia	17
Hypertension with chronic kidney disease	6
Sepsis	4
Systemic lupus erythematosus	2
Post liver transplant on tacrolimus therapy	1
Guillain Barre syndrome	1

Table 2: Frequency of location of vasogenic edema in patients with PRES

Location	Number (%) of cases
Parietooccipital lobe	30 (96.8%)
Frontal lobe	10 (32.2%)
Cerebellum	8 (25.8%)
Temporal lobe	5 (16.1%)
Basal ganglia	3 (9.6%)
Brainstem	1 (3.2%)

Table 3: Vasogenic edema grade in patients with and without hypertension

Patients with PRES(n=31)	Vasogenic edema grade (no of patients)					Group average
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
Hypertensives (n=13)	5	4	2	1	1	2.15
Normotensives (n=18)	8	4	4	2	0	2

VII. Conclusion

This study has several limitations due to its retrospective design. The mean time from onset of symptoms to MR imaging during the acute phase was not uniform and this might influence the results. Follow up imaging was not performed in all patients and clinical data were obtained from the available medical records. Patients with minimal symptoms at presentation may have been missed. In depth analysis of clinical variables to draw statistically sound conclusions was precluded by our limited sample size.

To conclude, Posterior reversible encephalopathy or reversible posterior leukoencephalopathy syndrome has a varied clinical and radiologic spectrum. Majority of these patients show complete recovery. Although several hypothesis are proposed the exact mechanism behind the development of vasogenic edema and MR imaging appearance of PRES are still not clearly defined. Because of the diverse factors postulated to be responsible for PRES and the fact that PRES is not always benign, clinicians should be aware about the various risk factors, imaging abnormalities and atypical manifestations in PRES. Early recognition of the disorder and prompt management by control of blood pressure, removal of the offending medications or treatment of associated diseases is essential to prevent irreversible brain damage.

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