Original Article

Clinical Profile and Outcome of Posterior Reversible Encephalopathy Syndrome in Hemodialysis Patients

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiologic entity characterized by headache, altered level of consciousness, seizures, visual disturbances, and reversible vasogenic subcortical edema. Hypertension and renal failure are well known principal risk factors for the development of PRES. However, risk factors and outcome of PRES has not been studied in patients on maintenance hemodialysis (MHD). The objective of this study is to characterize the factors predisposing to the development of PRES in patients on MHD. We performed a retrospective analysis in patients of MHD who were diagnosed with PRES between August 1, 2013, and July 31, 2015. Those with a history of cerebrovascular accidents/stroke, and epilepsy were excluded. We analyzed the clinical details, course, and laboratory data. One year follow-up data were noted in recurrence of PRES and mortality. A total of 18 patients were included for the final analysis. Of these, 13 (72%) patients were males. Majority of these patients were young and mean age was 21.1 years (6–50 years). Most of the PRES episodes developed shortly after initiation of MHD with mean duration of 2 months after initiation of MHD (1 month–3 years). All 18 patients had resistant hypertension. Eight (45%) patients had infection at the time of PRES episodes. Four patients had catheter-related bloodstream infection, 1 had pneumonia and 3 patients were recently diagnosed with pulmonary tuberculosis. Four (22%) patients developed recurrence of PRES and all these episodes developed within 2 months of index event. Seven (39%) patients underwent renal transplantation, and all received triple immune suppression and had uncontrolled hypertension in the perioperative period. However, none of these patients developed PRES after transplantation. All these patients had been maintaining stable graft function in the follow-up. All episodes of PRES were of generalized tonic–clonic seizure type and 6 of them presented as status epilepticus. None of them had any neurological sequel and no mortality at the end of 1 year. PRES is not uncommon in patients on MHD. Uncontrolled hypertension and infection are common predisposing factors. Renal transplantation is safe and not adversely affected by prior episodes of PRES in MHD.

Keywords: *Hemodialysis, hypertension, infection, posterior reversible encephalopathy syndrome*

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinic-radiologic entity characterized by headache, altered level of consciousness, seizures, visual disturbances, and reversible vasogenic edema.[1-3] Radiologically, commonly there is vasogenic edema within the occipital and parietal regions (~95% of cases), perhaps relating to the posterior cerebral artery supply. The edema is usually symmetrical. Although it is termed posterior, PRES can be found in a nonposterior regions, mainly in watershed areas, including within the frontal, inferior temporal, cerebellar and brainstem regions. Both cortical and subcortical locations are affected. PRES is associated with acute hypertension and often complicates the management of acute kidney injury (AKI) and chronic kidney disease (CKD).[1,2] There are very few case reports of PRES in hemodialysis patients, and this entity has not been studied systematically. The objective of this study is to characterize the factors predisposing to the development of PRES in patients on maintenance hemodialysis (MHD).

Materials and Methods

We performed a retrospective analysis in patients on MHD who were diagnosed with PRES between August 1, 2013, and July 31, 2015. Those with a history of cerebrovascular accidents/stroke, and epilepsy were excluded. PRES was diagnosed when patients presented with

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symptoms of headache, visual disturbances, seizures, altered sensorium, and suggestive radiologic findings. Other neurologic disorders were ruled out. Cerebrospinal fluid analysis was done when necessitated. We analyzed the clinical details, course, and laboratory data. Patients with sepsis were thoroughly investigated for the focus of infection and treated. Treatment of patients with PRES included anticonvulsants and control of hypertension. Antiepileptic drug, levetiracetam was used as the first choice. These patients were followed for 1 year for recurrence of PRES, neurologic sequelae, and mortality. Patients undergoing transplantation were monitored closely in the perioperative period for recurrence of PRES. Antiepileptics were continued for 3 months, then tapered and stopped.

Statistical analysis

For continuous variables, the results were expressed as mean ± standard deviation and range. Categorical variables were expressed as frequency and percentages.

Results

A total of 18 patients with PRES in the study period were included [Table 1]. They were predominantly male (13/18) and predominantly younger patients. Mean age was 21.11 ± 9.71 years (6–50 years). Underlying kidney disease was biopsy proven chronic glomerulonephritis (CGN) in 4, biopsy-proven chronic interstitial nephritis (CIN) in 2, IgA nephropathy in 2, lupus nephritis in 1, stone disease in 1, and medullary cystic kidney disease in 1. In the remaining 7 patients underlying kidney disease was not known. The median duration of initiation of hemodialysis to the onset of PRES was 2 months (1 month–3 years). All patients reported good compliance to antihypertensive medications except one who stopped all medicines for 2 days before the onset of PRES. All of them had resistant hypertension since the initiation of hemodialysis. The mean systolic and diastolic pressures were 211.15 ± 25.05 and 116.47 ± 19.66 mmHg, respectively, at the time of the episode. The average number of antihypertensive drugs used was 4.11 per patient. At presentation headache, visual symptoms, altered sensorium, and seizures were universal. All patients had generalized tonic–clonic type of seizures. Of these, 6 patients presented in status epilepticus.

Table 1: Clinical characteristics of study population (*n*=18)

Age (years)	21.1±9.7
Male, *n* (%)	13/18 (72)
Duration on HD	2 months (1 month to 3 years)
Mean number of anti-HTN drugs	4.11
SBP/DBP	211.15 ± 25.05/116±19
GTCS, *n* (%)	18/18 (100)
Recurrence of PRES, *n* (%)	4/18 (22)
Tuberculosis, *n* (%)	3/18 (17)
Sepsis, *n* (%)	5/18 (27)
Transplantation, *n* (%)	7/18 (39)
1 year survival, *n* (%)	18/18 (100)

HD: Hemodialysis, HTN: Hypertensive, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, PRES: Posterior reversible encephalopathy syndrome, GTCS: Generalized tonic-clonic seizure

Eight of the 17 patients (45%) had infection during the episode of PRES. Of these 8 patients, 3 patients were diagnosed recently with pulmonary tuberculosis and were initiated on first line anti-tuberculous medications. All were in their intensive phase. One patient was started on anti-tuberculous treatment (ATT) 1 week before the onset of PRES. The other two were on ATT for 1 month before the onset of PRES. Four patients had dialysis catheter-related bloodstream infection. Blood culture was positive for enterococcus in one and MSSA in the other. Both of them had catheters replaced. The other two had negative cultures and were treated empirically with vancomycin and amikacin. The other patient had pneumonia, required noninvasive positive pressure ventilator support and recovered.

Radiologic findings in the present study showed the involvement of parieto-occipital region (17 [94%] cases), frontal lobe (5 cases), temporal lobe (3 cases), and cerebellum (2 cases). In one case of lupus nephritis, isolated cerebellum was involved.

All patients were treated with levetiracetam and did not require a second antiepileptic drug for seizure control. Second episode of PRES with a recurrence of seizures occurred in 4 patients, and all these episodes recurred within 2 months of the index event. PRES was associated with bleed in one patient who had permanent neurologic deficits and loss of vision. No mortalities were reported in 1 year.

Overall, 7 (39%) patients underwent renal transplantation of which 1 was cadaveric and 6 were live related. All these patients received triple immunosuppression, which includes steroids, tacrolimus, and mycophenolate. They were monitored closely during the perioperative period for seizure recurrence. None had seizure recurrence despite uncontrolled blood pressure postoperatively. All of them achieved immediate and stable graft function on follow-up.

Discussion

Hypertension and renal failure are well known principal risk factors for the development of PRES. Recently Canney *et al*. published a retrospective analysis of 5 cases of PRES in end-stage renal disease (ESRD) population. In this study, 3 patients developed PRES within 4 weeks of initiation of HD and 2 patients were on immunosuppression.[4]

To the best of our knowledge, the present study is the largest study that examined the clinical profile of

PRES in dialysis population. All of our patients had resistant hypertension since the initiation of MHD. In our center, 55% of dialysis patients had uncontrolled blood pressure and mean BP in our dialysis population was 163/101 mmHg and not all these patients developed PRES. Thus, although the acute surge in blood pressure precipitates PRES, all the episodes of hypertensive emergencies were not associated with the development of PRES and additional trigger in the background of uncontrolled hypertension might precipitate PRES and need to be explored strongly. Episodes of PRES developed in an early period of MHD, and this could be due to disturbances in volume status of an individual. Recurrence was noted in few cases (4 of 18), but it was not associated with any long-term morbidity or mortality.

The etiology of PRES remains controversial. Understanding the exact pathophysiology of PRES still remains challenging. Of the two theories, the cytotoxic theory states that vasoconstriction and hypoperfusion lead to brain ischemia and subsequent vasogenic edema. The vasogenic theory states that severe hypertension leads to failed autoregulation, hyperperfusion and endothelial dysfunction which leads to vasogenic edema.[5] Endothelial injury seemed to play a central role in the pathophysiology of PRES.[5] PRES seemed to occur in association with infection and sepsis.[6,7] Endothelial injury is central to the development of sepsis. Eight of our patients with PRES had an infection. Three of them had pulmonary tuberculosis and were started recently on ATT. The pharmacokinetic interactions with antituberculous medications might lead to decreased levels of antihypertensive drugs.

Endothelial dysfunction was hypothesized as the possible factor leading to impaired cerebral autoregulation and vasodilatation. Sepsis-associated endothelial dysfunction could be a precipitating factor to PRES in these patients but needs further evaluation into the other possible triggers for PRES. Endothelial dysfunction could be the common denominator for sepsis and PRES.[7]

The calcineurin inhibitors, cyclosporine, and tacrolimus are known to cause neurotoxicity and can precipitate PRES.[8-11] Glucocorticoids, especially high-dose pulse methylprednisolone is a known trigger for PRES.[12,13] In the presence of these precipitants, even mild-to-moderate hypertension can trigger PRES.[11] Surprisingly, this has not happened in any of 7 patients who underwent renal transplantation. All these seven patients had uncontrolled hypertension in the immediate postoperative period. Despite the presence of multiple risk factors (tacrolimus, pulse methylprednisolone, and severe hypertension), none had a recurrence of PRES. What precipitated PRES in these patients while on their MHD program and what protected them from developing it posttransplantation in the presence of many risk factors, is not clear.

Limitations of our study were retrospective analysis, small sample size, and limited duration of follow up. To confirm these findings and to further explore insights in pathogenesis of PRES in this special population we need prospective studies involving larger sample size and long-term follow-up.

Conclusion

PRES in MHD patients is not uncommon. Uncontrolled Hypertension is essential but not sufficient to cause PRES. Infection is one of the very common predisposing factors. Renal transplantation is safe and not adversely affected by prior episodes of PRES in MHD. One year outcome of PRES is excellent, and survival is not influenced by PRES.

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Conflicts of interest

There are no conflicts of interest.

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