



POSTPARTUM SEIZURES: AN ENIGMA?

Obstetrics & Gynaecology

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ABSTRACT

Background: Seizures is an alarming clinical presentation during the postpartum period which can be caused by myriad of etiologies. It is important to accurately diagnose the underlying etiology and appropriately treat the condition in an order to improve maternal morbidity and mortality. The objective of this study is to study the clinical profile and diagnose the cause of seizures in postpartum period.

Methods: The data was collected over a period of 3 years from November 2016 to November 2019. All patients presenting with complain of seizures in the postpartum period (upto 6 weeks after delivery) were included in the study. Patients with history of seizures following trauma were excluded. Detailed history, clinical examination, investigations and neuroimaging were carried out in all the cases.

Results: A total of 36 patients were included in the study. The age of the patient varied between 19 to 30 years. Most of the patient were primigravida (n=28, 80%). The most common mode of delivery was by caesarean section (n=24, 68.6%). The most common associated clinical symptom other than seizures was headache (n=13, 37.1%). The most common cause of seizures was Posterior reversible encephalopathy syndrome (n=20, 48%) followed by eclampsia (n=10, 19%). The other causes included cerebral venous thrombosis, intracerebral hemorrhage, sub arachnoid hemorrhage, ischemic stroke and breakthrough seizures in patient with known epilepsy.

Conclusion: We found that Posterior reversible encephalopathy syndrome the most common cause of postpartum seizures in our case series. As clinical symptoms are common among the different etiologies, neuroimaging plays an important role in identifying the cause as few conditions could be overlapping. Accurate diagnosis helps in provision of the appropriate treatment and improves outcome of patients.

KEYWORDS

Postpartum seizures, pregnancy, eclampsia, Posterior reversible encephalopathy syndrome, stroke.

INTRODUCTION

Seizures are an uncommon presentation in the postpartum period. The causes of seizures in postpartum period can be classified into three groups, first due to a formerly established cause of seizures which is most common like an exacerbation of epilepsy, second with a new onset of seizures not related to pregnancy such as an undiagnosed brain malignancy, metabolic cause or infections and third group is the occurrence of seizures that are pregnancy related like eclampsia, posterior reversible encephalopathy syndrome and cerebral vein thrombosis.¹

Pre-eclampsia is defined as the new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman. Diagnostic criteria for mild pre-eclampsia are blood pressure greater than or equal to 140/90 mm Hg and proteinuria greater than or equal to 0.3 g in a 24-h urine specimen. Criteria for severe pre-eclampsia are two occasions of hypertension (i.e., blood pressure greater than or equal to 160/110 mm Hg) at least 6 h apart, proteinuria greater than 5 g per 24 h, and other signs of end-organ injury.² Eclampsia is defined as pre-eclampsia and a grand mal seizure in the absence of other conditions that could account for the seizures. Because pre-eclampsia and eclampsia are common, they are often the default diagnoses in pregnant and postpartum women who present with seizures. However there are other important neurological conditions which have overlapping clinical presentations with eclampsia, like posterior reversible encephalopathy syndrome, acute intra-cerebral haemorrhage, sub arachnoid haemorrhage etc. It is important to identify these sinister conditions and appropriately manage the same to improve clinical outcome of the patients.

Some of the aetiologies of postpartum seizures like hypertensive disorders influence maternal mortality. It is estimated that approximately 14% of the maternal deaths worldwide are due to hypertensive disorders which may present as seizures.³ Hence it is important to identify the cause of the seizures and manage appropriately which can significantly improve maternal morbidity and mortality. This present case series is focused on identifying the most common aetiologies, clinical profile and outcome of seizures in postpartum period.

Objective of the study

To study the natural history and clinical profile of patients presenting with seizures in the postpartum period and to identify the cause of seizures.

METHOD

This study was conducted at a referral tertiary care medical college hospital Emergency Department which receives approximately 30,000-45,000 patients annually. A retrospective data was collected over a period of 3 years from November 2016 to November 2019. Patients who were brought in to the Emergency department with complaints of seizures in the postpartum period were included in the study. The postpartum period was considered from the day of delivery till 6 weeks after the delivery. Patients who were brought with a history of seizures followed by trauma, toxic compound exposure, poisoning, and drug overdose were excluded from the study. Detailed history, clinical examination findings, laboratory investigation, radiological investigations like CT scan and MRI scan were carried out in all cases and patient were followed up till discharge to analyse the outcome. The results were analysed and descriptive statistics were used. Data were collected using a structured preformats meeting the objectives of the study. The ethical committee approval was taken to conduct the study from the Institutional Ethics committee Review board.

RESULTS

The demographic and the baseline characteristics are depicted in table no.1. In our study a total of 36 patients were included. The age of the patient varied between 19 years to 31 years. The mean maternal age being 23.31 years. Most of the patients were primigravida (n=28, 80%). The most common mode of delivery was by caesarean section (n=24, 68.6%).

Table no 1. Baseline characteristics of patients.

CHARACTERISTIC	PATIENTS (N=36)
Age (years)	23.31±3.169
Systolic blood pressure	141.43±26.473
Diastolic blood pressure	89.43±13.708
Gravidity	29 (80)
Primigravida	
Gravida-2	6 (17)
Gravida-3	1 (3)
History of preeclampsia	9 (25.7)
Mode of delivery	25 (68.6)
Normal	11 (31.4)
Caesarean section	

Data are mean±SD (95% CI), n (%).

The vital parameters were documented. 15 patients had a BP on arrival of more than 140/90 mmHg. The mean systolic blood pressure was

141.43 mmHg and the mean diastolic blood pressure was 89.43mmHg. All the patients presented with generalized tonic clonic seizures. On an average the patients experienced a mean of 2.34 episodes of seizures.

The most common associated clinical presentation among the patients was increased blood pressure (n=21, 60%) followed by headache (n=13, 37.1%). The different clinical symptoms experienced by the patients are depicted in table no2. The patients developed seizures as early as on the day of delivery within 3 hours (n=7, 19.4%), whereas 3 (8.6%) patients developed seizures as late as 13 days after the delivery. Majority of the patients developed seizures on the day of delivery. On an average, the patients experienced their first seizure on day 5.4 post-delivery.

Table no 2. Associated clinical presentation in the emergency department

CLINICAL SYMPTOM/SIGN	PATIENTS(N)
Headache	13 (37.1%)
Visual disturbances	10 (28.57%)

Elevated BP	15 (42.8%)
Vomiting	5 (14.2%)
Fever	2 (0.05 %)
Pedal Edema	6 (17.1%)

All the patients were initially stabilised in the Emergency room. Anti-hypertensive drug was given to patients with a blood pressure more than 160/100. The patients received either intravenous labetalol or Nifedipine or both. The patients with a clinical suspicion of eclampsia received intravenous magnesium sulphate. If the seizures were persistent then they were administered levetiracetam. The other anti-epileptics administered were Levetiracetam and Phenytoin.

All patients underwent neuroimaging upon admission. Majority of the patients underwent neuroimaging studies within 24 hours of arrival to the hospital. The patients initially underwent Computed Tomography (CT) scan of the brain. If the CT scan did not reveal any findings the patients were subjected to Magnetic Resonance Imaging (MRI) of the brain.

Table 3. Clinical profile of the study patients.

Case	Age	Other symptoms	Postpartum day of occurrence of seizures	Episodes of seizures (n)	Drug given for seizures	Anti hypertensive drug	Mannitol	Diagnosis	Days on ventilator (n)	Duration of hospital stay
1	28	None	9	1	None	None	Received	Ischemic Stroke	4	6
2	24	Headache	0	1	Magnesium Sulphate	Labetalol	Received	Eclampsia	3	5
3	19	None	10	5	Levetiracetam	None	Received	PRES	3	5
4	23	None	0	1	Magnesium Sulphate	None	Received	Eclampsia	3	12
5	22	Fever	8	7	Levetiracetam	None	Not received	PRES	3	5
6	25	Headache	6	3	Levetiracetam	None	Received	PRES	0	5
7	27	Vision disturbances, vomiting	11	2	Levetiracetam	None	Received	PRES	0	4
8	20	Headache	6	1	Levetiracetam	None	Received	PRES	0	3
9	30	None	4	1	Levetiracetam	Labetalol	Received	PRES and eclampsia	0	1
10	23	Vision disturbances	9	3	None	None	Received	Ischemic Stroke	1	12
11	23	None	1	1	Levetiracetam	None	Received	Breakthrough seizures	0	5
12	21	None	2	5	Levetiracetam	None	Not received	PRES	0	4
13	27	Vomiting	7	1	Levetiracetam	None	Received	PRES	0	6
14	24	Headache, Vision disturbances	13	1	None	Labetalol	Received	PRES	0	6
15	27	Headache, Vision disturbances	9	8	Levetiracetam	None	Received	SAH	0	5
16	31	Vision disturbances	7	7	Levetiracetam	Labetalol	Received	PRES	0	3
17	22	Headache	0	1	Magnesium Sulphate And Levetiracetam	Labetalol	Received	Eclampsia	0	8
18	20	Vomiting	8	2	Levetiracetam	Labetalol	Received	PRES	0	4
19	28	Headache, Vision disturbances	7	2	None	Nifedipine	Received	PRES and SAH	0	5
20	26	Vomiting	4	1	Levetiracetam	None	Received	CVT	0	5
21	19	Headache	0	1	Levetiracetam	Labetalol and nifedipine	Received	Eclampsia	0	6
22	21	None	1	1	Levetiracetam	Nifedipine	Received	Eclampsia	0	8
23	24	None	5	1	Levetiracetam And Phenytoin	None	Received	PRES and eclampsia	0	8
24	25	Headache, Vision disturbances, vomiting	6	1	Levetiracetam	None	Received	ICH	0	12

25	20	Headache	0	2	Levetiracetam	None	Received	Eclampsia	0	9
26	20	None	13	2	Magnesium sulphate, Phenytoin	None	Received	Eclampsia	3	10
27	21	Headache, Vision disturbances	2	1	Levetiracetam	Labetalol	Received	PRES	0	5
28	25	Headache, Vision disturbances	3	5	Levetiracetam	Labetalol	Received	PRES	0	6
29	24	None	5	4	None	None	Received	PRES	0	5
30	21	None	1	1	None	None	Received	PRES	0	2
31	23	None	6	2	Phenytoin	Labetalol	Received	Ischemic Stroke	5	10
32	22	None	3	2	Levetiracetam	Labetalol	Received	PRES	0	4
33	20	None	13	2	Phenytoin	None	Received	PRES	3	10
34	20	Headache, Vision disturbances	0	2	Levetiracetam	None	Received	Eclampsia	0	9
35	21	None	1	1	None	None	Received	PRES	0	2
36	21	Fever, altered mental status	0	1	Levetiracetam	None	Received	ICH	4	7

The final diagnosis in majority of the patients were done by radiological imaging. Out of 36 patients, 20 patients were diagnosed to have Posterior reversible encephalopathy syndrome (PRES). The MRI findings revealed patchy areas of T2 and FLAIR hyperintensities in bilateral parieto-occipital lobes and few patients had accompanied hyperintensities in the frontal lobe cortex as well which was suggestive of Posterior reversible encephalopathy syndrome (Figure no. 1)

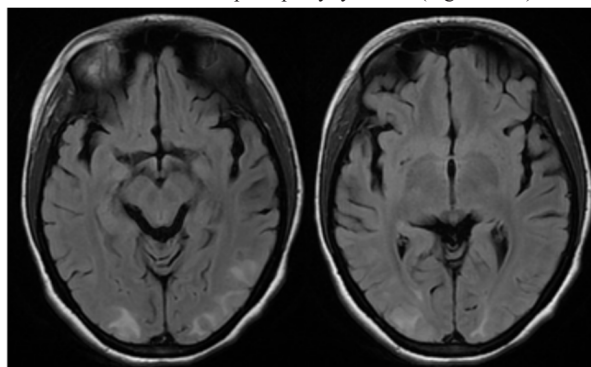


Figure no 1. Near symmetrical bilateral T2/ FLAIR hyper intensities seen in parieto-occipital, right frontal and left temporal lobe cortex and subcortical white matter features suggestive of Posterior Reversible Encephalopathy Syndrome (PRES).

The second most common cause of seizures among our study patients was eclampsia. 10 patients were diagnosed to have eclampsia. Among those 10 patients, two patients had MRI features suggestive of PRES. And one patient with eclampsia had sub arachnoid haemorrhage in the right frontal lobe along with features of PRES.

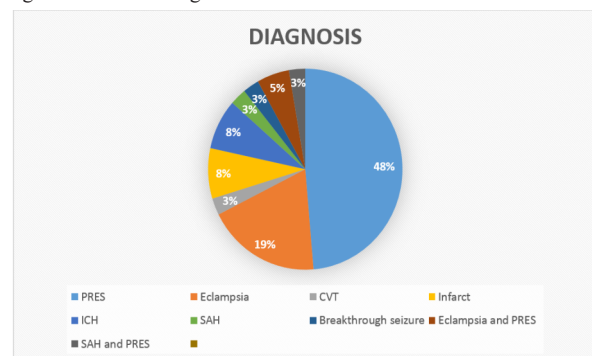


Figure No 2. Pie Chart Representing The Diagnosis

One patient had Acute cerebral venous thrombosis of right transverse sinus, sigmoid sinus, right internal jugular vein and bilateral superficial parieto-temporal cortical veins leading to acute infarct with haemorrhagic transformation involving the right temporo-parietal lobe.

Three patients were found to have intracerebral hemorrhage. One patient had acute atypical intraparenchymal haemorrhage involving left fronto temporal parietal cortex with breakthrough haemorrhage into the bilateral third and fourth ventricle with perilesional edema causing mass effect in the adjacent brain parenchyma with effacement of the ipsilateral lateral and third ventricle. The other patient had haemorrhage in the right gangliocapsular region with extension into the supratentorial and the infratentorial ventricular system with

midline shift and obstructive hydrocephalus (Figure no 3). The third patient had thalamic hemorrhage with interventricular extension.

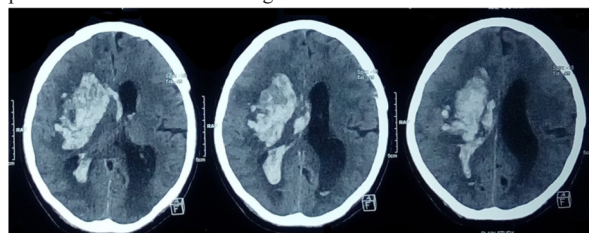


Figure no 3. Acute intracerebral hemorrhage in the right gangliocapsular region with extension into the ventricular system.

Two patients had sub arachnoid hemorrhage, out of them one was aneurysmal and the other was non aneurysmal. The former patient had Acute SAH along bilateral sylvian fissure, frontal and temporal cortical sulci, Acute SAH in suprasellar, quadrigeminal, prepontine, perimesencephalic, retrocerebellar cisterns and cisterna magna and visualised extent of cervical spinal canal with acute intraventricular hemorrhage in frontal horn of lateral ventricle, third and fourth ventricles causing mild obstructive hydrocephalus suspected aneurysmal rupture (Figure no 4). The latter had SAH in the right frontal lobe along with features suggestive of PRES.

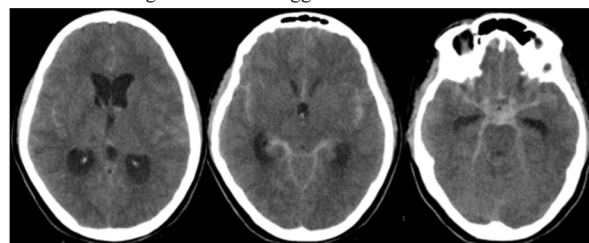


Figure no 4. Computed tomography of the patient with acute sub-arachnoid haemorrhage along bilateral sylvian fissure, frontal and temporal cortical sulci, Acute SAH in suprasellar, quadrigeminal, prepontine, perimesencephalic, and cisterna magna and visualised extent of cervical spinal canal with acute intraventricular hemorrhage in frontal horn of lateral ventricle, third and fourth ventricles causing mild obstructive hydrocephalus.

Among our study patients three had ischemic stroke. Two patients had right middle cerebral artery territory acute non-hemorrhagic infarct (Figure no 5). The other patient had pons, splenium and midbrain infarct with diffuse cerebral edema with hydrocephalus for which the patient underwent external ventricular drain placement for recurrent hydrocephalus.

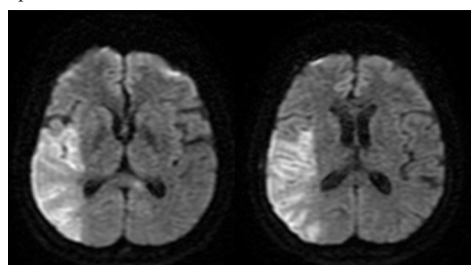


Figure no 5. Area of restricted diffusion seen in right parieto-temporal lobe cortex suggestive of acute non-hemorrhagic infarct in right parieto-temporal lobe cortex – Right MCA territory infarct.

One patient was a known case of epilepsy and presented with breakthrough seizures, neuroimaging was normal.

Most of the patients had a good neurological recovery except in two patients with intracerebral hemorrhage and the other patient with a large infarct who residual deficits. A serum lactate dehydrogenase levels was done in all patients and it was found elevated in all patients with eclampsia. Two patients with postpartum eclampsia developed HELLP syndrome. One patient with eclampsia and HELLP died due to coagulopathy and renal failure.

DISCUSSION

The occurrence of seizures in the postpartum period puts clinicians in a dilemma of myriad of possibilities. More often, eclampsia is considered as the default diagnosis in pregnant and postpartum women with seizures, until otherwise proven. However we have to consider other possibilities as well. Causes of postpartum seizures include postpartum eclampsia, epilepsy, hypoglycaemia, drug or alcohol induced or withdrawal, head trauma and intra cranial haemorrhage, brain tumor or abscess, hypertensive encephalopathy, cerebral vascular occlusion or ischemia, Meningitis, encephalitis, tetanus or HIV infection, Hypocalcemia, hypomagnesemia, hyponatremia or hypernatremia, Uremia, Pseudoseizure, Porphyria, Sturge-Weber syndrome and other rare conditions.

In our study we have found that the most common cause of seizures in the postpartum period to be Posterior reversible encephalopathy syndrome (PRES) (n=20, 55.55%). PRES initially described as reversible posterior leukoencephalopathy syndrome (RPLS) is an uncommon clinical-radiological entity characterized by a variety of symptoms, including headache, seizures, visual abnormalities and altered mental status, accompanied by radiologic findings of reversible vasogenic edema, typically located in bilateral parieto-occipital areas and subcortical white matter.⁴ This condition was initially described by Hinchee et al.⁵

The possible pre-disposing factors include eclampsia, severe hypertension, auto immune disorders, treatment with cytotoxic medication, post transplantation immunosuppression, and infection with sepsis.⁶ In our case series all the patients with PRES presented with seizures, 71.4% of the patients had headache, 38.9% of the patients had visual disturbances in the form of blurring of vision. 10 patients with PRES had a SBP>140mmHg and 6 (33.33%) patients had DBP of >90mmHg. A retrospective case series of patients with PRES done by Wen et al⁷ found that the most common clinical presentation was acute hypertension (86%), headache (81%), seizures (73%), visual disturbance (33%). In the same study they found that acute hypertension (>140/90mmHg) was present in 31 patients (86%), with nine patients (25%) had a systolic blood pressure of 180 mmHg or more. In our study 3 (15%) patients with PRES had a systolic blood pressure of >180 mmHg. In our study 11 of 20 patients with PRES underwent caesarean delivery (n=11, 61.1%) which was similar to the study done by Wen et al⁷ where they studied PRES in patients during antepartum and postpartum period, 17 of 21 postpartum PRES patients, underwent caesarean delivery.

A study done by Brewer I et al⁸ evaluated the occurrence of PRES in patients with eclampsia. Neuroimaging was carried out in all patients with eclampsia both antepartum and postpartum they found that features of PRES on MRI was present in all the patients with eclampsia. In our study we found that only 2 patients were diagnosed to have eclampsia with features of PRES on neuroimaging. Similar findings were seen in other studies where only 41–63% of imaged eclamptic women had clinical and radiologic findings of PRES. Richard Li et al¹² in their clinical study to investigate the factors which influence the clinical recurrence of PRES found that out of 28 patients studied only 2 patients had a pre eclampsia/ eclampsia with neuroimaging features suggestive of PRES.

Seizures are the hallmark of eclampsia. Symptoms that can precede seizures include persistent frontal or occipital headache, blurred vision, photophobia, right upper-quadrant or epigastric pain, and altered mental status. The incidence of hypertensive disorders of pregnancy is approximately 2.7%, with the incidence of pre-eclampsia and eclampsia at about 2.1 and 0.3 %, respectively¹³. Approximately 14% to 33% of patients with eclampsia occurs in postpartum period¹⁴. In our study a total of 7 (19.4%) patients with seizures were diagnosed to have eclampsia. The other symptom associated with seizures in

patients with eclampsia included headache (n=4) and one patient had vision disturbances in the form of blurring of vision.

Hypertension is a common presentation among patients with eclampsia, however it is not universal. In our study 3 (42.85%) patients had a blood pressure >140/90, however 4 (57.14%) patients had a blood pressure <140/90mmHg. It is reported that postpartum eclamptic seizures were less likely to have severe diastolic hypertension (≥ 110 mmHg) than women with antepartum eclampsia.¹⁵ Pulmonary edema, hepatic failure, hemolysis, elevated liver enzyme levels, low platelet count and disseminated intravascular coagulation are several well-recognized complications of eclampsia. 3 of the patients with eclampsia developed HELLP syndrome and one patient died due to Disseminated Intravascular coagulopathy and renal failure. 2 patients with eclampsia had features of PRES on MRI of the brain. The possible etiology endothelial cell dysfunction theory is now more widely accepted as the basic reason of pregnancy-related PRES. The synthesis and secretion of a variety of endothelial cell and neutrophil chemokines, and cytokines provoke a vicious cycle that results in disruption of vascular integrity and vasogenic edema, sometimes progressing to cytotoxic edema.⁷

The incidence of stroke is estimated to increase by 3 fold in pregnant women, possibly due to the relative state of hypercoagulability.¹⁷ As the pregnancy approaches term, many of the clotting factors increase. This is likely in expectation of the displacement of the placenta with subsequent release of pro thrombotic factors to prevent hemorrhage.¹⁸ These changes in prothrombotic factors are greatest in the third trimester and return to baseline at 3-week postpartum. The greatest risk is reported in the 2 days before and one day after delivery. Cardioembolism is the most common reported etiology¹⁷.

The incidence of non-hemorrhagic stroke reported was 18:100,000 pregnancies.¹⁹ In our study 3 patients developed ischemic stroke, two patients had large Middle cerebral artery infarct, one patient had splenium, pons and midbrain acute infarct with hydrocephalus. Ischemic strokes can mimic other more common complications such as eclampsia hence it should be considered whenever neurological deterioration is observed. Pre-eclampsia and eclampsia are major risk factors for both ischemic and hemorrhagic stroke during pregnancy. Hemorrhagic and ischemic stroke remain the most disabling complications of pregnancy. Out of the 3 patients who had ischemic stroke two of them underwent caesarean delivery. Caesarean delivery has been associated with peripartum stroke, although a causal relationship has not been well established²⁰.

Venous thromboembolism most commonly occur during pregnancy and puerperium owing to the hypercoagulable state. The incidence of venous thromboembolism during pregnancies include 0.76-1.72:1000²¹. More than 75% of cases of CVT occur in the postpartum period.²² The other common presenting complaint includes headache which is severe, diffuse and constant. Other findings include dizziness, nausea, seizures, papilloedema, lateralising signs, lethargy, and coma. One patient in the study group developed Acute cerebral venous thrombosis of right transverse, sigmoid, right internal jugular vein and bilateral superficial parieto-temporal cortical veins leading to acute infarct with haemorrhagic transformation involving the right temporo-parietal lobe. The patient presented with complaints of vomiting and seizures. She underwent right fronto-temporo-parietal decompressive craniotomy on second day of admission. A repeat CT scan of the brain was done on day 4 of admission which revealed acute atypical intraparenchymal haemorrhage with perilesional edema in the right temporo-parietal lobe cortex with mass effect and a midline shift on ipsilateral lateral ventricle and a midline shift of 4mm with mild cerebral edema.

Hemorrhagic stroke is an important cause of pregnancy related mortality. It is an uncommon presentation during pregnancy as well as postpartum period. The incidence of hemorrhagic stroke based on reported series is 6:100,000^{23,24}. In our case series three patients had hemorrhagic stroke. One patient had acute atypical intraparenchymal haemorrhage involving left fronto temporal parietal cortex with breakthrough haemorrhage into the bilateral third and fourth ventricle with perilesional edema causing mass effect in the adjacent brain parenchyma with effacement of the ipsilateral lateral and third ventricle. The other patient had haemorrhage in the right gangliocapsular region with extension into the supratentorial and the infratentorial ventricular system with midline shift and obstructive

hydrocephalus. The third patient had thalamic hemorrhage with intraventricular extension. Two patients had sub arachnoid hemorrhage (SAH), one had an aneurysmal SAH and the other patient had a non aneurysmal SAH in the right frontal lobe with associated features of PRES on neuroimaging. Both patients recovered well with no neurological deficits.

The possible pathophysiology of hemorrhagic stroke could be due to pregnancy associated changes where there is expansion of blood volume, vascular tissue remodelling in pregnancy with added risk from the strain and trauma of labour and delivery. Pregnancy increases the risk of hemorrhage more than that of ischemic stroke (relative risk of 2.5 and 28.5 during pregnancy and the postpartum period, respectively)²³. The most important pregnancy-related causes of hemorrhagic stroke includes eclampsia, intracerebral aneurysms and arteriovenous malformations and due to other causes like intracranial venous thrombosis, pregnancy induced hypertension leading to pial vessel rupture, intracranial vertebral artery dissection, Moya Moya disease, Posterior reversible encephalopathy syndrome and postpartum angiopathy.

CONCLUSION

Our study suggests that postpartum seizures include a heterogeneous mix of different conditions with some of them being life threatening. Although eclampsia is a common and important entity in patients with postpartum seizures we found that Posterior reversible encephalopathy syndrome remained the most common cause of seizures in our case series. As clinical symptoms are common among the different etiologies, neuroimaging plays an important role in identifying the cause as few conditions could be overlapping. Accurate diagnosis helps in provision of the appropriate treatment and improves outcome of patients.

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