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POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES)

Neurology

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ABSTRACT

Reversible posterior leukoencephalopathy syndrome (RPLS), better known as Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiological diagnosis characterized by confusion, seizures, headache, vomiting, and loss of vision with imaging studies indicating predominantly posterior leukoencephalopathy. PRES is the end result of various etiological factors that lead to blood brain barrier injury either by hyper- or hypoperfusion, endothelial dysfunction, changes in blood vessel morphology, hypocapnia or immune system activation.

KEYWORDS

Posterior reversible encephalopathy syndrome (PRES); Eclampsia; Hypertension; Encephalopathy; Vasogenic edema

Introduction:

Reversible posterior leukoencephalopathy syndrome (RPLS), better known as Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiological diagnosis characterized by confusion, seizures, headache, vomiting, and loss of vision with imaging studies indicating predominantly posterior leukoencephalopathy [1]. This syndrome was first reported in 1996 by Hinchey et al on a series of 15 patients having underlying acute hypertensive encephalopathy associated with renal insufficiency, eclampsia or were receiving immunosuppressive therapy after transplantation [1]. Although parieto – occipital lobes are predominantly involved in this entity, when regions of the brain other than the aforementioned lobes have predominant involvement, the syndrome is called atypical PRES, which in itself is a rare diagnosis [2]. Table 1 enumerates common locations of PRES [3].

Table – 1| Common locations of PRES
Parieto – occipital (most common)
Posterior frontal
Temporal
Thalamus
Cerebellum
Brainstem
Basal ganglia

Initially it was thought to have only white matter involvement; however, later it was observed that grey matter is also involved in this syndrome [4]. PRES can develop on the background of various conditions. Regardless of the underlying etiopathogenesis, the ultimate end result is cerebral vasogenic edema, the pathogenesis of which is still under debate [1, 5]. Classical description of PRES on T2-weighted and Fluid-attenuated inversion recovery (FLAIR) sequences images is of bilateral and symmetrical hyperintensity in the parietal and occipital lobe which is caused by focal or confluent vasogenic edema. Calcarine and paramedian occipital lobe is spared [6]. The most important feature of this syndrome is the reversibility of the imaging findings, which may take days to weeks following initiation of treatment. Reversibility of the lesion is also associated with better outcome whereas poor prognostic factors include brainstem involvement and intracranial hemorrhage. If treatment is not promptly initiated, PRES may progress to ischemia, massive infarction, and death [7, 8].

Etiopathogenesis:

The pathogenesis of PRES is not precisely known. Hypertension (HTN) is the most commonly identified cause of PRES, followed eclampsia, renal failure and immunosuppressive drugs [8]. Cerebrovascular autoregulation is supposed to maintain a constant rate of cerebral blood flow which is independent of fluctuations of systemic blood pressure. This is ensured by vasodilation of the cerebral arteries during hypotensive episodes. In contrast, during periods of hypertension, autoregulation results in cerebral vasoconstriction [9]. In healthy individuals, autoregulation operates usually between 50 and 150 mmHg of cerebral perfusion pressure, failure of which may predispose to cerebral ischemia during periods of hypotension or cerebral hyperperfusion and vascular leakage when blood pressure rises above the upper autoregulatory limit [10 – 13]. However, it is the rate of rise of blood pressure (BP) which is a more important factor in the pathogenesis of PRES than the absolute values [1].

The originally proposed hypothesis suggested that severe hypertension leads to cerebral autoregulatory vasoconstriction causing cerebral ischemia, and subsequent cytotoxic brain oedema. This hypothesis, however, fails to explain the reversible nature of the pathologic changes seen on imaging studies [14 – 16]. Moreover, 15%-20% of patients with PRES have either normal or low BP [17]. The recent, more acceptable theory suggests that elevation of blood pressure above the upper autoregulatory limit leads to failure of cerebral autoregulation with subsequent vasodilatation, hyperperfusion and extravasation of fluid in the interstitium leading to vasogenic brain oedema. These findings correlate with reversible nature of this syndrome as they resolve rapidly when blood pressure is lowered [7, 10, 18 – 22].

However, point against this hypothesis is that about 30% of patients with PRES show normal or only slightly elevated blood pressure values that do not necessarily exceed the normal upper autoregulatory limit, as would be expected in the context of cerebral hyperperfusion following autoregulatory failure [23]. Later, to explain the pathogenesis in this subset of patients, it was proposed that acute hypertension could cause endothelial dysfunction and breakdown of the bloodbrain barrier, even without blood pressure exceeding typical autoregulation range [24]. This hypothesis could explain the development of PRES in patients with (pre)eclampsia, sepsis or during treatment with immunosuppressive agents or cytotoxic medication [25 – 27]. According to this "toxic" theory, blood pressure elevations occur as a consequence of primary endothelial dysfunction [28].

As mentioned, in pre-eclampsia and eclampsia, the genesis of PRES is attributed to underlying endothelial activation and injury [29]. In a retrospective study, PRES was found in more than 90% of eclamptic and about 20% of preeclamptic patients having neurological symptoms. Compared with pregnant women with eclampsia or preeclampsia without PRES, significant elevations of hematocrit, serum creatinine, aspartate transaminase, alanine transaminase and lactate dehydrogenase values were noted [27]. Renal diseases have also been linked to PRES. Impaired renal function has been reported in

55% of all patients with PRES [30]. Beside endothelial dysfunction, the proposed mechanisms of PRES associated with immunosuppressive therapy, especially for cyclosporine, are hypercholesterolemia, hypomagnesaemia, aluminium overload, and drug levels above the therapeutic range [31 – 33]

Compared to solid organ transplantation, immunosuppressive agents are usually administered at higher dose in patients with bone marrow or stem cell transplantation which could possibly explain the higher incidence of PRES after nonsolid organ transplantation. However, it is still unclear whether PRES is linked to the dose of causative agents. Adding to this, plasma levels of immunosuppressive substances do not seem to correlate with the severity of clinical signs or imaging findings. Moreover, PRES has been observed up to several months after administration of cytotoxic agents [34, 35]. Nephrotoxicity from cyclosporine may lead to fluid overload, ultimately exacerbating hypertension and the altered bloodbrain barrier [31]. The mechanism for tacrolimus and interferon alpha is likely similar to that of cyclosporine [34]. Antiangiogenic drugs such as Bevacizumab, Sunitinib or Sorafenib may mediate increased vascular permeability, thereby contributing to vasogenic edema formation [30].

The posterior areas of the cerebral hemispheres seem to be particularly susceptible to various pathological processes, which is supported by clinical as well as imaging findings. This might be caused by a reduced density of sympathetic innervations in the posterior, compared to the anterior circulation [30, 36].

To summarize, PRES is the end result of various etiological factors (Table 2) [8], that lead to blood brain barrier injury either by hyper- or hypoperfusion, endothelial dysfunction, changes in blood vessel morphology, hypocapnia or immune system activation [3].

Table 2 – Etiology of PRES [8]

Common causes of PRES
· Hypertensive encephalopathy
· Eclampsia
· Renal failure with hypertension
· Immunosuppressive and cytotoxic agents
Uncommon causes
· TTP
· HUS
· Collagen vascular disease
o SLE
o PAN
o Behcet disease
· Acute intermittent porphyria
· Post organ transplantation
· ART in patient with HIV
Immunosuppressive drugs associated with PRES
· Cyclosporine A
· Interferon alpha
· Cisplatin
· Tacrolimus
· IVIG
· Erythropoietin
· Cytarabine

Symptoms and Signs:

PRES is characterized by a variety of neurological symptoms, usually associated with elevated arterial blood pressure. The onset may be acute or subacute, with symptoms developing within a few hours up to several days or even weeks [30]. Patients may have a presentation similar to that of encephalopathy, cortical venous thrombosis or a stroke mimic.

The most common clinical symptoms and signs are headache, seizures, vomiting, altered alertness and behaviour changes ranging from drowsiness to stupor, mental abnormalities including confusion and abnormalities of visual perception [1]. Up to 75% of patients may present with seizures [30]. However, seizures are likely a manifestation, rather than a cause, of PRES [4]. In view of frequent involvement of the occipital lobes, visual disturbances in the form of deterioration of visual acuity, visual field deficits including hemianopia and cortical blindness or visual hallucinations can be observed in about two third of all PRES patients [1]. Various studies have mentioned different frequencies of presenting symptom. As per Fisher M et.al, incidence of symptoms and signs in PRES are mentioned in Figure 1 [10].

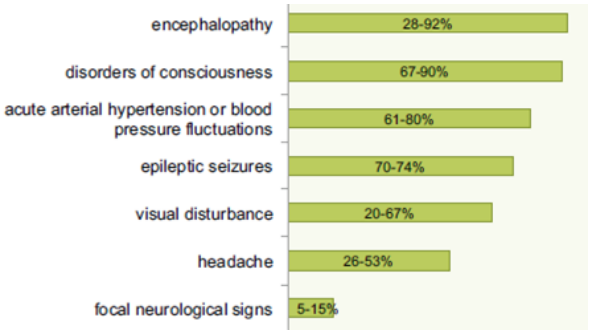

Figure 1: Incidence of neurological signs in patients with PRES [10].

Investigations:

Imaging Features:

CT scans usually show vasogenic edema with a bihemispheric distribution. As CT is less sensitive than MRI in detecting the initial subtle findings, initial CT may appear normal in up to 22% of cases [37]. Small and focal abnormalities which can be easily missed on CT are readily visible on MRI [1]. Among the routine MRI sequences, fluid attenuated inversion recovery (FLAIR) is the most sensitive in detecting subcortical and cortical lesions in PRES [2, 30]. Classically PRES has been described on T2-weighted MRI and FLAIR as bilateral and symmetrical regions of hyperintensity in the posterior parietal and occipital lobe which is caused by vasogenic edema. Calcarine and paramedian occipital lobe is spared (Figure 2) [1, 6, 26]. Subcortical white matter is usually involved, but even cortical grey matter can be involved, depending upon the severity of the disease. Predominant subcortical involvement is attributed to lower density of white mater in that area [37].

When regions of the brain other than the parieto-occipital lobes are predominantly involved, the syndrome can be called atypical PRES which is rare [2]. Three distinct primary imaging patterns of PRES have been described [5, 6, 8].

1. Superior frontal sulcus pattern (27 %)

Patchy edema predominates in the frontal lobes with more isolated involvement of mid and posterior aspect of superior frontal sulcus. The parietal and occipital lobes are variably involved.

2. Holohemispheric watershed pattern (23 %)

A confluent vasogenic edema spreads along 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.

3. Dominant parietal-occipital pattern (22 %)

In this pattern previously thought to be typical of PRES, the posterior part of the parietal and occipital lobes is predominantly involved.

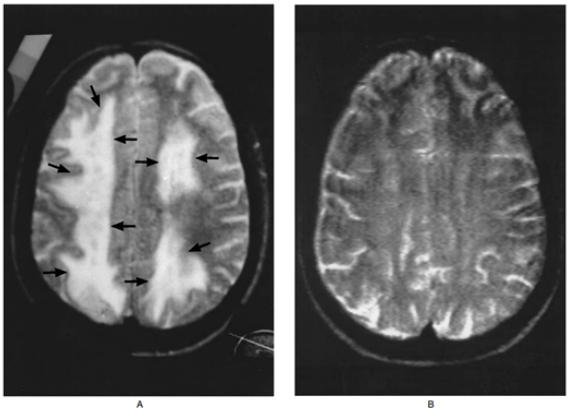

Figure 2: Imaging of PRES patient - In Panel A, the initial image shows widespread white-matter signal abnormalities (arrows). A follow-up scan (Panel B) is of poor quality but shows that the abnormalities have resolved [1].

Partial or asymmetric expression of these three primary patterns has also been described in 28 % of patients. In partial form, there is frontal lobe edema with sparing of parietal and occipital lobe whereas asymmetric form is characterized by unilateral absence of edema in either a parietal or an occipital lobe. Coexistence of partial and asymmetric form may also be noted [6]. Other atypical areas of distributions are temporal lobes, cerebellar hemispheres, brainstem, basal ganglia, deep white matter, and splenium [3]. Knowledge of these variations on imaging is important for recognizing PRES. Another variation reported is microhemorrhages which were noted in 65% of cases under observation [38]. However, its clinical correlation with symptoms could not be established. Therefore, the clinical relevance of microbleeds in PRES has yet to be determined.

Diffusion-weighted (DWI) MRI is the imaging modality of choice to reliably distinguish vasogenic oedema in PRES from cytotoxic oedema in the setting of cerebral ischemia [39]. DWI can also be used to monitor for ischemia as a complication of PRES [40]. On DWI, the hallmark of PRES lesions is a pattern of vasogenic oedema, but it may show T2 shine-through effect or pattern of ischemia [8]. Quantitative assessment of apparent diffusion coefficient (ADC) maps may show subtle involvement with PRES, which may go unnoticed on conventional MRI [36].

MRA must be added to MRI to identify an associated reversible vasoconstriction syndrome [26]. Vasculopathy has been observed in MR or conventional angiograms. Vasculopathic findings include focal vasodilatation, vasospasm (both diffuse and focal) and string-of-beads appearances which are usually located in the posterior circulation [40]. These findings are usually reversible on follow up. However, angiograms may show normal appearance of the vessels and is important in differentiating PRES from arterial infarcts [8].

Cerebral perfusion changes in PRES depend on whether it is a hyperperfusion or hypoperfusion mechanism [41]. Therefore, imaging studies on cerebral perfusion have reported conflicting results. Perfusion findings are therefore not very helpful in the diagnosis of syndrome. Increased perfusion has been observed in edematous zones confirming the hypothesis of cerebral hyperperfusion [42]. In contrast, single photon emission computed tomography (SPECT) and MR perfusion demonstrate cerebral hypoperfusion in lesion zones in PRES [43, 44]. Thus, PRES may be a dynamic process, with perfusion changing over time [45].

The extent of involvement has prognostic implications, and helps identify patients who need more aggressive treatment. Patient outcome correlates with the extent of combined T2 and DWI signal abnormalities [36]. High DWI signal intensity and low or normal ADC values are associated with cerebral infarction and may give the earliest warning of non-reversibility as vasogenic oedema progresses to cytotoxic oedema [8, 36]. ADC imaging can be of prognostic relevance: higher values have been associated with a reversibility of lesions [26].

Other Features:

Deranged liver and renal function along with electrolyte disturbance may be seen in patients with underlying eclampsia, renal disease, sepsis or those under immunosuppressive therapy [10, 31]. EEG may be necessary to ruleout convulsive epileptic seizures, status epilepticus and may also help in the evaluation of encephalopathy [46]. Lumbar puncture is done to exclude encephalitis or leptomeningeal involvement in patients with hemato-oncological disease. However, pathological alterations in cerebrospinal fluid (CSF) are nonspecific for PRES. Elevated CSF levels of albumin and an elevated CSF/serum albumin quotient as a manifestation of blood–brain barrier disruption have been reported in a series of 87 patients, whereas pleocytosis was rare [10, 47]. Figure 2 summarizes the diagnostic parameters [10].

Diagnostic tool	Finding
Laboratory data	Hypomagnesemia
	Lactate dehydrogenase ↑
	Liver function parameters ↑
	Creatinine ↑
	Albumin ↓
Cerebrospinal fluid	Albumin ↑
	Albuminocytologic dissociation
EEG	Diffuse theta slowing
	Delta slowing
	Rhythmic delta activity
	Sharp-slow wave activity
	Periodic lateralizing epileptiform discharges
	Diffuse or focal (symmetric) slowing of background activities
CT and MRI	Vasogenic edema
	Watershed distribution
	Parieto-occipital pattern
	Frontal and temporal lobe involvement
	Subcortical white matter lesions
	Bilateral, frequently symmetric distribution
	Hyperintense T2-weighted and FLAIR sequences
	Iso-, hypo-, or hyperintense lesions on DWI
	Facultative contrast enhancement
	Microbleeds, intracerebral hemorrhage possible
	Increased or decreased ADC values depending/indicating (ir)reversibility of lesions
Angiography	Vasoconstriction, vasospasm (diffuse or focal)

EEG electroencephalogram, *CT* computed tomography, *MRI* magnetic resonance imaging, *FLAIR* fluid-attenuated inversion recovery, *DWI* diffusion-weighted imaging, *ADC* apparent diffusion coefficient

Figure 3: Diagnostic findings in patients with PRES [10].

Diagnosis and Differential Diagnoses

Fugate et al. suggested the following criteria for the diagnosis of PRES [48]:

1. Acute onset of Neurological symptoms
2. Neuroimaging abnormalities of vasogenic edema (focal / confluent)
3. Reversibility of clinical and/or radiological findings

The differential diagnosis of the T2W confluent white matter hyperintensities is broad and is based on the distribution pattern of the lesions. Important considerations are basilar top syndrome, cerebral venous sinus thrombosis, acute ischemic stroke, trauma, vasculitis, encephalitis, demyelinating disorders, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and progressive multifocal leukoencephalopathy (PML) [8]. Sparing of the medial occipital lobe and thalamus, as well as MR angiography findings, rule out the possibility of basilar top syndrome. Venous infarction can be ruled out by showing normal venous structures. Distinguishing PRES from acute ischemic stroke is highly significant since hypertension in ischemic stroke should not be managed aggressively while in the case of PRES it should be controlled and actively managed [49].

Trauma can be ruled out by the clinical history and absence of any other radiological signs of trauma. Vasculitis is a difficult differential diagnosis to rule out. The typical pattern of distribution of PRES lesions can help. However, in atypical distribution of the lesions, vasculitis continues to be an important differential diagnosis. In these cases, reversibility of the lesions, if demonstrated, is important. The predominant involvement of white matter rules out encephalitis. The involvement of grey matter does not favor the diagnosis of demyelinating disorders [8].

One of the important differential diagnoses of PRES is reversible cerebral vasoconstriction syndrome (RCVS). In RCVS patients, the major cerebral arteries are affected and stroke occurs, while in PRES patients the small blood vessels, arterioles, and capillaries are affected [10]. There is a significant overlapping of clinical and radiological features between RCVS and PRES, suggesting that both conditions may represent a similar pathophysiologic spectrum [49, 50]

Treatment:

Despite of having a diverse etiological profile, general measures remain the same: management of airway, blood pressure control, anti-

epileptics, removing the disposing factors, and supportive care. With appropriate and timely responses, the patient usually has a complete recovery without any residual neurological sequelae and abnormal MRI findings [39]. The treatment of PRES is symptomatic, since no specific therapeutic strategy is currently available. Ideally patient should be admitted in an ICU and continuous hemodynamic monitoring should be done. In patients with markedly altered sensorium or seizure activity, need of intubation must be assessed. Temperature must be maintained near normal and hypoglycemia if present must be corrected. Laboratory evaluation be undertaken to provide insight on haematological, renal and liver parameters as well as electrolyte imbalance [39, 51].

Control of Blood pressure remains cornerstone of management. Continuous IV infusion is usually required to avoid fluctuations [51]. The choice of antihypertensive drugs, however is based on general recommendations for the management of hypertensive crisis or hypertensive emergency as in general population. [52, 53]. The aim is to bring down 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 [54]. However, despite of an established association of hypertension, there is no evidence based on prospective controlled studies, that strict blood pressure control limits neurologic injury, or results in a regression of clinical or imaging findings [10].

Anticonvulsive treatment is often indicated which should be administered according to the existing guidelines. Duration of treatment depends upon the clinical recovery as well as reversal of findings on imaging [26, 46]. Tapering off the dosage or discontinuation of causative agents usually leads to clinical improvement and/or a reduction in lesion size [34]. A positive correlation between the dose of the offending agent and the neuroloradiological manifestations has been proposed [10].

Prognosis:

Pre-existing diabetes mellitus and corpus callosum involvement were noted as predictors of poor outcome [55]. Reversibility of the lesions is the most important feature of PRES. When present it is associated with good prognosis in that subset of patients. The imaging features associated with poor prognosis and thus irreversibility of these lesions are 1) low ADC values in the lesions, 2) brainstem involvement, and 3) evidence of intracranial hemorrhage on initial imaging [8].

Conclusion:

- Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiological diagnosis characterized by confusion, seizures, headache, vomiting, and loss of vision with imaging studies indicating predominantly posterior leukoencephalopathy.
- Elevation of blood pressure above the upper autoregulatory limit leads to failure of cerebral autoregulation with subsequent vasodilatation, hyperperfusion and extravasation of fluid in the interstitium leading to vasogenic brain oedema.
- With appropriate and timely responses, the patient usually has a complete recovery without any residual neurological sequelae and abnormal MRI findings.

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