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General Medicine

STUDY OF ETIOLOGY AND CLINICAL MANIFESTATIONS OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME IN TERTIARY CARE HOSPITAL

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ABSTRACT **Background:** Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder. Even though PRES was first described over 20 years ago, our understanding of this entity is still limited due to lack of well-designed prospective studies with adequate follow-up. Hence the present study was undertaken to assess the clinical profile, etiologies and short-term outcome of patients with PRES. **Method:** A total 47 patients diagnosed with PRES were included in the study. History was taken, thorough physical, systemic, and neurological examination was done. Sign and symptoms, etiologies, laboratory data, and blood pressure levels were gathered. MRI brain was done, and radiological features were recorded. Patient's improvement of sign and symptoms was assessed at 3 months follow-up. Modified Rankin Scale (mRS) was used to assess the outcomes. **Results:** The commonest age group affected was between 21–30 years (59.6%) with female predominance (80.85%). Headache (87.2%), hemiparesis (12.8%) and pregnancy induced hypertension (70.21%) was the commonest symptom, sign, and aetiology of PRES respectively. On examination papillodema was seen in 19.14%. Commonest lobes involved in PRES was occipito-parietal (87.2%). Vasogenic edema was seen in all the patients. Symmetrical lesion on imaging was in 85.1%. Almost all patients had subcortical white matter changes (91.5%). Diffusion restriction was seen in 19.1%, irreversible complication (visual defects) in 2 and recurrent of PRES in 2 patients. 3 patients died and 44 were survived, of which 5 found to have slight disability. **Conclusion:** A thorough knowledge of PRES and high index of clinical suspicion in appropriate situations, together with radiological correlation, will aid in the early detection and treatment of PRES, reducing the risk of serious consequences.

KEYWORDS : Posterior reversible encephalopathy syndrome; Neurological; MRI brain; Modified Rankin Scale; Papillodema; Occipito-parietal; Vasogenic edema

INTRODUCTION

Hinchey and co-workers in 1996 first described a clinico-radiologic entity [1], in which patients presented with a symptom complex of sudden onset headache, altered sensorium, visual symptoms and seizures that, was later termed as Posterior Reversible Encephalopathy Syndrome (PRES) [2,3]. Though the term PRES denotes reversible encephalopathy, irreversible neurologic deficit occurs if prompt identification of the disease and early appropriate intervention is not done. PRES is often—but by no means always—associated with acute hypertension [4]. Clinically, PRES is characterized by headaches, seizures, reduced consciousness, visual and other focal neurological symptoms [5].

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. Key elements that are essential in its diagnosis include a combination of clinical features, radiological findings in the presence PRES of various risk factors. The neuroimaging has a major role in the diagnosis of this entity [6, 7]. Its recognition has improved markedly over the last few decades with increased availability of magnetic resonance imaging (MRI) [6]. MRI is the best exam to diagnose PRES although CT is also useful. 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 [8].

Although, etiological diagnosis of PRES should be identified early to allow prompt correction of the cause precipitating PRES. Blood pressure reduction, withdrawal of offending drug, termination of pregnancy – caesarean section, dialysis etc., may be required. Prompt treatment of the cause prevents irreversible complications and death. 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. Thus, we planned to carry out present study for better understanding of prevalence, natural history, and prognosis of this not so uncommon disease entity.

MATERIAL AND METHODS

After obtaining Institutional Ethical Committee approval and written informed consent from all the patients, this hospital based prospective longitudinal observational study was conducted in the Department of Medicine at Tertiary Care Teaching Hospital during a period from May 2019 to December 2021. All the patients with a clinical suspicion and radiological diagnosis of PRES admitted/referred to the Emergency department/Medicine department, were included in the study. During the study period, we identified 47 consecutive patients with PRES. Record review was done for the year 2017 and 2018 which showed average 30-35 patients were diagnosed as PRES. All diagnosis nosed patients had a clinical presentations and neuroimaging abnormalities consistent with PRES. Patients with subcortical white matter lesions other than PRES, infection– progressive multifocal leukoencephalopathy, vascular– posterior circulation stroke/ superior sagittal sinus thrombosis, neoplasms– gliomatosis cerebri, lymphoma, glioma, demyelination- acute disseminated encephalomyelitis, multiple sclerosis, dysmyelination- leukodystrophies like metachromatic leukodystrophy, severe hypoglycemia and hypotension were excluded from the study.

Following enrolment, a full medical history was acquired, and thorough general physical, systemic, and neurological examination was carried out. All available clinical records were screened for data known or suspected to be related to the development of PRES. Demographic details, neurological symptoms at the time of initial clinical presentation of PRES, predisposing disease/any precipitating factors, underlying diseases, laboratory data, and blood pressure levels at the time of onset of PRES related symptoms were gathered. Furthermore, laboratory parameters i.e., Heamoglobin, platelets, creatinine, Sr Bilirubin etc were acquired from available clinical records within a maximum range of 3 days from initial onset of PRES symptoms. Hypertension was diagnosed based on the criteria of Joint National Committee 8 (JNC 8) [9]. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the time of onset of PRES. Length of hospital stay and discharge status (home, inpatient rehabilitation/other hospital, and inhospital death) were acquired. Persistent neurological deficit if any was recorded. Ophthalmological testing performed by a trained ophthalmologist. Fundus examinations were carried out to screen the any retinal changes. The examination was done with the help of direct ophthalmoscope.

The MRI brain was done for all patients and the radiological features were recorded. In the study, FLAIR pictures, diffusion-weighted imaging sequences (DWI) containing ADC (apparent diffusion coefficient) map, T2 weighted sequences, and contrast-enhanced T1 weighted sequences were used as mode of diagnostic neuroimaging techniques. All patients underwent MRI imaging with T2 weighted, T2 FLAIR, T1-weighted, and diffusion weighted imaging sequences. Axial T1- and T2-weighted pictures were included in all the cases. The amount of edema and bleeding was determined using scans

(parenchymal hematoma, microbleeds, subarachnoid blood). The existence of cytotoxic edema components within the edematous areas was classified as either entirely vasogenic or as presence of cytotoxic edema components within the edematous areas.

The patient's improvement of sign and symptoms was assessed at 3 months follow-up examination. Repeat MRI was performed to assess the reversibility of lesion. Modified Rankin Scale (mRS) [10, 11] was used to assess the outcome in terms of disability, dependence for daily activities, recovered or death. Similarly, each surviving patient was interviewed for score determination based on modified Rankin Scale after 3 months follow up by trained physician.

Statistical Analysis

Data analysis was performed using SPSS (Statistical Package for Social Sciences) 20.0 software. Continuous data were described using measures of central tendency and dispersion. Categorical data were described using percentages. For normally distributed data, Independent Student t test, a parametric test was used to compare continuous variables between two groups whereas Mann– Whitney U test was used for skewed variables. A two-tailed p value <0.05 was considered statistically significant.

OBSERVATIONS AND RESULTS

A total of 47 consecutive patients with PRES were studied during the study period. Table 1 show the age and gender-wise distribution of PRES patients. PRES was common in females, with female: male ratio of 4:1. The commonest age group affected in both male and female was between 21–30 years with mean age of patient was 30.98±10.98 years.

Table 1: Age And Sex-wise Distribution Of Patients

Age group (Years)	Male	Female	Total	P value
≤20	00 (0.0%)	04 (10.5%)	04 (8.5%)	0.04
21-30	04 (44.4%)	24 (63.2%)	28 (59.6%)	
31-40	01 (11.1%)	07 (18.4%)	08 (17.0%)	
41-50	03 (33.3%)	01 (2.6%)	04 (8.5%)	
>50	01 (11.1%)	02 (5.3%)	03 (6.4%)	
Total	09 (100%)	38 (100%)	47 (100%)	-

Headache was the commonest symptom of PRES (87.2%) followed by seizures (70.2%) whereas hemiparesis (12.8%) was the most common sign of PRES as depicted in figure 1. Duration of headache ranged from ≤ 1 day up to 10 days, at the time of presentation to the hospital.

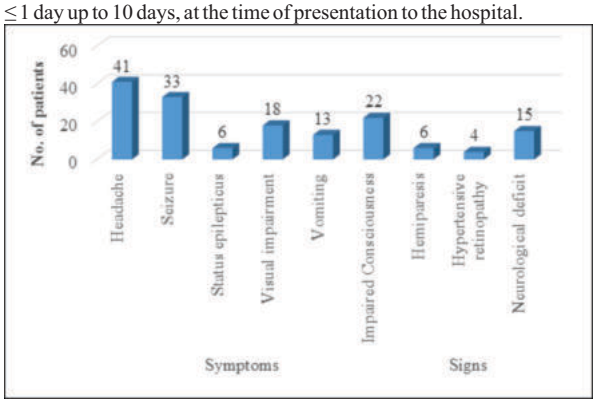

Figure 1: Signs And Symptoms Of PRES Patients (n=47)

The mean duration of onset of symptoms before presentation to the tertiary care centre was 3.06±2.67 days (Male: 2.56±1.87; Female 3.163±2.84). Study revealed only 19 (40.4%) patients of PRES had presented to the hospital within 24 hrs. Nine patients (19.1%) presented with symptoms within 48 hrs while 8 patients (17%) presented to the hospital within 72 hrs after onset of symptoms suspicion of PRES. Rest 11(23.4%) patients who were presented late after 72 hrs of onset of symptoms, (Table 2).

Table 2: Duration Of Sign And Symptoms Before Presentation To The Tertiary Care Hospital

Symptoms And Signs		Duration of symptoms (Hours)			P value
		Within 24 hrs (n=19)	24-72 hrs (n=17)	>72 hrs (n=11)	
Symptoms	Headache	18 (43.9%)	14 (34.1%)	09 (22%)	0.446
	Seizure	15 (45.5%)	10 (30.3%)	08 (24.2%)	0.411
	Status epilepticus	04 (66.7%)	01 (16.7%)	01 (16.7%)	0.0363
	Visual impairment	07 (38.9%)	07 (38.9%)	04 (22.2%)	0.954
	Impaired Consciousness	07 (31.8%)	08 (36.4%)	07 (31.8%)	0.366
Signs	Hemiparesis	02 (33.3%)	02 (33.3%)	02 (33.3%)	0.823
	Hypertensive retinopathy	01 (25%)	01 (25.0%)	02 (50.0%)	0.421
	ND <24 hrs (n=07)	03 (42.9%)	04 (57.1%)	00 (0.0%)	0.538
	ND >24 hrs (n=06)	02 (33.3%)	02 (33.3%)	02 (33.3%)	

Neurological deficit=ND

The commonest aetiology of PRES was pregnancy induced hypertension (PIH) followed by essential hypertension. Twenty-nine patients (61.7%) out of 47 cases were pregnancy related. All these patients were primigravida except one. Amongst the 29 patients, 14 (29.8%) had antepartum eclampsia, 10 (21.3%) had preeclampsia and 5 (10.6%) had postpartum eclampsia, (Figure 2).

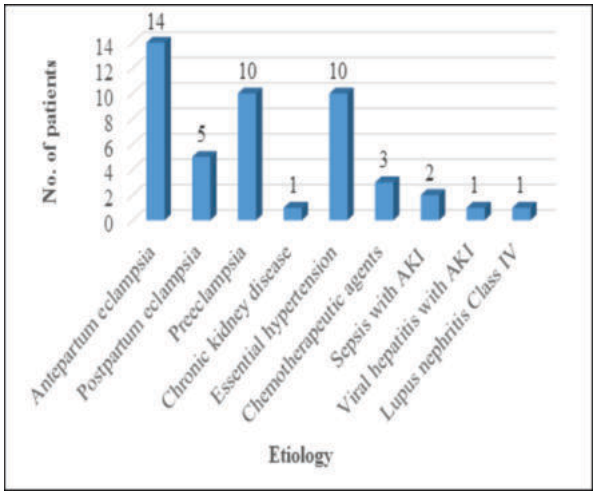

Figure 2: Etiology Of Posterior Reversible Encephalopathy Syndrome (n=47)

The mean SBP was observed to be 150.66±13.21 which was mainly attributed to PIH and essential hypertension. Laboratory examination revealed low haemoglobin (10.3±1.1 g/dl) among PRES patients, neutrophilic leukocytosis in a patients diagnosed with sepsis with AKI (2 Patients). Biochemical analysis revealed elevated serum creatinine. Liver function tests demonstrated an average alkaline phosphatase (ALP) of 128.32 IU/L among PRES patients as shown in table 3.

Table 3: Clinical And Laboratory Parameters

Parameters	Mean ± SD	
Clinical Parameters	Heart rate	98.1 ± 8.4
	Systolic Blood Pressure (mmHg)	150.66 ± 13.21
	Diastolic Blood Pressure (mmHg)	99.04 ± 10.14
Laboratory Parameters	Haemoglobin (gm/dl)	10.3 ± 1.1
	Total Leucocyte count	10.80 ± 2.07
	Platelets (lakh/µl)	2.09 ± 0.13
Biochemical analysis	Serum Creatinine (mg/dl)	1.52 ± 0.24
	Serum Sodium (mEq/lit)	135.48 ± 8.85
	Serum Potassium (mmol/lit)	3.44 ± 0.85
	Serum Chloride (mEq/lit)	101.36 ± 9.60
	Serum Bilirubin (mg/dl)	3.20 ± 1.00
Liver function tests	SGOT (U/L)	36.79 ± 6.92
	SGPT (U/L)	34.21 ± 4.49
	Alkaline phosphatase (IU/L)	128.32 ± 10.64

There was statistically significant difference between mean SBP, DBP and mean TLC among hypertensive patients and the individuals with underlying morbidities (p <0.05). SGOT and SGPT level found to be significantly increased among individuals with other morbidity at presentation as shown in table 4.

Table 4: Comparison Of Clinical And Laboratory Parameters With Hypertension And PRES Associated Underlying Morbidity

Variables		Individuals with hypertension at presentation*(n=39)	Individuals with other morbidity at presentation (n=08)	P value
Clinical Parameters	SBP (mmHg)	153.79±12.26	135.14±2.87	0.000*
	DBP (mmHg)	101.92±8.39	85.00±4.62	0.000*
Laboratory Parameters	Haemoglobin (gm/dl)	10.34±1.15	10.62±0.79	0.521
	Total Leucocyte count	10.40±1.43	12.72±3.44	0.003*
	Platelets (lakh/µl)	2.01±0.14	2.03±0.04	0.611
Biochemical analysis	Serum Creatinine (mg/dl)	1.49±0.25	1.62±0.48	0.157
	Serum Sodium (mEq/lit)	136.59±8.27	130.10±10.15	0.058
	Serum Potassium (mmol/lit)	3.34±0.83	3.93±0.86	0.075
	Serum Bilirubin (mg/dl)	3.23±1.08	3.07±0.49	0.694
Liver function tests	SGOT (U/L)	35.0±5.22	45.50±7.89	0.000*
	SGPT (U/L)	33.46±4.25	37.88±4.01	0.010*
	Alkaline phosphatase (IU/L)	127.87±10.94	130.50±9.36	0.531

Radiological Findings:

CT findings:

On CT scan, symmetrical lesions were found in 39 out of the 47 patients (83.0%) and eight patients had asymmetrical lesions (17.0%).

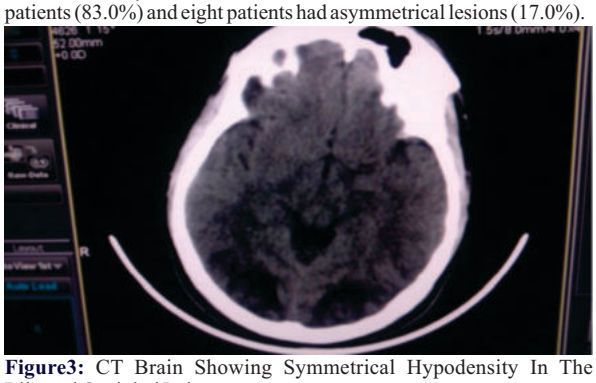

Figure3: CT Brain Showing Symmetrical Hypodensity In The Bilateral Occipital Lobes

Cerebral CT perfusion (CTP): CTP was performed to demonstrate increased cerebral blood volume (CBV) and cerebral blood flow (CBF). The imaging features of cerebral haemodynamic were consistent with PRES. Since there was hyperperfusion the CBF and CBV was significantly raised in 36 (76.6%) and 40 (85.1%) patients with PRES respectively.

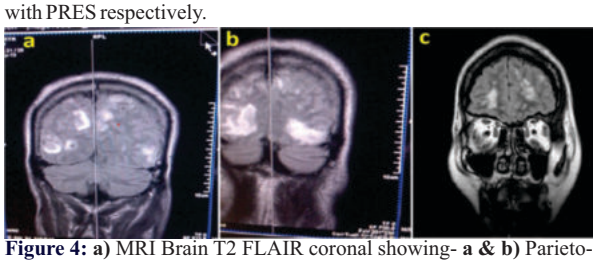

Figure 4: a) MRI Brain T2 FLAIR coronal showing- **a & b)** Parieto-occipital Hyperintensities In A Case Of PRES; **c)** Subcortical White Matter Hyperintensities In The Bilateral Frontal Lobes

MRI Findings:

The commonest lobe involved was parieto-occipital (87.2%) followed by temporal (44.7%), frontal (34.0%), cerebellum (25.5%) and other areas including brain stem (12.8%) and deep white matter (10.6%). Two patients with postpartum eclampsia had bilateral capsuleganglionic vasogenic edema with no diffusion restriction, one another patient with primary hypertension had bilateral capsuloganglionic, bilateral corona radiata, bilateral centrum semiovale, brainstem and cerebellar vasogenic edema without diffusion restriction.

Haemorrhage in PRES

Two patients (4.2%) 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. At presentation blood pressure was recorded to be higher among individuals with haemorrhage compared to patients without haemorrhage (175/110 mm Hg versus 152.4/100.3 mm Hg) although this difference was not statistically significant (P = 0.394).

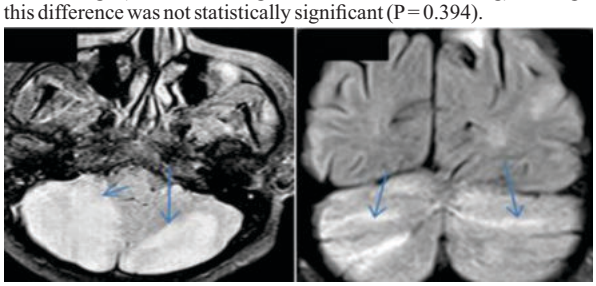

Figure 5: Hyperintense Signal Changes In Bilateral Cerebellar Hemispheres

VASOGENIC EDEMA- A PATHOGNOMIC OF PRES:

Vasogenic edema is the classical feature of PRES. It commonly presents with bilateral symmetrical vasogenic edema typically involving the sub-cortical white matter, predominantly in the bilateral occipital lobes. This presentation is called dominant parieto-occipital pattern. Diffusion weighted images (DWI) indicates typically in isodense or hypointense lesions with hyperintensity in ADC due to increase in apparent diffusion coefficient for water, indicative of vasogenic brain edema. Out of the total 47 PRES patients, subcortical lesions were found in 43 (91.5%) patients and cortical lesion was seen in 25 (53.2%).

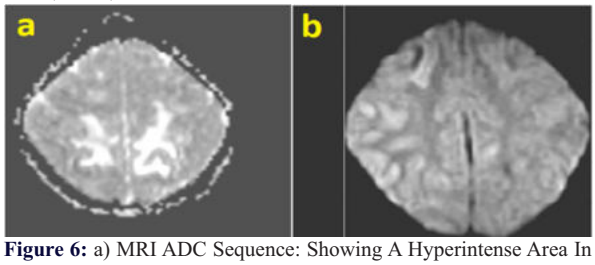

Figure 6: a) MRI ADC Sequence: Showing A Hyperintense Area In The Posterior Subcortical Region Of Brain; b) MRI Brain DWI Sequence Showing Isointense Area In The Corresponding Posterior Subcortical Region Suggestive Of Vasogenic Edema

Diffusion Restriction In Posterior Reversible Encephalopathy Syndrome:

Diffusion restriction was noted in 8 out of 47 patients i.e., 17% of the patients showed diffusion restriction. The sites included occipital and parietal regions (n = 8).

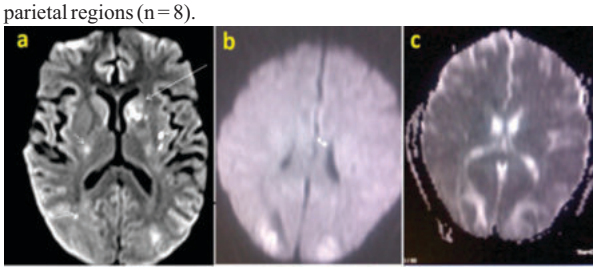

Figure 7: a) Diffusion restriction in a patient with posterior reversible encephalopathy syndrome with resolution of signal changes; b) DWI Brain occipital regions showing diffusion bright lesion in the bilateral–complication of PRES – Infarct showing Diffusion Restriction; c) ADC Brain showing hypointense lesions in the corresponding bilateral occipital region-complication of PRES - Infarct.

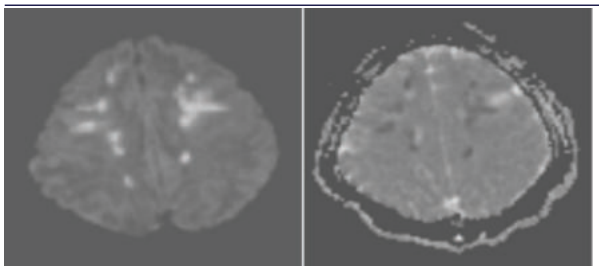

Figure 8: Showing Diffusion Restriction In The Bilateral Parietal Regions

The mean mRS score at presentation was 1.45±1.29, which was decreased to 0.49±1.48 at 3 months follow-up, this was statistically significant, (p=0.000). The outcome in terms of disability, dependence for daily activities, recovered or death are shown in table 5. At presentation, 9 (19.2%) patients had no symptoms while at 3 months follow up (n = 47), 83% (39) individuals were found to be asymptomatic as shown in table 5.

Table 5: Outcomes Based On Modified Rankin Scale (n=47)

Outcome		No. of patients	Percentage
At presentation	No symptoms (Score 0)	09	19.2
	No significant disability (Score 1)	22	46.8
	Significant disability (Score 2-5)	16	34.0
At follow up	No symptoms	39	83.0
	No significant disability	05	10.6
	Deaths	03	6.4

DISCUSSION

In the current study, PRES was common in females as most of the cases were pregnancy related. Maximum patients (45.7%) were in the 3rd decade of life. Thus, PRES is a disorder of young adults. The youngest participant was 15 years old, and the oldest participant was 61 years old. The age and sex distribution are similar to that reported in several other studies [12, 13]. Many studies conducted over worldwide have reported impaired consciousness as the commonest symptom of PRES [1,4,6]. However, in current series headache (87.2%) and seizures (70.2%) were the major symptoms of PRES at the presentation which is comparable with the study done by Yadav PK et al [14]. Previous studies [1, 6 and 15] documented hypertension in 67–80% of patients; in present study hypertension was noted in 70.21% of patients.

Despite the fact that all patients underwent extensive evaluation by a qualified ophthalmologist, visual complaints were recorded less frequently in present series while the frequency of most of the other symptoms was identical to that previously reported [1, 12]. The cause of this mismatch is unknown. One reason for this could be that several of our patients were suffering from 70 encephalopathy at the time of their initial evaluation and did not report any visual problems. Most of the patients had an acute increase in blood pressure. Eclampsia, primary renal illness, drug induced, and lupus were among the comorbidities in persons with high blood pressure. Three individuals had used steroids or immunosuppressants prior to the development of neurological symptoms. The majority of these patients had high blood pressure. In certain cases, these triggers may have contributed to endothelial damage and disruption of the blood–brain barrier. Before the onset of neurologic symptoms, one of the patients was given cyclosporine A. Cyclosporine A can alter the endothelium of the blood vessels and break the blood–brain barrier, but it can also raise arterial blood pressure. It is critical to consider PRES in conjunction with SLE in this case. In the present study, one patient had lupus nephritis associated with SLE and three others were given steroid and/or immunosuppressant treatment before onset of neurological symptom. In general, endothelial injury induced by vasculitis and/or its consequences, such as vascular spasm and angiopathy, was commonly seen in SLE patients [16]. Thus, PRES should be suspected when patients with SLE have acute headache and seizures, especially in those patients who have high blood pressure and are on immunosuppressive treatments [2, 17].

The frequency of involvement of commonest brain regions i.e., parietal and occipital in present study was similar to those described previously [1,2,15]. PRES is not solely a posterior phenomenon; rather, it presents in a gradient like pattern from posterior to anterior, likely reflecting sympathetic innervation gradients [7, 18, 19]. As a result, frontal lobe involvement was also found in one third of cases and was most commonly in the posterior portion of the superior frontal gyrus (anterior cerebral artery distribution). This distribution confirms that the posterior reversible encephalopathy syndrome is a misnomer because most cases involve anterior circulation structures as well. In present study, the symmetrical pattern was seen in 85.1% of the patients. Subcortical involvement was seen in 91.5% of the patients. Cortical involvement was seen in 25 out of the 47 patients i.e., 53.2% of the patients had cortical involvement. Recurrent PRES is a rare occurrence. In present study 2 patient (4.25%) had recurrent PRES.

Mortality is uncommon in PRES. Current study reports a mortality rate of 6.38%. One patient succumbed to death on day 2, one died on day 2 and another on day 5 of hospitalization. Mortality was associated with precipitating factor sepsis with AKI was noted in one patient. The mortality also could be attributed to late presentation to the health care centre. Among the 44 patients who survived, all were functionally independent over gradual period of time. Only 5 observed to have slight disability but can perform daily activities. Sufficient data were not available to compare this finding with those of other authors. We used IV methylprednisolone empirically in three patients who had absence of perception of light on ophthalmological examination. These patients recovered during the hospital stay. Steroids are known to help with vasogenic edema, so we utilised them in all patients after ruling out infections and paying close attention to blood pressure regulation. 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.

CONCLUSION

In the present study, majority of patients presented with headache and seizures. There is varied aetiology for PRES, ranging from commoner pregnancy related PRES to the rare causes like Lupus Nephritis class IV, Sepsis with AKI etc. as seen in present study. Hence a high index of suspicion and a thorough knowledge of conditions that could predispose to PRES is essential for the early diagnosis. Although, increased diffusion associated with vasogenic edema can be seen in diffusion MRI scans. Vasogenic edema-related lesions can be reversed. Prompt blood pressure control prevents irreversible complications. A high index of clinical suspicion in appropriate situations, together with radiological correlation, will aid in the early detection and treatment of PRES, reducing the risk of serious consequences.

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