

Reversible posterior leukoencephalopathy syndrome in a renal transplant patient

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■ ABSTRACT

Reversible posterior leukoencephalopathy syndrome is a clinical and radiological syndrome commonly associated with hypertensive encephalopathy, eclampsia or immunosuppressive agents. In renal transplant recipients it is usually described in patients on calcineurin inhibitor. A 64 year-old renal transplant recipient with slow graft function presented with seizures, renal insufficiency and hypomagnesaemia nine days after transplantation. Immunosuppression consisted of mycophenolate mofetil and steroids following an induction treatment with thymoglobulin. Magnetic resonance imaging showed bilateral symmetrical areas of increased attenuation involving the white matter of parietal, occipital and frontal lobes. With blood pressure control, serum magnesium correction, improvement in graft function and phenytoin, no further seizures were noted. Serial imaging demonstrated improvement and eventual resolution of abnormalities. We report this unusual case of reversible posterior leukoencephalopathy syndrome in a renal transplant recipient in the absence of calcineurin inhibitor treatment. Early recognition of this condition and correction of its risk factors seem paramount for its reversibility.

Key-Words:

Immunosuppressant drugs; renal transplant; reversible posterior leukoencephalopathy syndrome.

■ INTRODUCTION

Reversible posterior leukoencephalopathy syndrome (RPLS) is a clinical and radiological syndrome characterised by headaches, altered mental function, visual disturbances and seizures. It is associated with symmetrical white matter oedema predominantly located in the posterior cerebral hemispheres¹⁻⁶. It appears to be related to cerebral autoregulation and endothelial dysfunction disorder, with neuroradiology findings suggestive of vasogenic oedema^{1,5}. Its incidence is not well documented, but it is most commonly associated with malignant hypertension with encephalopathy, eclampsia, and treatment with immunosuppressant drugs, particularly calcineurin inhibitor (CNI), which are thought to impair endothelial function¹⁻³.

Volume overload, elevated blood pressure, electrolyte disturbances especially hypomagnesaemia, and impaired kidney function have been recognised as both risk factors and prognostic indicators for RPLS. RPLS is usually reversible within weeks if early and effective treatment is initiated, and the risk of recurrence is low. In renal transplant recipients RPLS has been previously described in association with CNI, including both ciclosporin and tacrolimus, generally resolving with drug suspension or a reduced dosage⁷⁻¹⁴.

In this report, we discuss an unusual case of a renal transplant patient who developed RPLS shortly after transplantation in the absence of CNI treatment.

■ CASE REPORT

A 64 year-old female presented via ambulance to the emergency department with two witnessed generalised tonic-clonic seizures at home.

She had a history of end stage renal disease secondary to analgesic nephropathy and hypertension. Prior to transplant she had been treated with peritoneal dialysis for three years and her hypertension was well controlled. She underwent a deceased donor renal transplant without complication. Her initial immunosuppression regimen included an induction with thymoglobulin (1.5mg/kg/day iv for 4 consecutive days), mycophenolate mofetil (MMF) (1000mg *po* bid) and methylprednisolone taper. Her initial post-operative course was notable for slow graft function, which was thought to be associated with prolonged cold ischaemic time (15 hours and 30 minutes). Her serum creatinine decreased from 8.6 mg/dl to 6.6 mg/dl on day 5 and 6.1 mg/dl on day 7 post-transplant. Urine output was adequate and the patient did not require dialysis. Her blood pressure was labile, though generally above normal, with a peak systolic blood pressure of 186 mmHg. She was discharged on day 7 post-transplant on MMF (1000 mg *po* bid), prednisone (20 mg *po* qd), valganciclovir (450 mg *po* qod), sulfamethoxazole/trimethoprim (80/400 mg *po* qod), metoprolol (50 mg *po* bid), simvastatin (20 mg *po* qd) and esomeprazole (20 mg *po* qd).

Two days after discharge, on post-operative day 9, she presented to the emergency department with generalised tonic-clonic seizures. Her history confirmed no recent headache, nausea, visual disturbance, focal

neurologic deficit or behavioural alterations. She had no prior history of seizure or neurologic condition and no new predisposing factors for seizure were identified. Her blood pressure on admission was 180/69mmHg and her husband confirmed most recent poor adherence to her antihypertensive therapy.

On initial examination, her airway was protected, ventilation and oxygenation were stable, she was lethargic and non-verbal, and she appeared stuporous. Cranial nerves 3-12 were intact, reflexes were preserved symmetrically and sensation to painful stimuli appeared bilateral. There was spontaneous movement of all four limbs. Fundoscopy did not demonstrate any papilloedema. (See Table 1 for initial and subsequent laboratory results).

The patient underwent head computed tomography (CT), which revealed a hypodense lesion in the left frontoparietal posterior region at the high convexity, as well as bilateral hypodensities in the posterior occipital lobes and near the midline, and a rounded hypodensity in the right basal ganglia that could represent an old lacunar infarction. Head magnetic resonance imaging performed on the same day revealed bilateral symmetric areas of abnormal T2 prolongation, predominantly involving the subcortical white matter of the posterior aspects of the parietal and, to a lesser extent, occipital and frontal lobes (Fig. 1). She was admitted to the hospital for further evaluation and management.

The initial focus of her management consisted of strict blood pressure control and treatment of her low serum magnesium levels. A neurology opinion was obtained, and it was felt that her current immunosuppressive regimen also might have contributed to RPLS. The MMF was accordingly stopped and she was started on azathioprine (75 mg *po* qd) and ciclosporin (300 mg *po*) in addition to phenytoin (200 mg *po* bid) for seizure prophylaxis. She slowly

Table 1

Laboratory results pre and post-transplantation (PT)

	Pre-transplantation	Day 1 PT	Day 3 PT	Day 5 PT	Day 7 PT	Day 9 PT	Day 11 PT	Day 13 PT
BUN (mg/dl)	59	51	69	95	111	85	70	62
Creatinine (mg/dl)	8.6	7	6.7	6.6	6.1	4.1	3	2.8
Na ⁺ (mmol/l)	137	142	133	134	140	138	135	130
Mg ⁺⁺ (mmol/l)			1.6	1.8	1.9	1.7	1.7	1.7

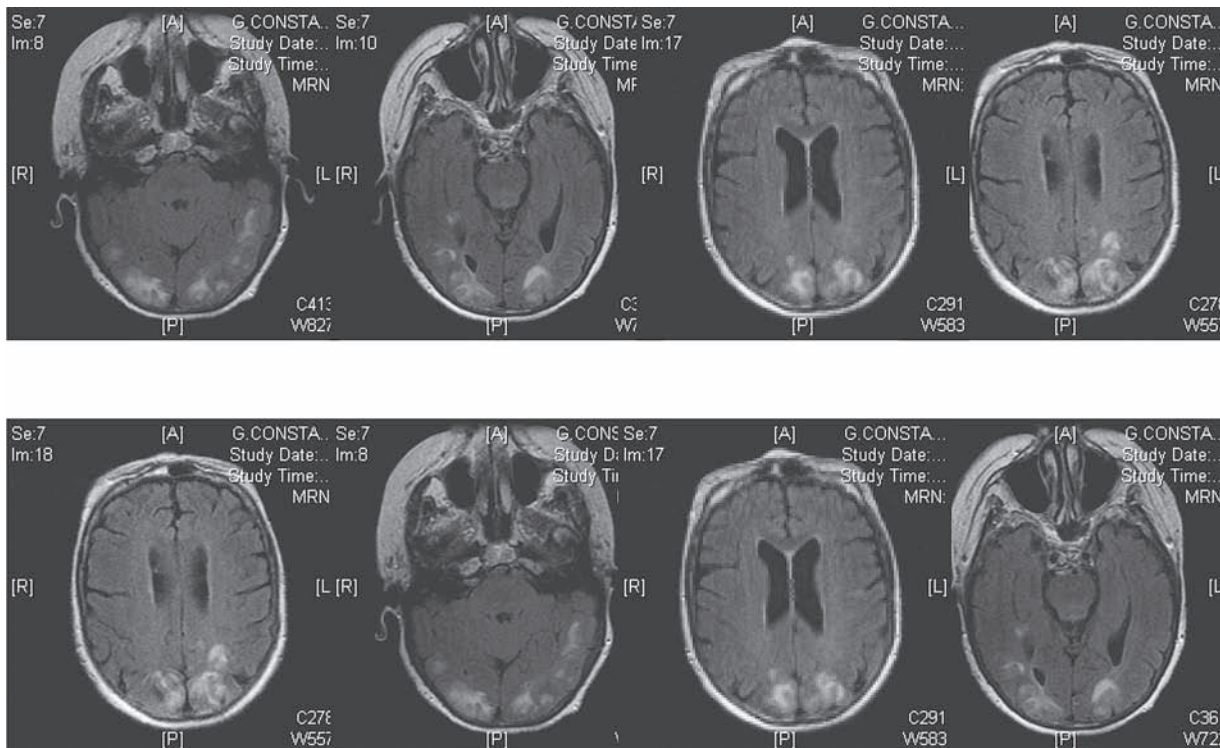


Figure 1

Bilaterally symmetric areas of abnormal T2 prolongation predominantly involving the subcortical white matter of the posterior aspects of the parietal and, to a lesser extent, occipital and frontal lobes, suggestive of Reversible Posterior Leukoencephalopathy.

improved over the next ten days, with no further seizure activity noted. Laboratory results over this period of time are presented in Table I. A repeat head-CT revealed complete resolution of the previously identified hypodense regions. She was eventually discharged to a rehabilitation facility on a regimen which included prednisone (20mg *po* qd), azathioprine (75 mg *po* qd), ciclosporin (300 mg *po* bid – trough whole blood level of 160 µg/L), phenytoin (200 mg *po* bid – blood level of 10.5 µg/mL), felodipine (10 mg *po* qd), labetalol (400 mg *po* bid), valganciclovir (450 mg *po* qod) and sulfamethoxazole/trimethoprim (80/400 mg *po* qod). Her kidney transplant function had improved significantly.

DISCUSSION

RPLS in renal transplant recipients is usually associated with the use of CNI (both ciclosporin and

tacrolimus)^{1,7-14}. Cellular injury appears to be the mechanism of action of CNI neurotoxicity through mitochondrial dysfunction¹⁶. This is to our knowledge the first reported case in which RPLS is described in a renal transplant patient without CNI maintenance immunosuppression.

Although RPLS usually has a subacute onset with other neurologic disturbances in addition to seizure, generalised tonic-clonic seizures may be the only manifestation of the syndrome, with multiple seizures more common than single events¹.

The neuroradiologic abnormalities identified in this patient have been similarly identified in previous reports, with vasogenic oedema involving the white matter in the posterior cerebral hemispheres^{1,2}. Although the involvement of the parieto-occipital lobes is the characteristic radiologic finding, potentially associated with a greater sympathetic innervation of the anterior circulation protecting

anterior regions from sudden increases in blood pressure, other areas, such as the frontal lobe, can be affected^{1,16}.

Elevation of blood pressure is an important risk factor for RPLS. It is postulated that sudden increases in blood pressure may exceed the autoregulatory capability of the brain vasculature¹⁵ related to an impaired endothelial dysfunction. RPLS is seen in patients with isolated hypertensive encephalopathy, and a key feature is that when the blood pressure is controlled, there is usually a rapid resolution of clinical and imaging abnormalities¹.

The association of RPLS with CNI is well documented, both in patients receiving ciclosporin or tacrolimus^{1,7-14}. While our patient was not on CNI, she did have several risk factors, including hypertension, hypomagnesaemia and underlying renal insufficiency. Treatment of her elevated blood pressure, correction of her serum magnesium and improvement in her kidney transplant function were major determinants in both the clinical and radiological resolution of the RPLS.

The presented patient had RPLS while on MMF with both clinical and radiological improvement after switching to azathioprine and ciclosporin. It is well known that MMF has important effects on the endothelium, which includes inhibition of endothelin-1 formation, reduced expression of adhesion molecules, enhanced prostaglandin I₂ release and reduced nitric oxide formation¹⁷. MMF may play a role in the endothelial dysfunction that could contribute to the RPLS, although other case reports and experimental studies are needed to clarify an association.

In conclusion, we report a case of RPLS in a renal transplant patient in the absence of CNI treatment. Early recognition of RPLS and its risk factors are important as appropriate management often results in rapid improvement of symptoms and signs.

Conflict of interest statement. None declared.

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