Review Article

Posterior reversible encephalopathy syndrome: A review with emphasis on neuroimaging characteristics

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ABSTRACT

Posterior reversible encephalopathy syndrome (PRES) is a clinical and radiological condition that involves the acute onset of headache, confusion, optical impairments, and seizures with accompanying vasogenic edema on brain imaging. PRES is a complex disorder with many causative factors, including underlying conditions such as hypertensive encephalopathy, eclampsia, collagen disease, and severe infection. Although the exact pathophysiological mechanism is not completely understood and remains controversial, the predominant proposed mechanism is endothelial dysfunction, which is preceded by hypertension, immunosuppressive agents, or cytotoxic medication. Magnetic resonance imaging (MRI) facilitates prompt diagnosis and treatment and leads to good outcomes. Findings are characterized by the following: hyperintensity on fluid-attenuated inversion recovery images and apparent diffusion coefficient mapping, and isointensity on diffusion weighted images involving the parieto-occipital or posterior frontal cortical–subcortical regions that are recognized in >90% of patients, and reversibility of neuroimaging abnormalities, with the latter being the most important. As an algorithm to standardize the diagnosis of PRES has not yet been developed, this review presents a diagnostic algorithm based on the types of MRI findings. This algorithm may provide a better understanding of the characteristics that compose PRES and bring us one step closer to the standardization of PRES diagnosis, helping clinicians evaluate individual features while also considering competing differential diagnoses.

1. Introduction

Over two decades have passed since posterior reversible encephalopathy syndrome (PRES) was first described in 1996 [1]. PRES is a neurological condition characterized by the acute onset of signs and symptoms that include seizures, disturbances to consciousness, headache, optical impairments and by neuroimaging findings of reversible subcortical vasogenic edema. Increasing use of brain magnetic resonance imaging (MRI) over the past two decades has led to the increased recognition of PRES, and clinicians in various fields encounter patients with PRES. The pathophysiology of PRES is not completely understood and remains controversial [2]. PRES is generally considered to be both radiologically and clinically reversible and typically has a good prognosis. However, diffuse edema or hemorrhage may cause complications or long-term neurological deficits, making accurate diagnosis of PRES essential for rapid and appropriate treatment to improve patient results and minimize complications. Therefore, it is necessary to investigate the imaging findings, clinical signs, and biochemical parameters of PRES to further predict prognosis. As there are currently no standard guidelines or diagnostic criteria for PRES, a diagnostic algorithm would help advance the radiological and pathophysiological research of this syndrome.

This review aims to present the pathophysiological, clinical, and radiological features and diagnostic approaches of PRES, emphasizing the clinical significance of imaging findings and their utility in developing a diagnostic algorithm.

2. Etiology and pathophysiological hypothesis

There are several comorbid conditions that may accompany PRES, including hypertension (53% of reported clinical cases), kidney disease (45%), malignancy (32%), dialysis dependency (21%), and transplantation (24%) [3,4]. The various factors that can cause PRES are presented in Table 1. Underlying conditions include hypertensive encephalopathy, eclampsia, collagen disease, and severe infection, and hemolytic uremic syndrome and thrombotic thrombocytopenic purpura are important contributing diseases. Certain drugs, including immunosuppressives, anticancer drugs, and antivirals, can be causative agents. Furthermore, it is necessary to consider certain medical histories, such as blood stem cell transfusion, rich erythrocyte transfusion,
cytokine administration (including erythropoietin), trauma, surgery, and angiography.

There are three main theories as to the pathophysiology of PRES. The first, the “breakthrough” theory, proposes a rapid increase in arterial blood pressure to a hypertensive crisis or emergency, which has been recognized at the onset of PRES in most patients [2]. The second is the “vasospasm theory,” which hypothesizes that neurological symptoms develop because of cerebral ischemia associated with vasospasm. The third theory is that PRES is caused by endothelial dysfunction due to circulating endogenous or exogenous toxins [5,7].

Compatible with this “toxic” theory, PRES is often recognized in patients with eclampsia or sepsis or during treatment with immunosuppressive drugs or cytotoxic medication [8–10]. The common factor is the existence of an endogenic toxin, triggered by eclampsia or sepsis, or an exogenic toxin, triggered by chemotherapy or immunosuppressive drugs. Furthermore, these toxins may induce endothelial dysfunction [11]. This toxic theory is one of systemic toxicity, perhaps with increased leukocyte trafficking that results in endothelial dysfunction. Hypoperfusion and vasoconstriction may lead to hypoxia with upregulation of vascular endothelial growth factor (VEGF); consequently, endothelial permeability increases. This process may be modulated by changes in blood pressure, with increased autoregulatory vasoconstriction and increasing blood pressure. A variation on the toxic theory is that the inducing factor is the excessive release of proinflammatory cytokines that lead to endothelial activation, release of vasoactive agents, increased vascular permeability, and edema. This mechanism may be considered the most relevant in PRES patients with autoimmune disorders or sepsis. Factors that lead to PRES cause activation of the immune system and release of cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1). These cytokines induce expression of adhesion molecules (intercellular adhesion molecule 1 and vascular cell adhesion molecule 1), which interact with leukocytes and cause them to produce reactive oxygen species and proteases that cause endothelial damage and consequent fluid leakage. TNF-α and IL-1 can also induce astrocytes to produce VEGF, which weakens the tight junctions of the brain vasculature. Thus, these cascades lead to vasogenic edema (Fig. 1) [11].

The breakthrough theory hypothesizes that blood pressure increases beyond the threshold of autoregulation of cerebral blood flow and that the blood brain barrier (BBB) collapses to develop vasogenic edema; whereas, the vasospasm theory hypothesizes that neurological symptoms develop because of cerebral ischemia associated with cerebral vasospasm. Thus, the two theories contradict each other. The breakthrough theory is dominant previously, although its limitations and contradictions have been pointed out in recent years [6]. If the breakthrough theory is the major cause, development of edema should be remarkable for cases with marked blood pressure rise. However, PRES develops even in patients with normal blood pressure, and greater brain edema is observed in patients with mild to moderate elevation of blood pressure than in patients with very high blood pressure. Moreover, further evidence against this hypothesis is that approximately 30% of patients with PRES present normal or only slightly elevated blood pressure that does not necessarily exceed the normal upper autoregulatory limit, as would be expected in terms of cerebral hyperperfusion [12]. Furthermore, brain edema can develop even in the case requiring vasopressors for shock. Therefore, the pathology of PRES cannot be sufficiently explained by the breakthrough theory alone.

In the context of vasospasm and PRES, it has been debated whether spasms are merely a result of injury to the blood vessels or whether they are actively involved in the pathology. Blood pressure rises in most cases of PRES. Although the causes are unclear, it has been pointed out that vasospasm of the whole body may be involved in the blood pressure elevation. Additionally, cerebral vasospasm potentially triggers simultaneous cerebral ischemia. Under the ischemic condition, malfunction of the BBB and cerebrovascular autoregulation occur remarkably and rapidly. In particular, the collapse is striking when hypertension is induced following ischemia, and strong vasogenic edema will occur.

Based on imaging findings, vasogenic edema is considered to be the main pathological feature of PRES. Endogeneous as well as exogeneous factors damage cerebrovascular endothelial cells in PRES. Ischemia is also caused by acceleration of endothelial damage by vasospasm. When hypertension occurs because of whole-body vasospasm in response to such damage, even if slight, autoregulation of the BBB and cerebral blood flow collapse instantly, thereby leading to vasogenic edema. The reason why PRES frequently develops in association with an elevation in blood pressure is probably because blood pressure increases in conjunction with vasospasm and damage to vascular endothelial cells, including ischemia. In a recent prospective study, of 68 patients with subarachnoid hemorrhage during induced hypertension, 5 patients developed PRES; an incidence of approximately 7%, and PRES occurred most often when mean arterial pressure was raised well above baseline to levels that exceed cerebral autoregulatory thresholds (> 140YmmHg) during aggressive, induced hypertension in subarachnoid hemorrhage [13]. These findings may also suggest the vasospasm theory. Therefore, both the breakthrough and vasospasm theories seem to underly the pathological condition of PRES (Fig. 1).

Basically, PRES is a reversible pathogenesis due to vasogenic edema; however, some patients subsequently experience cerebral infarction and cerebral hemorrhage due to brain cell and endothelial cell death. It is thought that the reason the posterior region is prone to being affected is that the control of the sympathetic nervous system is weaker in the vertebrobasilar system than in the internal carotid artery system and hence is more likely to collapse.
3. The clinical features of PRES

The main clinical symptoms of PRES are headaches, convulsions, disturbances to consciousness, and optical impairments [14]. Both focal and generalized epileptic seizures are very common and have been recognized in approximately two-thirds of all patients [4,15]. Optical symptoms are thought to be caused by functional impairments of the occipital lobe. Disturbances to consciousness may appear to varying degrees. There are also manifestations of hemiplegia, ataxia, and involuntary movements. Other symptoms include vertigo, tinnitus, and hearing loss, which may present in the early stages of the syndrome. High blood pressure accompanies 50% to 70% of cases, but there are only a few malignant cases of high blood pressure, conversely PRES may be caused by below normal blood pressure and shock [8,16].

4. The neuroradiological features of PRES

MRI is used to perform neuroimaging and is more sensitive for hyperintense lesions in T2-weighted or FLAIR sequences. The typical imaging findings of PRES are most apparent as hyperintensity on FLAIR images in the parieto-occipital and posterior frontal cortical and subcortical white matter (Fig. 2); less commonly, the brainstem, basal ganglia, and cerebellum are involved. Typical imaging findings for PRES are observed in the low-density area mainly around the white matter of the occipital and parietal lobes in a computed tomography (CT) scan during the acute phase (Fig. 3E) and as low- to equi-intensity signals under T1 and high-intensity signals in enhanced T2-weighted MRI images, which become more apparent on FLAIR images. Low- to equi-intensity signals are observed on diffusion-weighted images (DWI), and high-intensity signals are seen on the apparent diffusion coefficient (ADC) maps, and these findings are thought to be principally due to vasogenic edema (Fig. 2E, F) [16]. In PRES, the parietal-occipital lobe pattern (70%) is seen on T2-weighted images and FLAIR images [14,17]. This pattern is usually bilateral but in some cases is unilateral. Frontal grooves and watershed divide pattern are sometimes observed. On the other hand, atypical imaging findings of PRES are observed as lesions in the cerebellum, brainstem, basal ganglia, and spinal cord. It is advisable to confirm the high-signal range for ADC mapping to identify the angioedema (Fig. 3C) [16], and it is highly likely that the same region is reversible (Fig. 3B, F). However, the low-signal area in ADC indicates ischemia and could lead to neurological sequelae (Table 2). The contrast effect is observed in approximately 20% of cases, but no correlation has been established with severity or prognosis [14,17]. The presence of hyperperfusion is currently being debated. Other than MRI, single-photon emission computed tomography evaluation has been reported, with hypoperfusion in lesional areas in patients with PRES [18]. Perhaps the varying causative factors of PRES play a role in the different results with regard to cerebral perfusion reported by the authors. The neurological symptoms and radiographic anomalies of PRES usually resolve within a few days to a couple of weeks following treatment, particularly in the case of patients who are diagnosed and treated promptly. However, cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage, and other irreversible cerebral impairments may appear in some cases and leave lasting nerve damage or even result in death. Caution is required as PRES is not always clinically or neuroradiologically reversible. Reversible cerebral vasoconstriction is also observed, and its correlation with the pathology of the syndrome (RCVS) is recognized. Both the clinical and radiologic findings in PRES
are largely reversible, particularly in the case of the patients that diagnosed and treated promptly [9]. The presence of factors associated with severe radiological PRES, such as hemorrhage and diffusion restriction, affect the reversibility of radiological findings and have been shown to be associated with worse clinical outcome [19].

In summary, (1) severe hypertension leads to failed autoregulation, subsequent hyperperfusion, and endothelial injury/vasogenic edema and (2) vasoconstriction and hypoperfusion lead to brain ischemia and subsequent vasogenic edema [6,20]. This is important when considering the MRI findings of PRES. Both vasogenic and cytotoxic edema show signal hyperintensity on FLAIR. However, DWI only shows markedly high density for cytotoxic edema. In addition, ADC maps only display the diffusion component and are hyperintense in PRES, in contrast to being hypointense in cytotoxic edema that causes ischemia (cerebral infraction) (Table 2). Although abnormal MRI findings are almost always located only in the occipital and parietal lobes in most patients with PRES [21], many studies have shown that “atypical” variants abound [22], and it is the constellation of imaging findings along with clinical features that suggest PRES (Fig. 3).

5. Other clinical examination features of PRES

Recently, three retrospective cohort studies investigated the spectrum of cerebrospinal fluid (CSF) parameters in patients with PRES on a relatively large scale [23–25]. In these studies, elevated CSF protein level without CSF pleocytosis, which was called “albumino-cytologic dissociation,” was recognized as a common finding in the majority of patients with PRES. The radiographic severity of vasogenic edema positively correlated with total CSF protein levels in two of the studies [24,25], which might reflect the breakdown of the BBB due to the endothelial dysfunction as part of the pathophysiology of PRES. In addition, pleocytosis was rare in these studies and was an indicator for central inflammation in only a few PRES patients, which may represent an alternative pathophysiological mechanism caused by complications such as infarction or subarachnoid hemorrhage. These results might prove useful for the differential diagnosis and treatment of PRES.

Although most patients have generalized seizures as their initial presentation or epileptiform activities on electroencephalography (EEG) during the course of the syndrome, they do not subsequently develop chronic epilepsy during long-term follow-up [26,27]. In a recent EEG study, nonconvulsive seizures and epileptiform patterns, such as periodic discharges during continuous EEG monitoring, were observed in 23 out of 37 patients (62%) with PRES, occurring mainly in the posterior regions [28]. There was a high prevalence of nonconvulsive seizures and periodic discharges in critically ill patients with PRES, and those patients had worse outcomes as measured by the Glasgow Outcome Scale. Because nonconvulsive status epilepticus may lead to the development of secondary cytotoxic edema in patients with PRES, prompt recognition and treatment are needed in such patients.

6. Approaches to diagnosing PRES

At present, there are no diagnostic criteria for PRES, and both clinical and neuroimaging findings are often not specific. Therefore, it is important to perform a thorough differential diagnosis. As mentioned above, MRI is the key diagnostic examination when a patient presents
with acute development of neurological signs and symptoms and arterial hypertension or toxic conditions. Acute hypertension is associated with most cases of PRES, but it is not necessary for the diagnosis. The most common symptoms of PRES are seizures, headache, and optical impairments. Although onset is usually sudden, symptoms may also develop over several days. An important diagnostic feature of PRES is the reversibility of the clinical and radiological findings.

Several diagnostic criteria for PRES have been proposed based on retrospective cohort studies [29–33] and include the following: (1) presentation with acute clinical symptoms, (2) presence of a known risk factor for PRES, (3) reversibility of clinical and/or radiological findings, (4) ruling out of other possible causes of encephalopathy or vasogenic edema, (5) distributions of FLAIR hypointensities compatible with typical PRES imaging patterns, and (6) vasogenic edema as demonstrated by DWI and ADC [Fig. 3C, D]. However, since there are no guidelines to direct this assessment, clinical judgment is crucial. Although seizure is the most common clinical presentation, the signs and symptoms of PRES are nonspecific and may also be observed in other neurological disorders [34,35], thus necessitating brain imaging with the primary intent to exclude alternative diagnoses. It is fortunate that > 90% of PRES cases have typical radiological and clinical presentations [17,21,36]; for example, > 95% have a cortical-subcortical appearance of vasogenic edema, and > 95% involve the parieto-occipital region and high precentral/posterior frontal region. On the basis of these results, Gao et al. demonstrated an algorithm that was used to converge on the diagnosis of “typical PRES” in > 90% of patients who had parieto-occipital or posterior frontal cortical–subcortical appearance of vasogenic edema on FLAIR MRI findings [37]. However, the remaining approximately 10% of atypical PRES cases are overlooked by this algorithm. There are atypical PRES cases that are the uncommon central variants showing brainstem, basal ganglia, and cerebellum involvement [36,38–43]. We previously reported an “atypical” MRI appearance of involvement of the cerebellum, basal ganglia, and callosal splenium [Fig. 3] [38]. Such atypical MRI findings may mistakenly lead clinicians to diagnose other etiologies (such as stroke, hypoxic-ischemic injury, or an overdose of pain medication).

One of the most important features in the diagnosis of PRES may be the reversibility of the typical FLAIR MRI findings (Fig. 3). However, despite its name, the clinical and radiological findings of PRES are not always fully reversible [44–47]. The presence of factors associated with severe radiological PRES, such as hemorrhage and diffusion restriction, affect the reversibility of the radiological findings and have been shown to be associated with worse clinical outcome [48]. Therefore, reversibility is not a complete diagnostic factor. However, to increase the accuracy of the algorithm proposed by Gao et al., and given that reversibility of signs and symptoms has been reported in up to 90% of cases [44–47], reversibility should be added to typical FLAIR MRI.

<table>
<thead>
<tr>
<th>Image conditions (MRI)</th>
<th>Vasogenic edema</th>
<th>Cytotoxic edema</th>
<th>PRES</th>
<th>Cerebral infarction (Acute stage)</th>
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<tr>
<td>FLAIR</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N, then ↑</td>
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<tr>
<td>DWI</td>
<td>N</td>
<td>↑</td>
<td>N</td>
<td>N, then ↑</td>
</tr>
<tr>
<td>ADC</td>
<td>↑</td>
<td>↓</td>
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N, normal; PRES, posterior reversible encephalopathy syndrome; ↑, hyperintense signal; ↓, hypointense signal.

Fig. 3. Atypical MRI findings in PRES. A 38-year-old pregnant woman was admitted as an emergency case with a complaint of upper abdominal pain and headache at 29 weeks of pregnancy and development of HELLP syndrome. MRI shows hyperintense signal lesions in the cortical and subcortical white matter bilaterally in the cerebellar hemispheres (A) and in the occipital lobes, basal ganglia, and callosal splenium in both the fluid-attenuated inversion recovery sequence (B) and apparent diffusion coefficient mapping (C), but these lesions are not recognized in diffusion-weighted images (D), and CT shows hypointensity in the same lesions (E). The follow-up brain MRI performed 2 weeks later shows complete resolution of the lesions (F).

HELLP: hemolysis, elevated liver enzyme levels, and low platelet levels; MRI: magnetic resonance imaging; PRES: posterior reversible encephalopathy syndrome.
findings (Fig. 3).

Although PRES is a relatively rare disease, it is considered to be a differential diagnosis in various neurological, psychiatric, and ophthalmological disorders and is often misdiagnosed. Because the signs and symptoms of PRES are not specific, brain MRI is vital for diagnosis. Nevertheless, the diagnosis of PRES is not always possible through MRI findings, and clinical assessment is also important for an accurate diagnosis. The list of differential diagnoses of PRES is shown in Table 3. It is necessary to consider severe neurological conditions, such as encephalitis, RCVS, posterior circulation stroke, cerebral venous sinus thrombosis, and primary central nervous system vasculitis, as possible and differential diagnoses [49–51]. Although the neuroimaging of PRES is not specific, early MRI can lead to the correct diagnosis in most cases. However, misinterpretation of the MRI findings may lead to diagnoses of infarction, paraneoplastic demyelinating disorder, or acute disseminated encephalomyelitis. The onset of PRES may be so acute as to suggest a stroke. Patients who have developed occipital cerebral infarction due to thrombosis of the basilar artery may have visual loss, nausea, and ataxia that are similar to symptoms of PRES. However, symptoms of occipital cerebral infarction are not usually involved in seizures. Although cases of PRES characterized by cytotoxic edema may show radiological images similar to infarction with hyperintensity on DWI and low signal on ADC, DWI MRI and ADC mapping may help to differentiate between cerebral infarction and PRES [16,37,52–54] (Table 2). The most important differential diagnosis of PRES may be RCVS given that PRES and RCVS show similar clinical and angiographic findings and have similar risk factors, which are the postpartum period and the administration of vasoactive drugs. Further, MRI abnormalities with similar lesions as PRES have been observed in patients with RCVS, suggesting that PRES and RCVS may share the same pathophysiology.

Fig. 4 presents a simple algorithm that we propose for the analysis and diagnosis of PRES. This algorithm focuses on MRI findings, which are classified into typical and atypical, given that MRI findings are key in the diagnosis of PRES. This algorithm may provide a better understanding of the characteristics that compose PRES and act as a starting point for the standardization of the diagnosis of PRES, helping clinicians evaluate individual features while also considering competing differential diagnoses.

### Table 3

<table>
<thead>
<tr>
<th>Differential diagnoses of posterior reversible encephalopathy syndrome (PRES).</th>
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<tr>
<td>Infectious encephalitis</td>
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<tr>
<td>Herpes and others, Progressive multifocal leukoencephalopathy, Creutzfeldt–Jakob disease</td>
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<tr>
<td>Autoimmune encephalitis</td>
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<tr>
<td>Acute demyelinating encephalomyelitis, Multiple sclerosis</td>
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<tr>
<td>Other autoimmune encephalitis (e.g. Hashimoto’s disease, systemic lupus erythematosus, Behcet’s disease)</td>
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<tr>
<td>Paraneoplastic encephalitis</td>
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<tr>
<td>Malignancy or tumor</td>
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<tr>
<td>Lymphoma, gliomatosis cerebri, metastatic disease</td>
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<tr>
<td>Chemotherapy-related demyelinating disorder</td>
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<tr>
<td>Radiation necrosis</td>
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<tr>
<td>Cerebral ischemia (e.g. posterior stroke), Cerebral venous sinus thrombosis, Subcortical leukoaraiosis, CNS vasculitis, Reversible cerebral vasoconstriction syndrome</td>
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<tr>
<td>Toxic leukoencephalopathy</td>
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<tr>
<td>Osmotic demyelination syndrome</td>
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<tr>
<td>Metabolic encephalopathy</td>
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<tr>
<td>Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)</td>
</tr>
<tr>
<td>Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)</td>
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CNS; central nervous system.

Fig. 4. Proposed algorithm for the diagnosis of posterior reversible encephalopathy syndrome.
7. Conclusions

PRES is a rare condition caused by cortical-subcortical vasogenic edema visualized by typical MRI findings in the occipital and parietal lobes. The pathophysiology has not been elucidated but involves endotheliopathy of the posterior cerebral vasculature that results in failed cerebral autoregulation, posterior edema, and encephalopathy. The most common manifestations are seizures, headache, and optical impairments. PRES-associated clinical signs and symptoms and neuroimaging lesions are reversible in most patients. MRI is the diagnostic gold standard and is useful in the differential diagnosis. Vasogenic edema is usually visualized involving the peritreo-occipital or posterior frontal cortical–subcortical regions on FLAIR MRI. However, atypical PRES cases show brainstem, basal ganglia, and cerebellum involvement. MRI findings are characterized by hypertensive signals in FLAIR and ADC without DWI; this imaging technique facilitates the prompt treatment of patients, thereby resulting in good clinical outcomes. Although a diagnostic algorithm to standardize the diagnosis of PRES and facilitate future research regarding this disorder has not yet been developed, a key feature may be to classify the MRI findings into typical and atypical categories. Additional research is needed, and as more case reports and series are reported, additional clinical associations will be made, which will further our understanding of the pathophysiology of PRES and its manifestations and hopefully lead to improved treatment.

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Declaration of Competing Interest

We declare no competing interests.

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