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ORIGINAL ARTICLE

Posterior Reversible Encephalopathy Syndrome in Renal Disease

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ABSTRACT

Aims and Objectives: To identify the prevalence of posterior reversible encephalopathy syndrome in patients with renal disease at a single center over a two year duration and to analyse their clinical profile.

Materials and methods: A retrospective analysis of all patients admitted in the ICU under the department of Nephrology in the past 2 years at VPS Lakeshore Hospital and Research Centre, Kochi was done to look for patients with posterior reversible encephalopathy syndrome (PRES). Their presenting symptoms, degree of hypertension, immunosuppression status, recurrence rates, findings on imaging and prognosis after treatment was evaluated.

Results: In 636 intensive care unit (ICU) admissions under Nephrology, there were 6 cases of PRES. 4 were females and 2 were males. The median age was 27.6 years. 4 patients were cases of chronic kidney disease stage V on maintenance hemodialysis, one case was a case of CKD on conservative management and one patient had just undergone living donor kidney transplantation. 1 patient was on calcineurin inhibitors. Three patients (50%) had IgA Nephropathy, one (16.6%) had lupus nephritis, one (16.6%) had membranous nephropathy and one (16.6%) had chronic glomerulonephritis. Clinical features were seizures (50%) and confusion with depressed consciousness (50%). One patient had recurrence of PRES. Three patients (50%) had typical locations of radiological findings whereas three patients (50%) had findings in unusual areas. 5 patients (83.3%) had severe hypertension (BP>180/100mm Hg). All patients recovered completely and there was no mortality

Conclusions: posterior reversible encephalopathy syndrome can be seen in association with kidney disease in various scenarios with many atypical features such as atypical radiological distribution and absence of hypertension. It is an under-represented entity and merits further studies.

Introduction

Posterior Reversible Encephalopathy syndrome is a clinic-radiological condition characterized by radiologic evidence of posterior cerebral white matter edema along with a clinical syndrome comprising headache, seizures, encephalopathy, decreased consciousness and visual disturbances.

It is a fairly recent observation, having been first described by Hinchley in 1996. The incidence of this syndrome in kidney disease is unknown. Patients with kidney disease have numerous risk factors that may pre-dispose them to this condition, with uncontrolled hypertension, autoimmune disease and immunosuppressive medications being the common factors. PRES could be an under recognized entity in patients with kidney disease. In addition, there may be atypical presentations of PRES that may go unnoticed.

The hallmark of PRES is vasogenic edema. Pathogenesis can be explained by two theories, which are not mutually exclusive. Severe hypertension overwhelms cerebral autoregulation, leading to hyperperfusion, arteriolar dilatation, and vasogenic edema. Posterior regions of the brain may be more affected due to lack of sympathetic innervation. Another theory postulates that cerebral vasoconstriction causes vasogenic edema due to capillary leak. This article attempts to review the current theories about this condition as well as analyse few cases presenting at our centre.

Materials and Methods

A retrospective analysis of all patients admitted in the ICU under the department of Nephrology in the past 2 years at VPS Lakeshore Hospital and Research Centre, Kochi was done to look for patients with posterior reversible encephalopathy syndrome (PRES). Their presenting symptoms, degree of hypertension, immunosuppression status, recurrence rates, findings on imaging and prognosis after treatment was evaluated.

Results

Out of 636 total intensive care unit (ICU) admissions under Nephrology, there were 6 cases of PRES. 4 were females and 2 were males. The mean age was 27.6 years with the youngest being 15 years old, and the oldest being 51 years. 4 patients were cases of chronic kidney disease stage V on maintenance hemodialysis, one case was a case of CKD on conservative management and one patient had just undergone living donor kidney transplantation. 1 patient was on calcineurin inhibitors. Three patients (50%) had IgA Nephropathy, one (16.6%) had lupus nephritis, one (16.6%) had membranous nephropathy and one (16.6%) had chronic glomerulonephritis. Clinical features were seizures (50%) and confusion with depressed consciousness (50%). One patient had recurrence of PRES. Three patients (50%) had typical locations of radiological findings whereas three patients (50%) had findings in unusual areas. 5 patients (83.3%) had severe hypertension (BP>180/100mm Hg). All patients recovered completely and there was no mortality. Features are summarized in table 2

Discussion

Posterior reversible encephalopathy syndrome (PRES) is known by many synonyms, none of which may truly describe the entity. Various descriptions include reversible

posterior leukoencephalopathy syndrome, reversible posterior cerebral edema syndrome, hyperperfusion encephalopathy and brain capillary leak syndrome. This syndrome was first described by Hinchley[1] in 1996 in a case series of 15 patients, four of whom had varying degrees of renal impairment. The true incidence of the syndrome is unknown, although there are numerous case reports and series regarding PRES.

Not much is known about PRES in kidney disease. It is probably an under-reported entity since patients with kidney disease have multiple known risk factors such as hypertension, usage of immunosuppressive drugs. Neuroimaging findings can be diverse, and the int involving both anterior and posterior circulation territories. Ensity of hypertension may vary at presentation, leading to PRES being under-reported. There have been scattered reports of PRES in kidney disease, but systematic research is lacking. In Hinchey's original paper,[1] more than half of the patients had renal failure of varying degrees, and 80% had hypertension.

The following questions seem pertinent in understanding this syndrome.

1. Is hypertension always required for the diagnosis of PRES?
2. Are patients with renal disease more prone to PRES?
3. Is PRES exclusively limited to the posterior areas in the brain?
4. Is it a truly reversible process?

Hypertension seems to be a major contributing factor in PRES. The loss of cerebral autoregulation beyond a point leads to extravasation of fluid and blood products into the brain parenchyma due to loss of integrity of the blood brain barrier. Two factors play a role in this mechanism however- the rate of development of hypertension and underlying chronicity. It has been observed that rapidly increasing blood pressure may lead to PRES. In patients with renal disease, particularly those on renal replacement therapy, blood pressures remain chronically high due to various reasons. Therefore, PRES in this subgroup of patients tends to be associated with very high absolute values of blood pressure, unlike children who develop PRES at lower absolute values.

In addition to loss of cerebral autoregulation, endothelial dysfunction and cerebral ischemia also are instrumental in causing these symptoms.

The absence of hypertension is not necessarily against a diagnosis of PRES. In fact upto 20-30% of PRES may have near normal blood pressure[2] and close to 50% of drug induced PRES (calcineurin inhibitors) may not have hypertension at all[3]. Published case series by Hinchley, Ganesh et al[4] and Cannesy et al[5] all showed a small but significant number of patients who developed PRES without severe hypertension. The pathophysiology in these cases may be more related to endothelial dysfunction rather than the classic vasogenic theory alone. This 'cytotoxic' theory is additionally supplemented by an 'immune theory', which suggests a T cell mediated process. Thus it follows that the pathophysiology of PRES may be multifactorial. Possibly a multi-hit or a two hit process may have to be considered in selected cases, where the drug or immune mechanism provides the first hit, causes microvascular vasoconstriction, which is then compounded by hypertension and the classic vasogenic theory. This complex pathophysiology was borne out in a study by Rabenstein et al,

where there were no demonstrable correlations with either fluctuations in blood pressure or a significantly high BP at diagnosis[6]. In our case series, 5 out of 6 patients had uncontrolled hypertension at diagnosis.

Are patients with kidney impairment more prone to PRES than other organ involvement? In the larger published series of PRES, kidney disease features in some way in the patient populations studied (Table 1). Accounts differ. Upto 55% of patients with PRES are noted to have some degree of renal impairment[7]. In fact, in Table 1 all major case series have significant number of patients with renal disease. In a study by Burrus et al[8], patients with thrombotic thrombocytopenic purpura and PRES were studied. Here, there was some demonstrable association between kidney impairment and PRES, and none between PRES and hypertension. A possible common pathophysiology in TTP involving both brain and kidney has been suggested, either due to endothelial dysfunction or due to dysfunction of a common transporter protein. In any case, PRES is one of the differentials when a patient with TTP and renal dysfunction develops encephalopathy.

In the cohort of patients undergoing hemodialysis, hypertension is a major factor causing PRES as demonstrated in the study by Chandragiri et al[9]. Poorly controlled hypertension in this subgroup of patients may put them at a higher risk to develop PRES, however actual evidence is lacking in this regard. The modality of dialysis with respect to PRES has not been studied, however the case series by Olivera et al[10] demonstrated uncontrolled hypertension in all three of their cases who were on peritoneal dialysis. These required transitioning to hemodialysis, thus demonstrating the crucial need for volume control in patients on PD who may not be on as regular a follow up as hemodialysis patients. In our series, all five out of six patients had severe hypertension at diagnosis. Case number 3 had significant sepsis, with bilateral tuberculous psoas abscesses.

Canney et al raise an interesting point, that of a 'vulnerable period' for PRES in the dialysis population. 60% of the study subjects developed PRES within weeks of initiating dialysis. This is the period of establishing the correct 'dry weight' and great care should be taken in the interim, to avoid volume overload and fluctuations in blood pressure. This is especially so in anuric patients, where avoiding excess interdialytic weight gain assumes more significance.

The term 'posterior' in the description of this entity seems fair in so far as the numbers are concerned- majority of the cases have posterior area involvement. Radiological findings are typically bilateral areas of white matter edema, in the pareito-occipetal regions (Fig 1). However, other areas of the brain may also be involved, notably the frontal lobe, basal ganglia and the cerebellum. Although classically described as bilaterally symmetrical lesions, atypical forms may be confined to one hemisphere. Frontal lobe involvement may be as high as 68%[11]. In our series, 3 out of 6 (50%) patients presented with lesions in atypical areas. There did not seem to be any major difference in symptoms. Figures 2 and 3 demonstrate patients with PRES and atypical findings on MRI. In addition, although classically described as reversible, there have been documented cases of gliosis, infarcts, atrophy and even

hemorrhages in areas affected by PRES [12]. The long term effects of these irreversible changes are not well described. Therefore it follows that the diagnosis of PRES is not merely a radiological one, but rather a combined clinico-radiological diagnosis. A patient who presents with clinical features consistent with the diagnosis of PRES, along with radiological features on CT or MRI can be diagnosed with PRES.

Figure 1: CT Brain plain showing posterior cerebral hypodensities consistent with Posterior Reversible Encephalopathy

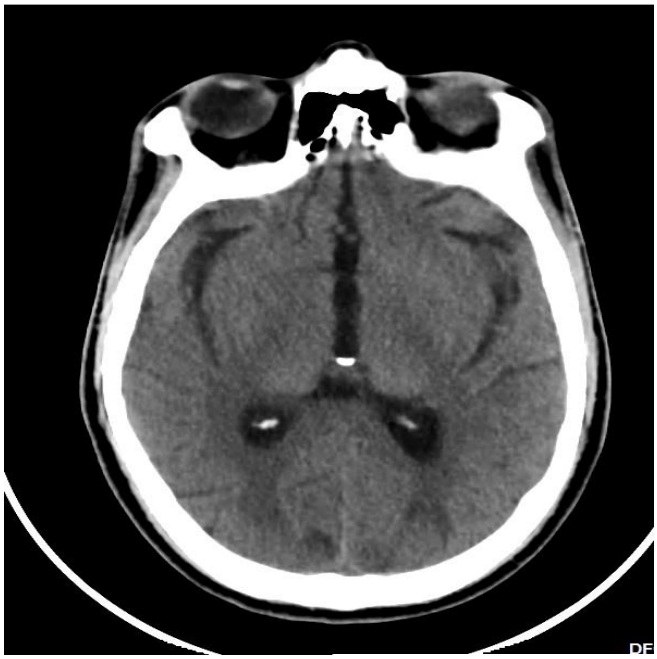


Figure 2: MRI Brain (T2/FLAIR) showing hyperintense signals in basal ganglia and frontal regions, features of atypical PRES

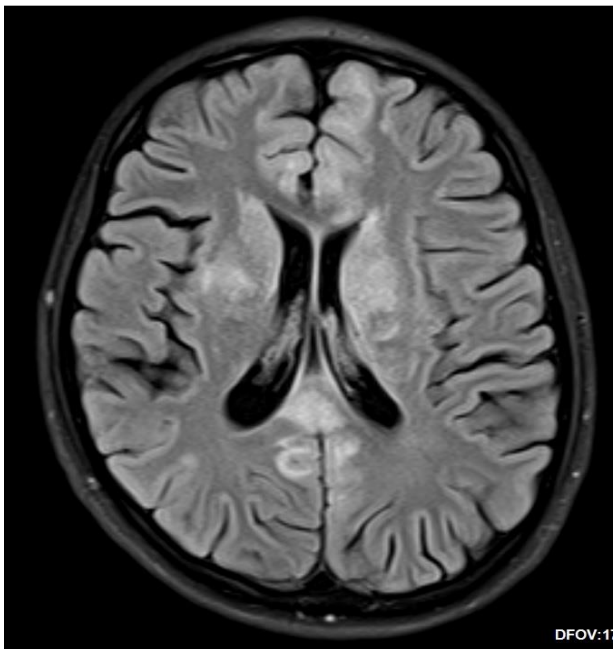
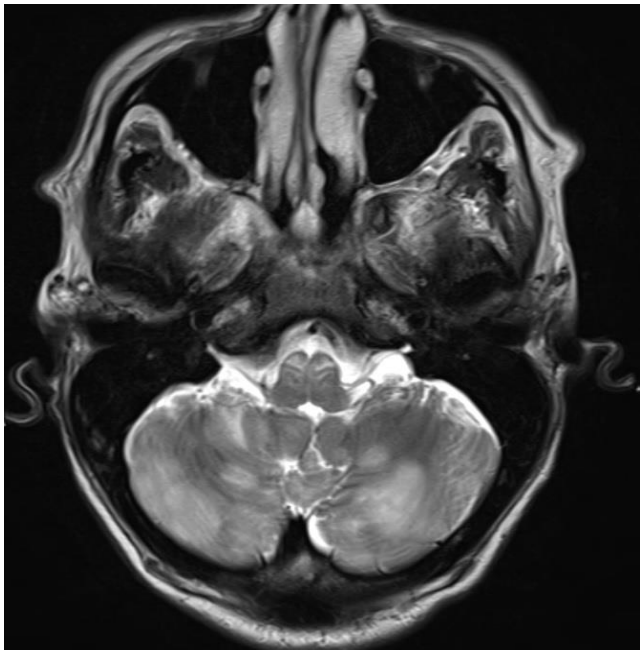


Figure 3: MRI Brain (T2/FLAIR) showing hyperintense signals in bilateral cerebellum, features of atypical PRES



PRES in the renal transplantation scenario is complex and multifactorial. Calcineurin inhibitor toxicity is the obvious causal candidate here, but serum levels of the CNI do not seem to correlate with neurotoxicity in multiple studies[13,14,15]. Our patient in this case series also had tacrolimus levels within the normal range. It is possible that CNI induced PRES may not be a dose related effect, but the mechanism of action appears obscure. In this situation, choosing an alternative immunosuppressive regimen is not without its own risks. Complete avoidance of CNIs may be achieved by conversion to an alternative regimen such as cyclosporine or mTOR inhibitor–based therapies, running the risk of rejections in the process. Reduction in drug dosage may be tried. Our patient in this series was maintained on calcineurin inhibitor with a target level of 6-7ng/dl.

The presence of PRES in patients with various levels of chronic kidney disease, including those on hemodialysis has been documented by few studies. Hu et al[16] describe a cohort of 42 patients with PRES, all of whom had a high mean presenting blood pressure. Canney et al's[5] 5 patients had significantly high blood pressure in 3 out of 5 cases. Considering the disease burden of chronic kidney disease and presence of multiple risk factors, clinicians must have a high index of suspicion in this subset of patients. In our case series, 5 out of 6 had varying degrees of chronic kidney disease, all had significant hypertension at presentation and one had recurrence.

Conclusions

- Posterior Reversible Encephalopathy syndrome is not unexpected in patients with renal disease, although true incidence is unknown.
- Uncontrolled hypertension is commonly associated with, although not necessary to diagnose PRES
- PRES need not be bilateral and confined to pareito-occipetal regions. Unilateral and atypical forms may occur.

Children may develop PRES at lower absolute levels of blood pressure than adults.

Table 1: Comparison of major case series of PRES

Case series	n	ESRD	Non ESRD Renal Failure	Transplant/ Immunosuppressed	Hypertension	Mortality	Recurrence
Hinchley et al	15	0	8	7	66% (10/15)	0	0
Canney et al	5	5		0	60% (3/5)	2	0
Ganesh et al	5	1	2	2	60% (3/5)	0	1
Burrus et al	13	0	Not available	Not available	Not available	Not available	Not available
Chandragiri et al	18	18	0	0	100%	0	4
Oliveria et al	3	3	0	0	100%	0	0

Table 2: General characteristics

Age/ Sex	Renal Function impairment	Kidney Disease	Hypertension (MAP>150/90mm Hg)	Calcineurin inhibitor	Symptoms	Recurrence	Distribution of lesion
15/F	Y (CKD on HD)	IgAN	Y	N	seizure	N	pareito occipetal
24/M	Y (Post tx)	IgAN	Y	Y	seizure	N	pareito occipetal
51/M	Y (CKD on HD)	IgAN	N	N	encephalopathy	N	b/l cerebellar, cerebral hemisphere brain stem
14/F	Y (CKD on HD)	Lupus nephritis	Y	N	seizure	N	cerebellum, gangliocapsule, fronto parietal -occipetal
45/F	Y (CKD on HD)	unknown	Y	N	encephalopathy	Y	pareito occipetal
17/F	Y (CKD)	Membranous nephropathy	Y	N	encephalopathy	N	gangliocapsular, pareital

Y-Yes; *N*-No; *CKD*-Chronic Kidney Disease; *IgAN*-IgA Nephropathy

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