

# Posterior reversible encephalopathy syndrome, a clinically diverse and challenging disorder

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## Abstract

The characterizing features of Posterior reversible encephalopathy syndrome (PRES) are broad and diverse, making early recognition and diagnosis challenging tasks. To illustrate the heterogeneous nature of PRES, we present three cases and discuss their clinical and radiological presentation.

## KEY WORDS

carboplatin, cytotoxic edema, hypertension, Miller Fisher syndrome, paclitaxel, posterior reversible encephalopathy, posterior reversible encephalopathy syndrome, seizure, vasogenic edema

## 1 | INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a clinoradiological disorder, characterized by acute neurological symptoms and neuroimaging findings of vasogenic edema in the posterior regions of the brain.<sup>1</sup> Accumulated knowledge from case reports and retrospective observational studies over the past two decades illustrate the diverse nature of this syndrome with respect to its clinical features, radiological lesion distribution and etiology, making it a diagnostic challenge.<sup>2,3</sup>

The clinical presentation of PRES is nonspecific in nature, including a constellation of neurological manifestations, ranging from clinically silent to coma and death.<sup>2</sup> Furthermore, the radiological findings associated with PRES are not consistent as typically described. Lesions are not always reversible, and cortical involvement and affliction of other brain regions have a higher incidence than previously stated.<sup>2,4,5</sup> PRES is associated with a number of medical conditions and therapeutic agents. Due to its multifactorial etiology, it spans multiple disciplines with cases in neurology, internal medicine, pediatrics, gynecology, rheumatology, surgery, oncology, and radiology.<sup>2,6,7</sup> It is our experience

that there is a lack of awareness of PRES within these fields, causing delay in diagnosis and treatment. To illustrate the heterogeneous nature of PRES, we present three cases and discuss their clinical and radiological features, etiology, and therapeutic approach.

## 2 | CASE PRESENTATIONS

An overview of the cases is provided in Table 1.

### 2.1 | Patient-1

A 64-year-old man with chronic renal failure and arterial hypertension underwent a cardiac bypass following a myocardial infarction. He developed a postpericardiotomy syndrome that was treated with a 1-month corticosteroid course. A month thereafter, he developed an acute, right-sided intense headache, ipsilateral blurry vision, photophobia, nausea, and vomiting. On admission the following day, his blood pressure (BP) was 215/140 mm Hg, heart rate (HR) 80 beats per minute (bpm), he was afebrile with normal

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oxygen saturation. Other than a right-sided homonymous hemianopia, he had a normal neurological examination. Computer tomography (CT) caput was normal. CT angiography (CTA) of the abdomen showed previously known severe atherosclerotic plaques in the wall of the abdominal aorta with approximately 50% stenosis of both renal arteries. Intravenous (iv) labetalol had no effect on BP, and iv nitroglycerin was started. Three hours later, his condition worsened with deteriorating level of consciousness, followed by generalized tonic seizures with postictal agitation. The seizures were terminated with iv benzodiazepine. Laboratory tests showed an elevated serum creatinine (212  $\mu\text{mol/L}$ ) and lactate (6.6  $\mu\text{mol/L}$ ) levels. Cerebrospinal fluid (CSF) analysis and electroencephalogram (EEG) were normal. Cerebral magnetic resonance imaging (MRI) showed bilateral, subcortical, and cortical hyperintense lesions on T2-weighted and fluid attenuation inversion recovery (FLAIR) sequences in the cerebellum, left thalamus and occipital and parietal lobes, with a right-sided predominance (Figure 1). The lesions were isointense on diffusion-weighted imaging (DWI) with an increased apparent diffusion coefficient (ADC) value, indicative of vasogenic edema. His condition improved significantly the day after, making a full clinical recovery within six days. Cerebral MRI, 6 weeks later, showed partial resolution with small lesions (gliosis) in the right parietooccipital region.

## 2.2 | Patient-2

A 53-year-old woman with hypothyroidism was diagnosed with stadium 4 uterine carcinosarcoma without distant metastasis and underwent a hysterectomy with bilateral salpingo-oophorectomy and small bowel resection. Preoperatively, she received three neoadjuvant therapy cycles with paclitaxel and carboplatin. Three and half weeks after the third cycle, she was admitted with focal seizures in her right-sided extremities followed by loss of consciousness. The seizures were terminated with iv benzodiazepine, and valproate was initiated. On examination, she had right-sided hemiparesis with reduced sensibility, ataxia in the lower extremities and positive Romberg's test. She was afebrile, her BP was 100/60 mm Hg, and the HR was 130 bpm. Laboratory tests were normal. CT caput showed bilateral hypoattenuated lesions in the parietal lobes. Suspecting brain metastasis, high-dose iv corticosteroids treatment was initiated. Cerebral MRI showed bilateral subcortical hyperintense parietooccipital lesions on T2-weighted sequences, with a left-sided predominance (Figure 1). There were no contrast enhancements. Lack of restriction on DWI with an increased ADC value indicated a vasogenic edema, and corticosteroid treatment was discontinued. MRI of the spine, EEG, and CSF analysis

was normal. Nerve conduction studies showed mild signs of bilateral sensory polyneuropathy in the lower extremities. She made a full clinical recovery within one week. Cerebral MRI taken a month later showed complete resolution of all lesions. Valproate treatment was discontinued, and she later received two more cycles of paclitaxel-carboplatin without complications.

## 2.3 | Patient-3

A 74-year-old man with hypertension, ischemic coronary disease, and type-2 diabetes had just finished an oral penicillin course for an upper respiratory infection. After 2 days of vertigo, he was admitted with an intense left-sided headache and diplopia. On examination, he had an incomplete left oculomotorius paresis and global areflexia. He was afebrile, his BP was 160/95 mm Hg, and HR was 80 bpm. His BP fell spontaneously to 135/80 mm Hg, no fluctuations in BP or other signs of dysautonomia were noted during the duration of his hospital stay. CT and CTA caput were normal. Laboratory tests including infectious parameters were normal. CSF analysis showed a borderline elevated protein level (0.73 g/L), but no pleocytosis. Cerebral MRI showed bilateral subcortical and cortical hyperintense lesions on T2-weighted and FLAIR sequences in the parietal and occipital lobes (Figure 1). Lack of restriction on DWI with an increased ADC value indicated vasogenic edema. Five days after admission, his condition worsened with bouts of confusion and visual hallucinations. He developed dysarthria and ataxia in his extremities. His left oculomotorius paresis progressed to complete plegia, and he also developed ptosis and oculomotorius paresis on the right side. Suspecting Miller Fisher syndrome (MFS), a five-day course of iv immunoglobulin (IVIG) treatment was administered. At the end of the IVIG course, his CRP and SR levels started to rise (>300 mg/L and 59 mm, respectively). However, the white blood cell count remained within normal range. An extensive panel of laboratory tests, including tests for paraneoplastic and acetylcholine receptor antibodies, viral serology, and bacterial and fungal cultures, was all negative. Chest x-ray, urinary analysis, and tests for intestinal pathogens were also negative. Deemed as an infection of unknown origin, an iv course with cefuroxime was started. A new lumbar puncture was performed 12 days later, CSF analysis (including cytology, viral serology, and IgG index) showed normal findings and no albumin-cytological dissociation. He was, however, positive for anti-GQ1b with a titer of 3200, supporting MFS diagnosis. Cerebral MRI performed 16 days thereafter demonstrated multiple cortical microinfarctions, predominantly in the left occipital lobe otherwise, complete resolution of the other cortical and

**TABLE 1** Cases overview

Patient	Age	Sex	Comorbidity	Triggering factor	Debut and progression	Presenting symptoms
1	64	M	Chronic renal failure Hypertension Atherosclerosis Coronary disease	Hypertension	Acute debut with rapid progression	Headache, nausea and vomiting, visual disturbances, deteriorating consciousness, and generalized seizure
2	53	F	Hypothyroidism Uterine carcinosarcoma	Paclitaxel-Carboplatin therapy	Acute debut with rapid progression	Focal seizures
3	74	M	Hypertension Coronary disease Type 2 diabetes	Miller fisher syndrome	Acute debut with gradual progression	Vertigo, headache, diplopia and visual hallucination

subcortical lesions. The patient made a full clinical recovery with normalization of eye motility within 2 months.

### 3 | DISCUSSION

Patient-1 had an acute debut, with headache, nausea, vomiting, visual disturbances, and seizures. Patient-2 presented with focal seizures, without prodromal symptoms or signs. Patient-3, on the other hand, had a phasic symptom presentation, debuting with vertigo, thereafter developing focal neurological signs, confusion, and visual hallucinations.

The clinical presentation of PRES varies widely, from clinically silent to death.<sup>2,8</sup> It can manifest with a myriad of neurological symptoms and signs, developing within hours to weeks.<sup>2</sup> The presenting symptoms are often nonspecific with confusion and deteriorating consciousness, headache, vertigo, nausea, and vomiting being most common.<sup>1,6</sup> Impaired visual acuity, hemianopia, visual hallucination, and anosognosia are frequent.<sup>1,6</sup> Focal or generalized seizures are reported in approximately 75% of cases, but status epilepticus is rare.<sup>6,7,9,10</sup> Focal neurological findings are also rare, among which hyperreflexia, ataxia, and paresis are the most common.<sup>2,4</sup>

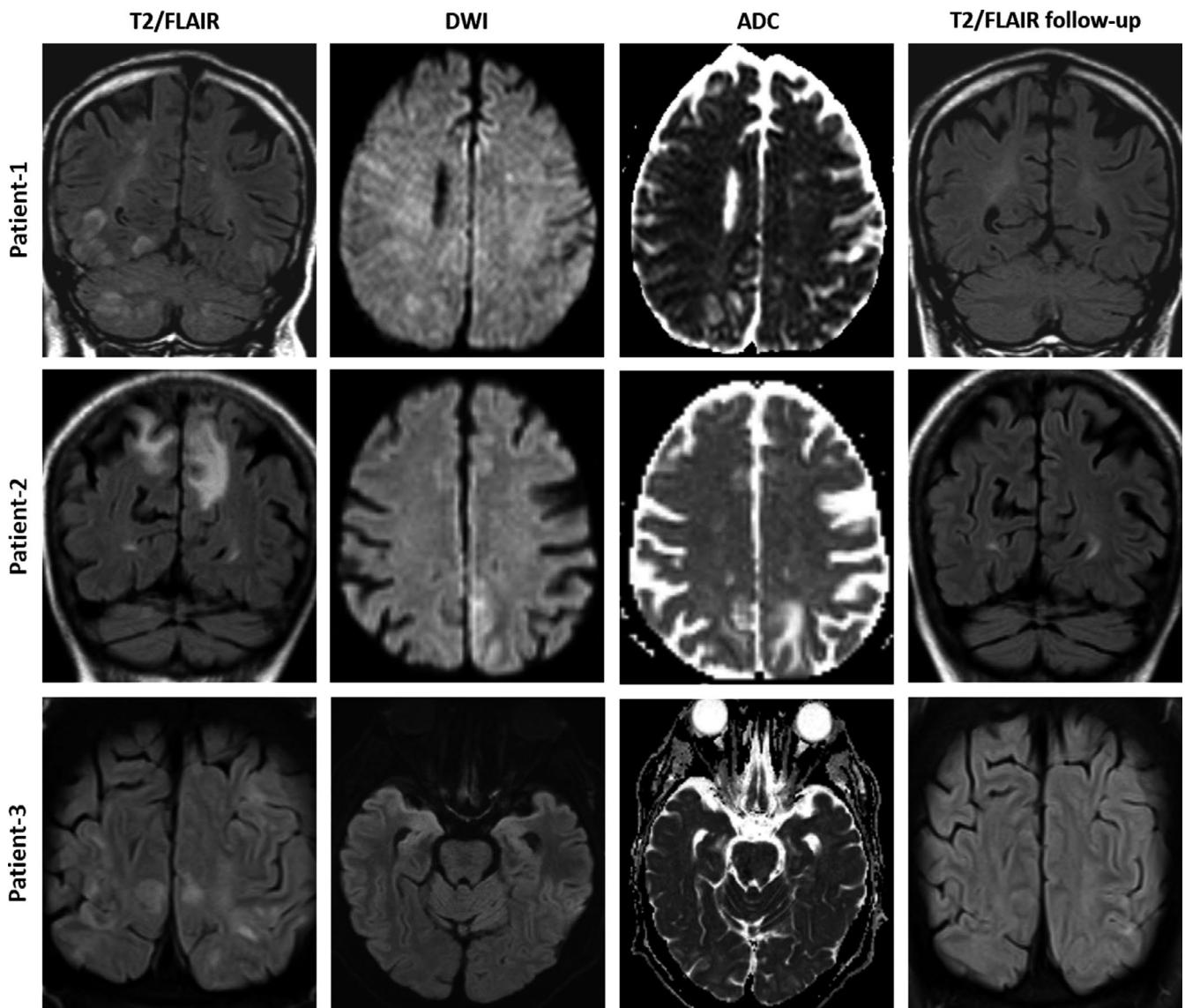
MRI is the principal diagnostic tool.<sup>5,7,10</sup> With the exception of patient-2, CT scans did not detect any of the lesions detected on MRI. Lesions have a hyperintense signal on T2-weighted and FLAIR sequences, characteristic of vasogenic edema. Usually, DWI with ADC map shows vasogenic edema with high ADC value, an indicator of their reversibility and thereby better prognostic outcome.<sup>5,11</sup> However, contrary to its name, not all PRES lesions are reversible.<sup>1,7</sup> Lesions with a low ADC value indicate cytotoxic edema with ischemia and irreversible damage.<sup>5</sup> Our three cases displayed subcortical vasogenic edema with a distribution pattern typical of the majority of reported PRES cases, affecting the posterior regions, the parietal and/or occipital lobes. Involvement of the cerebellar,

frontal, and temporal lobes and watershed areas has been shown to be more frequent than previously suggested.<sup>5,10,12</sup> Approximately 30% of PRES cases have an atypical distribution pattern, involving the brainstem, basal ganglia, thalamus, corpus callosum, and spinal cord.<sup>1,4,5,8,10-13</sup> PRES usually has a bilateral and relatively symmetrical distribution,<sup>1,5,11</sup> nevertheless an asymmetrical distribution is not unusual. Although rare, a unilateral form has been reported.<sup>4,6,11</sup> Furthermore, patient-1 and -3 had cortical lesions on MRI. Cortical involvement is shown to have a higher incidence than previously thought.<sup>12</sup> Patient-3 developed cortical microinfarctions despite the lack of cytotoxic edema on the initial MRI. His condition had a phasic progressive pattern, worsening significantly a week after symptom debut. Follow-up MRI, performed 16 days later, demonstrated multiple new cortical lesions with microinfarctions with complete resolution of previously demonstrated cortical and subcortical lesions. None of our cases displayed contrast enhancement or had hemorrhagic lesions. Hemorrhagic lesions, both hematomas and microbleeds, are associated with a poorer prognosis.<sup>5,7</sup>

Posterior reversible encephalopathy syndrome is associated with a number of medical conditions with different pathophysiological mechanisms. Hypertension, (pre) eclampsia, hypercalcemia, renal diseases, inflammatory, and autoimmune disorders are the most common underlying conditions.<sup>1,6,7,10</sup> PRES can also manifest after exposure to a number of therapeutic agents, particularly immunosuppressants and cytotoxic agents.<sup>2,7,10,14</sup> Patient-2 developed PRES following paclitaxel-carboplatin combination therapy. The toxicity of platinum analogues has been reported primarily in association with cisplatin, very rarely with carboplatin.<sup>14</sup>

Since PRES is often associated with hypertensive emergency scenarios, this led to the hypothesis that acute arterial hypertension is the principle pathophysiological mechanism behind PRES. As BP increases and exceeds the upper limits of the cerebral autoregulatory system, the ability to maintain a constant cerebral perfusion pressure is compromised. This causes

Presenting neurological signs	BP at presentation	MRI findings	Clinical recovery time	Resolution of MRI lesions
No focal signs	215/140 mm Hg	Bilateral, asymmetrical, subcortical and cortical vasogenic edema affecting the cerebellum, thalamus, occipital and parietal lobes	1 wk	Partial resolution (small area of occipital gliosis)
Hemiparesis and ataxia	100/60 mm Hg	Bilateral asymmetrical subcortical vasogenic edema affecting the occipital and parietal lobes	1 wk	Complete resolution
External ophthalmoplegia, ptosis, areflexia, mental deterioration, and confusion	160/95 mm Hg	Bilateral asymmetrical subcortical vasogenic edema in the occipital lobes	8 wk	Partial resolution (cortical microinfarctions)



**FIGURE 1** Cerebral MRI images showing coronal T2/FLAIR, axial DWI, and ADC map sequences at diagnoses of all three patients with coronal T2/FLAIR follow-up images

disruption of the blood-brain barrier (BBB) via vasodilatation and hyperperfusion, leading to vascular leakage and edema.<sup>15</sup>

However, 20%–40% of all PRES cases are reported to have either normal or mildly elevated BP,<sup>3,7</sup> as seen in our patient-2 and -3. Thus, the theory of hypertension as the main causative factor for PRES is not applicable to all cases. In these scenarios, the immune system is usually activated by either endogenous (autoimmune) or exogenous toxins (therapeutic agents), causing an inflammatory response damaging the BBB, impairing the autoregulatory mechanism causing vasoconstriction, hypoperfusion and subsequently ischemia and edema.<sup>10,15</sup> This argues the theory of endothelial dysfunction as the primary pathomechanism behind PRES development.

Posterior reversible encephalopathy syndrome is rarely associated with Guillain-Barre syndrome (GBS) and its different variants. The onset of PRES can either overlap with the clinical manifestations of GBS or, albeit rarely, precede it.<sup>16,17</sup> PRES in GBS patients is more commonly associated with IVIG therapy than as a direct consequence of the immunopathophysiology of GBS.<sup>17</sup> Patient-3 manifested PRES symptoms prior to developing clinical characteristics of MFS; furthermore, his condition improved following IVIG therapy. To the best of our knowledge, there are only five cases reporting comorbidity of PRES and MFS.<sup>16</sup> Three of these cases developed PRES following IVIG. The remaining two, similar to our case, manifested PRES prior to developing MFS symptomatology and therapeutic intervention.<sup>16</sup>

There are no clear therapeutic guidelines for PRES. Treatment is tailored on individual basis, with emphasis on early recognition and management of the underlying condition and its symptoms. There are also no recommendations or guidelines for hypertension and seizure treatment.<sup>2</sup> Antiepileptic medications are usually tapered off after recovery, since PRES patients rarely develop chronic epilepsy.<sup>9</sup> Where therapeutic agents are identified as triggering factors, the general consensus is to discontinue treatment.<sup>2</sup> However, no therapeutic paradigm exists on how to best achieve this. Furthermore, the risk for PRES recurrence following reexposure to the offending agent is unknown. Following recovery, patient-2 received two more cycles of paclitaxel-carboplatin without any complications.

Generally, the prognosis for PRES is good with the majority of patients making a full recovery within a few days to weeks. However, cytotoxic edema, hemorrhage, and delayed diagnosis can potentially lead to increased morbidity and mortality.

## 4 | CONCLUSION

Posterior reversible encephalopathy syndrome is a disorder with diverse clinical and radiological features. Etiologically, it is multifactorial, manifesting as complication in a number

of disorders where disruption of the BBB seems to be the common pathophysiological mechanism. There are thus far no clear therapeutic recommendations. Therefore, each patient requires an individual therapeutic approach depending on the underlying etiological factor.

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The authors have nothing to disclose.

## AUTHOR CONTRIBUTIONS

TC and FO: conceptualized and drafted the manuscript. FO and EB: involved in patient evaluation and follow-up. HT: provided radiology images and assessments. All authors: contributed to the writing and revision of the manuscript.

## CONSENT

Written consent was obtained from all patients.

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