



Neuro-imaging in severe hypertensive disorders of pregnancy and correlation with laboratory data: A study from North Indian tertiary health care institution

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Abstract

Introduction: Cerebral & visual disturbances, epigastric pain, nausea, and vomiting, pulmonary edema, impaired liver function of unclear etiology & thrombocytopenia. RBC morphology is the strongest predictor of abnormal radiographic findings. The only laboratory parameter that has been found to be abnormal a week prior to the development of neurological symptoms is serum Lactate dehydrogenase (LDH) level which is higher in the group that later developed hypertensive encephalopathy related brain oedema. Alteration in Liver function tests (LFTs) includes elevated levels of serum aminotransferase, namely, aspartate aminotransferase (AST) or alanine aminotransferase (ALT).

Methods: The study was conducted among 65 antenatal women diagnosed with pre-eclampsia and eclampsia at gestational age >20 weeks in the Department of Obstetrics and Gynaecology, Kamla Nehru State Hospital for Mother and child IGMC Shimla. Laboratory tests and neuroimaging findings were recorded for study purpose.

Results: About 17.6% of severe pre-eclampsia and 100% of eclampsia had findings observed on cranial MRI. In subjects with MR imaging findings, hematocrit, LDH, serum uric acid and ApTT were significantly higher than those without MR imaging findings. Subjects with MRI finding had abnormal RBC morphology whereas none of MR negative subjects had abnormal RBC morphology.

Conclusion: Neuroimaging in antenatals with severe hypertensive disorders might aid in better understanding of the poorly explained phenomenon. In addition this would be helpful in better management of the disorders along with their much dreaded complications. Patients with hypertensive disorders of pregnancy with deranged biochemical results should be subjected routinely to cranial imaging for the better perinatal outcomes.

Keywords: Antenatal women, Pregnancy induced hypertension, laboratory biochemical results, Neuro-imaging.

Introduction

Preeclampsia is a pregnancy-specific disorder clinically characterized by hypertension (blood pressure \geq 140/90 mm Hg) and proteinuria (\geq 300 mg in a 24-hour urine collection) occurring after 20 weeks of gestation in a previously normotensive patient. Preeclampsia can be severe or nonsevere. Criteria for Severe Preeclampsia are

Blood pressure of \geq 160 mm Hg systolic or \geq 110 mm Hg diastolic, recorded on at least two occasions at least 6 hours apart with patient at bed rest, proteinuria of \geq 5 g in 24 hours, oliguria (<400 ml in 24 hours), Cerebral & visual disturbances, epigastric pain, nausea, and vomiting, pulmonary edema, impaired liver function of unclear etiology & thrombocytopenia.

Eclampsia is the occurrence of convulsions or coma unrelated to other cerebral conditions in patients with signs and symptoms of preeclampsia. The seizures are generalized and may appear before, during, or after labor.³

RBC morphology is the strongest predictor of abnormal radiographic findings. The only laboratory parameter that has been found to be abnormal a week prior to the development of neurological symptoms is serum Lactate dehydrogenase (LDH) level which is higher in the group that later developed hypertensive encephalopathy related brain oedema¹¹. Alteration in Liver function tests (LFTs) includes elevated levels of serum aminotransferase, namely, aspartate aminotransferase (AST) or alanine aminotransferase (ALT). Renal perfusion and glomerular filtration rate are reduced. Plasma uric acid concentration is typically elevated in preeclampsia. The elevation exceeds the reduction in glomerular filtration rate and likely is also due to enhanced tubular reabsorption⁴.

Several studies have been conducted to correlate the various clinical and laboratory parameters with abnormalities on neuroimaging. Only a few studies provide information on predictors of outcome in eclamptic encephalopathy¹³. A study to determine the spectrum of cranial Magnetic Resonance Imaging findings in patients with severe preeclampsia & eclampsia and to evaluate their correlation with laboratory data has not been conducted in our institute in the past. The purpose of the study was to determine the spectrum of cranial Magnetic Resonance Imaging findings in patients with severe preeclampsia & eclampsia and to evaluate their correlation with laboratory data.

Materials and Methods

Study area and population: The study was conducted among the pregnant women attending antenatal clinic in the Department of Obstetrics and Gynaecology, Kamla Nehru State Hospital for Mother and child IGMC Shimla.

Study Design: Descriptive observational study.

Study Period: One year from July 2016 to June 2017.

Study Sample: As it was a time bound study, a total of 65 subjects (preeclampsia and eclampsia patients) were included in study.

Inclusion and Exclusion Criteria: Pregnant women diagnosed with pre-eclampsia and eclampsia at gestational age >20 weeks singleton pregnancy were included in the study while women with essential hypertension, liver disease, septicemia cortical vein thrombosis, tuberculoma, neurological infections, epilepsy, encephalitis, brain abscess, neurological tumors and cerebral malaria were excluded.

Study Tool: A study proforma was designed to collect and record socio-demographic parameters, antenatal history, previous medical and reproductive history, clinical signs and symptoms, laboratory investigations, ultrasonic findings, neuroimaging findings, plan and mode of delivery and maternal/foetal outcomes were recorded on the proforma.

Methodology: Standard case definitions were utilized to identify study participants. Patients with severe preeclampsia/eclampsia at 20 weeks or beyond were enrolled for this study. On admission detailed history was taken including warning signs and symptoms i.e. headache, blurring of vision, visual field scotomas, blindness, nausea/vomiting, pain epigastrium swelling feet. Time of onset of seizure, duration & type of seizure: tonic clonic movement, uprolling of eyeballs, frothing from mouth, deviation of head, post seizure confusion, number of seizures and any focal neurological deficit were also noted. These patients were managed in the emergency set up in labour room.

Sociodemographic variables were recorded on proforma, which was followed by general physical examination, obstetric examination (as per the proforma), various laboratory investigations (routine and specific) were done in the laboratory of this institution which is functional 24x7.

Renal sonogram was done in subjects with chronic hypertension and decreased urinary output. All

subjects enrolled for this study received antihypertensives and seizures prophylaxis with Magnesium Sulphate (Pritchards Regimen). Subjects at gestation <34 weeks received antenatal glucocorticoids for fetal pulmonary maturity. Pelvic and cervical assessment was done after stabilizing the patient and mode of delivery was decided accordingly. Caesarean section was done for the obstetric and medical indications only. Labour was monitored partographically. Second stage was cut short by prophylactic outlet forceps/ventouse. Labour and Neonatal parameters were recorded according to the performa.

Subjects with eclampsia, refractory eclampsia and severe preeclampsia with neurological symptoms severe enough to prompt neuroimaging were subjected to cranial MR imaging on 1.5 Tesla Magnetic Resonance Imaging system in Department of Radiodiagnosis at IGMC Shimla within 4 days of presentation. The standard protocol comprised of T1 Weighted images, T2 Weighted images, FLAIR sequence along with Diffusion Weighted images. Vasogenic edema which is the characteristic finding in PRES, showed hypo-intense signal on T1WI, hyper-intense signal on T2WI and FLAIR sequences and there was no diffusion restriction on Diffusion weighted images, whereas cerebral infarcts had shown diffusion restriction. The nature & distribution of the cerebral lesions, if any was noted. The clinical findings, laboratory data of all the patients with or without radiological findings on cranial MR imaging was compared and correlated.

Statistical Analysis: Data were entered into Microsoft Excel spreadsheet, cleaned and transferred to Epi Info version 7.2.2.6 software for analysis. Continuous variables were presented as mean scores \pm standard deviations while discrete variables as percentages and proportions of each. Pearson's Chi-squared was used to test the statistical significance of categorical data respectively. Mean of variables was compared using Independent t- test after checking normality

of data. Two tailed P value < 0.05 was considered as statistically significant for all analysis.

Ethical Considerations: Prior permission was taken from Institute Ethical Committee. Personal identifiers were omitted in order to maintain confidentiality and anonymity. Potential harms and benefits were explained to the patient and guardian before taking consent. Patient was free to leave the study at any point of time and this didn't affect her clinical care. No financial expenditure was incurred by the patient for the sake of study.

Results

The study recorded the findings of 65 Pre-eclamptic/Eclamptic antenatal women with gestational age more than 20 weeks and presenting with neurological symptoms. All 65 patients enrolled for the study were subjected to cranial MR Imaging. Table 1 shows the radiological findings of the subjects on Magnetic Resonance Imaging (MRI). About 36.9% subjects had findings on MRI. Posterior Reversible Encephalopathy Syndrome (PRES) was the most common (27.7%) finding followed by PRES with vasospasm (3.1%). One patient had radiological diagnosis of maxillary sinusitis on MRI and it was also regarded as MRI negative for the data analysis as the MRI of the brain was normal in this patient. About 63% of participants had no abnormality detected on MRI.

Table 1: Radiological Findings on Cranial Magnetic Resonance Imaging

Findings	No.	Percentage
Posterior reversible encephalopathy syndrome	18	27.69%
Posterior reversible encephalopathy syndrome with vasospasm	2	3.07%
Infarct	1	1.54%
CVT without infarct	0	0%
Atrophic changes	1	1.54%
Vasospasm	1	1.54%
Maxillary sinusitis	1	1.54%
No abnormality detected	41	63.07%
Total	65	

CVT: Cortical venous thrombosis

Table II depicts the various laboratory parameters of subjects with severe preeclampsia/eclampsia and their correlation with MRI findings. Several

lab parameters differed between MRI positive and MRI negative subjects. The difference was statistically significant for Hct (p-value 0.008), platelet count (p-value 0.023), serum LDH (p-value 0.0), S. uric acid(p-value 0.041) , APTT(p-value 0.002) and abnormal red cell picture (p-value \geq 0.05). The mean thrombocyte count (164739+/-103060/ μ l) was significantly higher in MRI

positive subjects, the possible explanation for this unusual finding could be that the subject with HELLP and DIC were excluded from the study. Moreover, the laboratory parameters analyzed were those of admission time and the cranial MRI was done within four days of delivery, due to the problems related to patient's safety as patient had to be transported over a distance of 2 kilometre for neuroimaging.

Table II: Relation of Various Lab Parameters with MRI Findings

LAB PARAMETERS	MRI negative			MRI positive			p-value
	Minimum	Maximum	Mean+/-SD	Minimum	Maximum	Mean+/-SD	
Hct(%)	23.2	42	35.830+/-5.213	32	45	39.18+/-2.93	0.008*
WBC(10^3 /ul)	9500	19880	14883+/- 2641	4900	19300	14226+/- 3892	0.423
Thrombocyte(μ l)	50000	238000	101269+/- 46382	50000	357000	164739+/- 103060	0.023*
LDH (U/L)	344	800	567+/- 122.03	479	1840	947.17+/- 338.5	0.00*
AST (U/L)	33	234	72+/- 58.8	28	234	75.87+/- 68	0.823
ALT (U/L)	18	334	85.86+/- 84.4	16	334	88.3+/- 111	0.921
ALP(U/L)	120	490	238+/- 81.09	66	547	222+/- 132	0.550
Uric acid(mg/dl)	4	8.6	6.102+/- 0.913	3.7	9.2	6.870+/- 1.58	0.041*
BUN (mg/dl)	8.5	22.0	12.683+/- 2.77	7	24.5	13.75+/- 5.26	0.287
Creatinine(mg/dl)	0.6	1.6	0.93+/-0.189	0.7	1.5	1.024+/-0.27	0.32
TSP(g/dl)	5	6.6	5.61+/-0.551	4.7	7	5.79+/-0.7	0.243
Albumin(g/dl)	2	5	3.298+/- 0.722	2.2	6	3.45+/- 0.82	0.491
PT(seconds)	10	12.8	11.35+/- 0.642	10	13.5	11.787+/- 1.25	0.071
APTT (seconds)	28	34	31.919+/- 1.32	30.6	39.2	34.109+/- 2.98	0.002*
24 hrs urine protein (mg)	200	6468	596+/-1332	220	1000	487+/-226.6	0.700
Abnormal red cell picture (No.)			0			16	0.00*

Table III: Relation of MRI Findings with Maternal variables

Parameter	Sub Group	MRI positive (n=23)%	MRI Negative (n=42)%	P-Value
maternal age	<20	3(13.1)	0	0.016*
	20-29	15(65.2)	35(83.3)	0.097
	30-39	3(13.1)	7(16.6)	0.69
	>40	2(8.7)	0	0.052
	Mean \pm SD	26.39 \pm 7.372	24.48 \pm 3.486	0.17
Gravidity	Primigravida	11(47.8)	27(64.3)	0.19
	multigravida	11(47.8)	15(35.7)	0.34
	postpartum	1 (4.3)	0	0.17
gestational age	20-23 wks 6 days	1(4.4)	0	0.17
	24-27 wks 6 days	4(17.4)	2(4.8)	0.09
	28-33 wks 6 days	6(26.1)	10(23.7)	0.83
	34-36 wks 6 days	6(26.1)	22(52.3)	0.04*
	>37 wks	5(21.7)	8(19.1)	0.79

Table IV: Lab Parameters and MRI Findings

Laboratory findings	Demirtas O et al ⁸ 2005		Junewar V et al ¹³ 2014		Present study 2017	
	MRI positive (n=18)	MRI negative (n=21)	MRI positive (n=27)	MRI negative (n=8)	MRI positive(n=23)	MRI negative(n=42)
Hct(%)	34.59±4.96	33.45±6.13 p-value-0.469	32.33±6.76	32.58±6.49 p-value-0.93	39.18+/-2.93	35.830+/-5.213 p-value-0.008*
WBC(10 ³ /µl)	12790±3250	13490±3220 p-value-0.748	7830±2230	8410±2000 p-value-0.51	14226+/- 3892	14883+/- 2641 p-value-0.423
Thrombocyte (µl)	245200±70030	264710±10488 p-value-0.432	185000±49000	200000±29000 p-value-0.42	164739+/- 103060	101269+/- 46382 p-value-0.023*
LDH (U/L)	792.40±186.08	605.48±184.51 p-value-0.006*	458.03±107.94	319.50±20.50 p-value-0.001*	947.17+/- 338.5	567+/- 122.03 p-value-0.00*
AST (U/L)	31.93±6.78	35.76±15.67 p-value-0.797	47.15±17.83	53.13±15.22 p-value-0.40	75.87+/- 68	72+/- 58.8 p-value-0.823
ALT (U/L)	25.60±8.67	26.24±18.89 p-value-0.712	46.48±16.12	53.13±16.14 p-value-0.32	88.3+/- 111	85.86+/- 84.4 p-value-0.921
ALP(U/L)					222+/- 132	238+/- 81.09 p-value-0.550
Uric acid (mg/dl)	5.61±1.17	4.41±1.83 p-value-0.010*	9.47±2.75	6.31±0.76 p-value-0.003*	6.870+/- 1.58	6.102+/- 0.913 p-value-0.041*
BUN (mg/dl)					13.75+/- 5.26	12.683+/- 2.77 p-value-0.287
Creatinine (mg/dl)	0.86±0.31	0.68±0.14 p-value-0.005*	1.11±0.41	0.74±0.14 p-value-0.019*	1.024+/-0.27	0.93+/-0.189 p-value-0.32
TSP(g/dl)					5.79+/-0.7	5.61+/-0.551 p-value-0.243
Albumine (g/dl)	2.87±0.57	2.99±0.55 p-value-0.584			3.45+/- 0.82	3.298+/- 0.722 p-value-0.491
PT(seconds)					11.787+/- 1.25	11.35+/- 0.642 p-value-0.071
ApTT(seconds)					34.109+/- 2.98	31.919+/- 1.32 p-value-0.002*
Abnormal red cell picture(No.)					16	0 p-value-0.00*

Bold numbers: values with significant p-value*

Discussion

The present study highlights the neuro-imaging findings in the antenatal cases suffering from hypertensive disorders of pregnancy and correlation of hematological and biochemical data of subjects with undergoing neuroimaging. In subjects with MRI findings haematocrit, LDH, uric acid and ApTT was significantly higher (p-value 0.008), (p-value 0.00), (p-value 0.041) and (p-value 0.02) respectively than those without MR imaging findings. Similarly Demirtas O et al and Junewar V et al also observed significantly higher levels of LDH and uric acid, although haematocrit and ApTT did not differ in relation to MRI findings. They did not observe any difference in the mean thrombocyte count between MR imaging positive and negative subjects.

The mean platelet count in the present study was higher in MR imaging positive subjects, which

was an unusual finding. Exclusion of subjects with DIC, HELLP and delay in neuroimaging could be the possible explanation as the patients had to be transported over a distance of 2 kilometers for neuroimaging.

The serum creatinine levels did not differ significantly in MRI positive and MRI negative subjects.

16/23(69.5%) subjects with neuroimaging findings had abnormal RBC morphology (p-value 0.00) Elevated LDH and abnormal RBC morphology are indicators of hemolysis. Elevated uric acid and serum creatinine are indicators of renal dysfunction. Endothelial injury yields to morphological disturbance in erythrocytes and microvascular hemorrhage. Therefore the brain lesions are found to be associated with high LDH levels, deranged renal functions and RBC

morphology. These lab parameters are the predictors of abnormal radiological findings

Conclusion:

The cause of severe preeclampsia & eclampsia has not yet been explained. Investigations of laboratory parameters associated with brain lesions detected on MR imaging might shed light on pathogenesis of the disease. Indicators of endothelial dysfunction i.e. abnormal RBC morphology, elevated LDH, deranged renal function tests were significantly associated with MRI positivity. Of all laboratory derangements the cranial MRI was found to have high sensitivity (91.30%) for LDH and high specificity (100%) for abnormal RBC morphology. We conclude that the brain edema in patients with preeclampsia-eclampsia syndrome is primarily associated with the laboratory based evidence of endothelial damage; more specific markers of endothelial dysfunction include fibronectin, tissue plasminogen activator, thrombomodulin, endothelin-1, and in particular Von willebrand factor. Measurement of the specific markers may be useful to evaluate endothelial integrity in patient who are preeclamptic, especially patient who are at risk of progression to hypertensive encephalopathy such as those with severe headache or other neurological signs and symptoms. If this screening result is abnormal treatment with appropriate antihypertensives & termination of pregnancy may be initiated before hypertensive encephalopathy develops. Neuroimaging should be done in such patients to rule out the neurological involvement.

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Conflict of Interest: None declared

Ethical Approval: Study was approved by the Institutional Ethics Committee

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