Case Report

An Unusual Case of Multifactorial Posterior Reversible Encephalopathy Syndrome (PRES)

Intensive Care Section

RASHMI TERESA MATHAI, SMITHA BHAT, K.S. BHAT

ABSTRACT

Posterior Reversible Encephalopathy Syndrome (PRES) is a clinico-neuroradiological entity which is characterized by headache, vomiting, altered mental status, blurred vision and seizures which can be detected by neuroimaging, demonstrating white-gray matter oedema and involving predominantly the posterior region of the brain.[1] We report a case of a hypertensive woman who presented with sepsis and Multi-organ Dysfunction Syndrome (MODS), underwent haemodialysis for acute kidney injury and subsequently developed PRES. She responded well to the treatment, as was evidenced by a complete resolution of her clinical and radiological findings. Vasogenic oedema due to the dysfunction of cerebral blood vessel autoregulation points towards the endothelium as the key factor in the pathogenesis of PRES in MODS, thus making it a potential therapeutic target.

Key Words: PRES, reversible encephalopathy, endothelium, sepsis, MODS

KEY MESSAGE

- The treating physician must have a high index of suspicion to consider PRES in the ICU setting and to order for appropriate neuroimaging.
- PRES can be prevented by controlling blood pressure fluctuations.

CASE REPORT

An adult female hypertensive presented to the Emergency Department with the chief complaints of dyspnoea and productive cough for 15 days, pedal oedema for 10 days and oliguria for 5 days. She had discontinued antihypertensives 10 days prior to the presentation.

On presentation, her blood pressure was 90/50mmHg, her heart rate was110/min, her temperature was 98.6°F and her respiratory rate was 28/min with SpO_2 96% on room air. She had icterus and bilateral pitting pedal oedema. Auscultation revealed bilateral rhonchi. The other systemic examinations were essentially normal. The ECG revealed non specific ST-T changes with tachycardia. The ABG showed severe metabolic acidosis with a pH of 6.81, $PaCO_2$ – 14 mmHg, PaO_2 – 114 mmHg, bicarbonate < 3 mEq/l with FiO_2 of 21% and an anion gap of 23.

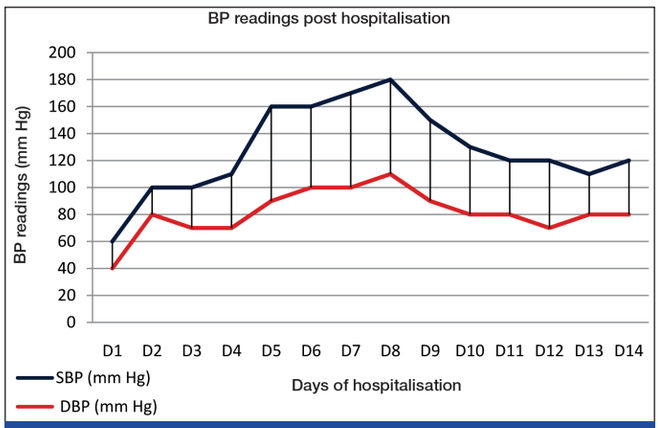
Her chest X-ray showed a prominent pulmonary vasculature. The ultrasonography of her abdomen and pelvis revealed normal sized kidneys with a bilateral increase in the cortical echogenecity. Mild, bilateral, pleural effusion was also noted.

A diagnosis of septic shock with severe metabolic acidosis and renal failure was made. The patient was admitted to the intensive care unit (ICU) with continuous NIBP monitoring, as her family could not afford intra arterial BP and central venous pressure monitoring. Inotropic support was initiated in the form of Inj. Dopamine at 5µg/kg/min, and Inj. Nor-adrenaline at 0.03µg/kg/min. A bicarbonate infusion was started for the severe metabolic acidosis. Piperacillin – tazobactam 4.5g intravenous twice daily was empirically started in view of the severe sepsis. Since her hypotension was refractory to dopamine and nor-adrenaline, intravenous hydrocortisone was given.

A 2D Echo was performed, which revealed mild mitral regurgitation and concentric left ventricular hypertrophy (LVH) with moderate pulmonary arterial hypertension (PAH); the left ventricular ejection fraction (LVEF) was 52%. The evidence of MODS was tabulated according to the 'Sequential Organ Failure Assessment' (SOFA), and the maximal SOFA score was found to be 12/24.

Hb: 13.4g%	S.sodium:127mEq/l, S.potassium:5.2mEq/l, S.chloride: 101mEq/l
TLC:24,200 /mm^3	S.Urea : 46mg/dl, S.Creatinine: 2.3mg/dl
DLC: $N_{68}L_{29}E_1M_2$	T.Bilirubin: 2.8mg/dl, SGPT/SGOT: 410/460
ESR: 4mm (end of 1st hr)	T.protein:6.1g/L,S.Albumin:3.3g/l; S.Globulin:2.75g/l; A/G:1.2
Platelet count: 3, 68, 000/ mm^3	Urine:++ proteinuria; RBC:35-40/HPF Pus cells: 15-20/HPF. No casts or crystals
PT/INR:12s/26.1s /2.29	Blood C/S: No organism isolated after 72hrs of incubation. Urine C/S: No bacteria isolated after 72hrs of incubation.
MP smear: negative	RBS: 143mg/dl, HIV/HBsAg/HCV: Non reactive
IgM Leptospira – negative	S.CPK: 153

[Table/Fig-1]: Lab Investigation



[Table/Fig-2]: BP reading post hospitalisation

(Slow Low-Efficiency Dialysis) was done as the patient had anuria. The inotropic support was tapered and stopped after her blood pressure (BP) stabilized on day 4. The next day, she was shifted to the ward, following which her BP readings increased consistently and she was started on Amlodipine 2.5mg once daily, which was increased to 5mg twice daily due to the persistently high BP readings.

The intravenous steroids and antibiotics were stopped on day 7 after she was afebrile for 48hrs.

On day 8, she had 3 episodes of generalized tonic clonic seizures (GTCS), which were preceded by focal seizures of the right upper limb. She was given a loading dose of fosphenytoin and was then shifted to the MICU. Her BP was constantly above 180/100 mm Hg.

She complained of headache and blurring of vision and was disoriented to time and place. The perception of light was absent, with intact pupillary reflexes, suggesting cortical blindness. Her fundus examination revealed grade 2 hypertensive retinopathy. Her blood biochemistry was normal.

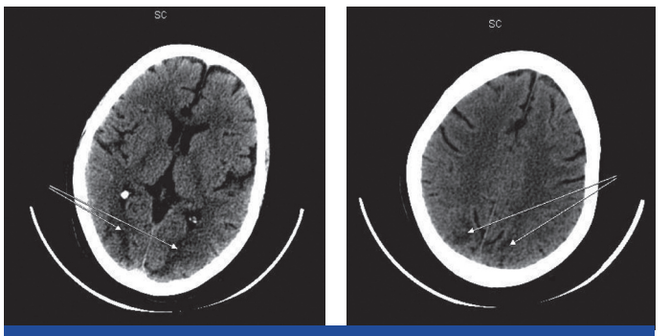
In view of the focal seizures with secondary generalization, MRI of the brain was ordered, which the patient could not afford. Hence,CT of the brain was done, which revealed hypodensities in the white matter of both the occipital lobes and the left centrum semiovale, which were suggestive of PRES (Table/Fig:3-6).

The patient was managed with antihypertensives and her vision was restored within the next 24 hours. Her antinuclear antibody (ANA) tests were negative and her thyroid function tests were normal. She was discharged on day 14 and she came for follow-up one month later. She was found to have no focal neurological deficits. Her vision was normal and a repeat CT of the brain did not reveal any abnormality. She is currently being maintained on anti-hypertensives.

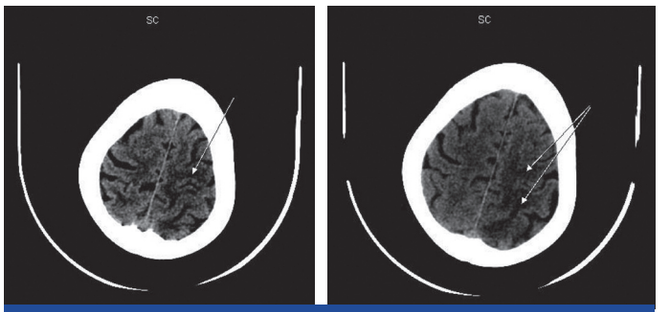
DISCUSSION

PRES is characterized by headache, seizures, visual disturbances, altered mental status, and focal neurological signs [1].The initiating factors include accelerated hypertension, eclampsia, sepsis, chronic kidney disease, haemolytic-uremic syndrome, and systemic lupus erythematosus. Additional reports have shown an association with chemotherapy, and glucocorticoids [2].

Normally, the cerebral vascular autoregulatory system maintains a constant perfusion in the brain over a range of systemic blood pressures. This is mediated by the sympathetic vascular innervation that normally protects the brain from marked increases in blood



[Table/Fig-3&4]: Axial view of the brain-CT image. Arrows pointing towards symmetrically located, bilateral hypodensities in the occipital regions affecting cortex and subcortical white matter.



[Table/Fig-5&6]: Axial view of the brain-CT images. Arrows pointing towards bilateral hypodensities in the fronto-parietal white matter, more prominent on the left side.

pressure. However, the posterior circulation is relatively less innervated, thus increasing its vulnerability to barotrauma and the breakdown of the blood-brain barrier [3, 4]. When the autoregulatory limits are exceeded, there is an interstitial extravasation of proteins and fluids, resulting in reversible vasogenic oedema, followed by small vessel rupture, leading to intracranial haemorrhage, ischaemia and infraction [5, 6].

The signal abnormality which is associated with PRES is commonly located at the gray-white matter junctions. The occipital lobes are a frequent location of cortical and sub-cortical haemorrhages. Angiography may show focal areas of constriction and narrowing of the proximal and peripheral vessels. This narrowing of the blood vessels will eventually lead to decreased cerebral blood flow (CBF) in the affected territories..

The pathophysiology of PRES in severe sepsis involves a complex, integrated response that includes the activation of lymphocytes, inflammatory mediators, and the haemostatic system. Central to this process is an alteration of the endothelial cell function. The cytokine response (TNF-α, IL-1) is believed to play a critical role in the development of the endothelial dysfunction [7, 8].

The high percentage of patients with PRES who have autoimmune disorders, support the theory that PRES is in part, caused by endothelial dysfunction, a process in which the host autoimmune response is essential. The endothelial cells become damaged by an inflammatory cytokine response, resulting in the leakage of fluid and protein into the interstitium. Autoimmunity has been recently implicated in PRES in association with neuromyelitis optica. This raises the possibility of the autoimmune-mediated disruption of the endothelial aquaporin [4] water channels, which may predispose to PRES [9, 10].

Hypertension is an adverse effect of high-dose corticosteroid therapy. The mechanism of corticosteroid-induced PRES is likely to be a steroid induced rise in blood pressure. However, dexam-

ethasone is known to cause PRES even without BP elevation. Given the widespread and multifaceted use of dexamethasone in patients with cancer, it is important to recognize PRES as a serious but reversible complication of high-dose corticosteroid use [11].

The endothelium plays a key role in causing many of the factors which predispose to PRES, and thus its potential role as a target to the treatment of PRES must be emphasized.

Our patient had multiple factors which contributed to the development of PRES, especially wide BP fluctuation, sepsis and renal failure. The possibility of steroids contributing to the condition was doubtful, as steroids were stopped 48 hours prior to the onset of the seizures.

SUMMARY

The treating physician must have a high index of suspicion to consider PRES and to order for appropriate neuroimaging. It is important to be aware of this condition because it is preventable by

A. The adequate control and prevention of blood pressure fluctuations.
B. Aseptic precautions to prevent nosocomial infections and sepsis.
C. The appropriate management of renal failure.

The physician must be aware of the usually reversible nature of PRES, for accurate prognostication. The key to the diagnosis in PRES is neuroimaging, but a suspicion must be raised by the clinician. Hence, the radiologists and the clinicians should be familiar with this under diagnosed syndrome. It is mostly a benign, reversible condition, especially once the causative factors are eliminated, but it can result in permanent deficits if it is improperly managed [12].

REFERENCES

[1] Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med* 1996; 334:494.
[2] Garg RK. Posterior leukoencephalopathy syndrome. *Postgrad Med J*. 2001 Jan;77(903):24-28.
[3] Stott VL, Hurrell MA, Anderson TJ. Reversible posterior leukoencephalopathy syndrome: a misnomer reviewed. *Intern Med J*. 2005 Feb;35(2):83-90.
[4] Lamy C, Oppenheim C, Méder JF, Mas JL. Neuroimaging in posterior reversible encephalopathy syndrome. *J Neuroimaging*. 2004 Apr;14(2): 89-96.
[5] Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev*. 1990;2(2):161-92.
[6] Bartynski W. Posterior Reversible Encephalopathy Syndrome, Part 2: Controversies Surrounding the Pathophysiology of Vasogenic Edema. *AJNR*. 2008 Jun 1;29(6):1043-49.
[7] Bartynski W.S, Boardman JF, Zeigler ZR, Shadduck RK, Lister J. Posterior Reversible Encephalopathy Syndrome in Infection, Sepsis, and Shock. *AJNR.* 2006 Dec;(27):2179-90.
[8] Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. *Blood*. 2003 May 15;101(10):3765-77.
[9] Matsushita T, Isobe N, Matsuoka T, Ishizu T, Kawano Y, Yoshiura T, et al. Extensive vasogenic edema of anti-aquaporin-4 antibody-related brain lesions. *Mult. Scler*. 2009 Sep;15(9):1113-17.
[10] Papadopoulos MC, Manley GT, Krishna S, Verkman AS. Aquaporin-4 facilitates the reabsorption of excess fluid in vasogenic brain edema. *FASEB J*. 2004 Aug;18(11):1291-93.
[11] Irvin W, MacDonald G, Smith JK, Kim WY. Dexamethasone-induced posterior reversible encephalopathy syndrome. *J. Clin. Oncol*. 2007 Jun 10;25(17):2484-86.
[12] Pande AR, Ando K, Ishikura R, Nagami Y, Takada Y, Wada A, et al. Clinicoradiological factors influencing the reversibility of posterior reversible encephalopathy syndrome: a multicenter study. *Radiat Med*. 2006 Dec;24(10):659-68.

AUTHOR(S):

1. Dr. Rashmi Teresa Mathai
2. Dr. Smitha Bhat
3. Dr. K.S. Bhat

PARTICULARS OF CONTRIBUTORS:

1. Corresponding Author.
2. MD, Dept. of Medicine
   Father Muller Medical College
   Kankanady, Mangalore, India.
3. MD, Dept. of Medicine
   Father Muller Medical College
   Kankanady, Mangalore, India.

NAME, ADDRESS, TELEPHONE, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Rashmi Teresa Mathai, MBBS
Dept of Medicine
Father Muller Medical College, Mangalore
Phone - +919663050783
E-mail: drrashmimathai@gmail.com

DECLARATION ON COMPETING INTERESTS:

No competing Interests.

Date of Submission: **Apr 20, 2011**
Date of peer review: **Jul 03, 2011**
Date of acceptance: **Jul 13, 2011**
Date of Publishing: **Oct 05, 2011**