Posterior reversible encephalopathy syndrome in a postpartum hemorrhagic woman without hypertension

A case report

Chon-Fu Lio, MD[b], Ying-Hua Lee, MD[c], Hung-Yen Chan, MD[d], Chang-Ching Yu, PhD[a], Nan-Jing Peng, MD[a,e], Hung-Pin Chan, MD[a,*]

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,

[a] Department of Nuclear Medicine, Kaohsiung Veterans General Hospital, Kaohsiung City, Taiwan, [b] Centro Hospitalar Conde de São Januário, Macao, China, [c] Department of Medicine, National Defense Medical Center, Taipei City, [d] Department of Emergency, E-Da Hospital, Kaohsiung City, [e] School of Medicine, National Yang-Ming University, Taipei City, Taiwan.

* Correspondence: Hung-Pin Chan, Department of Nuclear Medicine, Kaohsiung Veterans General Hospital, 386 Ta-Chung 1st Road, Kaohsiung, Taiwan 813, China (e-mail: markscience05@hotmail.com).

headache, and visual loss.[1,2] Hyperintensity lesions over the occipital and parietal lobes caused by subcortical vasogenic edema are diagnostic features of PRES.[3] There are numerous predisposing factors relating to the PRES, such as hypertension, chemotherapy, transplantation, hemolytic uremic syndrome, severe infection, malignancy, and depletive lumbar puncture.[4–8] Yet, hypertension was the most common comorbidity in patients with PRES.[9] 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]
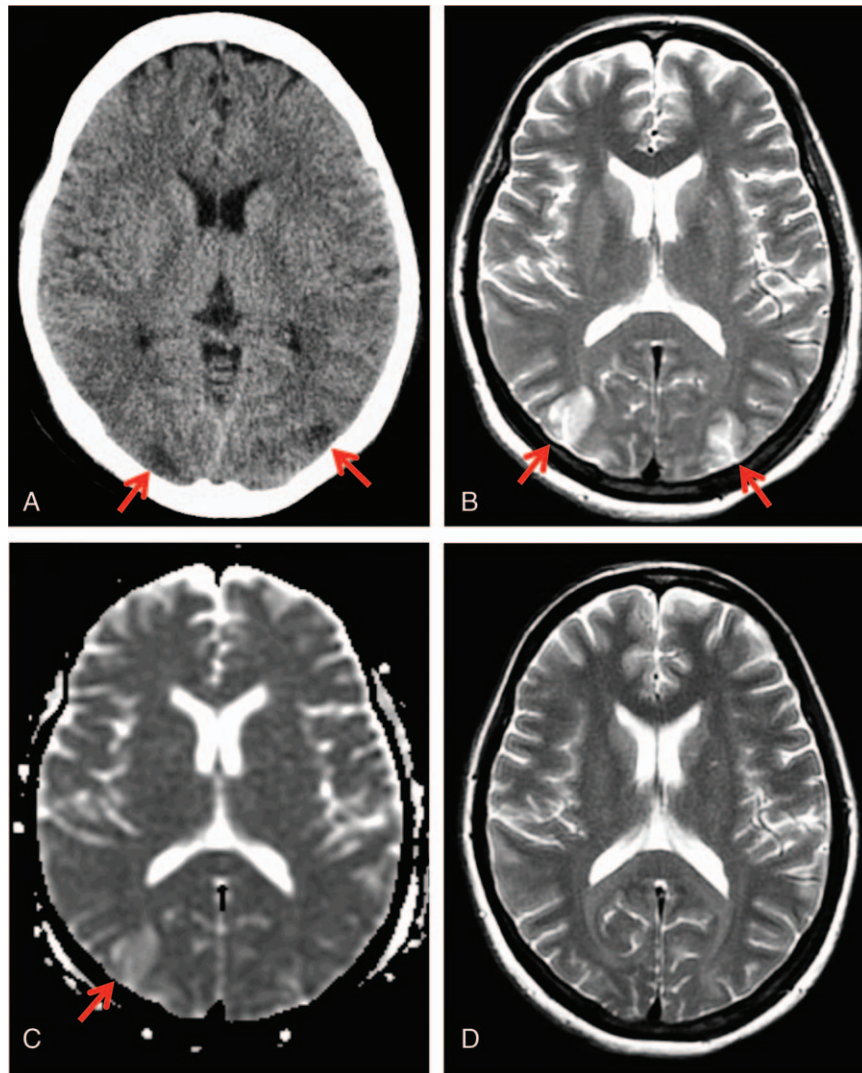
Figure 1. Brain abnormalities detected by CT and MRI. (A) Noncontrast CT showed hypodense lesions involving occipito-parietal regions (arrows). (B) T2-weighted MRI revealed foci of hyperintensity in temporal lobes and posterior occipito-parietal regions (arrows). (C) ADC maps showed no restricted diffusion 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.
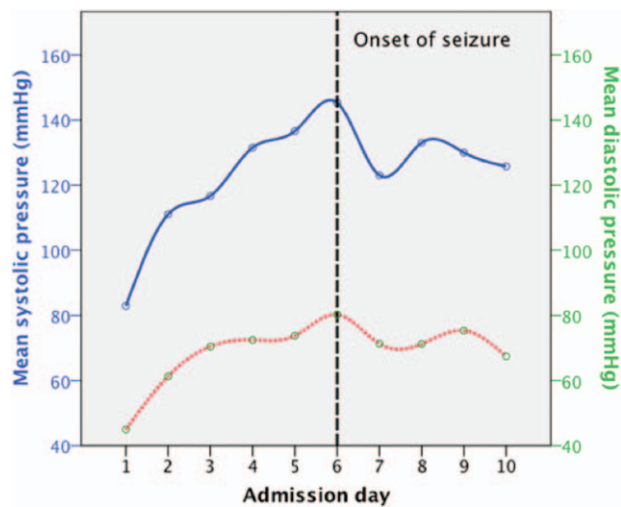
Figure 2. Curve for dynamic change of mean systolic and diastolic pressure in timeline during the first 10 d of hospitalization.

systemic lupus erythematosus (SLE), and polyarteritis nodosa.[14] To the best of our knowledge, it is the first case of PRES followed by PPH without underlying disease.

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.[14,15] On the contrary, another hypothesis suggested the dysfunction of endothelium leading vasoconstriction, hypoperfusion, and consequent ischemic edema.[16] 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.[16,17] On one hand, VEGF is a potent inducer of blood–brain barrier (BBB) permeability.[18] 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.[16,19,20] 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.[21] Previous research revealed large amounts of circulating TNF-α and VEGF were increased during pregnancy.[22] Since VEGF-induced BBB permeability is a well-recognized phenomenon,[18] 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.[23] However, sFlt1 drops dramatically during postpartum period while VEGF level remains plateau.[24] 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,[25] chemotherapy,[17] SLE,[26] and other autoimmune diseases.[27] Those conditions had been reported numerously in

patients with PRES as well. Hence, future study may clarify the correlation between the concentration of sFlt/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.[16] Some studies suggested that the brain edema might be a result rather than the cause of generalized vasoconstriction in PRES patients and PRES complicated with end organ dysfunction such as acute kidney injury had been described previously.[28–30] 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.[5,31–33] 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.[16,19,20] Interestingly, blood transfusions also produce pro-inflammatory[34,35] and microcirculatory effects[36] 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.[37,38] Since cerebral reperfusion injury is a well-known phenomena that reperfusion may exacerbate the injury initially caused by ischemia,[39] 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.[40,41] During literature review of normotensive

Table 1

Literature review of case report: the summary of demographic and clinical characteristic in posterior reversible encephalopathy syndrome patients without history of hypertension, preeclampsia, and eclampsia.

Number of included case, N	41	
Sex, N (%)	Female	Male
	39 (95.1%)	2 (4.9%)
Age, mean ± SD	47 ± 18.2	
Tentative causes of PRES	N	%
Infection/sepsis	3/41	7.3
Post-traumatic/surgery	4/41	9.7
Chemotherapy	5/41	12
Intracranial hypotension	3/41	7.3
Autoimmune disease	4/41	9.7
Blood transfusion	4/41	9.7
Electrolyte imbalance	5/41	12
Other	13/41	31
Presentation with shock	17/33	51
Hydration resuscitation	26/31	83

PRES = Posterior reversible encephalopathy syndrome, SD = standard deviation.

PRES (Table 1), we found that the vast majority of PRES patient 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 TRALI and TACO, in order to access the true prevalence of transfusion-related PRES. To minimize the transfusion-related adverse event, earlier studies had shown that restrictive transfusion, single-unit transfusion, and transfusion of leukoreduced blood product were advantageous.[46–48] 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,[49] 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[50] whereas elevated diffusion pattern is seen on diffusion-weighted imaging.[51]

In conclusion, we described a case of PPH-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.

Acknowledgments

References

[1] Kahana A, Rowley HA, Weinstein JM. Cortical blindness: clinical and radiologic findings in reversible posterior leukoencephalopathy syndrome: case report and review of the literature. Ophthalmology 2005; 112:e7–11.

[2] Granataa G, Grecob A, Iannellab G, et al. Posterior reversible encephalopathy syndrome—insight into pathogenesis, clinical variants and treatment approaches. Autoimmun Rev 2015;14:830–6.

[3] Fugate JE, Claassen DO, Cloft HJ, et al. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. Mayo Clin Proc 2010;85:427–32.

[4] Mathy I, Gille M, Van Raemdonck F, et al. Neurological complications of intravenous immunoglobulin (IVIg) therapy: an illustrative case of acute encephalopathy following IVIg therapy and a review of the literature. Acta Neurol Belg 1998;98:347–51.

[5] Ito Y, Niwa H, Iida T, et al. Post-transfusion reversible posterior leukoencephalopathy syndrome with cerebral vasoconstriction. Neurology 1997;49:1174–5.

[6] Pavlakis SG, Frank Y, Chusid R. Hypertensive encephalopathy, reversible occipitoparietal encephalopathy, or reversible posterior leukoencephalopathy: three names for an old syndrome. J Child Neurol 1999;14:277–81.

[7] Chiba A. Iatrogenic reversible posterior leukoencephalopathy syndrome. Nihon Naika Gakkai Zasshi 2007;96:1657–63.

[8] Nishio M, Yoshioka K, Yamagami K, et al. Reversible posterior leukoencephalopathy syndrome: a possible manifestation of Wegener's granulomatosis-mediated endothelial injury. Mod Rheumatol 2008; 18:309–14.

[9] Zhao ZY, He F, Gao PH, et al. Blood transfusion-related posterior reversible encephalopathy syndrome. J Neurol Sci 2014;342:124–6.

[10] Torocsik HV, Curless RG, Post J, et al. FK506-induced leukoencephalopathy in children with organ transplants. Neurology 1999;52: 1497–500.

[11] Frank Y, Pavlakis S, Black K, et al. Reversible occipital-parietal encephalopathy syndrome in an HIV-infected child. Neurology 1998; 51:915–6.

[12] Bakshi R, Shaikh ZA, Bates VE, et al. Thrombotic thrombocytopenic purpura: brain CT and MRI findings in 12 patients. Neurology 1999;52:1285–8.

[13] Baptista MV, Maeder P, Dewarrat A, et al. Conflicting images. Lancet 1998;351:414.

[14] Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. AJNR Am J Neuroradiol 2008;29:1036–42.

[15] Feske SK. Posterior reversible encephalopathy syndrome: a review. Semin Neurol 2011;31:202–15.

[16] Marra A, Vargas M, Striano P, et al. Posterior reversible encephalopathy syndrome: the endothelial hypotheses. Med Hypoth 2014;82:619–22.

[17] Kofler J, Bartynski WS, Reynolds TQ, et al. Posterior reversible encephalopathy syndrome (PRES) with immune system activation, VEGF up-regulation, and cerebral amyloid angiopathy. J Comput Assist Tomogr 2011;35:39–42.

[18] Argaw AT, Asp L, Zhang J, et al. Astrocyte-derived VEGF-A drives blood-brain barrier disruption in CNS inflammatory disease. J Clin Investig 2012;122:2454–68.

[19] Kim I, Moon SO, Kim SH, et al. Vascular endothelial growth factor expression of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin through nuclear factor-kappa B activation in endothelial cells. J Biol Chem 2001;276:7614–20.

[20] Nowak DG, Woolard J, Amin EM, et al. Expression of pro- and anti-angiogenic isoforms of VEGF is differentially regulated by splicing and growth factors. J Cell Sci 2008;121:3487–95.

[21] Papoutsis D, El-Attabi N, Sizer A. Postpartum posterior reversible encephalopathy syndrome (PRES) in a twin pregnancy complicated by preeclampsia-eclampsia: case report. Clin Exp Obstet Gynecol 2014; 41:351–3.

[22] Valdes G, Erices R, Chacon C, et al. Angiogenic, hyperpermeability and vasodilator network in utero-placental units along pregnancy in the guinea-pig (Cavia porcellus). Reprod Biol Endocrinol 2008;6:13.

[23] Espinoza J, Uckele JE, Starr RA, et al. Angiogenic imbalances: the obstetric perspective. Am J Obstet Gynecol 2010;203:17 e1–8.

[24] Palm M, Basu S, Larsson A, et al. A longitudinal study of plasma levels of soluble fms-like tyrosine kinase 1 (sFlt1), placental growth factor (PlGF), sFlt1: PlGF ratio and vascular endothelial growth factor (VEGF-A) in normal pregnancy. Acta Obstet Gynecol Scand 2011;90:1244–51.

[25] Horbinski C, Bartynski WS, Carson-Walter E, et al. Reversible encephalopathy after cardiac transplantation: histologic evidence of endothelial activation, T-cell specific trafficking, and vascular endothelial growth factor expression. AJNR Am J Neuroradiol 2009;30:588–90.

[26] Park SJ, Pai KS, Kim JH, et al. Could increased vascular endothelial growth factor induced by interleukin 17 be the cause of posterior reversible encephalopathy syndrome in systemic lupus erythematosus? J Rheumatol 2012;39:870.

[27] Carvalho JF, Blank M, Shoenfeld Y. Vascular endothelial growth factor (VEGF) in autoimmune diseases. J Clin Immunol 2007;27:246–56.

[28] Yan MT, Cheng CJ, Chen JS, et al. The case: a young man with acute kidney injury after exercise. The diagnosis: exercise induced acute kidney injury in hereditary renal hypouricemia. Kidney Int 2010;77:935–6.

[29] Mou LJ, Jiang LP, Hu Y. A novel homozygous GLUT9 mutation cause recurrent exercise-induced acute renal failure and posterior reversible encephalopathy syndrome. J Nephrol 2015;28:387–92.

[30] Mayama M, Uno K, Tano S, et al. Incidence of posterior reversible encephalopathy syndrome in eclamptic and patients with preeclampsia with neurologic symptoms. Am J Obstet Gynecol 2016;215:239.e1–5.

[31] Singh K, Gupta R, Kamal H, et al. Posterior reversible encephalopathy syndrome secondary to blood transfusion. J Clin Neurosci 2015;22:592–4.

[32] Huang YC, Tsai PL, Yeh JH, et al. Reversible posterior leukoencephalopathy syndrome caused by blood transfusion: a case report. Acta Neurol Taiwan 2008;17:258–62.

[33] Boughammoura A, Touze E, Oppenheim C, et al. Reversible angiopathy and encephalopathy after blood transfusion. J Neurol 2003;250:116–8.

[34] Bilgin YM, van de Watering LM, Versteegh MI, et al. Effects of allogeneic leukocytes in blood transfusions during cardiac surgery on inflammatory mediators and postoperative complications. Crit Care Med 2010;38:546–52.

[35] Fransen E, Maessen J, Dentener M, et al. Impact of blood transfusions on inflammatory mediator release in patients undergoing cardiac surgery. Chest 1999;116:1233–9.

[36] Roberson RS, Lockhart E, Shapiro NI, et al. Impact of transfusion of autologous 7- versus 42-day-old AS-3 red blood cells on tissue oxygenation and the microcirculation in healthy volunteers. Transfusion 2012;52:2459–64.

[37] Li Y, Gor D, Walicki D, et al. Spectrum and potential pathogenesis of reversible posterior leukoencephalopathy syndrome. J Stroke Cerebrovasc Dis 2012;21:873–82.

[38] Lee VH, Wijdicks EF, Manno EM, et al. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. Arch Neurol 2008;65:205–10.

[39] Pan J, Konstas AA, Bateman B, et al. Reperfusion injury following cerebral ischemia: pathophysiology, MR imaging, and potential therapies. Neuroradiology 2007;49:93–102.

[40] Sykora M, Diedler J, Turcani P, et al. Subacute perihematomal edema in intracerebral hemorrhage is associated with impaired blood pressure regulation. J Neurol Sci 2009;284:108–12.

[41] Skalidi SJ, Manios ED, Stamatelopoulos KS, et al. Brain edema formation is associated with the time rate of blood pressure variation in acute stroke patients. Blood Pressure Monit 2013;18:203–7.

[42] Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996;334:494–500.

[43] Golombeck SK, Wessig C, Monoranu CM, et al. Fatal atypical reversible posterior leukoencephalopathy syndrome: a case report. J Med Case Rep 2013;7:14.

[44] Huberlant V, Cosnard G, Hantson PE. Brain death in a septic patient: possible relationship with posterior reversible encephalopathy syndrome? Anaesth Intensive Care 2009;37:1017–20.

[45] Tinegate H, Birchall J, Gray A, et al. Guideline on the investigation and management of acute transfusion reactions. Prepared by the BCSH Blood Transfusion Task Force. Br J Haematol 2012;159:143–53.

[46] Jairath V, Kahan BC, Gray A, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. Lancet 2015;386:137–44.

[47] Kuroda S, Siesjo BK. Reperfusion damage following focal ischemia: pathophysiology and therapeutic windows. Clin Neurosci 1997;4:199–212.

[48] Jiwaji Z, Nunn KP, Conway-Morris A, et al. Leukoreduced blood transfusion does not increase circulating soluble markers of inflammation: a randomized controlled trial. Transfusion 2014;54:2404–11.

[49] Hacein-Bey L, Varelas PN, Ulmer JL, et al. Imaging of cerebrovascular disease in pregnancy and the puerperium. AJR Am J Roentgenol 2016;206:26–38.

[50] Schwartz RB, Jones KM, Kalina P, et al. Hypertensive encephalopathy: findings on CT, MR imaging, and SPECT imaging in 14 cases. AJR Am J Roentgenol 1992;159:379–83.

[51] Schwartz R, Mulkern R, Vajapeyam S, et al. Catheter angiography, MR angiography, and MR perfusion in posterior reversible encephalopathy syndrome. AJNR Am J Neuroradiol 2009;30:E19.