INTERNAL MEDICINE

□ CASE REPORT □

Posterior Reversible Encephalopathy Syndrome with Extensive Deep White Matter Lesions Including the Temporal Pole

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Abstract

Posterior reversible encephalopathy syndrome (PRES) typically affects the posterior subcortical white matter. We report the case of a 55-year-old man with atypical PRES, who had malignant hypertension and renal dysfunction. Magnetic resonance imaging of the brain revealed extensive vasogenic edema in the deep white matter including the temporal pole, as well as in the brainstem and cerebellum. Antihypertensive therapy and hemodialysis contributed to both clinical and radiological improvement. Involvement of the deep white matter including the temporal pole, which is rarely affected in an ischemic stroke, should be recognized as a potential sign of PRES.

Key words: posterior reversible encephalopathy syndrome, deep white matter, temporal pole, vasogenic edema, acute hypertensive nephrosclerosis

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Introduction

Posterior reversible encephalopathy syndrome (PRES) is an acute neurological disorder, which is typically reversible both clinically and radiologically (1). This clinical syndrome is commonly associated with severe hypertension, renal failure, autoimmune disorders, immunosuppressant therapy, and eclampsia. The common clinical manifestations include encephalopathy, seizures, headache, and visual disturbances. Brain magnetic resonance imaging (MRI) generally demonstrates vasogenic edema in the subcortical white matter and the cortex, which is typically confined to the posterior regions of cerebral hemispheres (1). We herein report an atypical case of PRES with reversible vasogenic edema in the deep white matter including the temporal pole, which is usually spared in an ischemic stroke (2).

Case Report

A 55-year-old man presented to our emergency department with a mild disturbance of consciousness. He had begun to make inadvertent mistakes at work three months before admission and had experienced a high degree of fatigue for the last month. On the day of admission, he was unable to stand up by himself and was brought to the hospital by his friend. He had had untreated hypertension (170/120 mmHg) for the last three years. He had a history of alcohol abuse, gastric ulcer, and a cleft lip palate. He had an unbalanced diet and had smoked 40 cigarettes a day for 25 years.

At admission, he was afebrile, and his blood pressure and pulse rate were 269/189 mmHg and 105 beats per minutes, respectively. He was mildly abstracted, had a disoriented perception of time, and it was difficult to communicate with him. A cranial nerve examination revealed no abnormalities, except for saccadic eye movement. The motor and sensory systems, including deep tendon reflexes, were unremarkable.

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He had an unstable gait due to cerebellar ataxia, and the findings for Romberg's sign were negative. The laboratory investigations revealed: hemoglobin, 12.8 g/dL; total leukocyte count, 14,050/mm^3; platelet count, 140,000/mm^3; serum creatinine, 8.43 mg/dL (0.3 mg/dL 3 years before admission); and urea nitrogen level, 106 mg/dL. He had mild hypokalemia (potassium, 3.0 mEq/L), and his renin (75 ng/mL·h; normal: 0.3-2.9) and aldosterone (1,930 pg/mL; normal: 35.7-240) levels were elevated, but the catecholamine levels were normal. He tested negative for autoantibodies, including antinuclear antibodies and anti-aquaporin 4 antibody. His antibody titers against herpes simplex virus and varicella-zoster virus were normal. He had macroscopic hematuria with no schizocyte. An arterial blood gas analysis showed: pH, 7.529; partial pressure of carbon dioxide (pCO_2), 28 mmHg; partial pressure of oxygen (pO_2), 108 mmHg; and HCO_3^-, 25.4 mmol/L. The findings from erebrospinal fluid test were normal. Based on the clinical picture of malignant hypertension with hypokalemia and hyperreninemia, he was diagnosed as having acute hypertensive nephrosclerosis with acute renal failure.

Brain computed tomography on admission revealed an extensive low-density area indicative of edema with swelling in the brainstem and cerebellum, and in the deep white matter (data not shown). Diffusion-weighted images (DWI)-MRI demonstrated mild hyperintensity (Fig. 1A-D), with an increased signal of an apparent diffusion coefficient (ADC) map of the brainstem, cerebellum, and deep white matter (Fig. 1E-H), which indicated vasogenic edema in these regions. Fluid-attenuated inversion recovery (FLAIR)-MRI showed increased signal intensity in the deep white matter including the temporal pole (Fig. 1I, K and L), as well as in the brainstem and cerebellum (Fig. 1I and J), with enlarged third and lateral ventricles (Fig. 1J). A spinal cord MRI was normal.

However, despite these remarkable MRI findings, his symptoms were relatively mild. Although the vasogenic edema in the deep white matter including the temporal pole was atypical, the involvement of the brainstem and cerebellum was compatible with a diagnosis of PRES. A provisional diagnosis of PRES caused by malignant hypertension with acute hypertensive nephrosclerosis was made. Antihypertensive therapy was initiated with continuous intravenous infusion of nicardipine; a subsequent oral treatment with amlodipine, enalapril, and carvedilol returned the blood pressure to the normal range. His consciousness completely improved over a few days, and signs of cerebellar ataxia gradually resolved. Because he developed oliguria after admission, hemodialysis was temporarily needed from Day 4. Renal biopsy revealed onion-skin thickening of the renal arteriolar walls (Fig. 2), which was consistent with the diagnosis of acute hypertensive nephrosclerosis. Magnetic resonance angiography of the brain showed no vascular stenosis (data not shown). FLAIR-MRI on Day 24 showed complete resolution of the vasogenic edema in the brainstem, cerebellum, and the temporal pole (Fig. 1M and N). The diffuse deep white matter abnormalities were significantly diminished (Fig. 1M, O and P) and further improvement of white matter signals was observed at 7 months (Fig. 1Q-T).

Discussion

The clinical and radiological manifestations of PRES were first described by Hinchey et al. in 1996 (3). The main symptoms and signs of PRES are encephalopathy (prevalence rate: 50-80%), seizures (60-75%), headache (50%), and visual disturbances (33%) (1). The brain MRI findings typically reveal reversible subcortical vasogenic edema located predominantly in the "posterior" circulation territories (4). Vasogenic edema in the "posterior" parietal or occipital lobe has been consistently reported, and an additional lesion is not uncommon in these cases. Although the pathophysiology of PRES is still not completely understood, rapidly developing hypertension is thought to impair the cerebral blood flow autoregulation, disrupt the blood-brain barrier, and cause hyperperfusion, resulting in vasogenic edema (1). In the normal physiological state, sympathetic activation induces cerebral vasoconstriction to protect the brain from severe hypertension. The posterior brain regions, however, are particularly susceptible to hyperperfusion, due to the relative lack of sympathetic innervation (1). Three major patterns of PRES have been noted in about 70% of patients (4): a holohemispheric watershed pattern (22.8%), a superior frontal sulcus pattern (27.2%), and a dominant parietal-occipital pattern (22.1%). However, atypical patterns have also been reported, including asymmetrical or unilateral lesions. Therefore, PRES may be associated with heterogeneous radiological signs.

The differential diagnoses of PRES include infectious or autoimmune encephalitis, malignancy, central nervous system (CNS) vasculitis, osmotic demyelination syndrome, and toxic leukoencephalopathy (1). In the present case, the reversible clinical and radiological manifestations with the underlying malignant hypertension and renal failure confirmed the diagnosis of PRES. His symptoms (disoriented sense of time and cerebellar ataxia) improved after the normalization of blood pressure even before the hemodialysis. Therefore, we believe that severe hypertension with acute hypertensive nephrosclerosis might have resulted in extreme hypertension and caused vasogenic edema.

Brain MRI on admission (Fig. 1A-L) demonstrated severe vasogenic edema in the deep white matter including the temporal pole, as well as in the brainstem and cerebellum. Although PRES typically involves the subcortical white matter including the U-fibers or the cortex, brainstem and cerebellar involvement has been reported in approximately 10% and 30% of cases, respectively (4). Although non-communicating hydrocephalus, possibly due to aqueductal stenosis via brainstem edema, may have affected the deep/periventricular white matter lesions (5), the hydrocephalus was too mild and temporary to cause such periventricular lesions. In the present case, the lesions in the periventricular

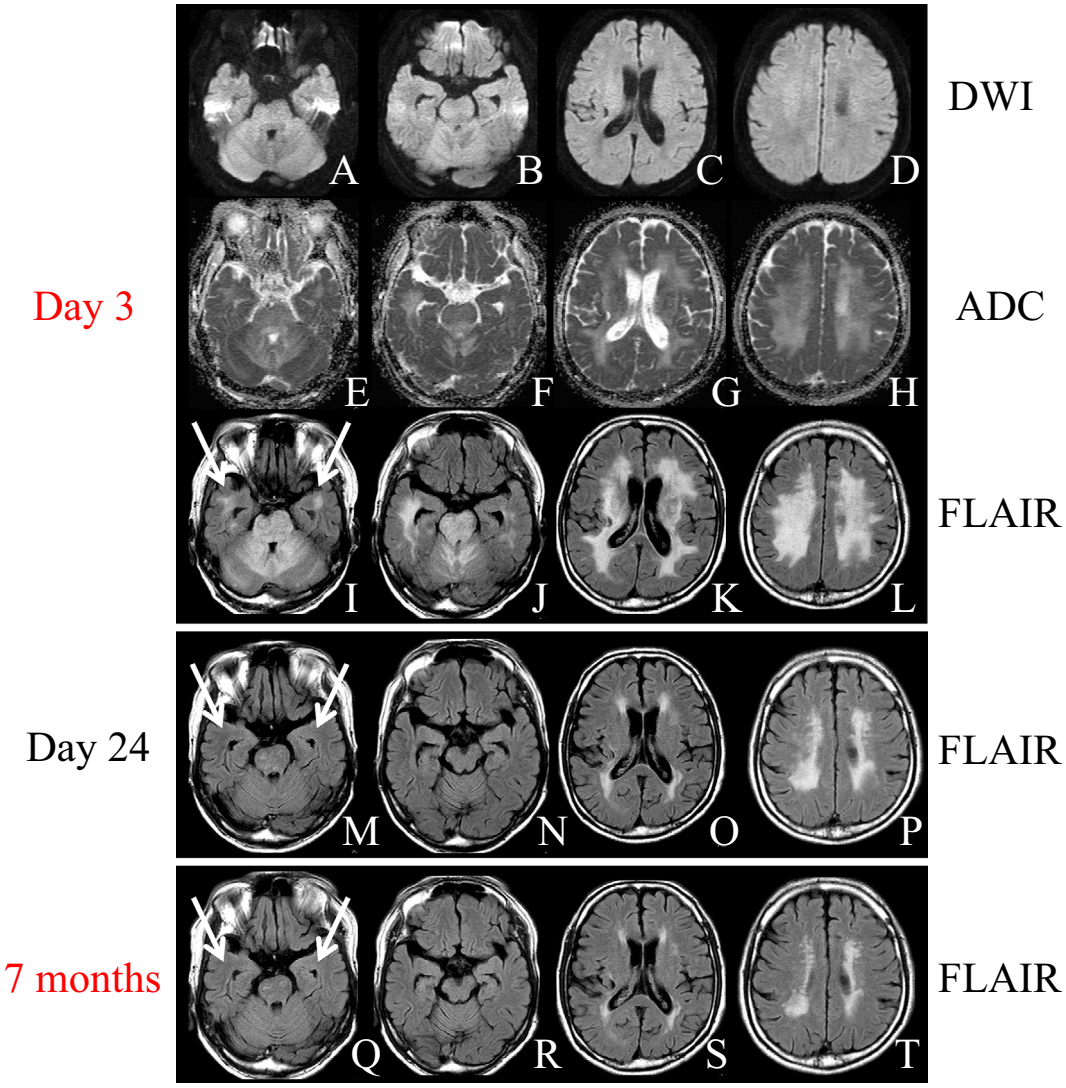

Figure 1. **The brain MRI axial sequences obtained on Day 3, Day 24, and 7 months after admission. DWI showed mild hyperintensity in the brainstem and cerebellum (A-D), and a modest hyperintense signal was observed in the affected areas on ADC mapping (E-H). FLAIR-MRI showed extensive hyperintensity of the infratentorial regions (I), not only in the brainstem and cerebellum (I, J) but also in the deep white matter (K, L) including the temporal pole (I; arrows). Neither the cortex nor the subcortical white matter was affected. The FLAIR image also demonstrated enlargement of the third ventricle and the inferior horn of lateral ventricles (J). FLAIR-MRI on Day 24 showed diminished brainstem and cerebellar edemas and resolution of hydrocephalus (M, N). Both the deep and temporal pole white matter abnormalities had also significantly improved (M; arrows, O, P). Follow-up MRI showed further improvement of the white matter signals at 7 months (Q-T).**

rim and cap, which were still present at 7 months after admission (Fig. 1S and T), might have been leukoaraiosis. Although deep white matter involvement had been reported in several cases of PRES, the vasogenic edema usually extends from the cortex or the subcortical white matter (4, 6). Our findings in the present case provide new insights into the vulnerable white matter regions in PRES, as the deep white matter was distinctively affected with no involvement of the cortex or the subcortical white matter including the U-fibers.

Li et al. reported two cases of PRES affecting the deep white matter but seemingly not the cortex or the subcortical white matter (7). One case was a 49-year-old man who presented with tonic-clonic seizures and postictal confusion. His initial blood pressure was 264/168 mmHg. Brain MRI revealed vasogenic edema in the deep white matter, pons, cerebellum, thalamus, and basal ganglia, all of which readily resolved with antihypertensive and antiepileptic therapy. The other case was a 50-year-old man who presented with headache, dizziness, and blurred vision. His initial blood pressure was 240/180 mmHg. FLAIR-MRI of the brain demonstrated confluent hyperintensity in the deep white matter. He showed remarkably rapid improvement, both clinically and radiologically, after antihypertensive therapy. Fugate et al. observed a mean peak systolic and diastolic blood pressure

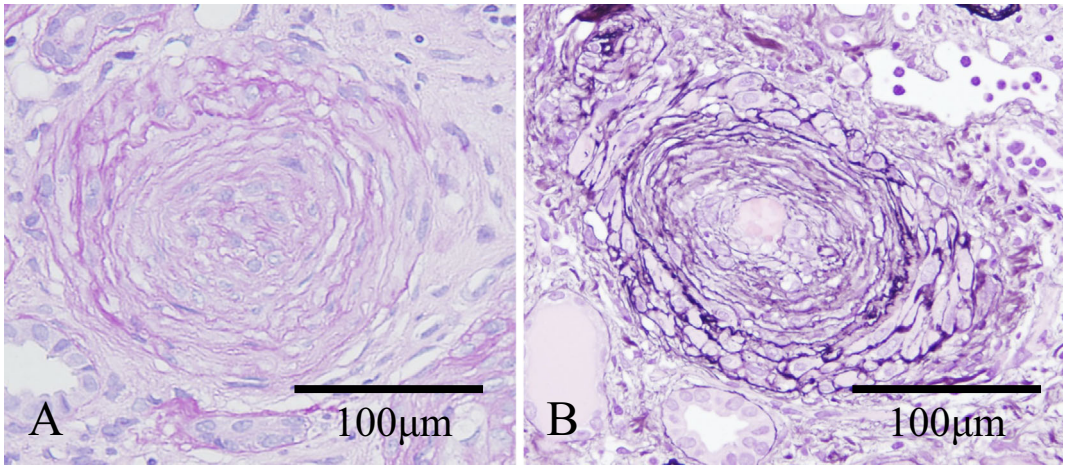

Figure 2. **PAS-stained (A) and PAM-stained (B) section of the renal biopsy specimen on Day 24 showing onion-skin thickening of the renal arteriolar walls. The scale bars indicate 100 μm. PAS: periodic acid-Schiff, PAM: periodic acid-methenamine silver**

of 191 mmHg and 104 mmHg, respectively, in 113 PRES cases (6). In comparison, the present case as well as the cases reported by Li et al. had extreme hypertension (systolic blood pressure >220 mmHg). A systolic blood pressure over 220 mmHg is generally accepted as extreme hypertension (8). No clear correlation has yet been identified between the vulnerable white matter lesions and the triggers of PRES (6). However, our observations suggest a potential correlation between extreme hypertension and the exclusive involvement of the deep white matter in PRES, although further accumulation of similar cases is needed to support this theory.

The deep white matter is fed mainly by the medullary arteries originating from the middle cerebral artery (MCA) (9). The region is typically associated with leukoaraiosis (10), which is caused by a chronic hypertensive state (11). Small vessels such as the medullary arteries are particularly vulnerable to impaired contractility under prolonged hypertensive conditions (12, 13). In addition, sympathetic innervation had been reported to be scarce in medullary arteries, similar to posterior brain regions (14). Extreme hypertension can exceed the threshold for sympathetic autoregulation of the MCA, and the lack of sympathetic innervation in the medullary arteries coupled with a reduction in the contractility may explain the vulnerability of the deep white matter to hyperperfusion. This hypothesis is supported by Li et al.'s and our cases, which show the involvement of the deep white matter in extreme hypertension-triggered PRES.

No previous study has reported the involvement of the temporal pole white matter in PRES, although the temporal lobe can be affected (6). The temporal pole white matter, which is included in the deep white matter, is also fed by the medullary arteries (15). Therefore, a similar mechanism of hyperperfusion may be suspected in the temporal pole white matter, which is usually spared in an ischemic stroke (2) and exclusively affected in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (16). The differential diagnosis includes cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) (17), myotonic dystrophy (18), neurosyphilis (19), and amyotrophic lateral sclerosis with dementia (20), but not PRES at present. However, based on our findings of the temporal pole white matter abnormalities in the present case, PRES should be considered in the radiological differential diagnosis of CADASIL.

In conclusion, we herein described an atypical case of PRES, with reversible vasogenic edema in the deep white matter including the temporal pole. It is important to recognize that PRES is a radiologically heterogeneous syndrome and such regions can be affected in PRES. In addition, PRES should be considered as a differential diagnosis of temporal pole white matter abnormalities, like CADASIL.

The authors state that they have no Conflict of Interest (COI).

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