Posterior reversible encephalopathy syndrome in obstetric patients. Report of three cases with literature review

S.O. Altinkaya[1], S. Nergiz[1], M. Küçük[1], H. Yüksel[1], Y. Dayanir[2]

[1]Department of Obstetrics&Gynecology, Adnan Menderes University, Faculty of Medicine, Aydın
[2]Department of Radiology, Adnan Menderes University, Faculty of Medicine, Aydın (Turkey)

Summary

Posterior reversible encephalopathy syndrome (PRES) is a serious clinico-neuroradiological maternal complication in pregnancy. Although it has various etiologies such as hypertensive encephalopathy, renal failure, autoimmune disorders, sepsis, multiple organ failure, and treatment with immunosuppressant or cytotoxic agents, pregnancy and postpartum complicated by hypertensive disorders more frequently lead to this condition. PRES is clinically characterized by headache, confusion, seizures, vomiting, and visual disturbances with radiographic vasogenic edema especially affecting symmetrical parietal and occipital lobes. The underlying pathophysiology is still a matter of debate. Prompt recognition and early intervention greatly improve the prognosis, so that obstetricians should be well aware of this rare entity. Timely imaging is of crucial importance especially in patients with an uncertain diagnosis for determining the appropriate treatment and preventing the possible development of neurologic deficits. In the present report, three cases of PRES are presented with clinical and radiological findings in pregnancies complicated by severe pre-eclampsia and eclampsia. The latest literature in the field is also carefully reviewed.

Key words: Encephalopathy; Eclampsia; Pre-eclampsia; Hypertension.

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a transient clinical neuroradiological entity characterized by clinical signs and symptoms including hypertension, headaches, generalized seizure activity, altered mental status, and visual disturbances, as well as characteristic findings on brain magnetic resonance imaging (MRI) scan [1]. It was first described by Hinchey *et al.* [2] in 1996; since then, both its clinical spectrum and underlying pathophysiology remain poorly understood. Despite its rarity, PRES is most commonly reported in the literature in association with pregnancies complicated by pre-eclampsia and eclampsia. Furthermore PRES is known to occur in a wide range of predisposing factors and causes, such as hypertension, solid organ and bone marrow transplantation, sepsis, autoimmune diseases, thrombotic thrombocytopenic purpura, renal failure and medication, and immunosuppressant and cytotoxic drugs [3-6].

Neuroradiological MRI findings usually include extensive symmetric bilateral hyperintensity in T2 weighted images of parietal and occipital subcortical white matter and in the corresponding cortical regions in patients with PRES [7]. However, frontal lobes, basal ganglia, cerebellum, and brainstem may also be affected [6,8]. Advances in radiology and increasing expertise in the field provide the rising diagnosis of PRES.

Although the underlying pathophysiology is not fully understood, several responsible factors have been proposed such as rapidly developing hypertension leading to a breakdown in cerebral autoregulation and vasogenic edema, especially in the posterior head region or endothelial dysfunction, or vasospasm with subsequent ischemia [8-10].

The prognosis of PRES is usually benign with complete reversal of clinical symptoms and radiological signs in case of early, adequate, and effective treatment which comprises control of elevated blood pressure and withdrawal of potentially offending agents. Despite its name, PRES may lead to permanent imaging abnormalities and secondary complications such as status epilepticus, intracranial hemorrhage, ischemic infarction, which may cause residual neurological sequel with substantial morbidity, and mortality [8, 11]. Therefore, medical awareness of PRES, which is a diagnostic challenge for obstetricians, is of crucial importance.

In the present report three cases of PRES are presented with clinical and radiological findings in pregnancies complicated by severe pre-eclampsia in one case, and by eclampsia in two cases. Neuro-imaging findings were emphasized. Latest literature in the field in obstetric patients is also carefully reviewed.

Case Report

Case 1 was a 27-year-old primigravida with singleton gestation and uneventful antenatal period. She presented with acute onset headache and one episode of seizure at 37 weeks. On arrival blood pressure was 140/90 mmHg. As she developed another tonic-clonic seizure at the time of ultrasonographic examination, a provisional diagnosis of eclampsia was made and

Revised manuscript accepted for publication June 24, 2013

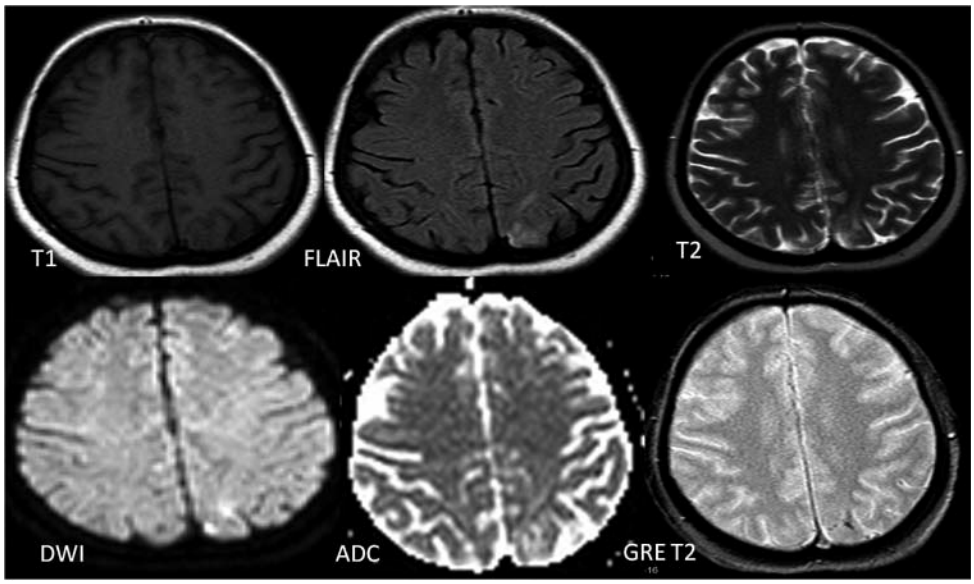

Figure 1. — T1, T2 -Weighted and FLAIR images show a region of vasogenic edema involving left occipital cortex and subcortical white matter without restricted diffusion and hemorrhagic transformation on diffusion maps and GRE T2 weighted images, respectively.

she was immediately shifted for an emergency cesarean section where she delivered a healthy baby. HELLP syndrome was diagnosed in postoperative period. She lost consciousness 25 hours after cesarean section associated with blood pressure values of 240/110 mmHg. She was referred to intensive care unit with tracheal intubation.

Case 2 was a 28-year-old primigravida who presented with amniotic fluid leakage at the 33rd gestational week. She was diagnosed with pre-eclampsia at the 31st week. As she complained of severe headaches and visual abnormalities and the blood pressure rose up to 180/100 on arrival, she was shifted for cesarean section. HELLP syndrome was diagnosed in postoperative period. She was referred to intensive care unit. About 30 hours after delivery the patient again complained of sudden visual abnormalities similar to those before the operation. No seizure activity was noted.

Case 3 was a 34-year-old woman at 31 weeks gestation. She presented with increased blood pressure and severe headaches. She stated that she did not come regularly for routine antenatal examinations and had a previous cesarean delivery. Her blood pressure on admission was 190/110 mmHg and urine laboratory evaluation showed 4+ proteinuria. As she developed severe headaches, visual abnormalities, and epigastric pain, emergency cesarean section was performed. Postoperatively she was taken to the intensive care unit. At postoperative first day she developed tonic-clonic seizure activity and HELLP syndrome.

All of the patients presented in the present report received appropriate antihypertensive treatment for blood pressure control as well as intravenous magnesium sulfate (MgSO4) treatment for seizure prophylaxis. In their neurologic evaluation no focally neurologic pathologic finding was examined. Ophthalmologic evaluation revealed residual perception of light, reactive pupils, and normal fundi in all cases. They were discharged from the hospital at 17th, 12th, and 14th postoperative days, respectively, with complete resolution of clinical and radiological features.

In all three patients MRI scan of the brain was performed. Axial T2 and fluid attenuated inversion recovery (FLAIR) MRI sequences demonstrated subcortical white matter hyperintensity lesions in occipital and parietal lobes in keeping with vasogenic edema. Additionally, case 2 also demonstrated white matter hyperintensity in T2 weighted FLAIR images in the pons. Diffusion weighted imaging (DWI) axial images demonstrated signal distortion secondary to edema but acute infarction was not suspected confirming PRES (Figure 1). Basal ganglia and capsula interna were normal.

Discussion

PRES is an acute rapidly evolving clinical condition characterized by clinical signs and symptoms including hypertension, headache, generalized seizure activity, altered mental status, and visual disturbances as well as characteristic findings on brain MRI scan [1]. Although the underlying pathophysiology of PRES is still a matter of debate, several theories have been suggested, the most widely accepted of which states that rapidly growing hypertension leads a breakdown in cerebral autoregulation, particularly in the posterior head region where there is a relative lack of sympathetic innervation. Hyperperfusion ensues with protein and fluid extravasation, producing focal vasogenic edema [8]. The second theory implicates endothelial dysfunction as it is defined in pre-eclampsia and eclampsia. A third theory proposes that vasospasm with subsequent ischemia may be responsible. It suggests that increases in the blood pressure lead to cerebral vasoconstriction and ischemia causing cytotoxic edema [8-10]. While the majority of cases resolve with treatment, PRES is not always reversible, not always limited to the posterior regions of the brain and not limited to the white matter. Irreversible neurologic deficits including delayed onset seizure disorder and even death have also been reported [9, 12].

Although literature is based mainly on case reports, few studies especially from neurology and radiology clinics are available. Fugate *et al.* [8] identified 120 cases of PRES in different clinical subgroups, of which seven were

obstetric cases. They reported that the most commonly involved brain regions were parieto-occipital lobes (94%), followed by the frontal lobe, temporal lobe, and cerebellum. They also found cerebellar involvement to be more frequent in patients with a history of autoimmunity and patients with sepsis were more likely to have cortical involvement. The location and severity of vasogenic edema were mostly similar in different groups. Mueller-Mang *et al.* [4] also indicated no difference in distribution of lesions and extent of disease between patients with or without pre-eclampsia/eclampsia. Roth and Ferbert [6] conducted a study on 21 patients and found no difference with regard to symptoms, cerebral imaging and outcome, apart from a difference in age, the premedical history, whereas headaches occurred more frequently in the pregnant group. Similarly Liman *et al.* [3] mentioned that headaches were more frequent as initial symptom. However, in contrast, Liman *et al.* [3] found major clinicoradiological differences between obstetric and non-obstetric patients pointing toward a less severe course of disease in obstetric group. Their results showed altered mental state and affection of thalamus, midbrain, and pons were less frequent in the obstetric group. They also concluded that obstetric group had less severe edema, less cytotoxic edema, hemorrhage and contrast enhancement, while more frequent complete resolution of edema and less frequent residual structural lesions were seen on follow up imaging.

Although PRES is known to occur in a wide range of predisposing factors and causes, it is most commonly reported in the literature in association with pregnancies complicated by pre-eclampsia and eclampsia. Wagner *et al.* [13] suggested that neuroimaging showed characteristics of changes of PRES in all seven of 13 eclamptic cases in whom neuroimaging studies were available. More recently Brewer *et al.* [14] reviewed 47 eclamptic patients in order to investigate the concurrence of PRES with eclampsia. They indicated that PRES is a core component of the pathogenesis of eclampsia as 46 of 47 (97.9%) of eclamptic patients revealed PRES on neuroimaging studies. Their results also demonstrated that severe systolic hypertension was present in 47% of patients. It is possible that blood pressure alone is not the exclusive cause, and that the endothelial dysfunction which is a hallmark of pre-eclampsia, is also a contributing factor. Alternatively, pregnancy itself may decrease the threshold at which an elevation in the blood pressure may lead to cerebral hyperperfusion and brain edema [15].

The widespread use of MRI technology has made PRES familiar to many clinicians in the last decade. Specific MRI techniques, such as FLAIR and DWI sequences have improved the ability to detect subcortical/cortical lesions and helped to clarify the underlying pathophysiological mechanism of cerebrovascular involvement, which results important for an appropriate therapeutic decision. DWI sequences of the brain are considered to be the gold standard. Cerebral edema is seen as an increased T2 weighted signal which may be tricky to detect if the lesions are small and subcortical, as they may be difficult to distinguish from adjacent cerebrospinal fluid (CSF). FLAIR sequences suppress the CSF signal and make these abnormalities more conspicuous. DWI signals and apparent diffusion coefficient (ADC) map values may help the radiologist to elucidate a diagnosis. Unlike areas of arterial infarction, lesions suspicious for PRES tend to display no restriction of diffusion on DWI. This lack of restriction of diffusion has led to the belief that the edema seen with PRES is not caused by cell swelling "cytotoxic edema" which is thought to occur with ischemia, but must be caused by leakage of fluid from the vasculature "vasogenic edema" [16, 17].

Here three cases of PRES are presented with clinical and radiological findings in pregnancies complicated by severe pre-eclampsia in one case, and by eclampsia in two cases. Severe headache was the initial symptom in all cases as it is indicated in the aforementioned studies [3, 6]. PRES was diagnosed on the basis of the results of neuroimaging studies. Published reports in the literature suggest an important question whether it is necessary to perform imaging studies routinely in patients with a classical presentation of eclampsia or not. Although PRES is most recently proven to be the core component of the pathogenesis of eclampsia, [14] several conditions such as acute stroke, intracranial emboli or hemorrhage, systemic diseases that are associated with central nervous system may mimic eclampsia. Differential diagnosis among these conditions, which is difficult on the basis of clinical findings alone, may not only affect treatment modalities but also act on long term neurological outcomes. Aggressive blood pressure control is the main target in PRES whereas acute stroke permits mild to moderate hypertension. Eventually timely imaging is of crucial importance especially in patients with an uncertain diagnosis for determining the appropriate treatment and preventing the possible development of neurologic deficits.

References

[1] Powell E.S, Goldman M.J.: "Posterior reversible encephalopathy syndrome (PRES) in a thirty-six-week gestation eclamptic". *J. Emerg. Med.*, 2007, *33*, 377.

[2] Hinchey J., Chaves C., Appignani B., Breen J., Pao L., Wang A, *et al.*: "A reversible posterior leukoencephalopathy syndrome". *N. Engl. J. Med.*, 1996, *334*, 494.

[3] Liman T.G., Bohner G., Heuschmann P.U., Scheel M., Endres M., Siebert E.: "Clinical and radiological differences in posterior reversible encephalopathy syndrome between patients with preeclampsia-eclampsia and other predisposing diseases". *Eur. J. Neurol.*, 2012, *19*, 935.

[4] Mueller-Mang C., Mang T., Pirker A., Klein K., Prchla C., Prayer D.: "Posterior reversible encephalopathy syndrome: do predisposing risk factors make a difference in MRI appearance?" *Neuroradiology*, 2009, *51*, 373.

[5] Li R., Mitchell P., Dowling R., Yan B.: "Is hypertension predictive of clinical recurrence in posterior reversible encephalopathy syndrome?" *J. Clin. Neurosci.*, 2013, *20*, 248.
[6] Roth C., Ferbert A.: "Posterior reversible encephalopathy syndrome: is there a difference between pregnant and non-pregnant patients?" *Eur. Neurol.*, 2009, *62*, 142.
[7] Finocchi V., Bozzao A., Bonamini M., Ferrante M., Romano A., Colonnese C., Fantozzi L.M.: "Magnetic resonance imaging in Posterior Reversible Encephalopathy Syndrome: report of three cases and review of literature". *Arch. Gynecol. Obstet.,* 2005, *271*, 79.
[8] Fugate J.E., Claassen D.O., Cloft H.J., Kallmes D.F., Kozak O.S., Rabinstein A.A.: "Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings". Mayo Clin. Proc., 2010, *85*, 427.
[9] Torrillo T.M., Bronster D.J., Beilin Y.: "Delayed diagnosis of posterior reversible encephalopathy syndrome (PRES) in a parturient with preeclampsia after inadvertent dural puncture". *Int. J. Obstet. Anesth.*, 2007, *16*, 171.
[10] Ito T., Sakai T., Inagawa S., Utsu M., Bun T.: "MR angiography of cerebral vasospasm in preeclampsia". *AJNR Am. J. Neuroradiol.*, 1995, *16*, 1344.
[11] Staykov D., Schwab S.: "Posterior reversible encephalopathy syndrome". *J Intensive Care Med.*, 2012, *27*, 11.
[12] Mirza A.: "Posterior reversible encephalopathy syndrome: a variant of hypertensive encephalopathy". *J. Clin. Neurosci.*, 2006, *13*, 590.
[13] Wagner S.J., Acquah L.A., Lindell E.P., Craici I.M., Wingo MT, Rose CH, *et al.*: "Posterior reversible encephalopathy syndrome and eclampsia: pressing the case for more aggressive blood pressure control". *Mayo Clin. Proc.*, 2011, *86*, 851.
[14] Brewer J., Owens M.Y., Wallace K., Reeves A.A., Morris R., Khan M., *et al.*: "Posterior reversible encephalopathy syndrome in 46 of 47 patients with eclampsia". *Am. J. Obstet. Gynecol.*, 2013, *208*, 468.e1. doi: 10.1016/j.ajog.2013.02.015. Epub 2013 Feb 7..
[15] Cipolla M.J.: "Cerebrovascular function in pregnancy and eclampsia". *Hypertension*, 2007, *50*, 14.
[16] Vijayalakshmi B., Sethna F., Manford M., Lees C.C.: "Posterior reversible encephalopathy syndrome in a patient with HELLP syndrome complicating a triploid pregnancy". *J. Matern. Fetal Neonatal Med.*, 2010, *23*, 938.
[17] Lee V.H., Wijdicks E.F., Manno E.M., Rabinstein A.A.: "Clinical spectrum of reversible posterior leukoencephalopathy syndrome". *Arch. Neurol.*, 2008, *65*, 205.

Address reprint requests to:
S.Ö. ALTINKAYA, M.D.
Kurtuluş Mahallesi 2018 Sokak
Elif Apartmanı 39/9
Aydin (Turkey)
e-mail: altinkayaozlem@yahoo.com