Cranial MR imaging with clinical correlation in preeclampsia and eclampsia

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Preeclampsia is a disease characterized by hypertension, peripheral edema, and proteinuria, which affects 4%-5% of all pregnancies. Many of the patients with preeclampsia present with headache, visual disorders, confusion, and depression of consciousness. The disease is referred to as eclampsia when seizure is a component (1).

Pathological conditions, which present with headache, visual disorders, seizure, and depression of consciousness, and that regress both clinically and neuroradiologically in a few weeks with the elimination of etiological factors have different names such as “posterior reversible encephalopathy syndrome” (PRES), “hypertensive encephalopathy”, “reversible posterior cerebral edema syndrome” and “posterior reversible leukoencephalopathy syndrome” (PRLS). Recently, the term PRES (3) has become preferable to the term PRLS (2), which was first described in 1996, because of the gray matter involvement accompanying white matter involvement in these patients. PRES can occur in conditions such as hypertension, preeclampsia/eclampsia, immunosuppressive treatment (cyclosporin A, tacrolimus), and uremia (1, 2, 4-7). Vasogenic edema, most prominently at the posterior regions of the cerebral hemispheres, and less commonly, the brain stem, cerebellum, and basal ganglia, is detected on computed tomography (CT) and magnetic resonance (MR) imaging examinations (1, 2, 4, 5, 7-9). Cytotoxic edema and irreversible brain damage occur if etiological factors remain or are not treated (10-12).

The cause of preeclampsia/eclampsia, which threatens the lives of mother and fetus, has not yet been explained. Investigation of the clinical parameters associated with brain lesions detected in preeclampsia/eclampsia cases might shed light to the pathogenesis of the disease (1, 2, 13). Schwartz et al. demonstrated that brain lesions detected in MR examination are associated with endothelial damage indicators, not hypertension (1). The purpose of this study was to determine the distribution and nature of cranial MR imaging findings in preeclampsia/eclampsia, and also to correlate them with clinical and laboratory data.

Materials and methods
A total of 39 patients diagnosed with preeclampsia (n=30) and eclampsia (n=9) between 2000-2003 composed the study group. Ten of the patients were evaluated retrospectively and 29 of them prospectively. Age range was 18-39 years (mean, 26.2 years). Two of the patients were diagnosed with HELLP syndrome (hemolysis, elevated liver enzymes, and thrombocytopenia). Two of the patients were admitted to the emergency department with prematurity rupture of membranes and were diagnosed with preeclampsia. Three of the patients had seizures in the postpartum period. All of the patients were discharged from the hospital following delivery and without sequela.
Age, systolic and diastolic arterial blood pressure, mean arterial blood pressure, hematocrite (Hct), mean eritrocite volume (MEV), white blood cell count (WBC), thromocyte, lacte dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT), urea, uric acid, albumin, globulin, and calcium (Ca) values of all patients were recorded. Mean arte
tial tension values were calculated with 1/3x (systolic pressure + 2 x diastolic pressure) formula. Cranial MR exami
nations were performed for all patients between the 1st and 7th day of the onset of clinical symptoms in a 0.5T
magnetic resonance imaging system. The examination protocol consisted of T1-weighted spin echo (axial and sag-
ittal) and T2-weighted spin echo axial sequences without intravenous con
trast material injection. Control MR examinations were performed for two
of the patients two months after the first examination.
Clinical and laboratory data of all patients, with or without pathological
findings on cranial MR imaging, were compared statistically. As HELLP syn-
drome is associated with fulminant hematological anomalies (14) and can er-
roneously affect laboratory results, MR findings of the two HELLP cases were
excluded from the statistical analyses of laboratory values. All statistical anal-
yses were performed with the SPSS 11.0 program for Windows. Mann-Whitney
U test and chi-square test were used for statistical evaluation and p<0.05 was
accepted to be statistically significant and p>0.005 was accepted to be statis-
tically insignificant. Data dependent upon verbal explanations were depict-
ed as frequency and %, data dependent upon laboratory parameters were
depicted as mean ±SD.

## Results
Of our 39 patients, 37 (94.9%) had headaches, 14 (35.9%) had visual dis-
orders, 9 (23%) had seizures, and 9 (23%) had depression of conscious-
ness. Cranial MR imaging was found to be normal in 21 patients (53.8%).
In the remaining 18 patients, cortical-subcortical lesions that were iso-/hy-
pointense on T1-weighted images and hyperintense on T2-weighted images
were detected. Subcortical white matter was affected in only 8 of these 18 patients (44.4%) and pathological sig-
nals were present in both the cortex and the white matter in the remaining
10 patients (55.6%). Anterior, poste-
rior, or parasagittal watershed zone involvement was present in 13 pa-
tients (72.2%). Clinical findings and distribution of lesions in patients with
MR findings are presented in Table 1. Pathological findings regressed in two
patients who had control examina-
tions about two months after the first
examination (Figures 1-3).
The clinical and statistical analyses of patients with or without MR
findings are shown in Table 2. When the patients with or without MR im-
age findings were compared, there was a statistically significant difference
regarding visual disturbances, depression of consciousness, and seizures,
but there was no significant difference regarding headaches. There was no sta-
tistically significant difference between the mean age of patients with or without MR imaging findings (Mann-Whit-
ney U test, p=0.097). Although patients with MR imaging findings showed
higher blood pressures as compared to those without MR findings, there was no statistically significant differ-
ence between the two groups (Mann-Whitney U test, p=0.074). In Table 3,
minimum and maximum mean blood

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*Statistically significant p values with chi-square test
pressure values, as well as their means, and statistical comparison of the patient groups with or without MR findings are given. Biochemical data, lactate dehydrogenase (LDH), uric acid, and creatinine levels were significantly higher in patients with positive MR findings than those without MR findings (Mann-Whitney U test, p=0.006, p=0.010, p=0.005, respectively).

**Discussion**

Pathogenesis in PRES patients is not yet fully understood, but a major causative factor is thought to be extravasation of fluid (15). Brain lesions detected in these patients might be related to a disturbance of the cerebral autoregulation mechanism and impairment of endothelial function (1, 8, 16). The cerebral autoregulation mechanism, consisting of myogenic and neurogenic components, maintains stable blood perfusion in normal individuals (1). Effective functioning of neurogenic mechanisms depends on sympathetic innervation. In PRES cases, direct toxic effects on endothelium or vessel distention, which depends on elevated blood pressure, decreases the effect of myogenic mechanisms (1, 4). In these cases, neurogenic mechanisms take over the regulation of cerebral perfusion; this way, posterior circulation areas, which are relatively sparsely innervated by sympathetic nerves, become more sensitive to blood pressure elevations. In PRES cases with hypertension, serum extravasation occurs when the elevation in blood pressure passes beyond the autoregulation capacity of brain blood vessels. Brain lesions are more commonly demonstrated in posterior areas in these cases. Vasoconstriction, which sympathetic innervation induces, moderately protects anterior circulation areas from overperfusion. In PRES cases without hypertension, direct endothelial cell dysfunction, which increases blood-brain barrier permeability, is thought to be responsible for the pathogenesis (1, 8).

In this study, various clinical and laboratory parameters in preeclampsia/eclampsia cases with and without positive brain MR imaging findings were compared. Brain lesions were found to be associated with high LDH levels, which is an indicator of hemolysis, and both high uric acid and creatinine levels, which are indicators of renal function disorder. Endothelial injury yields to morphological disturbances in erythrocytes and microvascular hemolysis; as a result, LDH level increases (1). The cause of endothelial injury in preeclampsia/eclampsia cases has not yet been demonstrated, but circulating endothelial toxins or endothelium antibodies are thought to be responsible (1). In previous studies, it has been demonstrated that in preeclampsia/eclampsia patients, high LDH levels occur before lesions appear in brain MR examination, and this finding shows that high blood pressure does not lead to endothelial injury (1, 17). Multiple organ involvement in preeclampsia/eclampsia cases is thought to be associated with an endothelial function disorder (17). Renal function disorder secondary to renal endothelial injury results in uric acid and creatinine increase.

In our study, there was no statistically significant difference between blood pressure values of cases with or without MR imaging evidence of brain lesions. But in cases of preeclampsia/eclampsia, brain lesions might occur although blood pressure values are normal but still higher than a patient’s routine normal blood pressure (1). When blood pressure values and results associated with laboratory parameters were evaluated together in our study, brain edema detected in preeclampsia/eclampsia was thought to be secondary to endothelial injury, rather than hypertension. These findings correlated with the findings of Schwartz et al. (1). But the distribution of brain lesions should also be evaluated in determining whether hypertension or endothelial injury is more responsible for the pathogenesis.
We considered that PRES cases might be evaluated in three groups according to pathogenesis. In the first group, brain edema develops only secondary to elevated blood pressure. In these cases, lesions occur only in cases of high blood pressure values, as there is no endothelial injury leading to fluid extravasation. Limits of cerebral autoregulation pass beyond the normal levels of blood pressure and vasogenic edema occurs in posterior circulation areas, especially in the occipital lobes and watershed zones, which are relatively sparsely innervated by sympa-

Figure 1. a, b. Eclampsia. A 23-year-old patient, 36 weeks pregnant, with headache for one week has been hospitalized for new onset visual loss and generalized tonic clonic convulsion. Axial T2-weighted MR image (a) shows high-signal lesion in the right head of caudate and partially the lentiform nucleus. Axial T2-weighted image at a superior level (b) shows bilateral parietooccipital high-signal lesions involving the cortex and the white matter.

Figure 2. a, b. Preeclampsia; cranial MR imaging of a 19-year-old patient, 38 weeks pregnant, with developing headache, visual loss, and depression of consciousness. Axial T2-weighted MR image (a) shows bilateral frontoparietal and occipital lesions involving the cortex and the white matter. Two months later (b) the lesions have disappeared except for minimal bilateral parietal subcortical hyperintensities (arrows).

Figure 3. a-c. Preeclampsia. Cranial MR imaging of a patient, 34 weeks pregnant, with headache for a few weeks and developing acute visual loss. Axial T2-weighted MR images (a and b) show hyperintensities in bilateral frontal and parietooccipital lobes, quite symmetrical, involving anterior and posterior watershed zones cortically and subcortically. Axial T1-weighted MR image (c) shows the lesions to be iso-/hypointense.
Arterial watershed zones have been demonstrated not be rich in sympathetic innervation as are posterior circulation areas (18). Cases of hypertensive encephalopathy occur in this group. Distribution of lesions in the second group is similar to the first group, but lesions might occur in cases of lower blood pressure values, even those close to normal. Endothelial injury plays a major role in the pathogenesis of these cases; as a result of a failure of the blood-brain barrier, fluid might leak into the interstitium in milder blood pressure elevations. As lesions occur especially in areas of low autoregulation capacity, acute blood pressure fluctuations are thought to be a major determinant in pathogenesis. In experimental studies, acute blood pressure elevations were shown to impair the autoregulation mechanism and cause fluid and blood leakage as a result of vasoconstriction and vasodilatation, especially in arterial watershed zones (19). Preeclampsia/eclampsia, cyclosporin-A, and tacrolimus toxicity are placed in this group (1, 5, 20, 21). In the third group, lesions predominantly occur secondary to endothelial injury; blood pressure elevations do not play a major role in pathogenesis. Symmetrical basal ganglion involvement is typical in these cases; thalamus, cerebellum, and brain stem involvement follow this. Occipital lobe and watershed zone involvement is not as prominent as they are in PRES cases with hypertension. Some kinds of uremic encephalopathy, especially hemolytic uremic syndrome, are placed in this group. (22). In uremic pathologies with renal hypertension, lesion distribution might be similar to the first two groups. By evaluating blood pressure measurements and the distribution of brain lesions, an understanding of pathogenesis might be possible in PRES cases with the classifications we suggest.

Lesions are generally iso-/hypointense on T1-weighted images, hyperintense on T2-weighted images, and petechial hemorrhage is rarely seen in patients with preeclampsia/eclampsia (1, 13, 24). Lesions with similar signal changes were demonstrated in all of our cases, but no findings of hemorrhage were detected. The occipital lobe is the most affected region in preeclampsia/eclampsia; parietal, frontal, temporal lobe, and basal ganglion involvement follow this. The cerebellum and brain stem might be involved in more severe cases (1, 24). The occipital lobe was involved in all of our cases. Lobar distribution of lesions was similar to other series in the literature, and watershed involvement was prominent in our cases. Watershed zone-distributed lesions evoke ischemia secondary to cerebral vasospasm, but as they are demonstrated not to be cytotoxic edema with diffusion weighted images, the possibility of ischemia is not an issue of concern (4).

If radiological and clinical findings occurring in PRES are easily recognized and treated immediately, they might be totally reversible (25). All the patients investigated in our study were discharged from the hospital without neurological deficit within 1-2 weeks. Control brain MR examination was performed in two of our patients two months after the first examination. Total recovery was detected in one of the patients and subcortical hyperintense lesions were present in a very limited area in the other patient. Ischemia, massive infarct, and death might occur if the disease is not recognized. Diffusion weighted MR imaging is used to distinguish ischemia-cytotoxic edema from vasogenic edema, which is present in PRES cases (4, 11, 12, 16). Cases that develop cytotoxic edema-ischemia as a complication of PRES have been reported (11, 12). It is accepted that massive vasogenic edema might cause an increase in tissue pressure and ischemia by impairing microcirculation (11).

Visual disorders, depression of consciousness, and seizures were more frequently detected in cases of preeclampsia/eclampsia with cerebral edema in MR imaging than in patients with normal MR examinations. Brain lesions were found to be significantly correlated with only seizure in the study of Schwartz et al. (4). This diversity might be explained by the widespread distribution of brain edema areas in our study. Seizure is thought to be secondary to the irritative effect of fluid in the cortex and white matter (1). Cerebral edema was present in our all cases with seizures. Depression of consciousness was demonstrated to be more frequent in cases with basal ganglion involvement in some studies (26). In 6 of the 10 (60%) patients with depression of consciousness in our study, basal ganglion involvement was present. There was no statistically significant difference between patients with or without MR imaging findings regarding headaches. The detection of visual disorders, depression of consciousness, or seizure in the follow-up of pregnant patients with preeclampsia/eclampsia should be a warning for possible brain lesions.

In conclusion, increased permeability of the blood-brain barrier related to endothelial injury plays a major role in the pathogenesis of preeclampsia/eclampsia. In cases where blood pressure elevations do not reach very high levels, intravascular fluid leaks into interstitium and vasogenic edema occurs. However, when the cerebral autoregulation mechanism is considered, the distribution of cerebral lesions in the posterior circulation and watershed zones, which are relatively sparsely innervated by sympathetic nerves, there is evidence that the main determinant of pathogenesis is acute fluctuations in blood pressure. When symptoms like visual disorders, depression of consciousness, or seizure develop during the follow-up of pregnancy, or indicators of endothelial injury are detected to be elevated, appropriate precautions to regulate blood pressure would be beneficial.

References