Posterior Reversible Encephalopathy Syndrome in a Patient with Severe Uremia without Hypertension

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Abstract

A 28-year-old man was admitted to our hospital with nausea, headache and weakness of the left hand. He had severe uremia without hypertension due to recurrent/chronic pyelonephritis. Brain magnetic resonance imaging showed reversible vasogenic edema in the brainstem and bilateral frontal centrum semiovale. All of his neurological symptoms immediately improved after the introduction of hemodialysis. When a patient with uremia presents with neurological symptoms, posterior reversible encephalopathy syndrome should be considered in the differential diagnosis even if high blood pressure is not observed. Brain magnetic resonance imaging may be helpful in such a case, and an appropriate therapy could be subsequently initiated.

Key words: posterior reversible encephalopathy syndrome, normotension, uremic toxins, brain magnetic resonance imaging, hemodialysis, endothelial dysfunction

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Introduction

Uremia causes a variety of neurological disorders that affect the central nervous and peripheral nervous systems. Reversible posterior leukoencephalopathy syndrome (RPLS) (1), otherwise known as posterior reversible encephalopathy syndrome (PRES), is a frequently encountered disorder in uremic patients with hypertension. This syndrome is a clinical entity that is characterized by headaches, vomiting, confusion, seizures, cortical blindness and other visual disturbances, and motor signs. PRES also has characteristic radiological findings of focal reversible vasogenic edema, typically in the posterior regions of the cerebral hemispheres (2, 3). Although PRES is most commonly encountered in association with acute hypertension, other conditions have been identified as etiological or risk factors without hypertension. We herein report a rare case of PRES with severe uremia without hypertension in which brain magnetic resonance imaging (MRI) showed lesions in the brainstem and frontal white matter.

Case Report

A 28-year-old man was admitted to our hospital with worsening nausea, headache, and weakness of the left hand. He was in his usual state of health until approximately 1 week before admission. One day before admission, weakness in the left hand developed and gradually worsened. His medical history was remarkable. At 3 years of age, he suffered from a renal abscess and was diagnosed as having bilateral vesicoureteral reflux. He was occasionally treated in an outpatient clinic due to complaints of a fever, however, he had not received adequate medical management after 18 years of age. On a previous visit at our hospital for a cold at 23 years of age, moderate renal insufficiency was observed (serum creatinine, 2.40 mg/dL). He had a recurrent low-grade fever, however, he had not received a recent checkup at the hospital.

On this admission, the patient was obese (body mass index, 32.5). His blood pressure was 120/72 mmHg, pulse was 66 beats per minute, and temperature was 36.5°C. He was anemic, but not icteric. Bilateral pretibial edema was...
Figure 1. MRI on the first day of admission. T2-weighted images and T2-weighted FLAIR images show increased signal intensities in the brainstem (Panel A, B) and a hyperintense signal in the bilateral (right > left) frontal centrum semiovale (Panel C). Diffusion-weighted images (DWI) show a hypointense signal in the brainstem (Panel A, B) and a hyperintense signal in the bilateral (right > left) frontal centrum semiovale (Panel C). T1WI: T1-weighted image, T2WI: T2-weighted image, FLAIR: T2-weighted fluid-attenuated inversion recovery, DWI: Diffusion-weighted images

present. Manual muscle testing revealed 3/5 in the left arm, and paresthesia was detected in the left hand. All other components of the neurological examination were normal.

The urinary protein level was 195 mg/dL and the urinary sediment was 1-4 erythrocytes, with 1-4 leukocytes per high-power field. His hematocrit was 23.9%, hemoglobin concentration was 8.6 g/dL, platelet count was 140,000/mm³, and leukocyte count was 5,230/mm³. His serum urea nitrogen level was 171.4 mg/dL, creatinine was 15.01 mg/dL, uric acid was 9.7 mg/dL, cholesterol was 84 mg/dL, total protein was 6.1 g/dL, and albumin was 3.9 g/dL. His serum sodium level was 143 mEq/L, potassium was 5.2 mEq/L, chloride was 112 mmol/L, calcium was 4.3 mg/dL, phosphorus was 13.5 mg/dL, and magnesium was 1.8 mg/dL. An arterial blood gas analysis was performed in room air with the following findings: pH, 7.135; partial pressure of carbon dioxide in arterial blood (PaCO₂), 24.0 mmHg; partial pressure of arterial oxygen (PaO₂), 140.0 mmHg; HCO₃, 7.7 mmol/L; and oxygen saturation, 98.4%. His C-reactive protein level was 0.66 mg/dL, immunoglobulin (Ig) G was 798 mg/dL, IgA was 266 mg/dL, IgM was 108 mg/dL, ferritin was 546 ng/mL, brain natriuretic peptide was 52.5 pg/mL, and beta 2-microglobulin was 25.31 ng/mL. His intact serum parathyroid hormone level was 795 pg/mL. His serum HbA1c level was 5.3% and the serum glucose concentration was 149 mg/dL. His serum complement level was normal, and circulating immune complexes were negative. Hepatitis B virus surface antigen, hepatitis C virus antibody, human immunodeficiency virus (HIV) antibody, and antinuclear antibody were all negative. The cardiothoracic ratio was 51.0%. Renal ultrasound and computed tomography (CT) showed bilateral atrophic and uneven kidneys. Hypertension was not observed during his clinical course.

Brain MRI was performed on the first day of admission. T2-weighted images (T2WI) and T2-weighted fluid-attenuated inversion recovery (FLAIR) images showed increased signal intensities in the brainstem (pons and midbrain) and bilateral (right > left) frontal centrum semiovale. Diffusion-weighted images (DWI) demonstrated bilateral (right > left) hyperintense signals in the frontal centrum semiovale and a hypointensity in the brainstem (Fig. 1). An apparent diffusion coefficient map (ADC map) was not available. Acute cerebral infarction was considered as a tentative diagnosis, however, his clinical symptoms were relatively mild compared with the MRI findings. Low doses of aspirin without any other medications were administered. Because of his severe uremia, hemodialysis was immediately started on the 1st hospital day for 3 hours with a blood flow rate of 120 mL/min and a dialysate flow rate of 500 mL/min using a 1.1 m² triacetate hollow fiber dialyzer. He un-
derwent hemodialysis treatments for three consecutive days, and maintenance hemodialysis was subsequently performed three times a week. His symptoms, including nausea, fatigue, and muscle weakness of the left upper extremities, were immediately diminished. On the 6th hospital day, he was almost symptom free. Brain MRI on the 8th hospital day showed the disappearance of the increased signal intensities on T2WI and T2-FLAIR in the brainstem and a hyperintensity in the frontal white matter on DWI (Fig. 2-4). With hyperintensities on T2WI and T2-FLAIR, the hyperintensity in the frontal white matter on DWI at the 1st hospital day appeared to be T2-shine through caused by vasogenic edema. PRES was diagnosed according to the patient’s clinical course and these radiological findings. On the 24th hospital day, he was discharged on regular intermittent hemodialysis without any neurological symptoms. The MRI findings returned to normal on the 40th day (Fig. 2-4).

Discussion

In this study, PRES was diagnosed in a severe uremic patient without hypertension according to his clinical course and characteristic MRI findings. His neurological symptoms and abnormalities on brain MRI improved with hemodialysis.

RPLS was first described by Hinchey et al. (1). They reported 15 cases of RPLS with different triggers. RPLS was later renamed as PRES because of its greater accuracy. PRES has been described in association with severe hypertension, preeclampsia or eclampsia, cerebrovascular events, renal disease, sepsis, autoimmune conditions, organ transplantation, and less frequently, following the administration of immunosuppressive agents, cytotoxic drugs, anti-angiogenic agents, and monoclonal antibodies (2, 3).

The underlying pathophysiology of PRES remains unknown, however, two main hypotheses have been proposed. The most popular hypothesis is the disruption of the blood brain barrier secondary to abrupt hypertension. The alternative hypothesis is endothelial dysfunction with cerebral hypoperfusion due to circulating toxins in sepsis, immunosuppressive agents, and autoimmune disease. Under both hypotheses, cerebral blood perfusion abnormalities lead to cerebral vasogenic edema (4). Because PRES can affect normotensive patients, as in our case, endothelial dysfunction may represent a common pathway in the pathogenesis of PRES in a variety of etiologies.

In renal diseases, PRES has been reported in association with acute or chronic renal failure (5-7), glomerulonephritis (8, 9), nephrotic syndrome (10), lupus nephritis (11, 12), and antineutrophil cytoplasmic antibody-associated vasculitis (13). PRES has also been reported in patients with chronic renal failure undergoing peritoneal dialysis (14, 15), after blood transfusions (16), or following the discontinuation of antihypertensive agents (17). At the initiation of hemodialysis, a case of PRES associated with dialysis disequilibrium syndrome was also previously reported (18). Acute hypertension was associated with the majority of PRES cases, and the main cause of hypertension was acute.
Figure 3. Serial MRI at the level of the midbrain. On the 1st day, FLAIR shows an increased signal intensity (A). The increased signal intensity was not observed on FLAIR on the 8th (B) and 40th days (C). Decussation of the superior cerebellar peduncle is slightly hyperintense on DWI (D-F).

Figure 4. Serial MRI at the level of the centrum semiovale. On the 1st day, FLAIR and DWI show increased signal intensities in the bilateral (right > left) centrum semiovale (A, D). These signal abnormalities are decreased on FLAIR and DWI on the 8th day (B, E), and disappear completely on the 40th day (C, F).
or chronic renal failure.

However, systemic hypertension was not present in our case. Immunosuppressive agents, cytotoxic drugs, antiangiogenic agents, and monoclonal antibodies were not used in our patient, and no underlying disease was present, except for severe uremia due to recurrent/chronic pyelonephritis. All of the patient’s neurological symptoms immediately improved with hemodialysis therapy. Therefore, severe uremia was determined to be the major factor in the development of PRES.

Kadikoy et al. reported a case of recurrent uremia-induced PRES in lupus nephritis without hypertension (11). In their case, PRES-related symptoms resolved after the initiation of dialysis, similar to our case. In addition, Kurukumbi et al. described a normotensive case of PRES with untreated HIV dialysis, similar to our case. In addition, Kurukumbi et al. speculated that endothelial dysfunction associated with untreated HIV infection and end-stage renal disease caused PRES without hypertension (19).

Uremic encephalopathy is a neurological syndrome that occurs in patients with acute or chronic renal failure. Numerous metabolic complications associated with uremia are considered to cause neurological manifestations in end-stage renal failure. A large number of solutes may have direct neurotoxicity or contribute indirectly to the pathogenesis of uremic encephalopathy by altering the blood-brain barrier. Several uremic toxins, mostly protein bound, have been shown to have specific endothelial toxicity. These uremic toxins include asymmetrical dimethyl arginine, homocysteine, advanced glycation end products, and more recently, p-cresyl sulfate and indoxyl sulfate (20). Our patient had a high blood urea nitrogen level of 171 mg/dL on admission. Azotemia can cause cytotoxic edema when some nitrogenous waste products, specifically guanidine compounds, enter the brain parenchyma and activate neuronal N-methyl-D-aspartate receptors. This ultimately leads to excitotoxic cell death (21). Endothelial dysfunction is a prominent feature of chronic renal failure. Patients with end-stage renal failure have baseline endothelial dysfunction secondary to severe uremia (22). However, which uremic toxins cause PRES in patients with end-stage renal failure are difficult to determine.

The neurological symptoms associated with PRES are typically severe. In a previous study of PRES, the main clinical manifestations were consciousness impairment (94%) and seizure activity (81%) (23). Consciousness was often severely impaired, with a median Glasgow Coma Scale of 9 (range, 3-14) at admission to the intensive care unit (23). In contrast, the clinical symptoms of our patient were relatively mild. In cases with mild neurological findings, including focal signs, PRES complicated by uremia might be overlooked, or occasionally it may be misdiagnosed, such as cerebral infarction. When a uremic patient presents with mild nonspecific or vague neurological symptoms, PRES should be considered in the differential diagnosis.

PRES is radiologically characterized by abnormalities of white matter and grey matter, predominantly affecting the posterior regions. DWI shows increased diffusion in the affected regions, suggesting vasogenic edema in these areas. The preferential involvement of the parietal and occipital lobes is explained by sympathetic nervous system innervation of the posterior cerebral circulation (24, 25). Fugate et al. reported that the most commonly involved location in PRES was the parieto-occipital brain region (94%), followed by the frontal lobe (77%), the temporal lobe (64%), the cerebellum (53%), the basal ganglia (34%), and the brainstem (27%) (26). Brainstem lesions were not observed in normotensive patients in their series. Although our patient was normotensive, the lesion extended to the brainstem (the pons and midbrain) in addition to bilateral frontal lesions. Some studies have suggested correlations, such as greater vasogenic edema in normotensive patients and a trend for basal ganglia involvement, in patients with preeclampsia or eclampsia. However, PRES can present with a variety of imaging findings on CT and MRI without a clear relationship between the clinical conditions and specific imaging findings of the severity or location of edema (26, 27). Katano et al. reported that an ADC map is useful in the differential diagnosis of a brainstem variant of PRES from central pontine myelinolysis in a uremic patient with hyponatremia (28). There are two mechanisms whereby DWI can show hyperintensity: T2 shine-through or truly reduced apparent diffusion. These mechanisms can be differentiated with an ADC map (29). The correct diagnosis of PRES in our patient may have been possible with MRI on the 1st hospital day if an ADC map had been available.

In conclusion, we herein described a severe uremic patient with normal blood pressure complicated by PRES involving the brainstem and frontal white matter. All of his neurological symptoms immediately improved after undergoing hemodialysis. When a patient with severe uremia presents with neurological symptoms, PRES should be considered in the differential diagnosis, even if high blood pressure is not observed.

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

References


