

Posterior Reversible Encephalopathy Syndrome: A Noteworthy Syndrome in End-Stage Renal Disease Patients

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Key Words

Cerebral edema · Hypertension · Peritoneal dialysis · Seizures

Abstract

Background: Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiologic entity characterized by headache, visual disturbances, seizures, and the presence of edema on MRI scan, predominantly in the posterior white matter. Regarding end-stage renal disease (ESRD) and PRES, only a few cases of children on peritoneal dialysis (PD) and adults on hemodialysis have been described in the literature. **Cases:** We report 4 cases of adult patients on PD who presented with PRES, all of which were due to hypertension and inadequate management of fluid balance. The patients expressed typical PRES symptoms such as headache, visual disorders, and tonic/clonic seizures. The patients recovered completely and the MRI lesions disappeared after strict control of volume status. **Conclusion:** Nephrologists should be aware of the syndrome, especially when they manage hypertensive ESRD patients not compliant with the fluid and diet restrictions. MRI scan is the only diagnostic tool for defining the syndrome. Early diagnosis is important, since complete remission is achieved after appropriate treatment.

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Background

Posterior reversible encephalopathy syndrome (PRES) was first introduced by Hinchey [1] in 1996 to describe a reversible syndrome presenting with headache, altered mental functioning, seizures, and visual disturbances accompanied by characteristic neuroimaging findings. The most typical neuroimaging finding is the presence of edema involving the white matter of the posterior portions of the cerebral hemispheres [1]. Complete remission of the symptoms and radiologic findings occurs after appropriate treatment [2]. The syndrome has been observed in numerous clinical conditions such as nephrotic syndrome, acute poststreptococcal glomerulonephritis, solid organ transplantation, bone marrow and stem cell transplantation, eclampsia, systemic lupus erythematosus, hemolytic uremic syndrome, and calcineurin inhibitors treatment [3–5]. The syndrome is well described in children [6], especially in those with kidney diseases [7]. Two cases of children on peritoneal dialysis (PD) presenting with PRES have also been described [8, 9]. Regarding adults, so far only a few cases of hemodialysis patients with PRES have been published [10, 11]. Here, we present 4 cases of adult patients on PD who presented with PRES due to fluid overload and hypertension.

Table 1. Clinical data of the patients (at admission)

	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	45	51	23	59
Primary renal disease	IgA nephropathy	hypertensive nephropathy	Alport syndrome	ADPKD
PD vintage	3 weeks	2 years	2 years	2 years
Blood pressure, mm Hg	200/120	190/90	180/110	240/145
Anihypertensive treatment	furosemide 125 mg valsartan 160 mg nebivolol 5 mg o.d.	furosemide 250 mg o.d. irbesartan 300 mg o.d. diltiazem 300 mg o.d. nifedipine 30 mg b.d. clonidine 150 µg q.d.s. terazosin 5 mg b.d.	valsartan 160 mg o.d. diltiazem 300 mg o.d. amlodipine 10 o.d. clonidine 150 µg b.d. nebivolol 5 mg o.d.	valsartan 320 mg o.d. furosemide 250 mg o.d. clonidine 150 µg q.d.s. metoprolol 25 mg b.d. doxazosin 2 mg q.d.s.
Erythropoetin	darbepoetin alpha 40 µg/week	methoxy polyethylene glycol-epoetin beta 100 µg/month	darbepoetin alpha 100 µg/week	darbepoetin 40 µg every 2 weeks

Neurologic examination and funduscopy were negative in all patients. o.d. = Once daily; b.d. = twice daily; q.d.s. = 4 times daily; ADPKD = autosomal dominant polycystic kidney disease.

Case Reports

Patient 1

A 45-year-old Caucasian woman with end-stage renal disease (ESRD) due to IgA nephropathy, on continuous ambulatory PD treatment for the last 3 weeks, presented with acute headache, diplopia, generalized tonic-clonic seizures, and high blood pressure (BP) (200/120 mm Hg). Her pharmaceutical treatment is shown in table 1. An MRI scan showed findings indicative of PRES (fig. 1). Biochemical results showed adequate dialysis, no electrolyte imbalance, and sufficient acid-base homeostasis (table 2). The patient received phenytoin in the first place. Intensified PD treatment reduced her body weight by 4 kg and her BP was reduced to 128/70 mm Hg with only valsartan 160 mg once daily. A second MRI scan 2 months after the incident showed findings within the normal range (fig. 1).

Patient 2

A 51-year-old Caucasian man on automated PD for 2 years due to hypertensive nephropathy showed generalized tonic-clonic seizures. Phenytoin was started to control the seizures. His BP was 190/90 mm Hg while he was on 6 antihypertensive agents (table 1). An MRI scan was indicative of PRES. The weekly Kt/V was 2 and electrolytes were within the normal range (table 2). After strict control of fluids, the patient's weight gradually decreased (5 kg) within a month, while his BP was 140/86 mm Hg with reduced antihypertensive treatment. Six months later a new MRI scan was normal and the phenytoin was stopped.

Patient 3

A 23-year-old Caucasian man started PD due to ESRD secondary to Alport syndrome. After 2 years on automated PD therapy, he presented with visual disturbances, intense headache, and

grand mal seizures. Phenytoin was initiated. His BP was uncontrolled for at least a few months before the event, and at the time of presentation it was 180/110 mm Hg. His treatment consisted of 5 antihypertensive drugs and erythropoetin (table 1). His laboratory findings were within the normal range for ESRD patients (table 2). An MRI scan showed PRES. Due to ultrafiltration failure the patient was transferred to conventional hemodialysis. His body weight gradually decreased by 4 kg, while antihypertensive treatment was adjusted to reduced drugs/doses. His BP was 146/89 mm Hg 3 months later. A second MRI scan 4 months after the incident showed complete remission and the phenytoin was withdrawn.

Patient 4

A 59-year-old Caucasian woman on PD for 2 years due to autosomal dominant polycystic kidney disease presented with acute headache and visual disturbances. Her BP was 240/125 mm Hg while on therapy with 5 antihypertensives (table 1). Biochemical results showed adequate dialysis, without any electrolyte imbalance and sufficient acid-base homeostasis (table 2). MRI showed findings indicative of PRES. Phenytoin was added to her treatment. The patient was transferred to conventional hemodialysis. Within a month her body weight had decreased by 14 kg and her BP was 110/68 mm Hg with reduced antihypertensive treatment. A second MRI scan 2 months after the incident showed no abnormal findings.

Discussion

In this article we present for the first time in the literature 4 cases of adult patients with ESRD on PD and PRES due to hypertension and fluid overload. Renal failure, ec-

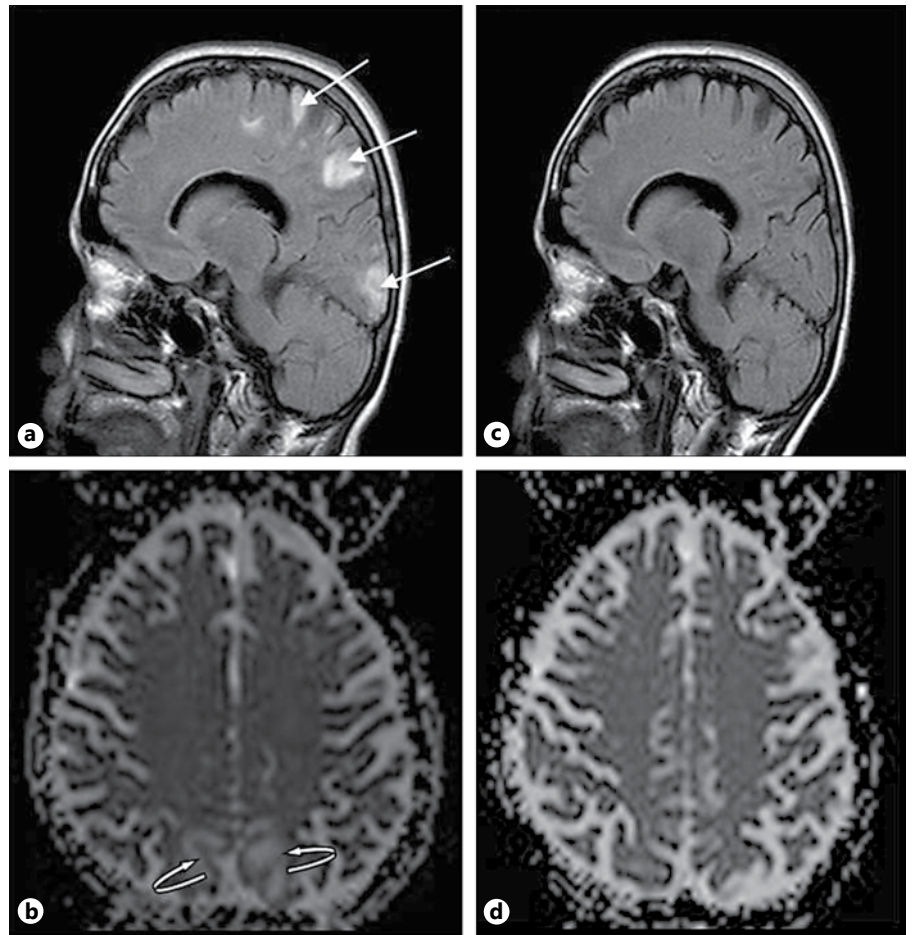


Fig. 1. Representative MRI of a patient with PRES. **a** Sagittal FLAIR (fluid-attenuated inversion recovery sequence) image demonstrates a hyperintense signal in the parietal and occipital lobes (arrows). **b** DWI (diffusion-weighted imaging) reveals that the areas of signal abnormality represent vasogenic edema (curved arrows). **c, d** MR images (FLAIR, DWI) 2 months later showed complete resolution of the lesions.

Table 2. Laboratory values of the patients

	Patient 1	Patient 2	Patient 3	Patient 4
Ure, mg/dl	162	150	118	108
Cr, mg/dl	9.7	17.6	15.9	6.4
K, mEq/l	3.5	4.9	3.7	4.2
Na, mEq/l	138	135	139	142
Ca, mg/dl	8.6	10.3	10	10
PTH, pg/ml	152	342	157	210
Kt/V	2.4	2	1.95	1.85
Hb, g/dl	10.1	10.9	13.1	10.7
Ht, %	33.7	34.2	36.3	31.5

Ure = Serum urea; Cr = serum creatinine; K = serum potassium; Na = serum sodium; Ca = serum calcium; P = serum phosphate; PTH = serum parathyroid hormone; Hb = hemoglobin; Ht = hematocrit; Kt/V = dialysis adequacy.

lampsia, immunologic diseases, sepsis, and treatment with immunosuppressive drugs are the most common conditions associated with PRES. So far, only few cases of PRES in adults on hemodialysis and children on PD have been described in the literature.

The most typical clinical presentation of PRES includes headache, visual disturbances, seizures, generalized tonic-clonic or partial seizures, and altered mental function which ranges from mild somnolence to frank confusion, stupor, or coma [12, 13]. In 70–80% of patients, PRES is accompanied by moderate-to-severe hypertension, while in another 20–30% the BP is normal or minimally elevated. However, PRES can occur without significant hypertension [7]. The symptoms may have a gradual or acute onset, are not specific, and can mimic a variety of neurological conditions, which should be excluded [3, 14]. An important differential diagnosis is hypertensive encephalopathy, which has been historically recognized as a neurological dysfunc-

tion induced by malignant hypertension regardless of imaging abnormalities.

The typical neuroimaging presentation of PRES is vasogenic edema predominantly involving the posterior white matter of the cerebral hemispheres, especially the bilateral parieto-occipital lobes. The radiographic lesions can also involve other areas such as the cortex, frontal lobes, basal ganglia, and brainstem [15–17]. There is no evidence to support a relationship between the clinical symptoms and specific imaging findings of the severity or location of the edema [18]. Complete resolution of the abnormalities has been observed after appropriate treatment, 8 days to 17 months after the first abnormal result [1].

Regarding the pathogenesis of the vasogenic edema, two hypotheses have been proposed: hyperperfusion due to autoregulatory failure of the cerebral vasculature and hypoperfusion due to vasoconstriction of the cerebral artery. The former theory suggests that severe hypertension exceeds the limits of autoregulation, leading to breakthrough, capillary bed injury, hyperperfusion, and brain edema [1, 19, 20]. The second theory of ischemia implies that vasoconstriction secondary to hypertension or autoregulatory compensation leads to reduced brain perfusion, ischemia, and subsequent vasogenic edema [21, 22]. This theory is supported by the expression of PRES in systemic conditions such as transplantation, sepsis, autoimmune disease, and chemotherapy [19]. The cascades of biologic mechanisms are similar in the above mentioned conditions and include: immune system activation, endothelial cell activation, endothelial injury, vascular instability (systemic vasoconstriction), systemic/organ hypoperfusion, and finally capillary leak [12]. However, none of them can completely explain the cascade of events leading to the expression of the syndrome.

The patients we present here expressed the typical PRES symptoms such as headache, visual disturbances, and tonic/clonic seizures. Three of them were treated for a respectable period of time with more than 3 antihypertensive drugs because of refractory hypertension. All of them presented with high BP levels at the onset of the syndrome. Overhydration was also evident due to diet noncompliance in 3 patients and ultrafiltration failure in the fourth. All patients had adequate values of Kt/V while PTH and electrolytes levels were within acceptable ranges. Three patients had hemoglobin values within the guidelines, while 1 patient had hemoglobin of 13.1 g/dl. Initial symptomatic treatment with phenytoin was started in all patients. Later, the drug was withdrawn in all of them after the gradual weight loss and subsequent reduction of BP. Three patients

were managed with strict fluid restriction, intensive PD, and intensive antihypertensive therapy. In one patient the transfer to hemodialysis was the only possible solution because of ultrafiltration failure. Follow-up scanning (MRI) was obtained in all patients and complete disappearance of the lesions was confirmed. None of our patients developed irreversible tissue damage thanks to early recognition of the syndrome and the immediate treatment.

The clinical presentation and neuroimaging findings of our cases are in agreement with the literature. Moreover, the history of hypertension and fluid overload seems to support the hyperperfusion theory. Although all of the patients we present had adequate Kt/V, the role of the uremic state cannot be overlooked. Patients on dialysis have an increased load of urea in comparison with normal individuals. This could make these patients more vulnerable to the pathophysiological changes which lead to the expression of PRES. Furthermore, erythropoietin was prescribed in all of our patients and its vasoconstrictive action cannot be neglected.

Euvolemia could be challenging in PD patients and PRES should be always considered as a possible complication. Nephrologists should be aware of the syndrome, especially when they manage hypertensive ESRD patients who do not comply with the fluid and diet restrictions. An MRI scan is the only diagnostic tool for defining the syndrome and should be done as early as possible. However, it is more important to prevent the appearance of the syndrome by treating it strictly and following up patients closely.

Disclosure Statement

The authors have no conflicts of interest to declare.

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