Clinico-radiological Profile and Its Association with Clinical Outcome in Patients with Posterior Reversible Encephalopathy Syndrome

Md. Rubel[1*] Akramul Azam[2] Syed Arif Uddin[3] Shemanta Waddadar[4]
Mohammad Rifat Kamal[5] Riyadh Muhammad Marzuk[6] Md. Hassanuzzaman[7]

Abstract

Background: Posterior Reversible Encephalopathy Syndrome (PRES) is a clinical-radiological condition that is generally reversible. However, a significant number of patients may experience permanent neurological sequelae, which can lead to a fatal outcome. The study aimed to find out the various causes, clinical symptoms, and imaging results of patients with PRES. It also aimed to understand how these factors are related to the patients' clinical outcomes.

Materials and methods: This prospective observational study comprised of 56 patients who fulfilled the criteria for the diagnosis of PRES from the Department of Neurology, Medicine, Gynae & Obstetric of Chittagong Medical College Hospital. The demographic and clinical data, imaging findings, and laboratory parameter were duly recorded.Patients' outcomes were assessed using modified Rankin Scale (mRS) scores one month after the initial symptoms of PRES.

Results: The mean age was 24.4±9.6 years and 91.1% were female. The most common symptoms were seizure (98.2%), headache (78.6%), blurred vision (60.7%), stupor (51.8%) and vomiting (41.1%). The most frequent precipitating cause was posttpartum pre-eclampsia / eclampsia (53.6%), followed by antepartum pre-eclampsia / eclampsia (30.4%), acute HTN (10.4%) and acute kidney injury (5.4%). The parieto-occipital region was the most common area of involvement (98.2%), followed by the frontal lobe/superior frontal sulcus (75%), temporal (51.8%), holohemispheric watershed (26.8%), cerebellum (10.7%), basal ganglia (8.9%) and brainstem (1.8%). Haemorrhage was seen rarely (7.2%). At discharge, 26.2% of the patients had a poor outcome (mRS>2), and at the one-month follow-up, 14.3% of the patients had a poor outcome. The only independent predictor for poor outcomes of PRES was the presence of diffusion restriction on MRI.

Conclusion: This study would enhance our understanding of PRES's nature in our context. However, prospective large-scale multicenter studies are necessary to establish factors that are independently associated with unfavourable outcomes in PRES.

Key words: Clinical features; Central nervous system; Posterior Reversible Encephalopathy Syndrome (PRES).

Introduction

PRES is a syndrome that affects the Central Nervous System (CNS) and can present with various clinical symptoms, which typically involve headache, altered mental status, seizures, and vision loss.[1] A wide range of conditions can result in the development of PRES, including the most common reported etiologies including preeclampsia/eclampsia, moderate to severe HTN, infection with sepsis, autoimmune disease such as SLE, multidrug chemotherapy regimens and hematopoietic malignancies.[2] The common imaging characteristics observed in cases of PRES typically include near-symmetrical vasogenic edema in the subcortical white matter, which may also spread to the adjacent cortex. These features are most effectively observed using FLAIR sequences.[3,4]

Typically, the prognosis of PRES is determined by the underlying pathology, while the outcome is determined by the immediate removal or treatment of such pathology.[5,6] The mortality rate for patients with PRES is between 3% and 7%, and it has been attributed to neurological injury caused by intracranial hemorrhage, diffuse cerebral edema, posterior fossa edema with brainstem compression, increased intracranial pressure and sepsis with multiorgan dysfunction

1. Medical Offcer
Khahrachari Zila Sadar Hospital, Khagrachari.
2. Assistant Professor of Neurology
Chittagong Medical College, Chattogram.
3. EMO
Rangamati General Hospital, Rangamati.
4. Junior Consultant of Neurology
Chittagong Medical College Hospital, Chattogram.
5. Assistant Surgeon
Bangladesh Institute of Tropical and Infectios Diseases (BITID) Chattogram.
6. Medical Officer
Upazila Health Complex, Banshkhali, Chattogram.
7. Professor of Neurology
Chittagong Medical College Hospital, Chattogram.

***Correspondence: Dr. Md. Rubel**
Cell : 01778 15 35 86
E-mail: rubelpmr@gmail.com

Submitted on 18.07.2023
Accepted on : 18.10.2023

syndrome.[6,7] There has been a reported residual neurological deficit in 10%-37% of patients with PRES.[5,6] Poor outcomes have been associated with certain factors includeischemia, hemorrhage, extensive vasogenicoedema, brainstem involvement, hyperglycemia, severe encephalopathy, etiology other than pre-eclampsia/ eclampsia, multiple comorbidities, SAH and corpus callosal involvement.[8-12] However, there are no clear conclusions regarding the relative impact of clinical factors, imaging findings, and laboratory parameters on the outcome of PRES.[13] Further investigation, especially prospectively, is necessary to understand the role of imaging findings, clinical symptoms, and biochemical parameters in predicting PRES prognosis.

The increased recognition and better understanding of this condition has been achieved through increased brain imaging in the past twenty years. However, all we know about PRES is based solely on a few small case studies from Bangladesh.[14-16] and observational studies conducted on other countries.[13] Therefore, further investigation was conducted into the clinical, radiological and outcome of PRES. Hence, we planned to prospectivelystudy the clinical symptoms, different imaging characteristics and their association with clinical outcomes in patients with PRES admitted to a tertiary hospital in Bangladesh.

Materials and methods

We conducted a prospective observational study in the Departments of Neurology, Medicine, Gynae and Obstetrics of Chittagong Medical College Hospital, from March to December 2020. The ethical and review committee at Chittagong Medical College has approved the study protocol (CMC/PG/2020/633, dated 11/03/2020). Verbal and written informed consent was taken from the caregivers of the patients.

We included consecutive patients who had age more than 12 years admitted to the hospital with the following criteria:

i) Acute onset neurological symptoms including headache, altered level of consciousness, seizure, visual disturbance or focal neurological deficit

ii) Typical or atypical MRI manifestations of PRES

iii) Had known risk factors of PRES.

We excluded the patients with clinical features not favoring PRES, patients with cerebral oedema due to ischemia, haemorrhage, inflammation, infection, or space-occupying lesions, and patients whose relatives refused to participate in the study.

Data collection included demography, coexisting past illness, sign, and symptoms, imaging, and biochemical features. The outcome was measured by the mRS score after 30 (±5) days of PRES onset. A mRS score of 0-2 was considered a favorable outcome, while a score above 2 was considered a poor outcome.[17]

SPSS version 23.0 (IBM SPSS Inc., USA) was utilized to analyze the data. Continuous data was presented in the form of mean ± SD or median, and with a 25%-75% interquartile range as appropriate. Categorical data was presented in numbers (Percentages). The Fisher's exact test was utilized to compare categorical variables andthe Mann-Whitney U test was utilized to compare continuous variables. First, a univariate analysis was done to find out the strength of the association between the collected variables and the 30 days outcome. Multivariate logistic regression analysis was performed in the second step, with the 30-day outcome as the dependent variable and variables found to be significant by univariate analysis as independent variables. The results were presented in terms of the Odds Ratio (OR) and the 95% Confidence Interval (CI) with $p<0.05$ being considered to be statistically significant.

Results

Patients' median age was 20.5 years (IQR, 18.5-26.7) and ranging from 12.5 years to 55 years. There was a female preponderance, with a female to male ratio of 10.2:1. The median duration of the interval of symptom onset to enrollment in the study was 7 hours with a range from 1 hour to 5 days. Seizure was the most prevalent symptoms followed by headache, blurred vision, stupor, and vomiting. The most frequent precipitating factor was a post-partum state with preeclampsia/ eclampsia followed by antepartum pre-eclampsia/ eclampsia, acute hypertension, and acute kidney injury (Table I).

Table I Clinical characteristics of the patients at admission (n=56)

Variables	n (%)/Median (IQR)
Age, years	20.5 (18.5-26.7)
Female	51 (91.1)
Precipitating causes	
Acute hypertension	6 (10.4)
Antepartum preeclampsia/ eclampsia	17 (30.4)
Post-partum preeclampsia/ eclampsia	30 (53.6)
Acute kidney injury	3 (5.4)
Chemotherapeutic drugs (Methotrexate)	1 (1.8)
Acute hemodialysis	1 (1.8)
Massive blood transfusion	1 (1.8)
Symptoms at presentation	
Seizure	55 (98.2)
Headache	44 (78.6)
Blurred vision	34 (60.7)
Stupor	29 (51.8)
Vomiting	23 (41.1)
Drowsiness	15 (26.8)
Nausea	8 (14.3)
Examination findings at presentation	
Cortical blindness	7 (12.5)
Focal neurological deficit	5 (8.9)
Coma	3 (5.4)
Systolic blood pressure, mm of Hg	160 (150-177)
Diastolic blood pressure, mm of Hg	100 (90-110)
Glasgow coma scale	10 (8-14)

The data were expressed as frequency (%) or median (IQR) as appropriate. IQR: Interquartile Range.

The most frequently involved area on brain MRI was parieto-occipital, followed by frontal lobe/superior frontal sulcus, temporal, holohemispheric watershed, cerebellum, basal ganglia and brainstem. The incidence of restricted diffusion, and hemorrhage was seen rarely (Table II).

Table II MRI features of the patients (n=56)

Variables	Frequency (%)
Individual site	
Dominant parieto-occipital	55 (98.2)
Frontal lobe	42 (75.0)
Holohemispheric watershed	15 (26.8)
Temporal lobe	29 (51.8)
Cerebellum	6 (10.7)
Basal ganglia	5 (8.9)
Brainstem	1 (1.8)
Corpus callosum splenium	2 (3.6)
Associated lesion	
Restricted diffusion	11 (19.6)
Focal parenchymal hemorrhage	1 (1.8)
Microhaemorrhage	3 (5.4)

Overall outcome in the study was good without any fatality. Themedian length of hospital stay was 7 days, and the median time of clinical resolution was 6 days (IQR:4-8 days) and ranged from 2 to 12 days. Respectively, 26.2% and 14.3% of the patients had poor outcome (mRS >2) at discharge and at one month follow-up (Figure 1).

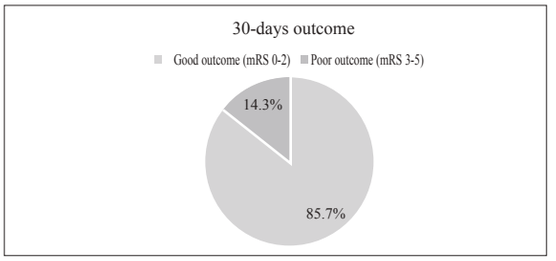

Figure 1 30-days outcome of the patients (n=56)

Among the different demographic and clinical characteristics only higher cerebral function and cortical blindness at enrollment were found to be associated with the 30-day outcome. Patients with good outcome had comparatively higher initial median GCS value compared to patients with poor outcome. Similarly, patients who were stuporous were more likely to have poor outcome at 30 days compared to their counterpart. Likewise, patients with cortical blindness on presentation were more likely to have poor outcome compared to their counterpart (Table III).

Table III Association between admission clinical characteristics with 30-day outcome

Variables	30-day outcome		
	Good (n=48)	Poor (n=8)	p value
Age, yrs.	20 (18-26)	23 (18-27)	0.841*
Sex			
Male	5 (10.4)	0 (0)	0.0339†
Female	43 (89.6)	8 (100)	
Cause of PRES			
Antepartum preeclampsia	14 (19.2)	3 (37.5)	0.688†
Postpartum preeclampsia	26 (54.2)	4 (50.0)	1.0†
Acute HTN	6 (12.5)	0 (0)	0.671†
AKI*	3 (6.3)	0 (0)	0.332†
Symptoms & Exam-findings			
Seizure	47 (97.9)	8 (100)	1.0†
Headache	39 (81.3)	5 (62.5)	0.348†
Blurred vision	29 (60.4)	5 (62.5)	1.0†
Stupor	21 (43.8)	8 (100)	0.005†
Coma	3 (6.3)	0 (0)	1.0†
Cortical blindness	4 (8.3)	3 (37.5)	0.021†
GCS**	10 (9-14)	8 (8-10)	0.03*
Focal neurological deficit	5 (10.4)	0 (0)	0.519†
SBP, mm of Hg ***	160 (150-180)	160 (150-170)	0.899*
DBP, mm of Hg	100 (90-110)	100 (80-120)	0.722*

Data were expressed as frequency (%) or median (Interquartile range), *p values were obtained from Mann Whitney U test, †p values were obtained from the Fisher exact test. * Acute Kidney Injury, ** Glasgow Coma Scale,*** Systolic and Diastolic Blood Pressure.

Among the imaging parameters only restricted diffusion on DWI was found to be associated with the 30-day outcome. Patient who had restricted diffusion on MRI were more likely to had poor outcome at 30 day compared to their counterpart (Table IV). However, for the 30-day outcome, the poor outcome was only associated with the presence of diffusion restriction (OR, 62.37; 95% CI, 2.71-143.1) among the four clinical and radiologic variables.

Table IV Association between admission imaging characteristics with 30-day outcome

MRI findings	30 day outcome		
	Good (n=48)	Poor (n=8)	p value
Dominent parieto-occipital	44 (97.9)	8 (100)	1.0†
Frontal lobe	35 (72.9)	7 (87.5)	0.667†
Holohemispheric watershed	14 (29.2)	1 (12.5)	0.428†
Temporal lobe	23 (47.9)	6 (75.0)	0.254†
Cerebellum	5 (10.4)	1 (12.5)	1.0†
Basal ganglia	4 (8.3)	1 (12.5)	0.552†
Brainstem	1 (2.1)	0 (0)	1.0†
Corpus callosum splenium	1(2.1)	1 (12.5)	0.268†
Restricted diffusion	5 (10.4)	6 (75.0)	<0.001†
Focal parenchymal hemorrhage	0 (0)	1 (12.5)	0.415†
Microhaemorrhage	2 (4.2)	1 (12.5)	0.714†

Data were expressed as frequency (%) or median (Interquartile range); *p values were obtained from Mann Whitney U test, †p values were obtained from the Fisher exact test.

Discussion

With the advent of neuroimaging, PRES has become an increasingly recognized clinical-radiological syndrome among a diverse patient population, ranging from children to older people, without any gender differences.[18] The present study included patients 12 years above only, and the median age was around 20 years. Most patients were women with a female. Series from other countries also reported similar distribution with female preponderance.[7,19,20] As the majority of the cases of the present series were female and the precipitating cause of PRES was pregnancy-associated preeclampsia/eclampsia, this might be attributed to the comparatively younger median age observed in the present study in contrast to other larger series.[2,20] However, PRES due to eclamptic encephalopathy had similar age distribution to the present study.[21,22]

In the current study, seizures have been reported as the most common presentation. GTCS was present in the majority (78.6%) of the cases, and status epilepticus occurred in (26.8%) of cases. Followed by seizure, the most prominent feature at presentation was an altered level of consciousness (In the form of drowsiness, stupor or coma), which was found in 47 (83.9%) cases. The third most common presentation was headache in the present study. These findings align with the other studies.[19,21-24]

The most common precipitating cause in the present study was post-partum preeclampsia/eclampsia, followed by antepartum preeclampsia/eclampsia, acute hypertension, and acute kidney injury. Preeclampsia/eclampsia was the dominant cause of PRES in previous case studies and series.[7,14-16,19]

Like McKinney et al., 98.2% were typically dominant parietooccipital, 75% frontal and 51.8% temporal regions of brain involvement in the present study.[25] PRES does not solely occur at the posterior, but rather shows a gradient-like pattern from the back to the front, likely indicating the sympathetic innervation gradient.[25] In the present study, haemorrhage was seen in (7.1%) where focal parenchymal haemorrhage was seen in only (1.8%) of cases and micro bleeding was observed in (5.4%) of cases. On DWI, diffusion restriction found in a minority (19.6%) of patients in the present study. Similarly, McKinney et al. found diffusion restriction less common in their study.[25]

Although the significant residual neurological deficit has been reported in earlier studies, in the present study, 82.1% of the patients were found to have no residual neurological deficit after 30 days of PRES.[5,6] Most of the patients in the present series were pregnancy-induced preeclampsia or eclampsia, which might have contributed to a favourable outcome in our cases. In a meta-analysis, Chen et al. showed promising preeclampsia/eclampsia-associated PRES outcomes.[13] Similar to a recent study, the entire cohort of the present study survived till 30 days following the event.[19] It is in line with the existing evidence where it was established that the aetiology of toxaemia of pregnancy had a more favourable and less severe course of the disease.[26,27,13]

The prognosis of PRES is still unclear, considering the role of different risk factors, imaging findings, and biochemical parameters. Prior research has established a correlation between the causes, location of lesions, atypical imaging results, and some biochemical markers with the clinical outcome of PRES under varying confounding settings. However, the results of those studies vary and are not fully conclusive.[12,20] In the present study, the only independent predictor found for poor outcomes was the presence of diffusion restriction. Diffusion restriction is generally associated with incomplete PRES recovery, reported by several earlier studies.[9,10,12,13,20]

Limitation

There was less case mix as most cases were pre-eclamptic/eclamptic patients. Radiological evidence of reversibility could not be obtained in our patients because there were no follow-up MRIs conducted after the resolution of neurological symptoms.Seriously ill patients with sepsis, multiorgan dysfunction and autoimmune disorders were not in the study group.

Conclusion

PRES was found to be a reversible disorder as the outcome of patients with PRES was excellent without any case fatality. Most patients were female, and preeclampsia/eclampsia was the most important contributory factor for this disorder, followed by acute hypertension. Neuroimaging demonstrated a higher frequency of combined typical and atypical distribution where the dominant parieto-occipital region was the most common site of involvement. The presence of diffusion restriction on MRI is a possible predictor of poor outcomes.

Recommendation

Further prospective studies on larger populations from different centres and case-mix with different aetiology, including pediatric groups, should be included in future studies to determine factors linked to unfavorable outcomes in PRES.

Acknowledgement

All the authors express their gratitude to the respondents.

Contribution of authors

MR-Acquisition of data, drafting & final approval.

AA-Data analysis, drafting & final approval.

SAU-Interpretation of data, critical revision & final approval.

SW-Acquisition of data, drafting & final approval.

MRK-Interpretation of data, critical revision & final approval.

RMM-Data analysis, drafting & final approval.

MH-Conception, critical revision & final approval.

Disclosure

All the authors declared no competing interests.

References

1. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med. 1996; 334:494–500.

2. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: Fundamental imaging and clinical features. AJNR Am J Neuroradiol. 2008; 29:1036–1042.

3. Casey SO, Sampaio RC, Michel E, Truwit CL. Posterior reversible encephalopathy syndrome: utility of fluid-attenuated inversion recovery MR imaging in the detection of cortical and subcortical lesions. AJNR Am J Neuroradiol. 2000; 21:1199–12061.

4. Gupta V, Bhatia V, Khandelwal N, Singh P, Singhi P. Imaging findings in pediatric posterior reversible encephalopathy syndrome (PRES) 5 years of experience from a tertiary care center in India. Journal of Child Neurology. 2016;31(9):1166-1173.

5. Gao B, Lyu C, Lerner A, McKinney AM. Controversy of posterior reversible encephalopathy syndrome: What have we learnt in the last 20 years? Journal of Neurology, Neurosurgery & Psychiatry. 2018;89(1):14-20.

6. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: Clinical and radiological manifestations, pathophysiology, and outstanding questions. The Lancet Neurology. 2015;14(9):914-925.

7. Kalaiselvan MS, Renuka MK, Arunkumar AS. Clinical features and outcomes of patients with posterior reversible encephalopathy syndrome. Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine. 2017;21(7):453-456.

8. Schweitzer AD, Parikh NS, Askin G, Nemade A, Lyo J, Karimi S, et al. Imaging characteristics associated with clinical outcomes in posterior reversible encephalopathy syndrome. Neuroradiology. 2017;59(4):379-386.

9. Hinduja A. Posterior reversible encephalopathy syndrome: clinical features and outcome. Frontiers in neurology. 2020;11:71.

10. Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion-weighted MR images. American Journal of Neuroradiology. 2002;23(6):1038-1048.

11. Alhilali LM, Reynolds AR, Fakhran S. A multi-disciplinary model of risk factors for fatal outcome in posterior reversible encephalopathy syndrome. Journal of the neurological sciences. 2014;347(1-2):59-65.

12. Moon SN, Jeon SJ, Choi SS, Song CJ, Chung GH, Yu IK, et al. Can clinical and MRI findings predict the prognosis of variant and classical type of posterior reversible encephalopathy syndrome (PRES)?. Acta radiologica. 2013;54(10):1182-1190.

13. Chen Z, Zhang G, Lerner A, Wang AH, Gao B, Liu J. Risk factors for poor outcome in posterior reversible encephalopathy syndrome: systematic review and meta-analysis. Quantitative Imaging in Medicine and Surgery. 2018;8(4):421-423.

14. Begum A, Khanam K. Posterior Reversible Encephalopathy Syndrome (PRES). Journal of Bangladesh College of Physicians and Surgeons. 2017;35(1):43-45.

15. Biswas R, Nessa SS, Gupta PS, Biswas S. Posterior Reversible Encephalopathy Syndrome (PRES): A case series in postpartum patients. Bangladesh Critical Care Journal. 2013;1(2):104-106.

16. Rashid F, Sattar MA. Postpartum Posterior Reversible Encephalopathy Syndrome A Case that can Press Hard an Obstetrician. Bangladesh Journal of Obstetrics & Gynaecology. 2016;31(1):46-49.

17. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: A literature review and synthesis. Stroke. 2007;38(3):1091-1096.

18. Roth C, Ferbert A. The posterior reversible encephalopathy syndrome: What's certain, what's new? Practical neurology. 2011;11(3):136-144.

19. Yadav PK, Sen D. Clinicoradiological profile and outcome of patients with posterior reversible encephalopathy syndrome. The Journal of the Association of Physicians of India. 2019;67(1):13-16.

20. Hinduja A, Habetz K, Raina S, Ramakrishnaiah R, Fitzgerald RT. Predictors of poor outcome in patients with posterior reversible encephalopathy syndrome. International Journal of Neuroscience. 2017;127(2):135-144.

21. Sardesai S, Dabade R, Deshmukh S, Patil P, Pawar S, Patil A. Posterior reversible encephalopathy syndrome (PRES): Evolving the mystery of eclampsia! The Journal of Obstetrics and Gynecology of India. 2019;69(4):334-338.

22. Junewar V, Verma R, Sankhwar PL, Garg RK, Singh MK, Malhotra HS, et al. Neuroimaging features and predictors of outcome in eclamptic encephalopathy: A prospective observational study. American Journal of Neuroradiology. 2014;35(9):1728-1734.

23. Granata G, Greco A, Iannella G, Granata M, Manno A, Savastano E, et al. Posterior reversible encephalopathy syndrome—insight into pathogenesis, clinical variants and treatment approaches. Autoimmunity reviews. 2015;14(9):830-836.

24. Lee VH, Wijdicks EF, Manno EM, Rabinstein AA. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. Archives of neurology. 2008;65(2):205-210.

25. McKinney AM, Short J, Truwit CL, McKinney ZJ, Kozak OS, SantaCruz KS, et al. Posterior reversible encephalopathy syndrome: Incidence of atypical regions of involvement and imaging findings. American Journal of Roentgenology. 2007;189(4):904-912.

26. Legriel S, Schraub O, Azoulay E, Hantson P, Magalhaes E, Coquet I, et al. Critically III Posterior Reversible Encephalopathy Syndrome Study Group (CYPRESS). Determinants of recovery from severe posterior reversible encephalopathy syndrome. PLoS One. 2012;7(9):e44534.

27. Patil VC, Agrwal V, Rajput A, Garg R, Kshirsagar K, Chaudhari V. Clinical profile and outcome of posterior reversible encephalopathy syndrome (PRES). Annals of Tropical Medicine & Public Health. 2015;8(4):105-112.