Posterior reversible encephalopathy syndrome in rapid progressive glomerulonephritis

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ABSTRACT

Introduction: Posterior reversible encephalopathy syndrome (PRES) is a neuro-radiological syndrome affecting the posterior cerebral regions and is associated with an accelerated rise in blood pressure, renal disease or autoimmune disorders. Our objective was to review the association of PRES with renal outcome. Materials and Methods: Retrospective review of all nephrology patients diagnosed with PRES from 2010 to 2013 at our institution. The diagnosis of PRES was based on the presence of clinical features such as headache, altered mental status, visual disturbances and seizures with positive radiological findings on either Magnetic Resonance Imaging or Computed Tomography of the brain. Their demographic and laboratory result were analysed in particular, progression to end stage renal disease (ESRD). Results: Seven patients (3 males: 4 females), median age of 21 (IQR 17-24) years were recruited. Majority had lupus nephritis except one patient who had crescentic IgA nephropathy. Median duration of their disease was 52.83 (IQR 3.3 - 58.17) months. Mean systolic and diastolic blood pressure were 186.43 ± 18.87 and 110.43 ± 14.02 mm Hg. Mean serum albumin and creatinine were 27.3 ± 8.7 g/L and 403.4 ± 183.6 umol/L respectively, at presentation. Two patients developed ESRD at the development of PRES whereas three patients progressed to ESRD at 2.73, 5.77 and 17.13 months. The other two patients had complete recovery of renal function to normal levels. All patients had full neurological recovery within one week. Conclusion: Development of PRES in patients with underlying chronic kidney disease may be a predictor of poor renal survival.

Keywords: Chronic kidney disease, end stage renal disease, hypertension, lupus nephritis, posterior reversible encephalopathy syndrome

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a neuro-radiological syndrome that is characterised by a wide range of neurological signs and symptoms (headache, altered mental status, visual disturbances and seizures) and accompanied by typical radiological findings (œdema of the posterior cerebral regions especially the parieto-occipital lobes). It was first described in 1996 as reversible posterior leukoencephalopathy syndrome in patients with renal insufficiency, hypertension or on immunosuppressive therapy. Other conditions associated with PRES include toxæmia of
pregnancy, solid organ transplantation and chemotherapy. \(^2\)\(^-\)\(^6\)

The pathophysiology is still unclear and several theories have been proposed. A widely accepted theory is the breakdown of the cerebral auto-regulation secondary to accelerated hypertension resulting in extravasation of proteins and fluids in the vulnerable posterior parts of the brain. \(^2\)\(^,\)\(^7\)\(^,\)\(^8\) Other theories involve endothelial dysfunction and vasospasm leading to focal areas of ischaemia, resulting in the syndrome. \(^9\)\(^-\)\(^11\) In the presence of an insult, endothelial cells become activated and are damaged by an inflammatory cytokine response from monocytes and lymphocytes, leading to leakage of fluid and proteins into the interstitium. \(^11\) PRES has also been associated with thrombotic thrombocytopenic purpura (TTP) and this also supports the theory of endothelial dysfunction. \(^12\) There is a significant association of PRES with autoimmune diseases with up to 45% of patients having an underlying autoimmune diseases (such as systemic lupus erythematosus; SLE). \(^1\) This further strengthens the theory of endothelial dysfunction which is an essential process in autoimmune diseases. \(^1\) Most studies have reported good neurological prognosis with reversal of neurological symptoms within one week.

PRES is a well recognised phenomenon in patients with renal insufficiency. Most reported cases of PRES in this subgroup population have been associated with hypertension. \(^2\) In renal insufficiency, development of hypertension is mediated by an impairment of renal auto-regulation following a significant reduction of functional renal mass. \(^13\) However, there is no data on the impact of PRES on renal outcome. Therefore, the aim of this study was to review the effects of PRES on patients with renal disease and assess its association with renal outcome.

**MATERIALS AND METHODS**

We retrospectively reviewed records of all patients under the follow-up at our institution over the last three years with a diagnosis of PRES. Demographic data collected include cause and duration of underlying disease, renal function, immunosuppressive regimen and clinical presentation. The diagnosis of PRES was made based on clinical features (headache, altered mental status, visual disturbances and seizures) with positive radiological findings on either Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) of the brain. Figure 1 demonstrates the classical MRI findings that are seen in patients with PRES.

We excluded all electrolyte, metabolic and other neurological diagnoses. All MRI/CT scans were reviewed and verified by a consultant radiologist. As all patients had full neu-

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**Fig. 1:** MRI demonstrating bilateral symmetrical hyperintensities involving the posterior parietal and occipital regions (arrows).
### RESULTS

There were seven cases of PRES in our cohort of 950 patients with glomerulonephritis during this three year period, giving an incidence of 0.74%. Details of the demographics, diagnosis and presentation are shown in Table 1. All patients with seizures received anti-convulsant therapy. The median age was 21 (IQR 17-24) years. Duration from diagnosis of disease to the development of PRES was

<table>
<thead>
<tr>
<th>Age/ Gender</th>
<th>Diagnosis</th>
<th>Clinical Presentation</th>
<th>Radiology Findings of PRES (MRI/CT)</th>
<th>Progression to ESRD (months)</th>
<th>Treatment for GN and HT</th>
<th>CNI prior to PRES</th>
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<td>21/F</td>
<td>SLE diagnosed 2008 - Relapsed in October 2012</td>
<td>Refractory hypertension with seizure in 2012</td>
<td>Hyperintensities of sub cortical and cortical of both posterior parietal and occipital regions</td>
<td>ESRD at presentation</td>
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<td>None</td>
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<td>Acute kidney injury with complete renal recovery in two weeks</td>
<td>High dose corticosteroids, Plasmapheresis, IV Cyclophosphamide</td>
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<td>Newly diagnosed SLE with LN - Class IV with MAHA (2012)</td>
<td>Headache, seizure and accelerated hypertension in 2012</td>
<td>Bilateral hypertensi- ties in cortical and subcortical occipital, posterior parietal and frontal lobes, as well as cerebellum</td>
<td>Acute kidney injury with complete renal recovery in 4 weeks</td>
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<td>SLE diagnosed 2004 LN - Class IV/V</td>
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<td>SLE diagnosed 2005 LN - Class IV/V with 75% crescents</td>
<td>Seizure and hypertension in 2011</td>
<td>Bilateral white matter hyperintensities in both occipital lobes</td>
<td>Progressed to ESRD in 5 months</td>
<td>High dose corticosteroids, Plasmapheresis, IV Immunglobulin, Low dose IV Cyclophosphamide, Rituximab</td>
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<td>CI 68 mg/dL, C4 23 mg/dL, ANA 1:400 homogenous, DsDNA positive</td>
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<td>33/M</td>
<td>SLE diagnosed -1998 AHA/ITP/refractory LN - Class III/V</td>
<td>Seizures in 2012</td>
<td>Hyperintensities of cortical and subcortical region and left posterior parietal lobe</td>
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### Table 1: Demographics and characteristic of patients with PRES.

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Two patients had ESRD at the time of development of PRES and received regular haemodialysis. One patient opted for long-term peritoneal dialysis. Three patients progressed to ESRD at 2.73, 5.77 and 17.13 months respectively, and they all opted for peritoneal dialysis. The two male patients who presented initially with rapidly progressive glomerulonephritis had complete recovery of renal function within four weeks of disease onset (Table 1). All patients had full neurological recovery within one week. As all patients presented with accelerated hypertension and were symptomatic, all received intravenous labetolol to control their hypertension, titrated to avoid a rapid decline in blood pressure. They were also initiated on oral anti-hypertensive therapy and adjusted to achieve target blood pressure of <130/80 mmHg.

Calcineurin inhibitor was stopped in the one patient who was receiving this for her SLE and was switched to an alternative immunosuppressive therapy. All patients received immunosuppressive therapy for their glomerulonephritis (Table 1).

**DISCUSSION**

Up till now, there are 109 reported cases of PRES. Of these, 85.1% are associated with underlying renal involvement. All our patients with PRES had either acute kidney injury, or acute on chronic kidney disease. All patients were hypertensive at the time of PRES development and in keeping with other studies. Although hypertension is associated with the development of PRES, the severity of hypertension is not significantly associated with the intensity of PRES.

A widely accepted mechanism of PRES is the breakdown of cerebral auto-regulation as a result of accelerated hypertension leading to extravasation of proteins and fluids, endothelial dysfunction leading to focal areas of ischaemia and disruption of the endothelial aquaporin-4 water channels in autoimmune-mediated disease.

In renal insufficiency, development of PRES is mediated by endothelial dysfunction which leads to fluid retention. Furthermore, there is stimulation of renin angiotensin system and impairment of renal auto-regulation following a reduction of functional renal mass which leads to hypertension. Hypertension and the administration of calcineurin inhibitors are considered to be the two principal risk factors for the development of PRES. However, to date there are no reported cases of PRES in liver/cardiac transplant recipients with high trough levels of calcineurin inhibitors. This suggests that either hypertension or renal impairment is a prerequisite factor in the development of PRES in patients on calcineurin inhibitors. Only one patient was on a calcineurin inhibitor prior to the development of PRES in our case series.

Apart from hypertension, PRES also has been described in both adult and paediatric patients with nephrotic syndrome. A low serum albumin, generalised oedema, un-
stable fluid status, increase in vascular permeability and renal insufficiency are the predisposing factors for the development of PRES. 19, 20 Other factors such as decreased intravascular oncotic pressure and increased permeability of capillaries in the nephrotic state could induce vasogenic oedema and fluid overload. Our entire study cohort demonstrated a low serum albumin.

In our case series, two patients presented with ESRD at diagnosis and the other three patients progressed to ESRD shortly after developing PRES. The three patients that progressed to ESRD had refractory disease with inadequate treatment of their lupus nephritis due to non compliance. PRES has been well reported in SLE. 23-25 The postulated pathogenesis of chronic kidney disease progression is either through blood pressure dependent mechanism or blood pressure independent mechanism. 26 We found in our patient with PRES, despite control of blood pressure, they still progress to ESRD indicating blood pressure independent mechanism. These effects are mediated by renin angiotensin system stimulation, hypoxia, cytokines and nitric oxide. 27, 28 These three patients had already chronic kidney disease with deteriorating renal function that was aggravated by PRES and hence the rapid progression to ESRD. Patients with renal disease have glomerular arterioles that are chronically inflamed and under continuous stimulation by the renin angiotensin system. Therefore, there is less recovery of the oedema and hence the progression of renal failure.

All patients were young and majority either had refractory disease or presented initially with rapidly progressive glomerulonephritis. Rapidly progressive glomerulonephritis can lead to a rapid increment in blood pressure which can then trigger PRES as seen in cases of lupus nephritis, post streptococcal glomerulonephritis and crescentic IgA nephropathy. 29, 30 However, the patients that presented for the first time with rapidly progressive glomerulonephritis had good renal recovery as the treatment was instituted early thereby reversing the effects of endothelial dysfunction and better control of hypertension.

Patients with PRES usually have full neurological recovery and this is in keeping with our findings. This is because the neurological disturbances like vasogenic oedema changes are transient as these patients have normal cerebral vasculature. This is also supported by the fact that our patients with first presentation of rapidly progressive glomerulonephritis had complete renal recovery. Treatment of PRES is based on antihypertensive and/or anti-convulsant therapies, the withdrawal of suspected drug and the treatment of SLE flare if present.

Our study has limitations in that it is a small cohort of patients and confounded by several factors that can also lead to progression to ESRD.

In conclusion, development of PRES can occur in acute or chronic kidney injury. In patients with chronic kidney disease who develop PRES, one can anticipate that they may progress to ESRD earlier.

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REFERENCES


