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Posterior reversible encephalopathy syndrome: Co-relation between MR perfusion and the clinico-pathological spectrum

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Abstract

Objectives: The study was aimed to assess the epidemiological profile and patient characteristics, various morphological patterns of posterior reversible encephalopathy syndrome (PRES) on MRI and various pathophysiological mechanisms on MR perfusion. *Methods:* It was a prospective and observational study done over a total of 40 patients. Standard sequences included T1 and T2-weighted sequences, FLAIR, DWI, SWI and MR perfusion. *Results:* Females were affected predominantly with F:M ratio of 12:1. The commonest age group affected was between 20-40 years. The most common symptom was headache. The commonest etiology being pregnancy induced(37.5%).Hypertension was reported in 70%,out of which 37.5% included pregnancy induced hypertension. The commonest region involved was occipital lobe seen in 85% of patients. Atypical PRES was seen in 42.5% of patients in the form of involvement of atypical locations; basal ganglia 10%, thalami 2.5% and cerebellum 2.5%; diffusion restriction 12.5% and hemorrhage 22.5%, out of which 10% had subarachnoid hemorrhage,10% has intraparenchymal hematoma and 2.5% had minute focal hemorrhage. rCBV and rCBF was decreased in 82.5% of patients and unchanged in 12.5% of the total number of patients supporting the hypoperfusion theory.
Conclusion: PRES predominantly involves female, hypertension is seen in most of the patients. The commonest lobes involved are the occipital and parietal lobes; however the incidence of atypical PRES is also seen in a significant number of patients. The basic pathophysiological mechanism is hypoperfusion.

Keywords: Posterior reversible encephalopathy syndrome, typical/atypical features, pathophysiology, MR perfusion.

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiologic entity that is characterized by an acute onset of various neurologic symptoms associated with vasogenic edema, in a predominantly bilateral parieto-occipital distribution showing high signal intensity on T2 weighted and FLAIR, low signal intensity on T1 weighted and rarely accompanied by diffusion restriction. The term PRES appears to be a misnomer as the condition is not always reversible, is not only confined to the posterior regions of the brain and can affect both white and grey matter. It is observed to have a female prevalence, secondary to its association with peripartum conditions and autoimmune diseases.[1,2] PRES affects both adult and pediatric populations, the age group varying between children as young as two years old and adults as old as 90 years old. However most cases are reported in people between 20 to 65 years.[3,4]

There are two leading theories regarding the pathophysiology of PRES.[5] According to the first hypothesis, elevation of blood pressure levels

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above the upper autoregulatory limit leads to cerebral hyperperfusion, which in turn causes vascular leakage and subsequent vasogenic edema.[6]

The second theory states that the syndrome is triggered by endothelial dysfunction caused by circulating endogenous or exogenous toxins[5] which leads to vasoconstriction of microcirculation, which is further worsened by hypertension and associated autoregulatory response.[7] Cerebral vasoconstriction may then be followed by hypoperfusion and ischemia, ultimately resulting in vasogenic edema characteristic of PRES.

METHODS

This study was done in the Department of Radiodiagnosis and Imaging, Sher-e-Kashmir institute Of Medical Sciences, Soura from June 2018 to June 2020 on patients referred from the Department of Neurology, Sher-e-Kashmir institute Of Medical Sciences, Soura. Ethical approval was obtained from the institutional ethical committee.

Inclusion criteria

Patients who on initial MRI showed cortical or subcortical FLAIR or T2 weighted hyperintensity with posterior predominance in a parieto-occipital distribution typical of PRES or FLAIR or T2 weighted hyperintensity in the brainstem, basal ganglia, or subcortical or cortical frontal regions without posterior predominance. In addition, the patient who had received a medication or experienced a condition known to cause PRES.

It was a prospective and observational Study and a total of 40 patients were studied. All MR studies were performed using 1.5 tesla MR system (Magnetom Avanto, Siemens Medical Systems, Erlangen,Germany). As a first step,i.v.Cannulation was performed using 18 or 20 gauge i.v. cannula. Saggital and axial T1-weighted images were obtained (Parameters400-600ms/15-25ms/5mm/2 [TR/TE/SLICE thickness/NEX]) (Figure 3). Axial fluid-attenuated inversion-recovery (FLAIR) images were obtained(Parameters7000-9000ms/110ms/5mm/2 [TR/TE/SLICE thickness/NEX]) (Figure 4). T2 weighted images were obtained (Parameters3000-4000ms/100-120ms/5mm/2[TR/TE/SLICE thickness/NEX]) (Figure 2). Diffusion weighted imaging was done (Parameters 7000-9000ms/110ms/5mm/4[TR/TE/SLICE thickness/NXA]).

MR perfusion was performed using dynamic susceptibility contrast MR imaging with gradient-echo sequence during dynamic bolus contrast administration. Standard dose of 0.1 mmol/kg of gadolinium dimeglumine bolus injection (antecubital;5mL/s) was given 10 seconds after initiating the scan. Relative cerebral blood volume (rCBV) was obtained from quantification of the area under the concentration- time curve. Multiple regional rCBV and rCBF region-

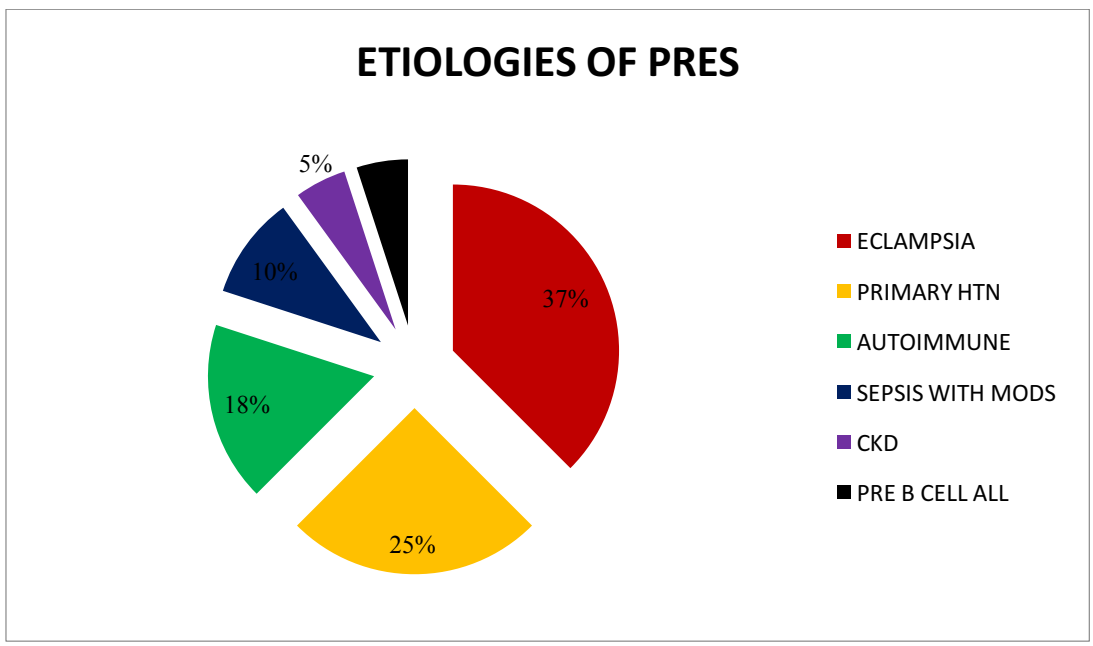

Figure 1. Etiologies of PRES

of-interest measurements were obtained in a healthy-appearing cortex and subcortical white matter as well as regions affected with PRES as identified on MR imaging (FLAIR sequence and T2).The regions of interest were chosen to avoid surface blood vessels that would inappropriately increase the rCBVamdr CBF measurements and ventricles that would falsely decrease the rCBV and rCBF measurements. Similarly 2 to 6 cortex measurements were obtained in the PRES lesions over representative regions, with careful attention not to extend into adjacent normal white matter or include dominant surface vessels. Average lesion rCBV and rCBF was referenced to average healthy brain rCBV and rCBF obtained for that patient.

RESULTS

There was a striking female predominance in patients with PRES, in this study, with 37 (92.5%) females and 3 (7.5%) males. The age distribution ranged from 7 years to 61 years. The most common age group was 20-40 years with 60% of patients in this age group. The most common presenting complaint being headache seen in 80% of patients. The second most common presenting complaint was impaired consciousness with 75% of patients . Seizures were the third most common presenting complaint, with 60% patients. Visual symptoms were present in 50 % of patients. The symptoms ranged from blurring of vision to cortical blindness. Focal neurological deficit was present in 20% of patients. The myriad etiologies of PRES in our study included eclampsia seen in 15 out of 40 patients (37.5%), followed by primary hypertension seen in 10 patients (25%), autoimmune disorders in 7 Patients (17.5%), sepsis with multiple organ dysfunction syndrome in 4 patients (10%). Others were chronic kidney disease and pre B cell ALL each in 2 patients i.e. 5% each (Figure 1). The number of patients associated with hypertension in our study were 28 out of 40 (70%). And out of them 15 had pregnancy associated hypertension and 13 had non pregnancy associated hypertension. Twelve out of 40 (30%) patients had normal blood pressure.

The region of brain most commonly involved on MRI was occipital lobe seen in 34 out of 40 patients (85%) followed by parietal lobe seen in 32 out of 40 patients (80%), temporal lobe seen in

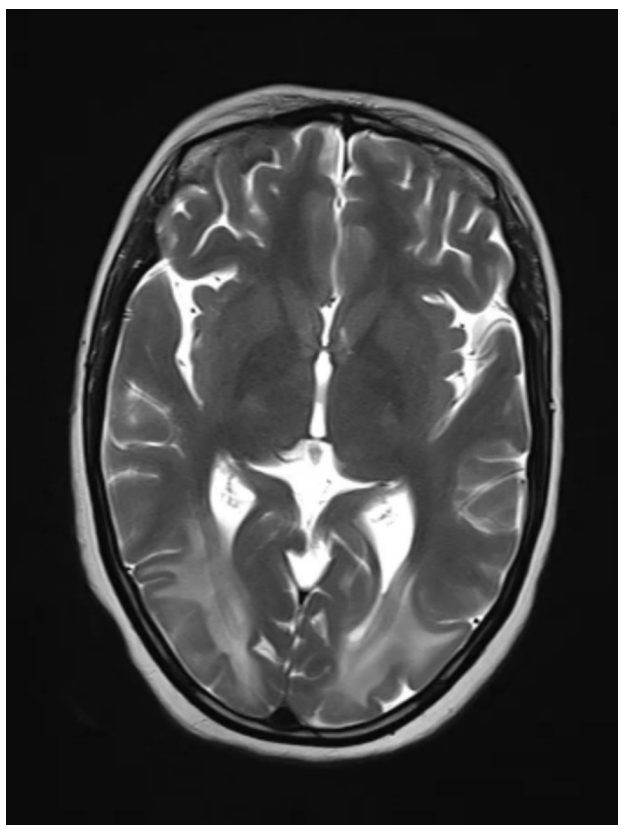

Figure 2. MRI Brain Axial T2 weighted image showing hyperintensity in bilateral; occipital lobes.

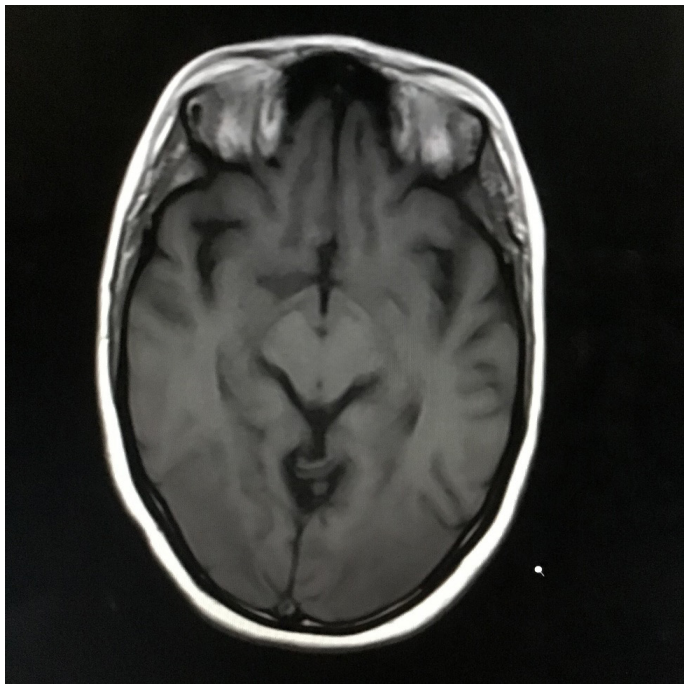

Figure 3. MRI Brain Axial T1 weighted image showing hypointensity in bilateral; occipital lobes.

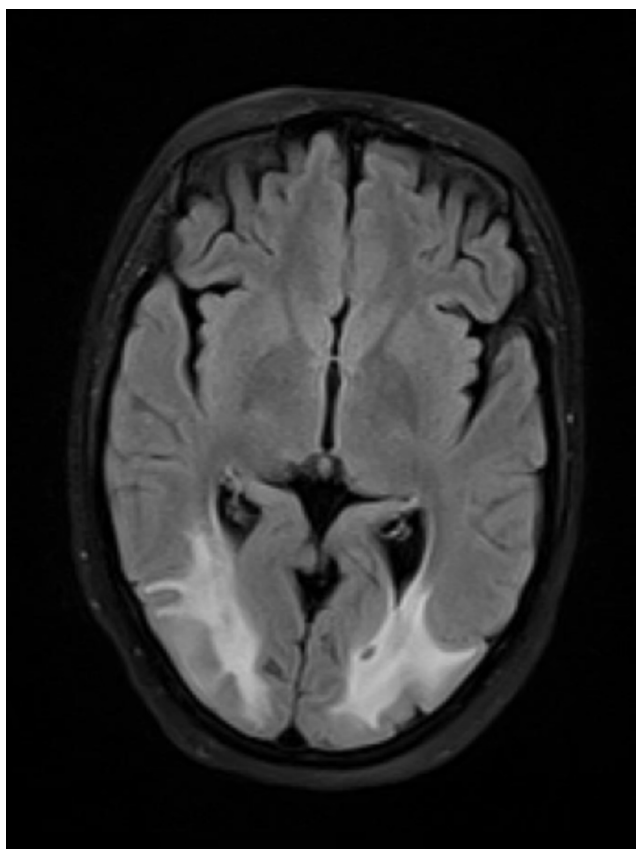

Figure 4. MRI Brain Axial FLAIR weighted image showing hyperintensity in bilateral; occipital lobes.

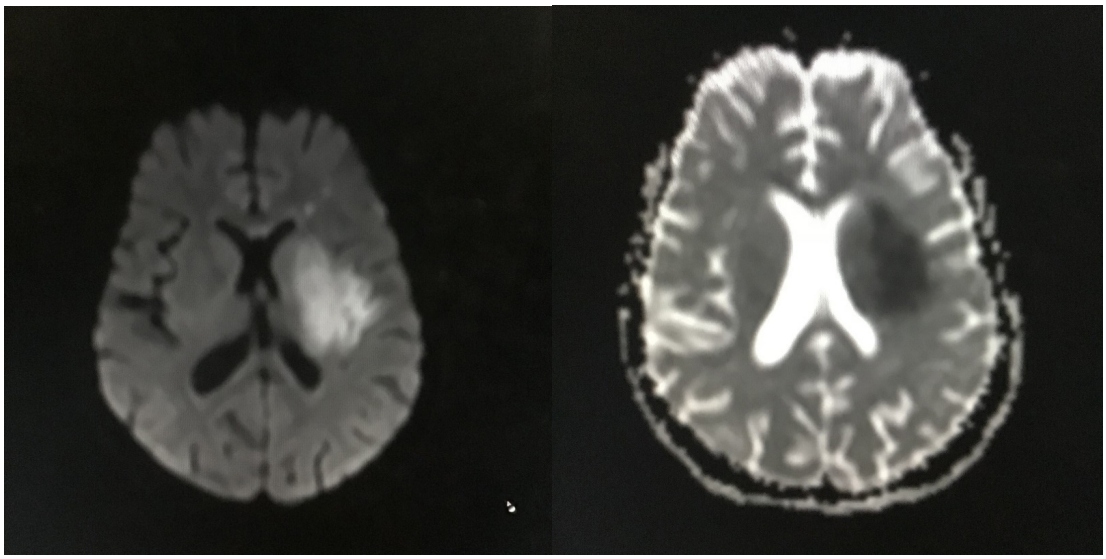

Figure 5. (A) DWI showing diffusion restriction in the left basal ganglia, (B) a significant signal drop on the ADC image.

9 out of 40patients (22.5%), frontal lobe seen in 5 out of 40 patients (12.5%). Four out of 40 patients (10%) had basal ganglia involvement,1patient (2.5%) had cerebellar involvement and 1 patient (2.5%) had thalamic involvement (Figure 7). Four patients (10%) had cortical laminar necrosis. Diffusion restriction was noted in 5 out of 40 patients with PRES i.e. 12.5% (Figure 5). Blooming foci on SWI were present in 9 out of 40 patients i.e. 22.5%. 9 out of 40 patients had hemorrhage in our study, out of which 4 (10%) had intraparenchymal hematoma and 4 patients (10%) had subarachnoid hemorrhage and 1 patient had minute focal hemorrhage (2.5%) (Figure 6). Twenty-three out of 40 patients (57.5%) in our study had typical PRES features while 17 patients (42.5%) had atypical PRES features. On perfusion MRI, 33 out of 40 patients (82.5%) had decreased rCBV and rCBF (Figure 8) while in 5 out 40 patients the rCBV and rCBF were normal

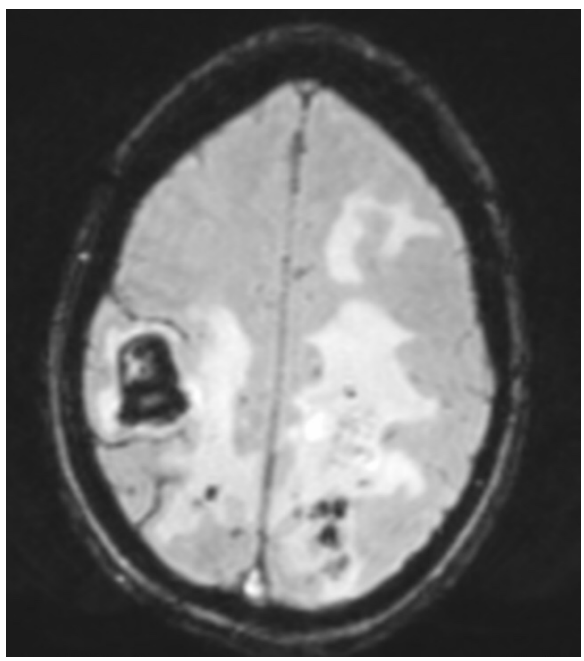

Figure 6. MRI Brain Axial SWI showing multiple blooming foci in both parietal lobes.

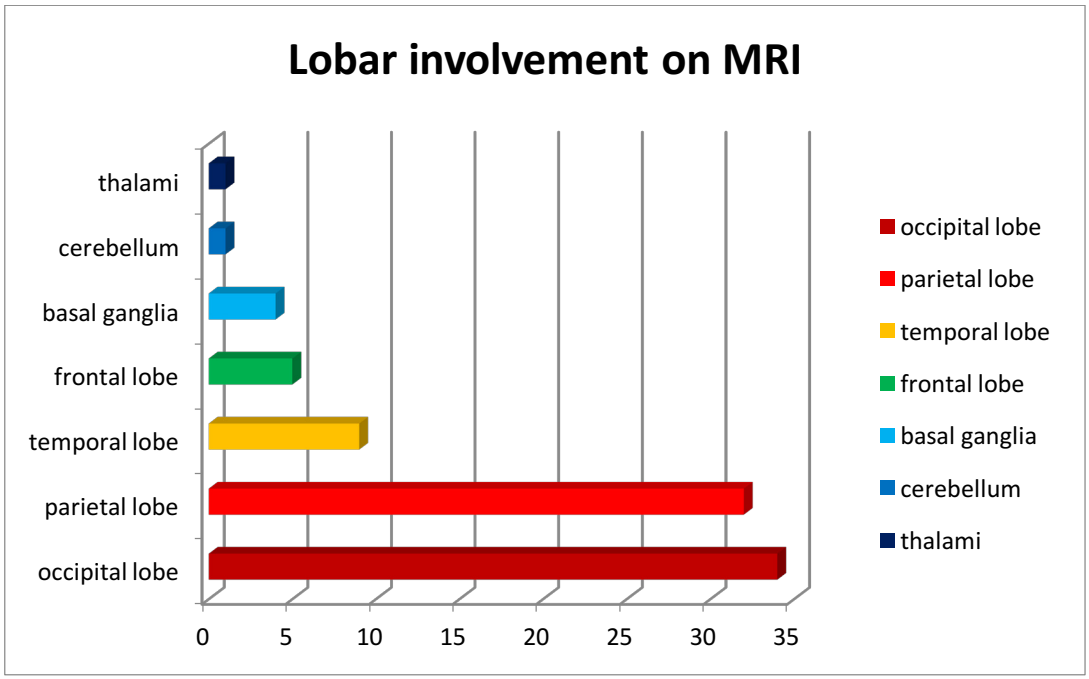

Figure 7. Lobar involvement on MRI in patients with PRES.

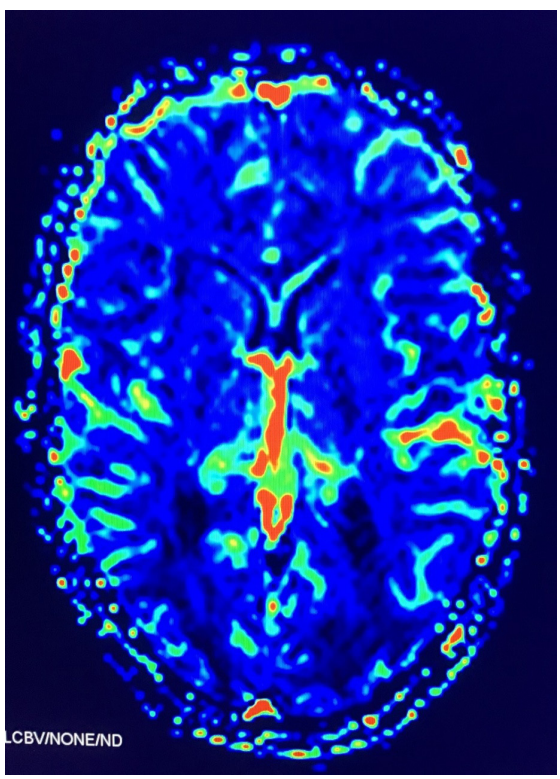

Figure 8. rCBV colour map demonstrates decreased blood volume in both occipital lobes.

(Figure 9). 2 patients had CKD with accelerated hypertension, they were excluded from perfusion MRI due to iv contrast contraindication in such patients.

DISCUSSION

PRES is predominantly seen in females. In this study also there was a marked predominance of females with 92.5 % of the total number of patients being females. The reason being that a substantial number of patients were pregnancy related and suffering from autoimmune diseases.

PRES has been reported in patients between 4 years to 90 years old.[8] Fugate and Rabinstein reported PRES in patients between 9-82 years of age.[11] Mc Kinney *et al*. reported that the youngest patient was 5 years old and the oldest was 80 years old.[16] In our study the youngest was 7 years old and the oldest was 61 years of age with a mean age of 33.02 years. The most common age group involved was between 20-40 years. A study done by Raman *et al*.[22] demonstrated the most common age group between 20-30years.

The commonest symptom of PRES in many studies across the world is seizures. McKinney *et al*.[16] reported seizures in 76% of cases. Fugate and Rabinstein reported that seizures were present in 74% of patients with PRES.[11] However the commonest symptom in our study was headache seen in about 80% of the total number of patients and seizures being the second most common symptom with 60 % of patients. This is consistent with the study done by Kumar and Sen.[9], they reported headache as the most common symptom seen in 83.3% of patients and seizures in 75% of cases.[9]

PRES has a varied etiology, however the most common cause of PRES in this study was pregnancy related PRES with over 37.5% of the patients followed by primary hypertension accounting for 25% of patients. Autoimmune diseases also involved a significant number of patients (17%). This finding is similar to that by Mueller-Mang *et al*.[17], Raman *et al*.[22] where pregnancy related PRES was the most common cause. In a study by Pande *et al*.[18], eclampsia was the second commonest etiology preceded by drug induced PRES.

In our study 70% of the total number of patients were hypertensive out of which 37.5% were pregnancy related. This is in consistence with a number of studies done worldwide. Hinchey *et al*.[1] and Muller Mang *et al*.[17] documented

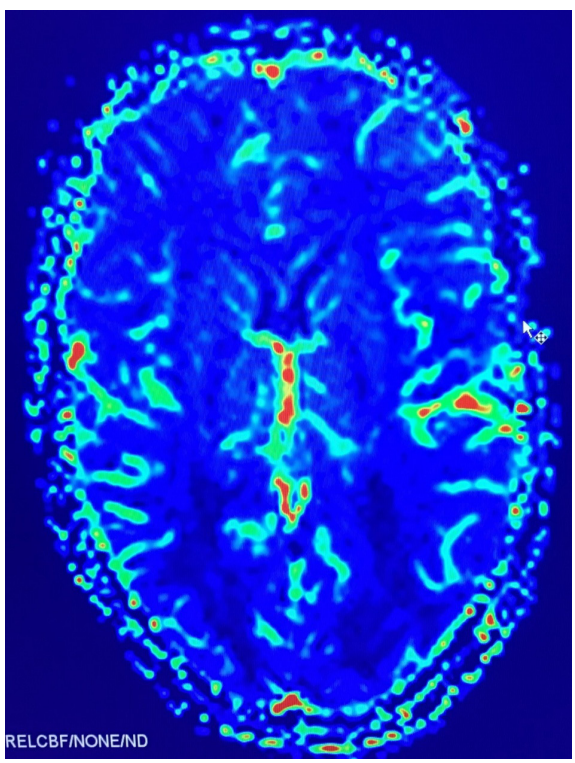

Figure 9. rCBF colour map demonstrates decreased blood flow in both occipital lobes

hypertension in 80% of patients. 61 % of patients were hypertensive in a study done by Fugate *et al*.[11] Bartynski *et al*.[5] reported hypertension in about 67% of the total number of patients.

As far as the lobar distribution of lesions on MRI is considered, parieto-occipital lobes are the most commonly involved as seen in a number of studies by Hinchey *et al*.[1], Bartynski *et al*.[2] (99%), Fugate *et al*.[11] (94%), Mc Kinney[16] (98.7%). In our study the most commonly involved lobes were occipital lobes accounting for 85%, closely followed by parietal lobes seen in 80% of patients. PRES is known to have a predilection for posterior territories of brain due to sparse sympathetic innervations of the verterbrobasilar circulation[11] which find support in our study as well.

Lesions have been reported at atypical locations like basal ganglia, cerebellum and brainstem. Fugate *et al*.[11] reported cerebellar involvement in 53% of cases and 34% showed basal ganglia involvement. Similarly Bartynski[2] demonstrated cerebellar lesions in 32% and basal ganglia in 13.9% of patients. In the study done by Mc Kinney[16] 34.2% had cerebellar involvement, 30.35% had thalamic lesions,18.4% has brainstem lesions and 11.8% had involvement of basal ganglia.

In our study 57.5% of patients had typical PRES features and 42.5% had atypical PRES in the form of involvement of atypical locations, hemorrhage and diffusion restriction. In our study 10% of the total number of patients had basal ganglia involvement, 2.5% demonstrated cerebellar lesions and 2.5% thalamic lesions. Kastrup *et al*.[19] in a cohort of 50 patients showed basal ganglia involvement in 1.6% and cerebellar involvement in 6.5% of patients. In a study done by Hefzy *et al*.[20] the incidence of hemorrhage was seen in 15.2%. The three types of hemorrhage included subarachnoid hemorrhage, intraparenchymal hematoma and minute focal hemorrhage. McKinney reported hemorrhagic lesions in 17.1% of patients.

In our study hemorrhage was noted in 22.5% of the total number of patients out of which 10% had subarachnoid hemorrhage, 10% had intraparenchymal hematoma and 2.5% had minute focal hemorrhage. Doss-Esper *et al*.[12] have proposed two hypotheses: 1) nonaneurysmal subarachnoid (sulcal) hemorrhage due to rupture of pial vessels secondary to severe hypertension and impaired cerebral autoregulation, and 2) post ischemic reperfusion injury resulting in multifocal brain haemorrhages.[12] Hefzy *et al*.[20] however observed that vasoconstriction of small and medium sized vessels leading to hypoperfusion, postischemic reperfusion might be a potential cause of hemorrhage in PRES. This is consistent with our observation of reduced CBV and CBF in patients with PRES.

Vasogenic edema predominates in PRES which can be differentiated from cytotoxic edema by DWI that shows diffusion restriction. In a case series of 76 patients, Mc Kinney[16] reported diffusion restriction in 17.3% of patients. Covarrubias *et al*.[8] showed diffusion restriction in 22% of patients. In another study by Junewar *et al*.[13], diffusion restriction was demonstrated in 33.3% of cases. In our study diffusion restriction was seen in 12.5% of patients. This finding is believed to be due to compromised microcirculation, either secondary to the mass effect of vasogenic edema or due to reactionary vasoconstriction.[13]With demonstration of hypoperfusion in patients with PRES in our study, we can corroborate the aforementioned findings.

The precise pathophysiological mechanism of PRES remains controversial. There are two leading hypotheses: According to one hypothesis, elevation of blood pressure levels above the upper autoregulatory limit leads to cerebral hyperperfusion, which may cause vascular leakage and resultant vasogenic edema.[6] However PRES is commonly seen in patients without hypertension as well and even in hypertensive patients the blood pressure rarely rises above the autoregulatory levels. The second hypotheses suggests that vasoconstriction secondary to evolving hypertension and endothelial activation, leads to reduced brain perfusion, ischemia and subsequent vasogenic edema.[14]

Few studies of perfusion MRI have been done in patients with PRES. Brubaker *et al*.[21] demonstrated decreased CBV and CBF within the affected regions when compared with the normal anterior brain parenchyma. Bartynski *et al*.[7] reported a significant reduction in the rCBV when compared with the healthy cortex. He also demonstrated vasculopathy in the form of focal vasoconstriction, focal vasodilatation, string of beads appearance and vessel pruning on MRA further strengthening the cause of hypoperfusion. Evidence of hyperperfusion in PRES is very minimal, and finds support in isolated case reports on Tc99m-HMPAO SPECT.[15] In our study 82.5% (33) of the total number of patients demonstrated decreased rCBV and rCBF in the affected regions when compared with the normal healthy appearing cortex. It remained unchanged in 12.5% of patients.

Average rCBV in PRES lesions and regions relative to a reference normal cortex was 41% and rCBF was 46%. Bartynski *et al*.[7] demonstrated a 61% decrease in rCBV as compared to the normal healthy cortex. Brubaker *et al*. recorded a lower average rCBV 28%, comparing the PRES lesions with the normal anterior part of the brain.

Two patients with CKD were excluded from perfusion MRI.

Our study backs the hypoperfusion theory. One the many reasons being that a significant proportion of patients in our study included eclamptic patients and those with autoimmune disorders.

There are various studies of PRES in pediatric patients with renovascular diseases, immunosuppressive therapy, hematologic malignancies and other systemic diseases.[14] In our study 2 children had pre Bcell ALL and PRES.

In conclusion, PRES develops more commonly in females, predominantly in the young to middle age group between 20-40 years. There is a varied etiology of PRES but the most common cause includes pregnancy induced followed by primary hypertension and autoimmune diseases. The imaging patterns of PRES included a predominantly posterior parieto-occipital distribution of lesions, however also involved the temporal and frontal lobes and atypical locations like basal ganglia, cerebellum and thalami. Though vasogenic edema is seen in the patients with PRES, Few patients also demonstrated cytotoxic edema in the form of diffusion restriction. We also noted hemorrhagic lesions in PRES. Abrupt rise in blood pressure undoubtedly causes PRES and the hyperperfusion theory does find support in the fact that a substantial number of patients are hypertensive, however there is little radiological evidence to support it. Also this theory is incomprehensive since PRES also occurs in normotensive patients. We found decreased rCBV and rCBF in the affected brain regions favouring the hypoperfusion theory which also goes on to explain the vasogenic edema, hemorrhage and diffusion restriction.

DISCLOSURE

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Conflict of interest: None

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