Posterior Reversible Encephalopathy Syndrome

Dimitre Staykov, MD¹, and Stefan Schwab, MD, PhD¹

Abstract
Posterior reversible encephalopathy syndrome (PRES) is characterized by headache, altered mental status, visual disturbances, and seizures. Radiological features typically include edema of the posterior cerebral regions, especially of the parietooccipital lobes. Atypical imaging features, such as involvement of anterior cerebral regions, deep white matter, and the brain stem are also frequently seen. Vasoconstriction is common in vascular imaging. Different conditions have been associated with PRES, but toxemia of pregnancy, solid organ or bone marrow transplantation, immunosuppressive treatment, cancer chemotherapy, autoimmune diseases, and hypertension are most commonly described. The pathophysiology of PRES is unclear and different hypotheses are being discussed. Posterior reversible encephalopathy syndrome is best managed by monitoring and treatment in the setting of a neurointensive care unit. The prognosis is usually benign with complete reversal of clinical symptoms within several days, when adequate treatment is immediately initiated. Treatment of severe hypertension, seizures, and withdrawal of causative agents represent the hallmarks of specific therapy in PRES. Delay in diagnosis and treatment may lead to permanent neurological sequelae. Therefore, awareness of PRES is of crucial importance for the intensivist.

Keywords
posterior reversible encephalopathy syndrome, reversible posterior leukoencephalopathy syndrome, hypertensive encephalopathy, eclampsia

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Introduction
The term reversible posterior leukoencephalopathy syndrome (RPLS) was first used in 1996 by Hinchey et al¹ to describe a condition characterized by transient headache, altered mental functioning, seizures, and loss of vision associated with findings of predominantly posterior leukoencephalopathy on imaging studies. In this case series of 15 patients, RPLS was associated with immunosuppressive or interferon therapy, eclampsia, renal disease, or autoimmune diseases.¹ The newly coined term RPLS, however, basically described an already known condition. The same clinical picture with findings of elevated mean arterial pressure (MAP) and similar radiological features was known as the hypertensive encephalopathy syndrome (HTE).²-⁴ Meanwhile the association of hypertension with RPLS is well documented, but hypertension is not always present in such patients, as the case series of Hinchey et al already demonstrates—³ of the 15 cases did not show episodes of elevated blood pressure. Particularly in patients treated with immunosuppressive therapy hypertension may be absent.¹ Therefore, the older term HTE seems indeed too restrictive for an appropriate naming. The newly introduced name RPLS has, however, also begun to cause controversy immediately after its publication.⁵ By now, an extensive body of literature on the syndrome has accumulated, and the term, including its “R,” “P,” and “L” parts, has been increasingly considered misleading for different reasons. First, as cases with nonreversible lesions and neurological deficits have been reported, names like “occipital—parietal encephalopathy,”⁶ or “potentially reversible encephalopathy syndrome”⁷,⁸ have been suggested to be more appropriate. The term “reversible” is still accepted by majority of authors as a part of the name of the condition, provided that it is supposed to suggest the reversibility of symptoms with adequate therapy, and should not imply, that lesions and clinical deficits must always resolve completely. Second, although the posterior localization of the lesions on imaging is most often seen, brain regions other than the occipitoparietal lobes are reported to be very frequently affected.⁹ Third, it has been shown, that the lesions on neuroimaging are not restricted to the white matter, as indicated by...
“leukoencephalopathy”. Although the linguistic debate surrounding the name of the syndrome has not been closed yet and different alternatives are still being used, over the last years the name RPLS has been increasingly replaced by “posterior reversible encephalopathy syndrome” (PRES). As the latter term better reflects the meanwhile increased knowledge about this condition and is widely accepted to be most appropriate, it will be further used in the present review.

**Clinical and Laboratory Characteristics of PRES**

The clinical picture of PRES includes several typical features: seizures, an acute encephalopathy syndrome, and visual disturbances.

Seizures commonly represent the first clinical manifestation of the syndrome and are the most frequently seen symptoms in PRES. Seizures are generalized in the majority of cases but may also have a focal onset with following secondary generalization. Multiple seizures are even more frequent and status epilepticus (SE) may also occur. The acute encephalopathy syndrome manifests with confusion, headache, vomiting, and altered consciousness from somnolence and lethargy to stupor and coma. Episodes of agitation may alternate with lethargic conditions. Severe disturbances of consciousness, especially after seizures, may result in intubation and mechanical ventilation, which was necessary in 39% of PRES cases in a recently reported larger case series. Visual disturbance in PRES varies from blurred vision to hemianopsia and complete cortical blindness. In such cases, denial of cortical blindness (Anton syndrome) may be observed. Other focal neurological signs such as paresis or sensory deficits have also been reported. Symptoms may develop acutely, or gradually over a period of several days. Blood pressure is normal or only minimally elevated on symptom onset in 20% to 30% of the patients. In the remaining 70% to 80%, hypertension is present on manifestation of PRES, the upper limits of autoregulation are however usually not reached. Lee et al report a mean peak systolic blood pressure of 187 mm Hg, range 80 to 240 mm Hg, within the day before presentation in 36 patients with PRES.

As PRES is seen within a wide palette of associated conditions, laboratory characteristics may vary considerably, depending on specific pathophysiology and organ involvement. However, laboratory evidence of endothelial injury, as indicated by thrombocytopenia, cell fragmentation with elevated schistocyte counts, and increase in lactate dehydrogenase, seems to be more frequently found across conditions associated with PRES. Cerebrospinal fluid findings are usually normal, rarely a mild protein elevation has been reported, however there are few studies available in patients with PRES. Lee et al report electroencephalographic findings of slowing in 22 of 28 examined patients, focal sharp waves are less frequently seen (3 of 28 patients), and in 3 of 28 patients electroencephalography was normal.

**Imaging Characteristics of PRES**

**Lesion Characteristics and Localization**

Magnetic resonance imaging (MRI) allows more precise characterization and recognition of PRES than computed tomography (CT) (Figures 1 and 2). The lesions in PRES usually show increased signal on T2- (Figure 2A) and fluid-attenuated inversion recovery (FLAIR) imaging with increased apparent diffusion coefficient (ADC) values (Figure 2C), indicating the presence of vasogenic edema. On diffusion-weighted imaging (DWI), majority of cases show no change in intensity in the corresponding areas with high T2 signal. A T2 shine-through effect with a slight hyperintensity on DWI is less commonly present (Figure 2B). Areas of restricted diffusion and hyperintensity on DWI are rarely observed. Such lesions with restricted diffusion may show ADC values, which appear normal and are surrounded by regions of vasogenic edema. Covarrubias et al describe this phenomenon as “pseudonormalized” ADC, because those changes have been observed by the authors to progress to infarction in 6 patients with PRES. Elevated DWI signal combined with decreased ADC usually indicates ischemic areas. There are, however, also reports of diffusion restriction with ADC decrease in PRES, with subsequent complete reversibility of imaging changes. Single voxel proton MR spectroscopy of the lesions may also
help differentiate between infarction and reversible changes in PRES. N-acetylaspartate decrease has been reported in PRES lesions, whereas lactate increase, a typical finding in ischemic areas, is usually absent.28-31

The most common location of white matter abnormalities in PRES is the posterior regions of the cerebral hemispheres, that is, the occipital lobe, the posterior parietal lobe, and the posterior temporal lobe.1,9,10,24 The frontal lobes are also very frequently involved (Figure 2).9,24 Atypical locations such as the cerebellum, the brain stem, the basal ganglia, the deep white matter, or the splenium of the corpus callosum are seen in approximately 10% to 30% of the cases.1,9,10,20,24 Cortex involvement is frequent (up to approximately 90%) and best recognizable by FLAIR imaging.10 Symmetrical edema is most commonly observed in PRES, asymmetrical or even strictly unilateral manifestations have, however, also been described.9,24 McKinney et al define 3 levels of severity of PRES distribution in a series of 76 patients, based on FLAIR imaging: mild, moderate, and severe.24 In their analysis, there was no significant correlation between edema severity and the occurrence of restricted diffusion, hemorrhage, contrast enhancement, or maximum systolic or diastolic blood pressure. Bartynski et al, however, did find a correlation. The authors suggest a 5-level grading scale for severity of edema in PRES, in which confluence and extension of the lesions to the ventricular system, as well as involvement of the cortex, the subcortical and deep white matter, and space-occupying effects of the lesions are taken into account.15 Among 25 patients with PRES associated with infection, sepsis, and shock, the authors found a significant correlation between the edema severity grade and blood pressure at the time of neurotoxicity. Interestingly, more severe edema was associated with a “normotensive” blood pressure. In contrast, “severely hypertensive” patients showed lower edema grades.15 Similar findings were reported by Bartynski et al for

Figure 2. Magnetic resonance images (MRI) of a patient with posterior reversible encephalopathy syndrome. Hyperintensive alterations in the occipital and frontal lobes on T2 imaging (A). A slight hyperintensity (T2-shine through effect) on diffusion imaging (B). Increased apparent diffusion coefficient (ADC) values in the corresponding areas indicate vasogenic edema (C). Kindly provided by Dr Marios Psychogios and Prof Michael Knauth, Neuroradiology Department, University of Göttingen, Germany.
patients with kidney transplants and PRES. The differing results of McKinney et al and Bartynski et al are probably best explained by the use of different edema grading scales with a better sensitivity of the 5-level grading scale.

Although various brain regions may be affected, certain patterns of lesion distribution appear to be more common. Bartynski et al have made an attempt to classify PRES lesion distribution and found 3 major patterns analyzing a large series of 136 patients with PRES: the first is a holohemispheric watershed pattern consisting of a linear distribution of edema spanning the frontal, parietal, and occipital lobes, with lesser involvement of the temporal lobes. This linear distribution of the lesions seems to be consistent with the anatomostic border zone between medial (posterior cerebral artery [PCA]; anterior cerebral artery [ACA]) and lateral (medial cerebral artery [MCA]) vessel branches. The severity of manifestation ranges from extensive to mild, with a “string of pearls” appearance of nonconfluent white matter lesions. The other 2 major patterns are a superior frontal sulcus pattern with predominant involvement of the mid-to-posterior aspect of the superior frontal sulcus with varying degrees of parietooccipital abnormality and a dominant parietooccipital pattern with involvement of the parietal and occipital lobes and variable temporal lobe manifestations. Each of those patterns was observed in approximately one fourth of the patients. The remaining patients showed incomplete or asymmetrical expression of the described lesion distribution patterns, partially with strictly unilateral abnormality. The imaging distribution patterns did not correlate with clinical features of the syndrome in that study. Analyzing lesion distribution in 24 patients with PRES, another work group found a significantly higher number of lesions and a trend for increased distribution in 3 of patients.11,24,25,36,37 In a recently published study on 151 patients with PRES, Hefzy et al report 3 different types of hemorrhage: minute (punctual) hemorrhage, sulcal (subarachnoid) hemorrhage, and focal hematoma. In this largest analysis focusing on hemorrhage in PRES, a borderline significant statistical trend ($P = .07$) for an association between the occurrence of hemorrhage and underlying etiology of PRES was found. When looking at allogenic bone marrow transplantation (allo-BMT; hemorrhage rate of 46.6%) and solid organ transplantation (hemorrhage rate of 11.7%), the authors identified a statistically significant difference. Focal hemorrhage rates were also significantly greater in allo-BMT patients. Patients with therapeutic anticoagulation or those taking aspirin were significantly more likely to develop PRES-associated hemorrhage, in contrast to patients with intrinsic coagulopathy. There was no association between hemorrhage occurrence and blood pressure. Even excluding the subset of allo-BMT patients, severe hypertension was less frequently associated with hemorrhage.36 This finding may indicate that hemorrhage in PRES is not directly caused by severe hypertension but rather a consequence of initial hypoperfusion and subsequent reperfusion injury.

### Vascular and Cerebral Perfusion Imaging

The state of cerebral perfusion in PRES is still a subject of controversy because of contradictory findings reported in different studies. Animal studies suggest that experimentally induced hypertension above the autoregulatory limit leads to breakdown of the blood–brain barrier, hyperperfusion, and leakage of fluid into the brain, with subsequent vasogenic edema.38 The evidence of hyperperfusion in the clinical setting of PRES is, however, not convincing. Single reports of hyperperfusion in PRES detected either by single-photon emission computed tomography (SPECT)39 or by MR-perfusion imaging40 have been published. There is, however, controversy on the interpretation of those findings.14,40

The majority of studies on cerebral perfusion imaging in PRES reports hypoperfusion in the affected areas with vasogenic edema.15,28,41-43 In studies using MR-perfusion imaging, a reduction of relative cerebral blood volume (rCBV) in the affected areas of the brain has been reported.41,43 Reductions in rCBV measured in edematous areas range from one third up to two thirds of reference normal cortical rCBV.41,43,44 In a large case series of women with eclampsia, brain perfusion assessed by SPECT has also demonstrated perfusion deficits in the predominantly affected watershed areas, in which PRES lesions occur.45 Hypoperfusion has also been reported using CT-perfusion imaging in a patient with PRES.46

These findings are usually coupled with vessel irregularities and vasospasm shown on vascular imaging.15,28,41,424 Catheter angiography41,47-51 and MR angiography studies15,28,41,42,52-54 in patients with PRES have demonstrated vascular abnormalities as focal vasoconstriction, focal vasodilatation, “string-of-bead,” or “string-of-sausages” appearance. Follow-up MR angiography usually demonstrates reversal of vascuopathy.41

### Conditions Associated With PRES

PRES has been associated with a variety of conditions and predisposing factors, which are summarized in Table 1.

Moderate-to-severe hypertension, commonly present in PRES, is reported in approximately 75% of cases.14 Hypertension has been recognized as a major factor in the setting of PRES,
PRES has been frequently described in the setting of allo-BMT or stem cell transplantation, as well as after solid organ transplantation, mostly in connection with cyclosporine or tacrolimus neurotoxicity. PRES occurs most commonly in the first month after allo-BMT, the remaining cases usually within 1 year after transplantation. The incidence of PRES seems to vary with different preconditioning regimens and comprises approximately 7-9% using myeloablative marrow preconditioning and cyclosporine immune suppression. Even higher incidences (approximately 16%) have been reported using higher dose myeloablative regimens, in contrast to a PRES incidence of only 3% when nonmyeloablative preconditioning was used. As higher incidence of graft versus host disease (GVHD) has been identified in patients developing PRES, GVHD effects have been suggested to play a role in the pathogenesis of PRES.

In solid organ transplantation, PRES incidence has been reported to vary between 0.4% and 6%. PRES seems to occur earlier in the course after liver transplantation—in most cases within 2 months—and markedly later after kidney transplantation. Systemic hypertension is more often noted after kidney transplantation compared to liver, lung, or heart transplantation, and hypertensive patients tend to develop less brain edema than normotensive patients with PRES. Transplant rejection and infection have been reported to often accompany PRES after solid organ transplantation.

High-dose multidrug cytotoxic chemotherapy has also been associated with PRES, especially in children with leukemia. Additionally, several chemotherapeutic drugs have been reported in connection with PRES: cytarabine, cisplatin, gemcitabine, tiazofurin, and bevacizumab. In recent years, reports of PRES in patients with connective tissue diseases, the majority of them with systemic lupus erythematosus (SLE) and also Wegener granulomatosis, polyarteritis nodosa, scleroderma, psoriasis, Graves disease, and rheumatoid factor positive arthropathy have accumulated. The particular role of the underlying connective tissue disease in the pathogenesis of PRES is not clear in those cases, because comorbidity like hypertension, renal involvement with renal insufficiency, infection, or recent immunosuppressive treatment with corticosteroids, cyclophosphamide, cyclosporine, mycophenolate mofetil, rituximab, and azathioprine, all factors separately associated with PRES, were present in most patients. Interestingly, withdrawal of putatively causative immunosuppressive drugs on one hand, and administration of high-dose corticosteroids or adjunctive immunosuppressive drugs, including cyclophosphamide or mycophenolate mofetil on the other hand have been reported to lead to successful treatment of PRES.

A recent study of 106 patients identified infection and sepsis as an important, though not yet recognized cause of PRES, particularly in relation to infection with gram-positive organisms. Infection and sepsis have been suggested to be responsible for one fourth of the cases with PRES in this study. This observation has, however, yet to be confirmed in other studies.
Rarely or anecdotally reported associations with PRES include hypomagnesemia, hypercalcemia, hypercholesterolemia, acute pancreatitis, intravenous immunoglobulin, linezolid treatment, Guillain-Barré syndrome, Ephedra overdose, triple H therapy, tumor lysis syndrome, hydrogen peroxide, contrast media exposure, corticosteroid treatment, influenza A infection, lysergic acid amide, and scorpion poison. 

**Pathophysiology of PRES**

The mechanism of PRES is still poorly understood and controversial. There are 2 commonly cited opposing hypotheses on the pathogenesis of PRES. The older hypothesis states that hypertension leads to autoregulatory vasoconstriction and hypoperfusion with resulting ischemia and cerebral edema. 

This idea was supported by findings of edema in the posterior cerebral regions combined with vasospasm on vascular imaging in patients with eclampsia and hypertension. 

The newer hypothesis suggests that severe hypertension exceeds the autoregulatory limits of the cerebral vasculature and leads to breakthrough of the blood–brain barrier, fluid leakage, and vasogenic edema. 

This more intuitive explanation has become popular in recent years, mainly because of the frequently reported benefit of emergent hypertension treatment with subsequent recovery of symptoms and alterations in imaging. 

Moreover, animal studies investigating the cerebral sequelae of severe hypertension have demonstrated breakthrough of the blood–brain barrier, hyperperfusion, and vasogenic edema when the upper limits of autoregulation are exceeded. 

However, the role of hypertension in PRES has not been sufficiently elucidated yet and continues to be the subject of controversy. 

In humans, the upper limits of autoregulation are usually reached at a mean arterial pressure (MAP) of 150 to 160 mm Hg. 

Due to the rich sympathetic innervation of cerebral vessels, sympathetic stimulation leads to increase of the upper limit of autoregulation by up to 30 mm Hg MAP. 

Those limits are also increased in patients with chronic hypertension. 

Given the considerable prevalence of moderate-to-severe hypertension in the setting of PRES (up to 75% of patients), it should be noted that observed blood pressure levels, although in some reported cases elevated quite severely, in the majority of cases it does not reach the upper limits of autoregulation. 

Furthermore, circumstances leading to increased levels of autoregulation are a common finding in PRES, for example, chronic hypertension, or increased sympathetic stimulation, as reported in patients treated with cyclosporine. 

Moreover, PRES is frequently seen without hypertension, as reported in patients with eclampsia, after allo-BMT or solid organ transplantation. 

In this subset of patients, however, “relative hypertension” may play a role. Women with eclampsia having borderline hypertensive blood pressure values (systolic pressure of less than 140 mm Hg) are often young primigravidas whose blood pressures have risen from markedly low baseline levels. 

The importance of this mechanism for the pathogenesis of PRES is yet still unclear. Some recent findings show that the severity of cerebral edema is inversely correlated to the blood pressure level in patients with PRES. 

Those observations have led to the speculation that increased blood pressure may represent a secondary event in the mechanism of disease, not causing edema by fluid leakage, but rather appearing as a reaction to hyperperfusion and ischemia, thus supportive for the older hypothesis of pathogenesis. 

Although animal studies underpin the hypothesis of breakthrough of the blood–brain barrier by increased MAP, those observations have been made on otherwise healthy animals, in contrast to the usually very complex systemic conditions associated with PRES in humans. Apart from hypertension, other common findings across underlying conditions may give further clues regarding the pathophysiology of PRES. 

Looking at the major conditions, in the setting of which PRES commonly occurs, namely transplantation, autoimmune disease, preeclampsia—eclampsia, cancer chemotherapy, infection, and sepsis, endothelial injury to a certain extent seems to be almost uniformly present. In allo-BMT, the combination of preconditioning regimens and following GVHD leads to release of proinflammatory cytokines and endothelial activation or injury. 

In solid organ transplantation, graft rejection related to a T-cell response is additionally associated with the development of antiendothelial antibodies, primarily against the allogenic transplant. 

On the other hand, immunologically active cells within a liver transplant may contribute to a GVHD similar mechanism of endothelial damage. 

Autoimmune diseases as SLE and Wegener granulomatosis are characterized by vasculitis. 

In toxemia of pregnancy, a placental maternal immune reaction is considered the underlying cause of cytokine release, endothelial activation, and injury. 

Furthermore, antiendothelial antibodies are more frequently found in women with eclampsia, as compared to healthy pregnancies (50% vs 16%). 

In cancer, immunologic reaction to cancer, or direct damage of the endothelium by chemotherapeutic drugs are possible mechanisms of endothelial injury. 

Endothelial activation in infection, triggered by bacterial endotoxins, and endothelial injury in sepsis represent an important part of the primary infection response and secondary septic response. 

Laboratory markers of endothelial injury, namely thrombocytopenia, cell fragmentation (schistocytes), and elevated lactate dehydrogenase, are commonly found across those conditions. 

Considering the important role of the endothelium in cerebral autoregulation and its vasodilator influence, endothelial injury in PRES-associated conditions may lead to vascular instability and vasoconstriction, with subsequent hyperperfusion. 

Cerebral hyperperfusion of the regions showing abnormalities on imaging in PRES, accompanied by evidence of vasculopathy and vasoconstriction on vascular imaging, has been indeed better documented, as compared to the sporadic reports of hyperperfusion. 

Therefore, the available evidence seems to be in better unison with the older hypothesis on the pathogenesis of PRES, which considers hyperperfusion central. In this context, the occurrence of edema patterns in the watershed areas of cerebral circulation is also better explained.
Speculations have been made in order to explain the predominant involvement of the posterior parts of the brain in PRES. One explanation has been proposed by Schwartz et al. The authors mention the evidence of a protective effect of sympathetic innervation of the cerebral vasculature against marked increases of blood pressure. Based on a histofluorescence study by Edvinsson et al, which has shown a less dense sympathetic innervation of the vertebrobasilar compared to the internal carotid system, Schwarz et al concluded that the vertebrobasilar system is more likely to be affected by increases in blood pressure and more susceptible to breakthrough of the upper limits of autoregulation. A newer study aiming at quantification of perivascular nerve fibres in human basal cerebral arteries has, however, shown exactly the opposite relation of innervation density in the circle of Willis, namely a higher perivascular sympathetic nerve density in the PCA and the posterior communicating artery (PCom), as compared to the rest of the basal cerebral arteries. The authors used a methodology of histologic preparation, which probably allows better representation of perivascular nerve fibers, especially of fibers within deeper layers of the vessel wall, as compared to the method used by Edvinsson et al. This finding allows the speculation that the higher density of sympathetic innervation of the PCA may contribute to increased vasoconstriction, hypoperfusion, and subsequent cerebral edema in the setting of endothelial injury in this part of the cerebral vasculature. This explanation would then better fit into the hypothesis of hypoperfusion as the central mechanism in the pathogenesis of PRES. The number of studies quantitatively investigating innervation density in human cerebral arteries is, however, still too small, the results controversial, and the correlation of those findings to clinical, imaging features, and hypotheses on the pathogenesis of a complex condition like PRES remains speculative. The repeated reports of different findings in the anterior and posterior parts of cerebral circulation, including in vivo functional studies using transcranial Doppler sonography, however, indicate the possible role of different innervation and vascular reactivity in the development of the imaging patterns in PRES.

Prognosis and Treatment of PRES
Natural History
With timely institution of adequate treatment, PRES is usually completely reversible within several days to several weeks. Incomplete recovery has, however, also been reported under adequate therapy. In a recent long-term follow-up report on patients with PRES, in approximately 25% of the cases, abnormalities on imaging did not resolve completely and clinical improvement often preceded improvement on imaging. Similar results have been reported in women with eclampsia within several months from the event. When studied 7 years postpartum, 40% of formerly eclamptic women have shown white matter lesions on imaging, as compared to 17% of patients with no eclampsia. It is important to point out that reversibility of PRES is not spontaneous and delay in diagnosis and treatment may lead to permanent damage to affected areas of the brain. Ischemia represents one of the major complications of PRES, occurring typically in the posterior border zone between the territories of the middle and posterior cerebral arteries. Patients with multiple seizures in the course of PRES are at an especially high risk of developing infarction. When hemorrhage occurs in PRES, focal parenchymal bleedings most likely lead to permanent clinical symptoms, as compared to minute, or sulcal bleeding.

Epilepsy may represent another long-term complication of PRES. Patients with hippocampal sclerosis, or permanent focal changes and temporal lobe epilepsy, which has developed months to years after an episode of PRES, have been reported. It appears plausible, that lesions in PRES, which evolve into permanently damaged areas, may cause seizures in the long-term course. The development of hippocampal sclerosis after PRES, however, may also be coincidental and this issue remains controversial.

To date, no data are available on the long-term neurocognitive consequences of PRES. Theoretically, the presence of permanent cerebral lesions in a considerable part of the patients who had suffered PRES may be reflected in a certain level of cognitive dysfunction. In a study using a questionnaire for cognitive functioning, formerly eclamptic women indeed reported cognitive impairment several years after complicated pregnancy. Objective neurocognitive testing performed in women several months after preeclampsia has also shown presence of cognitive deficits in such patients.

Recurrence of PRES has been infrequently documented in single-case reports. Relapsing PRES has been reported in patients after solid organ transplantation, chemotherapy, allo-BMT, autoimmune disease, sickle cell disease, and in a patient with a mitochondrial disorder. Multiple episodes of PRES in a single patient have been reported in children with renal disease and in a patient with SLE, for a total of 4 recurrent episodes of PRES that have been documented.

Differential Diagnosis and Treatment
The differential diagnosis of PRES includes a wide variety of acute neurological disorders with different etiologies. Several important conditions with prognostic and therapeutic implications should be considered: ischemic stroke and cerebral sinus thrombosis are usually easily ruled out by MRI and MR angiography. Inflammatory diseases, such as infectious (eg, viral) encephalitis, or autoimmune diseases like acute disseminated encephalomyelitis, can be excluded by cerebrospinal fluid examinations or negative bacteriological and virological tests. Other rare diseases, like mitochondrial disorders, or cerebral autosomal dominant arteriopathy with stroke and ischemic leukoencephalopathy (CADASIL), may also mimic the clinical and radiological appearance of PRES.

There are several important aspects in the treatment of PRES: (i) the removal or reduction of the causative drug,
(ii) aggressive management of blood pressure if hypertension is present, (iii) treatment of seizures and SE, and (iv) consideration of delivery by cesarean section in pregnant women with refractory symptoms.\(^{13}\) PRES is best managed in the setting of a neurocritical care unit with the possibility of close consultation with other specialties according to the underlying systemic condition, for example, oncology, rheumatology, obstetric critical care. Clinical and operative monitoring, that is, invasive blood pressure monitoring, monitoring of airways and oxygenation, and electroencephalographic monitoring in patients with seizures, are essential in the acute phase of PRES. Intubation and mechanic ventilation may be necessary in up to 39% of patients.\(^{11}\) General management also includes maintenance of homeostasis, sufficient hydration and arterial oxygenation, correction of hypoglycaemia, electrolyte disturbances, or coagulopathy.

Treatment of elevated blood pressure is considered central in the management of PRES. Generally, the goal of treatment is the reduction of mean blood pressure to premorbid levels. Intravenous antihypertensive drugs should be preferably used and blood pressure should be monitored with an arterial catheter. Intravenous nicardipine (5-15 mg/h) and labetalol (2-3 mg/min) are considered first-line medications in PRES.\(^{13}\) Hydralazine and diazoxide may also be used for antihypertensive treatment. As nitroglycerine has been reported to aggravate cerebral blood flow.\(^{13,171}\) The aim of the therapy in such patients is to lower the mean arterial pressure by no more than 15% to 25%. Antihypertensive treatment is usually recommended for sustained systolic blood pressure values of more than 160 mm Hg and diastolic blood pressure of at least 110 mm Hg.\(^{180,181}\)

Small reductions in blood pressure in the first 60 minutes with a target systolic value of approximately 140 to 155 mmHg and/or diastolic value of 90 to 105 mmHg have been recommended.\(^{182}\) Both intravenous hydralazine and labetalol have been shown to be safe for the management of hypertension in women with preeclampsia–eclampsia. Angiotensin-converting enzyme inhibitors should be avoided in pregnant women, because of their toxic effects on the fetal kidney.\(^{183}\)

Status epilepticus is a neurologic emergency, in which a single generalized epileptic seizure does not cease within 5 minutes of onset, or recurrent epileptic seizures occur without complete clinical or electroencephalographic recovery between the single events. A focal SE is considered present if a focal seizure continues for more than 30 minutes.\(^{184}\) Generalized SE has a mortality of up to 40% depending on the underlying condition and duration. Therefore, this condition particularly requires immediate, aggressive, and effective treatment in order to prevent neuronal damage or death.\(^{185}\)

After initial control of cardiorespiratory function and blood glucose level, the first-line treatment of SE consists of benzodiazepines, most commonly diazepam or lorazepam.\(^{185}\) Lorazepam is administered intravenously in boluses of 2 mg given slowly over 2 to 5 minutes, up to a cumulative dose of 10 mg. This treatment is usually followed by administration of second-line drugs such as phenytoin (15-18 mg/kg initially, maximal injection speed 50 mg/min) if SE persists after 20 minutes. In most countries, phenytoin is approved for the first-line treatment of SE. Third-line treatment of refractory SE usually consists of coma induction using anesthetics, such as propofol, midazolam, or barbiturates.\(^{185}\)

In pregnant women with eclampsia, magnesium sulfate has been shown to be effective in treatment and prevention of eclamptic seizures compared to traditional antiepileptic drugs, such as diazepam or phenytoin.\(^{186}\)

**Conclusion**

Since its description in 1996, many reports on PRES have accumulated in the literature. Although the pathophysiology of this condition has not been sufficiently elucidated yet, its clinical features and radiological appearance have been well documented. For the critical care physician, awareness of PRES is important, because immediate diagnosis and treatment initiation have the potential to result in a very good outcome, whereas delay in adequate therapy can lead to permanent neurological sequelae.

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