Posterior reversible encephalopathy syndrome in a postpartum hemorrhagic woman without hypertension
A case report
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Abstract
Rationale: Posterior reversible encephalopathy syndrome (PRES), which diagnosis is based on clinical symptoms and radiological features, is a neurotoxic disease characterized by a set of clinical manifestations, such as seizure, headache, visual, and/or consciousness disturbance. It is the first case of PRES followed by postpartum hemorrhage (PPH) without underlying disease.

Patient concerns: A 37-year-old healthy woman had PPH after caesarean section. Six days after delivery, headache occurred suddenly, followed by episodes of clonus seizure.

Diagnoses: Brain computed tomography showed ischemic stroke. However, magnetic resonance imaging revealed characteristics consistent with PRES.

Interventions: The patient received phenytoin for seizure control.

Outcomes: Seizure was under good control over the following days. Three months later, repeated magnetic resonance imaging showed complete remission.

Lessons: PRES may be triggered by PPH and is not necessarily secondary to typical predisposing factors such as hypertension or pre/eclampsia. Hormone fluctuation, increased blood pressure variation, and massive blood transfusion may be contributed to the development of PRES in our case. Also, it is necessary to rule out those life-threatening diseases, such as cavernoma hemorrhage, cerebral venous thrombosis, and ischemic stroke before the diagnosis of PRES.

Abbreviations: BBB = blood–brain barrier, FFP = fresh frozen plasma, MRI = magnetic resonance imaging, PICs = pro-inflammatory cytokines, PPH = postpartum hemorrhage, pRBC = packed red blood cells, PRES = posterior reversible encephalopathy syndrome, sFlt1 = soluble fms-like tyrosine kinase 1, SLE = systemic lupus erythematosus, TACO = transfusion associated circulatory overload, TRALI = transfusion-related acute lung injury, VEGF = vascular endothelial growth factor.

Keywords: case report, normotensive, posterior reversible encephalopathy syndrome, postpartum hemorrhage, reversible posterior leukoencephalopathy, transfusion

1. Introduction
Posterior reversible encephalopathy syndrome (PRES) is a rare disease and its diagnosis is based on clinical and radiological findings. Typical manifestations of PRES include seizures, headache, and visual loss. Hyperintensity lesions over the occipital and parietal lobes caused by subcortical vasogenic edema are diagnostic features of PRES. There are numerous predisposing factors relating to the PRES, such as hypertension, chemotheraphy, transplantation, hemolytic uremic syndrome, severe infection, malignancy, and depletive lumbar puncture. Yet, hypertension was the most common comorbidity in patients with PRES. Although exact pathogenesis of PRES is unclear, hyperperfusion of cerebral circulation may play an important role in hypertensive patients. However, the proportion of PRES was presented in normotensive patients. Here, we report a woman with postpartum hemorrhage (PPH) who developed PRES on the 6th day of admission. This patient had an initial presentation with hypovolemic shock and did not have other systemic disease. It is the first case of PRES followed by PPH without underlying disease. In the discussion part, we focus the potential causes and propose a “2-hits” hypothesis of PRES development.

2. Case report
A 37-year-old woman who did not have any systemic disease before was sent to Kaohsiung Veterans General Hospital emergency department due to PPH after caesarean section on
March 17, 2014. She had an altered state of consciousness. Fever, tachycardia, and hypotension (69/49 mm Hg) were noted. Although empiric antibiotics were given then, urine and blood culture showed negative results. Serum hemoglobin level was only 3.2 mg/dL, and hematocrit was 10.3%. Consequently, 8 U packed red blood cells (pRBC) and 6 U of fresh frozen plasma (FFP) were transfused in the following 24 h. Computed tomography angiography revealed intra-abdominal bleeding. Therefore, transcatheter arterial embolism for bilateral internal iliac artery was done on March 18, 2014. Yet, dyspnea occurred and she underwent tracheal intubation. Afterward, she was transferred to intensive care unit (ICU) for monitoring. On the 2nd day, she developed acute kidney injury (creatinine = 1.23 mg/dL) and aggressive hydration was given. She received transfusions with 4 pRBC and 4 FFP, and anemia had improved (hemoglobin 9.1 mg/dL). However, clonus seizure occurred twice on the 6th day with a surge of blood pressure (Fig. 2). Emergent computed tomography of the brain revealed several hypodense lesions in the occipital and parietal regions (Fig. 1A), and the tentative diagnosis was ischemic stroke. However, T2-weighted magnetic resonance imaging (MRI) revealed hyperintense foci in the posterior occipito-parietal region (Fig. 1B), without a restricted diffusion area in apparent diffusion coefficient maps (Fig. 1C), consistent with PRES. Blood pressure ranging from 139/72 to 153/81 mm Hg was noted on that day. Her seizure was alleviated after receiving phenytoin. After 8 days of ICU stay, she was transferred to general ward and discharged. Three months later, follow-up brain MRI revealed almost complete remission of signal abnormalities (Fig. 1D). She had no further seizure episodes during 6 months follow-up.

3. Consent

Written informed consent was obtained from the patient in this case report and we have permission to use the accompanying images.

4. Discussion

Triggering factors of PRES in normotensive patient included chemotherapy,[10] AIDS,[11] thrombotic thrombocytopenic purpura,[12] carotid endarterectomy hyperperfusion syndrome,[13]

Figure 1. Brain abnormalities detected by CT and MRI. (A) Noncontrast CT showed hypodense lesions involving occipito-parietal regions (arrows). (B) T2-weighted MRI revealed foci of hyperintensity in temporal lobes and posterior occipito-parietal regions (arrows). (C) ADC maps showed no restricted diffusion except an area of vasogenic edema (arrow). (D) T2-weighted MRI showed complete resolution 3 mo later. ADC = apparent diffusion coefficient, CT = computed tomography, MRI = magnetic resonance imaging.
Pathogenesis of PRES is not fully understood and 2 proposed hypotheses are contradictory. One hypothesis is that severe hypertension beyond the upper limit of cerebral vascular autoregulation leads to hyperperfusion and vasogenic edema. On the contrary, another hypothesis suggested the dysfunction of endothelium leading vasoconstriction, hypoperfusion, and consequent ischemic edema. Since a proportion of the PRES did not have severe hypertension, dysfunction of endothelium seems to be a reasonable mechanism in this situation. Recent evidences favored vascular endothelial growth factor (VEGF) played an important role in the pathogenesis of PRES. On one hand, VEGF is a potent inducer of blood-brain barrier (BBB) permeability. On the other hand, the expression of cytokines (such as TNF-α) and VEGF up-regulating adhesion molecules (ICAM-1, VCAM-1, and E-selectin) in endothelial cells during inflammation may cause vessel lumen narrowing. Eventually, a combination of hypoperfusion and increased BBB permeability may lead to brain edema. In this case, we believed that the endothelial dysfunction might be due to combined effects of pregnancy, increased blood pressure variation, and blood transfusion.

Women who have twins pregnancy or pre/eclampsia were reported to have higher incidence of PRES. Previous research revealed large amounts of circulating TNF-α and VEGF were increased during pregnancy. Since VEGF-induced BBB permeability is a well-recognized phenomenon, soluble fms-like tyrosine kinase 1 (sFlt1) secreted from placental tissue could neutralize the adverse effects of VEGF and therefore prevents leaky BBB in the prepartum period. However, sFlt1 drops dramatically during postpartum period while VEGF level remains plateau. Although it is unclear whether or not the loss of BBB protection from sFlt1 drop after removal of the placenta is a direct cause of PRES in postpartum women, it is obvious that a relatively high concentration of VEGF plays a crucial role in the pathogenesis of PRES. Recent studies had demonstrated that the elevated VEGF was related to transplantation, chemotherapy, SLE, and other autoimmune diseases. Those conditions had been reported numerous in patients with PRES as well. Hence, future study may clarify the correlation between the concentration of sFlt1/VEGF and the occurrence of PRES in pregnant patients.

Further, the effect of hypovolemic shock during PPH in the occurrence of PRES cannot be ruled out completely. Ischemic edema resulted from vasoconstriction and hypoperfusion was 1 hypothesis of the onset of PRES. Some studies suggested that the brain edema might be a result rather than the cause of generalized vasocostriction in PRES patients and PRES complicated with end organ dysfunction such as acute kidney injury had been described previously. Our patient also had acute kidney injury and liver impairment just before the onset of PRES. These findings correlated the hypothesis of hypoperfusion and it might play an essential role in occurrence of PRES in our postpartum hemorrhagic patient.

On the other hand, our patients received a massive amount of blood product and cases of blood transfusion-related PRES were reported previously. We have already recognized that certain pro-inflammatory cytokines (PICs) and adhesion molecules which cause vessel lumen narrowing may be part of the PRES mechanism. Interestingly, blood transfusions also produce pro-inflammatory and microcirculatory effects and adverse events of blood transfusion related to allergic reaction, transfusion associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI) are well recognized. In summary, which based on reasonable speculation, vasoconstriction resulted from acute hemorrhage, massive blood transfusion-related PIC production, and drop of sFlt1 after placenta removal may induce the onset of PRES by the combined effect of hypoperfusion, endothelial activation, and VEGF-related BBB permeability.

Although the patient’s seizure occurred on the day with the highest blood pressure (Fig. 2), the mean arterial pressure did not go beyond the upper limit of physiological regulation, which is 140 to 160 mm Hg. Since cerebral reperfusion injury is a well-known phenomena that reperfusion may exacerbate the injury initially caused by ischemia, it raises the safety concern of rapid fluid resuscitation in patients with high risk of PRES. Some studies also indicated that the increased variation of blood pressure was associated with subsequent brain edema in acute stroke patients. During literature review of normotensive

| Table 1 |
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| Literature review of case report: the summary of demographic and clinical characteristic in posterior reversible encephalopathy syndrome patients without history of hypertension, pre eclampsia, and eclampsia. |
| | Female, N (%) | Male, N (%) |
| **Number of included case, N** | 41 | 41 |
| **Sex, N (%)** | 39 (95.1%) | 2 (4.9%) |
| **Age, mean±SD** | 47±18.2 | |
| **Tentative causes of PRES** | | |
| Infection/sepsis | 3/41 (7.3%) | 7.3 |
| Post-traumatic/surgery | 4/41 (9.7%) | 9.7 |
| Chemotherapy | 5/41 (12) | 12 |
| Intracranial hypotension | 3/41 (7.3%) | 7.3 |
| Autoimmune disease | 4/41 (9.7%) | 9.7 |
| Blood transfusion | 4/41 (9.7%) | 9.7 |
| Electrolyte imbalance | 5/41 (12) | 12 |
| Other | 13/41 (31) | 31 |
| Presentation with shock | 17/33 (51) | 51 |
| Hydration resuscitation | 26/31 (83) | 83 |

PRES = Posterior reversible encephalopathy syndrome, SD = standard deviation.
PRES (Table 1), we found that the vast majority of PRES patients had the episode of shock (51%) and received hydration resuscitation (83%). Consequently, we propose a “2-hits” hypothesis of PRES. Activation of endothelium causing hypoperfusion may be the first “hit” and subsequent reperfusion injury due to increased blood pressure variation may be the second “hit.”

Although the outcome of PRES had been shown to be promising,[14,42] fatal PRES cases were reported occasionally.[43,44] Therefore, it is clinically crucial to prevent PRES in high-risk population. This case inspired us several directions for future study and clinical implication. Firstly, the relationship between blood pressure variation and subsequent PRES needs to be examined. It is unclear whether or not avoiding rapid fluctuation of blood pressure could prevent PRES in shock patient. Secondly, transfusion of blood products is very common during hospitalizations. Although just a few cases of transfusion-related PRES were reported, we believe that the true prevalence might be underestimated because of lacking awareness of PRES symptoms in shock patients with altered state of consciousness. The solution to this issue may be reporting PRES in hemovigilance system,[45] a register system for transfusion-related adverse event, such as eclampsia, cerebral venous thrombosis, arteriovenous malformation, or PRES such as those reported in hemovigilance system.[46,47] Hence, we may consider these strategies in postpartum hemorrhagic women. Finally, since several cerebrovascular disorders in pregnant women can also produce symptoms/signs similar to PRES such as eclampsia, cerebral venous thrombosis, arteriovenous malformation rupture, cavernoma hemorrhage, and ischemic stroke,[48] it is crucial to differentiate other life-threatening disease rather than PRES. MRI features of PRES include high signal intensity involving the cortex and subcortical white matter in occipital lobes on T2-weighted and fluid attenuation inversion recovery images[49–51] whereas elevated diffusion pattern is seen on diffusion-weighted imaging.[51]

In conclusion, we described a case of PHH-related PRES without underlying disease. Hormone fluctuation, increased blood pressure variation, and massive blood transfusion may be contributed to the development of PRES in our case.

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