Original Article

Exploring the Spectrum: An Original Observational Study of Posterior Reversible Encephalopathy Syndrome from Tertiary Center in Kerala

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Abstract

Introduction: Posterior reversible encephalopathy syndrome (PRES) is a disorder of subcortical vasogenic edema causing reversible neurologic dysfunction which includes headache, altered sensorium, seizures, and visual disturbances. It is a relatively rare disease with a myriad of nonspecific symptoms with similar presentations to that seen in other diseases such as stroke and cortical venous thrombosis. Hence, accurate diagnosis is needed for early detection to guide the management of such patients. This is a single-center retrospective study from June 2022 to May 2024 to identify the demographic profile, etiologies, imaging features, and prognosis of patients diagnosed with PRES. **Materials and Methods:** Diagnosis of PRES was made on the basis of clinical history, neurological examination, and magnetic resonance imaging brain after ruling out other possible differential diagnoses. The patients who satisfied Fugate *et al*. criteria were included in the study. The data were collected from the hospital database. Patients with alternate diagnoses were excluded from the study. **Results:** There were 22 patients diagnosed with PRES. There were 20 (91%) females among the cohort. Eighteen (82%) patients had headache. Fourteen (64%) patients had seizures all of which were generalized tonic–clonic seizures. All had positive imaging findings with 2 patients having leptomeningeal enhancement in the presence of normal cerebrospinal fluid findings. Blood pressure (BP) was normal in 5 (22%) patients. Most of the patients were postpartum without a prior history of hypertension or preeclampsia. **Conclusion:** PRES is a reversible entity with the imaging findings primarily involving the posterior part of the brain. It can also involve anterior circulation and spinal cord. Normotensive PRES is possible and should not be overlooked if the patient has all features of PRES but has normal BP. It has a female predilection with the most vulnerable state being immediate postpartum. Although recurrence is possible, PRES does not require long-term medications. Complicated PRES presents with SAH and intracranial hemorrhage.

Keywords: Atypical posterior reversible encephalopathy syndrome, headache, intracranial hemorrhage, posterior reversible encephalopathy syndrome, reversible posterior leukoencephalopathy syndrome

Introduction

Posterior reversible encephalopathy syndrome (PRES) was described initially in 1996 by an American neurologist Judy Hinchey.[1] It is also known as reversible posterior cerebral edema syndrome, posterior leukoencephalopathy syndrome,[2] hyperperfusion encephalopathy,[3,4] and brain capillary leak syndrome.[5]

It is a clinicoradiological syndrome[6] with symptoms including headache, nausea, vomiting, seizures encephalopathy ranging from mild agitation and confusion to coma, and visual disturbances. Occasionally, field defects such as hemianopia may occur. Elevated blood pressure (BP) is seen in most of the cases.

Pathophysiology

Few hypotheses have been postulated as to the pathogenesis of PRES. The first hypothesis is that PRES is due to the failure of

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autoregulation of cerebral blood vessels in response to acute changes in BP. This leads to hyperperfusion injury leading to impaired blood–brain barrier and vasogenic edema.[7,8]

Cerebrovascular autoregulation is a protective mechanism to preserve a continuous cerebral blood flow irrespective of systemic BP fluctuations. There is vasodilatation during hypotensive episodes and vasoconstriction during hypertensive episodes. It usually operates between 50 and 150 mmHg.[9] Various triggers such as acute BP rise and dysautonomia causing rapid fluctuations in BP can overwhelm the autoregulatory mechanisms. Hence, a rapid increase of arterial BP which exceeds the upper autoregulatory limit leads to cerebral hyperperfusion. Increased cerebral perfusion pressure attributes to additional blood–brain barrier dysfunction causing extravasation of plasma and macromolecules through tight junction proteins.[7,8]

The posterior areas of the cerebral hemispheres seem to be particularly susceptible, hence the name posterior reversible encephalopathy. This may be explained by the reduced density of sympathetic innervation in the posterior circulation compared to the anterior circulation. However, this hypothesis does not explain PRES in patients who have normal BP and in those with involvement of other parts of the brain including anterior circulation.

The second hypothesis is that the syndrome is triggered by endothelial dysfunction caused by circulating toxins which could be endogenous or exogenous. This could explain PRES in patients with preeclampsia, sepsis, and chemotherapy including immunosuppressive agents. One of the main functions of the vascular endothelium in the blood–brain barrier is the preservation of vascular integrity by interendothelial adhesion molecules. These endogenous or exogenous toxins could trigger vascular leakage and edema formation and also lead to endothelial activation resulting in the release of immunogenic and vasoactive substances. These vasoactive substances cause increased vascular permeability and edema formation.[7]

Below is an image to explain the etiopathogenesis of PRES in brief [Figure 1].

The risk factors for PRES[8,10,11] include hypertension, pregnancy, postpartum, sepsis, dysautonomia state such as in Guillain–Barre syndrome, autoimmune diseases such as SLE, kidney diseases, drugs such as immunosuppressants – azathioprine and tacrolimus, and chemotherapeutic agents.

The diagnosis is obtained based on criteria based on the study by Fugate *et al*.[6] which is the presence of all three of the following: (1) Clinical history of acute neurologic change including headache, encephalopathy, seizure, visual disturbance, or focal deficit; (2) Brain imaging findings of focal vasogenic edema; and (3) Clinical or radiologic proof of reversibility. Although there are no specific criteria, imaging plays a vital role in the diagnosis of PRES. Magnetic resonance imaging (MRI) of the brain is more sensitive and specific

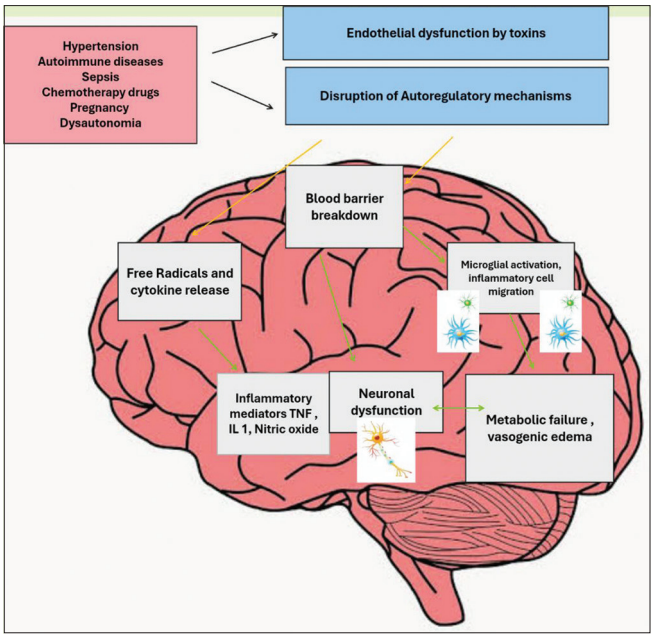

Figure 1: Image model explaining the probable etiopathogenesis of posterior reversible encephalopathy syndrome

than computed tomography (CT). The findings in MRI are hypointense T1, hyperintense in T2, and fluid-attenuated inversion recovery (FLAIR) sequences mainly in subcortical white matter with no true diffusion restriction. Gadolinium contrast enhancement may be patchy and leptomeningeal enhancement has also been reported in few cases. Susceptibility weighted imaging (SWI) is usually normal. If there is blooming and evidence of bleed, lesions in areas other than posterior cerebral regions, then the diagnosis of atypical/complicated PRES[8,22,23] can be made. MR angiography and MR venogram are normal – if abnormal suggests an alternate diagnosis.

The differential diagnosis is multiple as PRES has multiple nonspecific symptoms which include reversible cerebral vasoconstriction syndrome,[12,13] cortical venous thrombosis,[14] migraine with epilepsy,[15] hypertensive encephalopathy,[4] acute disseminated encephalomyelitis,[16] central nervous system vasculitis, and stroke.

Materials And Methods

This is a single-center retrospective cohort study from a tertiary care center in South India, Kerala. Data were obtained from electronic and physical medical records in our center. Diagnosis of PRES was made on the basis of clinical history, neurological examination, and MRI brain and after ruling out other possible differential diagnoses. Electroencephalogram (EEG) was performed in cases presenting with seizures. Cerebrospinal fluid (CSF) analysis was done in those cases, in which other differentials were considered. We analyzed the various etiologies, demographic profiles, and imaging characteristics of patients with PRES cases admitted to our hospital from June 2022 to May 2024 with age ≥18. Patients underwent standard care of management that includes BP

control, anti-seizure medications in case of seizures, and other supportive medications. Follow-up imaging was done in select cases 1–2 months after the initial diagnosis of PRES. The results were analyzed using SPSS Statistics software v.26 (IBM Inc, USA).

Results

We had 22 patients of whom 20 were female. Fourteen patients were postpartum females. The mean age was 33.95 years. The mean systolic BP (SBP) was 166 mmHg (range of 110–240 with standard deviation [SD] of 34) and diastolic BP (DBP) was 95 mmHg (range of 70–130 with SD of 16.8). BP was normal in 22% of patients (n = 5/22). Eighty-two percentage of patients had headaches (n = 18/22). Sixty-two percentage of patients had seizures (n = 14/22), altered mental status without seizures was present in 18% of patients (n = 4/22), and reduced vision in 18% of patients (n = 4/22) [Table 1]. The most common etiology was postpartum state without prior eclampsia/gestational hypertension [Table 2]. Three patients had coexisting eclampsia. All postpartum patients with the exception of two presented with seizures. The semiology was generalized tonic–clonic seizure in all patients. No patient presented with focal seizures or NCSE. The most common site of lesion found in MRI brain was T2 hyperintensity in the bilateral parieto-occipital region [Table 3]. Meningeal enhancement was seen in 9% of patients (n = 2/22). Both patients were postpartum with events occurring by 1st week of delivery. CSF of both patients was acellular with normal protein and sugar levels. Recurrence was seen in 4% of cases (n = 1). EEG was normal in all patients presenting with seizures except in two cases. One had mild intermittent theta range slowing and another patient with CKD/IgA nephropathy had occipital intermittent rhythmic delta activity. One patient had PRES presumed due to azathioprine/steroid intake as all other possible etiologies and differential diagnoses were ruled out. A male patient presenting with blurred vision and uncontrolled hypertension had T2 hyperintensities in the pons and cervical spinal cord which are atypical sites for PRES. Extensive workup for demyelination and vasculitis was negative and the lesions resolved after controlling BP [Figure 6]. Complicated PRES was in 9% (2/22) patients. Table 4 shows details of all twenty two patients.

MRI images of some of the cases diagnosed with PRES [Figures 2-8].

Discussion

This is a retrospective study from our center where we have treated patients with PRES with standard care of management. Treatment[10,17,24] included antihypertensives – nifedipine and IV nitroglycerin infusion; anti-seizure medications – levetiracetam and lorazepam; and antiedema medications – mannitol and hypertonic saline. After extensive Internet search, to our knowledge, this is the largest study in 2-year span with 22 patients diagnosed with PRES.[18] PRES has a favorable outcome with the MRI changes resolving after a few weeks.[19] All patients were tapered off the anti-seizure medications on subsequent 6-month follow-up. Those with renal failure or chronic hypertension were continued with antihypertensives.

Table 1: Distribution of various clinical presentations in posterior reversible encephalopathy syndrome

Clinical presentation	Number of cases (%)
Headache	18 (82)
Seizure	14 (64)
Visual disturbance	4 (18)
Altered mentation	4 (18)

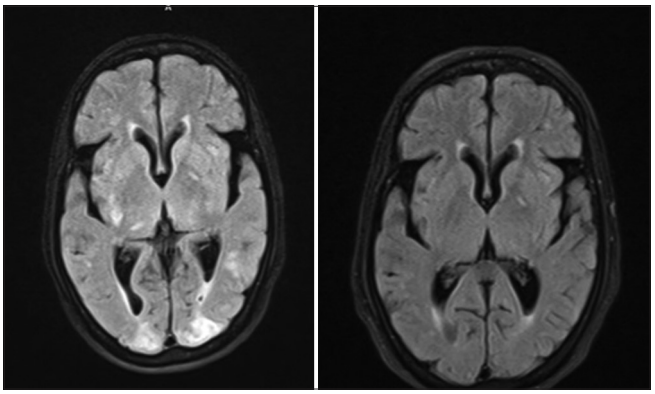

Figure 2: FLAIR Sequence showing left > right occipital hyperintensities and mild hyperintensity in right internal capsule area and follow-up imaging after 1 month shows resolution of lesions

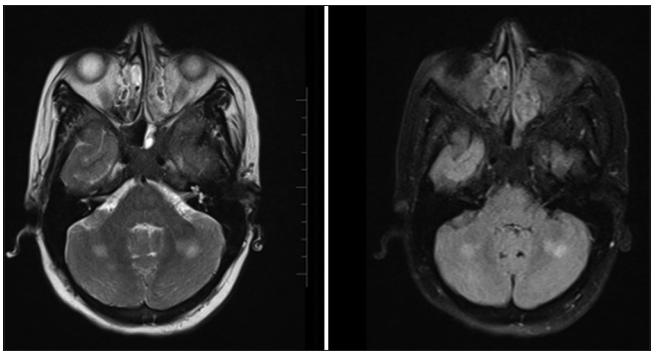

Figure 3: T2 and FLAIR sequences showing bilateral cerebellar hyperintensities

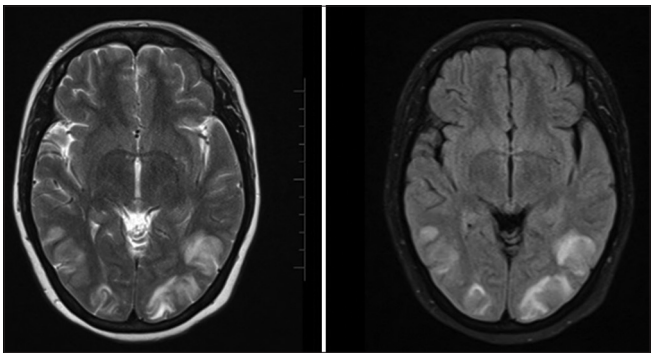

Figure 4: There are bilateral symmetrical T2 and FLAIR hyperintensities in the occipital region involving cortex and subcortex areas

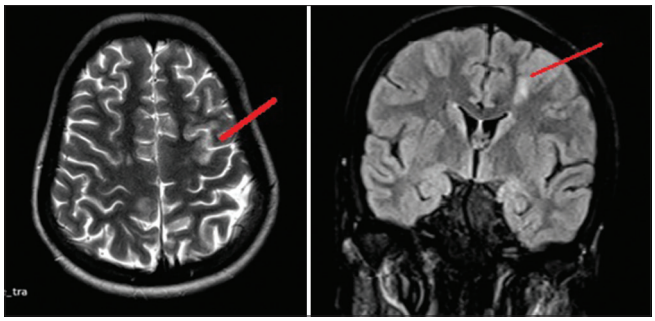

Figure 5: There is T2, FLAIR hyperintensity in left frontoparietal cortex

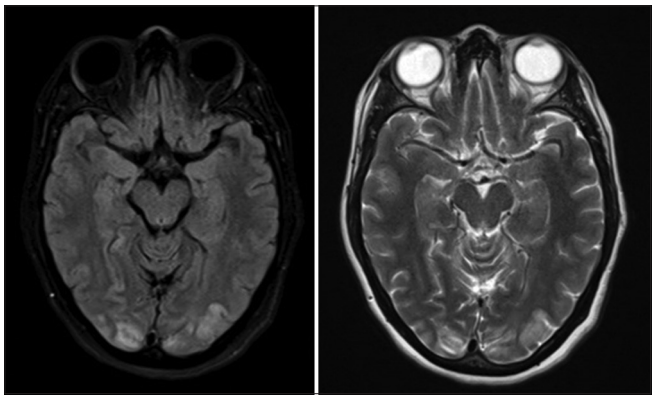

Figure 7: T2 and FLAIR hyperintensities in bilateral occipital regions

Similar to a case report by Vilas-Boas and Corte-Real,[20] one patient developed PRES while on azathioprine. Her BP recordings were normal during her previous admissions for inflammatory lesion in the cavernous sinus and were on prednisolone initially followed by the addition of azathioprine later. Patient presented with sudden-onset altered mental status, headache, and elevated BP of 200/110 mm Hg. Like a case report by Rouzi *et al*.,[21] one patient in our study had a recurrence of PRES. She was diagnosed with PRES in her second pregnancy in the postpartum period. She had a history of previous PRES in her first pregnancy. She was asymptomatic and not on any medications in between her pregnancies. Her BP remained stable throughout the period of pregnancy. Two patients in our study had complicated PRES.[22,23] One had intracranial hemorrhage with subarachnoid hemorrhage. Another patient had left temporal T2/FLAIR hyperintensity with blooming in SWI. Both patients had improved to normalcy within 3 months of follow-up. Although complicated PRES has a stormy course initially, it becomes reversible later. One male patient had an atypical site of involvement in the pons and spinal cord.[22,23,25,26] The usual MRI pattern is bilateral symmetrical T2/FLAIR hyperintensity of cortical and subcortical areas without diffusion restriction mainly in the occipital or parieto-occipital region.[24,25] There can be asymmetric lesions as well as in atypical[22] sites such as the spinal cord and brainstem. The second most common sites involved are frontal and cerebellar regions. Even though occipital regions are involved, only three patients had visual disturbance.[5]

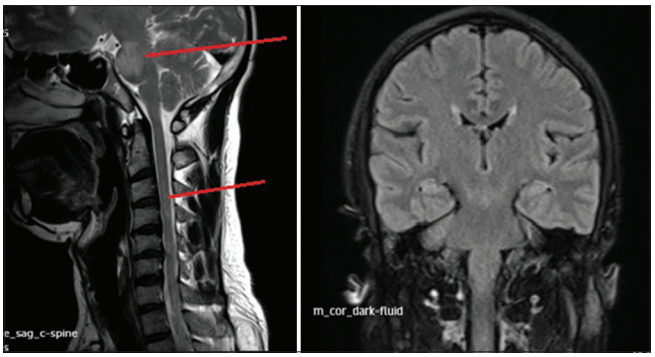

Figure 6: T2 Hyperintensities in pons, spinal cord in patient. Follow-up imaging on right, 2 months later after adequately controlling blood pressure showed resolution of the lesions

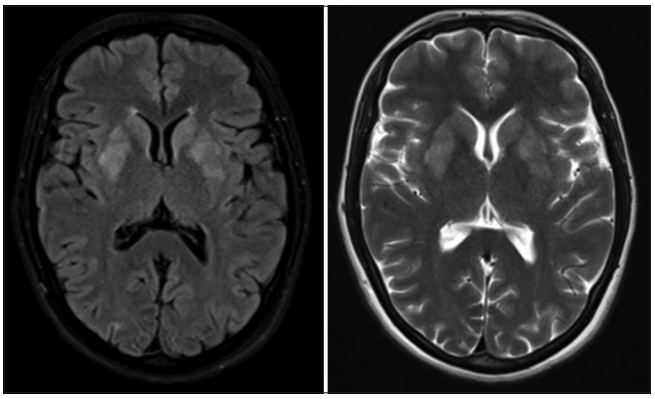

Figure 8: T2 and FLAIR hyperintensities in bilateral caudate and lentiform nuclei

Table 2: Etiologies of posterior reversible encephalopathy syndrome

Eriology	Number of cases
Postpartum	14
HTN	3
DM/new-onset HTN	1
Renal disease	2
GBS	1
Drugs	1

DM: Diabetes mellitus, HTN: Hypertension, GBS: Guillian–Barre syndrome

Table 3: Distribution of location of lesions in magnetic resonance imaging

Site of lesion	Number of cases, *n* (%)
Occipital	16 (73)
Parietal	13 (59)
Frontal	13 (59)
Brainstem	3 (13)
Thalamus	1 (4)
Basal ganglia	3 (13)
Spinal cord	1 (4)
Cerebellum	6 (27)

Table 4: Details of cases diagnosed with posterior reversible encephalopathy syndrome

Serial number	Sex	Age	SBP	DBP	Headache	Seizure	Comorbidities
Case 1	Female	19	130	80	Yes	Yes	Postpartum day 11
Case 2	Female	27	200	110	Yes	Yes	Postpartum day 8, eclampsia
Case 3	Female	43	180	100	0	Yes	GBS, schizophrenia
Case 4	Male	56	170	100	Yes	0	HTN
Case 5	Female	19	130	90	Yes	Yes	Postpartum day 5
Case 6	Male	38	240	120	0	0	Uncontrolled HTN
Case 7	Female	61	200	110	Yes	0	Present with altered mentation - azathioprine
Case 8	Female	19	130	70	Yes	Yes	Postpartum day 7
Case 9	Female	22	140	100	Yes	Yes	Eclampsia/postpartum day 2
Case 10	Female	36	130	70	Yes	Yes	Postpartum day 10
Case 11	Female	62	180	80	0	0	Present with altered mentation - DM
Case 12	Female	31	180	110	Yes	Yes	Postpartum day 7
Case 13	Female	32	170	100	Yes	Yes	Postpartum day 5
Case 14	Female	20	130	100	Yes	0	Postpartum day 5–15
Case 15	Female	24	160	80	Yes	Yes	Postpartum day 5, eclampsia
Case 16	Female	21	160	80	Yes	Yes	Postpartum day 6
Case 17	Female	30	110	70	Yes	Yes	Postpartum day 7
Case 18	Female	27	200	110	Yes	Yes	IgA nephropathy/CKD on HD
Case 19	Female	71	200	100	0	0	Present with altered mentation - HTN
Case 20	Female	21	130	80	Yes	Yes	Postpartum day 7
Case 21	Female	32	170	100	Yes	0	Postpartum day 10
Case 22	Female	36	210	130	Yes	0	CKD/IgA nephropathy

PRES: Posterior reversible encephalopathy syndrome. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, GBS: Guillain–Barre syndrome, HTN: Hypertension, CKD: Chronic kidney disease, IgA: Immunoglobulin A, DM: Diabetes mellitus, HD: Hemodialysis, MRI: Magnetic resonance imaging

Hypertension was defined as a SBP of ≥140 mm Hg or a DBP of ≥90 mm Hg.[27] Those patients who had normotensive PRES were all postpartum. MRI of those patients showed lesions in the occipital, parietal, and frontal areas. Renal failure/CKD/hypertension with PRES was seen in two patients with suspected IgA nephropathy suggesting autoimmune etiopathology.[28]

Limitations of our study were that this being retrospective in nature, it is prone to multiple biases such as recall and selection bias and also all other disadvantages of a retrospective study. Furthermore, our center does not handle oncology[29] patients and hence we have no experience and data regarding such cases, patients with solid organ/bone marrow transplants or those undergoing chemotherapy presenting with PRES. Another major limitation is the noninclusion of pediatric population.[30]

Conclusion

We have observed that PRES as the name suggests is reversible clinically and radiologically. From our study, we have found that all patients had favorable outcomes irrespective of site or the presence of hemorrhage. Imaging, especially an MRI brain in all patients with clinical history suggestive for PRES is essential. Our study confirms that PRES has female predilection. The most vulnerable group was postpartum women even when had no history of eclampsia/gestational hypertension. Complicated or atypical PRES and normotensive PRES are also possible. Treatment options are mainly symptomatic – controlling seizures, headache, and elevated BP. There are no specific drugs to prevent or treat PRES, but identification of the disease as early as possible and its management prevent further complications. However, till now, there are no imaging modalities or scoring systems or biomarkers to predict the severity, duration of illness in PRES, or its risk of recurrence. Further studies are needed in abovementioned aspects of PRES to provide better healthcare to all susceptible patients.

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Conflicts of interest

There are no conflicts of interest.

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