Posterior reversible encephalopathy syndrome (PRES): presentation, diagnosis and treatment

Anant Parasher, Rajat Jhamb

Medicine, Guru Teg Bahadur Hospital, New Delhi, India

Correspondence to
Dr Anant Parasher, Medicine, Guru Teg Bahadur Hospital, New Delhi 110095, India; anant02jan@gmail.com

Received 12 March 2020
Revised 9 April 2020
Accepted 10 May 2020

To cite: Parasher A, Jhamb R. *Postgrad Med J* 2020;**96**:623–628.

ABSTRACT

Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder which is characterised by variable symptoms, which include visual disturbances, headache, vomiting, seizures and altered consciousness. The exact pathophysiology of PRES has not been completely explained, but hypertension and endothelial injury seem to be almost always present. Vasoconstriction resulting in vasogenic and cytotoxic edema is suspected to be responsible for the clinical symptoms as well as the neuroradiological presentation. On imaging studies, Symmetrical white matter abnormalities suggestive of edema are seen in the computer tomography (CT) and magnetic resonance imaging (MRI) scans, commonly but not exclusively in the posterior parieto-occipital regions of the cerebral hemispheres. The management is chiefly concerned with stabilization of the patient, adequate and prompt control of blood pressure, prevention of seizures and timely caesarean section in obstetric cases with pre-eclampsia/eclampsia. In conclusion, persistently elevated blood pressures remain the chief culprit for the clinical symptoms as well as the neurological deficits. Early diagnosis by diffusion weighted MRI scans, and differentiation from other causes of altered sensorium i.e. seizures, meningitis and psychosis, is extremely important to initiate treatment and prevent further complications. Although most cases resolve successfully and carry a favorable prognosis, patients with inadequate therapeutic support or delay in treatment may not project a positive outcome.

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder which is characterised by variable symptoms, which include visual disturbances, headache, vomiting, seizures and altered consciousness.[1] Its association is seen with a number of conditions including hypertension, pre-eclampsia and eclampsia, renal failure, systemic lupus erythematosus (SLE) and the use of some immunosuppressive agents.[2 3] PRES was first described in 1996 by Hinchey *et al* and shortly after the description, two other case series were published.[2 4] This condition has been known by various names previously (reversible posterior leukoencephalopathy syndrome, reversible posterior cerebral oedema syndrome and reversible occipital parietal encephalopathy), but PRES is now the widely accepted term.[5 6] It is commonly, but not always associated with acute hypertension and is now increasingly being diagnosed, because of increased availability and improvement of brain imaging techniques.[7]

PRES can be considered to be the basis of the neurological manifestations of preeclampsia/eclampsia.[8] Cases can present in very early pregnancy (before the 20th week of gestation), as well as rarely in the late stages of pregnancy with intrauterine death.[9] Severe pre-eclampsia (defined as arterial blood pressure >170/110 mm Hg) is common in most women, but rare cases of PRES in pregnant women with normal blood pressure and without pre-eclampsia have also been described.[10] The major clinical conditions associated with PRES are represented in box 1.

Pathophysiology

The exact pathophysiology of PRES has not been completely explained, but hypertension and endothelial injury seem to be almost always present. Vasoconstriction resulting in vasogenic and cytotoxic oedema is suspected to be responsible for the clinical symptoms and the neuroradiological presentation.[11] Barring cerebral ischaemia or haemorrhage which can result in permanent damage, PRES is usually reversible.[1] Hypertension is the most common precipitating factor, with endothelial dysfunction playing an important role.[12] The various mechanisms explaining the pathophysiology of PRES include (i) failure of cerebral autoregulation causing vasogenic oedema, (ii) cerebral vasoconstriction and (iii) disruption of the blood brain barrier due to endothelial disruption.[5] Among the various theories that have been proposed for PRES, failure of brain autoregulation causing vasogenic oedema is presently the most accepted one.

Once the cerebral autoregulation, which maintains a constant blood flow to the brain despite alterations in the systemic pressures gets disrupted, increased, perfusion pressure causes extravasation of fluid by overcoming the blood brain barrier.[13–15] This can be briefly explained as follows. Cerebral blood flow is usually regulated by dilatation and constriction of vessels to maintain adequate tissue perfusion[15] which also avoids excessive increase in the intracerebral pressure. Sustained mean arterial pressure more than 150–160 mm Hg results in the breakdown of autoregulation mechanisms leading to hyperperfusion and cerebral vessel damage, resulting in interstitial extravasation of proteins and fluid, causing vasogenic oedema. Above 200 mm Hg mean arterial pressure (MAP), the changes start to become irreversible.[15] Chronic hypertension and atherosclerosis, which usually accompany PRES, are known to reduce the effectiveness of autoregulation.[16]

Although this theory explains why control of hypertension benefits these patients, it does not

Box 1 Conditions associated with PRES[45]

- Immunosuppressive/cytotoxic drugs.
- Hypertensive encephalopathy.
- Pre-eclampsia/eclampsia/HELLP syndrome.
- Autoimmune disorders, for example, SLE.
- Acute or chronic renal diseases.
- HUS/TTP.
- High dose steroids.
- Liver failure/transplantation.
- Endocrine dysfunction.
- Hypercalcemia/hyperparathyroidism.
- Bone marrow transplant.
- Massive blood transfusion.
- Porphyrias.

PRES, posterior reversible encephalopathy syndrome; SLE, systemic lupus erythematosus; HELLP, Hemolysis, Elevated Liver Enzymes and Low Platelet count; HUS/TTP, Hemolytic Uraemic Syndrome/Thrombotic Thrombocytopenic Purpura.

explain few things such as the occurrence of PRES in the absence of hypertension and the correlation of extent of the oedema and the severity of hypertension. Also, some positron-emission tomography based studies have actually demonstrated cerebral hypoperfusion instead of hyperperfusion.[7 14–17]

Another theory has implicated a systemic inflammatory state causing endothelial dysfunction as the cause of PRES.[15] Systemic inflammatory process such as sepsis, eclampsia, transplantation and autoimmune disease are usually associated with PRES, which can lead to reversible focal and diffuse abnormalities seen on angiographic studies. Vasoconstriction that occurs during cerebral autoregulation has a propensity to worsen pre-existing inflammatory endothelial dysfunction. This leads to further hypoxia and subsequent vasogenic oedema.[15] Although this theory explains well the role of endothelial dysfunction due to inflammation, it still does not explain the occurrence of PRES in the absence of inflammation.[16 17]

A simplified flowchart describing the pathogenesis of PRES has been shown in figure 1.

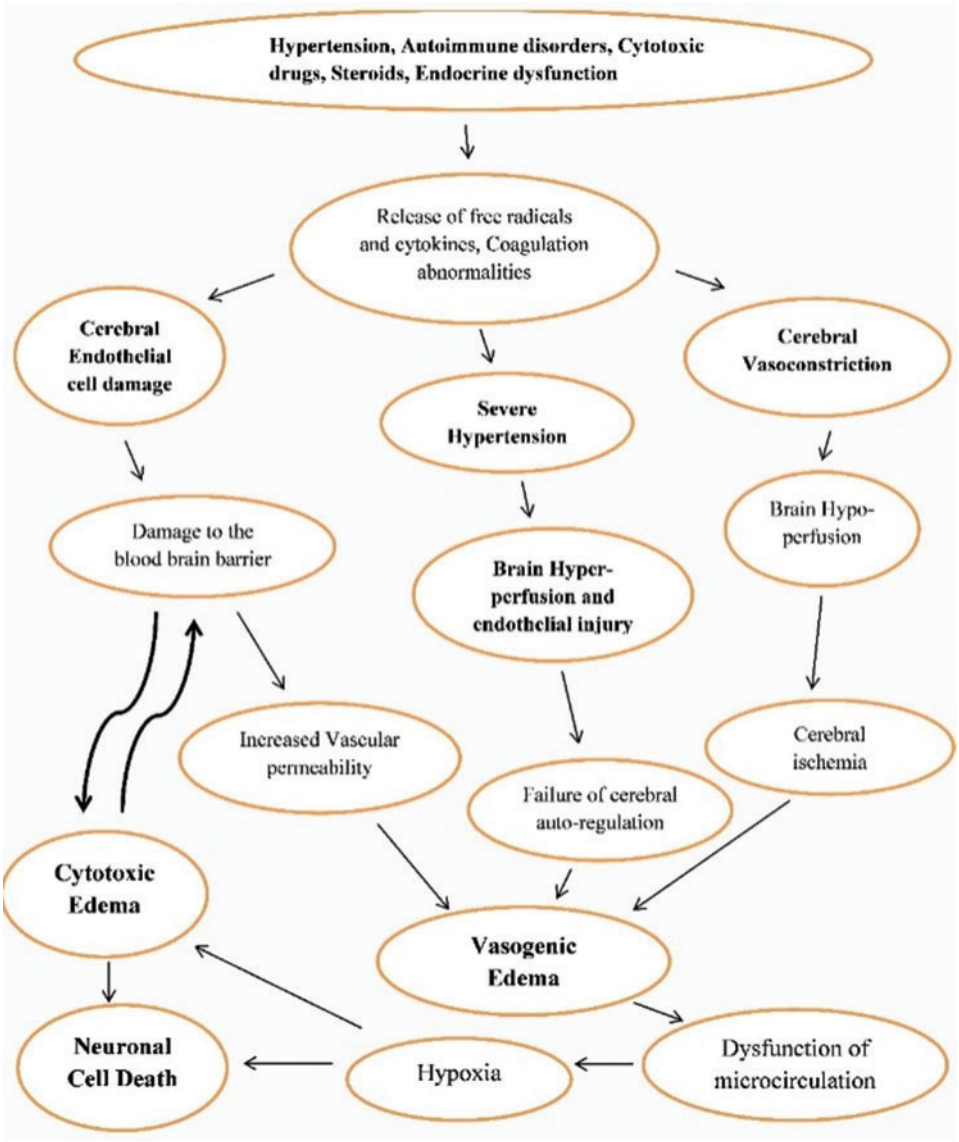

Figure 1 The pathogenesis of PRES.[6 18 19] PRES, posterior reversible encephalopathy syndrome.

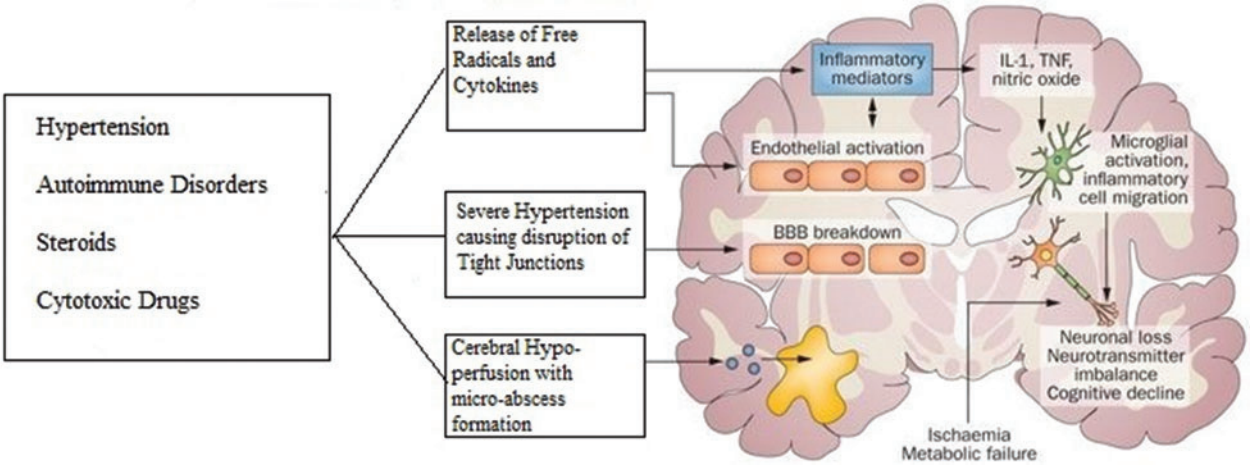

Figure 2 A representational diagram showing the pathophysiology of PRES. PRES, posterior reversible encephalopathy syndrome.

Breakdown of the blood brain barrier and endothelial dysfunction occurs in PRES with fluid and macromolecule extravasation into the interstitium. Increased concentrations of circulating cytokines (eg, tumour necrosis factor α, interleukin 1 and endothelin 1) activate endothelial cells and allow interaction and adhesion of circulating leucocytes(figure 2). The tight junctions are disrupted and vascular endothelial growth factor expression is increased, leading to increased vascular permeability and vasogenic oedema.

To complicate the matter further, not all the patients with PRES have hypertension, and cytotoxicity is thought to be the mechanism underlying cerebral oedema in these patients. The associated conditions include cytotoxic therapies (eg, ciclosporin, tacrolimus), infection/sepsis/shock, autoimmune disease and exposure to toxic agents.[6 18 19] The mechanism might be direct toxicity to vascular endothelium leading to capillary leakage and breakdown of the blood brain barrier, which triggers vasogenic oedema.[2] The damage may also be seen with non-toxic levels of these drugs.

Severe anaemia can be a predisposing factor for PRES due to the endothelial dysfunction caused by insufficient oxygen supply. This can further damage and disrupt the blood brain barrier.[20] Rapid blood transfusion in these patients may cause a rapid increase in total blood volume, with resultant cerebral blood flow overload. This acute cerebral hyperperfusion disrupts cerebral autoregulation and might result in the vasogenic oedema found in PRES.[5]

Clinical presentation

The symptoms of PRES are variable, ranging from visual disturbances which may present as blurred vision, homonymous hemianopsia and cortical blindness, to altered consciousness presenting as mild confusion, agitation or coma. Other symptoms may include nausea, vomiting and seizures. Status epilepticus is common, which may be generalised. Non-convulsive status can be prolonged and last for days in PRES and should be carefully observed. Drug intoxication and psychosis should be ruled out in these cases, so that treatment can initiated as early as possible.[5]

The most common symptoms seen in obstetric patients are seizures (45%), visual disturbances (34%), alteration of consciousness (19%)[1] and focal deficits (4%).[21] The degree of hypertension is not associated with the extent of cerebral lesions and oedema can also occur at lower levels of arterial blood pressure. This is chiefly due to ongoing endothelium damage, as indicated by the high lactic acid dehydrogenase (LDH) levels in laboratory tests.[22 23]

Imaging studies

The most common location of the lesions in PRES is the parietal-occipital lobe or 'posterior' area of the brain. Lesions may also be observed in the anterior regions, basal ganglia, brainstem and the cerebellum.[1 24 25] The characteristic imaging patterns in PRES are represented in box 2.[26] Symmetrical white matter abnormalities suggestive of oedema may be seen in the CT and MRI scans, but not exclusively in the posterior parieto-occipital regions of the cerebral hemispheres.[1 27 28]

Diffusion-weighted imaging is essential to distinguish between vasogenic and cytotoxic oedema.[1 29] Diffusion-weighted MRI is the modality of choice for confirming the diagnosis of PRES(figure 3) and to differentiate between reversible vasogenic and irreversible cytotoxic oedema, as compared with a CT scan, which can be normal in some cases of PRES. Radiologically detectable cerebral lesions may persist in some cases in spite of intensive monitoring and prompt aggressive therapy.[1]

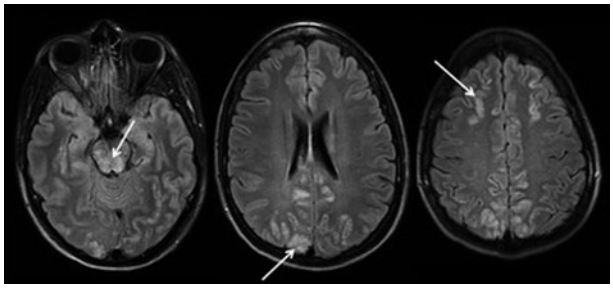

Figure 3 MRI with T2-flair-weighted images showing the typically hyperintense bilateral lesions indicating vasogenic oedema in the parieto-occipital regions as well as less common lesions in the frontal regions and brain stem (arrows).[27 28]

Box 2 Imaging patterns in PRES[5]

- Holo-hemispheric watershed.
- Superior frontal sulcus.
- Dominant parietal/occipital.
- Partial and/or asymmetric PRES.

PRES, posterior reversible encephalopathy syndrome.

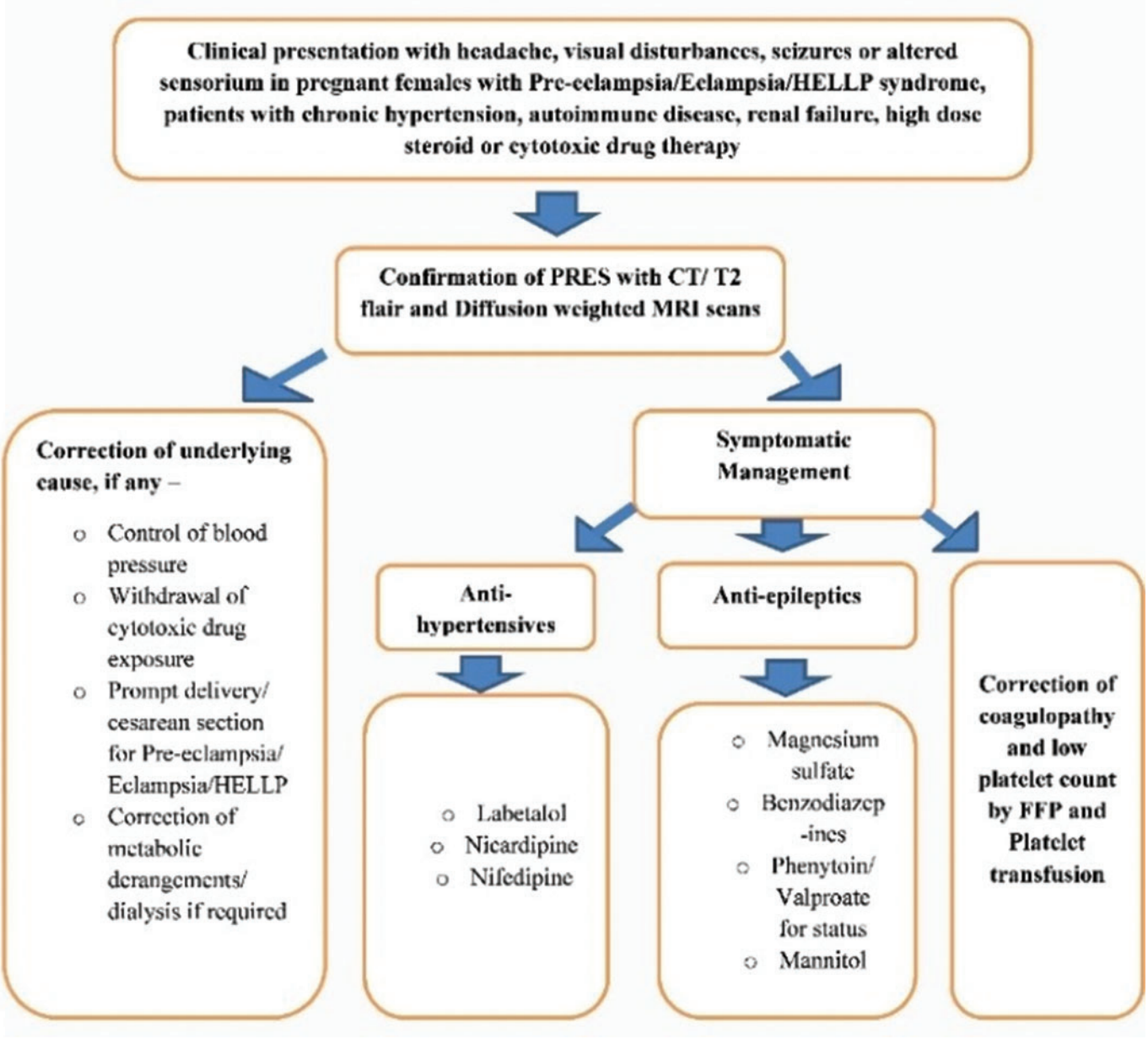

Figure 4 Management of PRES. PRES, posterior reversible encephalopathy syndrome.

Management

The key thing to remember in the management of PRES is early diagnosis and initiation of therapy. Many patients may require intensive care unit (ICU) care for aggressive management of their symptoms such as seizures, encephalopathy and status epilepticus.[30] The important points of therapy include:[31]

- Prompt induction of labour in cases of pre-eclampsia/eclampsia and HELLP.
- Immediate removal of the offending cytotoxic drugs/ immunosuppressants.
- Stabilisation of the patient with adequate hydration, along with correction of acidosis and electrolyte abnormalities, if any.
- Gradual reduction of blood pressure in patients with hypertension to avoid sudden hypoperfusion of vital organs.
- Prevention and management of seizures in pregnant women by magnesium sulfate. For seizures in non-pregnant patients presenting with PRES, first-line drugs used are diazepam, phenobarbital and fosphenytoin. Refractory cases can be started on propofol or midazolam.
- Dialysis for patients presenting with renal failure.
- Airway management and intubation in altered patients with a poor Glasgow Coma Score, as per the standard protocol.

PRES in non-obstetric cases

In cases of PRES caused by factors other than pre-eclampsia and eclampsia, the most effective therapy includes withdrawal of the offending agent, immediate control of blood pressure, anticonvulsive therapy and temporary renal replacement therapy (haemodialysis/peritoneal dialysis) if required. Aggressive treatment with corticosteroids and cyclophosphamide is effective in cases of SLE-related PRES.[5]

Main messages

- Posterior reversible encephalopathy syndrome is increasingly being recognised now due to better imaging techniques.
- Pathophysiology not completely elucidated, but hypertension, vasoconstriction and endothelial dysfunction seen to be important inciting factors.
- Management protocols need to be specific and well defined, especially in obstetric cases.

Current research questions

- Can posterior reversible encephalopathy syndrome (PRES) be predicted from early signs and symptoms in high-risk cases?
- What is the pathophysiology of PRES?
- Do early intervention, treatment and intensive care unit care have any effect on the prognosis of patients with PRES?

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PRES in pre-eclampsia/eclampsia

The majority of obstetric cases with pre-eclampsia and eclampsia are treated with a similar protocol. Initially, the mother needs to be stabilised by means of antihypertensive and antiepileptic drugs, especially labetalol, nifedipine and magnesium sulfate.[32] The underlying cause has to be removed without delay, and a caesarean section has to be performed to reduce feto-maternal stress. General anaesthesia is preferred if there are complications such as coagulopathy, seizures or thrombocytopenia. Neuroaxial anaesthesia should always be given for the majority of patients without any complications as due to the antihypertensive effect of sympathetic blockade, it is the least risky for the mother and fetus. Rapid reduction of blood pressure by more than 15%–25% should be avoided as it can worsen the cytotoxic oedema and compromise uteroplacental perfusion.[1] Magnesium sulfate can prevent convulsions and reduce cerebral oedema.[33] The use of thiopental, valproate or phenytoin has been reported only for status epilepticus in these patients.[34] Specific cerebral antioedema therapy with steroids or mannitol has not been found to be superior to magnesium sulfate in achieving neurological recovery.[35]

A concise overview of the management of PRES has been described in figure 4.

Prognosis and outcomes

PRES usually has a favourable prognosis among pregnant women, with resolution being rapid and complete after adequate therapy.[36] Permanent damage can persist in a few cases (6%) and death due to haemorrhage has been described in a couple of patients.[37–39] ICU care is advisable for postcaesarean patients to allow monitoring and sufficient recovery.[1] Recurrence of PRES is not uncommon in patients presenting with repeated episodes/flares of hypertensive crisis, renal failure, autoimmune conditions and multiorgan failure.[31]

Although prognosis is good for most patients, delayed diagnosis and treatment may lead to mortality or irreversible neurological deficits. Poor prognosis is associated with factors such as severe encephalopathy, chronic hypertension, neoplastic aetiology, delayed diagnosis of causative factor, multiple comorbidities, elevated C-reactive protein (CRP) and coagulopathy.[40 41] Involvement of the corpus callosum, extensive cerebral oedema or haemorrhage, restrictive diffusion and subarachnoid haemorrhage are the MRI features which predict a worse prognosis.[42–44]

CONCLUSION

PRES has been increasingly recognised in recent years and has been the cause of recurrent physician consultations for obstetric pre-eclamptic and eclamptic cases. In majority of patients, persistently elevated blood pressures remain the chief culprit for the clinical symptoms as well as the neurological deficits. Early diagnosis by diffusion weighted MRI scans, and differentiation from other causes of altered sensorium, that is, seizures, meningitis and psychosis, is extremely important to initiate treatment and prevent further complications. Reduction of blood pressure and seizure control remain the mainstays of therapy after prompt stabilisation of the patient and removal of any known toxic insult. Although most cases resolve successfully and carry a favourable prognosis, patients with inadequate therapeutic support or delay in treatment may not project a positive outcome.

Contributors AP did the research and final submission. RJ reviewed and edited the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Anant Parasher http://orcid.org/0000-0002-5573-3231

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