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POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES) : WHAT A PHYSICIAN SHOULD KNOW ABOUT!

Clinical Science

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ABSTRACT

Among the myriad of diseases that can cause acute reversible neurological dysfunctions, the Posterior Reversible Encephalopathy Syndrome (PRES) with its diverse etiology and varied presentation needs attention. At risk population includes those with chronic hypertension, eclempsia, auto- immune disease, chronic kidney disease and drug induced especially anti-cancer and immunosuppressant drugs. Once thought of its relation only to existing hypertension, its always reversibility and affection only to posterior cerebral cortex, the term PRES is now a misnomer as this is not always reversible and is not necessarily restricted to posterior region of brain with advancement in radiological diagnostic techniques, the kidney diseases as risk factor for PRES is getting more and more popularity in a good subset of patients. However a prompt diagnosis and rapid correction of underline cause makes it reversible both clinically and radiologically.

KEYWORDS

PRES, hypertension, seizure, posterior regions, reversibility.

INTRODUCTION

Posterior Reversible Encephalopathy Syndrome (PRES) is a clinico-radiological disorder characterised by the sudden onset of neurological symptoms associated with potentially reversible lesions affecting posterior cerebral white matter of brain. The differential diagnosis is broad due to the heterogeneity of symptoms which include seizure, headache, visual disturbance and altered mental status. Diagnosis is made using computerised tomography (CT) or, most commonly, magnetic resonance imaging (MRI), the latter using diffusion weighted imaging (DWI). Prompt recognition of this entity is extremely important, if the treatment is delayed, there is a risk of permanent brain injury.

The name of this condition has undergone a change since the first description of 15 cases in 1996 by Hinchey et al., who coined the term 'Reversible Posterior Leukoencephalopathy Syndrome'. The present term 'PRES' has been coined to reflect its association with elevated blood pressure[1].

The term reversible posterior leukoencephalopathy could be a misnomer as the condition may not always reversible and is not necessarily restricted to the posterior regions of the brain and can also affect both white and grey matter.

The epidemiology of PRES is largely unknown due to the paucity of large prospective series. The syndrome has been described both in pediatrics and adult age group and the median age at presentation is approximately 40 years based on existing registry data. Females appear to be affected more than males. The onset of disease is usually acute or sub-acute and subsequent course is of rapid progression for few next days. Clinical features usually disappear after appropriate treatment is started, and the majority of the patients recover completely.[2]

There are a variety of medical conditions associated with PRES namely hypertension, renal disease, dialysis dependency, malignancy, and transplantation. PRES has been observed in the context of many multi-system diseases that are commonly associated with kidney disease such as preeclampsia, vasculitis and systemic lupus erythematosus. It has also been reported in infection, sepsis and shock. **(Table 1)**

Despite these consistent associations with kidney disease risk factors, the literature regarding occurrence of PRES in individuals with established kidney disease is relatively sparse.

Table-1. Causes Of Posterior Leukoencephalopathy

Common

- Hypertensive encephalopathy
- Toxaemia of pregnancy
- Renal impairment with hypertension
  - *Renal failure
  - *Haemolytic-uraemic syndrome
  - *Acute glomerulonephritis
- Infection, sepsis, shock
  - * Immunosuppressive and cytotoxic drugs
  - *Cyclosporin A
  - * Interferon-alpha
  - * Cisplatin
  - * Tacrolimus
  - *Cytarabine
  - *Intravenous immunoglobulins
  - *Erythropoietin
  - *Gemcitabine
  - *Tiazofurin
  - *Kinase inhibitor

Uncommon

- Collagen vascular disorders
  - *Systemic lupus erythematosus
  - *Systemic sclerosis
  - *Wegener's
  - *Polyarteritis nodosa
  - *Antiphospholipid syndrome
- Thrombotic-thrombocytopenic purpura
- Acquired immunodeficiency syndrome
- Acute intermittent porphyria
- Following organ transplantation
- Following repeated blood transfusion

Clinical Presentation

PRES is a rapidly evolving condition and is clinically characterised by headache, altered alertness and behavior ranging from drowsiness to stupor, seizures, vomiting, altered mental status including confusion and diminished speech, abnormalities of vision and occasionally focal neurological signs.

The onset is usually subacute but may begin abruptly by a seizure.

Seizures are common at the onset and are usually initial manifestations of the disease but can also develop later. Seizures may begin focally but usually become generalized. Multiple seizures are more common than single events. Status epileptics may develop. Lethargy and somnolence are often the first signs noted. Temporary restlessness and agitation may alternate with lethargy. Stupor and frank coma may develop, but usually patients remain responsive to stimuli. Memory and the ability to concentrate are impaired, although severe amnesia is unusual.

Abnormalities of vision are nearly always observed and are the most characteristic clinical manifestation of this syndrome. Patients often report blurred vision or visual hallucination, hemianopia, visual neglect, and frank cortical blindness may occur. Some cortically blind patients also have denial of blindness (Anton's syndrome). Fundus examination along with pupillary responses are often normal. The tendon reflexes are often brisk, and some patients have weakness and incoordination of the limbs and gait ataxia.

Pathophysiology Of PRES

Before exploring the pathogenesis of PRES, let us first understand some concepts of cerebral blood flow. Auto-regulation refers to the ability of an organ to alter its vascular resistance and maintain normal blood flow despite changes in arterial pressure. This is particularly important in the brain, an organ that receives approximately 15% of cardiac output. Cerebral blood flow must be maintained constant despite fluctuations in systemic arterial pressure. In the setting of low blood pressure cerebral arterioles will dilate to increase flow to the capillaries. In contrast, high blood pressure will result in arteriolar vasoconstriction to limit flow downstream. Such is the sophistication of this system, the human brain can maintain normal perfusion within a range of mean arterial pressure between approximately 60 and 140 mm Hg.[3]

Beyond these thresholds of autoregulation brain injury will occur due to hypoperfusion or hyperperfusion, respectively. The hallmark of PRES is vasogenic edema. The advent of DWI has facilitated the differentiation of vasogenic edema from cytotoxic edema, the latter an irreversible phenomenon due to tissue infarction. Controversy exists, however, as to the pathogenesis of vasogenic edema in PRES and the role of hypertension. Two theories, recently reviewed by Bartynski, have been suggested.

In the most popular [Vasogenic] theory, severe systemic hypertension overwhelms the auto-regulatory capacity of the cerebral vasculature (principally arterioles) leading to hyper-perfusion, arteriolar dilatation, injury to the capillary bed and vasogenic edema. Sympathetic stimulation can raise the upper threshold of auto-regulation; therefore, the predilection of PRES for the posterior brain, where there is a relative lack of sympathetic innervation, adds weight to this hypothesis. Although logical, there are a number of problems with this theory. First, blood pressure is not always elevated in PRES, and this is particularly true in cases associated with immunosuppression and organ transplantation. In addition, the degree of vasogenic edema does not always correlate with the severity of hypertension.

The second [Cytotoxic] theory states that the principal problem is cerebral vasoconstriction that causes downstream hypo-perfusion, ischaemia and vasogenic edema due to capillary leak. This is seen in many cases in which the blood pressure is either normal or minimally elevated in many cases of PRES, and this suggests that Hypertension cannot be the sole cause of injury in all cases. PRES is often seen in autoimmune diseases, organ transplantation and pre-eclampsia, where systemic processes operate rather than hypertension.[4]

These pathophysiological mechanisms in these conditions include autoimmunity and endothelial cell activation and/or injury. Endothelial cell dysfunction can lead to altered vascular tone, vasospasm hypoperfusion and ischaemia. Vascular endothelial growth factor (VEGF) is produced by the cerebral vessels in response to hypoxia and this increases their permeability, thereby resulting in edema. This injury encountered in PRES, is usually located in the watershed areas of the brain (esp. in the posterior cerebral areas), which are most susceptible to hypo perfusion.

Both these theories are not mutually exclusive and may play roles together in many patients.

Heterogeneity Of PRES

Originally PRES was defined as a posterior phenomenon, but almost all areas of the brain can be affected. The classical pattern of vasogenic edema in the parietal or occipital region is still seen in a majority of cases. Frontal lobe involvement, however, has been reported to be as high as 68%. In the Berlin PRES study, involvement of frontal and temporal lobes occurred in one half of cases. Lesions involving the infra-tentorial region, particularly the cerebellum, were encountered in more than half of cases.

In large case series intracranial haemorrhage has been encountered in 15 to 32% of cases. In a study of haemorrhagic PRES, seizure and confusion were the most common presenting features; however, hypertension was surprisingly not a significant factor in the development of haemorrhage.

The Berlin PRES study demonstrated that, of those who had repeat imaging performed, 43% had incomplete resolution of edema on repeat MRI. A significant factor associated with incomplete resolution was higher MAP at presentation. The presence of haemorrhage also shows a worse outcome.

PRES In Chronic Kidney Disease

Renal dysfunction also appears to predispose the brain to posterior leukoencephalopathy, because of associated hypertension, chronic uraemia or fluid overload. Human recombinant erythropoietin is used to treat chronic anaemia in patients with end-stage renal failure. Erythropoietin aggravates hypertension which can lead to hypertensive encephalopathy.

PRES In End Stage Renal Diseases (ESRD)

Because of the consistent association of severe hypertension, autoimmunity, and organ transplantation with PRES it is expected to have a close association of renal disease namely ESRD with PRESS .However a literature search does not point to the frequency of PRES in CKD. In a larger published series of PRES, kidney disease does not feature prominently except in solid organ transplantation. PRES has been observed in a number of individuals receiving peritoneal dialysis. Most of these cases had significant hypertension at presentation and responded to BP control with or without ultrafiltration.

In some patients the onset of PRES was within weeks of commencing haemodialysis. This suggests a vulnerability period during which time patients were becoming accustomed to fluctuations in MAP by alterations to their 'dry weight.' A key learning point from these cases is the need for meticulous extracellular fluid volume and blood pressure control at the time of commencement of dialysis. Anuric patients in particular need very close monitoring and avoidance of long inter-dialytic gaps. In a recent review of three cases of PRES in haemodialysis patients, severe hypertension was the key clinical finding and responded well to strict volume control without the need for anti-hypertensive agents. Two of these patients developed PRES within three months of starting haemodialysis.

Clinically silent white matter lesions are common in individuals with kidney disease and probably reflect associated vascular disease. In an interesting study of patients undergoing their first haemodialysis, MR brain imaging was performed within 30 minutes before and after the dialysis treatment. Baseline imaging demonstrated a diffuse increase in apparent diffusion coefficient (ADC) in ESRD patients compared to controls indicative of interstitial edema. In the post-dialysis images, the ADC further increased particularly in the frontal lobes, suggestive of worsening interstitial edema. None of the patients who underwent haemodialysis experienced significant neurological symptoms. Brain imaging abnormalities without accompanying symptoms after dialysis has been reported elsewhere. It is likely, therefore, that dialysis patients do experience neurological sequelae of their treatment, but only a proportion comes to clinical attention.

PRES In Post Transplantation

The incidence of PRES post-transplantation varies depending on the type of organ transplanted. A retrospective single-centre study of 4222 solid organ trans- plants showed an overall incidence of PRES of 0.49%.[5]

In both kidney transplant and liver transplants, PRES was diagnosed at the time of co-existent infection or organ rejection. In the context of a complex transplant recipient with infection and/or rejection, it is

difficult to attribute a single aetiology to the development of PRES.

Typical Neuroimaging Features

Neuroimaging of PRES is typically associated with high signal intensity on T2 weighted images predominantly in the posterior regions of cerebral hemispheres, which is caused by subcortical white matter vasogenic edema. The most common affected areas are occipital lobes and posterior parietal lobes. The imaging abnormalities are often symmetrical, however asymmetrical involvement is not usual. MRI abnormalities of PRES are more better demonstrated on fluid-attenuated inversion recovery imaging (FLAIR), with nulling of the ventricular and subarachnoid CSF signal, the parenchymatous oedematous lesions esp. those in cortex are much better demonstrated on FLAIR images than on conventional T2 weighted images.[6-7] Supplemental diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) map images are helpful in distinguishing vasogenic edema, the predominant abnormality in PRES, from cytotoxic edema, which can also occur and may represent foci of irreversible ischemia as in case of "Top of Basilar Syndrome" which produces bilateral occipital lobe infarctions. Because vasogenic rather than cytotoxic edema is the principal basis for the lesions, regions demonstrating high signal intensity on T2-weighted images correspond to slightly increased or isointense signal intensity on diffusion-weighted images[8]. In ADC mapping, the hyperintense lesions on T2-weighted images correlate with increased ADC values (appear brighter). Most PRES lesions do not enhance on T1-weighted images. Contrast enhancement in the areas of T2 signal abnormality occurs in a few patients and may represent a dynamic feature related to the timing of imaging after the onset of symptoms and severity of lesions. Gadolinium enhancement in areas of T2 abnormality is inconsistent and typically not a striking finding.

Hypodense lesions of PRES are well visualised even with CT scan. An outstanding feature of PRES syndrome is reversibility of the imagine abnormalities. Complete reversibility is generally regarded as a defining feature of PRES. Resolution of PRES neuroimaging abnormalities probably occurs in the range of several days to weeks but if appropriate management is delayed, there is a great risk of permanent neurological damage because of ensuing cerebral infarction or hemorrhages.

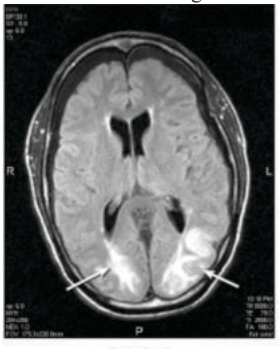

Figure 1.

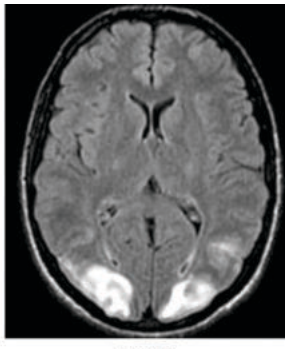

Figure 2.

MRI (flair image) showing Posterior Reversible Encephalopathy Syndrome (PRES). Arrows in figure 1, points to bilateral parietal lobe hyper-intensity that is characteristic of vasogenic edema in the Posterior Reversible Encephalopathy Syndrome, seen in women with end stage renal disease.

ATYPICAL NEUROIMAGING FEATURES

Although classic neuroimaging features of PRES with involvement of the posterior head regions are easily recognized, features that may generally be regarded as atypical are often present in patients, such as significant anterior involvement, cortical lesions, recurrent PRES episodes, foci of permanent injury, hemorrhage into lesions, and unilaterality. High signal intensity on T2-weighted image lesions can occur in regions other than the parieto-occipital areas, frequently involving the frontal lobes, basal ganglia, thalami, or brainstem. The PRES lesions typically do not exclude the anterior head regions. Frontal lobe involvement is a common feature seen in most of these patients. Similarly, PRES lesions do not have to be restricted to the white matter. Although white matter is predominantly involved, gray matter lesions, anterior lesions, and isolated brainstem involvement are becoming increasingly appreciated.[9-10]

Treatment

The posterior leukoencephalopathy syndrome needs to recognised promptly, as it is reversible and readily treated by controlling blood pressure, discontinuing the offending immunosuppressive agent or decreasing the dose and treatment of underlying sepsis. Delay in initiating the appropriate treatment may result in permanent damage to the brain. This highlights the need for meticulous extracellular fluid volume control during this potentially vulnerable period. In patients with solid organ transplantation where cyclosporine or tacralimus are thought to be the culprit, stopping these drugs acutely may lead to acute organ rejection and death. So close consultation with the transplant physician is important. Patients experiencing seizures become seizure free after resolution of imaging abnormalities and do not require long term anti-epileptic drug treatment.

CONCLUSION

PRES is an uncommon diagnosis among patients with renal diaeases. However, the varied clinical presentation and the increasing recognition of heterogeneous imaging findings make it difficult to be accurate about its true incidence. The reversibility of PRES is not always present, hypertension is a significant driver of brain injury, often in the setting of recent commencement of haemodialysis.

Thus, knowledge of posterior reversible ephalopathy syndrome is of great significance in day to day clinical practice. The cause of this syndrome is multifactorial. The mechanism of the syndrome is, probably, a brain-capillary leak syndrome related to hypertension, fluid retention, and possibly the cytotoxic effects on the vascular endothelium. Clinicians must be aware of this common clinico-radiological syndrome, as its recognition obviates unnecessary diagnostic procedures. Moreover, early treatment of this syndrome may prevent permanent neurological damage.

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