

Understanding Posterior Reversible Encephalopathy Syndrome

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Introduction

Posterior reversible encephalopathy syndrome (PRES) [1, 2] is a clinicoradiological entity that was well described by Hinchey et al. [3] in 1996 based on 15 cases, shortly after two other small case-series were published [4, 5]. This condition has been designated by a variety of names (reversible posterior leukoencephalopathy syndrome, reversible posterior cerebral edema syndrome, and reversible occipital parietal encephalopathy). PRES is now the accepted term [1, 2, 6] but has been challenged recently based on the risk of neurological impairment and up to 15 % mortality rate [7, 8]. PRES is characterized by variable associations of seizure activity, consciousness impairment, headaches, visual abnormalities, nausea/vomiting, and focal neurological signs. The cerebral imaging abnormalities are often symmetric and predominate in the posterior white matter (**Fig. 1**). Recognition of PRES has evolved with increasing availability of magnetic resonance imaging (MRI).

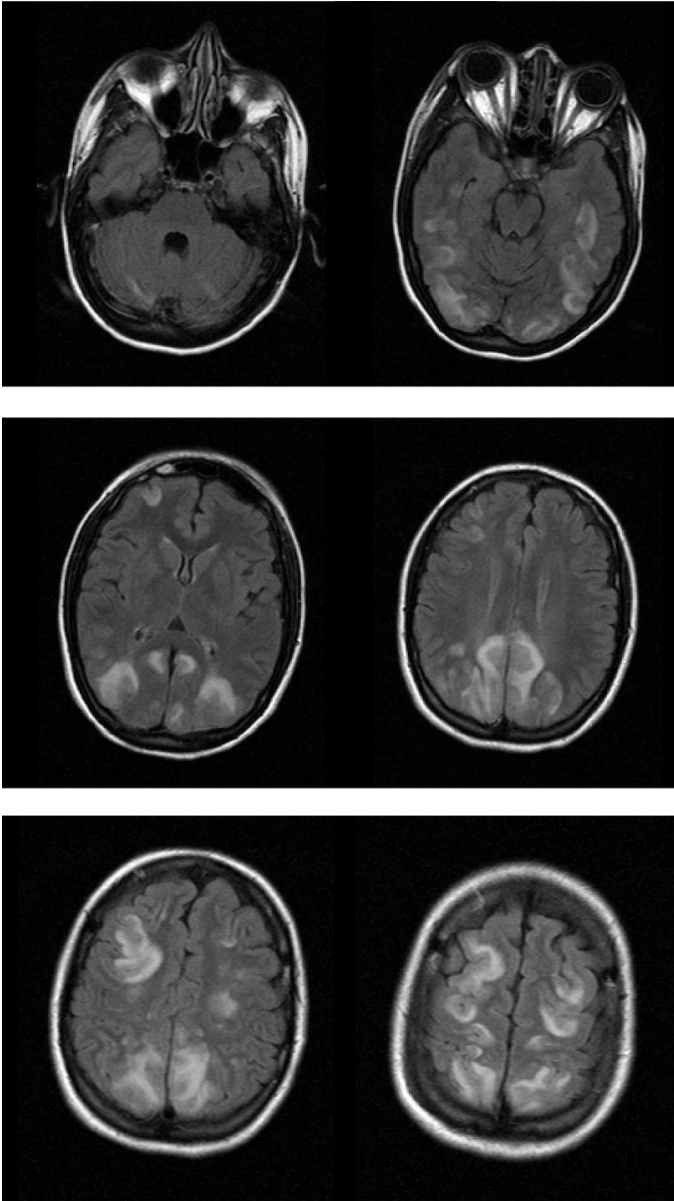
PRES can develop in association with a vast array of conditions. However, regardless of the underlying cause, the main abnormality is cerebral vasogenic edema, the pathogenesis of which is still under debate [1, 2]. PRES is typically reversible once the cause is removed. However, patients with severe manifestations of PRES, such as coma and/or status epilepticus, may require admission to the intensive care unit (ICU) [9, 10]. Moreover, permanent neurological impairment or death occurs in a minority of patients [5, 7, 8].

The objective of this chapter is to provide clinicians with guidance for diagnosing and treating patients with PRES. The diagnostic criteria are described in detail and management recommendations are given with an algorithm.

Epidemiology

The global incidence of PRES is unknown. The only epidemiological data come from retrospective studies of patients seen between 1988 and 2008 [3, 6–8, 10–13]. PRES has been reported in patients aged 4 to 90 years, although most cases occur in young to middle-aged adults, the mean age ranging across case-series from 39 to 47 years. There is a marked female predominance that may reflect some of the causes. Many patients with PRES have comorbidities, which may be severe conditions, such as bone marrow or solid organ transplantation, chronic renal failure, and chronic hypertension.

Mechanical ventilation is required in 35 % to 40 % of patients with PRES, for 3 to 7 days [7, 8]. Status epilepticus may require ICU admission [10]. No epidemi-



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Fig. 1. Cerebral magnetic resonance imaging in a patient with posterior reversible encephalopathy syndrome (PRES). Fluid-attenuated inversion recovery (FLAIR) sequence showing bilateral high-signal foci in the cerebellum, basal ganglia, and occipital, parietal, frontal, and temporal lobes

ological data are available on the subgroup of patients with PRES requiring ICU admission. Mean hospital length of stay was 20 days [7, 8].

Diagnosis

PRES is a clinicoradiological entity. The intensity and severity of clinical manifestations vary and may require ICU admission. Imaging findings also vary in severity. Thorough familiarity with the imaging criteria is crucial to the diagnosis. The combination of suggestive clinical manifestations and radiological criteria establishes the diagnosis of PRES. In doubtful cases, the clinical and radiological improvement that occurs once appropriate treatment is given confirms the diagnosis. Nevertheless, there are no consensual guidelines to validate diagnosis of PRES.

Clinical Manifestations of PRES

Typical presenting manifestations

The typical features of PRES consist of consciousness impairment, seizure activity, headaches, visual abnormalities, nausea/vomiting, and focal neurological signs (**Table 1**). Consciousness impairment may range in severity from confusion, somnolence, and lethargy to encephalopathy or coma. Consciousness impairment has been reported in 13 % [14] to 90 % [8] of cases. Seizure activity occurs in up to 92 % of cases [7]. The seizures are rarely isolated (23 %–28 %) [7, 8]. Secondary generalized seizures are common (53–62 %) [3, 8]. Status epilepticus, defined as

Table 1. Topographic distribution of clinical and radiological features in cohort studies of posterior reversible encephalopathy syndrome (PRES)

	Hinchey 1996 [3] n = 15	Casey 2000 [6] n = 16	Bartynski 2007 [11] n = 136	McKinney 2007[14] n = 76	Lee 2008 [7] n = 36	Burnett 2010 [8] n = 79
Clinical Features of PRES						
Consciousness impairment	10 (67 %)	NR	39 (26 %)	10 (13 %)	34 (94 %)	76 (90 %)
Seizure activity	11 (73 %)	NR	97 (71 %)	58 (76 %)	33 (92 %)	56 (70 %)
Headaches	8 (53 %)	NR	39 (26 %)	3 (4 %)	19 (53 %)	26 (31 %)
Visual abnormalities	10 (67 %)	NR	39 (26 %)	3 (4 %)	13 (36 %)	24 (29 %)
Nausea/vomiting	8 (53 %)	NR	39 (26 %)	NR	NR	NR
Focal neurological signs	NR	NR	NR	2 (3 %)	1 (3 %)	14 (17 %)
Acute hypertension	12 (80 %)	NR	91 (67 %)	NR	NR	62 (78 %)
Radiological Features of PRES						
Bilateral	15 (100 %)	11 (69 %)	> 98 (> 72 %)	NR	36 (100 %)	NR
Asymmetric	10 (67 %)	NR	21 (15 %)	2 (3 %)	NR	NR
Confluent	NR	2 (13 %)	31 (23 %)	44 (58 %)	2 (13 %)	12 (16 %)
Gray matter	4 (27 %)	NR	NR	22 (29 %)	16 (44 %)	NR
Posterior > anterior	14 (93 %)	15 (94 %)	30 (22 %)	NR	NR	NR
Occipital	14 (93 %)	NR	134 (99 %)	75 (99 %)	NR	NR
Parietal	13 (87 %)	8 (50 %)	134 (99 %)	75 (99 %)	NR	50 (67 %)
Frontal	7 (47 %)	14 (88 %)	93 (68 %)	60 (89 %)	22 (61 %)	61 (81 %)
Temporal	9 (60 %)	16 (100 %)	55 (40 %)	52 (68 %)	NR	62 (83 %)
Brainstem	2 (13 %)	NR	17 (13 %)	14 (18 %)	21 (58 %)	NR
Cerebellum	1 (7 %)	NR	41 (30 %)	26 (34 %)	21 (58 %)	NR
Basal ganglia	1 (7 %)	3 (19 %)	19 (14 %)	9 (12 %)	NR	NR

NR: None reported

ongoing continuous seizure activity for at least 5 minutes (continuous) or as more than two motor seizures without full recovery of consciousness in the interval (intermittent), has been described in 3 % [7] to 13 % [10] of patients. Visual abnormalities were found in 26 % [11] to 67 % [3] of patients and consisted of blurred vision (7 % [3]-18 % [8]), visual neglect (4 % [8]-27 % [3]), homonymous hemianopsia (4 % [8]-20 % [3]), visual hallucinations (3 % [7]-5 % [8]), and cortical blindness (8 % [8]-33 % [3]). Headaches and nausea/vomiting were reported in 26 % [11] to 53 % [3] of patients. Focal neurological signs were either not mentioned at all or reported in only 3 % [7, 14] to 17 % [8] of cases.

A frequently associated sign: Acute hypertension

Acute hypertension is not usually described among the main signs of PRES. However, hypertension has been reported in most studies [3-5, 7, 8, 11, 12], in 67 % [11] to 80 % [3] of patients. In one study, mean systolic blood pressure reached 187 (80-240) mm Hg [7]. It is worth noting that mean blood pressure defined as $[\text{systolic blood pressure} + 2(\text{diastolic blood pressure})/3]$ reflects cerebral autoregulation of blood flow. Acute hypertensive emergency was not significantly associated with the intensity of the clinical or radiological manifestations of PRES [11]. Therefore, high mean blood pressure is often observed in PRES but its level is not correlated to the severity of PRES.

Radiological Characteristics of PRES

The topographic distribution of radiological features reported in cohort studies is given in [Table 1](#) [3, 6-8, 11, 14].

The four radiological patterns of PRES [11]

Until recently, PRES was believed to consistently produce bilateral and symmetric regions of edema typically located in the white matter and predominating in the posterior parietal and occipital lobes. Occasionally, edema has been described in the frontal lobes, temporal, basal ganglia or cerebellum and brainstem in the posterior fossa, and cortical gray matter.

In a study of 136 patients, however, this pattern was found in only 26 % of cases [11]: Three radiological patterns were found in 99 patients, and incomplete forms of these three patterns in the remaining 37 patients ([Fig. 2](#)):

a. Holohemispheric watershed pattern (23 %) ([Fig. 2a](#))

A swath of confluent vasogenic edema extends through the frontal, parietal, and occipital lobes. Involvement of the temporal lobes is less marked. This topography matches the watershed zone between the anterior and posterior cerebral arteries, on the one hand, and the middle cerebral artery, on the other.

b. Superior frontal sulcus pattern (27 %) ([Figure 2b](#))

Patchy edema predominates in the frontal lobes along the superior frontal sulci. The parietal and occipital lobes are variably involved.

c. Dominant parietal-occipital pattern (22 %) ([Fig. 2c](#))

In this pattern previously thought to be typical of PRES, the posterior part of the parietal and occipital lobes is predominantly involved. The edema varies in severity from mild to extensive.

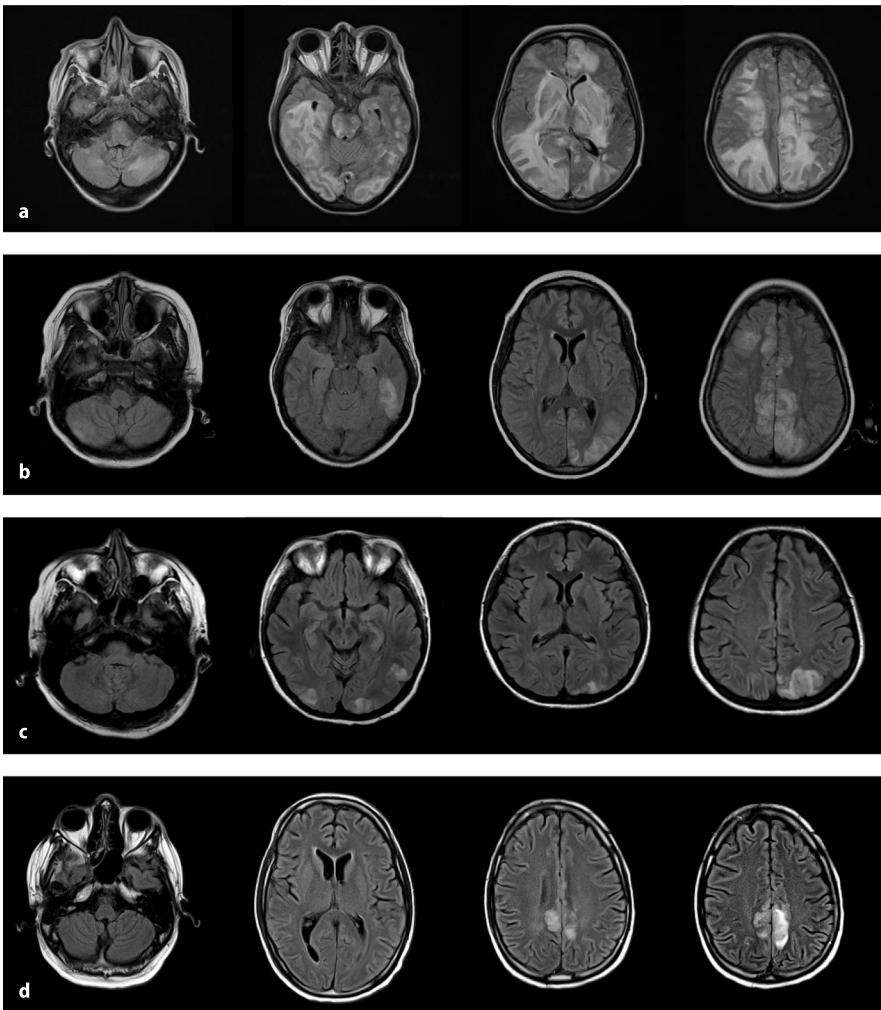


Fig. 2. Four main magnetic resonance imaging patterns of posterior reversible encephalopathy syndrome (PRES).

2a. Holo-hemispheric watershed pattern. Fluid-attenuated inversion recovery (FLAIR) sequences showing bilateral vasogenic edema in a linear pattern involving the white matter of the cerebellum, brainstem, and occipital, parietal, frontal, and temporal lobes. This pattern was found in 23 % of patients.

2b. Superior frontal sulcus pattern. Fluid-attenuated inversion recovery (FLAIR) sequences showing bilateral vasogenic edema in a non-confluent pattern involving the frontal sulcus area and, to a lesser degree, the white matter of the parietal, occipital, and temporal lobes. This pattern was found in 27 % of patients.

2c. Dominant parietal-occipital pattern. Fluid-attenuated inversion recovery (FLAIR) sequences showing bilateral vasogenic edema in the white matter of the occipital and parietal lobes. This so-called 'classic' pattern was found in 22 % of patients.

2d. Partial expression of the three primary patterns. Fluid-attenuated inversion recovery (FLAIR) sequences showing bilateral vasogenic edema in the white matter of the parietal and frontal lobes but not in the occipital lobes. This pattern can also be asymmetric. Partial and/or asymmetric forms of the three primary patterns were found in 28 % of patients.

d. Partial or asymmetric expression of the primary patterns (28 %) (Fig. 2d)

The partial form is defined as bilateral absence of edema in either the parietal or the occipital lobes. The frontal lobes are often involved. The asymmetric form is characterized by unilateral absence of edema in either a parietal or an occipital lobe. Finally, in the partial and asymmetric form, there is both absence of involvement of either the parietal or the occipital lobes and asymmetric abnormalities in the affected parietal or occipital lobes.

Roles for computed tomography and magnetic resonance imaging in the diagnosis of PRES

- Computed tomography (CT): In retrospective reviews, CT scans were available for review in 65 % [11] to 100 % [7] of cases. CT findings are often normal or nonspecific [11]. Hypodensities in a suggestive topographic distribution suggest PRES (Fig. 3).
- MRI: Cerebral MRI is the key investigation for the diagnosis of PRES. Proton-density and T2-weighted images show regions of high signal indicating edema. Fluid-attenuated inversion recovery (FLAIR) sequences also visualize the lesions. The use of FLAIR has been shown to improve the diagnosis of PRES and the detection of subcortical and cortical lesions in PRES [6]. T1-weighted images show low-intensity foci. Diffusion-weighted imaging (DWI) is normal but the apparent diffusion coefficient is increased [13]. Finally, enhancement is seen in about half the cases [11].

MRI is superior to CT for the diagnosis of PRES. Of 67 patients who had both CT and MRI at least 2 days after the clinical onset of PRES [11], 22 had both investigations on the same day and of these, only 7 (32 %) had contributive CT findings. Interestingly, the proportion of patients with contributive CT findings was 74 % on day 2, suggesting that repeated CT scanning may be helpful when MRI is unavailable. MRI has been performed in 84 % [11] to 100 % [7] of patients with PRES and both MRI and CT in 49 % [11] to 87 % [6].

Complications diagnosed radiologically at presentation of PRES

- Cerebral ischemia: Cerebral infarction is seen as high DWI signal intensity with a decrease in the apparent diffusion coefficient below 20 %. Cerebral infarction is among the early signs of non-reversible damage associated with adverse outcomes [13]. This complication was present at the acute phase of PRES in 9 (10 %) of the 82 patients with available DWI in one study [11] and in 5 (23 %) of 22 patients in another [13]. In this setting, every effort must be taken to exclude a reversible cerebral vasoconstriction syndrome defined as at least two narrowings per artery on two different cerebral arteries at brain magnetic resonance angiography (MRA) or at conventional angiography [15]. Ducros et al. reported a 9 % incidence of PRES in reversible cerebral vasoconstriction syndrome [15].
- Cerebral hemorrhage: Cerebral hemorrhage is uncommon in PRES (5 % [7] to 17 % [14] of patients). Reported cases were about evenly distributed in three categories, parenchymal hematoma, subarachnoid hemorrhage, and focal intraparenchymal hemorrhage measuring less than 5 mm in diameter [14, 16]. Cerebral hemorrhage may be more common among patients with allogeneic bone marrow transplantation or anticoagulant treatment, whereas

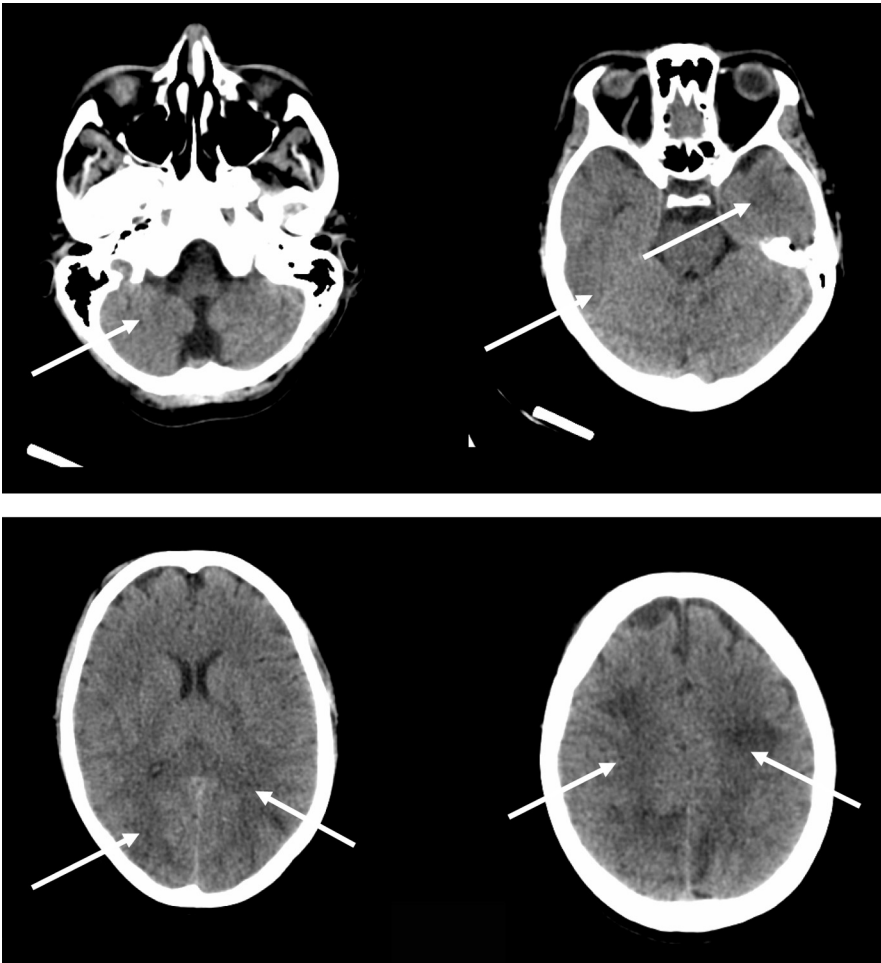


Fig. 3. Cerebral computed tomography in a patient with occipital, parietal, frontal, and temporal abnormalities suggesting posterior reversible encephalopathy syndrome (PRES). Several low-density areas are visible in the occipital, parietal, frontal and temporal lobes (white arrows).

blood pressure levels may have no influence on the bleeding risk [16]. A statistically significant association has been reported between edema severity on FLAIR sequences and bleeding risk [14].

In the presence of cerebral or subarachnoid hemorrhage, vascular imaging must rule out cerebral aneurysm and reversible cerebral vasoconstriction syndrome.

- Cerebral herniation: Posterior edema, particularly when located in the cerebellum and brainstem, may cause transtentorial cerebral herniation [17].

Retrospective Diagnosis of PRES after Regression of the Initial Clinical and Radiological Abnormalities

In some cases, the diagnosis of PRES remains in doubt. In this situation, regression of the clinical and radiological abnormalities with appropriate treatment supports the diagnosis. Thus, repeated brain imaging is helpful.

Differential Diagnosis

The non-specific clinical manifestations and multiplicity of radiological patterns raise diagnostic challenges. Many conditions may resemble PRES, including ictal or post-ictal state (with or without status epilepticus), progressive multifocal leukoencephalopathy (PML), severe leukoaraiosis, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), infectious encephalitis, acute disseminated encephalomyelitis, mitochondrial myopathy encephalopathy lactic acidosis and stroke-like episodes syndrome (MELAS), vasculitis, Creutzfeldt-Jakob disease, cerebral venous sinus thrombosis, and ischemic stroke (watershed or posterior cerebral artery territory) [18, 19]. The MRI characteristics of these conditions are reported in [Table 2](#).

Pathophysiology

The pathophysiology of PRES remains controversial. The two main hypotheses contradict each other. One involves impaired cerebral autoregulation responsible for an increase in cerebral blood flow (CBF), whereas the other involves endothelial dysfunction with cerebral hypoperfusion. This hypoperfusion hypothesis may be most relevant to cases of PRES associated with cytotoxic therapy. Under both hypotheses, the result of the cerebral blood perfusion abnormalities is blood-brain barrier dysfunction with cerebral vasogenic edema [2] ([Fig. 4](#)).

Cerebral Hyperperfusion Results in Vasogenic Edema by Exceeding the Capacity for Autoregulation of Perfusion Pressure

When mean arterial blood pressure (MAP) is within the 60–120 mmHg range, cerebral autoregulation via variations in vasoconstriction and vasodilatation keeps the CBF at about 50 ml/100 g/min in healthy individuals. To overcome this autoregulation mechanism, MAP must exceed 170 mmHg (systolic/diastolic blood pressure of 220/110 mmHg). However, a smaller MAP increase of only 50 mm Hg (systolic/diastolic blood pressure of 160/100 mmHg) in a patient with *de novo* hypertension is sufficient to trigger severe vasoconstriction [31].

Cerebral hyperperfusion leads to the release of the vasodilators nitric oxide (NO) and prostacyclin under the influence of endothelial agonists such as acetylcholine, norepinephrine, and substance P. Concomitantly, there is overproduction of catecholamines, vasopressin, thromboxane, and endothelin 1. These substances increase vasoreactivity and activate the renin-angiotensin-aldosterone system. Angiotensin II activates the gene expression of pro-inflammatory cytokines such as interleukin (IL)-6 and the transcription of nuclear factor-kappa B (NF- κ B), leading to direct cytotoxic effects on the blood vessel wall. This damage to the

Table 2. Differential diagnosis of cerebral magnetic resonance imaging (MRI) findings in patients with white matter abnormalities mimicking posterior reversible encephalopathy syndrome (PRES)

	T1	T2	FLAIR	DWI	ADC	Gd	GMD/WMD	Other characteristics
PRES [1–5, 11]	↓	↑	↑	↑ or →	↓ or →	0 or +	WMD >>> GMD	Typically bilateral and symmetric; located in the white matter of the posterior parietal-occipital lobes; but also involves the frontal lobes, temporal posterior fossa, or brainstem
Ictal/Post-ictal state [20]	↓	↑	↑	↑	↓	+	GMD >>> WMD	Theoretically, complete resolution of MRI changes in the area involved in the seizure activity
Progressive multifocal leukoencephalopathy (PML) [21]	↓	↑	↑	↑ (newer or active lesion) ↓ (older lesion)	↓ (newer or active lesion) ↑ (older lesion)	0 or +	WMD + cortical GMD – WMD junction (U fibers)	Multifocal lesions
Severe leukoaraiosis [22]	↓	↑	↑	↑	↑	0	WMD	Diffuse, confluent white matter abnormality around the frontal horn and/or the posterior part of the lateral ventricles (parieto-occipital) and in the centrum semiovale
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [23]	↓	↑	↑	↑	↓	0	WMD	Symmetric involvement of white matter and basal ganglia, dilated perivascular spaces
Infectious encephalitis [24]	↓	↑	↑	↑ or →	↓ or →	+	WMD and/or GMD	Depend on the stage of the disease and type of microorganism
Acute disseminated encephalomyelitis (ADEM) [25]	↓ or →	↑	↑	→	↑	+	WMD	Asymmetric multifocal lesions of less than 5 cm, confluent multifocal lesions of more than 5 cm, and multifocal lesions involving the basal ganglia

Table 2. (continued)

	T1	T2	FLAIR	DWI	ADC	Gd	GMD/WMD	Other characteristics
Mitochondrial myopathy encephalopathy lactacidosis and stroke-like episodes syndrome (MELAS) [26]	↑	↓	↓	→ or ↓	→ or ↑	0 or +	WMD + GMD	Lesions in parieto-occipital regions and cortex of the cerebrum, cerebellum, and adjacent white matter
CNS vasculitis [27]	↓	↑	↑	↓	↑	+	WMD + GMD	Depend on the underlying disease. Usefulness of brain perfusion MRI.
Creutzfeldt-Jakob disease [28]	→	↑	↑	↑	↓	0	GMD	Lesions of basal ganglia, caudate nucleus, striatum, and/or thalamus
Cerebral venous sinus thrombosis [29]	↑	↑	↑	↑ or → or ↓ depends on association with cerebral ischemia	↑ or ↓ depends on association with cerebral ischemia	0	GMD +/- WMD	Venous thrombus is seen on T2 echogradient as hypoT2 in the first day and as hyperT2 and hyperT1 signal in venous sinus between day 3 and day 30
Acute ischemic stroke (1–7 days) [30]	↓	↑	↑	↑	↓	0	WMD + GMD	
Subacute ischemic stroke (1–4 weeks) [30]	↓	↑	↑	↑ or →	↑	+	WMD + GMD	
Old ischemic stroke (> 1 month) [30]	↓	↑	↑	↑ or →	↑	0	WMD + GMD	

T1: T1-weighted imaging; T2: T2-weighted imaging; FLAIR: fluid attenuated inversion recovery; DWI: diffusion-weighted imaging; Gd: gadolinium enhancement; GMD: gray matter disease; WMD: white matter disease; CNS: central nervous system; →: isosignal; ↑: hypersignal; ↓: hyposignal

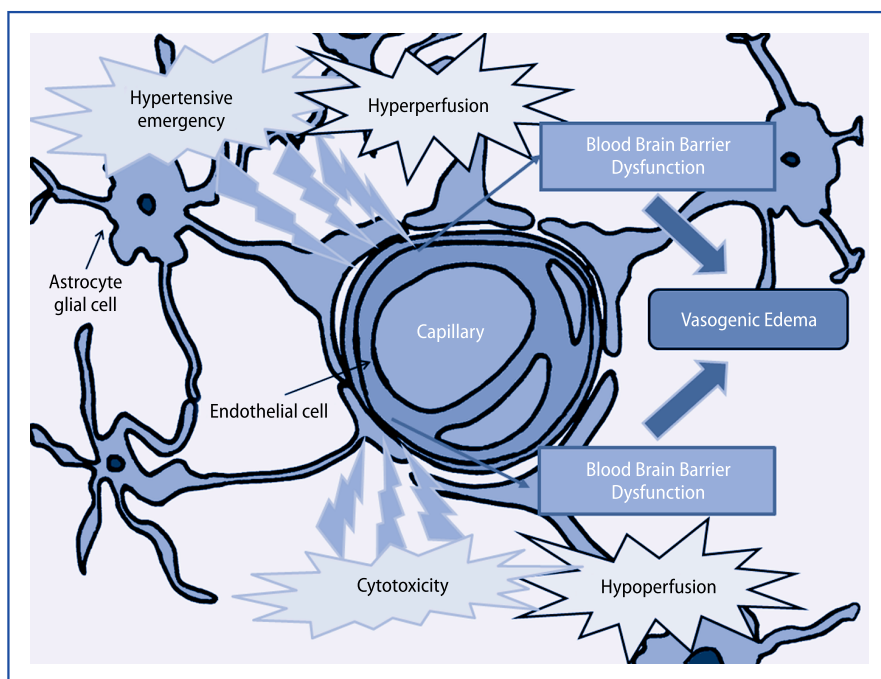


Fig. 4. This figure shows the two main hypotheses of posterior reversible encephalopathy syndrome (PRES) pathophysiology. One involves impaired cerebral autoregulation responsible for cerebral hyperperfusion and blood brain barrier dysfunction. The other is related to cytotoxicity and involves endothelial dysfunction, blood brain barrier alteration and cerebral hypoperfusion. Under both hypotheses, the result of the cerebral blood perfusion abnormalities is cerebral vasogenic edema.

vascular endothelium causes blood-brain barrier dysfunction and cerebral vasogenic edema [31].

Data supporting the hyperperfusion hypothesis have been reported. Thus, irrespective of the cause of PRES, hypertension is a feature in 67 % [11] to 80 % [3] of cases. In addition, a study involving single photon emission CT (SPECT) 99mTc-HMPAO imaging showed regional hyperperfusion in the occipital lobe and cerebellum [4].

Cerebral Hypoperfusion Related to Disruption of the Blood-brain Barrier Results in Vasogenic Edema

Not all patients with PRES have hypertension. In patients with PRES and normal blood pressure, cytotoxicity has been hypothesized to be the mechanism underlying the brain edema [2]. Causes of PRES without hypertension include eclampsia/preeclampsia, cyclosporine toxicity, and infection/sepsis/septic shock. The potential mechanisms vary with the cause. Immune system (T-cell) activation leads to endothelial cell activation with the release of various mediators such as histamine, free radicals, NO, bradykinin, and arachidonic acid [32]. These mediators activate the production of pro-inflammatory cytokines (e.g., tumor necrosis factor [TNF]- α , IL-1, IL-6, and interferon [IFN]- γ) [33–37]. Leukocyte trafficking

increases via the release of adhesion molecules (e.g., intercellular adhesion molecule [ICAM]-1, P-selectin, E-selectin, and cell adhesion molecule [CAM]-1) [2, 38]. Upregulation of endothelial surface antigens and the release of endothelin affect the local vascular tone [39]. All these changes result in vascular instability with vasoconstriction and downstream hypoperfusion. Blood-brain barrier dysfunction occurs, leading to vasogenic cerebral edema [2, 40].

This hypothesis is supported by studies involving catheter angiography, MRA, and MR perfusion imaging, which show cerebral hypoperfusion [41–43].

Pathophysiology of Complications of PRES: Cerebral Ischemia and Cerebral Hemorrhage

Ischemia following vasogenic edema may involve conversion to cytotoxic edema and may result from longer exposure to the initial source of toxicity [40]. However, the distinction between vasogenic and cytotoxic edema may be somewhat artificial, as both forms of edema probably co-exist in many conditions. Cytotoxic edema is defined as a pre-morbid cellular process characterized by induction of swelling of all cellular elements of the brain (neurons, glia, astrocytes, and endothelial cells) [44]. The swelling is indirectly related to ATP depletion with failure of the ATP-dependent Na^+/K^+ channel and diffusion of extracellular water according to the osmotic gradient into the intracellular sector. Cells in both the white and the gray matter are affected, and swelling is more severe in the astrocytes than in the neurons [44]. Compensatory mechanisms induce calcium overload and activation of proteases (cathepsin B, calpain, serine proteases), nucleases, and phospholipases (cytosolic Ca^{2+} -dependent phospholipase A2), leading to necrosis and apoptosis [45]. These phenomena are potentiated by mitochondrial damage related to ATP depletion [45].

Bleeding related to reperfusion injury is another potential complication of blood-brain-barrier dysfunction and cerebral edema. Oxidative stress with overproduction of reactive oxygen species (ROS) and oxidative damage to lipid membranes in the blood-brain-barrier causes vessels within ischemic foci to leak or rupture [44]. Leukocyte trafficking with endothelial cell adhesion and activation leads to proteolysis of catenin, a component of the endothelial cell-cell junction [46]. The resulting damage to microvascular endothelial cells causes edema and bleeding [44]. Proteolysis by matrix metalloproteinases and proteases secreted by activated leukocytes may cause bleeding after reperfusion injury [44].

Conditions Most Commonly Associated With PRES

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The list of conditions associated with PRES is increasing steadily.

Toxic Agents

Exposure to toxic agents is the most common condition associated with PRES, in 11 % [7] to 61 % [14] of cases. **Box 1** shows an exhaustive list of toxic agents known to be associated with PRES. This etiology has been the focus of specific studies. In a study of cyclosporine neurotoxicity in 16 patients, exposure duration at symptom onset ranged from 6 days to 5 years and the plasma cyclosporine levels were within the therapeutic range at diagnosis [5]. All patients had hypertension. Symptomatic treatment and cyclosporine withdrawal was followed by a full

Box 1. List of toxic agents known to be associated with posterior reversible encephalopathy syndrome (PRES)

Cancer chemotherapy agents (in combination) [8, 12, 14]
Cytotoxic agents
 Alkylating agents
 Cisplatin [48]
 Oxaliplatin [49]
 Carboplatin [50]
 Anti-metabolites
 Gemcitabine [48]
 Cytarabine [51]
 Methotrexate [52]
 Mitotic inhibitors
 Vincristine [53]
 Irinotecan hydrochloride [54]
 Others
 L-asparaginase [14]
Anti-angiogenic agents
 Bevacizumab [54]
 Sunitinib [55]
 RAF kinase inhibitor BAY 43–9006 [56]
Immunomodulatory cytokines
 Interferon-alpha [3, 57]
 Interleukin-2 [58]
Monoclonal antibodies
 Rituximab (anti-CD20) [59]
 Infliximab (anti-TNF- α) [60]
Intravenous immunoglobulins [61]
Anti-TNF- α protein
 Etanercept [62]
Anti-lymphocyte globulin [63]
Immunosuppressive agents
 Anticalcineurin agents [8]
 Cyclosporine A [3, 5, 10, 12, 14]
 Tacrolimus (FK 506) [3, 12, 14]
 Sirolimus [64]
 High-dose corticosteroid therapy (e.g., dexamethasone and methylprednisolone) [14]
Blood transfusion [65]
Other agents
 Granulocyte-stimulating factor [66]
 Antiretroviral agents [67]
 Linezolid [68]
 Erythropoietin [69]
 Cocaine [14]
 Ephedra sinica (traditional Chinese remedy) [70]
 Intravenous contrast agents [14]
 Lysergic acid amide [19]
 Carbamazepine [71]
 Intravenous caffeine [72]

TNF: tumor necrosis factor

recovery in 14 patients. One patient with an occipital lobe hemorrhage had permanent visual field impairment and another had severe bleeding with transtentorial herniation and died shortly after diagnosis.

Transplantation patients are at risk for PRES, as they are exposed to cancer chemotherapy and/or immunosuppressive therapy. PRES has been reported after bone marrow or stem cell transplantation and after solid organ transplantation. In a study of 27 patients with PRES after liver or kidney transplantation, the time from transplantation to PRES diagnosis was 2 months in liver transplant recipients and 1 year in kidney transplant recipients [47]. Common concomitants of PRES were cytomegalovirus or bacterial infection and moderately severe transplant rejection. Hypertension was a feature and was more severe in the kidney transplant group than in the liver transplant group.

Hypertension

Hypertension is the second most common condition associated with PRES, being present in 6 % [12] to 72 % [7] of cases. The first case-series, published in 1992, had 14 patients, all of whom recovered fully within 2 weeks after blood pressure control was achieved [4]. The main cause of hypertension was acute or chronic kidney failure. Cases associated with hypertension due to autoimmune disease or toxic exposures have been reported [19].

Infection/Sepsis/Septic Shock

Infections have been reported in 8 % [14] to 24 % of cases [12]. The most common situation was PRES onset within 2 weeks after a Gram-positive bloodstream infection, often with hypertension at diagnosis [12]. PRES has also been reported in patients with *Escherichia coli* bloodstream infection [73].

Preeclampsia/Eclampsia

Pre-eclampsia/eclampsia [3, 7, 8, 12, 14, 74] was present in 7 % [14] to 20 % [3] of patients with PRES. The outcome was usually favorable. Hypertension was a prominent feature at presentation. PRES onset occurred from 28 weeks' gestational age [74] to day 13 postpartum [3].

Autoimmune Disease

Autoimmune disease has been encountered in 8 % [14] to 10 % [12] of cases. PRES has been reported in patients with systemic lupus erythematosus [75, 76], systemic sclerosis [76], polyarteritis nodosa [77], Wegener's granulomatosis [78], thrombotic microangiopathy [79], polyangiitis [80], Takayasu arteritis [81], Hashimoto encephalopathy [82], and Crohn's disease [83].

Other Conditions

There are myriad conditions associated with PRES, sometimes only anecdotally. They include sickle cell disease [12], Guillain-Barré syndrome [84], hypomagnesemia [3], hypercalcemia [85], tumor lysis syndrome [86], porphyria [87], pheochromocytoma [88], and Cushing syndrome [89].

Outcomes

As indicated by the name of this syndrome, appropriate treatment is expected to ensure a full recovery. However, permanent complications and fatal cases have been reported, leading some authors to suggest that a better name may be “potentially reversible encephalopathy syndrome” [90]. Clinical findings returned to baseline in 35 % [8] to 100 % [3] of patients. Radiological recovery is more difficult to document, as all published studies were retrospective and repeated brain imaging was performed in only 44 % [8] to 87 % [11] of cases. Among patients with follow-up imaging studies, 49 % [6] to 75 % [3] had resolution of the initial abnormalities within 5 days [7] to 17 months [3]. Permanent neurological abnormalities are related to ischemia and/or bleeding. Recurrences have been reported in 6 % of cases [8].

Limited data are available on functional outcomes. In one study, the median modified Rankin Scale score was 2.5 at discharge, indicating mild-to-moderate disability [8]. Mild disability is defined as being capable of handling one’s own affairs without help but not of carrying out all previous activities; and moderate disability is defined as requiring help for some activities but being able to walk unassisted.

Death has been reported in up to 15 % [7, 8] of patients. However, the relative contributions of PRES and of associated factors to the fatal outcomes are unclear.

Management of PRES

PRES must be diagnosed early and investigations must be performed to identify the causative factors. Symptomatic treatment should be given immediately and the causative factors corrected without delay. ICU admission and life-supporting treatments may be required [9, 10].

Diagnostic Strategy

The diagnostic strategy for PRES is fairly well standardized (**Fig. 5**). After a careful history and thorough physical examination, investigations should be performed as appropriate, starting with the simplest and moving to the more sophisticated.

CT may be easier to obtain first. However, MRI must be performed, either as the first or as the second imaging study. MRI is considerably better than CT for the diagnosis of PRES and can provide information regarding many of the causes of PRES [1–3, 6, 7, 11, 13]. MRA must be added to MRI to identify an associated cerebral reversible vasoconstriction syndrome.

Electroencephalography (EEG) should be performed routinely to look for non-convulsive status epilepticus. Patients most likely to have non-convulsive status epilepticus are those in a deep coma or prolonged post-ictal state [10]. Lumbar puncture findings are not specific in PRES [7]. However, the cerebrospinal fluid (CSF) must be examined in patients with a fever or clinical suspicion of meningitis and when deemed appropriate by the attending physicians. Laboratory tests should be obtained routinely. Plasma anticonvulsant drug assays (including magnesium dosage) and qualitative tests for toxic agents or medications associated with seizures and other symptoms of PRES should be performed at the discretion of the attending physicians.

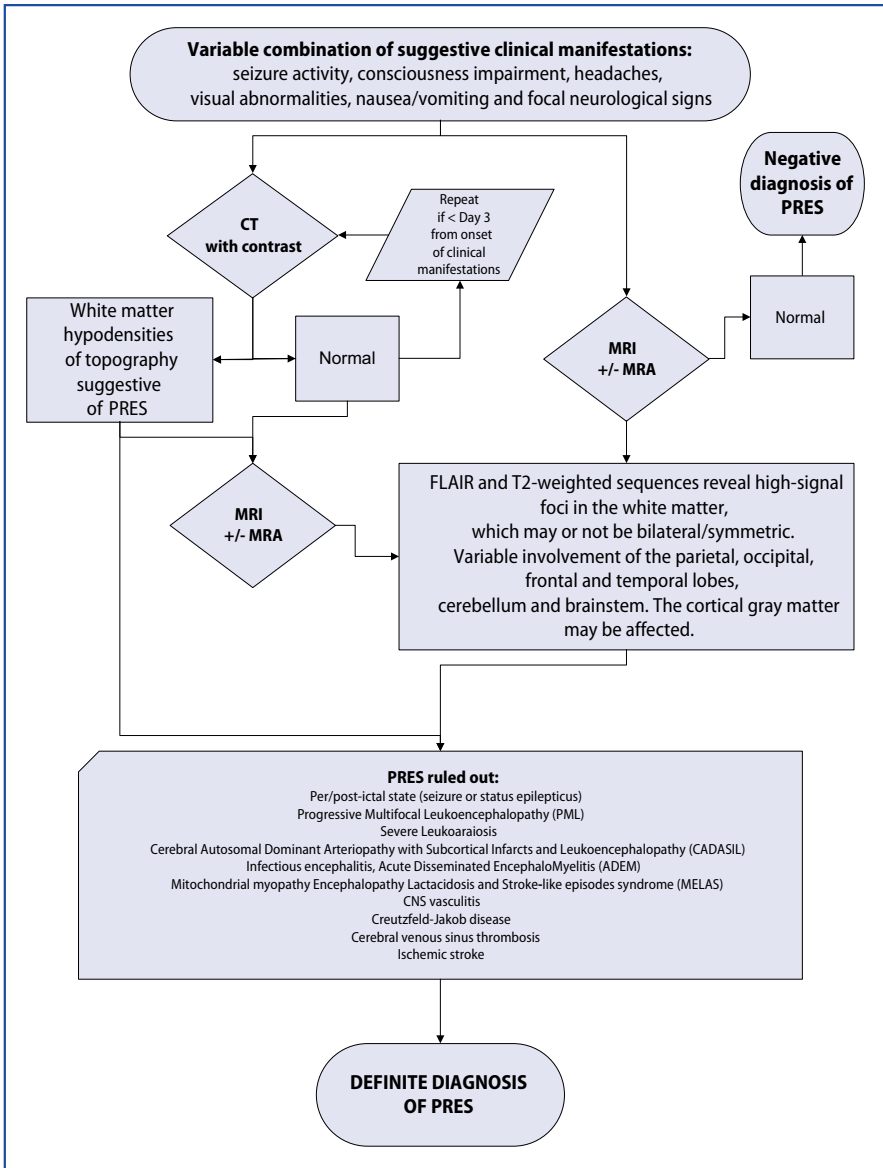


Fig. 5. Diagnostic strategy for posterior reversible encephalopathy syndrome (PRES). MRI: magnetic resonance imagery; MRA: magnetic resonance angiography; CT: computed tomography

A neurosurgical biopsy should be performed in patients who fail to respond to appropriate treatment and whose cerebral imaging studies show focal lesions of unknown or doubtful nature. Brain biopsy may show non-specific white matter changes consistent with vasogenic edema (activated astrocytes, scattered macrophages, and rare lymphocytes). Findings at a later stage include demyelination and anoxic neuronal alterations, sometimes with bleeding in the white and gray matter [91].

Treatment

The treatment strategy associates general measures with correction of the underlying cause of PRES (Fig. 6).

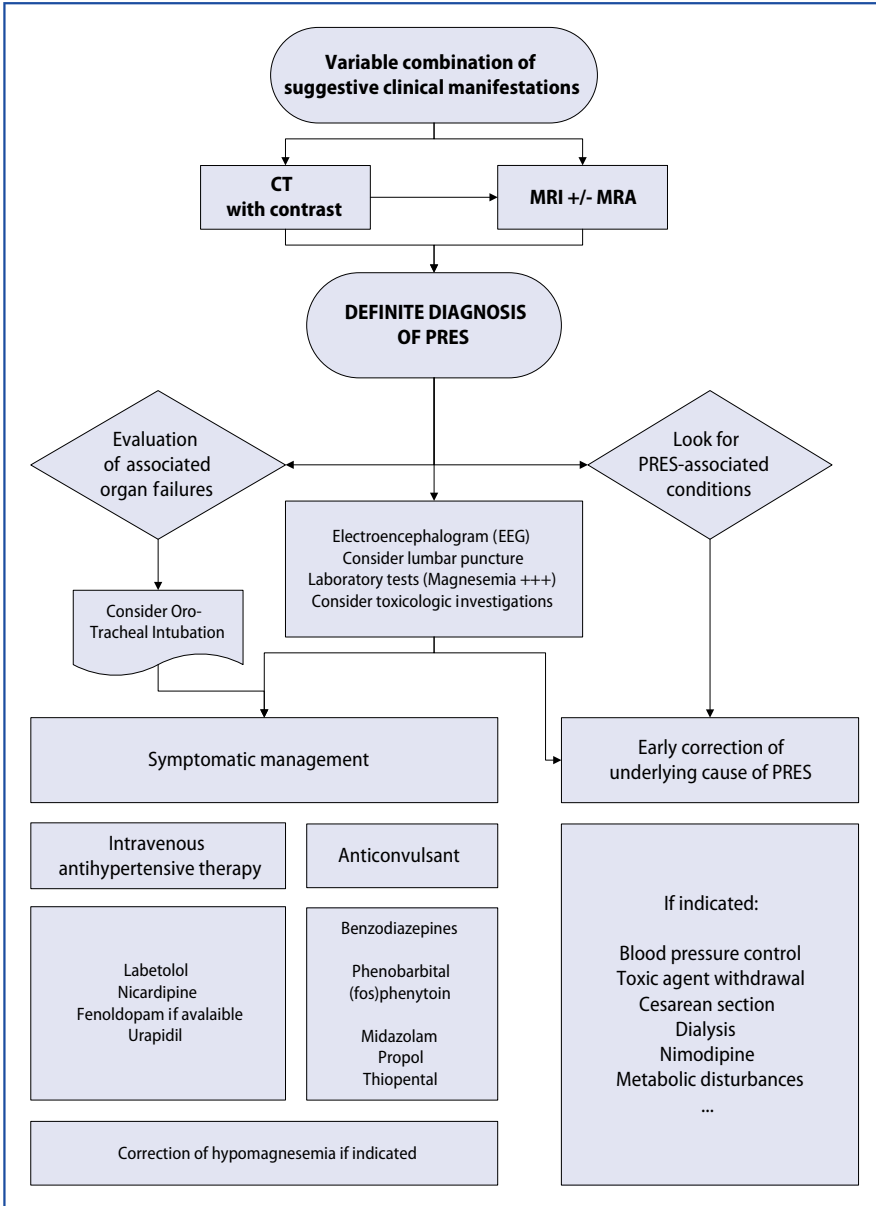


Fig. 6. Treatment of posterior reversible encephalopathy syndrome (PRES). MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; CT: computed tomography

General measures

Patients with PRES require the symptomatic measures usually taken in the ICU. Although most patients have stable hemodynamics, catecholamines are required occasionally. The need for upper airway protection should be evaluated continuously in patients with marked consciousness impairment or seizure activity. If endotracheal intubation is performed, rapid-sequence induction with etomidate and succinylcholine can be used, provided there is no evidence of hyperkalemia. Propofol or thiopental are also good choices, since they have anticonvulsant effects. Neuromuscular blocking agents may transiently mask seizures.

Hypoglycemia should be looked for routinely and corrected. If glucose is given, 100 mg of thiamine should be administered concomitantly, most notably when there is evidence of vitamin B1 deficiency. Patients should be routinely evaluated for hyperthermia and metabolic disturbances, in particular hypomagnesemia, which require prompt correction. Aspiration pneumonia may complicate the initial consciousness disorders.

Antiepileptic treatment, appropriate for the electrical and clinical pattern in the patient, should be initiated on an emergency basis and according to current guidelines. Patients with persistent seizure activity at ICU admission should be given intravenous benzodiazepines (clonazepam 1 mg or diazepam 10 mg) either before ICU admission or in the ICU. The dose can be repeated up to three times if necessary. Patients with continuing seizure activity despite intravenous benzodiazepines should receive standard complementary intravenous anticonvulsant drugs (phenobarbital 10 to 15 mg/kg, phenytoin 18 mg/kg, or equivalent dose of fosphenytoin). Patients with refractory status epilepticus need midazolam, propofol, or thiopental in titrated doses until remission of the clinical seizure activity. When the EEG reveals electrical status epilepticus, these anesthetic drugs are given in titrated doses to induce EEG burst suppression then as a continuous infusion for at least 12 hours [92].

Control of hypertensive emergency, if present, is an important part of the symptomatic management. The aim is not to normalize the blood pressure but rather to decrease the MAP by 20–25 % within the first 2 hours and to bring the blood pressure down to 160/100 mmHg within the first 6 hours [31, 93]. More rapid blood pressure reduction is not recommended since it can aggravate the cerebral perfusion pressure alterations and promote ischemia [94]. Intravenous antihypertensive drugs are necessary. Appropriate choices include labetalol, nicardipine, or fenoldopam if available [31, 94]. Urapidil has been suggested as a second-line agent, perhaps in combination with another agent [95].

Correction of the underlying cause of PRES

An early etiologic diagnosis allows prompt correction of the cause of PRES. Patients may require blood pressure control, withdrawal of cancer chemotherapy or immunosuppressive agents, Cesarean section, dialysis, or other interventions. Prompt correction of the cause is crucial to decrease the risk of ischemia or bleeding and therefore to avoid permanent disability or death [3].

Conclusion

This review highlights recent advances in the diagnosis, pathophysiological understanding, and management of PRES. Although the clinical presentation is

non-specific, most patients have a suggestive combination of symptoms. MRI is crucial for diagnosing PRES, monitoring the course, and assessing treatment effectiveness. MRA performed during MRI can be useful to identify associated cerebral vasoconstriction. Repeated cerebral imaging helps to support the diagnosis and identifies complications potentially responsible for permanent impairments. The pathophysiology of PRES remains controversial. However, the list of conditions known to be associated with PRES is increasing steadily. Early recognition and resolution of the underlying cause is the keystone of management. Persistence of the cause carries a risk of ischemia, bleeding, and death. Finally, studies are needed to identify factors of adverse prognostic significance and to develop neuroprotective strategies.

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