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Posterior Reversible Encephalopathy Syndrome: A Review

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a clinical-neuroradiological entity characterized by headache, vomiting, altered mental status, blurred vision and seizures as well as images suggesting white-gray matter edema involving in most cases posterior regions of the central nervous system, as demonstrated by magnetic resonance image. The development of PRES is most commonly associated with hypertensive encephalopathy, preeclampsia-eclampsia and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, and immunosuppressive/cytotoxic drugs. While usually reversible, the early recognition and treatment of this syndrome is important to prevent permanent neurological sequelae. The treatment is based in the management or withdrawal of the triggering factor. In this manuscript we will briefly review the pathogenesis, clinical scenario, diagnostic studies and management of PRES.

Key words: Reversible encephalopathy, hypertensive crisis, hypertensive emergency, eclampsia, immunosuppressants

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinical-neuroradiological entity, (1) initially described in 1996 by Hinchey and co-workers, as reversible posterior leukoencephalopathy syndrome. (2) This syndrome is characterized by headache, visual disturbances, seizures, altered mental status and radiological findings of edema in the white matter of the brain areas perfused by the posterior brain circulation. (3) While most cases are due to systemic hypertension (HTN), other conditions and entities have been identified as etiologic or risk factors in the absence of HTN, such as immunosuppressant drugs use, nephrotic state, sepsis, and systemic lupus erythematosus (SLE). (2,4-6)

Hypertension is an exceeding common medical disorder estimated to affect 20 to 30% of the adult population in first world countries and approximately 72 million people in the US. (7,8) Hypertensive encephalopathy which complicates poorly controlled HTN, is the most common cause of PRES. (7,8) In these patients the rate of increase of blood pressure (BP) is a more important factor in the development of PRES than the absolute BP levels. (9) The precise pathogenetic mechanisms leading to the development of PRES have not been identified. Nevertheless, regardless of the triggering factor, PRES involves the development of edema in the affected areas of the brain. (10-12)

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Etiology and Pathogenesis

Hypertension, hypertensive crises and their role in PRES

Normally, compensatory mechanisms in the central nervous

system (CNS) limit blood flow in the context of a sudden increase in systemic BP, avoiding fluid leakage from the intravascular space to the interstitium. This autoregulatory mechanism is facilitated by vasoconstriction as a result of an increase in sympathetic tone. (13) In PRES, this autoregulatory response is abnormal resulting in a breakdown of the normal blood brain barrier (BBB) and culminating in vasogenic brain edema. (14,15) There is an apparent predisposition for edema to occur in the posterior CNS areas, particularly in the occipitoparietal areas. (2) This is thought to be secondary to the partial lack of sympathetic innervation of the vasculature that emerges from the basilar artery; (8) however, other sites of the brain and cerebellum may be affected even when occipitoparietal areas are not involved. (1,10,16,17)

In non-hypertensive patients, cerebral blood flow is preserved while the mean arterial pressure (MAP) is maintained within a range of 60-120 mmHg. However, in patients with chronic HTN the auto-regulatory range is shifted to the left. Thus, while normotensive patients can develop PRES with an acute increase in BP rising to a MAP of 120 mmHg, among patients with chronic HTN the BBB disruption occurs with MAP levels greater than 150 mmHg. (8)

Chronic HTN is a relative *protective* factor in the development of PRES because in response to sustained high BP, the walls of large and small cerebral vessels become hypertrophic, this results in a reduction of the wall stress providing BBB protective effects. This compensatory response is not present in pregnancy-induced HTN. (14)

Vasogenic edema results from the combination of HTN and endothelial injury. (14) Since cases of PRES without HTN have been reported, endothelial dysfunction may represent a common pathway in the pathogenesis of PRES, regardless of etiology. Therefore, endothelial damage due to other risk factors such as diabetes mellitus, dyslipidemia, and smoking may indirectly play a role in the pathogenesis of PRES. (13)

The cytotoxic theory postulates that an acute rise in BP produces hypoperfusion leading to hypoxia resulting in endothelial damage with subsequent edema. It is possible that both the cytotoxic and vasogenic theories may explain the development of PRES, as vasogenic edema can progress into cytotoxic edema. Edema of any nature, can compromise the circulation of the affected sites producing hypoxia with subsequently adenosine triphosphate (ATP) depletion resulting in sodium-potassium pump failure therefore maintaining an osmotic gradient within the cells producing water intracellular swelling. (18,19) Thrombotic microangiopathy, a complication of hypertensive crises can induce PRES development. It is produced secondary to endothelial damage leading to coagulation cascade activation with a permeability increase, leading to perivascular edema. (7,20)

Pregnancy-induced PRES

In PRES associated with pregnancy-induced HTN, it is thought that pregnancy itself predisposes the brain to edema formation, particularly in late-pregnancy. (14) In animal model studies of pregnancy, the smooth muscle reactivity that leads to *forced* vasodilatation needs lower pressures to be produced. (21) For unknown reasons, in animals, in late-pregnancy state there is a vasoconstriction activity in cerebral arteries in response to serotonin exposure, while the contrary occurs in non-pregnant specimens, in which the response results in vasodilatation. (21) Pregnancy has direct effects on perivascular innervations by mechanisms not yet elucidated, particularly in pial vessels, in which nerves hypertrophy is produced. (22) This suggests that neurotransmitters may have a role in hypertensive *intolerance* that results in the genesis of PRES. (14)

It has been proposed that angiogenic factors may have a role in the prevention of PRES development, via diminishing endothelial dysfunction. (23,24) Among endogenous antiangiogenic factors both soluble vascular endothelial growth factor (VEGF) receptor and placental growth factor (PIGF) are found increased in pregnancy. (24) While as general rule preeclampsia-eclampsia treatment is achieved with delivery, for unknown reasons, PRES might be developed in the postpartum period. (16)

Exogenous etiological factors: drugs related in the development of PRES

The use of many drugs has been related with PRES pathogenesis; however, the exact mechanisms are yet to

be fully explained. Many theories have been suggested for this strong drug-disease relation, including drug-induced HTN, nephrotoxicity, direct neurotoxicity, and endothelial damage. (25,26)

Many immunosuppressant drugs have been associated with the development of PRES. (2,27,28) Oxaliplatin has been reported as a possible cause of PRES. Its influence in the syndrome occurs due to its pass through of the BBB with secondary fluid transudation and subsequent cerebral edema. (28) Bevacizumab, a recombinant humanized monoclonal antibody, produces PRES by both increasing BP and inhibiting vascular endothelial growth factor (VEGF). (24) Sunitinib is a tyrosine kinase inhibitor which also inhibits VEGF effects, via anti-VEGF receptor. (20) Moreover, glucocorticoids such as dexamethasone have been shown to induce PRES, although it is an uncommon steroids-use complication, and thought to be related to HTN secondary to its mineralocorticoid effects. (29)

Other cytotoxic agent related to the development of PRES is sirolimus, a drug that alters the metabolism of astrocytes with secondary structural changes leading to edema. (30) Gemcitabine, a synthetic pyrimidine nucleoside analogue antineoplastic agent has a well described neurotoxic effect and has recently been associated with PRES development. (25) Cyclosporine is a drug that has been related as an etiologic factor of PRES since it was first described in 1996. (2,31) The mechanism by which it induces the syndrome is explained by the increase in efferent sympathetic activity with possible acute HTN development, it has been linked more frequently when administered via intravenous (IV) access. It is also thought that it may have a direct activation of the central sympathetic neurons as it is able to cross the BBB. (31)

Vasopressive agents play a significant role in the development of acute new onset HTN, eventually leading to PRES pathogenesis. Midodrine, a selective α-1 adrenoreceptor agonist can increase both venous and arterial constriction therefore may produce HTN-induced PRES. (27)

Miscellaneous conditions

Red cell morphology abnormalities have been suggested to have a role in the development of PRES. (32,33) This is likely to be a consequence of endothelial action that produces structural derangement of erythrocytes resulting in abnormal morphology types such as schistocytes and anisocytes. This seemingly explains why the serum lactic dehydrogenase (LDH) is elevated in patients with PRES secondary to endothelial damage. (18,32)

Sepsis and septic shock also seem to have a role in the pathogenesis of PRES by two mechanisms: endothelial derangement and microcirculation disturbances. (5) Endothelial injury is caused by pathogenic agent virulence factors and mediators released in the context of an exaggerated immune response. (34,35) The microcirculation alterations seen in sepsis are secondary to leukocyte microvessels blockage reducing tissue perfusion and also due to alterations in vascular tone via vasoactive substances release. (5,35) Likewise, bacterial and viral infections may have a role as trigger factors rather than etiologic in the pathogenesis of PRES even when sepsis or septic shock have not been developed. (33)

Clinical features

The clinical spectrum of PRES include headache as the most common symptom; however, it may not be present in all cases. (2) Other common signs are consciousness alterations such as lethargy, stupor, and somnolence although coma may develop. Visual disturbances range from blurred vision to cortical blindness, and permanent visual field defects have been reported. (9) Seizures, or *status epilepticus* (SE), may present as the initial clinical picture in some cases. (2,3) Although rare, signs of motor dysfunction such as hemiparesis, dystonia and dysmetria may be present. (2)

Pyramidal tract signs, such as Babinski's reflex, hyper or hyporeflexia are possible, but uncommon clinical features. (28,29) Sluggish pupillary reflexes or frank myosis can be part of the clinical picture. (6,29) Brain stem involvement manifestations comprise dyspnea, anarthria, and dysphagia. (27,36) Memory disturbances and alteration to the faculty of concentration might be part of the clinical manifestations. (37) Intracranial HTN may be part of PRES, therefore on funduscopic examination papilledema and hemorrhages can be noted. Contralateral motor manifestations are present

when the edema comprises frontal circumvolutions or when basal ganglia are affected. (32) Recurrence is another clinical situation that could be present in 3.8% of the cases. (33)

Histopathological changes seen in PRES include hydropic axonal swelling and myelin edema which is shown as myelin pallor without tissue destruction. (38)

Diagnostic studies

Cerebrospinal fluid analysis

Invasive diagnostic methods such as lumbar puncture (LP) to evaluate cerebrospinal fluid (CSF) are not needed; however, in the setting of SLE or acquired immunodeficiency syndrome in which other causes of the neurological picture have to be ruled out, the CSF analysis serves as an important differential diagnostic tool. (39,40)

Image studies

Computed tomography (CT) scan findings are negative in almost all cases of PRES and when positive, it is difficult to distinguish between PRES and acute stroke. Therefore the image study of choice is the magnetic resonance imaging (MRI). (33,41)

The most common findings in image studies are radiological signs of edema in the white matter of posterior portions of the brain, particularly occipital and parietal areas, being in commonly bilateral; (2) however, different distribution has been reported, postfrontal cortical, subcortical white matter, cortex, brainstem, basal ganglia and cerebellum (**Figure 1** and **2**). (2,12,18) Covarrubias et al. (18) retrospectively found that occipitoparietal areas were involved in 100% of the cases of PRES and compromised anterior structures (i.e., temporal and frontal lobes) in more than 80%. Depending on the literature that is reviewed, frontal lobe lesions may occur in 68 to 82% of the patients. (12,18,41) The lentiform and caudate nuclei are seen to have affection in 11.8% of the cases of PRES. (12) With little prevalence the brain stem and the basal ganglia have been involved in some case reports. (12,41) Though its incidence is not suggested in the syndrome's name temporal lobe areas are affected in up to 91% of cases. (18)

Bartinsky and co-workers have described three different image patterns on the MRI for PRES lesions. (41) 1) holohemispheric water shed lesions (22.8%), consist in linear vasogenic edema that maybe present in the frontal-parietal and occipital lobe; 2) superior frontal sulcus pattern is seen in 27.2% of the cases with an anterior distribution; 3) dominant parietal-occipital pattern lesions may include both the white matter and the cortex in the posterior regions of the encephalus with an incidence of 22.1%. There is a subclassification within the three patterns which accounts for the remaining 27.9% of the lesions; it is described as a partial or asymmetric expression of the original patterns.

The neuroimaging differential diagnosis of PRES include neoplasms, encephalitis, inflammatory and infectious processes, demyelinating pathology and cerebrovascular accidents. (19) Diffusion-weighted magnetic resonance imaging (DWI) is the study of choice in PRES to discriminate between vasogenic and cytotoxic edema. Thereby, being helpful as a screening testing image method in the setting of ischemic complications of PRES indentifying irreversible tissue damage. (18)

Apparent diffusion coefficient (ADC) mapping, detects motion of water molecules, showing increased values in the acute phase of PRES, this can be useful to rule out other conditions that can mimic PRES, such as central pontine myelinolysis. (37) Vasogenic edema appears as an increase in diffusion in ADC mapping as a hyperintense signal. Alternatively cytotoxic edema has contrarily decreased in ADC. Because both, cytotoxic and vasogenic edema show an increase signal in DWI, the use of ADC is of great utility in differentiation of the two. (18,19)

Management

It is important to treat patients with PRES as soon as recognized to avoid the risk of irreversible lesions. (39) The treatment is based in the management or withdrawal of the triggering factor.

In the setting of hypertensive emergencies, intensive care unit (ICU) admission must be done in order to perform continuous hemodynamic, cardiac and neurological status close monitoring. (42) The current recommendations are to reduce the MAP in an initial rate of no more than 20-25% within the first 2 hours, as a rapid reduction of the MAP can

worsen the brain dysfunction by decreasing perfusion. (43) Thus, an IV, short half-life drug that permits easy titrating would be the best pharmacologic therapy in this context. While the current available antihypertensive agents includes several drugs, new rapid-acting IV medications (e.g. clevidipine) have gained acceptance as first choice for the management of hypertensive crises; (42) however, current guidelines are not available.

Preeclampsia-eclampsia related PRES management resides in the general recommendations for treatment of pregnancy-induced hypertension. While definitive treatment consists in prompt delivery (i.e. labor induction or cesarean section), general measures (e.g. IV fluids, thromboprophylaxis), BP control, prevention and/or treatment of seizures must be provided. (44) Even though hydralazine is the most common used antihypertensive agent in this scenario, it has been proven that calcium channel blockers, specifically dihydropyridines, decreased the rate of persistent high BP. (45) Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers are contraindicated in pregnancy. (8) In the setting of eclampsia, magnesium sulfate is known to be the drug of choice as compared with other anticonvulsant agents with proven decreased maternal mortality and diminishing recurrence of seizures episodes as well as infants outcome improvement. (46-48)

General measures have to be taken in the setting of complicated PRES such as in cases with seizures or SE (defined as generalized convulsions which last at least 5 minutes or two or more episodes between which there is not complete recovery of level of consciousness) (49) in which airway ensue, including invasive ventilation may be needed, anti convulsivant agents have to be given in this scenario, being IV lorazepam the most recommended drug. (50,51) Since pronounced metabolic or respiratory acidosis might be present, arterial blood gases screening should be obtained, in order to improve acid-base and/or airway management. (52) *Status epilepticus* that does not improve with correct administration of benzodiazepines, phenytoin, valproate or phenobarbital (i.e. refractory SE), (53) might be managed with continuous IV infusion of pentobarbital. (54) In order to determine treatment accomplishment it is necessary to achieved clinically and electroencephalographically complete absence of convulsion activity. (50)

Obstructive hydrocephalus is a rare complication of PRES, which is secondary to cerebrospinal fluid (CSF) circulation obstruction and peripheral structure edema. Surgical drainage methods may be needed such as external ventricular drain or ventriculoperitoneal shunt resulting in an improvement of the neurological picture, returning to the baseline within 3 days after the procedure, when the underlying cause is also treated. (55)

Conclusions

Cases of PRES have been widely reported since its first description and various factors such as etiology have been identified; however, numerous aspects regarding the pathogenesis of this entity are yet to be elucidated. Due to the vague, non-specific clinical scenario developed in patients with PRES, in order to establish early diagnosis of this condition, it is important to be cognizant of this entity as well as the possible causative factors involved on each case. The certain identification of this syndrome is achieved with head MRI specifically with DWI. More invasive procedures such as LP are neither necessary nor recommended. The main features obtained with MRI are high density areas suggestive of CNS edema mostly in the posterior white matter of the brain, although anterior structures and gray matter may also be involved. The treatment of PRES, as a secondary pathology, depends upon the determination of the underlying contributing condition; however, palliative therapy for symptoms that might worsen the outcome (e.g. seizures) must be provided, as well as strictly monitored BP control.

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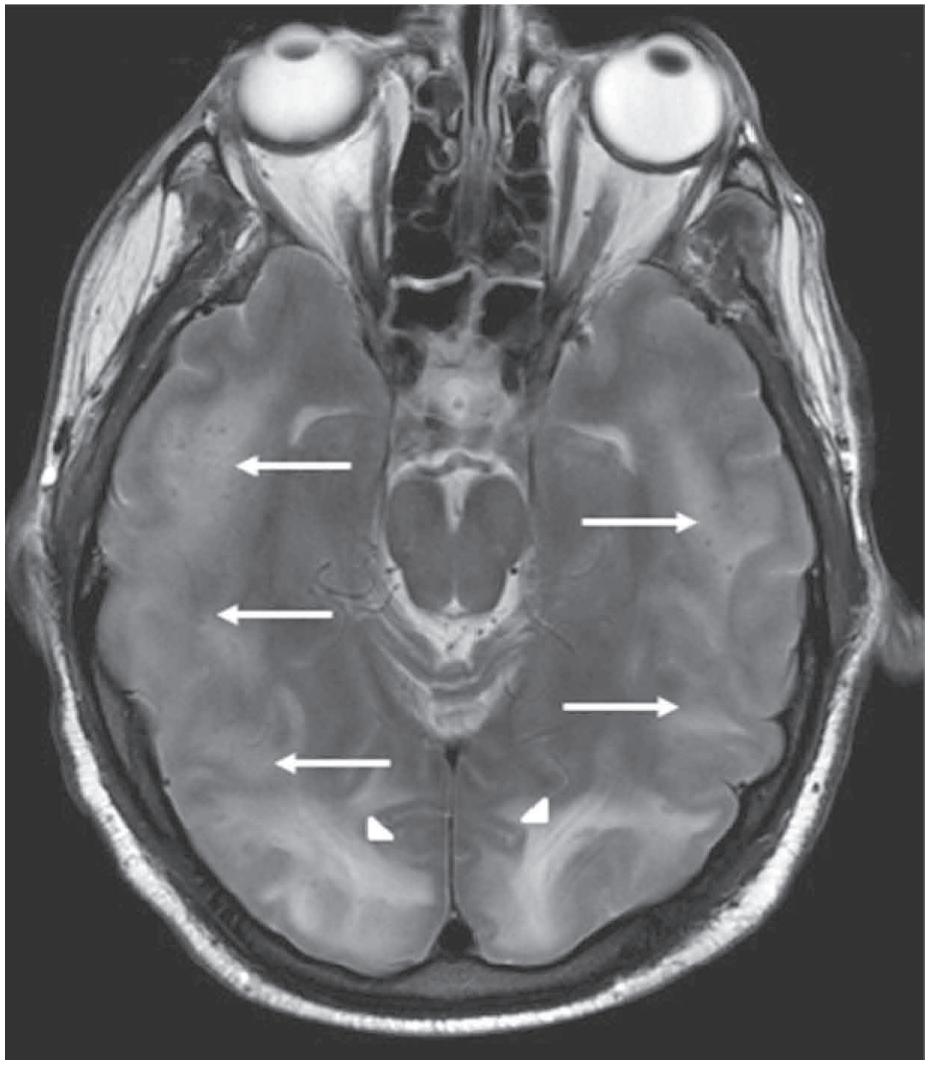
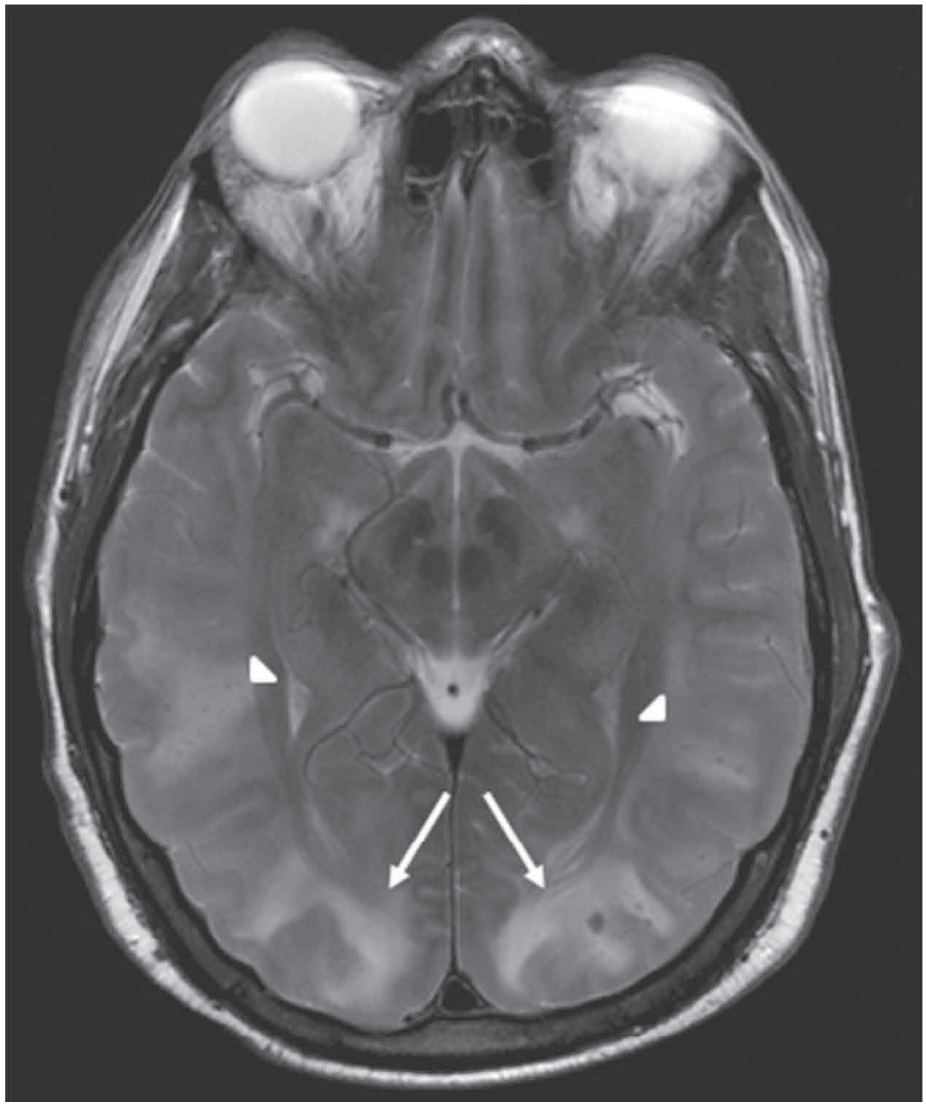
Figure 1. Axial T2 weighted magnetic resonance imaging (MRI) image showing bilateral subcortical holohemispheric edema.



Legend:
Axial T2 weighted MRI from a patient with PRES showing bilateral high-density areas in the white matter of both cerebral hemispheres (arrows). This image also demonstrates posterior predominance of the edema, revealing zones with more hyperintense signal in both occipital lobes (arrow heads).

Figure 2. Axial T2 weighted magnetic resonance imaging (MRI) revealing bilateral subcortical white matter temporooccipital edema.



Legend:
Axial T2 weighted MRI demonstrating areas of hyperintense signal in occipital (arrows) and parietal (arrowheads) lobes bilaterally, with higher density in the occipital regions, findings compatible with PRES.

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