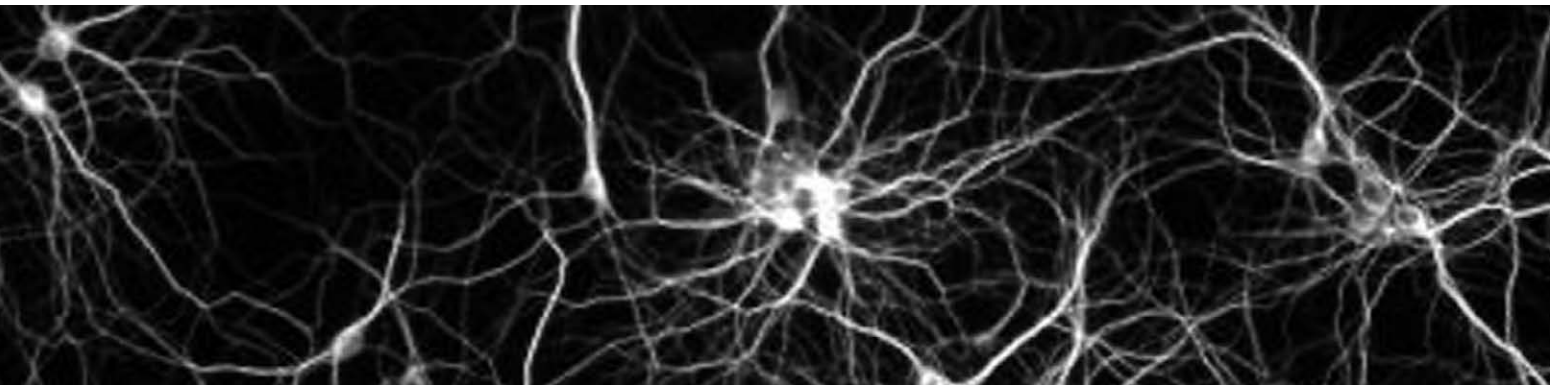

Definition and historical overview of posterior reversible encephalopathy syndrome

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ABSTRACT – Posterior reversible encephalopathy syndrome (PRES) is a clinical and radiographic syndrome characterized by nonspecific neurological symptoms and characteristic imaging findings of symmetrical usually posterior-predominant cerebral white matter vasogenic oedema, although other regions of the brain may be affected in atypical forms of PRES. There are numerous causes of PRES. The most common conditions associated with it are moderate to severe hypertension, preeclampsia, and eclampsia, the use of immunosuppressant and cytotoxic drugs, autoimmune disorders, bone marrow, stem cell or solid organ transplantation, infection with sepsis and shock, and acute or chronic kidney disease. The precise pathophysiological mechanism behind PRES has yet to be fully clarified. The hypertensive and cerebral hyperperfusion theory proposes the loss of autoregulation in the posterior circulatory area of the cerebrovascular system due to large and sudden increases in blood pressure as the main cause. The endothelial dysfunction theory proposes endothelial injury caused by circulating toxins and the consequential increased permeability of the blood-brain barrier as the primary cause of the development of vasogenic oedema. Clinical presentation is nonspecific. The most common clinical presentation includes headache and impaired visual acuity, and in more severe cases visual loss, epileptic seizures, altered mental status, and altered levels of consciousness. T2-weighted/FLAIR sequences on magnetic resonance imaging (MRI) play a fundamental role in the diagnosis of PRES. The treatment is aimed at eliminating the cause if possible. PRES is usually reversible, and prognosis is good if the cause is recognized and removed.

Keywords: Posterior reversible encephalopathy syndrome, PRES, magnetic resonance imaging, vasogenic oedema, hypertension

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INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a rare clinical entity, which first got its name in 2000 when it was used by Casey *et al.* (1). PRES was first described in 1996 by Hinchey *et al.* in a study of 15 patients. They used the term "reversible posterior leukoencephalopathy syndrome (RPLS)" which was characterized by clinical symptoms such as headache, confusion, disturbances of consciousness, visual impairment, and seizures. These symptoms correlated with the typical neuroimaging features consisting of posterior-predominant cortical or subcortical white matter oedema within the parietal and occipital lobes. It was the involvement of subcortical white matter that made them add the prefix "leuko" in the name which suggests only white matter involvement (2). However, imaging findings in the setting of PRES are not often exclusively confined to the white matter, and often extend to involve the overlying cerebral cortex, basal ganglia, brainstem, and cerebellum, which is why this name is not completely satisfactory (3). PRES in literature is also often referred to as "reversible posterior cerebral edema syndrome", "posterior leukoencephalopathy syndrome", "reversible occipital-parietal encephalopathy", "hypertensive encephalopathy", "hyperperfusion encephalopathy" and "brain capillary leak syndrome". While PRES most commonly manifests on imaging as cortical or subcortical oedema within the parietal and occipital lobes, it may also occur in an atypical fashion with the involvement of other regions such as the frontal lobe, temporal lobe, basal ganglia, thalamus, brainstem, or cerebellum, and even spinal cord without the involvement of the cerebral hemispheres (1,4,5,6).

Therefore, none of these names are completely satisfactory as the syndrome is not often restricted to either the white matter or the posterior regions of the brain, and it is not always reversible. PRES is potentially reversible and patient prognosis is often positive with timely recognition and removal of the inciting factors leading to PRES. However, death and permanent neurological damage have been reported in a small number of patients, as has the recurrence of PRES in 6% of the cases. Hence, in 2016 Kabre and Kamble proposed a new terminology "potentially reversible encephalopathy syndrome" (7).

PATHOPHYSIOLOGY

The precise pathophysiological mechanism underlying the development of PRES has yet to be fully clarified (8). There are two main proposed theories for the pathophysiology of PRES. The hypertensive and cerebral hyperperfusion theory describes severe arterial hypertension as the key factor for the development of PRES (9), proposing that the primary cause of vasogenic oedema is the loss of autoregulation in the posterior circulatory area of the cerebral vascular system due to large and sudden increases in blood pressure, which leads to cerebral hyperperfusion and consequential blood-brain barrier dysfunction, causing vascular leakage (10). The area of the central nervous system supplied by the posterior circulation show predilection for brain oedema, compared to the area supplied by anterior circulation, due to the lack of sympathetic tone of basilar artery vasculature (9). Likewise, the cortex is less prone to oedema, as it is structurally more tightly packed, unlike the white matter (11). This theory is based on the fact that hypertension is a common occurrence in patients with PRES, on reports of cerebral hyperperfusion in patients imaged with TcPPm-HMPAO single-photon emission computed tomography (SPECT), and on animal studies showing the development of cerebral hyperperfusion and vasogenic oedema with experimentally elevated blood pressure (12). However, the development of PRES in patients with normal or mildly increased blood pressure, as well as studies demonstrating cerebral hypoperfusion in patients with PRES, and lack of correlation with the degree of the severity of hypertension and brain oedema, point to the shortcomings of this theory (8).

A related vasoconstriction and cerebral hypoperfusion theory describes cerebral ischemia as a key factor in the pathophysiology of PRES. According to this theory, extreme hypertension results in focal vasoconstriction due to autoregulatory compensation, leading to reduced cerebral perfusion and local ischemia, which causes blood-brain barrier breakdown and the development of vasogenic oedema (13, 14). This sequence of events, leading to the development of PRES, was noticed in patients being treated with immunosuppressive agents such as cyclosporin A and tacrolimus (14). Even though cerebral infarction is an unusual occurrence in patients with PRES, there is a possibility that it develops due to microcirculation compression caused by vasogenic oedema. Some imaging studies that have used magnetic resonance (MR) perfusion have shown reduced brain perfusion in patients with PRES. This theory is also supported by the evidence of vasculopathy as demonstrated using catheter angiography in patients with vasoconstriction and hypoperfusion, as well as by the common occurrence of typical PRES imaging

features in watershed distribution. Nevertheless, it is considered that cerebral ischemia does not play a big part in the pathophysiology of PRES in most patients (15, 16).

The second major theory is the endothelial dysfunction theory, which proposes endothelial injury caused by various circulating endogenous or exogenous toxins as the primary cause of PRES. Circulating toxins cause endothelial injury which causes further release of vasoconstrictive and immunogenic agents, leading to vasoconstriction, increased vascular permeability, and the development of vasogenic oedema. According to this theory, the development of PRES is due to immune system activation that induces endothelial dysfunction suggesting that hypertension and vasoconstriction are not the primary causes in the pathophysiological mechanism of PRES. Cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1), induce the expression of adhesion molecules which interact with circulating leukocytes and trigger the release of reactive oxygen species (ROS) and proteases, leading to endothelial injury and vascular leakage (17). These cytokines also trigger astrocytes to produce vascular endothelial growth factor (VEGF), which leads to the weakening of endothelial cell tight junctions and the breakdown of the blood-brain barrier. Additionally, VEGF activates the vesiculo-vacuolar organelle, thus creating the main way for the extravasation of fluids and macromolecules (18). Also, increased levels of leukocyte adhesion molecules have been registered in preeclampsia, solid organ transplantation, allogenic bone marrow transplantation, infection, sepsis, and shock (8). In their study, Marra *et al.* showed that increased levels of VEGF in patients with preeclampsia result in a fivefold increase in vascular permeability (17). Likewise, in one case of PRES following heart transplantation, a brain biopsy showed endothelial activation, T-cell trafficking, and endothelial VEGF expression (17, 19).

In patients with normal arterial blood pressure, cytotoxic medications may have a direct effect on vascular endothelium, causing endothelial dysfunction, and capillary leakage, leading to blood-brain barrier breakdown and axonal swelling, and subsequently vasogenic oedema (20).

Elevated levels of endothelial dysfunction markers, such as lactate dehydrogenase and abnormal red blood cell morphology, can be found in patients with preeclampsia, and they usually arise prior to the clinical syndrome. They also correlate better with the extent of cerebral oedema, than changes in blood pressure (21, 22). More specific markers of endothelial dysfunction seen in patients with preeclampsia include fibronectin, tissue plasminogen activator, thrombomodulin, endothelin-1, and von Willebrand factor (23, 24). These markers have also been registered in other states associated with PRES, such as chronic kidney failure, lupus nephritis, and hemolytic uremic syndrome (25). Although in patients with thrombotic thrombocytopenic purpura who developed PRES, hypertension and renal insufficiency usually occurred simultaneously, a case was reported in which these two complications were absent, suggesting endothelial dysfunction as the primary factor in the development of PRES (26, 27).

The theory of endothelial dysfunction is based on the fact that up to 30% of patients with PRES do not have elevated arterial blood pressure levels that are necessary for the breakdown of the autoregulation mechanism of the cerebral vasculature (28,29), and can also explain the development of PRES in patients who are going through chemotherapy or immunosuppressive therapy, and in systemic conditions characterized by endothelial damage and the absence of severe hypertension, such as sepsis, preeclampsia, and after bone marrow transplantation (30,31).

Another theory on the pathophysiology of PRES was recently published, which suggests arginine vasopressin (AVP) hypersecretion as a possible mechanism in the development of PRES. Numerous conditions associated with PRES, such as sepsis and eclampsia, have also been associated with AVP hypersecretion. In their study, Largeau *et al.* hypothesized that increased AVP secretion or AVP receptor density will lead to activation of vasopressin V1a with consequent cerebral vasoconstriction, endothelial dysfunction, and cerebral ischemia with resultant cytotoxic oedema, which may ultimately lead to increased endothelial permeability and subsequent vasogenic oedema. This theory is significant as it creates the possibility for pharmacological treatment of PRES by targeting the AVP pathway (32).

Although the pathophysiology of PRES is still a controversial topic and the exact pathophysiological mechanism remains unclear, blood-brain barrier dysfunction is generally accepted as the initial step for the formation of vasogenic oedema with predominantly affected posterior circulation of the central nervous system, regardless of whether the underlying cause is arterial hypertension or endothelial damage caused by circulating toxins. Still, it should also be kept in mind that the underlying cause may be a combination of interrelated processes, due to the heterogeneous nature of PRES (33).

ETIOLOGY

PRES is a rare syndrome, but the causes are numerous. The most common conditions associated with the development of PRES are moderate to severe hypertension, preeclampsia, eclampsia, the use of immunosuppressant and cytotoxic drugs most commonly in patients with hematopoietic malignancies, and in the setting of bone marrow, stem cell, or solid organ transplantation, infection with sepsis and shock, autoimmune disorders, and acute or chronic kidney disease that can ultimately lead to renal insufficiency (8, 34, 49). In their study, Fugate *et al.* found that hypertension was the causative factor in 61% of patients, cytotoxic drugs in 19%, sepsis in 7%, preeclampsia or eclampsia in 6%, and multiple organ failure in 1% of patients, while autoimmune disorders were present in 45% of patients (35).

Although some patients with PRES are normotensive at presentation, in most of them their blood pressure is higher compared to the initial value of blood pressure, while a minority of them are truly normotensive, and sometimes even hypotensive (1, 34). However, according to some studies, it also appears that PRES may be more common in patients with various comorbidities, such as systemic lupus erythematosus (SLE) (50,51,52), cryoglobulinemia (53), thrombotic thrombocytopenic purpura (TTP) (26), and hemolytic uremic syndrome (HUS) (54,55), and in patients on immunosuppressive and cytotoxic drugs, such as cyclosporine (52, 56), or cisplatin (20). They also noticed a higher incidence of renal failure in hypertensive patients with PRES, which may suggest a role for fluid overload, electrolyte disturbances, or uremia (57).

The development of PRES has also been described in patients who took immunosuppressive and immunomodulatory drugs as part of treatment for malignant or rheumatologic conditions and after transplantation of bone marrow, stem cells, and solid organs (35). These medications have a well-known neurotoxic effect, which has not been fully explained. PRES can develop in patients after several months of using these drugs, during the maintenance phase, which means that elevated or toxic levels of medications are not necessary for the development of PRES. Likewise, previous exposure to these medications does not appear to have a protective effect (25). One of the most common immunosuppressive agents associated with the development of PRES is cyclosporine. It is indicated after solid organ and bone marrow transplantation, and in the prevention of graft rejection after solid organ, allogenic bone marrow, and stem cell transplantation, and in the prevention of graft-versus-host disease (GVHD), but it is also extremely nephrotoxic and neurotoxic (56). Hypertension, hypomagnesemia, and hypocholesterolemia have been known to enhance the neurotoxic effect of cyclosporine, and in turn, cyclosporine may exacerbate hypertension by inhibiting nitric oxide production (58). Other common chemotherapeutic agents associated with the development of PRES include platinum-containing drugs, CHOP/R-CHOP regimens (cyclophosphamide, doxorubicin, vincristine, prednisone or prednisolone, rituximab), and gemcitabine (59,60). Apart from them, PRES can also occur with the use of other medications such as sirolimus (61), tacrolimus (62), interferon alpha, bevacizumab (63, 64), and tyrosine kinase inhibitors (pazopanib, sorafenib, sunitinib) (35).

Autoimmune disorders associated with the development of PRES include SLE, cryoglobulinemia, polyarteritis nodosa (PAN), TTP, granulomatosis with polyangiitis (GPA), inflammatory bowel diseases (Crohn's disease, ulcerative colitis), rheumatoid arthritis (RA), Sjörgen syndrome and neuromyelitis optica (35). High percentage of patients with PRES suffering from an autoimmune disorder supports the theory of endothelial dysfunction as a mechanism of PRES. However, it is still unclear whether the primary cause of PRES is the presence of one of these disorders, or if PRES is caused due to the use of medications for treatment of these disorders. Leroux *et al.* conducted a study on a group of 46 patients with SLE who developed PRES, but the role of SLE itself in the development of PRES was not clear, because 95% of patients already had arterial hypertension, 91% had reduced kidney function, 54% received immunosuppressive therapy, and 43% received intravenous steroids (65).

PRES was also described in patients with sepsis, and acute and chronic kidney disease (35, 66). In patients with SLE, renal dysfunction is a particularly important risk factor (66).

PRES can occur in any age group. Some cases of PRES have been described in the pediatric population. Although most cases of PRES in children have been described in oncology patients, especially those after stem cell transplantation (67, 65), a study by Gupta *et al.* showed that most likely kidney disease is the most common cause of PRES in the pediatric population (68).

IMAGING

PRES is typically presented on neuroimaging findings as posterior-predominant bilateral and sym-

metric vasogenic oedema involving subcortical white matter, with a common parieto-occipital lesion distribution pattern (34). However, the paramedian parts of the occipital lobe are usually not affected, which helps distinguish PRES from bilateral posterior cerebral infarctions (35). In PRES, T2-weighted and FLAIR sequences on MRI often show focal or confluent areas of increased signal in the posterior-predominant subcortical white matter (36). In addition to the posterior parts of the hemispheres, the frontal lobes (up to 68%), especially the upper frontal gyrus, are also often affected by the oedema. Although they are uncommon, isolated posterior fossa lesions are increasingly described (25,37). In a small number of patients, temporal lobe oedema has also been described (37).

In addition to the typical posterior-predominant pattern involving parietal-occipital regions, other patterns of lesion distribution can be observed on MRI and have been described by Bartynski and Boardman in their study (37). In Fig. 1 we show a less common pattern of central PRES due to hypertension, which resolved completely after therapy. Likewise, the use of FLAIR sequences on MRI improved sensitivity and enabled detection of peripheral and cortical lesions, which turned out to be much more common (25). Therefore, four other patterns of oedema distribution in PRES have been described: holohemispheric watershed pattern, superior frontal sulcus pattern, a dominant parietal-occipital pattern, and partial or asymmetric expression of these primary patterns. In the holohemispheric watershed pattern, vasogenic oedema involves the frontal, parietal and occipital lobes. Superior frontal sulcus pattern is characterized by the prominent involvement of the frontal lobe with varying parietal-occipital involvement, while the partial or asymmetric expression of these primary patterns refers to the bilateral or unilateral lack of signal in parietal-occipital regions (25, 37).

PRES may present with atypical imaging findings, in terms of regions involved or different types of lesions not related to vasogenic oedema that can cause further complications such as cerebral hemorrhage, diffusion restriction, or contrast enhancement/imbibition (38,39). Atypical regions that may be involved include the brainstem, cerebellum, basal ganglia, thalamus, corpus callosum, and the spinal cord. A study by McKinney *et al.* conducted on 124 patients with PRES, showed the involvement of the brainstem and basal ganglia without the presence of cortical or subcortical oedema in as many as 4% of patients (40). They also conducted an additional study consisting of 76 patients with PRES, which showed involvement of thalamus involvement in 30,3% of patients, cerebellum in 34,2% of patients, brainstem in 18,4%, and basal ganglia in 11,8% with unilateral involvement in 2,6% of patients (4). Liman *et al.* studied a cohort of 96 patients diagnosed with PRES, and in more than 50% of patients found infratentorial involvement, predominantly in the cerebellum and pons, whilst around 25% of patients showed basal ganglia and thalamus involvement (5). In their study, Kastrup *et al*. described the involvement of the basal ganglia in 1,6% of patients, and of the cerebellum in 6,5% of patients (6). The involvement of the spinal cord in patients with PRES is exceptional, and only a few cases have been described, with confluent and expansive areas of increased signal found in the central part of the spinal cord as shown on the T2-weighted sequence on MRI (41).

PRES may be complicated by cerebral hemorrhage. Several patterns of cerebral hemorrhage have been described, such as large hematomas causing compression of surrounding structures, subarachnoid hemorrhage (SAH), or multiple focal microhemorrhages (<5 mm) (42). The overall rate of cerebral hemorrhage in patients with PRES ranges from 15% to 65%, with the higher percentage reflecting the greater number of reported cases (43). The exact mechanism of cerebral hemorrhage in PRES is still unknown. In a study conducted by Hefzy *et al.* on a group of 151 patients, 15% of cases of cerebral hemorrhage were recorded, with the incidence being highest in cases of immunosuppression, more commonly in patients following bone marrow transplantation than in solid organ transplantation. No difference in the incidence of cerebral hemorrhage was observed in patients with normal, slightly elevated, or extremely elevated blood pressure (38). McKinney *et al.* observed that the proportion of patients who developed cerebral hemorrhage was much higher (64,5%), due to the increased use of SWI (susceptibility-weighted imaging), as it is more sensitive in the detection of hemorrhage (44).

In addition, PRES may be complicated by the development of cytotoxic oedema as indicated by diffusion restriction. Areas of reduced diffusion are usually small, punctate, and are located within confluent lesions of vasogenic oedema. Since vasogenic oedema is a characteristic imaging finding in PRES, MRI by FLAIR, diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) help us in differentiating types of oedema. Isointense or hyperintense signal on DWI and hyperintense signal on ADC sequence are a feature of

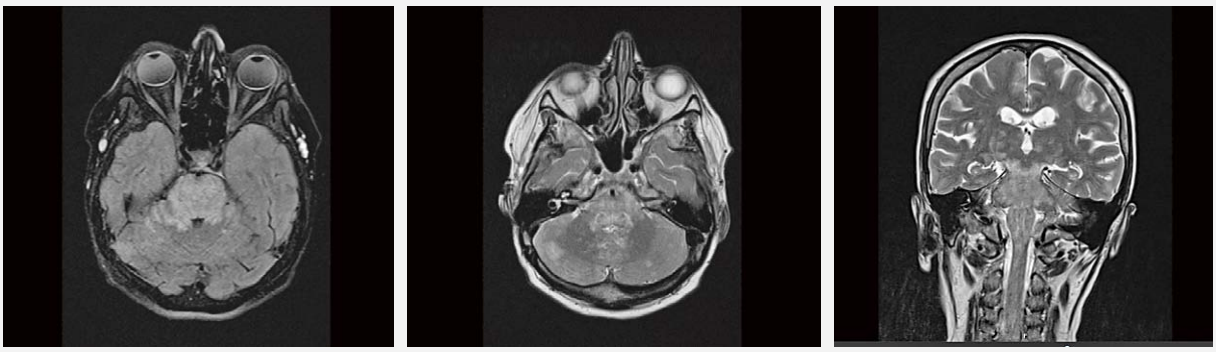

Fig. 1. *Brain MRI of a 59-year-old hypertensive female patient with renal impairment showing typical hyperintense changes in brain stem and in cerebellar both hemispheres on T2/FLAIR sequences.*

vasogenic oedema, while hyperintense signal on DWI and hypointense signal on ADC sequence are characteristics of cytotoxic oedema (45). According to data from previously published studies, approximately 10% - 33% of patients with PRES develop cytotoxic oedema (46,47), which is thought to be a consequence of late treatment, resulting in persistent hyperperfusion and vessel injury caused by the mass effect of vasogenic oedema on the surrounding tissue, which ultimately leads to ischemia and brain infarction (4).

Superficial leptomeningeal enhancement is the most common pattern seen on MRI. Additionally, a nodular and, in a third of patients, a combined leptomeningeal and gyral cortical pattern can be described too (39,41).

MR angiography often shows vasculopathic changes in patients with PRES. In their study, Bartynski *et al.* discovered evidence of diffuse or focal vasoconstriction in 87% of patients (48).

TREATMENT OPTIONS

Treatment of PRES is aimed at removing the primary condition leading to PRES and includes symptomatic treatment. In cases of hypertension, treatment is aimed at gradual and careful blood pressure lowering (69), while in cases of preeclampsia/eclampsia, it is aimed at the timely delivery of the baby as well as careful blood pressure lowering (70). In cases of PRES induced by cytotoxic or immunosuppressive agents, prompt removal of the drug is usually recommended and leads to clinical and radiological improvement (69,71). Seizures are treated with parenteral benzodiazepines (diazepam) (69), while magnesium sulphate is used for seizure prophylaxis in the setting of preeclampsia/eclampsia (70). It is important to promptly recognize and treat conditions that are known to contribute to the development and poor prognosis in patients with PRES, such as electrolyte disturbances, volume overload, uremia, and sepsis. Hypomagnesemia is a common finding in patients with PRES, and it is believed that magnesium supplementation may be useful in the treatment of PRES (69, 72).

CONCLUSION

PRES is a rare clinical and radiographic syndrome with numerous causes and characteristic neurological symptoms and imaging findings, although it may present with atypical imaging findings too. The exact pathophysiological mechanism has yet to be fully clarified and remains a controversial topic. PRES is usually reversible. If the cause is recognized and removed, the prognosis is generally good, and most patients recover within a few weeks. Unfortunately, a certain number of patients die or are left with permanent neurologic deficits.

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