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Case Report

Unilateral posterior reversible encephalopathy syndrome characterized with a long and gradually exacerbating course over 3 years and that presented propofol infusion syndrome – A case report

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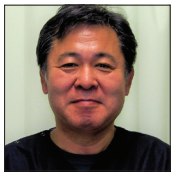

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ABSTRACT

Background: Posterior reversible encephalopathy syndrome (PRES) is characterized by acute neurological symptoms and vasogenic edema, and most patients wholly recover. We report a unilateral PRES patient characterized by a gradual onset followed by propofol infusion syndrome (PRIS) due to general anesthesia therapy.

Case Description: A 32-year-old woman had ovarian dysfunction treated by Kaufmann's treatment for 17 years. Three years ago, she developed seizures, and photophobia and myoclonus sometimes occurred. This time, she had strong photophobia and nausea for 3 months and then developed tonic-clonic seizures for 3 min. Her blood pressure and laboratory test on admission were all within normal limits. She presented no neurological deficits at admission, but the T2-weighted image (T2WI) showed a high-intensity area (HIA), and arterial spin labeling (ASL) image described cerebral blood flow (CBF) increase in the left parieto-occipital region. We diagnosed PRES and started anticonvulsants, antihypertensive, and steroid pulse therapy. However, her aphasia and neuroimaging findings worsened, so we started general anesthesia treatment with propofol on day 29. On day 32, she suddenly developed multiple organ dysfunctions due to PRIS. After intensive care with other sedatives over 2 months, the systemic status and neurological symptoms gradually improved almost as before the onset. On day 90, HIA in the T2WI in the lesion became small, and CBF was severely downregulated in the ASL image.

Conclusion: Unilateral PRES's pathophysiology and the association with the female hormone remain unknown. Some patients undergo gradual onset and long-term courses, and we should care for PRIS during PRES treatment.

Keywords: Kaufmann's treatment, Ovarian dysfunction, Posterior reversible encephalopathy syndrome, Propofol infusion syndrome, Status epilepticus

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a clinical and neuroradiologic entity that involves an acute onset of neurological symptoms and vasogenic edema. It is characterized by relatively acute-onset symptoms of headache, visual disturbance, altered mental status, and

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seizures. The neuroimaging typically reveals that patchy areas of vasogenic edema generally occurring bilaterally in the posterior parietal and occipital lobes.[1,2,7,8] Its prognosis is usually favorable, and most patients wholly recover.[22] However, about 40% of PRES patients require intensive care monitoring and treatment due to severe complications such as status epilepticus, cerebral ischemia, intracerebral hemorrhage, or intracranial hypertension.[5] PRES with gradual onset has rarely been reported.[4,20] Furthermore, some PRES patients undergo intractable courses,[7,8] but such difficult cases were rarely reported.[24,26] Therefore, we herein report a rare case who developed unilateral PRES characterized with a not acute but long and gradually exacerbating course over 3 years, followed by propofol infusion syndrome (PRIS) due to general anesthesia therapy for status epilepticus that needed 2-month intensive care.

CASE DESCRIPTION

A 32-year-old woman had ovarian dysfunction and had been undergoing Kaufmann's treatment for 17 years. Kaufmann's treatment is the sequential administration of estrogen and progesterone cyclically for a fixed period. In her Kaufmann's treatment's 28 day cycle, she had been taking 0.625 mg conjugated estrogens for the first 10 days, both 0.625 mg conjugated estrogens and medroxyprogesterone 5 mg for the next 11 days, and nothing for the rest of the 7 days. Three years ago, she developed seizures with the right upper extremity flexion, left upper extremity extension, and conjugate deviation to the right, which led to systemic convulsion. She was then treated with fosphenytoin, levetiracetam, and midazolam, and the convulsion was relieved. However, photophobia and myoclonus seizures sometimes occur, so she had taken levetiracetam 1000 mg/day as an outpatient. Her symptoms had repeated about once per 3 months, but her blood pressure had been within an optimal range.

Since 3 months ago in this year, she had been feeling strong photophobia and nausea. She then developed tonic-clonic seizures for 3 min and was transported to our emergency department. Her blood pressure was 124/77 mmHg, and laboratory test results were all within normal limits. She did not present any neurological deficits at admission, but the head computed tomography (CT) revealed a low-density area (LDA) in the left occipital lobe. The diffusion-weighted image (DWI) and T2-weighted image (T2WI) showed high-intensity area (HIA), and arterial spin labeling (ASL) image described cerebral blood flow (CBF) increase in the same region. These findings suggested brain edema [Figure 1]. We diagnosed unilateral PRES and started nicardipine to decrease her systolic blood pressure to around 110 mmHg and increased levetiracetam from 1000 mg/day to 3000 mg/day. Edaravone 60 mg/day was also administered for a week. However, she gradually developed motor aphasia and apraxia, and the HIA in the T2WI in the parieto-occipital region enlarged, and CBF was further upregulated in the ASL image on day 12 [Figure 2]. Therefore, we started glycerol 400 mL/day continuously. We administered magnesium sulfate 4 g/day for 3 days. However, her aphasia and apraxia further worsened, so we started perampanel 2 mg/day and steroid pulse treatment (hydrocortisone 500 mg/day for 2 days, 300 mg/day for 3 days, 200 mg/day for 2 days, 100 mg/day for 2 days, and 50 mg/day for 2 days) on day 26. She developed total aphasia, and her apraxia worsened so that she could not perform daily living activities.

On day 29, the HIA in the T2WI in the left parieto-occipital region enlarged to the temporal lobe, and CBF was further upregulated in the ASL image. Gadolinium-enhanced magnetic resonance imaging was performed, but the lesion was not enhanced; thus, malignant glioma seemed negative [Figure 3]. We diagnosed status epilepticus due to PRES and started general anesthesia treatment with intubation. Her weight was 75 kg, so we started continuous administration of 1% propofol 40 mL/h, but we could not obtain her sedation. We also started midazolam 10 mg/h and fentanyl 0.5 mg/day as continuous administration and got her sedated.

On day 32, she suddenly developed multiple organ dysfunctions with a serum creatinine kinase level of 25,770,000 IU/L. We diagnosed PRIS, and she was transported to another advanced medical care center. After intensive care with vasopressors, continuous hemodiafiltration, and prone position respiratory therapy with sedation by midazolam and dexmedetomidine, her systemic status and consciousness gradually improved. She was extubated on day 68, and continuous hemodiafiltration ended on day 76. Her consciousness finally improved as that before the onset, but intention tremor was present as a subsequent complication. During the intensive care, electroencephalography did not reveal any epileptiform patterns, and laboratory cerebrospinal fluid (CSF) and blood tests associated with autoimmune and inflammatory diseases were all negative; anti-viral antibodies, anti-myelin oligodendrocyte glycoprotein antibody, anti-N-methyl-D-aspartate receptor antibody, and anti-aquaporin 4 antibody were negative in both CSF and blood serum. Anti-nuclear antibody, anti-double-stranded deoxyribonucleic acid antibody, Ro/La antibody, serine proteinase 3-anti-neutrophil cytoplasmic antibody, and myeloperoxidase-anti-neutrophil cytoplasmic antibody were all negative. Serum C3, C4, and CH50 levels were 72 mg/dL, 44.3 mg/dL, and 39.9 U/mL, respectively. Serum pyruvate and lactate levels were increased to 1.15 mg/dL and 25.7 mg/dL each.

She was transported back to our hospital on day 89 and has continued mainly physical therapy for gait disorder due to disuse syndrome rather than higher cognitive training. Her aphasia and apraxia had already disappeared, and she has walked without any assistance. On day 90, HIA in the T2WI in

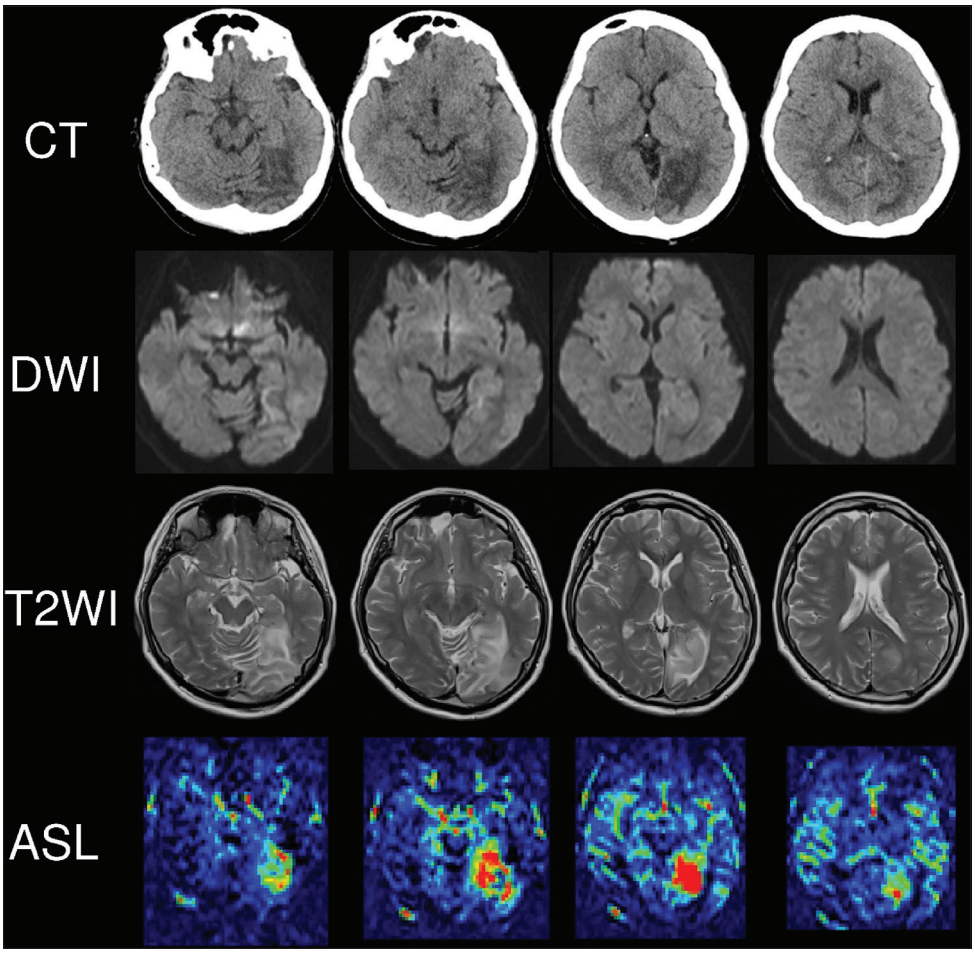

Figure 1: Neuroimaging on day 1. Head computed tomography revealed a low-density area in the left occipital lobe. The diffusion-weighted image and T2-weighted image showed high-intensity area, and arterial spin labeling image described cerebral blood flow increase in the same region.

the parieto-occipital region a bit became small, and CBF was severely downregulated in the ASL image. Magnetic resonance spectroscopy did not reveal the peak of lactate [Figure 4].

DISCUSSION

We herein reported a rare case who developed PRES characterized by a long and gradually exacerbating course over 3 years and needed intensive care for seizures with general anesthesia therapy. She had ovarian dysfunction and had been undergoing Kaufmann's treatment. In this case, there are five notable points; pathophysiology related to female hormones, unilateral variant PRES, gradual onset and improvement, development of PRIS after PRES, and differential diagnosis.

Pathophysiology

There are two leading theories on PRES's pathophysiology: hypertension and cerebral hyperperfusion theory, and endothelial dysfunction theory.[5,7] Both theories are related to dysfunction of the cerebrovascular autoregulation, leading to cerebral edema with various symptoms.[1,5] Our case did not have hypertension, and her blood pressure on admission was within the optimal range of 124/77 mmHg. Therefore, endothelial dysfunction seemed to play a key role in this case.

The endothelial dysfunction theory's common factors are the presence of endogenic (preeclampsia, sepsis, and autoimmune disorders) or exogenic (chemotherapy and immunosuppressive agents) toxins.[15,17] PRES occurs 90% of eclamptic and 20% of preeclamptic patients, and it is presumably because cytokines associated with pregnancy may occur endothelial dysfunction.[16] On the other hand, estrogen, which is vigorously increased during pregnancy, affects the vascular endothelial nitric oxide synthase and nitric oxide production, which prevent atherosclerotic vascular changes,[21] and also has an anti-inflammatory effect on the endothelial cells.[3] PRES associated with gonadotropin-releasing hormone agonists, which led to low estrogen status, was also reported.[14] As a similar disease of vascular dysfunction,

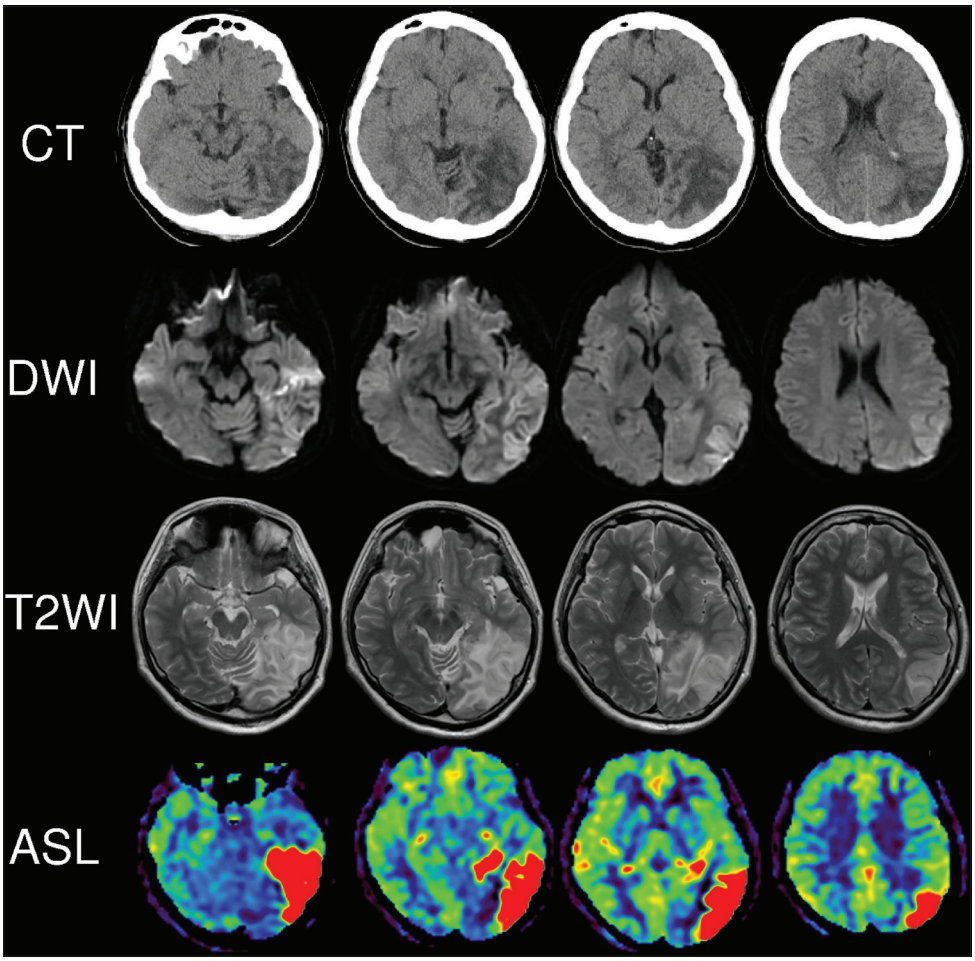

Figure 2: Neuroimaging on day 12. Head computed tomography revealed an enlarged low-density area in the left parieto-occipital lobe. The diffusion-weighted image and T2-weighted image also showed the enlarged high-intensity area, and arterial spin labeling image described further cerebral blood flow increase in the same region.

reversible cerebral vasoconstriction syndrome was reported in the setting of hormonal ovarian stimulation for intrauterine insemination.[6] In our report, she had ovarian dysfunction and had been undergoing Kaufman's treatment for 17 years. Of course, these associations between a female hormone and PRES development are the only speculation. Furthermore, PRES incidence may be higher in women,[12] but the actual gender difference associated with the PRES development is still unknown.[1,2,7,13] Although it is unknown whether favorable or adverse effect ovarian dysfunction and Kaufmann's treatment had on the cerebral vascular function and endothelial cells, our patient's pathophysiology may be associated with those female hormonal dynamics, which attenuated endothelial functioning.

Unilateral variant PRES

As a unique point of our case, she showed unilateral lesions in the left hemisphere. Typically, PRES presented bilateral and symmetrical lesions.[1,7,13] In addition to PRES with the atypical locations, such as the cerebellum, basal ganglia, thalamus, brainstem, and spinal cord, unilateral PRES has been established as the disease concept.[2,13] In Khan's report, our case is categorized into the unilateral variant PRES, which involves one cerebral hemisphere.[13] These types were mainly reported in the setting of preexisting vascular abnormalities that affected cerebrovascular hemodynamics. As another report, Mc Kinney reported that 2.6% (2 out of 76 PRES patients) mimicked neoplasm with unilateral lesions after bone marrow transplantation and cyclosporine therapy.[18] However, our case did not have any vascular abnormalities or bone marrow transplantation and cyclosporine therapy. Therefore, this is a unique point of our case that unilateral variant PRES observed in the young woman who had been undertaking Kaufmann's treatment.

Gradual onset and prolonged recovery course

PRES's prognosis is usually favorable, and 75%–90% of patients wholly recover with a mean time to full clinical recovery about 2–8 days.[7] Roth and Ferbert reported their

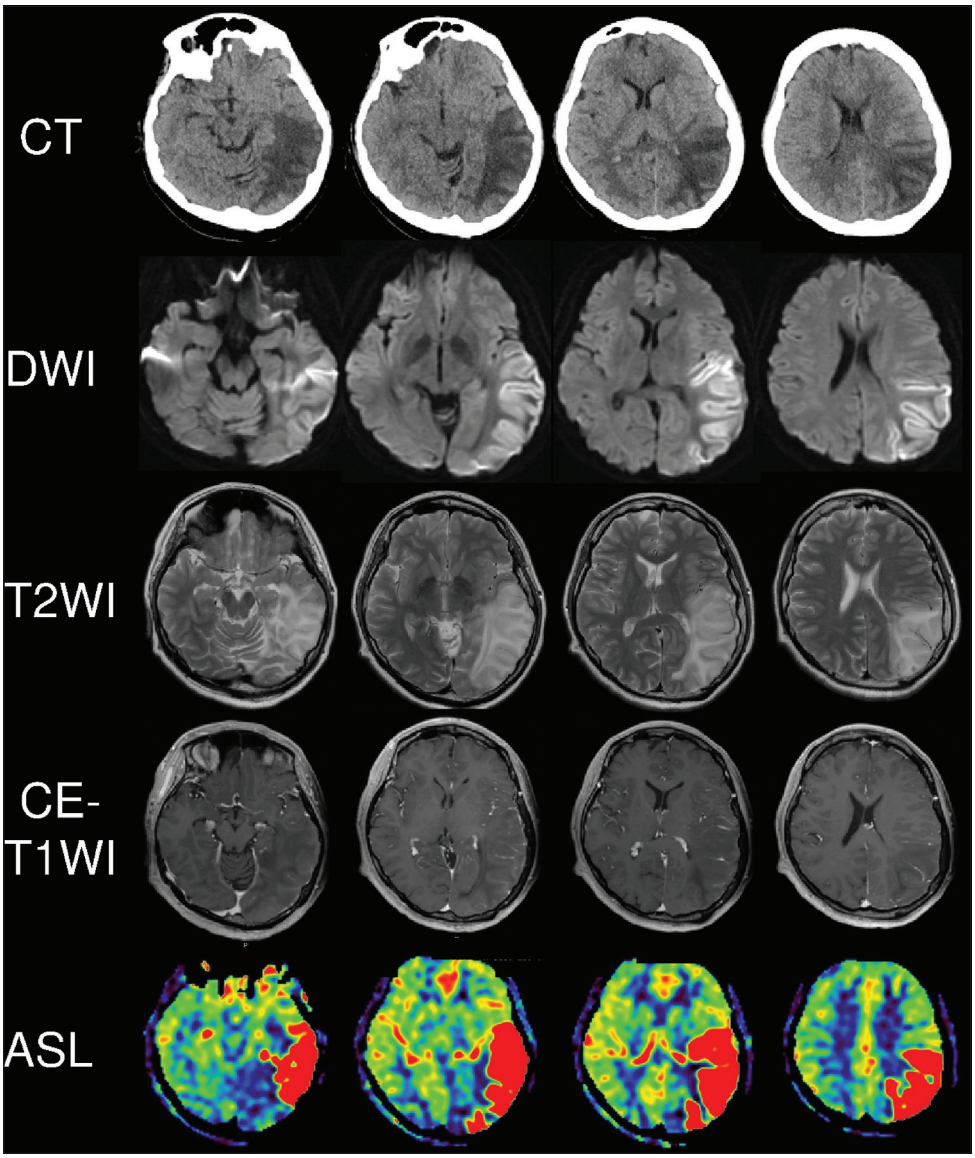

Figure 3: Neuroimaging on day 29. Head computed tomography revealed a further enlarged low-density area from the left parieto-occipital lobe to the temporal lobe. The diffusion-weighted image and T2-weighted image also showed the enlarged high-intensity area. Gadolinium-enhanced T1-weighted image reveal that the lesion was not enhanced and arterial spin labeling image described strong cerebral blood flow increase in the same region.

23 PRES patients, and their patients were treated in an intensive care unit for a mean duration of 3.9 days.[22] PRES seems an acute-onset and favorable outcome disease, but PRES patients with gradual and prolonged onset were also reported. De Seze reported a PRES patient due to hypertension who presented progressive headaches followed by blurred vision over 1 month, treated by antihypertensive therapy for 3 months.[4] Oishi reported a PRES patient due to hypertension who presented gait difficulty, which gradually worsened over 4 months. The neurological symptom improved 1 week after antihypertensive and steroid pulse therapy.[20] On the other hand, PRES patients with prolonged recovery courses were reported. Tlemsani reported a case developed PRES under anti-vascular endothelial growth factor agents and with a history of hypertension.[26] The symptoms were relieved 1 month after anticonvulsants, corticosteroids, or antihypertensive therapy. Shiga reported a case associated with diabetic nephropathy and uremic encephalopathy. After treatment for the electrolyte imbalance and dehydration, the symptoms gradually improved, and the patient was discharged on day 15, but 6 months were needed for neuroimaging improvement.[24] Both cases acutely developed PRES, but the symptoms needed a long time to improve. Compared to these previous reports, our patients had a long and gradual onset

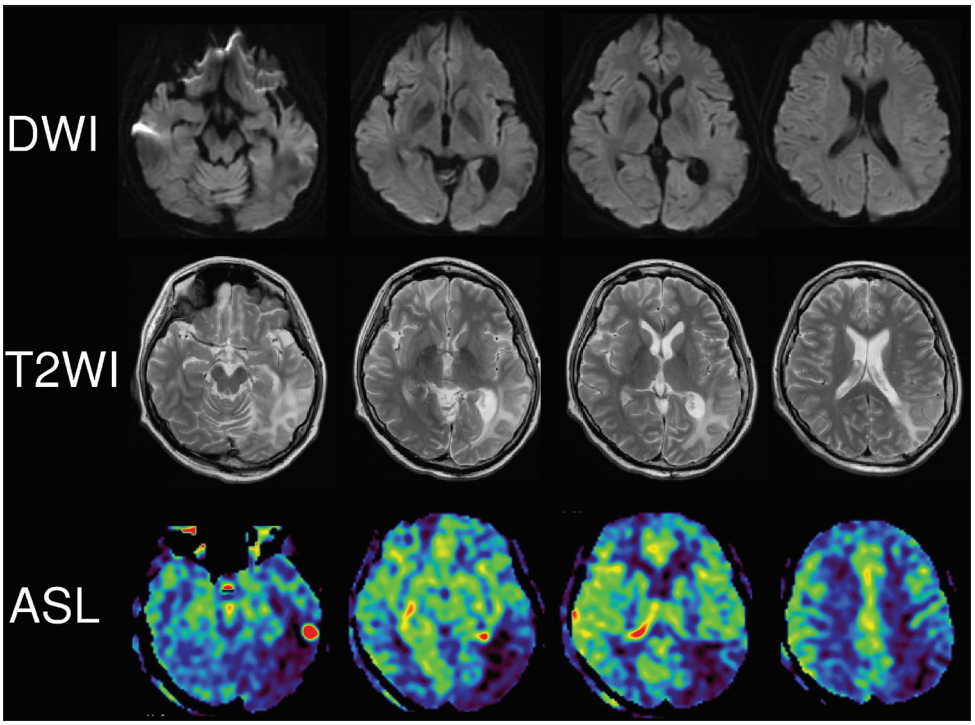

Figure 4: Neuroimaging on day 90. The lesions improved a bit in the diffusion-weighted image and T2-weighted image. Arterial spin labeling image described severely decreased cerebral blood flow in the same region.

for 3 years and underwent intensive care for about 2 months. This gradual onset and prolonged and difficult treatment course were rare. Our case suggests that even if the symptoms developed gradually, the treatment for PRES could be difficult, and the recovery would take longer.

Propofol infusion syndrome

Propofol is used for treating refractory status epilepticus. PRIS is a rare but often fatal syndrome characterized by lactic acidosis, lipidemia, and cardiac failure, associated with propofol infusion over prolonged periods. The incidence of PRIS during treatment for status epilepticus is about 39%, and the mortality rate is up to 6%.[9] The risk factors for the development of PRIS are inappropriate propofol doses (>83 μg/kg/min)[9] and duration of administration, carbohydrate depletion, severe illness, and concomitant administration of catecholamines and glucocorticosteroids.[19] We infused a bit much propofol as 88 μg/kg/min with glucocorticosteroids. These are things to reflect on, and we should have used less propofol and have administered benzodiazepine sedatives and performed frequent laboratory tests to notice PRIS's development.

Differential diagnosis

Based on the clinical course and radiological findings, we raised progressive malignant glioma and mitochondrial myopathy encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) as differential diagnoses. The incidence of malignant gliomas is approximately 5/100,000, and malignant gliomas constitute 35–45% of primary brain tumors. Gadolinium-enhanced T1-weighted image usually reveals enhanced lesion in the progressive glioma,[11] but our case did not reveal such enhanced lesion; therefore, malignant glioma may be negative in our case.

MELAS is a mitochondrial disorder caused by mutations in the genes in mitochondrial DNA. MELAS can be another differential diagnosis because MELAS and PRIS's pathophysiological mechanism commonly involves mitochondrial disorder that leads to insufficient energy generation. PRIS patient with the genetically proven mitochondrial disease[23] and MELAS patient who developed PRIS were also reported.[25] MELAS could not be ruled out, but laboratory tests, radiological findings of our patient did not meet the diagnostic criteria,[10] and we did not perform pathological or genetic tests. We should have tested these tests and proceeded with a differential diagnosis. If she has MELAS's symptoms continuously, we will perform a further investigation on MELAS.

CONCLUSION

We herein reported a rare case who developed unilateral PRES characterized with a not acute but long and gradually exacerbating course over 3 years, followed by PRIS due to

general anesthesia therapy for status epilepticus that needed 2-month intensive care. PRES's pathophysiology remains unknown, and further studies on the association, especially female hormone and PRES, are needed. We also should care for prolonged clinical course and PRIS during PRES treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Anderson RC, Patel V, Sheikh-Bahaei N, Liu CS, Rajamohan AG, Shiroishi MS, *et al*. Posterior reversible encephalopathy syndrome (PRES): Pathophysiology and neuro-imaging. Front Neurol 2020;11:463.
2. Brady E, Parikh NS, Navi BB, Gupta A, Schweitzer AD. The imaging spectrum of posterior reversible encephalopathy syndrome: A pictorial review. Clin Imaging 2018;47:80-9.
3. Cossette É, Cloutier I, Tardif K, Donpierre G, Tanguay JF. Estradiol inhibits vascular endothelial cells pro-inflammatory activation induced by C-reactive protein. Mol Cell Biochem 2013;373:137-47.
4. De Seze J, Mastain B, Stojkovic T, Ferriby D, Pruvo JP, Destée A, *et al*. Unusual MR findings of the brain stem in arterial hypertension. AJNR Am J Neuroradiol 2000;21:391-4.
5. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. J Neurol 2017;264:1608-16.
6. Freilinger T, Schmidt C, Duering M, Linn J, Straube A, Peters N. Reversible cerebral vasoconstriction syndrome associated with hormone therapy for intrauterine insemination. Cephalalgia 2010;30:1127-32.
7. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: Clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol 2015;14:914-25.
8. Garcia JM, Stillings SA, Leclerc JL, Phillips H, Edwards NJ, Robicsek SA, *et al*. Role of interleukin-10 in acute brain injuries. Front Neurol 2017;8:244.
9. Hwang WS, Gwak HM, Seo DW. Propofol infusion syndrome in refractory status epilepticus. J Epilepsy Res 2013;3:21-7.
10. Japan Intractable Diseases Information Center Journal Mitochondrial Disease; 2020. Available from: https://www.nanbyou.or.jp/entry/335. [Last accessed on 2020 Nov 01].
11. Kao HW, Chiang SW, Chung HW, Tsai FY, Chen CY. Advanced MR imaging of gliomas: An update. Biomed Res Int 2013;2013:970586.
12. Kawakita K, Abe Y, Kirizume K, Shinohara N, Kawai N, Tamiya T, *et al*. Posterior reversible encephalopathy syndrome: Five case reports. Nihon Kyukyu Igakukai Zasshi 2012;23:357-63.
13. Khan IR, Pai V, Mundada P, Sitoh YY, Purohit B. Detecting the uncommon imaging manifestations of posterior reversible encephalopathy syndrome (PRES) in adults: A comprehensive illustrated guide for the trainee radiologist. Curr Probl Diagn Radiol 2020. Doi: 10.1067/j.cpradiol.2020.11.002.
14. Lee M, Kim TH, Kim SJ, Jee BC. Posterior reversible encephalopathy syndrome in a woman who used gonadotropin-releasing hormone agonists: A case report. Obstet Gynecol Sci 2019;62:69-72.
15. Marra A, Vargas M, Striano P, Del Guercio L, Buonanno P, Servillo G. Posterior reversible encephalopathy syndrome: The endothelial hypotheses. Med Hypotheses 2014;82:619-22.
16. Mayama M, Uno K, Tano S, Yoshihara M, Ukai M, Kishigami Y, *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.
17. McDermott M, Miller EC, Rundek T, Hurn PD, Bushnell CD. Preeclampsia association with posterior reversible encephalopathy syndrome and stroke. Stroke 2018;49:524-30.
18. McKinney AM, Short J, Truwit CL, McKinney ZJ, Kozak OS, SantaCruz KS, *et al*. Posterior reversible encephalopathy syndrome: Incidence of atypical regions of involvement and imaging findings. AJR Am J Roentgenol 2007;189:904-12.
19. Mirrakhimov AE, Voore P, Halytskyy O, Khan M, Ali AM. Propofol infusion syndrome in adults: A clinical update. Crit Care Res Pract 2015;2015:260385.
20. Oishi C, Okano H, Uegama K, Kobayashi K, Nagane M, Chiba A, *et al*. Brainstem variant of reversible posterior leukoencephalopathy syndrome with a prolonged clinical course: A case report. Rinsho Shinkeigaku 2008;48:737-41.
21. Ross R. The pathogenesis of atherosclerosis: A perspective for the 1990s. Nature 1993;362:801-9.
22. Roth C, Ferbert A. Posterior reversible encephalopathy syndrome: Long-term follow-up. J Neurol Neurosurg Psychiatry 2010;81:773-7.
23. Savard M, Dupré N, Turgeon AF, Desbiens R, Langevin S, Brunet D. Propofol-related infusion syndrome heralding a mitochondrial disease: Case report. Neurology 2013;81:770-1.
24. Shiga Y, Kanaya Y, Kono R, Takeshima S, Shimoe Y, Kuriyama M. Posterior reversible encephalopathy syndrome of the midbrain and hypothalamus-a case report of uremic encephalopathy presenting with hypersomnia. Rinsho Shinkeigaku 2016;56:43-7.
25. Shimizu J, Tabata T, Tsujita Y, Yamane T, Yamamoto Y, Tsukamoto T, *et al*. Propofol infusion syndrome complicated with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes: A case report. Acute Med Surg 2020;7:e473.
26. Tlemsani C, Mir O, Boudou-Rouquette P, Huillard O, Maley K, Ropert S, *et al*. Posterior reversible encephalopathy syndrome induced by anti-VEGF agents. Target Oncol 2011;6:253-8.

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