Posterior Reversible Encephalopathy Syndrome in End-Stage Kidney Disease: Not Strictly Posterior or Reversible

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Key Words
Posterior reversible encephalopathy syndrome · End-stage kidney disease · Haemodialysis · Magnetic resonance imaging · Hypertension

Abstract
Posterior reversible encephalopathy syndrome (PRES) is an uncommon clinico-radiological condition that can result in severe brain injury. The pathogenesis of cerebral vasogenic edema, the hallmark of PRES, is not fully understood. Despite its name, there is substantial heterogeneity both in terms of imaging findings and outcome. Relatively little is known about PRES in kidney disease despite the clustering of risk factors including hypertension, autoimmune disease and immunosuppression. In a retrospective observational study of incident end-stage kidney disease patients in Southwest Ireland over a ten year period, we discovered five cases of PRES representing an incidence of 0.84% in this patient population. These five cases highlight the variability in clinical presentation and the potentially life-threatening nature of this condition. We provide an in-depth review of the existing literature regarding PRES in terms of its pathogenesis and heterogeneity, as well as the experience of PRES in ESKD patients. PRES appears to be rare in the ESKD population but could be under-recognized. Marked hypertension is a cardinal risk factor in this population, associated with extracellular fluid volume expansion. Neuroimaging findings can be diverse involving both anterior and posterior circulation territories. Three of the five patients described had commenced haemodialysis within four weeks of their presentation. These patients may be particularly vulnerable to microvascular brain injury, which can be devastating. This emphasises the need for clinicians to pay meticulous attention to extracellular fluid volume control during this potentially hazardous period.

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological disorder characterised by the abrupt onset of neurological symptoms associated with potentially reversible lesions on brain imaging. The differential diagnosis is broad due to the heterogeneity of symptoms which include seizure, headache, visual disturbance and altered mental status. Diagnosis is made using computerised tomography (CT) or, most commonly, magnetic resonance imaging (MRI), the latter using diffusion weighted imaging (DWI). The epidemiology of PRES is largely unknown due to the paucity of large prospective series. Although PRES can affect people of all ages, the median age at presentation is approximately 40 years based on existing registry data [1, 2]. Females appear to be affected more than males [1].
The nomenclature of this condition has been the subject of much debate ever since its original description in 1996 [3]. Hinchey et al. observed a consistent pattern in both neurological symptoms and brain imaging findings in 15 patients and coined the term 'Reversible Posterior Leukoencephalopathy Syndrome'. The nomenclature changed over subsequent years to 'PRES' in an effort to popularise the diagnosis and reflect its association with elevated blood pressure [4]. However, the appropriateness of the acronym PRES has been questioned, specifically with regard to the reversibility of the lesions and the anatomical restriction to the posterior compartment of the brain [5].

There have been scattered reports of PRES in kidney disease but it has never been researched in a systematic fashion. In Hinchey’s original paper, over half of the cases had an abnormal serum creatinine, one third had a serum creatinine over 3 mg/dl (265 μmol/l) and hypertension was present in 80% of cases. PRES has been observed in the context of many multi-system diseases that are commonly associated with kidney disease such as pre-eclampsia, vasculitis and systemic lupus erythematosus. PRES has also been encountered following solid organ transplantation and with the use of calcineurin inhibitors. Despite these consistent associations with kidney disease risk factors, the literature regarding PRES in individuals with established kidney disease is relatively sparse. We describe our experience of PRES in five patients with end-stage kidney disease (ESKD) along with a critical review of the existing literature. Details of the cases are summarised in table 1.

### Cases

#### Case 1

A 15-year-old female presented with rapidly progressive glomerulonephritis secondary to granulomatous polyangiitis. Her serum creatinine at presentation was 1,191 μmol/l and she was commenced on haemodialysis. She received induction immunosuppression in the form of pulsed intravenous methylprednisolone in combination with plasma exchange and mycophenolate mofetil. Her symptoms improved and she was discharged home on maintenance haemodialysis three times per week for four hours. She continued on mycophenolate mofetil and oral prednisolone. Twelve days later she was readmitted with generalised tonic-clonic seizures. She was hypertensive on admission with a blood pressure (BP) of 150/110 mm Hg (mean arterial pressure (MAP) 123 mm Hg). Her blood pressure was initially managed using intravenous labetalol. She was admitted to the intensive care unit and commenced on continuous renal replacement therapy. Repeat MR imaging 3 weeks later demonstrated complete resolution of the aforementioned lesions.

| Age, years | 15 | 64 | 43 | 20 | 56 |
| Gender | Female | Male | Male | Male | Female |
| Cause of ESKD | ANCA-associated vasculitis | Hypertension | Anephric | Lupus nephritis | Diabetic nephropathy |
| Recent initiation of HD (<4 weeks) | Yes | No | Yes | Yes | No |
| Recent immunosuppression | Yes | No | No | Yes | No |
| Clinical presentation | Seizures | Ataxia | Headache, seizures | Headache, seizures | Altered mental state |
| BP (MAP), mm Hg | 150/110 (123) | 198/140 (159) | 180/111 (134) | 162/114 (130) | 202/91 (128) |
| Cerebral involvement | Bilateral frontal and parietal lobes | Left parietal and bilateral occipital lobes | Left frontal and parietal lobes (haemorrhagic) | Right occipital, left parieto-occipital lobes | Right hemisphere |
| Outcome | Resolution | Resolution | Death | Resolution | Death |

ANCA = Anti-neutrophil cytoplasmic antibody; BP = blood pressure; ESKD = end-stage kidney disease; HD = haemodialysis; MAP = mean arterial pressure.
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his day four-hour haemodialysis. His BP on admission was

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tional transitional cell carcinoma ultimately requiring bilateral ne-

Case 2
A 64-year-old male with a background of stage 5 chronic kid-

casey disease (CKD) and longstanding hypertension was admitted

with ataxia and speech disturbance. He had stopped taking his an-

ti-hypertensive medications in the previous 4 months. His BP on

admission was 198/140 mm Hg (MAP 159 mm Hg). On examina-

tion he was found to be dysarthric and had reduced lower limb

power and poor co-ordination. Serum creatinine was 940 μmol/l

on admission and he was commenced on haemodialysis. MRI

brain revealed extensive edema involving thalami, midbrain and

upper pons. Scattered areas of restricted diffusion were seen in

both occipital lobes and in the left parietal-occipital area. His BP

was managed using a combination of anti-hypertensive medica-

tions and frequent ultrafiltration. He was discharged with full res-

olution of his symptoms 3 weeks later.

Case 3
A 43-year-old male presented with severe headache, vomit-

ing, expressive dysphasia and seizures. He had a background of recur-

rent transitional cell carcinoma ultimately requiring bilateral ne-

phrectomy. In the four weeks prior to this period he was established

on maintenance haemodialysis. His BP post-operatively was ini-

tially low but started to increase over subsequent weeks. This was

being managed by progressive reduction in dry weight with alter-

nate day four-hour haemodialysis. His BP on admission was

180/111 mm Hg (MAP 134 mm Hg). He was commenced on

CVVH and parenteral antihypertensive therapy (intravenous labetalol infusion). An MRI brain revealed extensive bilateral vaso-

genic edema with secondary haemorrhage in the left frontal and

parietal lobes with consequent subfalcine herniation. Findings

were in accordance with the haemorrhagic variant of PRES. An

EEG showed an excess of diffuse slow wave activity, consistent

with a moderate diffuse encephalopathy. Despite intensive ultrafil-

tration, anti-hypertensive and anti-seizure medications, his condi-

tion deteriorated. He died 24 h later from brainstem compression.

Case 4
A 20-year-old male presented to the ER with multiple gener-
alised tonic-clonic seizures. He also complained of headache and

blurred vision. He had a background of ESKD secondary to lupus

nephritis. He was started on haemodialysis three weeks prior to

this period and was attending the dialysis unit for four hours three
days per week. The primary indication for dialysis was extracellular

fluid volume expansion and poorly controlled hypertension.

This was in the context of a severe systemic flare of his lupus neces-
sitating high-dose steroids (prednisolone 40 mg daily), nine ses-
sions of plasma exchange and four doses of rituximab. On arrival

his BP was 162/114 (MAP 130 mm Hg). He was poorly responsive

with decreased muscle tone throughout and up-going plantar re-

sponses. A non-contrast CT brain showed foci of low attenuation

involving the subcortical white matter in the right occipital lobe

and left parieto-occipital region. Subsequent MRI revealed high-

signal areas in the frontal lobe white matter as well as the grey and

white matter of the occipital lobes bilaterally. His BP was con-

trolled with a combination of anti-hypertensive medications and

frequent ultrafiltration. Repeat MRI two weeks later demonstrated

complete resolution of these abnormal areas.

Case 5
A 56-year-old lady presented with acute onset confusion, vomit-

ing and myoclonus. She had a background of ESKD, hypertension,

coronary artery disease and longstanding type 1 diabetes mellitus.

She had been receiving intermittent haemodialysis for three-and-a-
half hours 3 days per week for 2 years. Her blood pressure was being

managed with a combination of ramipril, amiodipine and bisoprol-

ol. Shortly into her admission to hospital she had further deteriora-

tion in her mental state with fluctuating levels of alertness. This

coincided with worsening hypertension (peak BP 202/91 mm Hg,

MAP 128 mm Hg). EEG demonstrated a diffuse slow wave pattern

in keeping with metabolic encephalopathy. On day 12 of her admis-

sion, she experienced multiple seizures and was transferred to the

intensive care unit where she was intubated, sedated and com-

menced on CVVH. MRI brain revealed extensive edema with dif-

fusion abnormalities primarily involving the right hemisphere,

portions of which showed restricted diffusion suggesting foci of

superimposed infarction. Her blood pressure remained labile and

she continued to have seizure activity. She subsequently developed

multiple organ dysfunction syndrome and died.

Discussion
Pathophysiology of PRES
Before exploring the pathogenesis of PRES, we will

first revisit some concepts of cerebral blood flow. Auto-

regulation refers to the ability of an organ to alter its vas-

cular resistance and maintain normal flow despite chang-

es in arterial pressure [6]. This is particularly important in

the brain, an organ that receives approximately 15% of
cardiac output. Cerebral blood flow must be maintained constant despite fluctuations in systemic arterial pressure. In the setting of low blood pressure cerebral arterioles will dilate to increase flow to the capillaries. In contrast, high blood pressure will result in arteriolar vasoconstriction to limit flow downstream. Such is the sophistication of this system, the human brain can maintain normal perfusion within a range of mean arterial pressure between approximately 60 and 140 mm Hg [7]. Beyond these thresholds of autoregulation brain injury will occur due to hypoperfusion or hyperperfusion, respectively.

The hallmark of PRES is vasogenic edema. The advent of DWI has facilitated the differentiation of vasogenic edema from cytotoxic edema [8, 9], the latter an irreversible phenomenon due to tissue infarction [10]. Controversy exists, however, as to the pathogenesis of vasogenic edema in PRES and the role of hypertension. Two theories, recently reviewed by Bartynski [11], have been suggested. Table 2 provides a summary of the conceptual differences between the two hypotheses. In the most popular theory, severe systemic hypertension overwhelms the autoregulatory capacity of the cerebral vasculature (principally arterioles) leading to hyper-perfusion, arteriolar dilatation, injury to the capillary bed and vasogenic edema. Sympathetic stimulation can raise the upper threshold of autoregulation; therefore, the predilection of PRES for the posterior brain, where there is a relative lack of sympathetic innervation, adds weight to this hypothesis. Although logical, there are a number of problems with this theory. First, blood pressure is not always elevated in PRES [2, 3, 12], and this is particularly true in cases associated with immunosuppression [2] and organ transplantation [13, 14]. In addition, the degree of vasogenic edema does not always correlate with the severity of hypertension [13].

In the second theory, the principal problem is cerebral vasoconstriction that results in downstream hypo-perfusion, ischaemia and vasogenic edema due to capillary leak. Again the strongest argument in favour of this hypothesis is the recognition that blood pressure is either normal or minimally elevated (i.e., below the upper autoregulatory threshold) in a significant proportion of PRES cases. Hypertension therefore cannot be the sole driver of injury in all cases. Indeed PRES is often encountered in the context of a systemic process such as autoimmune disease [15], organ transplantation [13, 14] and pre-eclampsia [16]. These conditions share many pathophysiological features including upregulation of the acquired immune response and endothelial cell activation and/or injury. Endothelial cell dysfunction can lead to altered vascular tone, vasospasm, sustained hypoperfusion and ischaemia. Cerebral vessels respond to hypoxia by secreting vascular endothelial growth factor (VEGF) and increasing their permeability, thereby resulting in edema [11]. The concept of hypoperfusion is further supported by the location of injury encountered in PRES, which is consistent with the so-called watershed areas of the brain [1]. These observations support the notion that a systemic process causing endothelial dysfunction results in a cascade of events culminating in cerebral vasoconstriction, hypoperfusion and ischaemia.

Although there is some evidence to support either theory, retrospective study design, varying terminology and different imaging modalities all make it difficult to choose one theory over another. They may not be distinct from...
one another. For instance, in our cohort, although hypertension was a common feature among all five patients, the peak MAP was below the recognised upper limit of autoregulation in four cases. Other authors have proposed an upper MAP threshold of 116 mm Hg to define clinically severe hypertension in the context of PRES [2, 12]. Using this cut-off all five of our cases would have been classified as having severe hypertension. Two of the patients (cases 1 and 4) had a co-existent systemic inflammatory disorder with recent exposure to potent immunosuppressive agents. It is plausible that another process could reduce the upper autoregulatory threshold by altering vascular dynamics, thus increasing the potential for hypertension-mediated injury.

**Heterogeneity of PRES**

A key observation from the cases described earlier is the heterogeneity both in terms of lesion distribution and clinical outcome. Despite the original definition of this disorder as a posterior phenomenon, potentially all areas of the brain can be affected. The classical pattern of vasoergic edema in the parietal or occipital region is still seen in a majority of cases. Frontal lobe involvement, however, has been reported to be as high as 68% [1]. In the Berlin PRES study, involvement of frontal and temporal lobes occurred in one half of cases [2]. Lesions involving the infra-tentorial region, particularly the cerebellum, were encountered in more than half of cases.

One of our patients had a haemorrhagic variant of PRES. In large case series intracranial haemorrhage has been encountered in 15 to 32% of cases [2, 12]. In a study of haemorrhagic PRES, seizure and confusion were the most common presenting features; however, hypertension was surprisingly not a significant factor in the development of haemorrhage [12]. Two of the five patients described died during their admission emphasizing the serious and potentially life-threatening nature of this condition. The Berlin PRES study demonstrated that, of those who had repeat imaging performed, 43% had incomplete resolution of edema on repeat MRI [2]. A significant factor associated with incomplete resolution was higher MAP at presentation. The presence of haemorrhage also portends a worse outcome [12].

**PRES in ESKD**

Given the fact that hypertension is a significant factor in the development of PRES, and the consistent associations of PRES with autoimmune diseases and immunosuppressive drugs, one would anticipate a high incidence of PRES in individuals with ESKD. Based on current literature, this does not appear to be the case. The cases described earlier were found by interrogating the incident ESKD database of South West Ireland. Of a total of 592 cases of incident ESKD over a ten-year period, 5 cases of PRES were discovered representing an incidence of 0.84% in this population. In the larger published series of PRES, kidney disease does not feature prominently outside the realm of solid organ transplantation. PRES has been observed in a number of individuals receiving peritoneal dialysis. Most of these cases had significant hypertension at presentation and responded to BP control with or without ultrafiltration [17–20].

In three of the five patients described here, the onset of PRES was within weeks of commencing haemodialysis. This suggests a vulnerability period during which time patients were becoming accustomed to fluctuations in MAP by alterations to their ‘dry weight.’ A key learning point from these cases is the need for meticulous extracellular fluid volume and blood pressure control at the time of commencement of dialysis. Anuric patients in particular need very close monitoring and avoidance of long inter-dialytic gaps. In a recent review of three cases of PRES in haemodialysis patients, severe hypertension was the key clinical finding and responded well to strict volume control without the need for anti-hypertensive agents. Two of these patients developed PRES within three months of starting haemodialysis [21].

It is possible that pre-existing brain injury could predispose to PRES in dialysis patients. Clinically silent white matter lesions are common in individuals with kidney disease and probably reflect associated vascular disease [22]. In an interesting study of patients undergoing their first haemodialysis, MR brain imaging was performed within 30 minutes before and after the dialysis treatment [23]. Baseline imaging demonstrated a diffuse increase in apparent diffusion coefficient (ADC) in ESKD patients compared to controls indicative of interstitial edema. In the post-dialysis images, the ADC further increased particularly in the frontal lobes, suggestive of worsening interstitial edema. None of the patients who underwent haemodialysis experienced significant neurological symptoms. Brain imaging abnormalities without accompanying symptoms after dialysis has been reported elsewhere [24]. It is likely, therefore, that our dialysis patients do experience neurological sequelae of their treatment, but only a proportion comes to clinical attention. In our cases the onset of neurological symptoms was outside the dialysis or immediate post-dialysis period, and severe hypertension was the predominant feature. This, along with the particular imaging findings, favoured PRES as the diagnosis.

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PRES in ESKD

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Transplantation

The incidence of PRES post-transplantation varies depending on the type of organ transplanted. A retrospective single-centre study of 4222 solid organ transplant patients showed an overall incidence of PRES of 0.49% [13]. The incidence of PRES in kidney transplant recipients (KTRs) was 0.35%. Some interesting observations emerged from this study. KTRs with PRES had much higher MAP at presentation than liver transplant recipients (LTRs) but, surprisingly, lower grades of vasogenic edema. LTRs developed PRES much earlier in the post-transplant period than KTRs, often in the setting of severe infection. This is not unexpected given the comparatively poor health status of individuals with liver disease who require emergent transplantation. In both KTRs and LTRs, PRES was diagnosed at the time of co-existent infection or organ rejection. In the context of a complex transplant recipient with infection and/or rejection, it is difficult to attribute a single aetiology to the development of PRES.

Conclusion

PRES is an uncommon entity among patients with ESKD. However, the varied clinical presentation and the increasing recognition of heterogeneous imaging findings make it difficult to be accurate about its true incidence. The reversibility of PRES has to be questioned given our experience and that of other centres. In our experience hypertension was a significant driver of brain injury, often in the setting of recent commencement of haemodialysis. This highlights the need for meticulous extracellular fluid volume control during this potentially vulnerable period.

References