OBSTETRICS

Posterior reversible encephalopathy syndrome in 46 of 47 patients with eclampsia

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OBJECTIVE: We sought to investigate the concurrence of posterior reversible encephalopathy syndrome (PRES) with eclampsia and to describe the obstetric, radiological, and critical care correlates.

STUDY DESIGN: This was a single-center, 2001-2010 retrospective cohort study of all patients with eclampsia who underwent neuroimaging via magnetic resonance imaging (MRI) or computerized tomography (CT) with or without contrast.

RESULTS: Forty-six of 47 of eclamptic patients (97.9%) revealed PRES on neuroimaging using 1 or more modalities: MRI without contrast, 41 (87.2%); MRI with contrast, 27 (57.4%); CT without contrast, 16 (34%); CT with contrast, 7 (14.8%); and/or magnetic resonance angiography/magnetic resonance venography, 2 (4.3%). PRES was identified within 24 hours of presentation. Laboratory findings can also vary, depending on the underlying associated condition.

PRES, but patients will also present with signs of encephalopathy such as altered mental status, headaches, nausea, and vomiting. Visual disturbances are also common, varying from mild blurry vision to complete cortical blindness. Hypertension is associated with the majority of cases, although blood pressure may be normal or only mildly elevated in up to 20-30% of cases. In the series of 36 patients presented by Lee et al, the mean systolic blood pressure was 187 mm Hg (range, 80–240 mm Hg) within 24 hours of presentation. Laboratory findings can also vary, depending on the underlying associated condition.

Neuroimaging findings of PRES have been described in scores of eclamptic patients since the 1996 report of Hinchey et al, usually in single case reports or small case series. How often PRES occurs in association with eclampsia is unknown. To our knowledge, there is no large patient series exploring the relationship between eclampsia and the concurrence of PRES. The purpose of this study was to determine what percentage of eclamptic women at our institution displayed findings of PRES when neuroimaging studies were undertaken. We also sought to determine which treatment modalities were used to manage these patients and to explore how well these interventions had an impact on overall patient outcome.

MATERIALS AND METHODS

This project was a single-center, retrospective cohort study inclusive of the years 2001-2010, which was approved by the institutional review board at the University of Mississippi Medical Center. Inclusion criteria were pregnancy or within 6 weeks postpartum; neuroimaging via magnetic resonance imaging (MRI) or MRI and/or magnetic reso-
The medical records of patients with eclampsia who underwent cranial imaging were identified, evaluated, and pertinent data extracted. If neuroimaging was not undertaken for an eclamptic patient, no further data accrual was undertaken.

**Imageing analysis**

The imaging modalities used included MRI, MRA, and CT both with and without contrast. The diagnosis of PRES was made by radiologists using the standard radiological criteria for PRES. PRES has a unique MRI and CT imaging appearance, which is demonstrated as subcortical and gyral T2-weighted and fluid attenuated inversion recovery (FLAIR) signal hyperintensities that become more diffuse as the extent of edema increases. Focal areas include symmetric multilobar/hemispheric edema with predominant involvement of parietal and occipital lobes. In addition, frontal lobes and the inferior temporal-occipital junction are also focal areas, less commonly the cerebellum. This group of women included both antepartum and postpartum eclampsia.

**Statistical analysis**

Maternal race, gravida, mode of delivery, systolic hypertension, imaging modality, site of lesions, and treatment modality was analyzed via a χ² analysis. Maternal age, body mass index (BMI), gestational age at delivery, days in-house, and the time to return to normalcy were analyzed using a Student t test. Data are expressed as mean ± SD. A P < .05 was considered significant.

**Results**

Forty-seven of 123 women considered to have eclampsia (38.2%) underwent neuroimaging studies during the 10 year period of 2001-2010 at our academic institution. The findings from all 47 patients who underwent neuroimaging are reported in the current study. Among the 47 study subjects were 23 women with antepartum eclampsia and 24 women with postpartum eclampsia. In cases of postpartum eclampsia, on average, the patient experienced her first seizure on day 6 (range, 0–14 days).

There was not a significant difference in self-reported maternal ethnicity between women with antepartum and postpartum eclampsia (P = .729; Table 1). Neither were there any significant differences in maternal age (P = .506), maternal BMI (P = .143), or gravidity (P = .777; Table 1) between the 2 groups.

Women who had antepartum eclampsia primarily delivered via cesarean section (74%), whereas 67% of the women with postpartum eclampsia had vaginal deliveries (P = .001; Table 1). Women with antepartum eclampsia also delivered earlier than women with postpartum eclampsia (P = .002; Table 1) and had a longer hospital stay than women with postpartum eclampsia (P = .026; Table 1).

There was a significant difference in systolic pressures between women with antepartum or postpartum eclampsia (P = .001; Table 1). Significantly more...
women with antepartum eclampsia (44%) had systolic blood pressures between 140 and 159 mm Hg ($P = .039$; Table 1) compared with women with postpartum eclampsia, whereas 54% of women with postpartum eclampsia had systolic blood pressures between 160 and 180 mm Hg, which was significantly more compared with women with antepartum eclampsia ($P < .0001$; Table 1). In addition, no women with antepartum eclampsia developed systolic pressures greater than 180 mm Hg, whereas 13% of women with antepartum eclampsia had systolic pressures greater than 180 mm Hg ($P = .002$; Table 1). All study subjects had singleton gestations. There were no maternal deaths in the current study.

Headache was the most common presenting symptom (87.2%) followed by altered mental status (51.1%), visual disturbance (34%), and nausea/vomiting (19.1%). A diagnosis of PRES was made in 46 of 47 women (97.9%) who were considered to have eclampsia. This diagnosis was made using 1 or more imaging modalities including MRI without contrast ($n = 41$), MRI with contrast ($n = 27$), CT without contrast ($n = 16$), CT with contrast ($n = 7$), and/or MRA/magnetic resonance venography ($n = 2$). There was not a significant difference in the imaging modality used when women with antepartum eclampsia were compared with women with postpartum eclampsia ($P = .984$; Table 2). Radiological evidence of PRES was found in multiple sites between women who developed eclampsia in the antepartum (87%) and postpartum (88%) periods. There was not a significant difference in the site of lesions between the 2 groups ($P = .705$; Table 2).

Full data regarding the use of various treatment modalities were available for 38 of the 47 patients (80.8%) and is reported in Table 2. Magnesium sulfate given as an initial intravenous bolus followed by a continuous infusion was utilized all of these women. Supplantal therapies included intravenous antihypertensives (labetalol, hydralazine, or nifedipine), diuretic agents, and potent glucocorticoids. The corticosteroids used in these patients included either intravenous (IV) dexamethasone or betamethasone for enhanced fetal lung maturation or maternal treatment for concurrent hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. There was a significant difference in treatment modality, in which women with antepartum eclampsia were treated with steroids significantly ($P = .001$) more often than women with postpartum eclampsia.

We made an intensive effort in this retrospective study to determine the length of time that it took for these women to return to normalcy following the initial eclamptic seizure and whether the use of various treatments altered this time period. Normalcy was defined clinically as the absence of visual problems, headache, nausea/vomiting, or altered sensorium. The mean time from seizure to normacy was 36.5 hours when a diuretic was given, 34.8 hours when antihypertensives were given, and 32.9 hours when corticosteroids (IV dexamethasone) were utilized (range, 9—135 hours for all interventions because the patients with the shortest and longest stays received all 3 treatments). For the 19 patients who received corticosteroids after the initial seizure, the mean time between steroid initiation and a return to normalcy was 17 hours. The Figure demonstrates the time to return to normalcy based on antepartum and postpartum eclampsia. There was not a significant difference between the groups when magnesium sulfate was administered ($P = .977$), with or without antihypertensives ($P = .955$), diuretics ($P = .778$), or steroids ($P = .829$; Figure).

**Comment**

The present series of patients is the largest single institutional series of imaged eclamptic patients with evidence of PRES in the United States that has been published to date. Consistent with the

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**Table 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Antepartum, n (%)</th>
<th>Postpartum, n (%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging modality used</td>
<td></td>
<td></td>
<td>.984</td>
</tr>
<tr>
<td>MRI without contrast</td>
<td>20 (87)</td>
<td>21 (88)</td>
<td></td>
</tr>
<tr>
<td>MRI with contrast</td>
<td>14 (61)</td>
<td>13 (54)</td>
<td></td>
</tr>
<tr>
<td>CT without contrast</td>
<td>8 (35)</td>
<td>8 (33)</td>
<td></td>
</tr>
<tr>
<td>CT with contrast</td>
<td>3 (13)</td>
<td>4 (17)</td>
<td></td>
</tr>
<tr>
<td>MRA/MRV</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Site of lesion</td>
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<td></td>
<td>.705</td>
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<tr>
<td>Occipital lobe</td>
<td>18 (78)</td>
<td>17 (71)</td>
<td></td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>17 (74)</td>
<td>19 (79)</td>
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</tr>
<tr>
<td>Temporal lobe</td>
<td>6 (26)</td>
<td>7 (29)</td>
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</tr>
<tr>
<td>Frontal lobe</td>
<td>12 (52)</td>
<td>17 (71)</td>
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</tr>
<tr>
<td>Basal ganglia/cerebellum</td>
<td>5 (22)</td>
<td>6 (25)</td>
<td></td>
</tr>
<tr>
<td>Multiple areas</td>
<td>20 (87)</td>
<td>21 (88)</td>
<td></td>
</tr>
<tr>
<td>Treatment modality used (results from 0.01938 patients reported)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>19 (100)</td>
<td>19 (100)</td>
<td></td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>17 (89)</td>
<td>16 (84)</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>13 (68)</td>
<td>12 (63)</td>
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<tr>
<td>Steroids</td>
<td>13 (68)</td>
<td>6 (32)</td>
<td></td>
</tr>
</tbody>
</table>

CT, computed tomography; MRA/MRV, magnetic resonance angiography/magnetic resonance venography; MRI, magnetic resonance imaging; PRES, posterior reversible encephalopathy syndrome.

*Women with antepartum eclampsia were treated with steroids significantly more often than women with postpartum eclampsia.

recently published summary of current knowledge about PRES by Sraykov and Schwab, the current study revealed several important findings that are suitable for emphasis. First, advanced neuroimaging techniques such as magnetic resonance imaging and/or computerized tomography indicated the presence of PRES in every patient with eclampsia; a single patient without evidence of PRES was later determined to have an underlying seizure disorder. Second, although headache (87%) and visual disturbance (34%) were common symptoms presaging eclampsia and PRES, they were not universal nor was severe systolic hypertension (47%) a constant feature. Third, PRES was identified often in multiple areas of the brain, not just the occipital region, consistent with the findings of others. In addition, the results from this study reconfirms a recent study from the Mayo Clinic, in which all eclamptic patients who underwent imaging had clinical and radiological findings of PRES.

Of great importance, the authors believe that aggressive comprehensive and meticulous medical management may have been a factor in facilitating complete maternal recovery over a usually brief hospitalization averaging 4 days without a single maternal death.

The evidence from our report supports the hypothesis that PRES is the primary central nervous system injury in patients with eclampsia. Some of the changes in normal pregnancy include substantially increased levels of antiangiogenic growth factors and cytokines entering the maternal circulation. However, during normal pregnancy the blood-brain barrier (BBB) adapts to prevent these circulating permeability factors from entering the brain and leading to vasogenic brain edema. Interestingly plasma from preeclamptic women has been found to increase BBB permeability, thereby suggesting that an increase in BBB permeability could permit passage of damaging antiangiogenic and antiendothelial proteins into the brain to cause the neurological complications of eclampsia.

Because not all patients with eclampsia exhibit significant hypertension or substantial proteinuria prior to the first seizure and because brain imaging with MRI prior to seizure in eclamptic women has revealed evidence of vasogenic edema, the primary explanation for the pathogenesis of neurological symptoms and cerebral edema formation during eclampsia is that it represents a form of PRES like that seen in other disease processes such as hypertensive encephalopathy.

With PRES there is a loss of autoregulatory capacity, BBB disruption, and subsequent vasogenic edema around cerebral arteries and arterioles. So-called normotensive eclampsia may actually represent a clinical state caused by diminished autoregulatory capacity or enhanced permeability of the BBB or both. In addition, PRES has been demonstrated in a patient with severe preeclampsia without seizure, and it has been demonstrated to precede eclamptic convulsion. These findings are suggestive of PRES as an antecedent to eclamptic seizure as opposed to the result of an eclamptic seizure.

The cerebral pathology of patients with severe preeclampsia who suffer seizure(s) may be due to microangiopathy of the cerebral vessels, often with hypertension contributing. Microangiopathy and/or malfunction of the cerebral vasculature may be related to circulating levels of antiangiogenic factors such as soluble fms-like tyrosine-1 (sFlt-1) and soluble endoglin (sEng), which have been demonstrated to be at higher levels in patients with eclampsia compared with those with severe preeclampsia.

In some animals exposed to high levels of sFlt-1 and sEng, researchers have observed choroid plexus with the loss of endothelial fenestrae resembling the glomerular endotheliosis of preeclampsia. Interestingly, a study by Fugate et al found that 45% of women with PRES also had autoimmune disease, which implicates endothelial dysfunction as a possible pathophysiological mechanism. Women with preeclampsia and animal models of preeclampsia, in which endothelial dysfunction is a key feature, also have some of the characteristics of autoimmune disease, such as increases in interleukin-17 and T helper 17 lymphocytes.

Treatment of eclampsia, and thus PRES, is best accomplished using magnesium sulfate; however, the effect of magnesium sulfate in the prevention and treatment of eclampsia likely is multifactorial. In the peripheral vasculature or cerebrovasculature, magnesium sul-
fate may act as a vasodilator to decrease peripheral resistance or relieve vasoconstriction. In the central nervous system, magnesium sulfate may also protect the BBB and thereby limit cerebral edema formation as well as act through a central anticonvulsant action.29

Control of hypertension is also considered a core management component for PRES treatment.2 Antihypertensive treatment using intravenous labetalol, hydralazine, or nicardipine is usually recommended for the prevention of severe systolic hypertension of more than 160 mm Hg and/or severe diastolic hypertension of more than 105-110 mm Hg.32,33 Gradual correction to target levels of 140-155 mm Hg systolic and 90-105 mm Hg diastolic are advisable to protect the mother and to avert compromised uteroplacental blood flow. Intravenous dexamethasone is widely used for the treatment of cerebral edema, especially in patients with intracranial tumors because of its long biological half-life, its low mineralocorticoid activity, and its well-described effect in minimizing vasogenic peritumoral edema.34-36

In addition to these clinical data, studies in experimental animals have shown that administration of IV dexamethasone leads to a reduction of poststroke brain edema.37 Thus, there is accumulating evidence to suggest a possible role for potent glucocorticoids along with magnesium sulfate and blood pressure control in pregnant patients with PRES/ecclampsia.38 This is supported by our findings in the present study showing faster normalization of central nervous system function following eclampsia when IV dexamethasone is given for HELLP syndrome or intramuscular betamethasone is given to enhance fetal lung maturation.

The current study used MRI and CT imaging to identify the abnormal T2/FLAIR signals associated with PRES. Diffusion-weighted imaging is also capable of distinguishing between vasogenic and cytotoxic edema and can be used to identify PRES. Differentiating the underlying etiology of PRES based on imaging alone is not possible at this time, despite the advanced imaging techniques (ie, brain perfusion imaging, magnetic resonance spectroscopy), but as the current study and others have shown, neuroimaging in conjunction with clinical diagnosis can help identify eclamptic patients with PRES.8

Our study shares the same shortcomings of any retrospective investigation, including selection bias. Because of logistical, cost, or consideration of value to patient management in individual cases, only 47 of 123 eclamptic patients had neuroimaging requested by the physicians who were caring for this patient group. In addition, we do not have information regarding women with severe preeclampsia who had neuroimaging. There was no consistent protocol in place to direct who would or who would not undergo neuroimaging, which introduces a selection bias in regard to the patients who were neuroimaged; utilization increased during the last half of the decade that spanned the course of study as greater interest in the information provided led to more frequent ordering of the test.

It is possible that a smaller percentage of eclamptic patients may have exhibited PRES had all patients been studied uniformly. Every medical record for patients discharged with a diagnosis of eclampsia were scrutinized carefully to identify all those who underwent neuroimaging; the same research nurse recorded the data from the medical records of all patients and the same physicians (J.B. and A.A.R.) interpreted the radiological reports for consistency and accuracy.

Another limitation to our study is the fact that radiologists were not blind to the diagnosis of the patient because this study was done retrospectively. Future studies will include a reanalysis of images by a radiologist blinded to patient diagnoses. For patients with eclampsia/PRES, critical care providers inclusive of obstetrician-gynecologists and maternal-fetal medicine subspecialists must be cognizant of similar mechanisms of disease development between eclampsia and PRES. In the authors’ opinion, this knowledge should be translated into a rapidly initiated, comprehensive management program including intravenously infused magnesium sulfate, blood pressure control, intensive maternal-fetal surveillance, meticulous medical care, timely delivery, and potent glucocorticoids, especially if evidence of HELLP syndrome is also present.

Because PRES was found in almost 100% of patients with probable eclampsia, a randomized, prospective, placebo-controlled, and blinded trial is now underway for patients with eclampsia to receive IV dexamethasone or placebo soon after an eclamptic seizure and to assess benefit if any when given in combination with magnesium sulfate therapy.

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REFERENCES


