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Differentiation of cytotoxic and vasogenic edema in a patient with reversible posterior leukoencephalopathy syndrome using diffusion-weighted MRI

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ABSTRACT
In recent years reversible posterior leukoencephalopathy syndrome (RPLS) has become increasingly recognized. It represents an uncommon entity related to multiple pathologies, the most common being hypertensive crisis. The underlying pathophysiological mechanism is proposed to be one of vasogenic edema, without infarction; however, differentiation from cytotoxic edema can be crucial for therapeutic and clinical outcome. Diffusion-weighted magnetic resonance imaging (DWI), including calculation of the apparent diffusion coefficient (ADC), may be helpful for differentiation. We present a case of a healthy young woman in the 40th week of gestation, with no prior complications, who suddenly developed RPLS with vasogenic edema, which was differentiated with DWI and quantification of ADC. Follow-up cranial MRI showed complete remission. Pre-eclampsia could not be proven according to pathognomonic laboratory findings.

Key words: • *diffusion magnetic resonance imaging* • *reversible posterior leukoencephalopathy syndrome*

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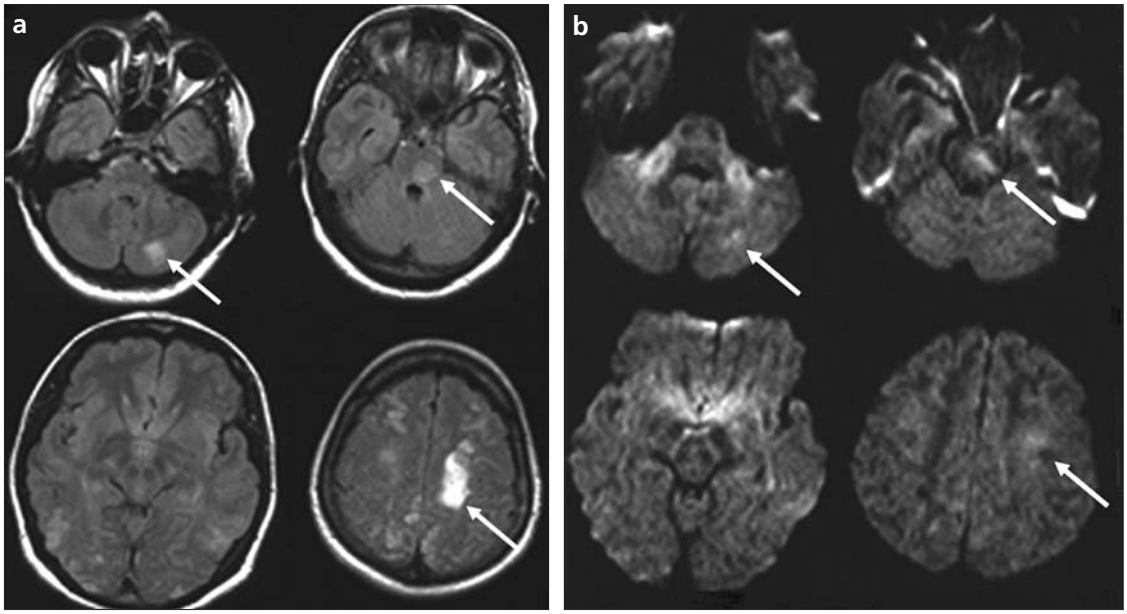
Major clinical symptoms leading to the tentative diagnosis of reversible posterior leukoencephalopathy (RPL) are headache, seizures, and visual loss, combined with accelerated arterial hypertension. In recent years, this entity has become increasingly recognized by the term RPL syndrome, which was first used by Hinchey et al. in 1996 (1). Causes and associations include hypertensive encephalopathy (1–4), eclampsia (5), thrombotic thrombocytopenic purpura (TTP)/hemolytic-uremic syndrome (HUS) (6–8), and immunosuppressive drugs, such as in cyclosporine-induced neurotoxicity (9–11). In addition to medical history and leading clinical symptoms, there are characteristic radiological findings in magnetic resonance imaging (MRI), the imaging modality of choice (12–14). Recapitulating the term RPL is misleading, as the condition is not always reversible and not necessarily bound to posterior regions of the brain. Furthermore, it can affect both white and grey matter. Therefore, it has also been described as occipital-parietal encephalopathy (15) and alternatively as posterior reversible encephalopathy syndrome (PRES) (12, 13). The underlying pathophysiological mechanism is proposed to be one of vasogenic edema, without infarction (14, 16–18); however, differentiation from developing cytotoxic edema can be decisive for treatment and outcome (18). Additionally, it is vital to recognize and treat the condition in a timely fashion in order to prevent further and permanent brain damage. We present the case of a healthy young woman in the 40th week of gestation that developed RPL, with no prior complications with regard to eclampsia. We focused on the use and potential of diffusion-weighted magnetic resonance imaging (DWI) and quantification of the apparent diffusion coefficient (ADC).

Case report

A 31-year-old gravida 2, para 1 woman in the 40th week of gestation was admitted to the hospital. She did not experience any prior complications during her pregnancy. The medical checkups at hand, including clinical history, laboratory results, and blood pressure, revealed no pathological findings. During hospitalization she suddenly developed hypertension (blood pressure, 170/110 mmHg), combined with severe bifrontal headache that was followed by a tonic-clonic seizure. History concerning seizures, drugs, neurological, or other underlying illnesses was negative. Her echocardiogram was normal. Serum electrolytes, blood urea-nitrogen level, serum creatinine, liver enzymes, and coagulation tests (PTT, INR) were in the normal range. Further laboratory tests, especially those focusing on hypoglycemia, eclampsia, and HELLP-syndrome (hemolysis, elevated liver enzyme levels, and low platelet count) returned no significant pathological findings. A cesarean section was performed without any complications. Postoperatively, 2 additional secondary generalized



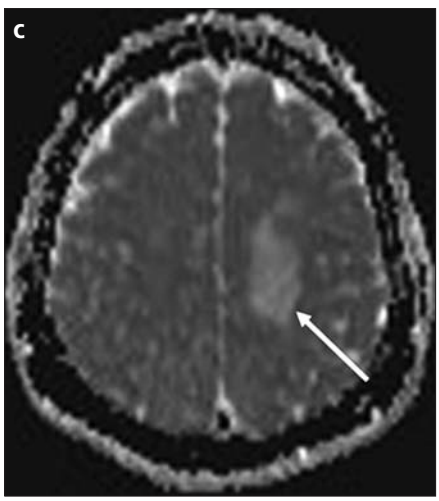


Figure 1. a–c. A 31-year-old woman in the 40th week of gestation with reversible posterior leukoencephalopathy. Initial transverse FLAIR MR images **(a)** were with abnormal signal intensity *(arrows)*, particularly in the supratentorial white matter and adjacent cortex in the occipital, frontoparietal, and temporal lobes bilaterally, with predominance in the left centrum semiovale. Further hyperintense signal alterations *(arrows)* in the left hemisphere of the cerebellum and left paramedian central brainstem are seen. Corresponding diffusion-weighted MR imaging (DWI) **(b)** demonstrated hyperintense signal alterations *(arrows)* in the areas of FLAIR signal abnormalities. Apparent diffusion coefficient (ADC) mapping **(c)** revealed increased diffusion in the left centrum semiovale (hyperintense signal), indicating vasogenic edema *(arrow)*. None of the hyperintense signal alterations on DWI showed decreased ADC values, as would be expected in an ischemic brain with cytotoxic edema.

tonic-clonic seizures occurred, focally prefaced with convulsion of the left hand. Her blood pressure at that time was 179/110 mmHg. The neurological examination revealed a right-sided hemiparesis. No retinal hemorrhages or papilledema was seen in fundoscopic examination. Electroencephalography (EEG) showed evidence of left frontal focal delta activity.

Cranial T2-weighted (T2W) MR images and fluid-attenuated inversion recovery (FLAIR) images demonstrated hyperintense signal changes, particularly in the supratentorial white matter and adjacent cortex in the occipital, frontoparietal, and temporal lobes bilaterally, with predominance in the left centrum semiovale (Fig. 1a). Additionally, hyperintense signal alterations were located in the left hemisphere of the cerebellum and left paramedian central brainstem (pons). DWI demonstrated slightly increased diffusion in most of these regions, as well as in the cerebellum and brainstem (Fig. 1b). The ADC was elevated, demonstrating vasogenic edema (Fig. 1c). There was no enhancement of the lesions after administration of contrast agent. Cerebrospinal fluid contained 23 µl white cells (90% granulocytes), cerebrospinal fluid protein level was elevated (905 mg/l), and lactate (2.46 mmol/l) and albumin (573 mg/l) were slightly increased in terms of a reactive pleocytosis after the grand-mal seizures and epidural anesthesia for the caesarean section. Microbiological or viral involvement, especially aiming at Herpes (HSV), Varicella zoster (VZV), Epstein-Barr (EBV), and Cytomegalovirus (CMV) encephalitis were excluded. Vasculitis serology was also negative. The patient was treated with the anticonvulsant carbamazepine (Timonil retard®) and cabergolin (Dostinex®) for ablactation. The initial systemic heparinization was aborted after exclusion of intracranial sinus thrombosis, arterial stenosis, and cardiac embolism by using MRI, Doppler echocardiography and transthoracic echocardiography, respectively, and the patient was switched to low-dose heparinization ($2 \times 5{,}000$ IE). Blood pressure then returned to the normal range (130/85 mmHg). Follow-up cranial MRI 2 days later demonstrated respective regression of the supra- and infratentorial signal changes, in terms of reversible posterior leukoencephalopathy syndrome (Fig. 2a, b). Along with the patient's blood pressure returning to the normal range, the right-sided hemiparesis rapidly improved. On the third day of hospitalization the patient was transferred to the local hospital in complete clinical remission. A follow-up cranial MRI 3 months later demonstrated complete resolution of the pathological signal alterations (Fig. 3).

Discussion

RPL syndrome encompasses a spectrum of disorders, including pre-eclampsia, which is a condition of hypertension occurring during pregnancy, typically indicated by fluid retention and high blood pressure (5, 18). Other neurological findings include head-

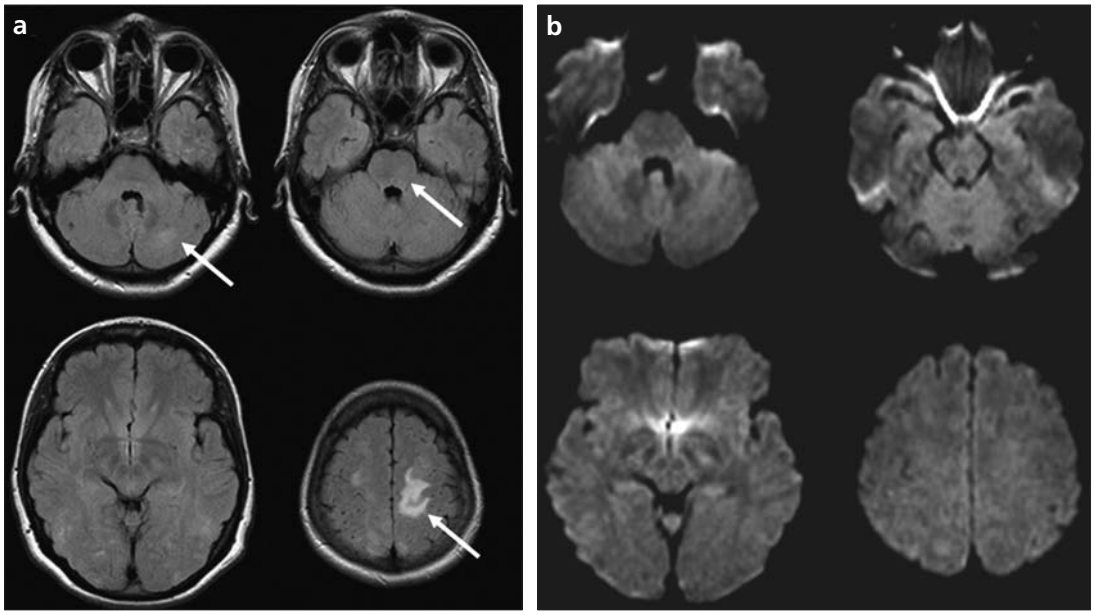


Figure 2. a, b. Two days after the initial MRI, repeat MRI demonstrates considerable regression of the multiple supra- and infratentorial hyperintense signal abnormalities on transverse FLAIR images **(a)** *(arrows)* and diffusion-weighted MRI **(b)**. Apparent diffusion coefficient map was normalized.

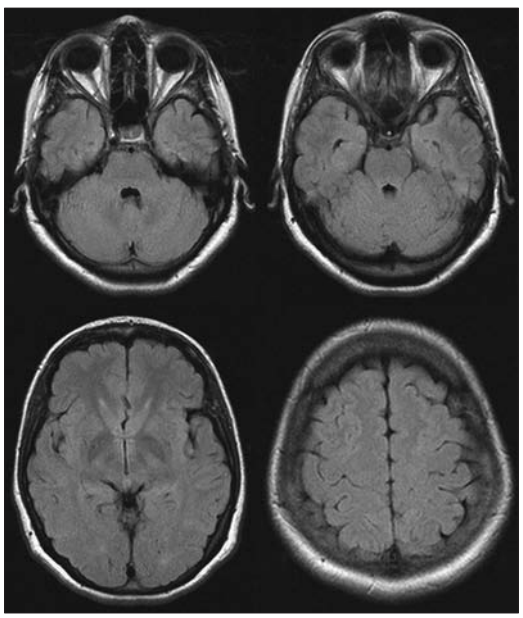


Figure 3. Follow-up MRI 3 months after treatment demonstrates complete resolution of the pathological signal alterations on transverse FLAIR images. Diffusion-weighted MR imaging and apparent diffusion coefficient mapping *(not shown)* revealed no pathological findings.

aches and loss of vision. In patients following organ or bone marrow transplantation, the differential diagnosis is often infective encephalitis. The characteristic distribution of lesions on MRI is often helpful in this regard (1, 7).

Two major hypotheses on the pathology of posterior leukoencephalopathy are currently discussed in the literature: the cytotoxic and the vasogenic theory (14, 18). The first hypothesis refers to a sudden increase in blood pressure, followed by cerebral vasoconstriction with cerebral ischemia and cytotoxic edema formation (12, 19–21). The second hypothesis relies on the conjecture that elevated blood pressure overcomes cerebral autoregulation, leading to cerebral vasodilatation and vasogenic cerebral edema (1–3, 17, 20).

Regarding these 2 hypotheses, it is important to differentiate between vasogenic and cytotoxic edema, due to different management strategies. Schneider et al. (4) suggests dividing the non-uniform pool of patients with RPL into 2 subgroups: patients with hypertensive encephalopathy and those with toxic encephalopathy. In patients who develop vasogenic edema, blood pressure reduction and supportive measures are the first-line treatment, while patients with cytotoxic edema and infarction need more aggressive approaches following treatment schedules from other etiologies, such as subarachnoidal hemorrhage with vasospasm.

Previously reported neuroimaging findings include reversible CT hypodensities and hyperintensities on T2W and FLAIR (1, 2) images. In this context, DWI, including quantification of ADC, is the imaging modality of choice. These new MR techniques describe the movement of water molecules using 2 metrics, mean diffusivity (MD) and fractional anisotropy (FA), which represent the magnitude and directionality of water diffusion, respectively. Cytotoxic edema is caused by acute ischemia and infarction, with subsequently decreased ADC through a reduction in the diffusibility of protons (22, 23). This elicits a bright signal on DWI and is believed to reflect increased intracellular and decreased extracellular fluid resulting from decreased Na^+ and K^+-ATPase activity. However, on DWI, vasogenic edema

can also be visualized as increased signal intensity (T2 shine-through effect) (24). Spillover effects of T2 and spin density on DWI account for this effect (25). Consequently, quantification of ADC (ADC mapping) is necessary to differentiate cytotoxic edema from vasogenic edema. High ADC values are consistent with highly mobile water in areas of vasogenic edema.

In our case, the hyperintense signal alterations on DWI did not show decreased ADC values, as would be expected in an ischemic brain with cytotoxic edema leading to irreversible brain damage. Therefore, the signal abnormalities on DWI represented vasogenic edema. These findings were consistent with the fact that the neurological impairment of our patient (right hemiparesis) rapidly improved over 24 h. Follow-up MRI demonstrated complete resolution of the diffusion and T2 signal abnormalities, confirming reversible vasogenic edema, owing to the fact that cytotoxic edema formation and infarction lead to irreversible brain defects or gliosis, and consequently result in permanent hyperintense signal alterations, for example, on FLAIR images (14, 18).

MRI changes in RPL have been shown to occur typically in the territory supplied by the posterior circulation, with anterior circulation abnormalities only seen in more severe cases (13, 26). This might be due to less sympathetic innervation of the vertebrobasilar posterior cerebral arteries in comparison to the anterior cerebral vasculature (2, 3, 17), leading to minor ability of the posterior brain to protect itself from an acute increase in blood pressure. Yet, there might be other abnormalities or imbalances in patients with only mildly elevated blood pressure that predispose to blood-brain barrier damage (17, 20). In the presented case, the anterior and posterior territory were involved, showing vasogenic edema in the frontal, temporal, and occipital lobes, and the brainstem (27). Synergistically, it might also interfere with the sympathic tone, leading to vasogenic edema at blood pressure levels that would usually be well tolerated (17). RPL occurs more commonly in puerperium or eclampsia, at a time when fluid accumulation might increase the tendency for cerebral edema to develop (1, 5).

RPL syndrome needs to be treated promptly, as any delay might result in permanent brain damage (12, 16, 17). Therapy involves the reduction of blood pressure, withdraw of possible triggering agents, and use of anticonvulsants in those with seizures. Seizures usually disappear once radiological abnormalities have resolved (14) and medication is no longer necessary. In the presented case, clinical and imaging follow-up demonstrated complete remission.

In conclusion, the exact pathophysiology of hypertensive encephalopathy in the non-uniform pool of patients with RPL is not completely understood. It is assumed to originate from a vasculopathy of the posterior circulation due to diminished adrenergic autoregulation in combination with a dysfunction of the endothelial cells (4). MRI is the modality of choice, not only to exclude differential diagnoses, such as infective encephalitis, sinus thrombosis, and cerebral ischemia, but with DWI and quantification of ADC in particularly, to further differentiate vasogenic from cytotoxic edema. This is mandatory to differentiate hypertensive encephalopathy from toxic encephalopathy, especially because of different prognoses and therapeutic approaches.

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