Tacrolimus-Associated Posterior Reversible Encephalopathy Syndrome after Solid Organ Transplantation

Qisi Wu^a Christian Marescaux^c Valérie Wolff^c Mi-Young Jeung^d
Romain Kessler^e Valérie Lauer^c Yangmei Chen^b

^aThe Second Affiliated Hospital and ^bDepartment of Neurology, The Second Affiliated Hospital, Chongqing Medical University, Chongqing, PR China; ^cStroke Unit and Department of Neurology, University Hospital of Strasbourg, ^dDepartment of Radiology B, University Hospital of Strasbourg, and ^eDepartment of Pulmonology, Nouvel Hôpital Civil, Strasbourg, France

Key Words

Posterior reversible encephalopathy syndrome · Tacrolimus · Solid organ transplantation

Abstract

Tacrolimus (TAC) is an immunosuppressant drug discovered in 1984 by Fujisawa Pharmaceutical Co., Ltd. This drug belongs to the group of calcineurin inhibitors, which has been proven highly effective in preventing acute rejection after transplantation of solid organs. However, neurotoxicity and nephrotoxicity are its major adverse effects. Posterior reversible encephalopathy syndrome (PRES) is the most severe and dramatic consequence of calcineurin inhibitor neurotoxicity. It was initially described by Hinchey et al. in 1996 [N Engl J Med 1996;334:494–450]. Patients typically present with altered mental status, headache, focal neurological deficits, visual disturbances, and seizures. Magnetic resonance imaging is the most sensitive imaging test to detect this. With the more deep-going studies done recently, we have learnt more about this entity. It was noted that this syndrome is frequently reversible, rarely limited to the posterior regions of the brain, and often located in gray matter and cortex as

well as in white matter. Therefore, in this review, the focus is on the current understanding of clinical recognition, pathogenesis, neuroimaging and management of TAC-associated PRES after solid organ transplantation.

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Introduction

The introduction of the calcineurin inhibitor (CNI) cyclosporine (CsA), and later of tacrolimus (TAC), with 100 times more potent immunosuppressive activity than that of CsA by weight, revolutionized posttransplantation immunosuppressive therapy in the 1980s [1]. These drugs effectively prevent acute rejection episodes and significantly prolong patient and graft survival [2, 3]. As demonstrated in large, prospective, randomized, multicenter solid organ transplantation (SOT) trials, when compared with CsA, TAC further reduced the 6-month/1-year incidence of biopsy-proven acute rejection. Post-transplant survival and treatment failure rates in the TAC groups were at least equal to or better than those for CsA. Furthermore, other metabolic benefits were seen in TAC

groups, such as lowered incidence of hyperlipidemia and cosmetic changes (gum hypertrophy, hirsutism) [4–6]. In contrast to 1997, when 77% of patients were discharged on CsA, 82% were started on TAC in 2006 [7]. However, the incidence of neurotoxicity which is one of the major adverse events of CNIs was higher in patients receiving TAC rather than CsA [8]. TAC-induced neurotoxicity has been well documented particularly in SOT recipients. As both sensory-motor functions may be adversely affected, patients thus present with a wide range of neurological and psychiatric disorders. Mild symptoms include tremor, neuralgia, and peripheral neuropathy. Severe symptoms could be manifested as psychoses, hallucinations, cortical blindness, seizures, cerebellar ataxia, motor weakness, or posterior reversible encephalopathy syndrome (PRES) [2, 9–15]. As an uncommon complication related to significant morbidity and mortality if it is not expeditiously recognized [9], TAC-associated PRES after SOT has recently been increasingly reported.

Posterior Reversible Encephalopathy Syndrome

PRES was initially described by Hinchey et al. [16] in 1996 as a cliniconeuroradiological entity, characterized by typical neurological deficits, distinctive magnetic resonance imaging (MRI) features, and a usually benign clinical course. Although hypertensive urgency, eclampsia, immunosuppressive drugs (CsA and TAC) and acute intermittent porphyria were first reported as predisposing factors causing PRES, it is a syndrome which can have variable causes (table 1).

Prevalence and Clinical Features of TAC-Associated PRES in SOT

The frequency of patients affected by CNI-induced neurotoxicity has been reported to vary from 7 to 32% [2, 17]. According to emerging research in the USA covering 4,222 patients who had undergone SOT from 1998 to 2006, the overall incidence of PRES after SOT is 0.49% [18], which is much lower than that suggested by older reports or studies (1–6%) [19]. However, Wong et al. [20] reported that the incidence of TAC-induced PRES is approximately 1.6%. Minor variation in the PRES incidence was noted between SOT subtypes from 0.34% in the kidney or kidney-pancreas group to 0.84% in the small bowel group, but differences were not statistically significant [18].

Table 1. Causes of PRES

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- Hypertensive encephalopathy [16]
 - Preeclampsia [68], eclampsia [16], HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome [69], thrombotic thrombocytopenic purpura [70], hemolytic uremic syndrome [71]
 - Immunosuppressive drugs (CsA, TAC, sirolimus) [16, 67]
 - Antineoplastic drugs (cisplatin [72], cytarabine [73], infliximab [74])
 - High-dose steroid therapy [75]
 - Intravenous immunoglobulins [76]
 - Renal diseases (nephrotic syndrome [77], patient on hemodialysis for end-stage renal disease [78])
 - Liver failure (cirrhosis [79])
 - Endocrine dysfunctions (pheochromocytoma [80])
 - Hypercalcemia [81] or hypomagnesemia [52]
 - Massive blood transfusion [82] or erythropoietin therapy [83]
 - Acute intermittent porphyria [84]
 - Collagen vascular disorders (systemic lupus erythematosus [85], polyarteritis nodosa [86], Behçet's syndrome [87])
 - Other causes (contrast medium exposure, scorpion poison, stimulant abuse, digitoxin intoxication, *Averrhoa carambola* ingestion) [88]
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The clinical picture of PRES is characterized by an acute or subacute encephalopathy with headache, vomiting, focal neurological deficits, altered mental status, visual impairment and seizures [21, 22]. Seizures may begin focally but usually become generalized. Additionally, in approximately 70–80% of patients, moderate-to-severe hypertension is observed [18, 23]. Recent research compared the clinical characteristics of PRES between different SOT subgroups in which statistically significant differences were found. As in patients who had undergone liver transplantation, PRES developed in the first 2 months after the transplantation. These patients had generally normotensive blood pressure and greater brain vasogenic edema, whereas in patients who had undergone kidney transplantation, PRES developed 1 year later. These patients had severe hypertension at presentation but had much less brain vasogenic edema [18, 24]. Normally, clinical symptoms resolve after a mean of 5.3 days [21]. But late recognition of this syndrome, poor control of hypertension, prolonged seizures, the inability to correct or diagnose the triggering metabolic abnormality, or persistence in the use of the culprit drugs may, potentially, result in permanent neurological deficit and cerebral infarcts. The multiple cerebral infarctions may result in early dementia.

Fig. 1. A 19-year-old patient with mucoviscidosis underwent a bi-pulmonary and hepatic transplantation. Seven days after the surgery, the patient presented with sudden-onset generalized tonic-clonic seizures, altered mental status and headache. Axial MR im-

ages showed **a** bilateral posterior subcortical hyperintensities on FLAIR. **b**, **c** DWI reveal abnormal signal hypointensities in the same region, with high ADC in a pattern typical of PRES.

Fig. 2. In the same patient, 2 months after the transplantation, confusion developed again. **a** FLAIR MR images reveal cerebral hyperintense signal changes in the subcortical white matter of the parietal lobe and deep white matter including internal capsules, insular regions and corpus callosum with predominance in the splenium. Additionally, there are hyperintense signal alterations also located in caudate nucleus. **b** Corresponding DWI demon-

strates increased diffusion particularly in the periventricular white matter and corpus callosum with isointense signal in the rest of the areas. **c** Except for corpus callosum with reduced ADC values which suggested cytotoxic edema, those areas with increased signal intensity on FLAIR have increased ADC values suggesting a vasogenic edema.

Neuroimaging

It has been well established that vasogenic edema rather than cytotoxic edema plays a pivotal role in TAC-associated neuroimaging characteristics of PRES supported by MRI manifestations [25–29] (fig. 1). Nevertheless, cases of a coexistence of vasogenic and cytotoxic edema suggesting irreversible damage have been described [25, 28–30] (fig. 2). Therefore, although computed tomography

can be used preliminarily to detect hypodense lesions of posterior encephalopathy, MRI is the gold standard of diagnosing this syndrome. Fluid-attenuated inversion recovery (FLAIR) sequence is the most sensitive sequence for recognition of cortical and subcortical edema in PRES where hyperintense signal alterations are more prevalent than on conventional sequences [31]. Furthermore, new MR techniques, including diffusion-weighted MRI (DWI) and apparent diffusion coefficient (ADC) map-

Fig. 3. A 48-year-old patient with silicosis underwent a bipulmonary transplantation. Five months after the transplantation, the patient suddenly developed confusion. **a, b** FLAIR demonstrates asymmetric cerebral increased white matter signal intensity affecting cerebellar, parietal and frontal areas. **c, d** Corresponding T₂* reveals a lesion of decreased signal intensity in the right cerebellum and multiple hypointense signal changes in the two cerebral hemispheres, suggesting hemorrhagic lesions.

ping, which can be elaborated from DWI, enable the measurement of net movement of water molecules in the brain using different metrics and reliably distinguish the type of edema in these patients [27–29].

In the case of a cytotoxic edema in which water molecules are translated from the extracellular to the intracellular compartment, it is characterized by hyperintensity in diffusion-weighted images and hypointensity in ADC mapping (fig. 2b, c) whereas in the case of a vasogenic edema, where there is an increase in the extracellular water and thus an increased diffusion, DWI shows an iso- or hyperintense signal but in ADC maps the signal intensity is increased [29] (fig. 2b, c). However, a significant debate has developed in recent literature regarding the various DWI phenomena of PRES. In the patients with PRES, although the most common appearances on diffusion-weighted images are isointense lesions result-

ing from a balance of T₂ effects and increased water diffusibility, a hypo- and hyperintense signal can also be visualized due to further increased diffusibility and T₂ shine-through effect, respectively [25, 32–34] (fig. 1b, 2b). In this regard, the quantification of ADC becomes essential for the discrimination of this vasogenic edema from cytotoxic edema in these patients. Covarrubias et al. [35] found that pseudonormalized normal ADC values in the areas of DWI hyperintensity may represent the earliest sign of nonreversibility as severe vasogenic edema progresses to cytotoxic edema with a worse outcome in patients with PRES. Mueller-Mang et al. [32], on the other hand, showed that the clinical outcome in their patients did not differ according to DWI abnormalities. In addition, abnormal gadolinium enhancement and hemorrhage (fig. 3c, d) were also described as less common manifestations in PRES. Hence, it is advisable that the

sequences (FLAIR, DWI and ADC) and even T_2^* and gadolinium-enhanced T_1 -weighted imaging where the degree of enhancement could relate to the cause of PRES (CsA or TAC) should be included in MR protocols for suspected PRES, not only for the correct identification of the lesions but also for preventing deleterious workups or therapies [25, 29].

Apart from a significantly higher number of involved brain regions and a tendency for basal ganglia involvement in patients with PRES associated with preeclampsia-eclampsia, the MRI appearance of patients with PRES does not seem to be influenced by predisposing risk factors [32]. Typically, the lesions of PRES reported in the literature are bilateral and symmetric in the cortical and subcortical regions of the parietal and occipital lobes (fig. 1a). However, in most patients, lesions were rarely limited to the posterior regions of the brain and asymmetric involvement of at least one brain region (fig. 3a, b) or even a unilateral variant was observed [25, 32]. Posterior frontal (51.5–78.9%), temporal (33–68.4%), cerebellum (33.3–43%), brainstem (18.4–30%), thalamus (30.3%), and basal ganglia (11.8%) can be involved, which used to be called atypical PRES but with a higher incidence than commonly perceived [16, 25, 28, 31, 32] (fig. 2a, 3a, b). Hence, McKinney et al. [25] suggested that the term ‘multifocal’ or simply removing ‘posterior’ from the term ‘posterior reversible encephalopathy syndrome’ may be a more appropriate terminology given the common involvement of the regions supplied by the anterior circulation.

Pathogenesis

It is known that neurological alterations after CNI therapy are associated with brain structures showing high calcineurin expression [36]. But the precise mechanism for the development of subcortical and cortical edema in PRES is still incompletely understood. From a historical perspective, two major hypotheses on the pathology of PRES are currently being discussed in the literature: the hyperperfusion and hypoperfusion theory. The first hypothesis which is more current and popular refers to systemic hypertension. Severe hypertension leads to the transient disruption of the autoregulation system consisting of a myogenic and a neurogenic response which will lead to cerebral vasodilatation; this, therefore, allows extravasation of fluid and blood into the brain parenchyma [37] and causes vasogenic cerebral edema. The main evidence supporting this theory comes from stud-

ies with single photon emission tomography [38] and as mentioned earlier DWI [27]. However, an inconsistency of this hypothesis is that many patients develop the syndrome with relative normotension.

Alternatively, vasospasm with brain hypoperfusion and presumed ischemia has been demonstrated. This theory is supported by the magnetic resonance angiography evaluation of a patient with CsA-induced PRES with documented prolonged reversible vasospasm [39] and it was noted that PRES occurred in 9% of patients with reversible cerebral vasoconstriction syndrome [40]. Several autopsy studies confirmed a predominance of ischemic microinfarcts or fibrinoid necrosis and cerebral vasculitis may occur [41–43]. Moreover, Bartynski and Boardman [24] reported decreased blood volume in reversible posterior leukoencephalopathy syndrome lesions on MRI perfusion coupled with a high rate of vasculopathy which was also seen in 2 cases of a recent series of patients with PRES and was considered to be responsible for some of the irreversible injury, presumably ischemic in nature [21, 44]. These features suggest that the primary mechanism of PRES could be associated with reduced cerebral flow. In contrast, hypertension, at some level, may reduce the vasogenic edema and exert a protective effect limiting the development of PRES [24]. Additionally, experimental data have indicated direct cytotoxic effects on the brain capillary endothelial cells with TAC which is similar, but less severe than those of CsA [45]. However, because of the large number of different chemotherapeutic and immunosuppressant agents that are associated with PRES, some publications focused on an immunogenic process as a theory for possible endothelial dysfunction or demyelination in patients with PRES [46–49]. This seems to be specifically associated with CNIs (TAC and CsA). According to a recent article by Bartynski [46] and along with the previously described immunogenic theory, enhanced systemic endothelial activation, leukocyte trafficking, and vasoconstriction, alone or in combination, would result in brain and systemic hypoperfusion in the majority of patients with PRES. Thus, we cannot deny that immune-mediated states may contribute to the increased risk of PRES in a subset of patients. Moreover, it has been demonstrated that TAC has a more significant effect on causing urinary magnesium wasting and hypomagnesemia when compared with CsA, which might partly explain the higher incidence of renal impairment and encephalopathy in patients receiving TAC [50–52]. Hypomagnesemia, which has been reported to predispose to hypertension, renal impairment, and TAC-induced encephalopathy after transplantation [50, 52],

could promote vasoconstriction [53]. But the precise mechanism by which hypomagnesemia causes encephalopathy is not clear. Therefore, we are in favor of the opinion voiced by Lee et al. [54] that although there are a variety of superficially unrelated precipitants involved in the process, all the triggers are presumably unified by a final common pathway, possibly dysfunction of cerebral autoregulation.

Management

As an effective medication for eclampsia seizures, the mechanism of action of magnesium sulfate has been further studied, in which the vasodilatory effect in the peripheral vasculature and the cerebrovasculature along with its effect on protecting the blood-brain barrier and possible effect on the cerebral endothelium to limit vasogenic edema has been proposed [55]. Consequently, a further discussion of magnesium supplementation and its potential in treating or preventing other brain injury disorders, even TAC-associated PRES, has recently been raised [55, 56]. However, the fact that mesenteric arteries are significantly more sensitive to magnesium sulfate as a vasodilator than the cerebral arteries [57] made it difficult to achieve consensus regarding the best possible use of magnesium supplementation in treating or preventing PRES, and there is controversy regarding the safety of treatment for neurological conditions as well as the specific mechanisms of action of magnesium sulfate remain unclear. Nevertheless, close serum magnesium level monitoring has been strongly recommended so as to avoid the possible TAC-associated complications induced by hypomagnesemia [50].

TAC-associated PRES may be reversed in most patients by substantially reducing the dosage of TAC or discontinuing the drug. But the conflicts between the prevention of episodes of rejection after transplantation and neurotoxicity from TAC always bewilder physicians. Therefore, TAC therapeutic drug monitoring still remains the main approach to aid physicians to obtain the ideal balance between therapeutic efficacy and the occurrence of adverse events, which still has its limitations. A well-recognized phenomenon is that immunosuppressant blood levels do not appear to correlate with PRES and some patients have experienced permanent or even fatal neurological damage even after dose reduction or discontinuation [58], suggesting the possibility of idiosyncrasy. A trial following 827 adult liver transplant recipients who received TAC as their primary immuno-

suppressant over a 5-year period focused on those who required a switch of TAC because of neurotoxic side effects [59]. The findings of this retrospective study confirmed the existence of this neurotoxicity-prone population, who should be carefully considered as a high-risk group for this undesirable CNI complication. Furthermore, research of Yanagimachi et al. [60] and Yamauchi et al. [61] showed that the polymorphisms in CYP3A5, ABCB1 and MDRI genes were linked to CNI-related neurotoxicity. It was reported that patients carrying at least 1 CYP3A5*1 allele have a lower TAC concentration to dose ratio when compared with nonexpressors (CYP3A5*3/*3) in kidney, liver, lung, and heart transplant recipients [62]; it is obvious that individual pharmacogenetics could affect whole blood TAC concentrations and, consequently, increasing TAC concentrations may lead to an increase in drug-related adverse effects [63]. These preliminary results explained the interindividual variability of neurotoxicity at a genetic level and, furthermore, indicated that genetic polymorphisms might be useful to predict the susceptibility of a patient with an increased risk for TAC-related neurotoxicity rather than a pure concentration-based approach [64]. In this high-risk group for undesirable TAC complications, choosing a different immunosuppressive protocol or aiming at a lower threshold for stopping TAC might eventually allow to reduce the incidence of TAC-associated PRES and improve clinical outcome [64]. Some physicians recommended that CsA should be chosen when patients experience TAC-related adverse events [65]. Moreover, sirolimus was noted without early or late episodes of major neurotoxicity when used in heart transplant recipients [66]. It was proven that it could be relatively safely used in SOT patients with severe neurological symptoms ascribed to or exacerbated by CNIs [2]. However, in patients after blood stem cell transplant, a case of PRES due to sirolimus was recently reported [67]. Additionally, numerous ongoing studies aim to determine the most effective immunosuppressive protocols while minimizing drug-related side effects. Some studies have investigated the impact of the TAC formulation on reducing TAC-associated side effects. A once-daily extended release formulation of TAC has been developed, which has been tested in conversion studies in both stable and novo kidney and liver transplant recipients. The result showed that it is equally efficacious but has a similar toxicity profile as the conventional TAC formulation when the same trough levels are targeted [63, 64].

Conclusions

PRES induced by TAC can usually be diagnosed on the basis of a characteristic clinical and radiographic pattern and is usually reversible by reducing the dosage or withholding the drug for a few days. Failure to recognize its heralding symptoms may potentially increase morbidity in SOT. However, by studying this entity in a deep-going way, it was discovered that this syndrome is frequently reversible, rarely limited to the posterior regions of the brain, and often located in the gray matter and cortex as

well as the white matter [21]. Future studies are warranted to fully understand the clinical spectrum and underlying pathophysiology of this disorder. With regard to management, there is a tendency that personalized drug therapy with novel approaches in clinical TAC therapeutic drug monitoring will better predict the dose-concentration-response relationship, and a close serum magnesium level monitoring might also contribute to prevent immunosuppressant neurotoxicity and finally improve patient care.

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