PRES in Children Undergoing Hematopoietic Stem Cell or Solid Organ Transplantation

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abstract

Posterior reversible encephalopathy syndrome (PRES) is a clinical neuroradiologic entity that is becoming increasingly well known and documented in pediatrics. It is characterized by a variable association of seizures, headache, vomiting, altered mental status, visual disturbances, and seizures, as well as imaging suggesting white-gray matter edema involving the posterior regions of the central nervous system in most cases. The pathophysiology of PRES remains unclear. Although PRES has been associated with a widespread range of clinical conditions, namely infections, adverse drug events, autoimmune diseases, and many others, its onset after hematopoietic stem cell and solid organ transplantation remains the most commonly reported. Historically, PRES has proved to be generally reversible and associated with good clinical outcomes; however, severe complications, sometimes life-threatening, can also occur. Most reported cases of childhood PRES after hematopoietic stem cell or solid organ transplantation have been case reports or series across a broad spectrum of different transplant settings, and no clear consensus exists regarding how best to manage the syndrome. Thus, in this article, we provide a comprehensive review of the pathophysiological, clinical, and diagnostic aspects of PRES in children, with a specific focus on the transplant scenario. Differential diagnoses with other neurologic complications after pediatric transplantation are reviewed, and crucial issues in the management of PRES and the development of future research are ultimately addressed.

It has been almost 20 years since the seminal report by Hinchey et al,1 which first reported a reversible, predominantly posterior leukoencephalopathy associated with subcortical edema without infarction. Today, this defined clinicoradiologic entity is commonly identified as posterior reversible encephalopathy syndrome (PRES). It is characterized by a variable association of seizures, headache, vomiting, visual disturbances, and impaired consciousness, typically accompanied by radiologic findings showing a posterior-predominant pattern of bilateral gray and white matter edema.1,2 Although PRES is usually reversible, it can lead to life-threatening complications and permanent neurologic damage if not promptly recognized and treated.3 Since the report by Hinchey et al,1 PRES has been associated with many other clinical conditions, namely infections, drug-related adverse events, and autoimmune diseases.4,5 In pediatrics, PRES has become known over the past 10 years as an entity increasingly diagnosed in different clinical settings, such as kidney diseases,6 vasculitis and hematologic...
Diseases (e.g., sickle cell disease, hemophagocytic lymphohistiocytosis). PRES in adults and children, however, remains mostly described as a complication of both solid organ transplantation (SOT) and allogeneic hematopoietic stem cell transplantation (allo-HSCT). Consistent with the increase in transplant procedures in children, PRES has emerged as a considerable concern for pediatricians involved in this field.

The incidence of PRES in children who have undergone an organ or hematopoietic stem cell transplant (HSCT) has ranged from 1% to 10%, similar to the 1% to 8% rate for adults. Expertise in the peculiar field of PRES in this childhood population remains lacking, and it is a topic of growing interest among pediatricians. The aims of this review, then, are to address from a pediatric prospective the many aspects concerning the pathogenesis and clinical and radiologic features of PRES in these transplanted children and to provide a useful guide for the management of PRES after transplantation.

**Pathophysiology and Risk Factors**

The pathophysiology of PRES remains unclear and is still debated. Two competing theories exist, both of which entail blood-brain barrier dysfunction and leakage of fluid into the interstitium, leading to the development of cerebral vasogenic edema. The first theory identifies hypertension as the "primum movens." Specifically, a rapid increase in blood pressure overcomes the cerebral vessels' autoregulatory mechanism with cerebral hyperperfusion, causing injury to the capillary bed and vasogenic edema. On the basis of this theory, the predominant involvement of the posterior cerebral area in PRES might occur because sympathetic innervation, which has the ability to increase the upper limit of autoregulation, is less represented in the vertebrobasilar circulation compared with the carotid system. Approximately 20% to 30% of patients with PRES have normal or only slightly high blood pressure. In fact, whereas the hypertension/hyperperfusion theory has been the most popular, a second pathogenetic theory of PRES speculates on T-cell/endothelial cell activation, resulting in leukocyte trafficking and systemic cerebral vasconstriction and cerebral hypoperfusion (Fig 1). In these cases, endothelial dysfunction and subsequent cerebral edema could be induced by the cytotoxicity of immunosuppressive therapy, infections, and autoimmune diseases. Hypoxia increases endothelial permeability through the activation of the vascular endothelial growth factor, causing vasogenic edema. Several imaging studies have supported this hypothesis, revealing brain hypoperfusion in patients with PRES. Neuroimaging studies have documented vasospasm, hypoperfusion, and ischemia and autopsy studies have confirmed a predominance of ischemic microinfarcts or cerebral vasculitis. As a consequence, some authors have hypothesized that systemic hypertension could be a reactive and protective response rather than a cause of PRES because of the ability to improve perfusion and reduce cerebral edema. In contrast, increasing hypertension could stimulate cerebral autoregulatory vasconstriction; and this stimulation, together with toxicity-induced vasconstriction, might result in further brain hypoperfusion, inducing ischemia. Finally, vasospasm might also play a role in the genesis of local ischemia and cerebral edema. This second theory might be relevant in the transplantation setting, in which the putative involvement of the vasculature and endothelial damage to it seem to play critical roles in the pathophysiology of many transplant-associated complications, namely microangiopathy, veno-occlusive disease, and graft-versus-host disease (GVHD).

Peculiarities in the pathophysiology of PRES are certainly present across different transplantation settings. These differences are evident between HSCT and SOT, in both of which endothelial damage and activation, cytokine release, and T-cell recruitment can occur through various mechanisms (i.e., chemotherapy-induced damage before HSCT, onset of acute GVHD, graft rejection, etc). Moreover, it seems that even in SOT, particularly kidney and liver transplantation, the pathophysiology of PRES could present different peculiarities, possibly influencing the respective time of onset. Many triggers and risk factors for PRES after SOT and HSCT have been described. GVHD prophylaxis with calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporine A (CSA), has been recognized as a major trigger of PRES in patients who underwent HSCT. The use of lower doses of the same drugs for immunosuppressive treatment after SOT has been credited with lowering the incidence of PRES in these patients. Medication withdrawal often results in the alleviation of toxicity, despite a frequent lack of correlation in the literature between circulating blood levels of CNIs and the occurrence of PRES. In fact, CSA and FK-506 levels have been found to be in the therapeutic ranges at the onset of many cases of PRES. CNIs could cause direct endothelial dysfunction mediated by enhanced systemic endothelial activation, leukocyte trafficking, and vasconstriction or demyelination in patients with PRES.

CNI administration was associated with chronic hypomagnesemia, and magnesium is a competitive antagonist of calcium that has vasodilatory effects on cerebral
vasculature, as well as a blood-brain barrier protective effect. Thus, it has been suggested that hypomagnesemia might be associated with PRES because it enhances CNI neurotoxicity.\textsuperscript{25,28} There have been fewer reports of PRES development in association with other immunosuppressive agents used mainly in SOT, particularly sirolimus.\textsuperscript{29} Because a high incidence of GvHD has been noted in patients with PRES after allo-HSCT, acute GvHD has been suggested to contribute to the pathophysiology of PRES.\textsuperscript{25,30} The administration of fludarabine during the conditioning regimen was also recognized to be a risk factor for the development of PRES in adult recipients after HSCT.\textsuperscript{31} In a cohort of
allografted children, we demonstrated significant relationships of the use of steroids and the use of cord blood as a stem cell source with the development of PRES.\textsuperscript{32}

With regard to SOT, transplant rejection, cytomegalovirus, and bacterial infections have all been identified as being associated with PRES.\textsuperscript{6,9,10,21} Moreover, the few studies available in the literature on the risk factors significantly predisposing children who undergo SOT to the development of PRES have recognized risk factors similar to those of HSCT, mainly hypertension and the use of CNI and other immunosuppressive drugs such as sirolimus.\textsuperscript{10,21,29}

**CLINICAL MANIFESTATIONS, DIAGNOSIS, AND COMPLICATIONS**

**Clinical Features**

The onset of symptoms is usually rapid, reaching their peak in 12 to 48 hours. Prodromes have rarely been described and have consisted mainly of tiredness and headache.\textsuperscript{33} The severity of the clinical manifestations varies among patients and can require intensive care management to support vital functions.\textsuperscript{2,4} Symptoms of PRES typically improve within 1 week, and complete clinical recovery is usually obtained earlier than neuroimaging resolution.

Seizures, usually with occipital onset, are the primary, and often presenting, manifestation of PRES.\textsuperscript{4,34–36} They frequently start with nonconvulsive focal signs, such as gaze deviation, oculolentic movements, visual hallucinations, and impaired consciousness. Evolution to a convulsive, often bilateral, seizure is common. Status epilepticus (SE), also frequently presenting with nonconvulsive features, has been described in these patients as well.\textsuperscript{27,37}

Other common symptoms of PRES, often associated with seizures, in descending order of frequency are as follows: nonepileptic visual disturbances, such as cortical blindness, hemianopsia, and blurred vision; headache, usually bilateral; various grades of impaired consciousness until coma; and nausea and vomiting. Only occasionally do patients with PRES show focal neurologic signs, including hemiparesis and aphasia.\textsuperscript{2,31}

PRES tends to present earlier in HSCT than in SOT.\textsuperscript{13,26} In a series of adults with PRES after allo-HSCT, the median time to onset was 30 days, with 82\% of cases developing PRES within 100 days.\textsuperscript{13} Consistent with these data, we reported a series of 14 allo-grafted children with PRES,\textsuperscript{11} of whom all but 1 patient developed PRES during the first 100 days after HSCT, with a median time of 65 days; in 1 case, PRES occurred at day 352.

In contrast, research has documented differences in PRES onset after liver and kidney transplantation.\textsuperscript{21} Specifically, PRES appeared to occur within 2 months after liver transplantation and was associated with mild rejection, cytomegalovirus, or systemic bacterial infection. In contrast, patients who underwent kidney transplantation developed PRES after $\geq$1 years, coinciding with moderate rejection or bacterial infection.\textsuperscript{9,10,21,38} Ghosh et al\textsuperscript{6} also described a case of early onset of PRES within 2 weeks after a pediatric kidney transplant.

**Neuroimaging**

MRI is the gold standard for the diagnosis of PRES. The typical lesion in PRES consists of vasogenic edema, located predominantly in the subcortical white matter with frequent involvement of the cortex (Fig 2A). These lesions show a high signal on T2-weighted images and fluid attenuated inversion recovery (FLAIR) sequences: the latter sequences are more sensitive for the detection of subcortical and cortical lesions.\textsuperscript{39} Diffusion-weighted imaging is required to differentiate PRES from ischemic stroke. In the majority of patients the administration of gadolinium chelates does not reveal any contrast enhancement of the brain tissue; nevertheless, in some cases, it may show mild signs of disruption of the blood-brain barrier. Although gadolinium can be helpful to exclude possible differential diagnosis (progressive multifocal leukoencephalopathy, opportunistic infections), its administration has to be carefully evaluated in transplanted children at high risk of acute and/or chronic renal failure.

Most patients show involvement of both hemispheres,\textsuperscript{1,39–41} sometimes asymmetrically. Predominantly parieto-occipital involvement is usually observed (from 50\% to 99\% of cases), whereas the frontal and temporal lobes are affected in half of cases.\textsuperscript{1,39,42} The cerebellum, basal ganglia, and brainstem are involved in approximately one-third of cases.

As transplanted children can present with a wide spectrum of acute neurologic complications, the evaluation with MRI is fundamental to obtain a secure diagnosis of PRES. However, computed tomography (CT) is usually the first investigation recommended for children with acute neurologic complications after transplantation, mainly to exclude hemorrhagic events related or not to PRES. Unfortunately, the CT findings in PRES are sometimes normal or nonspecific. A study comparing the different sensitivities of both assessment modalities after PRES found negative or nonspecific radiologic patterns on CT scans in more than half of patients, whereas MRI was able to detect typical PRES lesions in all the cases.\textsuperscript{40}

**EEG**

Performing EEG at the onset of neurologic symptoms in children who have undergone transplantation is an important tool for distinguishing...
between an epileptic and nonepileptic nature of specific neurologic signs. Intercritical EEG recordings during the acute phase of PRES often reveal encephalopathic changes, such as focal slowing and/or periodic lateralized epileptiform discharges involving unilateral or bilateral parieto-occipital or temporal-occipital regions. EEG could be particularly useful to diagnose nonconvulsive SE. In nonconvulsive SE due to PRES, EEG usually shows continuous or near-continuous rhythmic epileptic discharges involving unilateral or bilateral parieto-occipital or temporo-occipital regions, and associated with subtle clinical signs, such as gaze deviation and altered mental status. Considering the difficulty in diagnosing nonconvulsive SE, we suggest EEG monitoring for detecting subtle electrographic seizures in patients with suspected PRES.

**Laboratory Tests**

Laboratory tests are recommended to exclude metabolic disturbances and electrolyte imbalances, namely hyponatremia, hypocalcemia, and particularly hypomagnesemia. Furthermore, renal and liver function, as well as the dosages of plasma levels of immunosuppressant agents, should be evaluated. The coagulative function must be investigated due to the possible risk of hemorrhagic complications. Cerebrospinal fluid findings are not specific in PRES; however, lumbar puncture should be performed in children with fever or clinical suspicion of meningitis to exclude central nervous system (CNS) infections.

**Complications**

Although considered to be a benign self-limited entity, sometimes the occurrence of PRES has been described in association with potential life-threatening events. Severe cerebral hemorrhage, cerebellar herniation, and refractory SE have been reported as complications in some patients diagnosed with PRES. These events may not be always directly caused by PRES, but they can share with PRES many pathogenic aspects. Cerebral hemorrhage is reported to be associated with PRES in 5% to 19% of cases and usually manifests as parenchymal hematoma, small hemorrhages <5 mm in size, or subarachnoid hemorrhage. Intracerebral hemorrhages (ICHs) in the context of PRES are usually small, but lethal cases associated with massive ICHs have been described. The risk of ICH is significantly higher after allo-HSCT than after SOT, and patients receiving therapeutic anticoagulation were statistically more likely to develop hemorrhages. Other studies have supported a relationship between PRES and associated ICH and bleeding diathesis or coagulopathy in both the HSCT and SOT settings. In our experience, 20% of patients with PRES after allo-HSCT presented with cerebral hemorrhage (Fig 2C). None of these patients presented with bleeding diathesis at the time that complications emerged.

A rare but catastrophic complication of PRES is the occurrence of cerebellar herniation (Fig 2D) as a consequence of severe edema of the posterior fossa structures (cerebellum and brainstem). We observed this complication in 2 of 26 patients. In both patients, cerebellar edema was present from the beginning of PRES, suggesting that patients with cerebellar or brainstem involvement should be closely monitored for the appearance of neurologic signs and symptoms of cerebellar herniation, such as neurologic deterioration, gradual consciousness impairment with

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**FIGURE 2**

A, FLAIR T2-weighted MRI image of typical bilateral posterior vasogenic edema during the acute phase of PRES. B, Complete resolution of the vasogenic edema. C, CT scan showing a hemorrhagic complication of PRES in the right hemisphere. D, T2-weighted MRI image of cerebellar swelling and herniation during PRES.
hypotension, and bilateral mydriasis. A prompt diagnosis of this complication is essential because of the possible need of neurosurgical posterior fossa decompression and/or placement of a ventricular drain.

Finally, another possible cerebrovascular complication of PRES, until now reported only in settings other than pediatric transplantation, is the development of cerebral ischemic stroke. This complication has mainly been described in adult patients, and the few cases reported showed poor outcomes.46,48

**DIFFERENTIAL DIAGNOSIS**

PRES occurring after HSCT or SOT must be distinguished from other acute neurologic complications, namely CNS infections, metabolic disturbances (electrolyte imbalances or multiple organ failure), cerebrovascular disorders, and CNS involvement by an underlying disorder (Table 1).9,11,13 The frequency of transplant-related complications differs depending on the type of transplant. In the context of pediatric liver or combined liver and small bowel transplant,38 the most frequent causes of neurologic disorders described in the literature include metabolic encephalopathy, followed by PRES, CNS infection, and cerebrovascular accident. With regard to renal transplantation, PRES assumes a major role in the onset of neurologic complications, followed by CNS infection and hypertensive encephalopathy.6

PRES represents the main etiology for neurologic complications after pediatric allo-HSCT.3,11,49,50 Other causes of neurologic disturbances, in descending order of frequency, include the following: CNS infection, CNS involvement by the underlying disease, encephalopathy of unknown origin, metabolic disturbances, or neurotoxicity of certain drugs (ie, busulfan).

Instrumental, radiologic, and laboratory findings can help differentiate PRES from other common complications after transplantation. Ictal and/or postictal abnormalities on EEG (rhythmic epileptiform activity, periodic lateralized epileptiform discharges, and/or slowing) in the posterior regions of the brain are particularly suggestive of PRES.27

Although cerebral images are usually normal or scarcely informative in cases of metabolic derangement or CNS involvement by hematologic disease, CNS infections are associated

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CSF, cerebrospinal fluid; JCV, John Cunningham Poliomavirus; NCSE, nonconvulsive status epilepticus; PCR, polymerase chain reaction; PLED, periodic lateralized epileptiform discharge; PML, progressive multifocal leukoencephalopathy; PTLD, posttransplant lymphoproliferative disease; WM, white matter.
with heterogeneous, but suggestive, imaging findings spanning from an abscess lesion, a focal lesion surrounded by perilesional edema (ie, in the case of a cerebral Epstein-Barr Virus (EBV)-posttransplant lymphoproliferative disorders), or diffuse edema.11 In bacterial meningitis, abnormal thickening and enhancement of the leptomeninges are detectable on MRI with contrast enhancement. In the case of CNS aspergillosis, CT or MRI can detect vasculopathy and multiple septic infarcts involving the basal ganglia, thalami, and the corticomedullary area, often in association with hemorrhage and abscess formation.51 In patients with clinical suspicion of CNS infection or involvement by hematologic disease, cerebrospinal fluid analysis and related blood examinations are useful in reaching a diagnosis. Diffusion-weighted imaging is required to differentiate PRES from cerebrovascular disorders, such as ischemic stroke.

OUTCOMES

The clinical and radiologic reversibility of PRES has been extensively described since its first description,1,33 but over the years, the recognition of nonreversible cases has revealed the heterogeneous evolution of this syndrome.52–54 Globally, limited and conflicting data are available on functional outcomes. Some authors have reported good outcomes in children with PRES after SOT or allo-HSCT because all of their patients recovered from symptoms and none developed neurologic abnormalities.6,11,26 However, other studies have noted the presence of residual or late-onset neurologic sequelae or epilepsy secondary to permanent brain lesions.4,52 The impact of PRES on survival rates is particularly difficult to define because the relative effects of PRES and other factors (baseline disease, therapies) remain unclear. Moreover, data concerning mortality rates after PRES have derived mainly from case reports or small retrospective studies, from which it is difficult to draw accurate conclusions.

Our pediatric patients who developed PRES after allo-HSCT had a higher mortality rate than patients who were free from neurologic disturbances (5-year survival: 32.3% vs 45.8%).11,32 This finding was also emphasized in a large study of allo-HSCT in adults.13

RECOMMENDATIONS FOR MANAGEMENT AND FOLLOW-UP

Supportive care is the cornerstone of treatment of patients with PRES after SOT or HSCT. The management of these patients can require an ICU or intermediate care unit admission to allow for continuous monitoring of vital and cerebral functions and, in particular, to avoid the upper airway obstruction and respiratory failure that can occur in patients with impaired consciousness or seizures (Fig 3). Antiepileptic drugs (AEDs) should be administered as early as possible to control ongoing seizures. Benzodiazepines (diazepam 0.5 mg/kg given rectally [maximum of 10 mg] or intravenous midazolam 0.1–0.2 mg/kg over 2–3 minutes followed by continuous infusion at rates of 0.5–2 µg/kg per minute, titrated to efficacy) are often used as first-line agents. In patients with refractory seizures, intravenous phenytoin (15–18 mg/kg at a rate of 1 mg/kg per minute; maintenance at 5 mg/kg per day divided twice daily) or phenobarbital (10–15 mg/kg at a rate of 1–2 mg/kg per minute; maintenance at 5 mg/kg per day divided twice daily) or an anesthetic with anticonvulsant effects, such as propofol or thiopental, might be required. We suggest obtaining an EEG as soon as possible at the onset of neurologic signs/symptoms; in addition, serial EEG recordings should be obtained during the acute phase to monitor treatment efficacy and to investigate for the presence of nonconvulsive seizures. Hereafter, EEG follow-up is not required in patients who fully recover after PRES.

A particularly controversial issue is the duration of antiepileptic therapy after PRES. In most studies, AEDs were discontinued after the patients were seizure-free for at least 3 to 6 months.4 Other studies, however, have suggested continuing AEDs on a longer-term basis.52 Considering the occasional or provoked nature of seizures, our practice is to administer prophylactic treatment with AEDs (benzodiazepines and/or phenytoin) only during the acute phase of the neurologic complications. We then discontinue AEDs upon MRI evidence of edema resolution.11 We believe that prolonged prophylactic treatment with AEDs is unnecessary in patients with occasional or provoked seizures due to PRES, but it should be considered in cases of later development of secondary epilepsy.

Blood pressure is commonly measured at least once per day in patients undergoing transplantation, but in case of PRES the monitoring should be switched to a more intensive way and tailored according to specific clinical conditions. Little pediatric experience is available on the best pharmacologic approach for lowering blood pressure in children with PRES. In the case of severe hypertension during the acute phase of PRES, blood pressure should be lowered gradually after excluding cerebral infarction. Arterial pressure should be reduced by ~25% within the first hour, followed by subsequently slower reduction.55 Indeed, a sudden reduction in blood pressure is not recommended because it can worsen the cerebral perfusion pressure and promote ischemic lesions. In these cases, vasodilators (sodium nitroprusside: 0.53–10 µg/kg per minute via intravenous infusion56) and calcium channel blockers (nicardipine: 1–3 µg/kg per minute via
intravenous infusion\textsuperscript{56,57} are commonly used antihypertensive agents.

In nonemergency cases specific classes of antihypertensive drugs should be used preferentially because transplanted children are at risk of specific comorbidities such as renal failure or being exposed to concurrent medical conditions. Examples include the use of angiotensin-converting enzyme inhibitors (enalapril: 0.08 mg/kg per day administered orally up to 5 mg/day, once or twice a day\textsuperscript{56}) in children with concomitant proteinuric renal diseases.

After the clinical recovery of PRES, patients should be treated for hypertension until predisposing risk factors are present. In any case the efficacy of antihypertensive prophylaxis to prevent PRES recurrence is not documented.

In an attempt to remove potential promoting factors, patients should be evaluated for metabolic disturbances, particularly hypomagnesemia, and for bleeding diathesis, either of which can require prompt correction.\textsuperscript{44}

Upon the occurrence of PRES, in most studies, ongoing CNI treatment was discontinued, and a different immunosuppressant agent was introduced (CSA to tacrolimus, or vice versa), with monitoring of the drug level according to the individual GvHD and rejection risks, respectively.\textsuperscript{13,31,58}

Discontinuation of other agents potentially involved in PRES pathogenesis should be considered (Table 2).

Neuroimaging is also needed upon the appearance of symptoms to obtain a correct diagnosis. CT is usually the first investigation recommended at the onset of an acute neurologic complication after transplantation, mainly to exclude hemorrhagic events. Nevertheless, MRI must be performed to define secure diagnosis and the extent of encephalopathy. Moreover, neuroimaging must be obtained during PRES, at the appearance of new focal neurologic deficits and/or at the occurrence of neurologic deterioration, to exclude complications, such as ICH and cerebral herniation. Patient follow-up using neuroimaging studies has been controversial. Some authors have reported that in the presence of typical initial imaging findings and clinical presentation with subsequent total clinical recovery, a follow-up study is redundant because there is strong evidence in the literature of the reversible nature of cerebral lesions.\textsuperscript{58} However, as mentioned above, PRES can lead to persistent brain damage.\textsuperscript{41} The ideal timing for repeat brain imaging to document radiologic recovery is unclear, although improvements in abnormalities have usually been reported 7 to 15 days after symptom onset.\textsuperscript{26,31}

**PROSPECTIVES**

Although substantial advances have been made in recent years within the transplantation
community in the recognition and management of PRES, several questions remain unanswered. The risk factors predisposing one to developing PRES remain an open issue. The modification of identifiable risk factors before or during transplantation would significantly impact the outcomes. Few studies involving large series of patients and variables are available.\textsuperscript{13,32}

A significant role of hypertension in the onset of PRES has been suggested across different transplant settings, but the exact nature of this role remains unclear; clarification would have significant implications for transplant patients, who are usually exposed to drugs that promote hypertension. Other potential promoting factors, such as baseline disease, electrolyte abnormalities, concurrent infections, and plasma levels of CNIs, have not yet been elucidated. Moreover, researchers have yet to identify a circulating serologic biomarker possibly implicated in the development of PRES. Many candidates are of potential interest: inflammatory cytokines, such as tumor necrosis factor $\alpha$, interleukin-1, and interferon-$\gamma$; markers of endothelial activation, such as p-selectin, e-selectin, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1; and endothelin-1 upregulation.

The role of neuroimaging in the diagnosis of PRES has been well defined; nevertheless, it would be interesting to investigate whether new functional neuroimaging methods, such as magnetic resonance (MR) perfusion, arterial spin-labeled MR, and MR spectroscopy, could play major roles in understanding the pathophysiology of PRES.

Once a diagnosis has been made, the withdrawal or modification of immunosuppressive drugs is the primary matter of concern for transplant physicians. Studies focusing on the reliable switching of immunosuppressive drugs and the identification of a safe alternative immunosuppressant regimen, although challenging to conduct, would have undisputed importance because for both HSCT and SOT the availability of relatively new drugs (ie, belatacept or mammalian target of rapamycin [mTOR] inhibitors) for allograft rejection and GvHD prophylaxis are now encouraging the development of a variety of alternative combinations of immunosuppressive schedules to be studied. Moreover, each pediatric transplant community should emphasize the development of a uniform management strategy for PRES in terms of the optimal timing for reevaluation with MRI and subsequent follow-up.

Pediatricians who care for child transplant patients have certainly become increasingly accustomed to recognizing and managing PRES over the years. Nevertheless, PRES remains an intriguing and evolving matter of interest in the field of neurologic complications after pediatric organ or hematopoietic stem cell transplantation, and new knowledge is needed.

\section*{Acknowledgments}

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\begin{table}[h]
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\textbf{Drugs Associated With PRES of Potential Use During Transplantation} & \textbf{Source} \\
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\textbf{Cytotoxic agents} & \\
Antimetabolites & \\
Gemcitabine & Bartynski (2) \\
Cytarabine & Bartynski (2) \\
Methotrexate & Dicuonzo et al (59) \\
Fludarabine & Beitinjaneh et al (31) \\
\hline
\textbf{Monoclonal antibodies} & \\
Rituximab (anti-CD20) & Zito et al (60) \\
Infliximab (anti-TNF-$\alpha$) & Zarnvar et al (61) \\
Alemtuzumab (anti-CD52) & Gookeley et al (62) \\
\hline
\textbf{Immunosuppressive agents} & \\
\textbf{CNIs} & \\
Cyclosporine & Bartynski et al (25) \\
Tacrolimus & Hammerstrom et al (63) \\
mTOR inhibitors & \\
Rapamycin & Qin et al (64) \\
Sirolimus & Moskowitz et al (65); Bodkin and Eidelman (66) \\
Purine analogs & \\
Azathioprine & Facchini et al (67) \\
\hline
\textbf{Antibiotics} & \\
Linezolid & Nagel et al (68) \\
Ciprofloxacin & Ali (69) \\
\hline
\textbf{Growth factors} & \\
Granulocyte-stimulating factor & Stübgen (70) \\
Erythropoietin & Delanty et al (71) \\
Human immunoglobulins & \\
Antilymphocyte globulin & Belmouaz et al (72) \\
Greaves et al (73) \\
\hline
\textbf{Miscellaneous} & \\
Corticosteroids & Zama et al (32); McKinney et al (42) \\
Intravenous contrast agents & McKinney et al (42) \\
Carbamazepine & Furuta et al (74) \\
Epinephrine & Gharaawy et al (75) \\
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\caption{Drugs Associated With PRES of Potential Use During Transplantation}
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mTOR, mammalian target of rapamycin; TNF, tumor necrosis factor $\alpha$. 

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THE HIGH COST OF TIPPING: The other day I took a young friend of mine out to dinner at a very casual establishment. We ordered drinks and food at the bar and put the number given to us by the barkeeper by our seats at a large communal table. A few minutes later the server brought us our food. At the end of dinner I cleared our dishes and then went to the bar to pay. The barkeeper typed in a few items on the iPad and pushed it to me to sign. Generally speaking, I am a reasonably generous tipper but I was perplexed. The iPad showed I could automatically add 25%, 30%, or 35% to the bill (the percentage was based on the total bill including the tax which in Burlington, Vermont is 10%). To enter another number I would have to calculate the amount on my own and manually enter it into the iPad.

As reported in The New York Times (Business Day: January 31, 2015), tip creep is common. In the 1940s, a 10% tip was the norm. A 15% tip at sit down restaurants has been considered the norm for many years. However, now most feel that 20% is what is expected. Nowadays, restaurants, cab drivers, coffee shops and anyone using ubiquitous electronic payment tools offer automatic tipping options that generally include much more generous tips. For example, after purchasing a cup of specialty coffee, the buyer may be offered the option of tipping $1, $2, or $3 – which could mean a tip of 75%. Several of my children have worked very low wage jobs, so I am a great supporter of raising the minimum wage, but I am still having a bit of trouble with some tipping suggestions. Fortunately, I can multiply by 10% in my head very quickly and always carry some bills in my wallet so, if confronted with a suggested tip amount with which I do not agree, I have options other than blindly accepting.

Noted by WVR, MD
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