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Posterior Reversible Encephalopathy Syndrome After Renal Transplant: A Simple Solution for a Complicated Patient

David Haughey Sriram S. Narsipur

Upstate Medical University, Syracuse, N.Y., USA

Key Words

Posterior reversible encephalopathy syndrome · Posterior reversible leukoencephalopathy syndrome · Renal transplant · Encephalopathy · Tacrolimus

Abstract

Background: Posterior reversible leukoencephalopathy syndrome (PRES) is characterized by an acute neurologic dysfunction coupled with characteristic findings on brain imaging. PRES occurs in the setting of hypertensive emergencies, eclampsia and as a neurotoxic effect of immunosuppressive agents. While overwhelmingly reversible without residual deficits when promptly recognized, vague symptomatology may delay the diagnosis of PRES. ***Results/Summary:*** A 50-year-old man who had undergone a recent kidney transplant was admitted to our clinic due to multiple episodes of seizure. He had no prior history of seizures or alcoholism. His transplantation had been without complication; he was discharged and given prednisone, tacrolimus, mycophenolate, acyclovir, trimethoprim-sulfamethoxazole, atenolol and enalapril. On the day of presentation, he experienced a severe headache, blurred vision and tonic-clonic seizure-like activity. His neurologic examination was limited by sedation, although no focal deficits were evident. Laboratory studies were unremarkable. A lumbar puncture revealed normal opening pressure, negative Gram stain, benign CSF analysis and India ink preparation. An MRI of the brain revealed bilateral enhancing parietal-occipital lesions, seen prominently on FLAIR sequence. Tacrolimus and all other medications were continued. The patient remained afebrile and normotensive and was extubated on the second hospital day. The patient reported no neurologic symptoms and was discharged on the third hospital day after a full recovery. ***Conclusions:*** While the outcome of PRES is typically benign, a delay in diagnosis may lead to permanent neurologic deficits, and misdiagnosis can be lethal. The cornerstone of treatment is removal of the offending agent

Sriram S. Narsipur, MD
Upstate Medical University
750 East Adams Street CWB 343
Syracuse, NY 13210 (USA)
E-Mail Narsipur@upstate.edu

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or treatment of the underlying etiology. A clinical picture of headache, visual abnormalities, altered mentation and seizures is sufficient to prompt an empiric discontinuation of agents known to cause PRES. Calcineurin inhibitors such as tacrolimus are known to cause PRES, and in our patient, discontinuation led to a complete clinical resolution.

Introduction

Posterior reversible encephalopathy syndrome (PRES) is characterized by an acute neurologic dysfunction, coupled with characteristic neuroradiologic findings. PRES occurs in hypertensive emergencies, eclampsia and as a toxic effect of immunosuppressants, among other associations. When promptly recognized, PRES is rapidly reversible without residual deficits, however, vague symptomatology may delay diagnosis.

Case Description

A 50-year-old male was air-lifted to our institution due to multiple episodes of seizure. Five days before, he had undergone a deceased donor renal transplant for end-stage renal disease secondary to focal segmental glomerulosclerosis. He did not have a history of seizure, disorder or alcoholism. The transplant happened without any complications; post-transplant urine output was adequate and the patient remained normotensive. Discharge medications included prednisone, tacrolimus, mycophenolate, acyclovir, trimethoprim-sulfamethoxazole, atenolol and enalapril. On the day of presentation, he experienced severe headache, blurred vision and tonic-clonic seizure-like activity as reported by his wife, who worked as a paramedic. In the Emergency Department, IV lorazepam and intubation led to a cessation of seizure activity. The patient was afebrile with systolic blood pressure in the 170s, heart rate approximately 100 and oxygen saturation 100% while intubated. The neurologic examination was limited by sedation, although his pupils were approximately 3 mm and reactive to light with no evident focal deficits. Labs evidenced BUN and creatinine of 24 and 0.9 mg/dl respectively, glucose was 104 mg/dl and the remainder of the BMP was unremarkable (see table 1 for other results). WBC count was 10.1×10^6 cells/μl, hemoglobin and hematocrit were 10.0 g/dl and 30.3%, respectively (unchanged from baseline values). A lumbar puncture revealed a normal opening pressure, negative Gram stain, benign CSF analysis (0 WBC, 117 RBC, glucose 68 mg/dl, protein 47 mg/dl) and negative India ink preparation. The tacrolimus level was at 5.0 ng/ml. A CT of the head, with and without contrast, did not exhibit hemorrhage, masses or areas of infarction. A CTA of the head and neck did not evidence acute pathology; no hemodynamically significant vessel stenosis or dissection was observed. An MRI of the brain revealed prominent bilateral enhancing parietal-occipital lesions on FLAIR and T2 sequences and small areas of hyperintensity in the left periventricular white matter on diffusion-weighted images (fig. 1, fig. 2). Tacrolimus and all other medications were continued. Levetiracetam was started, mainly for seizure prophylaxis. The patient remained afebrile and normotensive and was extubated on the second hospital day. The patient reported no neurologic symptoms and was discharged on the third hospital day after a full recovery. At his 1-month follow-up, the patient remained neurologically asymptomatic; his CNS lesions were completely resolved on repeat MRI and an alternative immunosuppressive regimen of cyclosporine was well tolerated.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Discussion

PRES classically presents as headache, visual abnormalities, focal neurologic deficits, altered mentation and seizures [1]. In addition to tacrolimus and other calcineurin inhibitors, PRES is associated with hypertensive emergency, eclampsia/pre-eclampsia, sepsis, connective tissue disease/vasculitis, cancer chemotherapy and bone marrow/solid organ transplant [1]. MRI findings are essential for diagnosis. Vasogenic edema is typically evident in the deep white matter of the occipital and parietal lobes [2]. It is crucial to differentiate patients with PRES from those with 'top of the basilar' syndrome (i.e. bilateral infarctions of the occipital lobes). While seizure is a dominant feature of PRES and is rare with 'top of the basilar' syndrome [3], differentiation may hinge on imaging. In the former, affected areas are hypointense to isointense while in the latter, acutely infracted areas undergo restricted water diffusion and thus appear hyperintense [4]. Further, in PRES, the calcarine and paramedian regions of the occipital lobe are usually spared while they are invariably affected in 'top of the basilar' syndrome [5]. In our patient, MRI diffusion weighted image signals were mostly isointense and the calcarine and paramedian structures were spared.

Tacrolimus-induced neurotoxicity may be mild and involve both sensory and motor functions including tremor, neuralgia, and peripheral neuropathy. More severe symptoms include psychoses, hallucinations, cortical blindness, seizures, cerebellar ataxia, more weakness, and – as described here – PRES. The frequency of calcineurin inhibitor-induced neurotoxicity among solid organ transplant recipients ranges from 7 to 32%, but the incidence of PRES after solid organ transplant is only 0.49% (Bartynski [6]).

The mechanistic explanation for PRES is incomplete. Two major hypotheses, one involving hypoperfusion and the other hyperperfusion, dominate the literature. Current theory favors hypertension and transiently failed autoregulation as the cause of vasogenic edema (rather than cytotoxic edema). Both myogenic and neurogenic responses lead to cerebral vasodilatation and subsequent extravasation of fluid and blood into the brain parenchyma. An inconsistency of this theory, however, is that some individuals can develop PRES with relative normotension. Alternatively, endothelial dysfunction and vasoconstriction-mediated hypoperfusion may also play a role [1, 6]. In addition, calcineurin inhibitors may have direct cytotoxic effects on brain endothelium resulting in dysfunction or demyelination in patients with PRES (Bartynski [6]).

Management involves prompt recognition and control of the inciting event (i.e. antihypertensives for blood pressure control and removal of offending drugs). Our patient had tacrolimus levels within the target range; however, toxicity can occur at 'therapeutic' levels [7]. He also presented with hypertension exceeding the range of autoregulation. This may have contributed to the development of PRES. However, the hypertensive episode was brief and resolved without additional anti-hypertensive therapy. Further, tacrolimus causes endothelial damage and PRES in the absence of hypertension [8]. Given appropriate clinical and radiologic findings, a prompt reduction or discontinuation of medication known to cause PRES is prudent and prevents permanent neurologic deficits. Clinical symptoms typically resolve within 1 week.

Magnesium sulfate, a known effective medication for eclampsia-induced seizures, may have some vasodilatory effects on both peripheral and cerebral vasculature, and a protective effect on the blood-brain barrier and reduction in vasogenic edema has been proposed. As a result, and at a minimum, monitoring magnesium levels and possible correction to the normal range has been proposed.

Conclusion

While the outcome of PRES is typically benign, delayed diagnosis may lead to permanent neurologic deficits and misdiagnosis can be lethal. Definitive management involves removal of the offending agent or treatment of the underlying etiology. Calcineurin inhibitors such as tacrolimus, even at 'normal' serum levels, are known to result in toxicity, including PRES. Given appropriate neuroimaging findings, a clinical picture of headache, visual abnormalities, altered mentation and seizures is sufficient to prompt empiric discontinuation of agents known to cause PRES. In our patient, discontinuation of tacrolimus and conversion to cyclosporine led to a complete clinical resolution and a resolution of abnormalities on neuroimaging. Another option, conversion to the mTOR inhibitor sirolimus, was considered but has also been reported to be associated with PRES.

Acknowledgements

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Disclosure Statement

The authors declare that they have no competing interests.

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Table 1. Laboratory studies at admission

Variable	Admission value	Reference range
Sodium, mmol/l	141	133–145
Potassium, mmol/l	4.1	3.3–5.1
Chloride, mmol/l	105	96–108
Bicarbonate, mmol/l	25	22–29
BUN, mg/dl	**24**	6–20
Creatinine, mg/dl	0.9	0.5–1.2
Glucose, mg/dl	104	65–110
Calcium, mg/dl	9.0	8.4–10.2
Magnesium, meq/l	1.3	1.3–2.1
Total protein, g/dl	**5.7**	6.4–8.3
Osmolality	296	275–300
White blood cell count, 10^3/μl	**10.1**	4–10
Red blood cell count, 10^6/μl	3.07	4.6–6.1
Platelet count, 10^3/μl	207	150–400
Hemoglobin, g/dl	**10.0**	13.5–18
Hematocrit, %	**30.3**	41–53
Oxygen saturation, %	99	94–100
FIO2	0.60	
P_{CO2}, mm Hg	**30**	35–40
P_{O2}, mm Hg	**237**	95–100
pH	**7.49**	7.38–7.44
INR	0.91	
PT, s	12.6	12.5–14.9
PTT, s	**23.5**	24.0–32.4

Abnormal values are in bold.

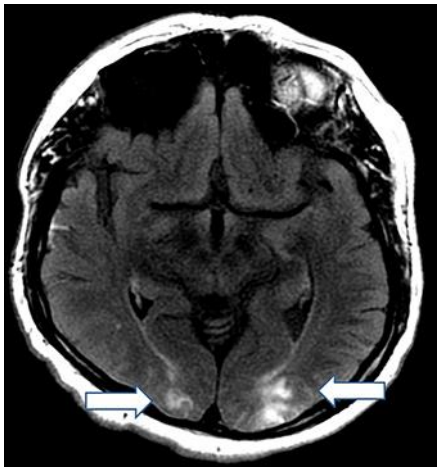

Fig. 1. MRI of the brain revealed prominent bilateral enhancing parietal-occipital lesions on FLAIR and T2 sequences and small areas of hyperintensity in the left periventricular white matter on diffusion-weighted images.

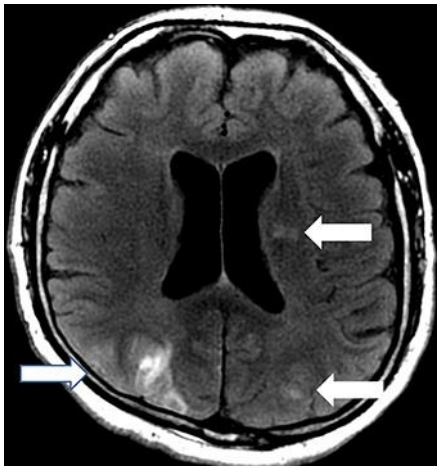

Fig. 2. MRI of the brain revealed prominent bilateral enhancing parietal-occipital lesions on FLAIR and T2 sequences and small areas of hyperintensity in the left periventricular white matter on diffusion-weighted images.