A Prospective Study of Cranial MRI in Eclampsia And Severe Preeclampsia

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Abstract:

BACKGROUND: This study was planned with an aim to identify the nature and distribution of cranial lesions on magnetic resonance imaging (MRI) and its correlation with clinical and laboratory data in eclampsia and severe preeclampsia.

MATERIAL AND METHODS: 40 patients admitted for indication of severe preeclampsia or eclampsia with or without neurological signs were first stabilized and then underwent cranial MRI. Following MRI they were divided into two groups; Group MP (n=24) including patients with positive finding on the cranial MRI and Group MN (n=16) which included patients with normal Cranial MR imaging. Nature and distribution of the lesions were documented and statistical comparison was made on the basis of clinical findings, arterial blood pressure and laboratory data in both the groups. Patient with cerebral changes in the MRI were also called back for repeat MRI postnatal after two 2 months.

RESULTS: Out of the 40 patients who underwent cranial MRI 24 patients had cerebral changes (Group MP) whereas 16 patients had normal scan (Group MN). In 21 out of 24 (87.5%) MRI finding positive patients the finding was consistent with diagnosis of posterior reversible encephalopathy syndrome (PRES). The most commonly involved areas in patients with PRES were parietal (85.7%,), frontal (71.42%) and occipital lobe (71.42), followed by temporal lobe (38.09) and basal ganglia (33.33) and cerebellum. All the patients who were diagnosed with PRES had a normal MR scan on the follow up at two months after the initial presentation. There was a significantly greater incidence of seizures and neurological disturbances in patients with positive MRI findings as compared to patients with no MRI findings (p<0.001). There was no statistical difference between the blood pressure measurements of the two groups. Markers of endothelial dysfunction like Serum LDH (p=0.002) Serum creatinine (p=0.006) and abnormal red blood cell morphology (0.002) was significantly higher in patients with positive MRI findings compared to MRI Finding Negative group.

CONCLUSION: Our study suggests that PRES is the core component of the pathogenesis of cerebral findings of eclampsia and development of PRES is associated with endothelial dysfunction and not elevated blood pressure alone.

Keywords: Posterior reversible encephalopathy syndrome, PRES, Eclampsia, Severe Preeclampsia, MRI, Endothelial dysfunction

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I. Introduction:

Obstetric literature defines eclampsia as new onset of seizures in a woman with preeclampsia, whereas preeclampsia is defined as blood pressure greater than140/90 mm Hg with significant proteinuria after 20 weeks of pregnancy.1,2 Preeclampsia is considered severe in the presence of multiorgan involvement such as pulmonary edema, seizures, oliguria, thrombocytopenia, abnormal liver enzymes in association with persistent epigastric or right upper quadrant pain, or persistent severe central nervous system symptoms (altered mental status, headaches, blurred vision or blindness). Eclampsia is one of the commonest causes of maternal death with hospital incidence in India ranging from 1 in 500 to 1 in 30. Maternal mortality in India due to eclampsia is 2 to 30% and perinatal mortality is 30 to 50%.3 Although numerous organs are affected by hypertension in

pregnancy, cerebrovascular involvement is the direct mechanism of death in 40% of patients.4,5 The precise mechanism that is responsible for the development of seizures is not clear, but proposed theories include cerebral vasospasm, edema, and the possibility that severe hypertension might disturb cerebral autoregulation and disrupt the blood-brain barrier (BBB); these changes are similar to those described for hypertensive encephalopathy. In fact, the neurologic symptoms of eclampsia are often interpreted as a form of hypertensive encephalopathy.6, 7 Recently the term Posterior reversible encephalopathy syndrome (PRES) has been coined to better explain the cerebral MRI changes observed in eclampsia. However PRES is not merely limited to eclampsia but also observed in patients on immunosuppressive treatment (cyclosporine A, tacrolimus), autoimmune disorders, uremia, hypertension, HIV syndromes, organ transplantation and acute intermittent porphyria.6-8 PRES is characterized by predominant involvement of white matter primarily in the territory of the posterior circulation. The pathology is mostly reversible; however with delay in treatment permanent cerebral injury may occur.6-8 The purpose of this study was to evaluate the Cranial MRI changes in patients suffering from eclampsia and severe preeclampsia and to correlate these changes with clinical and laboratory data.

MATERIAL AND METHODS: This study was conducted in Vardhman Institute of Medical Sciences, Pawapuri, Bihar from September 2017 to May 2018. MRI was done IGIMS, Patna as there is no facility of MRI in VIMS, Pawapuri.

PATIENT SELECTION: 40 patients diagnosed with eclampsia or severe preeclampsia admitted to the department of obstetrics and gynecology in our institute were enrolled into this prospective study. Women with pregnancy less than 20 weeks, known history of hypertension, epilepsy, known demyelinating disorders or cerebrovascular accidents were excluded from the study.

Parturients with contraindication for MRI e.g. Presence of metallic implants, pacemaker or claustrophobia were also excluded from the study.

After well informed consent these patients underwent cranial MR imaging and were divided into the following two groups Group MP (N=24): Patients with positive finding on the cranial MR imaging Group N (N=16): Patients with normal Cranial MR imaging.

II. Methodology:

All pregnant ladies who were admitted for indication of eclampsia or severe preeclampsia with or without neurological signs were first stabilized and antihypertensive agents were given to control blood pressure and Injection magnesium sulphate was started according to Pritchard regime for seizure control.

Laboratory investigations such as Hematocrit (Hct), white blood cell count (WBC), thrombocyte count, lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT), urea, uric acid, albumin, globulin, and PT/a PTT values of all patients were recorded. Also all the women underwent fundoscopic eye examination of both eyes by ophthalmology senior resident to rule out the presence or absence of any hypertensive retinopathy.

These patients once stabilized were counseled before subjecting to MRI. The written consent was taken either from the patient herself or from her relative. A questionnaire from X-ray department to exclude any condition that may be contraindication for MRI was also duly filled up by the attending medical officer.

The radiologist concerned was informed earlier prior to sending the patient. Patients who were admitted late at night or public holiday were stabilized and sent to MRI room the next morning during office hours. All the data required along with the patient sign and symptoms were recorded in the proforma designed for this study.

Patient with cerebral changes in the MRI were called back for repeat postnatal MRI after two 2 months. MRI was performed using 1.5T magnetic resonance imaging system. The examination protocol consisted of T1 weighted spin echo (axial and sagittal), T2 weighted spin echo (axial sagittal and coaxial) sequences, Fluid attenuated inversion recovery (FLAIR) imaging. All statistical analyses were performed with the SPSS 18.0 program for Windows.

Student's unpaired T was used for statistical evaluation of continues variable (age, weight, gestational period, duration of stay and lab data). A p-value<0.05 was accepted to be statistically significant. Data dependent upon verbal explanations were depicted as frequency and %, data dependent upon laboratory parameters were depicted as mean \pm SD.

III. Results:

Out of the 40 patients who underwent cranial magnetic resonance imaging (MRI) 24 patients had cerebral changes (Group MP) whereas 16 patients had normal scan (Group MN). The demographic characteristics in both the groups were comparable (table 1). Also the perinatal outcome was similar in both the groups. In 21 out of 24 (87.5%) MRI finding positive patients the finding was consistent with diagnosis of posterior reversible encephalopathy syndrome (PRES). In the remaining 3 patients with positive MRI finding two were diagnosed to be having old lacunar infarcts and one had superficial cortical vein thrombosis.

The most commonly involved areas in patients with PRES were parietal (85.7%), frontal (71.42%) and occipital lobe (71.42), followed by temporal lobe (38.09) and basal ganglia (33.33) and cerebellum. Except one patient who had isolated occipital lobe involvement all the patient exhibited involvement of multiple areas of brain (Table 2). Out of 24 patients with positive MRI findings 3 patients were diagnosed with Severe Preeclampsia at the time of obtaining the MRI. 2 of these 3 (66.66%) patients developed seizures on postnatal day 2 (Table 3). All these three women had MRI findings consistent with diagnosis of PRES. All the patients who were diagnosed with PRES had a normal MRI on the follow up at two months after the initial presentation.

There was a significantly greater incidence of seizures [87.5% (21 out of 24 vs. 0 out of 16, P<0.001)] and neurological disturbances [79.1% (19 out of 24 vs. 0 out of 16, P<0.001)] in patients with positive MRI findings as compared to patients with no MRI findings. In both the groups the most common symptom was headache with nearly every patient in both group presented with complaint of headache (87.5% in MRI Finding Negative group) (Table 4). No complication was observed in any of the patients.

There was no statistical difference between the blood pressure measurements of the two groups. Several laboratory values differed between the patient groups (Table 5). Serum LDH (586.5 U/L \pm 169.1 vs. 777.6 U/L \pm 172.8, P=0.02), Serum creatinine (1.62 \pm 0.71 mg/dl vs. 1.06 \pm 0.46 mg/dl 6 9, P=0.009), Serum AST (98.75 \pm 84.62 IU/L Vs. 44.95 \pm 54.15 IU/L, P=0.001), and Serum ALT (71.38 \pm 53.70 Vs. 43 \pm 56.17, P=0.006) levels were significantly higher, in patients with radiologic abnormalities, as compared with those without radiologic abnormalities.

The number of patients with abnormal red blood cell morphology was significantly higher in patients with positive MR findings [(79.1%) 19 out of 24] as compared to MRI Finding Negative group [(18.7%) 3 out of 16, P<0.05]. Whereas the white blood cell count (17029±6515 Vs. 11286±5242, P=0.004) was significantly higher in individuals with radiologic abnormalities. 2 out 3 patients diagnosed with severe preeclampsia with positive MRI findings had abnormal red cell morphology. Both these patients went on to develop seizures on post natal day 2.

Demographic characteristic	MP Group (n=24)	MN Group (n=16)	p Value
Age(Years)	23.91±4.49	24.31±4.23	0.782
Weight (kg)	56.375±5.61	57.93±7.08	0.442
Gestational Period (Weeks)	35.41±3.75	36.31±4.37	0.493
Gravida			
Nulliparous	17(70.83%)	11(68.75%)	0.873
Multiparous	7(29.17%)	5(31.25%)	
Religion			
Hindu	17(70.83%)	9(56.25%)	0.343
Muslim	7(29.17%)	7(43.75%)	
Duration of stay in Hospital (Days)	5.75±1.96	5.87±2.8	0.357

Vaginal	18(75%)	8(50%)	0.104
Caesarean section	6(25%)	8(50%)	_
Perinatal Outcomes			
Live Births	19 (79.16%)	13 (81.25%)	
IUD	5 (20.8)	3 (18.75%)	

Mode of Delivery

TABLE 1: DEMOGRAPHIC DATA OF PATIENTS IN THE TWO STUDY GROUPS

*Group MP= Group with abnormal cranial MRI findings, Group MN= Group with normal cranial MRI findings

Patient No.	Frontal	Parietal	Temporal	Occipital	Basal Ganglia
1.	-	-	-	+	-
2.	+	+	+	+	-
3.	-	+	-	-	-
4.	+	+	+	+	+
5.	+	+	-	-	+
6.	+	+	+	-	-
7.	+	+	+	+	+
8.	+	+	-	-	-
9.	+	-	+	+	+
10.	+	+	+	+	-
11.	+	+	-	+	+
12.	-	+	-	+	-
13.	+	+	+	+	+
14.	+	+	+	+	-
15.	-	+	-	-	-
16.	+	-	-	+	-

17.	+	+	-	+	-
18.	-	+	-	-	-
19.	+	+	-	+	-
20.	-	+	-	+	+
21.	+	+	-	+	-
Total (n=21)	15(71.42%)	18(85.71%)	8(38.09%)	15(71.42%)	7(33.33%)
	PRES IN MR	I FINDINGS POSIT	IVE GROUP		

(PRES): Posterior reversible encephalopathy syndrome

	No. of Patients	Patients with positive MRI finding		
Eclampsia	21	21		
Severe Preeclampsia	19	3		
TABLE 3: DISTRIBUTION OF PATIENTS IN THE GROUP				

WITH POSITIVE MRI FINDINGS (N=24)

Clinical Finding	MP Group (n=24)	MN Group (n=16)	*p Value	
Headache	21 (87.5%)	15 (93.75%)	0.519	
Seizures	21 (87.5%)	0	<0.001*	
Mental status changes	19 (79.16%)	0	<0.000*	
Visual Disturbances	17 (70.83%)	7 (43.75%)	0.087	
TABLE 4: CLINICAL FINDINGS IN PATIENTS IN THE TWO STUDY GROUPS				

*Chi square test (df=1)

Lab Value	MP Group (n=24)	MN Group (n=16)	*p Value
Systolic BP (mmHg)	172.75±14.33	178.25±19.58	0.244
Diastolic BP (mmHg)	117.83±10.72	119.12±11.47	0.485

Mean BP (mmHg)	136.14±11.06	138.83±13.56	0.524
HCT (%)	36.63±7.92	36.06±6.46	0.815
WBC	17029.17±6515.83	11286.88±5242.35	0.006*
Platelets	202875±60341.28	207937.51±44557.78	0.750
LDH (IU/L)	777.67±172.89	586.56±169.18	0.002*
AST (IU/L)	98.75±84.62	44.94±54.15	0.001*
ALT (IU/L)	71.38±53.70	43±56.17	0.006*
Uric acid (mg/dl)	5.74±1.43	6.16±1.19	0.423
ALP (IU/L)	480.75±329.61	320.25±194.75	0.057
Urea(mg/dl)	29.71±10.36	26.25±6.35	0.273
Serum Albumin(g/dl)	2.97±0.47	2.88±0.58	0.657
Serum Globulin(g/dl)	2.23±0.39	2.14±0.36	0.560
Creatinine (mg/dl)	1.59±0.71	0.97±0.38	0.006*

PT (seconds)	13.83±1.05	13.88±0.96	0.857		
aPTT (seconds)	29.63±2.06	30.56±3.39	0.622		
Abnormal red cell picture	19 (79.16%)	3 (18.75%)	0.002*		
TABLE 5: BLOOD PRESSURE AND LABORATORY DATA IN PATIENTS WITH MRI FINDING POSITIVE AND MRI FINDING NEGATIVE GROUP					

*student independent T test, HCT-Hematocrit, WBC-white blood cells count, LDH-lactate Dehydrogenase, AST-aspartate transaminase, ALT-alanine transaminase, ALP-alkaline phosphatase, PT-prothrombin time, aPTT-activated partial prothrombin time.

IV. Discussion:

There has been significant debate over the cause of seizures and neurological symptoms in women suffering from eclampsia and preeclampsia. Radiological findings of eclampsia have shown varying degrees of hemorrhage, cerebral edema, and vasculopathy.9-11 However various studies have demonstrated that the primary pathology behind the neurological symptoms is posterior reversible encephalopathy (PRES).12-14 This syndrome represents a type of hypertensive encephalopathy and has been postulated to result from acute elevations in arterial blood pressure resulting in autoregulatory breakthrough in cerebral circulation leading to blood brain barrier (BBB) disruption and vasogenic edema.12-14 Our study aims at identifying the nature and distribution of the cranial lesions on magnetic resonance imaging in women suffering from eclampsia and severe preeclampsia, and also correlate these findings with clinical and laboratory data obtained from these patients.

In the present study 87.5% (21 out of 24) women who had a positive MRI findings had cranial lesions which were consistent with the diagnosis of PRES as described by the various reports.14, 15 In these women the cerebral lesions were not limited to specific sites and were rather identified in multiple areas of brain and not just occipital region of brain. In our study 87.5% of patients with positive MRI had lesions in parietal region, followed by frontal (70.83%), occipital (62.5%), temporal (33.33%), Basal ganglia (33.33%) and venous sinuses (33.33%). Similar findings have been observed in a recent study conducted by Mayo Clinic in which all eclamptic patients who underwent imaging had clinical and radiological findings of PRES.16

It has been postulated that seizure induced neuronal excitation and increased sympathetic outflow releases large amounts of epinephrine and norepinephrine into the circulation resulting in increased peripheral vascular resistance causes acute hypertension and PRES-like symptoms including autoregulatory breakthrough and edema formation.17-19

However PRES has been demonstrated in women with severe preeclampsia without seizure, and it has been demonstrated to precede eclamptic convulsion.20 In our study, out of 21 patients with positive MRI findings 3 patients were diagnosed with severe Preeclampsia. Two of these three (66.66%) patient developed seizures on postnatal day 2. All these three patients had MRI findings consistent with diagnosis of posterior reversible encephalopathy syndrome (PRES). These findings suggest that PRES is an antecedent to eclamptic seizure and not the result of an eclamptic seizure.

Hypertension has been postulated as the cause of PRES, leading to exceeding of the autoregulatory breakthrough of blood brain barrier, fluid leakage and vasogenic edema however, not all patients with eclampsia exhibit significant hypertension prior to the first seizure.15 In a study conducted by Schwartz et al, twenty-eight patients with preeclampsia and neurologic symptoms underwent cranial MR imaging.

In their study they observed that baseline and maximal mean arterial blood pressures were not significantly different between the two groups, nor were the relative increases in blood pressures from 1st trimester levels.15 Very similar findings were observed in our study where we made the observation that that there was no significant difference between the groups on basis blood pressure.

Thus it can be concluded that elevated blood pressures is not the sole cause of PRES. This observation is supported by the fact that PRES can also be observed in conditions like cyclosporine toxicity and uremic encephalopathy where BP is normal.8We observed in our study that the presence of brain edema at MR imaging in patients who presented with preeclampsia-eclampsia and neurologic symptoms was associated with abnormal red blood cell morphology and elevated LDH levels. These findings indicate microangiopathic hemolysis, which suggests endothelial damage. Endothelial dysfunction is considered to be central to the multiple-organ pathophysiology of preeclampsia-eclampsia.21, 22

Patients who had brain edema also had evidence of more severe systemic disease than those who had normal MR imaging findings. Serum, Serum AST, Serum ALT levels and white blood cell concentration, were significantly higher, in patients with radiologic abnormalities, as compared with those without radiologic abnormalities, these changes suggest significantly greater hepato-renal insult in patients having positive findings on MR scan.

Interestingly 2 out 3 patients diagnosed with severe preeclampsia with positive MRI findings had abnormal red cell morphology. Both these patients went on to develop seizures on post natal day

2. This finding is consistent with the findings of previous studies20 in which investigators have shown that endothelial damage in patients with preeclampsia-eclampsia is not a result of hypertension but actually precedes substantial blood pressure increases. The endothelial dysfunction experienced by these patients is more likely related to circulating endothelial toxins or antibodies against the endothelium.

In conclusion cerebral edema in patients with preeclampsia-eclampsia syndrome is primarily associated with laboratory- based evidence of endothelial damage; blood pressures, although elevated in all patients, are not significantly different in those with or without brain edema. endothelial dysfunction leads to disruption of red blood cells and results in abnormal red cell morphology and release of LDH in the serum.24

Routine availability of investigations like red blood cell morphology and LDH levels led us to use them as indicators of endothelial dysfunction. However, more specific markers of endothelial dysfunction like Von willebrand factor, fibronectin, tissue plasma activators, thrombomodulin and endothelin-1 have also been found to be raised in patients with preeclampsia.23,24 These specific markers may we used to screen the patients who are at risk for development of PRES, like patients with severe preeclampsia or neurological disturbances.

Our study is limited by the fact that it was conducted on a small patient population. Also one of the limitations of our study was the use of non-specific markers of endothelial dysfunction. Larger studies using more specific markers of endothelial dysfunction are needed to further validate our findings.

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