

Clinical, Etiological and Imaging Profile of Posterior Reversible Encephalopathy Syndrome: A Prospective and Follow-Up Study

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Abstract

Background: Although first described more than two decades ago, posterior reversible encephalopathy syndrome (PRES) continues to be enigmatic. We prospectively followed consecutive patients of PRES both clinically and radiologically for a better understanding of natural history, symptomatology, and prognosis of this not so uncommon entity. **Patients and Methods:** The current study included 22 consecutive patients of PRES who were followed both clinically as well as radiologically at a tertiary care institute in Northern India from December 2014 to June 2016. **Results:** Mean age was 30.68 ± 12.68 years. The most common symptoms included altered sensorium (77.3%), headache (72.7%), seizures (63.6%), vomiting (36.4%), and visual disturbances (22.7%). About 94.5% of patients had parieto-occipital signal changes on neuroimaging. Magnetic resonance imaging (MRI) ($n = 20$) revealed involvement of sites considered atypical for PRES in 95% (frontal [55%], temporal [40%], cerebellum [40%], basal ganglia [15%], deep white matter [10%] and brainstem [10%]). Diffusion restriction, haemorrhage, and contrast enhancement were seen in 30%, 22.2%, and 25% of patients. At 3 months follow-up, modified Rankin scale was 0 in 19 patients and 1 in 1 patient. Two (9.1%) patients died. Eight (36.4%) patients had eclampsia, 5 (22.7%) each had chronic kidney disease and essential hypertension whereas 2 (9.1%) each had immune-mediated disorders and drug-induced PRES. None of the clinical or imaging features predicted outcome in PRES. **Conclusion:** Atypical MRI presentations of PRES are common, and there is a need to keep a strong index of suspicion for the diagnosis of PRES. The prognosis of PRES is good, and most cases show excellent recovery, particularly if underlying etiology can be treated satisfactorily.

Keywords: Eclampsia, hypertension, posterior reversible encephalopathy, posterior reversible encephalopathy syndrome

INTRODUCTION

Ever since its first description by Hinchey *et al.*^[1] in 1996, many cases of posterior reversible encephalopathy syndrome (PRES) have been reported worldwide.^[2,3] Diagnosis of PRES is based on a constellation of clinical and radiological findings, the common clinical symptoms being altered consciousness, seizures, headaches as well as visual disturbances, and common radiological findings being reversible signal changes in the subcortical white matter areas of the brain. The common radiological changes on noncontrast computed tomography (CT) scan of brain include hypodense lesions in areas supplied by posterior cerebral circulation while magnetic resonance imaging (MRI) of brain often reveals areas of vasogenic edema as hypointense areas on the T1-weighted MR images and hyperintense areas on the T2-weighted/fluid-attenuated inversion recovery (FLAIR) MR sequences, with lack of diffusion restriction.^[2,3]

In spite of unique clinical presentation and a characteristic radiology, the uncommon occurrence and varied presentation of PRES can result in diagnostic difficulties resulting in unnecessary diagnostic and therapeutic interventions. Furthermore with increasing use of MRI in neurology, more and more atypical presentations of PRES are being recognized, knowledge of which is essential to correct diagnosis appropriate management. Furthermore, natural history of PRES has not been delineated in detail. Although conventionally thought to be reversible, recent studies have

suggested that this may not always be true with a reported mortality rate of 15%^[4,5] and a significant risk of subsequent neurological impairment.^[3-7]

Despite a well known entity for the past two decades, much of the information regarding PRES has come from poorly conducted prospective studies or retrospective data. In addition, there is remarkable lack of studies from Indian subcontinent.^[8] Thus, we planned to carry out this study for better understanding of prevalence, natural history, and prognosis of this not so uncommon disease entity.

Aim and objectives

1. To study etiological, clinical, and radiological profile as well as outcome of PRES in North Indian population

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- To evaluate association of various clinical and radiological parameters with final outcome in PRES.

PATIENTS AND METHODS

The current prospective longitudinal observational study was conducted at a tertiary care institute in Northern India from December 2014 to June 2016. During this period, we identified 22 consecutive patients with PRES who were included in the study. As we planned at least 3 month follow-up for each patient, recruitment of patients was limited to the first 15 months of the study period. The study was approved by Institutional Ethics Committee and written informed consent was obtained from all the patients before inclusion in the study. The inclusion criteria for the study are listed below:

- Age >14 years
- Variable combination of clinical manifestations suggestive of PRES: seizure activity, consciousness impairment, headaches, visual abnormalities, nausea/vomiting, and focal neurological signs
- Brain imaging consistent with diagnosis of PRES: Two neuro physicians and an experienced neuroradiologist should have a consensus that MRI signal abnormalities are consistent with PRES
- Clinical or radiological proof of reversibility (at least partial)
- Patients willing to give written informed consent.

Care was taken to exclude conditions which may mimic PRES, including but not limited to encephalitis, acute disseminated encephalomyelitis, central nervous system vasculitis, cerebral venous sinus thrombosis, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episode, Creutzfeldt Jacob disease and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, through relevant clinical and laboratory data.

Once enrolled, detailed history was obtained and thorough general physical, systemic and neurological examination was carried out. All the relevant clinical and radiological data were noted on a predesigned pro forma. Hypertension was diagnosed on the basis of Joint National Committee 8 criteria.^[9] All the patients underwent detailed laboratory testing, MRI brain as well as ophthalmological testing by a trained ophthalmologist. Visual evoked potentials (VEPs), fundus examination, visual field charting, electroencephalography (EEG), and cerebrospinal fluid (CSF) analysis were carried out whenever deemed necessary. Modified Rankin scale (MRS) scoring^[10] was used as an outcome measure for the degree of disability or dependence both at presentation and at 3 months follow-up.

Imaging studies were reviewed by an experienced neuroradiologist, and discrepancies were reviewed to come to a consensus. All patients underwent MRI imaging with T2 weighted, T2 FLAIR, T1-weighted, and diffusion-weighted imaging sequences. Additional sequences like contrast-enhanced T1-weighted and time-of-flight intracranial MR angiography, were done whenever deemed necessary.

A diagnosis of PRES was considered whenever typical imaging findings were seen as described by Bartynski and Boardmann:^[11]

- Dominant parieto-occipital (PO) pattern
- Holohemispheric watershed pattern
- Dominant superior frontal sulcus pattern
- Asymmetrical or partial expression (A/P) of the three primary patterns.

The imaging findings were also described according to their site, i.e., frontal, parietal, occipital, temporal, deep white matter, basal ganglia/thalami, brainstem, and cerebellum as well imaging characteristics.

Statistical analysis

Data were analyzed using IBM-Statistical Package for the Social Sciences, version 22 (Armonk, New York, IBM corp) and Microsoft excel build 14.07200.5000 32bit ©2010 Microsoft corporation. Continuous parametric variables, for example, age, blood pressure, pulse rate, complete biochemistry, complete hemogram, clinical symptoms with duration, etc., were analyzed by applying analysis of variance test, whereas skewed variables were analyzed using Mann–Whitney U test/Kruskal–Wallis H test.

Data were expressed in frequency, percentage, mean, median and standard deviation (SD) as per variability of data. Two-tailed $P \leq 0.05$ was considered statistically significant with 95% confidence interval.

RESULTS

Demographic features

Mean (\pm SD) age was 30.68 ± 12.68 years (range 15–68 years). Maximum patients ($n = 9$, 40.90%) were in the 3rd decade of age followed by five (22.72%) in the 4th decade. Thus, PRES is a disorder of young adults. Females ($n = 17$, 72.3%) dominated the study group.

Clinical features

In the current study, the most common presentation was encephalopathy ($n = 17$; 77.3%), followed by headache ($n = 16$; 72.7% [holocranial-10; occipitocervical-5; left hemicranial-1]), seizures ($n = 14$; 63.6% [generalized tonic-clonic in all; mean 1.428 seizures per person]), vomiting (36.4%), visual disturbances ($n = 5$; 22.7% [2-no perception of light; 3-blurring of vision with visual acuity more than 3/60]), hemiparesis (5.6%), facial palsy (5.6%), and dizziness (5.6%). Headache persisted for >2 weeks among 6 (27.7%) individuals. Two patients died during the study. At 3 months follow up ($n = 20$), all individuals were free from headache. All individuals with seizures received antiepileptic drugs and were seizure free without any recurrence at 3 months follow-up. Patients with absent light perception received five doses of intravenous methyl prednisolone (1 g daily) and recovered completely during the hospital stay. Remaining patients improved spontaneously with meticulous control of blood pressure. Hypertension was noted in 20 (90.9%)

patients. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) pressures were 173.09 mmHg and 99.18 mmHg whereas peak SBP and DBP were 250 mmHg and 134 mmHg, respectively. Six (27.3%) patients [patient number 6, 7, 13, 17, 19, 20 in Tables 1 and 2] needed mechanical ventilation. These results are summarized in Table 1.

Radiological features

Twenty-one (94.45%) patients had CT/MRI changes in the PO regions similar to the changes which are classically stated in the literature. The MRI findings ($n = 20$) are summarized in Table 2. The most striking feature noted in our study group was the predominance of involvement of atypical sites on MRI ($n = 19$; 95%), i.e., involvement of areas beyond the classically described posterior circulation territory. Atypical sites of signal changes included frontal ($n = 11$; 55%), temporal ($n = 8$; 40%), cerebellum ($n = 8$; 40%), basal ganglia ($n = 3$; 15%), deep white matter ($n = 2$; 10%), and brainstem ($n = 2$; 10%) [Figures 1 and 2].

Hemorrhage in posterior reversible encephalopathy syndrome

Five (22.72%) patients had hemorrhagic PRES. In all these patients, cerebral venous sinus thrombosis was ruled out by MR venography. During the follow-up period, there was resolution in the hematoma volume and all the patients were asymptomatic clinically. Admission blood pressure was recorded to be higher among individuals with hemorrhage compared to patients without hemorrhage (179.20/106.80 mm Hg versus 173.09/99.18 mm Hg, although this difference was statistically insignificant ($P = 0.6$) [Figures 1 and 2].

Diffusion restriction in posterior reversible encephalopathy syndrome ($n = 20$)

Six (30%) of patients had restricted diffusion on MR imaging. The sites included occipital and parietal regions ($n = 6$), cerebellum ($n = 3$), temporal/brain stem/basal ganglia ($n = 1$ each) [Figure 1].

Contrast enhancement ($n = 16$)

Four (25%) individuals had evidence of contrast enhancement. Four individuals did not undergo gadolinium enhanced evaluation primarily due to deranged renal function tests. The

sites of contrast enhancement included parietal regions ($n = 3$) followed by frontal ($n = 2$) and temporal ($n = 1$) regions.

Follow-up data

Two (9.1%) patients succumbed to their illness. One of these had bilateral renal masses suggestive of renal malignancy. She (patient 6 in tables) presented with altered sensorium and tachypnea and was diagnosed to have PRES with aspiration pneumonia and sepsis. She was managed in our intensive care unit and succumbed on day 2 of the illness. Another patient (patient 7 in tables) developed HELLP syndrome with multi-organ dysfunction and acute kidney injury in setting of eclampsia. She was managed in intensive care unit but succumbed on day 5 of illness secondary to ventilator associated pneumonia with sepsis and septicemic shock. On detailed analysis, we could not find any clinical or imaging parameter which could predict final outcome in PRES at presentation, though there was a trend between need for mechanical ventilation ($P = 0.065$) and poor outcome.

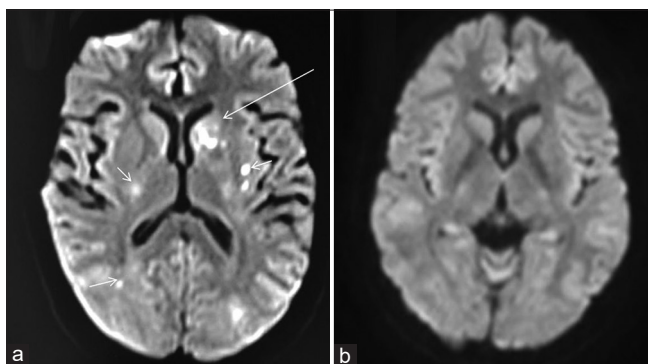


Figure 1: Diffusion restriction in a patient with posterior reversible encephalopathy syndrome (a) with resolution of signal changes (b) at follow up

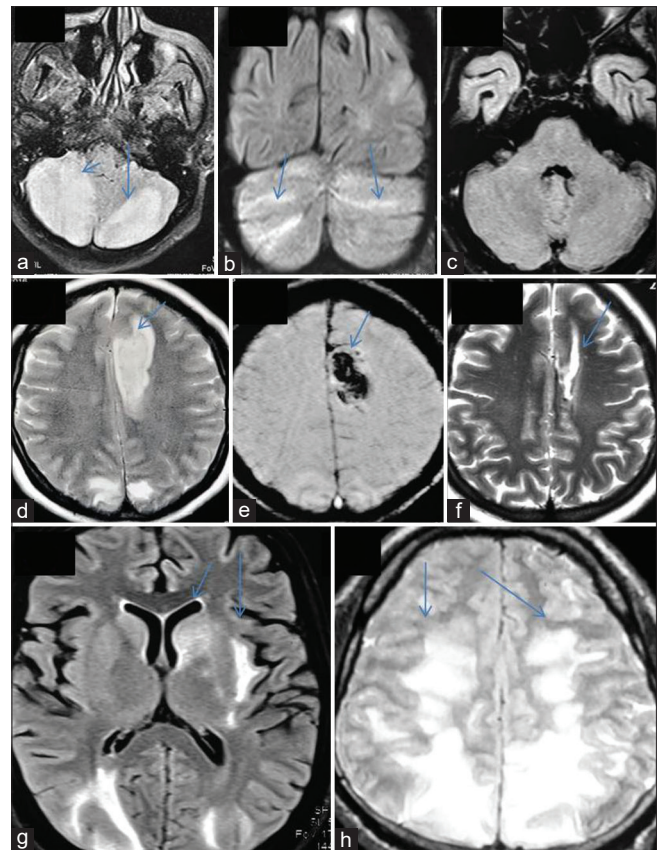


Figure 2: Some uncommon imaging findings in posterior reversible encephalopathy syndrome. fluid-attenuated inversion recovery images showing hyperintense signal changes in bilateral cerebellar hemispheres (a and b, blue arrows) followed by resolution at follow up (c). T2 weighted (d) and susceptibility weighted imaging (e) showing right sided frontal cortical and subcortical hemorrhage with signal changes which resolved leaving an gliotic scar at follow up imaging (f). (g and h): T2 weighted images showing left insular and basal ganglionic signal changes (g) and extensive subcortical white matter changes (h)

Table 1: Clinical features of the patients in the study group

Age (years)	Sex	Encephalopathy	Seizures	Head-ache	Visual disturbance	Vomiting	Other	Primary disease	Possible etiology for PRES
45	Female	+	+	-	-	-	-	Wegeners granulomatosis, pauci-immune glomerulonephritis	HT
34	Female	-	-	+	-	-	Right hemiparesis, right UMN CN VII	Essential hypertension	HT
60	Male	-	-	+	-	+	Vertigo	Chronic kidney disease stage 5, Hypertension	HT
68	Female	+	+	-	-	-	HT retinopathy	Essential hypertension	HT
27	Female	-	-	+	+	-	-	Essential hypertension	HT
31	Female	+	+	+	-	+	-	Renal lymphoma, chronic kidney disease Stage 5	HT
28	Female	+	+	+	-	-	-	Antepartum eclampsia, HELLP syndrome	HT
15	Male	+	+	+	+	+	HT retinopathy	Chronic kidney disease stage 5	HT
16	Female	+	+	-	-	+	-	Viral hepatitis, acute kidney injury	HT
32	Female	+	+	-	-	-	-	DRES syndrome (dapsone induced), ARDS	Drug induced
23	Female	+	+	+	+	+	-	Antepartum eclampsia	HT
25	Female	+	+	+	-	-	-	Antepartum eclampsia	HT
31	Male	+	-	+	-	-	-	Disseminated tuberculosis, Aspergillosis	Drug induced
25	Female	+	+	+	-	-	-	Postpartum eclampsia	HT
20	Male	-	-	+	+	+	-	Essential hypertension	HT
31	Female	+	-	-	-	-	-	Postpartum eclampsia	HT
30	Male	+	+	+	-	+	-	Organophosphate poisoning, acute kidney injury	HT
22	Female	+	+	+	-	-	HT retinopathy	Lupus nephritis class IV	HT
20	Female	+	+	+	-	-	-	Eclampsia	HT
35	Female	+	+	+	-	-	-	Eclampsia	HT
25	Female	-	-	+	+	-	HT retinopathy	Essential hypertension	HT
30	Female	+	-	-	-	+	-	Eclampsia	HT

CN=Cranial nerve, +=Present, -=Absent, HT=Hypertensive, PRES=Posterior reversible encephalopathy syndrome, ARDS=Adult respiratory distress syndrome, UMN=Upper motor neuron, HELLP=Hemolysis, elevated liver enzymes and low platelet counts, DRES=Drug rash with eosinophilia and systemic symptoms

All the remaining patients were followed up for a minimum of 3 months both clinically and by MRI. MRS score at admission was 5 in 16 patients, 4 in 2 patients, and 3 in 4 patients. At 3 months follow-up, MRS was 0 in 19 patients and 1 in 1 patient. Thus, all the patients were functionally independent at follow-up. Followup MRI at 3 months revealed complete resolution of signal abnormalities in 16 (80%) and partial resolution of signal abnormalities in four (20%) patients. All four individuals with partial resolution had hemorrhages. All these four patients are doing well during follow-up period.

Neuro-ophthalmological and other investigation findings

In the current study, all patients underwent ophthalmology evaluation at presentation and at follow-up. Fundus examination did not reveal disc edema in any patient. There were changes suggestive of hypertensive retinopathy in 4 (18.2%) patients. VEPs (Goggle) were done at presentation only in all five patients with visual disturbances. Both the patients without visual perception and one patient with visual disturbances had absent waveforms. At follow-up, flash VEPs were normal in all these patients. Bedside EEG was done in all patients with encephalopathy. However, it could be done

Table 2: Magnetic resonance imaging findings in the study group

Location of change	Hemorrhagic	Diffusion characteristic	IV contrast	MRA	Follow-up scan
P, O, F	Nil	Restricted	Not done	Not done	Resolved
P, O, F	Left frontal	Restricted	Enhancement over left frontal hematoma	Normal	Partially resolved
O, T	Right O-T	No restriction	Not done	Normal	Partially resolved
P, O, F	Nil	No restriction	Not done	Normal	Resolved
P, O, left CBLL	Nil	Restricted	Not done	Normal	Resolved
Not done (diagnosis made on basis of CT scan findings)	Nil	Not done	Not done	Not done	-
Not done (diagnosis made on basis of CT scan findings)	Nil	Not done	Not done	Not done	-
P, O, BS	Focal left temporal ICH	No restriction	Not done	Not done	Resolved
BG, T, DWM	Nil	No restriction	Not done	Not done	Resolved
P, O, F, CBLL	Nil	No restriction	B/L F, P, O	Normal	Resolved
P, O, T, F, CBLL, BS	Right P-T	Restricted	Enhancement over P-T hematoma	Normal	Partially resolved
P-O, CBLL, BG	Nil	No restriction	Not done	Normal	Resolved
B/L Temporal	Nil	No restriction	Not done	Normal	Resolved
P, O, F, T, CBLL	Sulcal SAH	No restriction	Not done	Normal	Resolved
P, O, F, CBLL	Nil	Restricted	Not done	Normal	Resolved
P, O	Nil	No restriction	Not done	Normal	Resolved
P, O, F	Left parietal	No restriction	Enhancement bilateral P-O	Not done	Partially resolved
P, O, CBLL	Nil	No restriction	Not done	Not done	Resolved
P, O, T, F	Nil	0	Not done	Not done	Resolved
P, O, T, F, CBLL	Nil	0	Normal	Normal	Resolved
P, O, F, CBLL, T	Nil	1	Normal	Not done	Resolved
P, O, T	Nil	0	Not done	Not done	Resolved

BG=Basal ganglia, BS=Brainstem, B/L=Bilateral, CBLL=Cerebellum, DWM: Deep white matter, F=Frontal, MRA=Magnetic resonance angiography, O=Occipital, P=Parietal, PO=Parieto-occipital, T=Temporal, SAH=Subarachnoid hemorrhage, CT=Computed tomography, IV: Intravenous, ICH=Intracerebral hemorrhage

in only seven patients during acute phase in whom it revealed diffuse slowing (theta-4; delta-3). Multifocal spikes were seen in three patients. None of the patients had evidence of electrical status. Follow-up EEG done at 3 months before tapering of antiepileptic drugs was normal in all ($n = 20$) patients. CSF examination done in three patients (number 9, 13, and 18) did not reveal any biochemical abnormality.

Etiology of posterior reversible encephalopathy syndrome ($n = 22$)

In the current study, eight (36.4%) patients had eclampsia, five (22.7%) had chronic kidney disease, five (22.7%) had essential hypertension and two each (9.1%) had immune mediated disorders and drug-induced PRES (one-dapsone; one-probably secondary to anti-tubercular/antifungal drugs).

DISCUSSION

Although PRES has been described approximately 20 years back, our knowledge about this entity continues to be plagued by lack of well conducted prospective studies with good follow-up. In the current study, we prospectively followed 22 patients of PRES with complete clinical, ophthalmological

and MRI data both at presentation and at 3 month follow-up to delineate its clinico-radiological profile and prognosis in a comprehensive manner.

Demographic profile and clinical features

The age and sex distribution in the present study was similar to that reported in several other studies.^[1,8,12] The main reason for female preponderance in current series is probably related to the fact that eclampsia accounted for 36.4% of all cases.

In the current series, the most common cause of PRES was eclampsia (36.4%) followed by hypertension and chronic kidney disease (22.7% each). Our findings are in direct agreement with three studies^[12-14] and in contrast to three studies who reported hypertension^[15] and dugs^[1,16] as the most common causes for PRES. The difference in etiologies in different series is likely related to differences in patient profile of various centers.

Regarding clinical features, though frequency of most of symptoms was similar to that reported previously,^[1,8] visual symptoms were reported less commonly in our series despite the fact that all patients underwent detailed evaluation by a trained neuro-ophthalmologist. The reason for this discrepancy

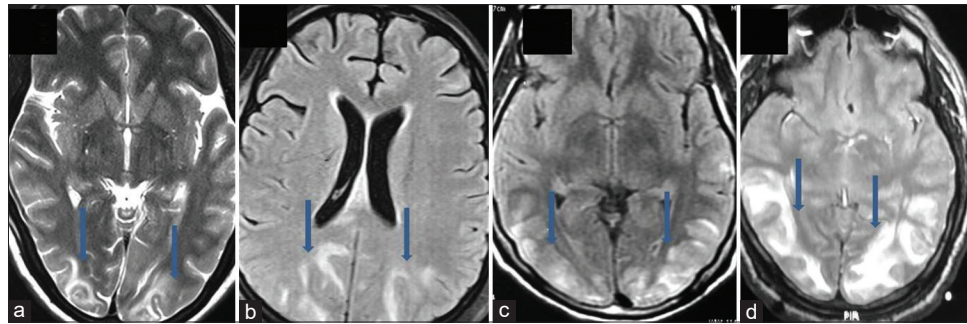


Figure 3: Typical sites of involvement in posterior reversible encephalopathy syndrome. Bilateral parieto-occipital lobe signal changes on T2 weighted (a and d) and fluid-attenuated inversion recovery images (b and c) in different patients

is not clear. One reason for this may be that many of our patients were in encephalopathy at time of initial evaluation and thus they did not report visual disturbances.

Neuroimaging findings

The frequency of involvement of commonest brain regions (parietal and occipital) [Figure 3] in current series was similar to those described previously.^[1,5,17] The involvement of atypical sites in present series was in accordance with several previously described studies.^[12,16,18] In addition to involvement of atypical sites, we also noted presence of hemorrhages, diffusion restriction and contrast enhancement on MRI, features which are considered atypical for PRES. Knowledge of atypical radiological presentations of PRES will help primary care physicians as well as neurologists in more accurate diagnosis and better management of PRES. The comparison of atypical neuroradiological findings in different series is shown in table three.

Outcome in posterior reversible encephalopathy syndrome

Mortality is uncommon in PRES. Our study reports a mortality rate of 9.09%. Two individuals succumbed to death on day 2 and day 5 of hospitalization, respectively. Hinchey *et al.*^[1] did not report mortality in his study group. Highest mortality was noted by Lee *et al.*,^[15] who reported mortality rate of 15.1%. Both our patients who died had serious underlying multisystem disorders. Among the remaining 20 patients who survived, all were functionally independent at 3 month follow-up with MRS score being 0 in 95%. Sufficient data were not available to compare this finding with those of other authors. Regarding radiological recovery, nearly 75% of patients in our series showed complete radiological recovery at 3 months follow up similar to previously reported series.^[1,15,16,18,19] We used intravenous methylprednisolone empirically in two patients who had absence of perception of light on ophthalmological examination. Both these patients recovered during the hospital stay. Steroids are known to benefit vasogenic edema and we used steroids in both the patients after ruling out infections and with meticulous attention to control of blood pressure. However, it should be noted that steroid use may be associated with PRES and thus future well conducted prospective studies are needed before their routine use can be recommended in PRES. On detailed analysis, we could not find any clinical

or imaging parameter which could predict final outcome at time of presentation. Our findings were in contrast to a meta-analysis done by Chen *et al.*,^[20] who reported presence of brain hemorrhage to be associated with poor and toxemia to pregnancy to be associated with good outcome in PRES (pooled odds ratio being 4.93 [95% confidence interval [CI]: 3.94–6.17; $P < 0.0001$] for hemorrhage and 0.24 [95% CI: 0.15–0.40; $P < 0.0001$] for toxemia of pregnancy, respectively). The main reason for this discrepancy is likely related to small sample size of our study and the fact that most of patients showed good outcome in our cohort.

CONCLUSION

The present study has given important insights into clinico-radiological profile of PRES. Atypical MRI presentations are common and there is a need to keep a strong index of suspicion for diagnosis of PRES in appropriate clinical settings. With a mortality of <10%, we reaffirm the fact that, a catastrophic presentation of PRES does not foster a sinister outcome. In the absence of severe systemic disease and multiorgan dysfunction, we noted the outcome of PRES to be excellent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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