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LETTER TO THE EDITOR

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ABOUT COVER

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CASE REPORT

Calcineurin inhibitors-related posterior reversible encephalopathy syndrome in liver transplant recipients: Three case reports and review of literature

Yu Gong

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Abstract

BACKGROUND

Posterior reversible encephalopathy syndrome (PRES), characterized by acute neurological deterioration and extensive white matter lesions on T2-fluid attenuated inversion recovery magnetic resonance imaging (MRI), is increasingly associated with calcineurin inhibitors (CNI)-related neurotoxicity. Prompt diagnosis is crucial, as early intervention, including the modification or discontinuation of CNI therapy, strict blood pressure management, corticosteroid treatment, and supportive care can significantly improve patient outcomes and prognosis. The growing clinical recognition of CNI-related PRES underscores the importance of identifying and managing this condition in patients presenting with acute neurological symptoms.

CASE SUMMARY

This report describes three cases of liver transplant recipients who developed PRES. The first case involves a 60-year-old woman who experienced seizures, aphasia, and hemiplegia on postoperative day (POD) 9, with MRI revealing ischemic foci followed by extensive white matter lesions. After replacing tacrolimus, her symptoms improved, and no significant MRI abnormalities were observed after three years of follow-up. The second case concerns a 54-year-old woman with autoimmune hepatitis who developed headaches, seizures, and extensive white matter demyelination on MRI on POD24. Following the switch to rapamycin and the initiation of corticosteroids, her symptoms resolved, and she was discharged on POD95. The third case details a 60-year-old woman with hepatocellular carcinoma who developed PRES, evidenced by brain MRI abnormal-ities on POD11. Transitioning to rapamycin and corticosteroid therapy led to her full recovery, and she was discharged on POD22. These cases highlight the critical importance of early diagnosis, CNI modification, and stringent management in improving outcomes for liver transplant recipients with CNI-

related PRES.

CONCLUSION
Clinical manifestations, combined with characteristic MRI findings, are crucial in diagnosing PRES among organ transplant recipients. However, when standard treatments are ineffective or MRI results are atypical, alternative diagnoses should be taken into considered.

Key Words: Posterior reversible encephalopathy syndrome; Calcineurin inhibitors; Liver transplantation; Prognosis; Case report

Core Tip: Liver transplantation is the only curative option for end-stage liver disease. The rise in liver transplants is accompanied by an increase in the occurrence of neurological complications. The etiology of calcineurin inhibitor (CNI)-related posterior reversible encephalopathy syndrome (PRES) remains unclear, and there are no established preventive measures. Optimal treatment strategies are still a matter of debate. CNIs, although widely used in liver transplants, come with various side effects. Therefore, when new neurological symptoms arise in liver transplant patients on CNIs who meet the diagnostic criteria for PRES, a cerebral magnetic resonance imaging should be promptly conducted to provide diagnostic evidence. Initiating treatment promptly upon confirming the diagnosis is essential for enhancing clinical outcomes.

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INTRODUCTION

Complications affecting the central nervous system, such as headaches, seizures, altered mental status, hemiplegia, sensory dysfunction, and visual impairments, frequently occur following solid organ transplantation. These complications are primarily caused by infections, the neurotoxic effects of immunosuppressive agents, and metabolic disturbances like hypernatremia or hypomagnesemia. They contribute to prolonged hospital stays, increased intensive care unit admissions, and are associated with higher mortality rates[1,2]. Both solid organ and stem cell transplant patients have a high incidence of posterior reversible encephalopathy syndrome (PRES)[3-5], The incidence of PRES in solid organ transplant patients ranges from 0.4% to 6%. In addition to certain medications, such as immunosuppressants, other factors contributing to the development of PRES include hypertension, renal dysfunction, and metabolic distur-bances [6], PRES is also associated with severe infections, reduced renal function, autoimmune diseases, and eclampsia[7]. Studies[5,8-12] have indicated that PRES can affect individuals across all age groups, with a higher prevalence observed in middle-aged women.

Previous studies have suggested that neurotoxicity related to calcineurin inhibitors (CNIs) occurs in an estimated 1% to 4% of solid organ transplant recipients[2,13,14]. While neurotoxicity and nephrotoxicity are significant adverse effects of immunosuppressive drugs[15-17], the pathophysiology of CNI-related PRES remains a subject of debate. Some researchers propose that it is linked to vasogenic edema and dysregulation of cerebral blood flow, particularly within the posterior cerebral circulation[8,15]. As a result, reversible subcortical white matter lesions, primarily in the posterior cortex of the cerebral hemisphere, typically appear on magnetic resonance imaging (MRI) within one to three months after organ transplantation. These lesions indicate a dysfunction in the regulation of the posterior cerebral circulation.

In 1996, Hinchey *et al*[16] first reported that CNIs could cause PRES. A retrospective analysis[18] involving 4222 solid organ transplant recipients found that the incidence of PRES was 0.49%. In this report, we present three cases of female liver transplant recipients diagnosed with CNI-related PRES, all of whom experienced favorable clinical outcomes. Additionally, we have summarized the clinical features of PRES through a literature review.

CASE PRESENTATION

Chief complaints

Case 1: A patient experienced a single episode of upper gastrointestinal bleeding six months ago, following a diagnosis of decompensated cirrhosis in 2010.

Case 2: A patient was diagnosed with autoimmune hepatitis in 2014, which was complicated by cirrhosis with decompensation, recurrent abdominal distension, and hepatic encephalopathy.

Case 3: A patient presents with a chief complaint of having discovered a liver mass 3 months ago.

History of present illness

Case 1: The patient was admitted to the hospital on June 16, 2016, and underwent orthotopic liver transplantation at the Hepatic Surgery Department of Zhongshan Hospital affiliated with Fudan University. Post-surgery, her postoperative immunosuppressive regimen consisted of tacrolimus, mycophenolate mofetil, and methylprednisolone, with maintenance of tacrolimus trough levels between eight to ten ng/mL.

On June 15th, 2016 [postoperative day (POD) 9], the patient suddenly developed neurological symptoms, including seizures and episodes of staring spells accompanied by aphasia, which eventually led to hemiplegia affecting the left limb and loss of consciousness. A cerebral hemorrhage was ruled out based on cranial computed tomography (CT) findings, while the initial cranial MRI revealed ischemic foci localized within the bilateral frontal lobes, with no significant involvement of the white matter regions (Figure 1A).

Subsequent laboratory investigations, including serological assays and electroencephalographic studies, returned unremarkable results, leading to the initiation of antiepileptic therapy with levetiracetam, clonazepam, and alprostadil, along with adjunctive neuroprotective agents. Despite these interventions, there was no significant improvement. Follow-up cranial MRIs conducted on POD22 revealed a continuous linear area of hyperintense abnormal signals involving the left posterior parietal region on diffusion-weighted imaging (DWI), along with patchy hyperintensities in the periventricular white matter and pontine areas bilaterally, as seen on fluid attenuated inversion recovery (FLAIR) sequences (Figure 1B).

Consequently, the possibility of CNIs-associated PRES was considered, leading to a transition in the immunosuppressive regimen from tacrolimus to rapamycin, with high-dose methylprednisolone totaling 1680 milligrams administered. This resulted in a favorable response regarding clinical symptoms. Subsequent evaluation with a third cranial MRI performed on POD66 demonstrated persistent aberrant signaling confined to the periventricular regions, displaying hypointensity during T1-weighted imaging and slight hyperintensity during T2-weighted imaging (Figure 1C).

Case 2: The patient was admitted to the hospital on July 19th, 2022, and underwent orthotopic liver transplantation at Zhongshan Hospital affiliated with Fudan University. Her postoperative immunosuppression regimen included tacrolimus, mycophenolic acid, and methylprednisolone, with the tacrolimus trough concentration maintained between 8 and 10 ng/mL. Although her liver function recovered rapidly and her blood electrolyte levels remained relatively stable, her blood pressure consistently remained elevated at approximately 160/90 mmHg.

However, on July 22nd, 2022 (POD4), the patient experienced transient delirium and hypoxemia, which improved with oral Zyprexa and supportive high-flow oxygen therapy. On August 13th, 2022 (POD24), the patient presented with acute neurological symptoms, including headache, restlessness, transient loss of consciousness, and limb convulsions. Neurological examination showed unresponsiveness to stimuli and an inability to cooperate with physical assessments; however, the bilateral pupils were equal in size with intact direct and consensual light reflexes. Symmetrical bilateral frontal lines and nasolabial folds were present, along with involuntary movements in both limbs. Additionally, both Pap and Kirsch signs were negative. The initial cerebral MRI on August 13th, 2022 (POD24), revealed a subdural hemorrhage in the left temporal lobe and extensive white matter demyelination (Figure 2A). The differential diagnoses included secondary epilepsy, immune-mediated white matter lesions, and subdural hemorrhage. Methylprednisolone was initiated following a neurological consultation, and levetiracetam and topiramate were administered while tacrolimus was replaced with rapamycin. Strict blood pressure control was maintained throughout the patient's stay in the intensive care unit, resulting in relatively stable vital signs. A follow-up cerebral MRI on August 30th, 2022 (POD43), revealed multiple demyelinating lesions in the brain along with a persistent subdural hemorrhage in the left temporal region (Figure 2B).

However, the diagnosis of osmotic demyelinating disease was under debated due to the absence of electrolyte disturbances was observed throughout the course of the illness. After replacing tacrolimus with rapamycin and administering a cumulative dose of 1580 mg of methylprednisolone, the neurological disorder gradually resolved.

Case 3: The orthotopic liver transplantation was successfully performed at Zhongshan Hospital, affiliated with Fudan University, on May 23rd, 2023. She was placed on an immunosuppressive regimen comprising tacrolimus, mycophenolic acid, and methylprednisolone, resulting in peak tacrolimus trough levels reaching up to 12.1 ng/mL. The initial recovery period was uneventful until the early morning of June 3rd, when she experienced a sudden-onset headache associated with elevated blood pressure (160/100 mmHg), leading to a loss of consciousness lasting approximately five minutes, accompanied by frequent limb convulsions. These symptoms necessitated tracheal intubation and sedation with midazolam, along with antiepileptic therapy using levetiracetam. Following prompt intervention, the patient regained consciousness and remained seizure-free by June 5th. Her initial cerebral MRI suggested potential PRES (Figure 3A). Consequently, tacrolimus was replaced with rapamycin, and the methylprednisolone dose was increased to 80 mg twice daily. Follow-up imaging revealed the resolution of brain lesions (Figure 3B). The absence of subsequent symptoms led to her discharge on June 17th, 2023 (POD22).

History of past illness

Case 1: The patient reported no personal or family history of hypertension, diabetes mellitus, cardiopulmonary disease, specific medication use, or genetic conditions within her family lineage.

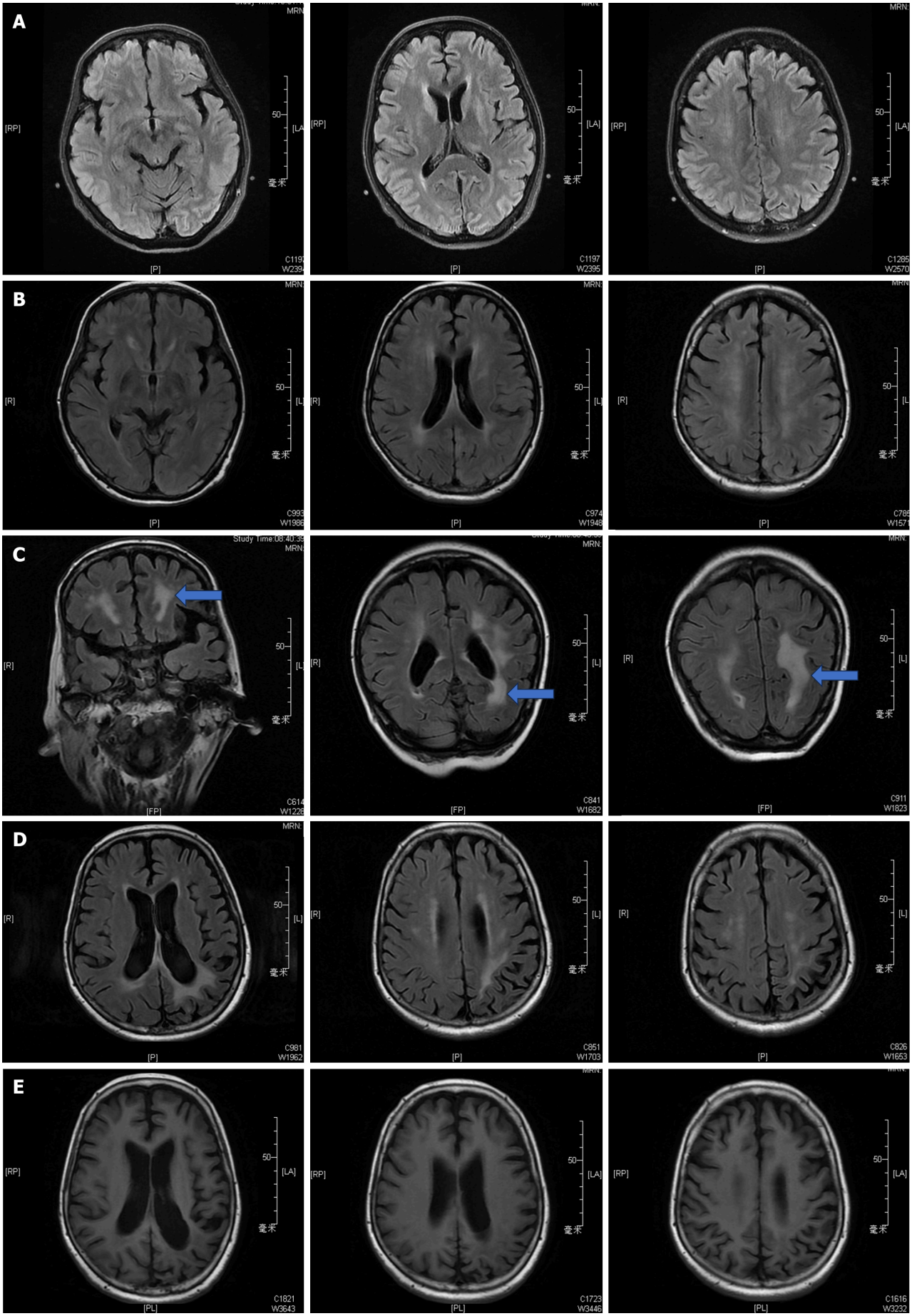

Figure 1 Cranial magnetic resonance imaging findings in patients monitored long-term (2016–2019). A: On June 15th, 2016 [postoperative day

(POD) 9], the cerebral magnetic resonance imaging (MRI) showed ischemic lesions in the bilateral frontal lobes, without noticeable white matter involvement; B: On June 27th, 2016 (POD 22), the MRI revealed a linear high signal in the left posterior parietal region on diffusion-weighted imaging and patchy high signals in the white matter and pons around both sides of the ventricles in fluid attenuated inversion recovery sequences; C: On August 12th, 2016 (POD 66), the MRI continued to show abnormal signals in the white matter surrounding the bilateral ventricles, with low signal intensity on T1-weighted images and slightly elevated signal intensity on T2-weighted images; D: On May 11th, 2018, the MRI still displayed abnormal signals in the white matter around the bilateral ventricles, with low signal intensity on T1-weighted images and slightly elevated intensity on T2-weighted images; E: On May 23th, 2019, the MRI showed no significant abnormalities in the white matter on T1-weighted and T2-weighted images.

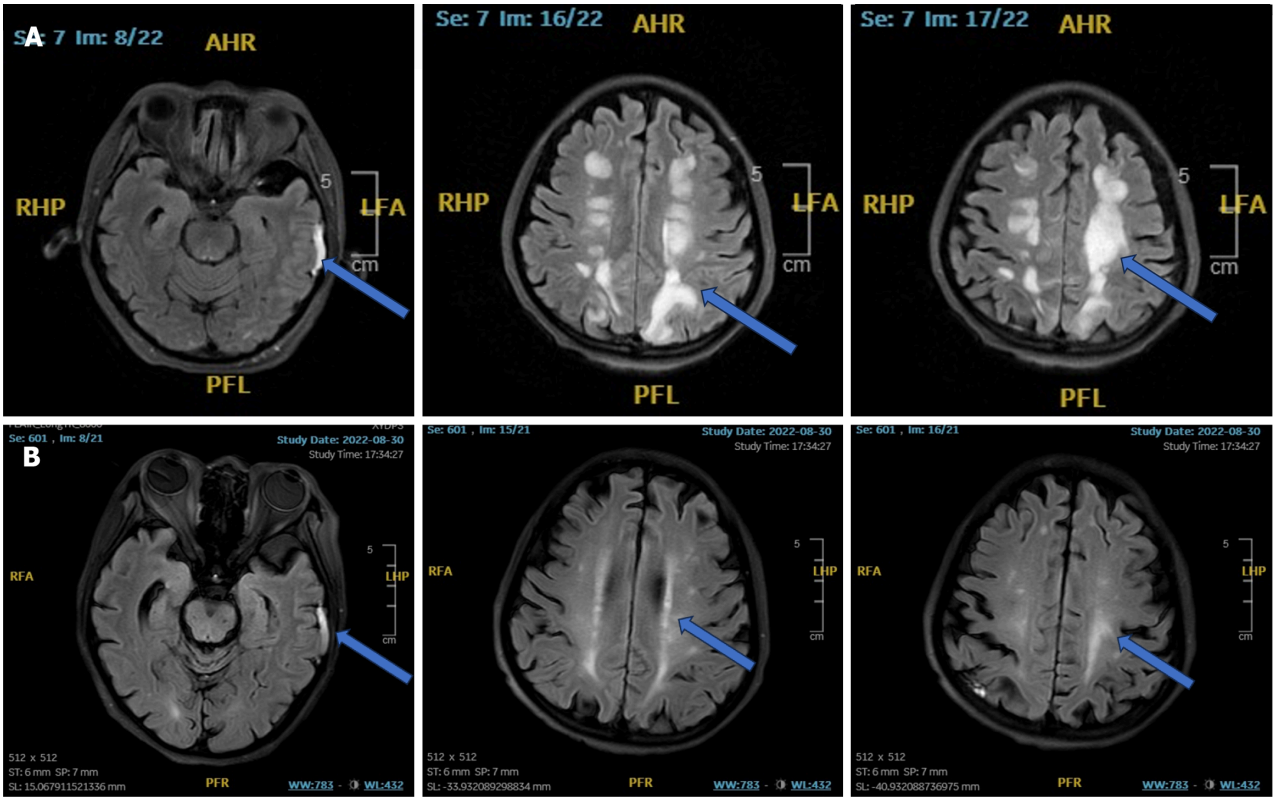

Figure 2 The white matter lesions in the patient's brain showed gradual resolution over 90 days. A: Initially, multiple areas with low signal on T1-weighted images (T1WI) and high signal on T2-WI fluid attenuated inversion recovery images (FLAIR) were observed bilaterally beneath the cerebral cortex, in the corona radiata, and the centrum semiovale, as indicated by the blue arrows. No significant abnormalities were noted on diffusion-weighted imaging (DWI). Curvilinear high signal shadows on T1WI and T2WI-FLAIR were also observed in the left temporal subdural region; B: Later, the blue arrows highlight multiple linear regions with low T1WI signal and high T2WI-FLAIR signal, with no evident abnormalities on DWI, along both sides of the cerebral cortex, corona radiata, centrum semiovale, lateral ventricle, and left basal ganglia. Widening of the fluid space was noted under the left medial temporal pole. AHR: Anterior to horizontal right; PFL: Posterior to frontal left; LFA: Left frontal anterior; RHF: Right horizontal frontal.

Case 2: She had no history of hypertension, diabetes, cardiopulmonary diseases, specific medication use, or genetic disorders in her family.

Case 3: The patient has no history of any other illnesses.

Personal and family history

All of patient has no reported comorbidities, and there is no family history of genetic disorders.

Physical examination

Case 1: On June 15th, 2016 (POD9), the patient experienced a sudden onset of neurological symptoms, including seizures, staring spells, aphasia, and hemiplegia affecting the left limb, culminating in a loss of consciousness. Cerebral hemorrhage was ruled out based on cranial CT imaging, while initial cranial MRI revealed ischemic foci localized within the bilateral frontal lobes without significant involvement of the white matter. Subsequent laboratory investigations, including serological assays and electroencephalographic studies, yielded unremarkable results, prompting the initiation of antiepileptic therapy with levetiracetam, clonazepam, and alprostadil, along with adjunctive neuroprotective agents. Despite these interventions, no significant improvement was observed.

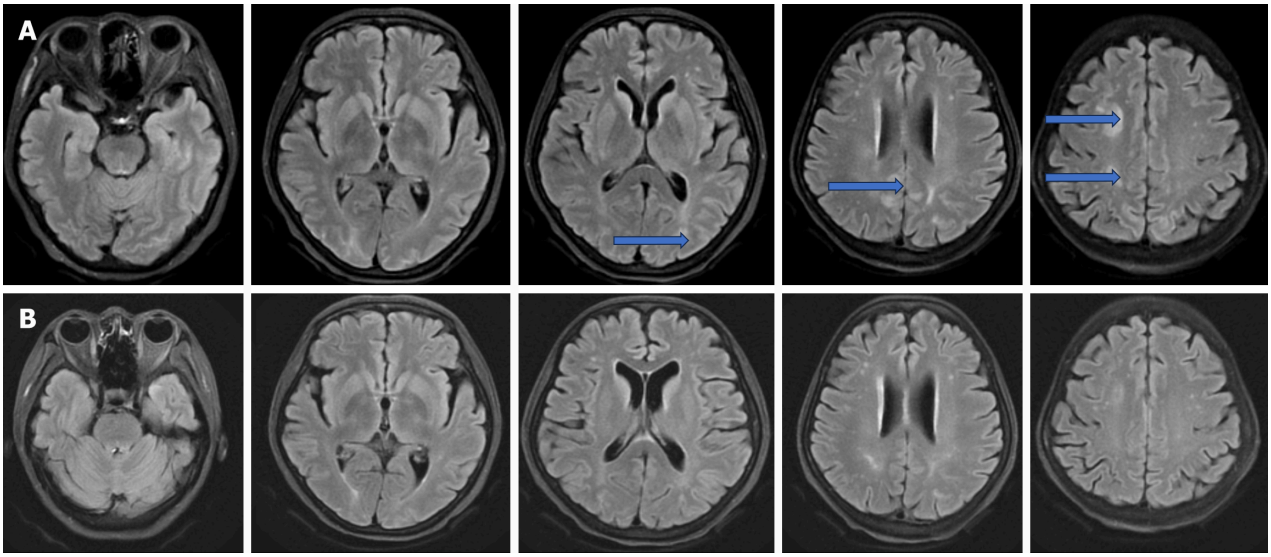

Figure 3 Head magnetic resonance imaging of the liver transplant patient revealed significant recovery in brain white matter damage on postoperative day 22. A: Scattered areas in the right frontal lobe and bilateral parietal cortex showed slightly decreased T1 signals and slightly increased T2 signals, as indicated by the blue arrows. No significant diffusion-restricted changes were observed on diffusion-weighted imaging (DWI). Specks and flaky abnormal signal shadows were detected beneath the cerebral cortex and near the lateral ventricles on both sides. T1WI displayed low signal intensity, while T2WI and fluid attenuated inversion recovery images (FLAIR) showed high signal intensity. No abnormal high signals were evident on DWI; B: Patchy T1 and T2 signals were noted in the right frontal and bilateral parietal cortex, with no apparent diffusion-restricted changes on DWI or notable abnormal enhancement post-contrast. Specks and flaky abnormal signal shadows were observed beneath the cerebral cortex and near the lateral ventricles on both sides. T1WI showed low signal intensity, whereas both T2WI and FLAIR revealed high signal intensity, with no abnormal high signals detected by DWI.

Case 2: On August 13th, 2022 (POD24), the patient presented with acute neurological dysfunction characterized by headache and restlessness, followed by transient disturbances of consciousness and limb convulsions. Neurological examination revealed unresponsiveness to stimuli and inability to cooperate with physical assessments; however, bilateral pupils were equal in size with intact direct and consensual light reflexes. Symmetrical bilateral frontal lines and nasolabial folds were observed, along with involuntary movements in both limbs. Both the Pap sign and Kirsch sign were negative. The initial cerebral MRI on August 13th, 2022 (POD24) demonstrated a subdural hemorrhage in the left temporal lobe as well as extensive white matter demyelination.

Case 3: In the early morning of June 3rd, 2023, the patient experienced a sudden-onset headache accompanied by elevated blood pressure (160/100 mmHg), leading to a loss of consciousness lasting approximately five minutes, along with frequent limb convulsions. These symptoms required tracheal intubation, followed by sedation with midazolam and antiepileptic therapy with levetiracetam. After these prompt interventions, the patient regained consciousness and remained seizure-free by June 5th, 2023.

Laboratory examinations

After liver transplantation, the hematological parameters, hepatic and renal function, electrolyte levels, infection markers, and tacrolimus trough concentration in these three patients gradually normalized in the early stage.

Imaging examinations

Case 1: Firstly, cerebral hemorrhage was ruled out in this patient based on cranial CT findings, while initial cranial MRI revealed ischemic foci localized within the bilateral frontal lobes, with no significant involvement of the white matter regions (Figure 1A). Subsequent laboratory investigations, including serological assays and electroencephalographic studies, yielded unremarkable results, prompting the initiation of antiepileptic therapy with levetiracetam, clonazepam, and alprostadil, along with adjunctive neuroprotective agents. Despite these interventions, no significant improvement was observed. Subsequent cranial MRIs conducted on POD22 revealed persistent linear hyperintense signals involving the left posterior parietal region on DWI, along with patchy hyperintensity within the periventricular white matter and pontine areas bilaterally, as discerned using FLAIR sequences (Figure 1B).

As a result, the possibility of CNI-associated PRES was considered, leading to a transition in the immunosuppressive regimen from tacrolimus to rapamycin, along with an additional course of intravenous methylprednisolone totaling 1680 milligrams, which yielded a favorable response in terms of clinical symptoms. Subsequent evaluation *via* a third cranial MRI performed on POD66 demonstrated persistent aberrant signaling confined to the periventricular regions, displaying hypointensity during T1-weighted imaging and slight hyperintensity during T2-weighted imaging phases (Figure 1C).

Ultimately, a definitive diagnosis of CNI-induced PRES was established based on the concordance between clinical presentation and radiologic evidence. Despite persistent abnormalities observed across successive cranial MRIs, the patient remained hemodynamically stable and was ultimately discharged with normal hepatic function, undergoing

regular follow-up extending beyond three years. The white matter lesions gradually resolved and were no longer detectable by the follow-up in 2019 (Figure 1D and E).

Case 2: On August 13th, 2022 (POD24), the patient experienced acute neurological symptoms, including headache and restlessness, followed by brief episodes of impaired consciousness and limb convulsions. Neurological assessment revealed a lack of response to stimuli and an inability to cooperate with physical examinations. However, the pupils were equal in size with preserved direct and consensual light reflexes. The patient exhibited symmetrical bilateral frontal lines and nasolabial folds, along with involuntary limb movements. Both Pap and Kirsch signs were negative. An initial cerebral MRI conducted on August 13th, 2022, revealed a subdural hemorrhage in the left temporal lobe and extensive white matter demyelination (Figure 2A). The differential diagnosis included secondary epilepsy, immune-mediated white matter lesions, and subdural hemorrhage. Consequently, methylprednisolone therapy was initiated following neurological consultation. Levetiracetam and topiramate were prescribed, and tacrolimus was replaced with rapamycin. Blood pressure was meticulously controlled during the patient's stay in the intensive care unit, resulting in relatively stable vital signs. A follow-up cerebral MRI on August 30th, 2022 (POD43), showed multiple demyelinating lesions in the brain, along with a persistent subdural hemorrhage in the left temporal region (Figure 2B).

Case 3: The initial cerebral MRI indicated the possibility of PRES (Figure 3A). Consequently, tacrolimus was replaced with rapamycin, while the methylprednisolone dosage was increased to 80 mg twice daily. Follow-up imaging showed a resolution of the brain lesions (Figure 3B).

MULTIDISCIPLINARY EXPERT CONSULTATION

Given the patient's history of tacrolimus use following liver transplantation, and the absence of other neurological conditions such as demyelinating diseases and progressive multifocal leukoencephalopathy (PML), modifications to or cessation of CNI therapy were implemented. Additionally, stringent blood pressure control, corticosteroid treatment, and supportive care were provided for the three patients.

FINAL DIAGNOSIS

Case 1

A definitive diagnosis of CNIs-induced PRES was established based on the concordance between the clinical presentation and radiologic findings.

Case 2

The diagnosis of osmotic demyelinating disease was debated due to the absence of electrolyte disturbances during the illness. However, after replacing tacrolimus with rapamycin and administering a cumulative dose of 1580 mg of methylprednisolone, the neurological symptoms gradually resolved. Consequently, a diagnosis of CNIs-related PRES was confirmed.

Case 3

The diagnosis of CNIs-induced PRES was confirmed based on cerebral MRI findings.

TREATMENT

Case 1

The immunosuppressive regimen was modified by switching from tacrolimus to rapamycin and was further augmented with an additional course of intravenous methylprednisolone, totaling 1680 mg.

Case 2

Tacrolimus was replaced with rapamycin, and methylprednisolone was administered continuously, totaling 1580 mg.

Case 3

Tacrolimus therapy was transitioned to rapamycin, while the dose of methylprednisolone was increased to 80 mg twice daily.

OUTCOME AND FOLLOW-UP

Case 1

Notwithstanding enduring abnormalities evident across successive cranial MRI, the patient remained hemodynamically stable ultimately achieving discharge normative hepatic function undergoing regular follow-up extending beyond three years. The white matter lesions in the patients gradually resolved and were no longer detectable by the follow-up in 2019 (Figure 1D and E).

Case 2

The patient was discharged from the intensive care unit on September 29th, 2022 (POD81). Consequently, confirmation of CNI-related PRES led to her discharge on October 13th, 2022 (POD95).

Case 3

The patient's subsequent symptom resolution led to her successful discharge on June 17th, 2023 (POD22).

In summary, three patients exhibited complete recovery of their neurological symptoms without any complications and were discharged from the hospital in a favorable clinical condition.

DISCUSSION

Despite an increasing number of case reports and reviews addressing postoperative neurological complications in solid organ transplant recipients, the precise pathogenesis remains unclear and is thought to be associated with factors such as infections, immunosuppressive drugs, and electrolyte imbalances[19-21] such as hypomagnesemia, uncontrolled or persistent hypertension, significant fluctuations in blood pressure, as well as pre-existing cerebral lesions[9] and even infections. Previous studies have indicated that the prevalence of tacrolimus-induced PRES ranges from 1% to 6%[16,22]. Neurological symptoms were observed in over 80% of liver transplant recipients within the first three months after the operation[9]. However, some patients experienced the onset of PRES more than a year after liver transplantation[16,23]. The prognosis of patients with PRES varied depending on their clinical condition, with the majority experiencing complete recovery without any long-term effects[4,8,13,22], However, unfortunately, a small number of patients still succumb to the illness[24].

According to published reports, CNIs, particularly tacrolimus, are often implicated as a common trigger for PRES in liver transplant recipients[17,21,22,25]. However, neurotoxicity associated with CNIs is frequently observed even when tacrolimus trough levels are within the normal range. This occurs because tacrolimus, being a lipid-soluble drug, can cross the blood-brain barrier and directly exert toxic effects on the lipid-rich regions of white matter[7,8,12]. Given these considerations, reducing the dosage of tacrolimus or switching to alternative immunosuppressants may be a potentially safer and more effective approach. It is worth noting, however, that cyclosporin, another immunosuppressant, also has the potential to cause neuraxial edema[26]. Although the pathophysiology of PRES remains unclear, endothelial damage is believed to be one of the key mechanisms in the development of CNI-related PRES[8]. It has been suggested that CNIs may induce reversible vasogenic edema, leading to the disruption of cerebral blood vessel autoregulation, particularly affecting the posterior cerebral circulation. Vascular integrity is maintained by inter-endothelial adhesion molecules, while circulating toxins may trigger vascular leakage and subsequent edema[26,27]. In immune disorders and other systemic conditions, dysfunction in cerebrovascular regulation can result in hyperperfusion in the posterior cerebral circulation. This phenomenon explains the tendency for involvement of the frontal and occipital lobes in PRES, as observed in MRI findings that predominantly show changes in these regions. While magnetic resonance angiography of the brain typically appears normal in PRES cases, it can sometimes reveal focal vasoconstriction or vasodilation patterns suggestive of central nervous system (CNS) vasculitis. Additionally, magnetic resonance venography, which is usually unremarkable in PRES cases, can be helpful in ruling out sagittal sinus thrombosis[28,29].

Reports on the clinical manifestations of PRES include a range of atypical neurological symptoms[8]. Therefore, the onset of new headaches and transient fluctuations in blood pressure in liver transplant recipients should not be overlooked, as these may be early symptoms of PRES. The use of CNIs and timely cerebral imaging are crucial for early diagnosis. With prompt treatment, including transitioning to rapamycin and corticosteroid therapy, patients with PRES can experience rapid recovery, often accompanied by significant improvements in cerebral structural changes as seen on MRI scans[2,8,29]. Therefore, special attention should be given to newly occurring headaches, limb convulsions, transient loss of consciousness, and new persistent hypertension in post-transplantation patients. In addition to routine cerebral imaging scans, lumbar puncture may be performed in immunocompromised individuals to assess for encephalitis. Furthermore, brain biopsy has been recommended as a diagnostic tool for identifying the underlying cause in patients unresponsive to initial treatments.

Currently, the primary treatments for PRES focus on providing supportive care, including maintaining stable vital signs, closely managing blood pressure, replenishing electrolytes, adjusting the tacrolimus dosage or switching immunosuppressive medications, and administering antiepileptic drugs as needed[11,30]. Early diagnosis can enable most patients to benefit from these treatments. However, the routine use of corticosteroid therapy for treating PRES-associated vasogenic edema remains controversial due to the lack of evidence supporting its efficacy[8], some studies support that corticosteroid therapy often preceded the onset of PRES and was not significantly associated with the extent of vasogenic edema, suggesting it did not reduce the edema. However, according to our cases, the cautious administration of corticosteroid therapy, when not contraindicated, effectively ameliorated clinical symptoms and potentially had

a positive impact on cerebral lesions.

The duration of cerebral lesions varied among PRES patients. In the first female patient, cerebral lesions persisted for approximately three years before gradually resolving in the affected white matter areas. In contrast, the cerebral lesions in the third patient resolved rapidly within 10 days after symptom onset. Furthermore, it was challenging to determine the presence of preexisting brain lesions in certain recipients prior to surgery due to the potential oversight of atypical clinical symptoms. Transplant candidates over 60 years old may already have localized white matter lesions due to cerebrovascular diseases. Although the prognosis for all three patients was relatively favorable, each had distinct clinical durations. Therefore, routine cerebral imaging scans are strongly recommended for organ transplant candidates, particularly those over 60 years old, and especially if they exhibit sharp fluctuations in perioperative blood pressure, electrolyte disturbances, hypoalbuminemia, or underlying infections or autoimmune diseases.

Finally, as reported in the literature, most patients with PRES have a favorable prognosis. However, if treatment is unsuccessful, it is important to promptly consider other neurological conditions, such as CNS infections, primary epilepsy, and PML[30-33]. PML which resulting from the reactivation of John Cunningham (JC) virus infection, typically occurs in immunocompromised individuals. Although PML is rare in liver transplant recipients, it is associated with a high mortality rate. The diagnosis of PML primarily relies on clinical manifestations, cerebral imaging, and polymerase chain reaction techniques to detect JC virus replication in cerebrospinal fluid.

CONCLUSION

In conclusion, while the neurotoxicity of CNIs is a significant factor, other variables also require careful evaluation in all organ transplant candidates. These include assessing comorbidities, prior medication history, preoperative cerebral imaging, and pre-existing viral infections. Additionally, independent risk factors for postoperative neurological complications include alcoholic liver disease, metabolic disorders, preoperative mechanical ventilation, model for end-stage liver disease scores exceeding 15, advanced age, elevated preoperative blood bilirubin levels, decreased platelet counts, severe lung infections, and renal insufficiency. Careful consideration of these factors is essential for optimizing patient outcomes post-transplantation[14,18,22,34,35]. Therefore, it is imperative to have a comprehensive understanding of the pathogenesis, conduct a thorough assessment of risk factors, and implement effective preventive measures. Prompt diagnosis and timely treatment are also critical. Moreover, further investigation into specific therapies for CNI-related PRES is warranted in order to improve patient outcomes.

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FOOTNOTES

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