Calcineurin Inhibitors Associated Posterior Reversible Encephalopathy Syndrome in Solid Organ Transplantation

Report of 2 Cases and Literature Review

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Abstract: Posterior reversible encephalopathy syndrome (PRES) is a rare neurologic side effect of calcineurin inhibitors (CNIs) with poorly understood clinical features.

We report cases of 2 patients with PRES developing after kidney transplantation and summarize PRES clinical features through a literature review.

The 1st case was a 28-year-old man who received a kidney transplant from a deceased donor. Initial immunosuppressive therapy consisted of tacrolimus/mycophenolate mofetil/prednisolone. He developed headache and blurred vision with visual field loss 15 days after transplantation and generalized seizures 4 days later. The 2nd case was a 34-year-old man who received a living kidney transplant. His initial immunosuppressive therapy comprised tacrolimus/mycophenolate mofetil/prednisolone. Two months after transplantation, he developed seizures. Both patients were diagnosed with PRES based on neurologic symptoms and magnetic resonance imaging (MRI) findings; they recovered after switching from tacrolimus to either a cyclosporine or a lower tacrolimus dose. CNI-associated PRES is an acute neurological syndrome with seizures, encephalopathy, visual abnormalities, headache, focal neurological deficits, and nausea/vomiting. It is always accompanied by hypertension. A fluid-attenuated inversion recovery signal MRI scan typically shows reversible subcortical white matter changes in the posterior cerebral hemisphere that usually occur within the 1st month after transplantation. CNI-associated PRES has a generally favorable prognosis with early diagnosis and prompt treatment including alternating or discontinuing CNIs and blood pressure control.

CNI-associated PRES should be considered in patients exhibiting acute neurological symptoms after transplantation. Early diagnosis and immediate treatment are critical for a favorable prognosis.

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES), 1st described in 1996 by Hinchey et al, refers to a clinical presentation of reversible subcortical vasogenic brain edema caused by endothelial injury resulting from abrupt changes in blood pressure changes or direct effects of cytokines on the endothelium. This leads to the breakdown of the blood–brain barrier and excessive exudation into the brain parenchyma. PRES often presents as a variable combination of altered consciousness, seizure activity, headache, visual abnormalities, nausea/vomiting, and focal neurological signs. Brain imaging studies usually reveal vasogenic edema predominantly involving the bilateral parieto-occipital regions.

Renal failure, blood pressure fluctuations, cytotoxic drugs, autoimmune disorders, and pre-eclampsia or eclampsia have been proposed to be causally related to PRES. In recent years, calcineurin inhibitors (CNIs), including tacrolimus that are widely used as primary immunosuppressive agents in organ transplant recipients, are attributed to neurotoxicity in 20% to 40% of solid organ transplant (SOT) recipients. In a cohort of 4222 patients who underwent SOT from 1998 to 2006, the overall incidence of PRES after SOT was 0.49%. Minor variations in PRES incidence were noted between SOT types; it was reported to occur in 0.34% of the kidney group and in 0.84% of the small bowel group. CNIs were indicated as one of the causative factors. As PRES in the setting of SOT is rare, there are no standard guidelines for its diagnosis and management, especially as the mechanism underlying neurotoxicity remains unclear and controversial. We herein present the successful management of 2 kidney transplant recipients with CNI-associated PRES.

CASE REPORTS

Case 1

A 28-year-old man received a kidney from a donation after cardiac death in May 2015. His history included an infarct in the left occipital region that was accidentally found in 2014; the patient had no history of seizures (Figure 1A). He was prescribed nifedipine 30 mg bid, and his blood pressure on average was 120–130/70–85 mm Hg. After transplantation, the graft functioned well with his serum creatinine level decreasing to 106 μmol/L on the 3rd day. His maintenance...
Case 2

A 34-year-old male presented to our hospital after 1 seizure episode. Two months before, he underwent a living related kidney transplant with no complications; his posttransplant urine output was adequate, and he remained normotensive. His medications at discharge included prednisone, tacrolimus 1.5 mg bid, and mycophenolate 1000 mg bid. On the day of presentation, he experienced only 1 seizure episode that resolved 30 seconds later without any treatment. He did not have a history of seizure. He was afebrile with systolic blood pressure in the range of 130 mm Hg. Laboratory tests including creatinine and electrolyte measurements were within normal limits, and his neurological examination was unremarkable. The tacrolimus trough level was 7.9 ng/mL. His cranial computed tomography (CT) excluded hemorrhage, mass lesions, and areas of infarction. A cranial MRI revealed localized subcortical areas of increased T2 signal/edema and markedly increased T2 FLAIR signal in the left temporal lobe with 1 small hypointense area in the center of the lesion, and scattered, small hypointense areas in the centrum semiovale (Figure 2A). Tacrolimus was reduced to 0.5 mg bid, and levetiracetam was started for seizure prophylaxis. The patient reported numbness in the right buccal region with no other neurological symptoms and was discharged 3 days after admission with full recovery. At the 2-month follow-up evaluation, the patient remained neurologically asymptomatic except for numbness in the right buccal region. Repeat MRI showed complete resolution of the temporal lesions except for the persistent central area with signs suggesting hemorrhage. The lesions in the centrum semiovale remained and showed signs suggestive of demyelination (Figure 2B).

Informed consent was obtained from both patients for the publication of this case report. The study was approved by the West China Hospital Institutional Review Board.

DISCUSSION

We performed a systematic review of existing literature and published reports to provide a comprehensive overview of PRES. The literature search was based on the following criteria: SOT recipients, PRES caused by CNI toxicity, and cases with complete PRES clinical course including symptom presentation, image characteristics, treatment, and outcomes. Thirty-seven studies were included for further analysis (Table 1). 1.5–40 As all included studies were case reports or small case series, the exact prevalence of CNI-associated PRES could not be estimated. However, at our institution, among a total of 1596 kidney transplants (1519 living and 77 donation after cardiac death) performed as of July 2015, the incidence of CNI-associated PRES was 0.13%. In our literature analysis of these 37 studies, CNI-associated PRES was diagnosed in 50% to 77% of transplant recipients who manifest altered consciousness and seizures.5,6

Time of Onset

The time of onset of CNI-associated PRES varied among studies. Our literature analysis determined the median time to onset after organ transplantation as 17 days (range; 24 hours to 5 years). Overall, 25.5% (14/55), 38.2% (21/55), 12.7% (7/55),...
and 16.4% (9/55) of the cases occurred between 0 and 7 days after transplantation, respectively; only 7.3% (4/55) occurred beyond the 1st year after transplantation. There was no difference in time of CNI-associated PRES onset across different transplantation types ($P = 0.07$). The median time to onset was 12, 17.3, 14, and 17.6 days after transplantation in heart, liver, lung, and kidney transplant recipients, respectively. There was a trend toward an earlier occurrence of PRES in transplant recipients receiving CsA than those receiving tacrolimus (median time to onset; 12 vs 26 days, respectively, $P = 0.077$).

**Clinical Features**

As reviewed by Fugate and Rabinstein, PRES-related clinical symptoms and signs can be classified into the following 7 categories: encephalopathy, seizure, headache, visual disturbances, focal neurological deficits, status epilepticus, and nausea/vomiting. Both our patients had seizures as the initial presentation; in addition, the 1st patient also had headache and visual disturbances. The literature review showed that among CNI-associated PRES cases, the percentage of patients presenting with seizures, encephalopathy, headache, visual disturbances, focal neurological deficits, status epilepticus, and nausea/vomiting were 77.5% (55/71), 62% (44/71), 29.6% (21/71), 22.5% (16/71), 22.5% (16/71), 1.4% (1/71), and 8.5% (6/71), respectively. The most common symptom combination was seizures/encephalopathy (38%, 27/71), followed by seizures/headache (22.5%, 16/71), seizures/visual disturbances (14.1%, 10/71), visual disturbances/headache (14.1%, 10/71), and visual disturbances/encephalopathy (9.9%, 7/71).

Majority of patients presented with encephalopathy, which comprised confusion (21.1%), lethargy (18.3%), altered consciousness (15.5%), coma or stupor (11.2%), and irritability (8.5%). Disorientation (4.2%), asterixis (5.6%), and loss of memory (2.8%) were uncommon. Visual disturbances consisted of cortical blindness (4/71), homonymous hemianopsia (3/71), blurred vision (3/71), hallucination (1/71), opsinclonus (1/71), and nonspecific visual alterations (4/71). Hemiparesis occurred in 8.5% (6/71) of the patients and was a prominent and distinctive feature of focal neurological deficits; this was followed by hemiplegia (4.2%, 3/71), speaking difficulties (4.2%, 3/71), and weakness of the extremities (4.2%, 3/71).

Our patients had no acute hypertension or pronounced blood pressure fluctuations. However, systemic hypertension was documented in 69% (40/58) of patients who experienced CNI-associated PRES according to the literature review. There was no difference in age between patients with and without hypertension (23.1 ± 18.4 vs 32.8 ± 18.5 years, $P = 0.069$). Hypertension was documented in 83%, 71.4%, 54.5%, and 58.8% of kidney, heart, liver, and lung recipients, respectively. Hypertension was significantly higher in male patients (81.3% vs 53.8%, $P = 0.025$) and in those receiving CsA as the initial CNI (80% vs 60.6%, $P = 0.097$).

CNI toxicity is regarded as one of the etiologies of PRES; CNI levels are always above the upper limit of therapeutic window. The literature analysis revealed that the mean CsA concentration was 296 ± 200 ng/mL (range, 44–778 ng/mL) and mean tacrolimus concentration was 17.9 ± 12 ng/mL (range, 4.1–56 ng/mL) in patients with CsA-associated PRES. However, in both our patients, the trough levels of tacrolimus were within the normal range, suggesting that CNI levels are not necessarily above the upper limit of the therapeutic window in CNI-associated PRES cases. As most studies did not consistently report the reference normal range of CNIs, we set the higher limits for tacrolimus and CsA at 10 and 200 ng/mL, respectively, for our literature analysis and determined that CsA and tacrolimus levels higher than these limits were reported in 68.6% (35/51) of patients diagnosed with CNI-associated PRES. Finally, CNI-associated PRES in the presence of therapeutic drug levels was more likely to occur in patients receiving CsA than in those receiving tacrolimus (40%, 8/20 vs 25.8%, 8/31, $P = 0.286$).

**Neuroimaging**

As FLAIR sequences in MRI scans can highlight anatomical details to a higher resolution and render brain tissue edema more easily than conventional T2-weighted spin echo MRI by suppressing signals from the cerebrospinal fluid and gray–white matter, suppressing signals from the cerebrospinal fluid and gray–white matter...
| Author                      | Year | No. SOT | CNI (No.) | Hypertension (No.) | Clinical symptoms (No.) | Image Characteristic (No.) | Treatment | Outcomes |
|----------------------------|------|---------|-----------|-------------------|-------------------------|----------------------------|-----------|----------|
| Hinchey et al⁴              | 1996 | RT: 1   | LT: 4     | CsA: 2 TAC: 3     | Seizures: 3, cortical blindness: 1, lethargy: 2, asterixis: 2, left hemiparesis: 1, confusion: 1 | Occipital lobe: 4, temporal lobe: 2, parietal lobe: 4, frontal lobe: 3, internal capsule: 1, pons: 1, centrum semiovale: 1 | Decreased doses or withdrawal | Recovered |
| Lanzino et al⁸              | 1997 | LT: 1   | HT: 1     | CsA: 2            | Seizures: 2, lethargy: 1, right hemiplegia: 1 | Temporal lobe: 1, occipital lobes: 1, parietal lobe: 1, occipital lobe: 1 | No | Recovered |
| Nakamura et al⁹             | 1998 | LT: 2   | TAC: 2    | Unknown           | Seizures: 2, confusion: 2, headache: 1 | Parietal lobe: 1, occipital lobe: 1 | Replace with CsA or discontinuation of TAC | Recovered |
| Wennberg¹⁰                 | 1998 | HT: 1   | CsA: 1    | Unknown           | Seizures: 1, confusion: 1 | Occipital lobes: 1, parietal lobe: 1, occipital lobe: 1 | Decreased doses | Recovered |
| Fruhauf et al¹¹             | 2003 | LT: 1   | TAC: 1    | Unknown           | Seizures: 1, coma state: 1, flaccid tetraplegia: 1 | Parietal lobe: 2, occipital lobe: 2 | No | Died |
| Lepoivre et al¹²            | 2003 | LuT: 2  | CsA: 2    | Unknown           | Seizures: 2, headache: 1, visual trouble: 1 | Parietal lobe: 2, occipital lobe: 2 | Replace with TAC | Recovered |
| Marchiori et al¹³           | 2004 | LT: 1   | CsA: 1    | Unknown           | Seizures: 1 | Occipital lobes: 1 | Decreased doses | Recovered |
| Ishikura et al¹⁴            | 2006 | RT: 10  | CsA: 6    | TAC: 4            | Seizures: 8, cortical blindness: 2, lethargy: 4, left hemiparesis: 1, confusion: 3, headache: 4, coma: 2, stupor: 1 | Frontal lobe: 8, temporal lobe: 2, occipital lobe: 7, cerebellum: 1 | Decreased doses | Recovered |
| Akutsu et al¹⁴              | 2008 | RT: 2   | CsA: 1    | TAC: 1            | Coma: 1, paralysis: 1, confusion: 1 | Parietal lobe: 2, occipital lobe: 1 | Replace with TAC or reduced dose of TAC | Recovered |
| Hernandez et al¹⁵           | 2008 | LT: 1   | TAC: 1    | Unknown           | Seizures: 1 | Frontal: 1, occipital, parietal: 1 | No | Died |
| Perez Menendez-Condé et al¹⁶| 2008 | LT: 1   | TAC: 1    | Unknown           | Headache: 1, confusion: 1, disorientation: 1, vision trouble: 1 | Parietal: 1, periventricular: 1 | Replace TAC with rapamycin | Recovered |
| Soi V¹⁷                    | 2008 | RT: 1   | TAC: 1    | No                | Confusion: 1, disorientation: 1, seizure: 1 | Parietal lobe: 1, occipital lobe: 1 | Discontinuation of TAC | Recovered |
| Dzudie et al¹⁸              | 2009 | HT: 2   | CsA: 2    | Yes: 2            | Headache: 1, disorientation: 1, tremor: 1, seizure: 2, vision trouble: 1 | Frontal lobe: 1, occipital lobe: 2, cerebellum: 1, lenticular: 1 | Reduced dose then replace with everolimus | Recovered |
| Heidenhain et al¹⁹          | 2009 | LT: 1   | TAC: 1    | Unknown           | Coma: 1 | Pontine: 1, occipital: 1 | No | Recovered |
| Izquierdo Pajuelo et al²⁰   | 2009 | RT: 1   | TAC: 1    | Unknown           | Seizure: 1 | Occipital: 1 | Discontinuation of TAC | Recovered |
| Baldini et al²¹             | 2010 | LT: 1   | TAC: 1    | No                | Seizure: 1, altered mental status: 1, headache: 1 | Frontal lobe: 1 | Discontinuation of TAC | Recovered |
| Study | Year | Type | CNI | Yes | No | Seizure | HA | VT | Hemi | LBM | Location | Outcome | Treatments |
|-------|------|------|-----|-----|----|-------|-----|-----|------|-----|---------|---------|------------|
| Navarro et al | 2010 | HT | CsA | 4 | No | | 4 | | | | | | Recovered |
| Oda et al | 2010 | LIT | CsA | 1 | No | | 1 | | | | | | Recovered |
| Tsang et al | 2010 | LuT | TAC | 2 | Yes | 3 | 2 | | 2 | 1 | 1 | | Recovered |
| Santos et al | 2011 | LT | CsA | 1 | | | | | | | | | Recovered |
| Cadavid-Aljure et al | 2011 | RT | TAC | 1 | No | | 1 | | | 1 | | | Recovered |
| Lunardi et al | 2012 | LT | CsA | 1 | No | | 1 | | | | | | Recovered |
| Rosso et al | 2012 | LuT | CsA | 1 | No | | 3 | | | | | | Recovered |
| Shao et al | 2012 | BT | TAC | 1 | No | | 1 | | | | | | Recovered |
| Teotonio et al | 2012 | HT | TAC | 1 | No | | 1 | | | | | | Recovered |
| Yamada et al | 2012 | RT | CsA | 1 | No | | 3 | | | | | | Recovered |
| Barbas et al | 2013 | Muti-T | TAC | 1 | No | | 1 | | | | | | Recovered |
| Facchini et al | 2013 | LuT | Unknown | | | | | | | | | | Recovered |

**Note:**
- TAC: Tacrolimus
- CsA: Cyclosporine
- PRES: Proliferative Reversible Encephalopathy Syndrome

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| Author           | Year | No. SOT | CNI (No.) | Hypertension (No.) | Clinical symptoms (No.) | Image Characteristic (No.) | Treatment                                      | Outcomes                        |
|------------------|------|---------|-----------|-------------------|-------------------------|---------------------------|-----------------------------------------------|----------------------------------|
| Fitzgerald et al | 2013 | LT: 1   | TAC: 1    | Yes: 1            | Seizures: 1, altered mental status: 1 | Frontal: 1, parietal: 1, middle brain: 1 | Replace with Rapamycin and blood pressure control | Recovered                       |
| Loar et al       | 2013 | HT: 1   | TAC: 1    | Yes: 1            | Headache: 1, altered mental status: 1 | Frontal: 1, parietal: 1, occipital: 1 | Reduce dose of TAC, then replace with ATG and following CsA | Difficult in speech,              |
| Arimura et al    | 2014 | LuT: 4  | TAC: 3 CsA: 1 | Unknown          | Decrease of consciousness: 1, seizure: 3 | Parietal: 4, occipital: 3, cerebellum: 2, frontal: 3 | Reduce dose of TAC, replace CsA with TAC | Recovered for 3, left             |
| Hayes et al      | 2014 | LuT: 1  | TAC: 1    | Yes: 1            | Seizure: 1              | Parietal: 1, occipital: 1, corpus callosum: 1 | Reduce dose of TAC and add rapamycin | Recovered                       |
| Singh et al      | 2014 | LT: 1 RT: 3 | TAC: 6   | Yes: 3            | Seizure: 4              | Parietal: 4, occipital: 3, frontal: 3, temporal: 1, cerebellum: 1 | Reduce dose of TAC and blood pressure control | Recovered                       |
| Ueda             | 2014 | RT: 1   | TAC: 1    | Unknown           | Visual trouble: 1, headache: 1, paralysis: 1, coma: 1 | Unknown                   | Replace with CsA and rapamycin               | Recovered                       |
| Harirchian et al | 2015 | RT: 1 HT: 2 | CsA: 3   | Yes: 1            | Confusion: 3, headache: 1, vision trouble: 1, seizure: 3, hemiplegia: 1 | Parietal: 2, occipital: 3 | Replace CsA with TAC | Recovered                       |
| Haughey and Narsipur | 2015 | RT: 1   | TAC: 1    | Unknown           | Visual trouble: 1, headache: 1, seizure: 1 | Parietal: 1, occipital: 1 | No                                | Recovered                       |

BT = bowel transplant, CsA = cyclosporine A, HT = heart transplant, LT = liver transplant, LuT = lung transplant, RT = renal transplant, SOT = solid organ transplant, TAC = tacrolimus.
matter contrast, it is the appropriate modality to detect brain tissue edema in CNI-associated PRES. In all 75 cases reviewed, neuroimaging abnormalities were detectable on initial presentation in all cases but one and were usually located in the subcortical white matter, sometimes extending into the deeper white matter or the cortex. Occipital (76%, 57/75), parietal (61.3%, 46/75), and frontal (40%, 30/75) lobes, either bilaterally or unilaterally, were the most common regions involved. Temporal lobes were involved in 21.3% (16/75) of the patients. Other sites included the cerebellum (12%), centrum semiovale (6.7%), pons (5.3%), corpus callosum (5.3%), basal ganglion (4%), thalamus (2.7%), internal capsule (2.7%), corona radiata (1.3%), and hippocampus (1.3%). Coexistent ischemic lesions were detected in 2 cases, and hemorrhagic lesions were reported in 2 other patients. Both our patients had typical subcortical white matter edema. However, our patients are distinct from previously reported cases due to the coexisting lesions in the center of white matter edema, which was a source of initial confusion during differential diagnosis.

Management and Clinical Outcomes

A timely diagnosis is critical for PRES management. Although most patients have mild symptoms and signs and have a reversible course, if PRES is not recognized and treated early, it can lead to severe and life-threatening situations. Thus, the elimination of predisposing factors is crucial. As tacrolimus was suspected to be the causative agent, it was replaced with CsA in our 1st patient with low tacrolimus trough levels, whereas its dose was reduced in our 2nd patient with high tacrolimus trough levels. The literature review also revealed that the substitution of CNIs with other immunosuppressive agents (43.7%) (switching to another CNIs, 26.8%; replacing CNIs with sirolimus, everolimus, mycophenolate mofetil, or hydrocortisone, 16.9%) and lowering the CNI dose (22.5%) were the most commonly applied primary approaches, followed by temporal CNI cessation (19.7%), CNI discontinuation (9.9%), and no intervention (4.2%). However, CNI substitution did not improve the neurologic symptoms or imaging abnormalities in rare cases, most likely as CsA and tacrolimus exhibit similar pharmacologic effects. In such cases, replacing CNIs with non-CNIs is the appropriate approach.

Both our patients had complete recovery with no major neurological sequelae. The literature review showed that 89.3% of the patients with CNI-associated PRES had a full recovery and an additional 10.7% recovered with residual neurologic sequelae, including persistence of vigilance alteration, deterioration of visual acuity, epilepsy, amnesia, difficulties with speech, hemiparesis, and homonymous hemianopia, dysarthria and sporadic myoclonias, and visual field defects. Death occurred in 5.3% of the patients within the 1st year due to complications not related to PRES. Patients with hemorrhagic lesions recovered with neurologic sequelae, as did our 2nd patient who complained of numbness in the right buccal region.

Both our patients had imaging abnormalities that resolved, albeit slowly, during follow-up. The literature analysis revealed that the resolution of neuroimaging abnormalities might take an additional 24 more days on average than the resolution of neurologic signs (median: 6 vs 30 days, respectively, P < 0.001) after the treatment.

CONCLUSIONS

CNI-associated PRES is a rare clinical syndrome with acute neurological symptoms including seizure, encephalopathy, visual abnormalities, headache, focal neurological deficits, and nausea/vomiting. FLAIR MRI reveals reversible subcortical white matter changes in the posterior cerebral hemisphere. Lesions usually occur within the 1st month after transplantation. Radiological findings do not always correlate with the severity or type of clinical presentation. CNI-associated PRES generally has a favorable prognosis, but neurological sequelae may occur particularly if it is complicated by intracranial hemorrhage. Early diagnosis and prompt treatment, including adjustment of dose or discontinuation of CNIs, and blood pressure control in those with hypertension may be helpful.

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