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POSTPARTUM HELLP SYNDROME ASSOCIATED WITH POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

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ABSTRACT

Haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome is a poorly understood, life-threatening multisystemic condition related to pregnancy with a rapid onset, typically observed in patients with severe pre-eclampsia. Various mechanisms may lead to diffuse endothelial damage associated with HELLP and possible brain involvement.

A comprehensive review of PubMed, Embase and Cochrane databases was conducted to examine the clinical, laboratory and radiological features associated with postpartum HELLP syndrome, particularly its potential association with posterior reversible encephalopathy syndrome (PRES). This review was prompted by a rare case we encountered. The literature review identified 10 articles documenting this association during pregnancy and 7 articles reporting it in the postpartum period.

Our patient developed multiple organ dysfunction (renal, hepatic, haemolysis and thrombocytopenia) postpartum associated with an arterial hypertensive profile. The patient experienced seizures along with the maintenance of an arterial hypertensive profile resistant to pharmacological therapy. Brain magnetic resonance imaging allowed the diagnosis of PRES and pituitary adenoma/apoplexy. Follow-up led to complete recovery.

KEYWORDS

Haemolysis elevated liver enzymes and low platelets syndrome, HELLP, posterior reversible encephalopathy syndrome, PRES, obstetric emergencies

LEARNING POINTS

- Early identification of posterior reversible encephalopathy syndrome (PRES) is essential after diagnosis of haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome.
- Early magnetic resonance imaging is required to identify PRES lesions and guide therapy.
- There needs to be an opportunity to discuss therapeutic options.

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INTRODUCTION

The syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP) is a life-threatening, poorly understood pregnancy-related multisystem condition with a rapid onset and is typically seen in patients with severe pre-eclampsia. It is associated with generalised vasospasm, microthrombi formation and coagulation defects. Although most cases of HELLP syndrome develop during the third trimester of pregnancy it can also manifest, albeit less frequently, in the postpartum period[1]. Various mechanisms are associated with gestational hypertensive disorders and can lead to diffuse endothelial damage that causes multiple organ dysfunction, with possible brain involvement[1]. We report a rare case of postpartum HELLP syndrome associated with posterior reversible encephalopathy syndrome (PRES). PRES is a radiographic clinical syndrome with heterogeneous aetiologies that are grouped together due to similar findings in neuroimaging studies[2]. The pathophysiology is still largely unknown but appears to be related to disordered cerebral autoregulation and endothelial dysfunction[2]. It should always be considered in women with acute hypertensive disorders such as pre-eclampsia, associated with epileptic seizures or other neurological symptoms during pregnancy and in the postpartum period[3]. Brain magnetic resonance imaging (MRI) is crucial for the diagnosis of PRES[3]. PRES is typically reversible with appropriate medical and supportive care, and prompt diagnosis and treatment are crucial to avoid complications such as death or permanent neurological damage[2,3].

The case presented shows a complete resolution of symptoms due to early diagnosis and immediate therapy. To explore the association between HELLP syndrome and PRES, we conducted a systematic review in several databases, including MEDLINE (PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, IBECS, BIOSIS, Web of Science, SCOPUS, conference abstracts and grey literature (Google Scholar and the British Library). The search covered publications from inception to June 2022. We used a combination of keywords encompassing different terms for PRES (posterior leukoencephalopathy syndrome), PRES, reversible posterior leukoencephalopathy syndrome (RPLS) and RPLS along with HELLP. This search produced a total of 11 relevant studies, shown in *Table 1*.

CASE DESCRIPTION

A 36-year-old woman with a history of depression developed pre-eclampsia at 35 weeks of gestation. She presented to the emergency department at 35 weeks and two days, referred by her primary care provider for hypertension with proteinuria. No other abnormalities were noted during the physical examination. The blood pressure measured in the obstetric emergency department was 146/82 mmHg, and laboratory tests revealed a urine protein/creatinine ratio of 2.528 mg/mg. The patient continued to be monitored in the maternity ward. Prenatal corticotherapy was started to promote foetal lung maturation. On day 3, hepatic cytolysis (alanine aminotransferase 95 U/l and aspartate aminotransferase 100 U/l) and renal dysfunction (SCr 1.8 mg/dl) developed. The patient presented with pre-eclampsia and was urgently admitted for a caesarean section. The procedure was complicated by significant blood loss (estimated >1,000 ml) leading to an emergency hysterectomy and bilateral salpingectomy. The patient was admitted to the intensive care unit (ICU) the same day with a diagnosis of class I HELLP syndrome. Upon admission to the ICU, the blood smear revealed moderate anisopoikilocytosis, with the presence of some elliptocytes and rare schistocytes, as well as mild anisochromia and polychromasia. Blood tests revealed thrombocytopenia (36 $\times 10^3$/µl), acute kidney injury, metabolic acidosis, hyperkalaemia and nephrotic proteinuria (5.3 g/g) with severe hypoalbuminemia (1.96 g/dl). The combination of these findings suggested a thrombotic microangiopathy. A multidisciplinary discussion involving haematology, immunology, internal medicine, obstetrics and nephrology was held in the ICU, leading to the decision to initiate a daily plasmapheresis regimen. On day 5, the patient started the daily plasmapheresis regimen with fresh frozen plasma replacement therapy associated with corticosteroid therapy (three days with a bolus of 250 mg/day followed by a maintenance dose of 60 mg/day). During this period, the patient maintained a hypertensive profile, requiring continuous labetalol infusion along with a regimen of various oral antihypertensives. On day 11 while in the ICU, she presented a focal seizure characterised by amaurosis, right hemiparesis and anisocoria (dilated right pupil) with persistent hypertension. The hemiparesis resolved within five minutes, but the patient continued to have amaurosis and anisocoria. Increasing the dose of labetalol failed to control the blood pressure, and isosorbide dinitrate infusion was started.

An urgent head CT scan was performed, revealing PRES – later confirmed with a cerebral MRI, as shown in *Figure 1*. T2/FLAIR hyperintensities were observed in the subcortical/juxtacortical white matter of the parietal (more pronounced on the left), occipital and posterior frontal regions, as well as in the posterosuperior aspect of the cerebellar hemispheres (also more pronounced on the left), and in the left splenium of the corpus callosum. A small focus of diffusion restriction is seen in the left parietal region.

Hormonal testing, including thyroid function and prolactin levels, were within normal limits. Cortisol levels were not checked as the patient was taking corticosteroids. The patient was started on anti-epileptic medication with levetiracetam, with resolution of all neurological symptoms and no further seizures. On discharge, the patient remained thrombocytopenic, but with levels above 134 $\times 10^3$/µl so plasmapheresis was stopped on day 12. Captopril, 50 mg three times a day, effectively controlled the patient's blood pressure, and isosorbide dinitrate and labetalol were discontinued.

With resolution of all major dysfunctions, the patient was discharged from the ICU on day 15. Five days later, she was

Study	Age (years)	Gestation (weeks) age (weeks)	Symptoms and signs	Laboratory findings	Brain CT	Brain MRI		Outcomes
						T2 and FLAIR	Diffusion	
Ateş et al., 2015[3]	29	35	Headache, peripheral oedema, blurred vision, hypertension	Class 1 HELLP, hypertransaminasaemia, thrombocytopenia, elevated LDH, schistocytes, altered renal function, proteinuria	-	Hyperintensities in the right occipital lobe, left cerebellum and right thalamus	No restriction	Complete recovery
Hegde et al., 2009[4]	21	-	GTC seizures, altered sensorium, generalised oedema, naso-oral bleeding, hypertension, oliguria	Class 1 HELLP, hypertransaminasaemia, thrombocytopenia, elevated LDH, altered renal function, proteinuria	Bilateral ill-defined hypodensities in the posterior temporal, parieto-occipital, high frontal and parietal lobes; bilateral watershed territory hypodensities with focal doubtful loss of grey-white matter differentiation	-	-	Complete recovery
Marano et al., 2003[5]	30	32	GTC seizures, drowsiness, tiredness, anuria	Class 2 HELLP, hypertransaminasaemia, thrombocytopenia	-	Bilateral asymmetric hyperintensities in the subcortical parieto-occipital lobes	-	Complete recovery
Morton et al., 2005[6]	26	28	GTC seizures, confusion, tongue lacerations, epigastric pain, oedema, visual disturbance, hypertension	Class 2 HELLP, hypertransaminasaemia, thrombocytopenia, altered renal function, proteinuria	Hypodensities in the right frontal and both occipital lobes	-	-	Complete recovery
Orgul et al., 2017[7]	40	24	Seizures, headache, visual loss, hypertension	Class 1 HELLP, hypertransaminasaemia, thrombocytopenia, proteinuria	Bilateral hypodensity in the occipital lobes and hyperaemia in the falx cerebri	Hyperintensities in both posterior hemi spheres	-	Complete recovery
Özden et al., 2020[8]	29	36	Headache, nausea, vomiting, epigastric pain, visual loss, hypertension	Class 1 HELLP, hypertransa minasaemia, thrombocytopenia, elevated LDH, hyperbilirubinaemia, altered renal function, proteinuria	First interpretation: bilateral hypodensities in white matter substance, especially in the occipital lobes, and general oedema. Second interpretation: no signs of PRES.	-	-	Complete recovery
Sarbu et al., 2018[9]	24	35	Drowsiness, weariness in the limbs with gait difficulties, hypertension	HELLP, hypertransaminasaemia, thrombocytopenia	Bilateral symmetric hypodensity of the basal ganglia	Symmetric hyperintensities in the lenticular and caudate nuclei, and internal and external capsule	Mild restriction in some areas	Complete recovery
Tetsuka et al., 2017[10]	38	29	Headache, drowsiness, delirium, abdominal pain, hypertension	Class 1 HELLP, hypertransaminasaemia, thrombocytopenia, elevated LDH, hyperbilirubinemia, altered renal function	-	Hyperintensities in the cortical-subcortical white matter in the occipital lobes, basal ganglia and callosal splenium	No restriction	Complete recovery
Vijayalakshmi et al., 2010[11]	28	16 (triploid pregnancy)	Headache, peripheral oedema, puffiness of the fingers, morning sickness, hemiparesis, epistaxis, epigastric pain, visual disturbance, hypertension	Class 1 HELLP, hypertransaminasaemia, thrombocytopenia, hyperbilirubinemia, reduced haptoglobin, altered renal function, proteinuria	Bilateral hypodensities in the basal ganglia and internal capsule, more on the right side	Bilateral, almost symmetrical, hyperintensities in the head of the caudate nucleus, external capsules and basal ganglia	Minor restriction in the right periventricular area	Complete recovery
Zemple et al., 2017[12]	21	32-35	GTC seizures, hypertension	Class 1 HELLP, hypertransaminasaemia, thrombocytopenia, altered renal function	Hypodensities in the parieto-occipital lobes and indistinct areas of basal ganglia, putamen and thalamus	-	-	Complete recovery
Incognito et al., 2023[13]	19	38	GTC seizures, hypertension	Class 2 HELLP, hypertransaminasaemia, thrombocytopenia, increased LDH	Normal	Focal cortical-subcortical hyperintensities in the left occipital lobe, parietal and frontal lobes bilaterally, and the cerebellum bilaterally	-	Complete recovery; Small areas of oedema in the right frontal lobe on MRI

Abbreviations: LDH, lactate dehydrogenase; GTC, generalized tonic-clonic seizure.

Table 1. Patient's hypercoagulable test results.

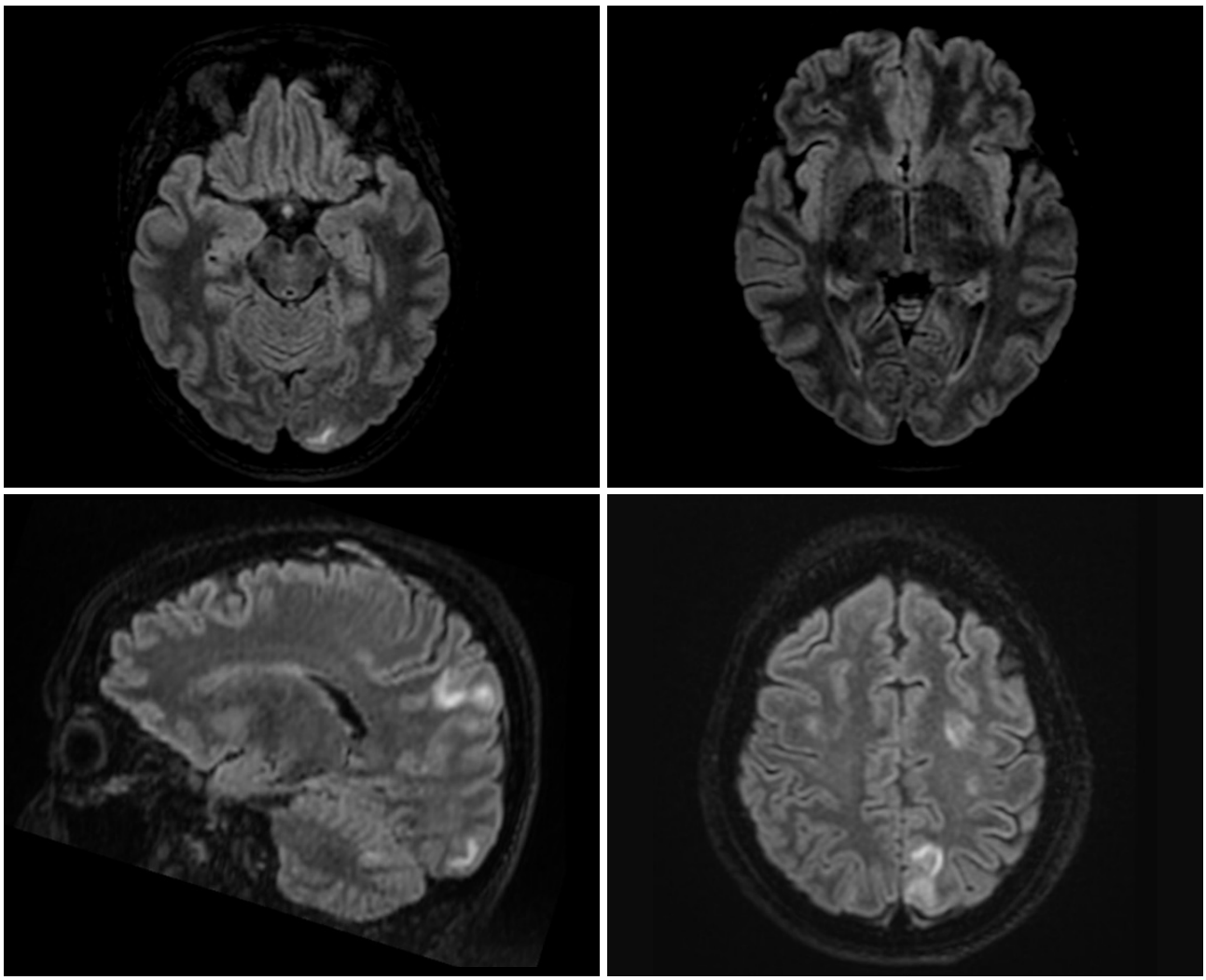


Figure 1. Magnetic resonance images of the PRES brain lesions.

discharged from the hospital. Follow-up appointments were scheduled with both endocrinology and nephrology; genetic testing revealed no defect. A follow-up MRI was performed twelve months after the event and showed resolution of the PRES lesions. The patient has annual MRIs without any changes, and at her last appointment she reported no new complaints and laboratory tests were normal.

DISCUSSION

This report describes a rare case of HELLP syndrome associated with PRES, that developed immediately after childbirth (postpartum). HELLP syndrome, a serious complication of pregnancy, typically occurs in the third trimester[1]. However, as in this case, it can also manifest postpartum in about one third of cases[1]. The estimated incidence of HELLP syndrome in specialised obstetric units is 7.6 per 1,000 deliveries[1]. Microvascular injury, possibly triggered by hypertension or immunological mechanisms, is thought to be the underlying cause[1].

The patient did not have chronic hypertension, an atypical presentation for HELLP syndrome, as only 20% of cases occur in the absence of this[1]. Blood tests showing anaemia with haemolysis, elevated liver enzymes and low platelet count confirmed the diagnosis of postpartum HELLP syndrome. The patients' ADAMTS13 levels were not measured. The platelet count is an important prognostic factor. In this case, the patient presented with class 1 HELLP syndrome with a platelet count of 36 $\times 10^3$/µl.

In terms of management, delivery is the definitive treatment for gestational hypertensive disorders[2]. Neurological disorders are rare, occurring in 4.5% of class 1 patients, but carry a high risk of morbidity and mortality[2]. PRES is a rare neurological disorder that causes sudden onset of headache, seizures, confusion and visual disturbances[2]. The symptoms of PRES usually develop quickly over a period of hours or days[2]. In some cases, people with PRES may also have trouble walking, weakness or numbness on one side of the body[4]. The exact aetiology of PRES remains unclear[2]. Several factors may contribute to its development, including hypertension, pre-eclampsia, eclampsia, kidney failure and the use of certain medications[5,6].

All these precipitating factors were excluded in the patient by clinical history and laboratory investigations. The most probable aetiology was pre-eclampsia/eclampsia, related to the hypertensive profile that the patient maintained despite optimal antihypertensive therapy. The patient presented with an acute hypertensive episode followed by a focal neurological deficit, which was interpreted as a focal seizure.

The diagnosis of PRES is primarily based on clinical presentation and neuroimaging findings[7,8]. MRI is the most used imaging modality and typically shows reversible subcortical white matter and/or posterior cortical oedema in a watershed distribution[9].

Management of PRES focuses on addressing the underlying cause and providing supportive care[2]. Treatment may involve antihypertensive medications, management of pre-eclampsia or eclampsia, dialysis for acute kidney injury or withdrawal of the causative medications[2]. Supportive care includes monitoring of vital signs, fluid management, seizure prophylaxis and management of neurological symptoms 2]. The prognosis for PRES is generally good[10]. With prompt treatment, most patients (70–90%) make a full recovery within weeks to months[11,12]. However, some patients may experience long-term neurological sequelae such as visual problems, cognitive impairment or motor deficits[8,9].

Our patient's seizures were controlled with levetiracetam and magnesium sulphate. Blood pressure control was initially achieved with labetalol and isosorbide dinitrate, followed by a switch to oral captopril. PRES is not always reversible, and the outcome is variable[13]. Prompt diagnosis and appropriate treatment can lead to complete reversal of clinical and neuroradiological findings with favourable outcomes[2,10]. The ideal time to repeat brain imaging to document recovery is unclear, but in the largest reported clinical series with confirmed neuroimaging improvement, resolution typically occurs within a few days[2]. The MRI, six months after discharge from the ICU, showed complete resolution of the PRES lesions.

The strength of our case report is the rarity of the association between these two entities: PRES and HELLP syndrome. Also, our review of the literature regarding diagnosis and physiopathology. Limitations include the small number of cases described and the lack of consensus regarding therapy.

CONCLUSIONS

Our study highlights a rare association between postpartum HELLP syndrome and PRES. While PRES in the postpartum period is poorly understood, its pathophysiology remains controversial, and the number of known comorbidities is increasing. Importantly, patients with PRES do not always present with typical symptoms, making MRI a critical tool for diagnosis. This case highlights the importance of considering PRES as a differential diagnosis in women presenting with seizures, headaches and altered mental status. Early recognition and intervention are crucial for full recovery.

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