

Posterior Reversible Encephalopathy Syndrome After Transplantation: a Review

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Abstract Posterior reversible encephalopathy syndrome (PRES) is a rare neurological disease. Recently, an increase in the number of transplantations has led to more cases being associated with PRES than what was previously reported. Calcineurin inhibitors (CNIs) are major risk factors for PRES in posttransplantation patients. The mechanisms of the development of PRES remain to be unclear. The typical clinical symptoms of PRES include seizures, acute encephalopathy syndrome, and visual symptoms. The hyperintense signal on fluid-attenuated inversion recovery image is the characteristic of the imaging appearance in these patients. In addition, other abnormal signals distributed in multiple locations are also reported in some atypical cases. Unfortunately, PRES is often not recognized or diagnosed too late due to complicated differential diagnoses, such as ischemic stroke, progressive multifocal leukoencephalopathy, and neurodegenerative diseases. Thus, this review emphasizes the importance of considering the possibility of PRES when neurological disturbances appear after solid organ

transplantation or hematopoietic cell transplantation. Moreover, this review demonstrates the molecular mechanisms of PRES associated with CNIs after transplantation, which aims to help clinicians further understand PRES in the transplantation era.

Keywords Posterior reversible encephalopathy syndrome · Transplantation · Calcineurin inhibitors · Etiology · Physiopathology · Therapy

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitors
ADC	Apparent diffusion coefficient
CNIs	Calcineurin inhibitors
CsA	Cyclosporine A
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
DWI	Diffusion weighted MRI
EBV	Epstein–Barr virus
FLAIR	Fluid-attenuated inversion recovery
HSCT	Hematopoietic stem cell transplantation
MRI	Magnetic resonance imaging
ODS	Osmotic demyelination syndrome
PAI-1	Plasminogen activator inhibitor-1
PKA	Protein kinase A
PKC	Protein kinase C
PRES	Posterior reversible encephalopathy syndrome
PTLD	Posttransplantation lymphoproliferative disorder
T1WI	T1-weighted image
T2WI	T2-weighted image
TAC	Tacrolimus
SOT	Solid organ transplantation

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Introduction

Posterior reversible encephalopathy syndrome (PRES), initially described by Hinchey [1] in 1996, is a neurological disturbance coupled with different clinical symptoms and appearances of distinctive imaging features. The etiology of this syndrome is complicated, varied, and often includes hypertensive encephalopathy, eclampsia, immunosuppressive drugs, and autoimmune diseases [1, 2]. So far, the mechanisms of PRES development are still unknown. Seizures, acute encephalopathy syndrome, and visual symptoms are the typical clinical symptoms of PRES [3–5]. The fluid-attenuated inversion recovery (FLAIR) images usually show an abnormal and reversible increased signal, mostly distributed in the parietal and occipital lobes. However, the abnormal signal can also be distributed in the posterior frontal, temporal lobe, cerebellum, brainstem, thalamus, and basal ganglia. The incidence of atypical distribution and imaging appearances may even be higher than what is commonly seen in the literature [5–7]. The management of PRES is still unclear. Although this disease is reversible, permanent neurological deficits and cerebral infarcts may appear because of late recognition of this syndrome and persistence in the incorrect usage of drugs [5].

PRES after transplantation, as a rare complication, should not be ignored, especially in developing countries, where the numbers of transplantations are rising rapidly. There is an upward trend of the reports about PRES with an increasing number of transplantations. There are about 160 publications that have mentioned PRES after transplantation since the disease was first reported in 1996. More than 80 publications regarding PRES after transplantation have been published from 2010 to 2014, including 78 cases that report after solid organ transplantation (SOT) or hematopoietic cell transplantation (Table 1) [8–31]. There have been significant advances in PRES research after transplantation in the past 4 years, but only few review articles concerning PRES after transplantation. The aim of our paper is to review the prevalence, mechanism, diagnosis, differential diagnoses, and management of PRES and to help clinicians to consider the possibility of PRES appearing as a neurological disturbance after transplantation.

Prevalence

PRES is increasingly recognized as a neurological disturbance with various clinical symptoms and characteristic images. PRES can occur in both male and females as well as in adults and children. The incidence of PRES after SOT is approximately 0.5–5 % [10, 13, 15, 25]. One study [32], which evaluated 4222 patients that underwent transplantation, reported that the incidence of PRES after SOT is about 0.49 %, with a similar incidence among subtypes. Another study considered

that the incidence of PRES after lung transplantation is closely 5.7 %, while only 12 cases had been published among 25,755 lung transplant recipients from 1999 to 2009 [24]. Meanwhile, the incidence of PRES after allogeneic hematopoietic stem cell transplantation (HSCT) is 1.1–20 % [14, 16, 17, 33].

The etiology of PRES is complicated and varied, including hypertensive encephalopathy, eclampsia, immunosuppressive drugs, and autoimmune diseases [1, 2, 5]. There are also other risk factors, such as the following: hypomagnesemia, hypocholesterolemia, vasoactive agents, erythropoietin, blood transfusion, antineoplastic drugs, peritoneal dialysis, and parathyroid hormone-related peptide [19, 34, 35]. Immunosuppressive drugs, especially calcineurin inhibitors (CNIs), are widely used for preventing acute rejection reaction in patients with various transplantations. Seventy-five patients with PRES seem to be related with immunosuppressive drugs in 78 transplantation patients from 2010 to 2014. One study proposed that PRES can occur in patients receiving CNIs after kidney, allogeneic peripheral blood stem cell, liver, and lung transplantations [36]. CNIs may be a major risk factor for PRES in posttransplantation patients. In addition, hypertension is sometimes accompanied with PRES after transplantation. Hypertension presents in approximately 70–80 % of patients [2, 4]. Fifty-six percent of the patients may have a history of hypertension [37]. High-dose corticosteroid use, ischemia reperfusion during surgery, the use of multiple medications, and antibiotics may be associated with PRES after SOT and hematopoietic cell transplantation, as well [11].

Clinical Features of PRES

The features of PRES after transplantation include clinical symptoms and neuroimaging. The typical clinical symptoms are involved in seizures, acute encephalopathy syndrome, and visual symptoms. Dysarthria, incoordination of the limbs, paresis, sensory deficits, and visual hallucinations are atypical clinical symptoms. The characteristic neuroimaging is a hyperintense signal, distributing in the parietal and occipital lobes on FLAIR images. Other magnetic resonance sequences can also show the specific appearances of PRES. Furthermore, angiography and magnetic resonance angiography (MRA) are also useful diagnosis approaches for PRES.

Clinical Symptoms

Seizures, acute encephalopathy syndrome, and visual symptoms are the mainly clinical symptoms of PRES after transplantation. One study identified 120 cases of PRES, which reported that seizures (74 %), encephalopathy (28 %), headache (26 %), and visual disturbances (20 %) are the clinical presentations of PRES [38]. The acute encephalopathy syndrome includes confusion, headache, vomiting, altered

Table 1 The clinical presentation and management of 80 PRES patients after solid organ transplantation and hematopoietic cell transplantation (reported from 2010 to 2014)

Patient	Transplantation	Symptoms	ISD	Management ^a
1–3	Lung transplantation	SE	TAC	Lower dose
4–7	Lung transplantation	MSC/SE/AC	TAC/CsA	Switch drug
8	Lung transplantation	SE	CsA	Discontinue
9	Lung transplantation	VS	None ^b	Others ^c
10	Lung transplantation	SE	TAC	Reduce and add others ^d
11	Renal transplantation	VS, HD, AC, paralysis	TAC	Switch drug
12	Renal transplantation	HD, SE, VS	MF	Switch drug
13	Renal transplantation	HD, VS, VT, SE, AC, hemiparalysis	Rapamycin	Switch drug
14	Renal transplantation	SE, MSC, HD	TAC	Lower dose
15–33	Liver transplantation	SE/MS/HD	TAC/CsA	Switch drug
34	Liver transplantation	Aphasia	TAC	Switch drug
35	Liver transplantation	SE, MSC	TAC	Lower dose
36	Liver transplantation	Vertigo, SE	TAC	Lower dose
37	Liver transplantation	VS, MSC, visual hallucinations	TAC	Switch drug
38	Heart transplantation	SE, HD, MSC	TAC	Discontinue
39	Small bowel transplantation	HD, VS, SE	TAC	Reduce and add others ^d
40	Multivisceral transplantation	HD, AC, VS, SE	TAC, sirolimus	Discontinue
41–59	Hematopoietic cell transplantation	SE/HD/VS/MS/AC	TAC/CsA	Switch drug
60–65	Hematopoietic cell transplantation	HD/VT/SE/VS/MS/AC	TAC/CsA	Discontinue
66	Hematopoietic cell transplantation	AC, VS, HD, VT, gait disturbances	TAC	Discontinue
67–76	Hematopoietic cell transplantation	SE/MS/VS	TAC	Hold and continue
77–78	Hematopoietic cell transplantation	HD/AC/VT/SE	None ^b	Others ^c

ISD immunosuppressive drugs, SE seizures, MSC mental status changes, AC altered consciousness, VS visual symptoms, HD headache, VT vomiting, MF mycophenolate mofetil

^a Management means the management of immunosuppressive drugs, including switching the culprit drugs to other immunosuppressive drugs, lower dosage of the immunosuppressive drugs, reducing the culprit drugs accompanied with adding other similar drugs, discontinuing the culprit drugs, and continuing using the culprit drugs

^b The immunosuppressive drugs was not used, when the patients showed the symptoms of PRES

^c Other managements do not include the management of immunosuppressive drugs

^d The dose of the culprit drugs was reduced, and another immunosuppressive drug was added

consciousness, and mental status changes [4, 9, 10, 22, 29]. Visual symptoms involve hemianopsia [4], loss of visual acuity [11], visual blurring [11], blindness [20], and diplopia [30]. Seizures with secondary generalization, multiple seizures, and status epilepticus are reported as the common symptoms in some literatures [4, 26]. Status epilepticus is also reported as a main manifestation of PRES after pediatric HSCT [14]. Residual epilepsy may be continued despite clinical and neuro-radiological normalization in PRES patients [12]. In addition, other atypical symptoms like dysarthria, incoordination of the limbs, paresis, sensory deficits, and visual hallucinations can occur in PRES [10, 23, 30, 31]. One study suggested that the incidence of atypical distribution and imaging appearances may even be higher [7]. Intracranial hemorrhage can occur simultaneously in PRES, with an incidence of approximately 15 %. Intracranial hemorrhage is more common after allogeneic bone marrow transplantation than after SOT [31, 39].

The time course of PRES presentation varies in posttransplantation patients. PRES typically develops within 2–3 months after liver transplantation [5, 15]. The timing is even later in renal transplantation patients [32]. Some cases showed an onset time within 1 week after transplantation [10, 11, 19, 25, 26, 29, 40]. Therefore, PRES can occur during acute and subacute onset neurological disturbances after transplantation. The time course of PRES may be associated with the type and dosage of CNIs and the organ of transplantation surgery.

Neuroimaging

The MRI is one of the most useful imaging tools for diagnosing PRES. MRI scan usually shows an abnormal and reversible increased signal on FLAIR images, which is the most sensitive sequence for recognition of cortical and subcortical edema in PRES [5]. The hyperintense signal alterations on

FLAIR images usually distribute in the parietal and occipital lobes. The lesions also appear as iso-intense or hyperintense signals on T1-weighted images (T1WI) and hyperintense signals on T2-weighted images (T2WI) [41, 42]. Diffusion-weighted MRI (DWI) and apparent diffusion coefficient (ADC) are instrumental in distinguishing the type of edema in PRES lesions. Hyperintense on the DWI and hypointense in the ADC mapping are the characteristics of a cytotoxic edema, whereas an iso-intense or hyperintense signal in DWI and hyperintense in ADC are typical presentations of a vasogenic edema. Vasogenic edema can generally be completely reversible; however, severe vasogenic edema can exacerbate cytotoxic edema, leading to worse outcome [2, 4–6]. PRES can also be identified in other MRI imaging. Gadolinium enhancement, hemorrhage, and restricted diffusion have been observed in some patients with PRES [7, 12, 18, 21, 24, 43]. The abnormal signal of PRES can be distributed throughout the posterior frontal, temporal lobe, cerebellum, brainstem, thalamus, and basal ganglia [7, 10, 11, 24, 43]. In addition, angiography is another measure for PRES patients. Angiography can reveal focal or diffuse vasoconstriction, vasodilatation, or a “string-of-beads” appearance [43]. One study also mentioned that the dilation and constriction in the secondary and tertiary branches of intracranial artery could be observed in PRES patients by angiography and MRA [2].

Differential Diagnosis

It is often very difficult to recognize PRES at the beginning, since this syndrome has various atypical symptoms and imaging appearances. The diagnosis of PRES was further confirmed in most cases, when neuroimaging showed a reversible lesion. Clarity of the differential diagnoses of PRES is needed in order to make a diagnosis. Encephalopathy associated with ischemia, thrombosis, hemorrhage, infection, immune-inflammation, and others are general differential diagnoses. Most diseases mentioned above can be distinguished by symptoms, radiography, and laboratory examinations. Here, we present some differential diagnosis for PRES in Table 2.

Osmotic Demyelination Syndrome

Osmotic demyelination syndrome (ODS) is a neurological disorder with new onset neurological symptoms and a recent rapid increase in serum sodium. Typical MRI lesions of ODS reveal hypointense images on T1WI and hyperintense images on FLAIR and T2WI [44]. The incidence of ODS is higher in liver transplant recipients than the general population [45]. However, the distributions of lesions are common in the striatum and pons. Mental status changes, movement disorders, dysphagia, and dysarthria are major presentations [44–46]. Monitoring serum sodium may also be helpful in identifying

the disease. Of patients, 50–67 % may have good outcomes, but even in those patients who have made a complete or nearly complete clinical recovery, imaging findings do not improve [44, 46].

Posttransplantation Lymphoproliferative Disorder

Posttransplantation lymphoproliferative disorder (PTLD) is a heterogeneous disease with variable benign or malignant types and unspecific symptoms. The incidence varies from 1 to 2 % after kidney transplantation to 20 % after small bowel transplantation [47, 48]. The risk is 20–120-fold higher in the posttransplantation patients than in the normal subjects [47, 49]. PTLD is also a malignant complication of cyclosporine A (CsA) with an incidence between 2 and 4 % [50]. PTLD in the central nervous system is a more rare form but has been increasing with the rise in popularity of SOTs. Focal neurological deficits, headaches, and altered mental status are common symptoms of central nervous system PTLD. Neuroimaging usually reveals multiple contrast-enhancing mass lesions in supratentorial, lobar, periventricular, corpus callosum, basal ganglia, and pituitary [47, 51, 52]. Epstein–Barr virus (EBV) deoxyribonucleic acid (DNA), biopsy, and cerebrospinal fluid (CSF) cytology and immunology are measures for the distinction between PTLD and PRES [47, 48, 53]. Prognosis is variable but not reversible. Rate of survival depends on the malignant degree, early detection, and timely treatment [48].

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease due to John Cunningham (JC) virus, which leads to a destructive infection of oligodendrocytes in immunosuppressed patients. Seventy-nine percent PML occurs in AIDS patients. The usage of immunosuppressant in organ transplantation recipients is associated with the development of 5 % PML [54]. The clinical symptoms are usually nonspecific and variable, including limb weakness, cognitive deficits, speech or visual difficulties, ataxia, seizures, and headache [55]. Radiographic characteristic of PML is single or multifocal white matter lesion, which may become confluent and large with the progression of this disease. The lesions of PML are generally hypointense on T1WI and hyperintense on T2WI, with high signals on the DWI and normal-to-low signals in the ADC. The parietal, occipital, and frontal lobes are the most frequent sites of PML. The lesions can occasionally be seen in the pontomesencephalon, basal ganglia, and cerebellum in PML patients [54, 56]. The neuroimaging appearance can also reveal mass effects and enhancements [55, 57]. JC virus DNA in CSF and proton magnetic resonance spectroscopy (MRS), which reveals low levels of N-acetylaspartate, high levels of choline, and elevated levels of lactate and variable myo-inositol in PML patients, may be

Table 2 The differential diagnoses of posterior reversible encephalopathy syndrome

Disease	Prevalence	Clinical symptoms	Neuroimaging	Distribution	Other examination	Prognosis
PRES	0.5–5 % after SOT	Seizures; acute encephalopathy syndrome; visual symptoms	Hyperintense on FLAIR; iso-/hyperintense on T1WI; hyperintense on T2WI	Parietal and occipital lobes	Angiography and MRA	Reversible and benign
ODS	Higher in liver transplant recipients	Mental status changes; movement disorders; dysphagia; dysarthria	Hypointense on T1WI; hyperintense on FLAIR and T2WI	Striatum and pons	Serum sodium	50–67 % have good outcomes; neuroimaging do not improve
PTLD	20–120-Fold higher in the posttransplantation patients	Focal neurological deficits; headaches; altered mental status	Multiple contrast-enhancing mass lesions	Supratentorial; lobar; periventricular; corpus callosum; basal ganglia; pituitary	EBV DNA; CSF cytology/immunology; biopsy	Variable but not reversible
PML	5 % PML is associated with immunosuppressants usage	Limb weakness; cognitive deficits; speech/visual difficulties; ataxia; seizures; headache	Hypointense on T1WI; hyperintense on T2WI; high signals on the DWI; normal-to-low signals in the ADC	Parietal, occipital, and frontal lobes	JC virus DNA; MRS; biopsy	Stabilization or remission; brain herniation or death

PRES posterior reversible encephalopathy syndrome, *ODS* osmotic demyelination syndrome, *PTLD* posttransplantation lymphoproliferative disorder, *PML* progressive multifocal leukoencephalopathy, *SOT* solid organ transplantation, *AIDS* acquired immune deficiency syndrome, *FLAIR* fluid attenuated inversion recovery, *T1WI* T1-weighted image, *T2WI* T2-weighted image, *DWI* diffusion-weighted MRI, *ADC* apparent diffusion coefficient, *MRA* magnetic resonance angiography, *EBV* Epstein–Barr virus, *DNA* deoxyribonucleic acid, *MRS* magnetic resonance spectroscopy, *CSF* cerebrospinal fluid

helpful in distinguishing PML from PRES [56]. Brain biopsy is the gold standard of PML. The outcome of PML ranges from stabilization or even remission to brain herniation or even death [54, 58].

Management and Prognosis

PRES following transplantation is reversible, when culprit drugs are discontinued or decreased early, or when related symptoms are controlled immediately such as hypertension or seizures. Unfortunately, permanent neurological deficits and cerebral infarcts may appear because of late recognition of this syndrome or persistent use of culprit drugs. The occurrence of intracranial hemorrhage also worsens the prognosis. Increasing studies suggested that not all PRESs are reversible [17, 59]. Therefore, timely and effective treatments for PRES after transplantation are essential for the outcomes of patients.

Management of Immunosuppressive Drugs

CNIs may be one of the major risk factors for PRES in post-transplantation patients. Management of immunosuppressive drugs is one of the primary tasks. However, there are several strategies for managing culprit immunosuppressive drugs. In some studies, the drugs were switched or substituted [9, 10, 20]. Some cases lowered the dosages of immunosuppressive drugs [11, 60]. A reduction of the culprit drugs accompanied with adding other similar drugs can also be seen in some other cases [18, 26]. Moreover, other studies have reported some cases in which CsA was ceased without substitution [24, 61].

In a study of 19 patients after hematopoietic allogeneic stem cell transplantation [17], 40 % of the patients survived without using tacrolimus (TAC) to manage PRES. About 40 % of the patients survived when TAC was continued. Meanwhile, 50 % of the patients who were switched to another agent survived and were eventually discharged. The results of this study suggest that there is no difference among these strategies, since the survival percentages were similar. In addition, another study showed that switching the immunosuppressive regimen may be detrimental and even fatal. It is recommended to completely cease treatment of CNIs as a treatment of PRES [62]. However, some cases that switch the immunosuppressive regimen have good outcomes [9, 20, 24, 25, 27, 30]. So, the management of immunosuppressive drugs still needs more researches. In most cases, reducing the dosage, switching the immunosuppressive drugs, or cessation of treatment are still the therapeutic strategy of PRES. Continuing using the culprit drugs should be discreet. The risk of rejection after transplantation should be taken into consideration. Meanwhile, therapeutic effects and related risks should be weighed.

Symptomatic Treatment

Seizures, one of the typical clinical symptoms of PRES after transplantation, should be controlled immediately. Uncontrolled seizures may shorten life span and increase the risk of death significantly. Approximately 20–30 % of patients with epilepsy are not fully controlled with available drugs [63]. The efficiency and adverse effects of the antiepileptic drug should be considered. Since there are several advantages and limitations for each drug, it is often difficult to choose appropriate antiepileptic drugs. One review [64] discussed all relevant data about epilepsy and other comorbidities, which concluded that gabapentin, levetiracetam, pregabalin, and topiramate are the most appropriate antiepileptic drugs to treat epilepsy in patients with liver transplantation. Additionally, the most appropriate drugs in kidney transplantation are benzodiazepines, lamotrigine, and valproic acid. The most appropriate drugs in bone marrow transplantation are gabapentin, levetiracetam, lamotrigine, and topiramate.

Blood pressure is often high in PRES patients. Of patients, 32–52 % have high blood pressure after transplantation. In all these cases, antihypertension treatments were used for controlling blood pressure. A treatment regimen of a diuretic plus an angiotensin-converting enzyme inhibitor (ACEI) is often recommended in patients with cerebrovascular disease [65]. Intravenous antihypertensive agents are necessary in patients with hypertensive emergency, which decrease blood pressure by 25 % [66]. However, some articles suggest that hypertension is a compensatory way to improve cerebral blood flow [15]. Thus, controlling blood pressure should be appropriate and prudent. The management of hypertension in PRES patients after transplantation still needs more evidence-based studies.

In addition, other symptoms, such as vomiting, mental status changes, and intracranial hemorrhage, should be examined since all of these are associated with patient outcomes. Monitoring vital signs, maintenance of arterial oxygenation, sufficient hydration, and correction of coagulopathies and electrolyte disturbances are general strategies for managing PRES patients.

Prognosis

The prognosis of PRES is generally reversible and benign. Seventy-two percent of patients present a reversion of imaging abnormalities with a mean duration of 41 days [67]. Recurrence of PRES is also infrequent and benign [13, 27]. Only a part of the patients after transplantation were reported to become worse, even died. But the death is rarely directly related with PRES [15]. However, one study included 302 patients, who underwent allogeneic HSCT, which suggested that the 1-year survival rate is significantly inferior in patients who developed PRES [68]. Permanent neurological deficit and

cerebral infarcts also appear in some cases [69]. Therefore, early diagnosis and appropriate treatments are still essential for a good recovery of patients.

Pathophysiology Mechanisms

Until recently, there was a lot of controversy about the mechanism of PRES. There are two major hypotheses, which included the hyperperfusion and hypoperfusion theories [5, 40, 70, 71]. The first theory suggests that severe hypertension leads to transient impairment of autoregulation, causing cerebral vasodilatation and vasogenic cerebral edema. The other theory suggests that the neurotoxicity of culprit drugs and hypertension induces autoregulatory vasoconstriction, leading to hypoperfusion, ischemia, and edema. Hyperperfusion remains the most popular hypothesis for the development of brain edema that occurs in PRES. Endothelial dysfunction and disruption of the blood brain barrier are another mechanisms, which lead to the development of PRES. There are several clinical and neuroimaging evidences about the occurrence of hypertension, failed autoregulation, and vasogenic cerebral edema [5, 70]. However, the molecular mechanisms of PRES after transplantation are still unclear. Here, we review the molecular mechanisms of PRES, which are mainly associated with CNIs after transplantation.

TAC and CsA are both CNIs, which are the main immunosuppressant drugs after transplantation. They are widely used for preventing acute rejection, since they provide potent inhibitory effects on T lymphocyte activation in patients with various transplantations. TAC (the Japanese drug FK506), a macrolide immunosuppressant, was discovered in 1984 [72]. TAC binds to the FK506-binding protein 12 (FKBP12) in the cytoplasm. The complex then inhibits the activity of calcineurin, and the signal transduction pathways in T cells are also downregulated [73–76]. CsA, a cyclic 11-amino acid peptide, was discovered earlier than TAC. CsA binds to cyclophilin and forms a complex, which can inhibit calcineurin and block the phosphatase activity, causing a decrease in T lymphocyte activation [74, 76, 77].

The Mechanism of Vasogenic Cerebral Edema in CNIs Induced by PRES

The final pathophysiological manifestation of PRES is brain edema. Previous studies suggested that severe hypertension exceeds the potential of autoregulation and the autoregulation dysfunction leads to vasogenic cerebral edema. In some cases, neuroimaging shows evidence of vasogenic cerebral edema, such as increased diffusions consistent with vasogenic edema in DWI and ADC [6, 25, 29]. In the posttransplantation patients, CNIs may participate in the formation of vasogenic

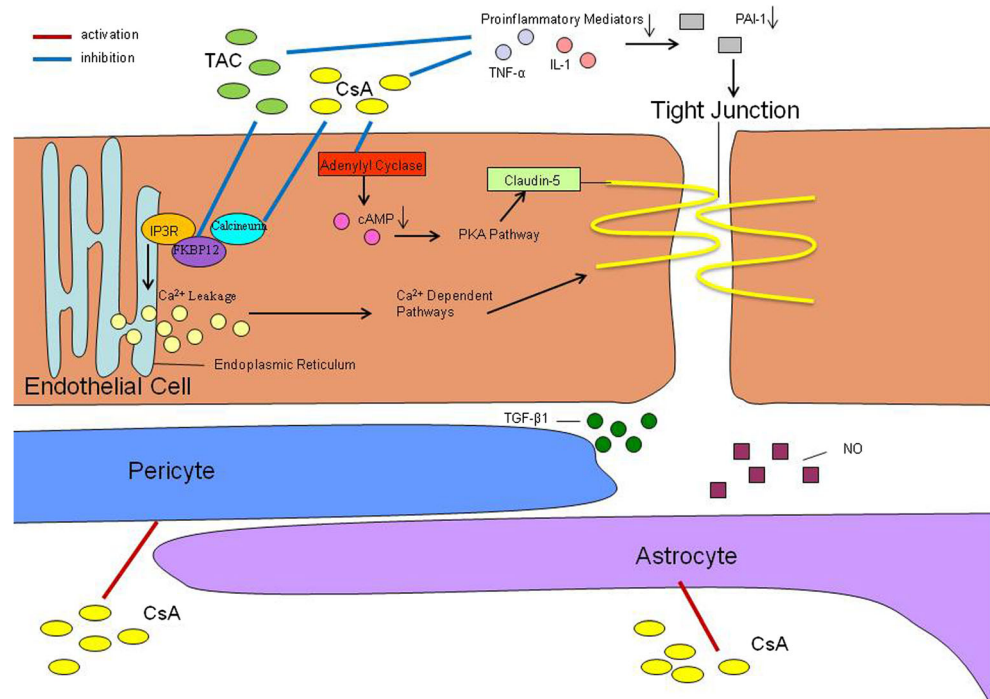
cerebral edema in PRES through multiple molecular mechanisms.

Vasogenic edema of PRES may be caused by the dysfunction of the blood–brain barrier. There are two aspects of blood–brain barrier dysfunction induced by CNIs: (1) hyperpermeability of the blood–brain barrier and (2) the inhibited expression of P-glycoprotein (Fig. 1). Previous studies have shown that CsA and TAC can damage the tight junction and the cell membrane directly and that CsA can induce apoptosis on the brain capillary endothelial cells [78, 79]. This leads to an increased permeability of the blood–brain barrier. Moreover, it is known that TAC can induce a calcium ion leakage from the endoplasmic reticulum [77, 80, 81]. FKBP12 binds to inositol 1,4,5-trisphosphate receptor (IP3R), which is associated with regulation of IP3-mediated Ca^{2+} flux. Calcineurin anchors to the IP3R via FKBP12 which participates in the regulation of the receptor [77, 80, 82]. When TAC dissociates FKBP12–IP3R complex or CsA inhibits calcineurin, the binding of calcineurin to the FK506–FKBP12 complex is stimulated, resulting in the phosphorylation of IP3R by protein kinase C, causing an increase in Ca^{2+} flux [77, 80, 83]. The increased intracellular Ca^{2+} can disrupt the tight junctions, which is the major constitution of the blood–brain barrier, via Ca^{2+} -dependent pathways [84–88]. Eventually, permeability of the blood–brain barrier is increased because of the disruption of the tight junction. In addition, CsA can decrease cAMP formation by inhibiting adrenomedullin-induced activation of adenylyl cyclase. The expression and phosphorylation of claudin-5 are weakened via a PKA pathway, when the

intracellular cAMP concentration is decreased. This causes an increased permeability of the brain–blood barrier by the loosening of the intercellular junctions [89–91]. Furthermore, another current study showed that plasminogen activator inhibitor-1 (PAI-1) increased the tightness of the brain endothelial barrier in a dose-dependent manner [92]. Previous research also reported that the inducers of PAI-1 involve the product of proinflammatory mediators, such as tumor necrosis factor- α and interleukin-1 [93, 94]. However, the production of the proinflammatory mediators is suppressed by CNIs through inhibiting the transcription of genes of early T cell activation [75]. Thus, the permeability of the blood–brain barrier may be influenced by this mechanism indirectly.

Several previous studies demonstrated that CsA can cause dysfunction of P-glycoprotein, which leads to the breakdown of the blood–brain barrier, via several ways. P-glycoprotein is an adenosine triphosphate (ATP)-dependent transmembrane transport protein and critical component of the blood–brain barrier. One such way is to decrease production of transforming growth factor- β 1 (TGF- β 1) in brain pericytes or to cause the dysfunction of nitric oxide (NO) production in astrocytes [77, 78, 89, 95, 96]. The inhibition of P-glycoprotein activity by CsA is also shown by using PET of ^{11}C -verapamil distribution into the brain [97]. Interestingly, the effect of CsA on NO production is still controversial. Some experiments demonstrated that CsA induces NO synthase expression and causes an increase of NO [77, 98, 99]. However, other experiments showed that CsA reduces NO

Fig. 1 Schematic illustration of the mechanism of vasogenic cerebral edema in PRES associated with CNIs. The blood–brain barrier is formed by endothelial cells, pericytes, and astrocytes. CsA and TAC can injure the tight junction of the endothelial cells via causing the Ca^{2+} leakage, weakening the expression and phosphorylation of claudin-5, and decreasing the production of PAI-1. CsA also decreases the production of TGF- β 1 in brain pericytes and causes the dysfunction of NO production in astrocytes, leading to the hyperpermeability and dysfunction of P-glycoprotein



synthase expression [100, 101]. The effect of NO production by CsA may be dependent on the dose of CsA. In any way, the dysfunction of the NO production may contribute to the endothelial dysfunction, which leads to the permeability variation. Moreover, a study found that CsA causes hyperpermeability and P-glycoprotein (P-gp) dysfunction by inhibiting TGF- β 1 production [96]. However, another study concluded that CsA does not induce TGF- β 1 biosynthesis. It is the cell type and concentrations used that the different effects on TGF- β 1, caused by CsA, depend on [102].

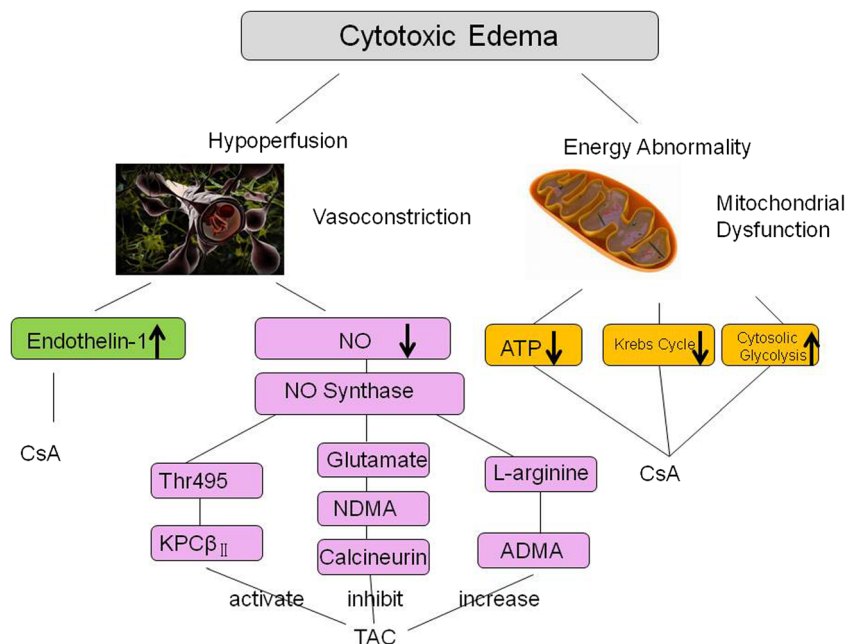
The hyperpermeability of the blood–brain barrier and the inhibited expression of P-gp eventually result in brain swelling which is termed vasogenic cerebral edema. The dysfunction of the blood–brain barrier may be transient or improved by discontinuing or decreasing CNIs. As far as we know, acute hypertension is also a major cause of PRES and can change the function of the blood–brain barrier. During acute hypertension, the increased NO may increase permeability and contribute to disruption of the blood–brain barrier [103–105]. It is also reported that the change of Ca^{2+} may be responsible for the permeability and disruption of the blood–brain barrier in acute hypertension [106]. These mechanisms, resulting in the development of PRES, may commonly exist in CNIs and hypertension. Hypertension can disrupt the blood–brain barrier via other ways, such as inflammation and oxidative stress [107, 108]. Recently, it is found that short-term hypertension impairs the antioxidant defense system in the brain by diminishing claudins and gene transcription in the endothelial cells of the blood–brain barrier, which causes changes to the blood–brain barrier [109]. More studies are needed for further understanding of the development of PRES.

The Mechanism of Cytotoxic Edema in PRES Associated with CNIs

Most neuroimaging of PRES reveals vasogenic cerebral edema; nevertheless, a coexistence of vasogenic and cytotoxic edema exists in several cases. The DWI of these cases also shows restricted diffusions of the lesions [5, 7, 10]. Moreover, the previous mechanism also mentions that autoregulatory vasoconstriction, caused by several pathogenic factors, leads to the hypoperfusion and results in ischemia and edema. Severe vasogenic edema progressing to cytotoxic edema may represent an early sign of irreversible damage. Currently, the molecular mechanisms about the development of cytotoxic edema in PRES associated with CNIs have not been reviewed. Here, we conclude that the development of cytotoxic edema caused by CNIs may be involved in two ways: vasoconstriction resulting in hypoperfusion or mitochondrial dysfunction resulting in energy abnormality (Fig. 2).

The endothelin-1 and decrease of NO may contribute to the vasoconstriction in cerebral artery. One study found that CsA-mediated capillary disruption causes the release of endothelin-1, which plays a significant role in CsA-induced endothelial dysfunction [110]. Their experiment also described that endothelin-1 gene is expressed during capillary breakdown by CsA. Another study reported that the use of CsA is associated with an increase in plasma levels of endothelin-1 [111]. However, other literatures considered that CsA does not elevate the level of endothelin-1 but increases the expression of the endothelin receptor [100]. In any way, endothelin-1 may play a role in endothelial dysfunction and may cause vasoconstriction of the arteries in the brain. Besides, TAC has been reported to decrease the production of NO in several

Fig. 2 Schematic illustration of the mechanism of cytotoxic edema in PRES associated with CNIs. CsA can cause the release of endothelin-1 leading to vasoconstriction and decrease the concentration of ATP leading to mitochondrial dysfunction. TAC can decrease the production of NO via several ways. Vasoconstriction resulting in hypoperfusion and mitochondrial dysfunction resulting in energy abnormality may lead to hypoxia that causes cytotoxic edema eventually



ways. TAC inhibits calcineurin and decreases the dephosphorylation of NO synthase [112]. Calcineurin is also reported to directly modulate N-methyl-D-aspartic acid (NMDA) receptors. Hence, TAC affects NMDA-stimulated neurotransmitter release indirectly and inhibits glutamate-induced NO synthase activity [113, 114]. In addition, TAC can increase asymmetric dimethylarginine (ADMA), an endogenous NO synthase inhibitor, which competes with L-arginine to block NO synthesis [115, 116]. Moreover, TAC can activate KPC β_{II} , which is an isoform of conventional PKC. The activated KPC β_{II} phosphorylates endothelial NO synthase at its inhibitory site Thr495 and reduces the production of NO [81, 117].

CsA is associated with mitochondrial dysfunction, which results in abnormal cerebral energy metabolism. Even in the therapeutic range of CsA in transplant patients, ATP concentration is also decreased by 20 %, accompanied by the inhibition of the Krebs cycle and a reduction of NAD⁺ concentration [118–120]. Moreover, 4 to 10 h after CsA perfusion, cytosolic glycolysis shows an increase, which compensates for the inhibition of mitochondrial glucose metabolism. Lactate concentration is increased in the rat brain after 6 days of CsA treatment [120]. Furthermore, CsA can induce hyperpermeability and P-gp dysfunction after hypoxia/reoxygenation injury [121]. So when the shortage of cerebral energy metabolism is compensated, CsA may still cause the dysfunction of the blood–brain barrier.

Vasoconstriction resulting in hypoperfusion and mitochondrial dysfunction resulting in energy abnormality may lead to hypoxia that causes cytotoxic edema in PRES associated with CNIs, which plays a significant role in the progression of the disease. However, some mechanisms may possibly participate in the development of cytotoxic edema with TAC-induced leukoencephalopathy as well. The mechanism concerning the reversal of cytotoxic edema in the PRES requires further study.

The etiology of PRES includes hypertensive encephalopathy, eclampsia, immunosuppressive drugs, and autoimmune diseases. All of these are systemic factors. How do these systemic factors cause a disease in the brain? These may be associated with the sensitivity of white matter, the difference of hypoxia tolerance, and the difference of vascular development. The mechanism of the PRES is also probably related to the differences in gene expression. More researches and clinical cases are the keys to make the pathophysiological mechanism of PRES more clear.

Conclusion

PRES is rare in daily clinical work and has an upward trend related to the increasing number of the transplantations. The usage of CNIs can be a major risk factor for PRES in

posttransplantation patients. The complicated differential diagnoses and late recognition may make the early diagnosis difficult. A familiarity with atypical clinical presentations, uncommon neuroimaging, and various differential diagnoses is necessary for early diagnosis. Also, the therapeutic effects and related risks should be measured when dealing with immunosuppressive drugs. Reviewing pathophysiology mechanisms of PRES may also provide novel management approaches and methods. However, the effects of inflammation and oxidative stress and the mechanisms of the reversal of cytotoxic edema after PRES should be further studied.

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