Review Article

Posterior reversible encephalopathy syndrome during the peripartum period: report of four cases and review of the literature

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Abstract: Posterior reversible encephalopathy syndrome (PRES) is a cliniconeuroradiologic disorder affecting the brain’s occipital and parietal lobes characterized by altered mental status, seizures, headache and blurred vision. Eclampsia is one of the main causes of posterior reversible encephalopathy. We aimed to discuss here literature guided clinical and radiologic findings of four women who had experienced status epilepticus at peripartum period and diagnosed as PRES.

Keywords: Posterior reversible encephalopathy syndrome, seizure, peripartum period

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a cliniconeuroradiologic diagnosis affecting occipital and parietal lobes, in which reversible changes occur in the central nervous system, associated with typical features on Magnetic resonance imaging (MRI) or computerized tomography (CT) brain imaging. This rapidly evolving neurologic entity is characterized by mental state changing, seizure, headache, visual disturbances which extents blurred vision to cortical blindness and posterior transient changing on neuroimaging [1-3]. The diagnosis is made up with patient past history, physical and radiologic examination. With early recognition and aggressive treatment, complete resolution of symptoms occurs within two weeks but delayed diagnosis and treatment could result in persistent neurologic deficits and disability or death. Hemorrhagic PRES, severe, and malignant presentations of PRES frequently lead to poor outcomes [2, 4]. We discussed here literature guided clinical and radiologic findings of four women who had experienced status epilepticus state at the peripartum period and diagnosed as PRES.

Case 1

A 31-year-old previously healthy woman presented to the delivery suite at 40 weeks of gestation for induction of labor. During pregnancy glucose intolerance had been controlled with diet alone. Along with labor period her blood pressure remained stable and she has not hypertension in past medical history. Caesarean/section (S/C) was performed under epidural anesthesia, and was uneventful. The immediate postoperative course was completed without any complication, no hypertension attack was recorded, and the woman was discharged home after second days of delivery. She was admitted to Emergency Department (ED) again following seventh days of postpartum period due to having a generalized tonic-clonic seizure which she was experienced at home. She complained of severe headache and visual disturbances that had been increasing in intensity over the preceding four days. She was agitated, disorientated and confused far longer than the usual postictal phase. Her blood pressure remained normal throughout course. A full blood count, urea and creatinine were within normal limits. A CT scan of her head revealed...
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no abnormalities. However, MRI showed high signal intensity in both occipital lobes consistent with PRES (Figure 1).

Case 2

A 27-year old woman, 34 weeks of gestation, due to status epilepticus and sever hypertension (160/100 mmHg) was admitted to intensive care unit (ICU). Hematologic and biochemical test results were all normal, except proteinuria. 15 mg/kg phenytoin intravenously was supplemented to the patient initially. Additionally 300 mg/day phenytoin was administered for maintenance. First day of admission the patient, confused, and patient’s cooperation and orientation were decreased. With Noxious stimulus, the patient response was flexor on four extremities, but other neurological findings and reflexes were all normal limits. MRI showed hyper intense imaging on T2, fluid attenuated inversion recovery (FLAIR), diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) weighted sequences on bilateral parietooccipital lobes cortical and sub cortical areas, especially prominent on left side of the brain (Figure 2). Cranial MRI venography was normal limits. The patient clinic was compatibles with PRESS syndrome. Electroencephalograph (EEG) showed diffuse slow and irregular ground activity. Second day of admission S/C was performed by senior gynecologist to the patient. After controlling of seizure, conscious was completely cleared and motor functions were come back normal limits beyond second days of admission. Seventh days of admission control cranial MRI showed remission of the lesions. The patient’s arteriolar tensions remained within normal limits except that first day of admission. Patient was discharged from hospital as an outpatient follow up plan.

Case 3

A 23-year old women, fourth gestation, after normal spontaneous vaginal birth, second postpartum day with headache, nausea, vomiting, blurred conscious and generalized tonic-clonic seizure where was experienced 3 times was admitted to ED with diagnosis of status epilepticus. Initial blood pressure was 180/100 mmHg, T2 weighted sequences indicated patch shaped signal enhancement and diffusion and ADC weighted series showed hyperintense findings on bilateral parietooccipital lobes, frontal area, cerebellar hemisphere, basal ganglia, and brainstem (Figure 3). Venography was normal limits. EEG showed normal pattern. Except proteinuria, all biochemical test results were normal limits. Patient’s neurologic examination revealed, bilateral midsized pupils, normal funduscopic examination and posticus somnolence, and there was no meningeal irritation findings. Babinski reflex was extensor response on left side but motor functions examinations and deep tendon reflexes were all within normal limits. The patient’s clinic and radiologic imaging were compatibles with PRESS syndrome. For controlling of seizure 15 mg/kg phenytoin was supplemented initially to the patient by intravenous route in ED. Additionally 300 mg/day phenytoin was administered for maintenance. For cerebral edema concomitantly antiedematous treatment was infused. Second day of admission the patient had clear consciousness and, after 7 days motor muscle power score and control MRI were obtained normal limits (5/5). During admission period blood pressures were determined as all normal. Because of clinically and laboratory test result were normal, the patient was discharged from clinic as an outpatient follow up plan. Because of the cerebral lesions disappeared which was seen after 1 month later performed MRI and EEG was normal ground activity anti-epileptic treatment was continued for 3 month and discontinued by gradually.
Case 4

A 18-year-old female, first gestation, had alive fetus via normal spontaneous vaginal birth, at 12th hours of postpartum period the patient referred to ED with complaints of headache, nausea, vomiting, and blurred vision. Initial blood pressure was 170/120 mmHg. At the time of examination and observation in ED, the patient had complex partial status epilepticus. For controlling of seizure 15 mg/kg phenytoin a rate of 40 mg/minute was infused initially to the patient by intravenous route and patient transferred to ICU. Cranial MRI showed patch shaped signal enhancement at T2 weighted sequences and hyperintense vasogenic edema findings on DWI and ADC weighted series on bilateral frontal and parietal areas sub cortical and deep white matter. Venography was within normal limits. EEG showed diffuse slow and irregular ground activity. Neurologic examination revealed postictal state and confusion, pupil sizes and funduscopic examinations were all normal. Bilateral babinski reflex had extensor response, there was no meningismus finding. Deep tendon reflexes normal and motor power scores were 5/5 on upper extremities and 3/5 on lower extremities. Laboratory test results were normal limits. The patient received antiedematous treatment for cerebral edema and anti-ischemic treatment in ICU. Phenytoin maintenance dose was implemented as 500 mg a day. Because of patient had seizure attacks extra 10 mg/kg phenytoin was added to daily phenytoin treatment during ICU admission. Conscious cleared and motor functions come back to normal after second day of ICU admission. Cerebral lesions were regressed on

Figure 2. MRI showed hyper intense imaging on T2. A: FLAIR sequences, coronal views shows hyperintensity on bilateral pariato-occipital lobes; B: DWI shows bilateral occipital involvement; C: ADC imaging shows bilateral occipital involvement.

Figure 3. T2 weighted sequences indicated patch shaped signal enhancement and diffusion. A: High signal intensity in brainstem; B: Bilateral frontal area and basal ganglia involvement; C: Frontal and occipital lobe involvement.
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Table 1. The alterations of cytotoxic and vasogenic edema in DWI and ADC maps

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<tr>
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<th>Vasogenic edema</th>
<th>Cytotoxic edema</th>
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<tr>
<td>DWI</td>
<td>+ Increased signal intensity</td>
<td>++ Increased signal intensity</td>
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<tr>
<td>ADC</td>
<td>Increased signal intensity</td>
<td>Decreased signal intensity</td>
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<td>Evolution</td>
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Discussion

This picture which has also been known by many other names such as PRES, hyperperfusion encephalopathy, brain capillary leak syndrome, hypertensive encephalopathy, posterior encephalopathy, occipito-parietal encephalopathy, and toxemic posterior encephalopathy was described first time by Hinchey et al. in 1996. Although PRES is usually described in post-partum patients who have had high blood pressure, this is not always the case [5-9]. Etiologic factors are listed as hypertension, eclampsia-preeclampsia, immunosuppressant and chemotherapeutic medications such as; Cyclosporine A, tacrolimus, interferon alpha, corticosteroids, etc. some renal disease such as lupus nephritis, acute glomerulonephritis, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, transplantations, infections including influenza A, sepsis, shock, toxemia, pregnancy, autoimmune disease, some vaccinations such as measles etc. One of these factors may be the triggers of PRES in patient. The significant minority of cases that occur in the absence of hypertension has challenged the traditional notion of PRES. Some authors speculated that hypertension not sufficient cause for the disorder but blood pressure (BP) surges could act as a trigger. Eclampsia might be a good prognostic factor for PRES [10-15].

Although the hemodynamic mechanisms underlying PRES are not yet clear, three theories have been suggested up to the present. 1) The current more widely accepted theory suggests that severe hypertension leads to failed autoregulation, subsequently causing hyperperfusion with endothelial injury/vasogenic edema. Although commonly mentioned, several problems exist with the hypertension/hyperperfusion theory, since PRES is seen in absence of hypertension in 20% to 40% of patients. 2) The earlier, original theory suggests that hypertension or rapid BP change leads to cerebral auto-regulatory vasoconstriction, ischemia and subsequent brain edema. 3) More recently, it has been suggested that the immune system triggering with T-cell activation, endothelial activation, and T-cell trafficking, accompanying vasculopathy with vasoconstriction results in sustained hypoperfusion and PRES edema [8, 11].

The first theory is defined as vasospasm which is result from overt activation of cerebral auto regulation that may leads to reversible ischemia at potentially risky border zones of brain vasculature. But most of cases, vasospasm is not detected in large vessels. Even if some cases show hypo perfusion on SPECT brain perfusion tests, most of cases are seen hyper perfusion findings [16]. Now hypo perfusion theory has more acceptance than other theories among authors. Homeostatic mechanism exerts effort to provide regular blood flow to brain by auto regulation. When systemic blood pressure decreased, auto regulation threshold values are tend to further slipping down. Distal arterioles dilate to increase cerebral blood flow. On the other hand, when systemic blood pressure elevated, auto regulation threshold values are tend to further higher levels. So as to increase cerebral blood flow and prevent hypo perfusion, cerebral arterioles are contracted and thus systemic vascular resistance is enhanced. For cerebral auto regulation there is well known an upper limit on animal models at time of spontaneous overt blood pressure increases. When limit is exceeded, already contracted arterioles will not be further contraction and at that time they are forced to become dilatation. The dilatation firstly initiates small segments and then proceeds along with all vessels. If threshold level is exceeded, which leads to breakdown of the blood–brain barrier and extravasation of fluid, macromolecules, and
even erythrocyte extraversions are seen in brain parenchyma [17, 18]. Because of its’ structure is more compact and organized, cerebral cortex resists against large cerebral edema. The edema shows tendency to spread towards subcortical white matter by continuing of blood-brain barrier destruction [19]. After recovery of blood-brain barrier, edema is absorbed slowly by slow from subcortical white matter. In this process, sympathetic nervous system (SNS) also plays a role. It is known that SNS innervation is poorer on posterior circulation than anterior circulation do with a consequent reduced auto-regulation of already impaired cerebral areas [3, 20]. This situation may explain in some degree of posterior territory susceptibility and radiologic findings which is seen in PRES.

Histological evaluation of PRES is uncommon and often obtained late in the course of complex systemic disease. Biopsy/autopsy obtained during acute toxicity demonstrates vasogenic edema, parallel to observations seen on DWI. Activated/reactive astrocytes, scattered macrophages, and T-cell lymphocytes have been commonly noted without inflammation, ischemia, or neuronal damage. Late autopsy studies have generally demonstrated evidence of demyelination and myelin pallor along with evidence of ischemia, neuronal anoxic damage, laminar necrosis, or older hemorrhage in the white matter and cortex [21].

The intensity and severity of clinical manifestations of PRES vary, but headache, mental state chancing, seizure, and occipital lobe related symptoms are usually present. The symptoms may emerge acute or sub-acute manner, but seizure is almost always present that may be focal but usually generalized and status epilepticus also seen. Mental state chancing may range from alertness or drowsiness to deep coma and eventually death [20] Visual disorders may extent from mild blurred vision to cortical blindness. DTRs are usually norm active but some cases may contain weakness and incoordination. Laboratory findings can also vary, depending on the underlying associated condition [1, 6, 13]. In our cases, we observed status epilepticus, headache, disorders of consciousness and visual acuity at diagnosis. Two cases had hypertension and two had normal blood pressure. All of the patients’ neurological examination was normal limits except mental state chancing. Only two patients had slow wave activity on EEG.

A neuroimaging study usually shows bilateral and symmetric brain edema in subcortical regions of the parietal and occipital lobes (98%), corresponding to typical manifestation of PRES, in which vasogenic edema rather than cytotoxic edema may play a pivotal role in neuroimaging. However, the lesions can also extend to other cerebral structures, such as the frontal lobes (68%), the temporal lobes (40%), the cerebellar hemispheres (30%), the basal ganglia (14%), the brain stem (13%) and the deep white matter, in particular the splenium of the corpus callosum (10%). Even though involvement is unilateral (28%), this must not mean that the diagnosis does not stand [22, 23]. On CT, diffuse hypodense areas show the affected regions, but best depicted by MRI [24]. On MRI, lesions appear as iso-intense or low signal intensity on T1-weighted images, and high signal intensity on T2-weighted images and FLAIR. However, FLAIR imaging was judged superior to proton density and T2-weighted spin-echo for detection of supratentorial brain lesions. Furthermore, FLAIR sequences allow better characterization of the lesion location [22, 25, 26]. Tree of the cases had parietal-occipital lobe involvement. In our cases cerebellar hemispheric involvement observed only second and third cases, brainstem and basal ganglia involvement was seen only third case.

In these cases new MR techniques, including DWI and ADC, reliably distinguish not only vasogenic/cytotoxic edema but also laminar cortical infarct with a decrease and an increase in the diffusion coefficient respectively and DWI has proved to be an accurate and a relatively quick method for early diagnosis which enable the measurement of net movement of water molecules [22, 24]. ADC maps, which can be elaborated from DWI, allow quantitative measurement of the diffusion of water molecules, which is altered in pathologic conditions. A restricted diffusion such as a cytotoxic edema is characterized by hyperintensity in DWI and hypointensity in ADC maps. Other hand vasogenic edema, where there is an increase in the extracellular water and thus an increased diffusion, DWI show an iso- or hyperintense signal whereas in ADC maps the signal intensity is increased. Evaluation with DWI of patients with PRES show increased diffusion, with elevated values of
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ADC, the alterations in T2-weighted images, demonstrating the presence of vasogenic edema. Nevertheless there have been described cases of coexistence of vasogenic with cytotoxic edema. Authors have hypothesized a possible evolution of lesions from an early reversible vasogenic edema to a later irreversible ischemic damage if not properly treated (Table 1) [23, 27]. Diffusion weighted and ADC series showed hyperintense image which was compatible with vasogenic edema in 1, 2 and 3 numbered cases. In fourth case, the lesions were viewed isointense on DW and hyperintense on ADC images. This was considered meaningful in terms of vasogenic edema. Among none of our cases, cytotoxic edema was observed.

The lesions generally resolved with appropriate treatment in days or weeks. Prompt diagnosis and treatment are the key points to achieving good clinic outcomes [28]. Main steps of treatment consist of identifying and management of the precipitating factors control and preventing of seizures and strict blood pressure control. Correction of systolic blood pressure is necessary to prevent worsening of the cerebral edema, but caution must be implemented in certain groups to prevent undesired effects [29]. Systolic BP should be amid to maintain at approximately 105 to 125 mm Hg. Nicardipine and labetalol are common agents used for blood pressure control because their quick onset and easy titratable [30]. Term or near-term pregnancies may be delivered, but in some cases where fetal viability is at question, medical management may be appropriate. Eclamptic seizures are treated with magnesium sulfate, whereas seizures of other etiologies can be treated with benzodiazepines for example lorazepam or diazepam. Refractory seizures may be treated with barbiturates such as phenytoin or Phenobarbital. Malignant presentations should include prompt referral for neurocritical care and neurosurgical examination and aggressive management of underlying conditions, in particular coagulopathies [4, 30].

In conclusion PRES is potentially a reversible condition with definitive treatment despite its dramatic presentation. An understanding of this syndrome must encourage practitioners not to conduct unnecessary repeated imaging. We will advocate routine use of MRI in suspected case of PRES which give significant information. In particular, for differential diagnosis of PRES and ischemic infarct, DWI should be performed to avoid delayed diagnose and treatment.

Disclosure of conflict of interest
None.

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