Recurrent and atypical posterior reversible encephalopathy syndrome in a child with peritoneal dialysis

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Posterior reversible encephalopathy syndrome (PRES) is a clinical and radiologic entity characterized by headache, seizures, visual changes, altered mental status, and focal neurologic signs. Typically, PRES involves the parieto-occipital lobes; however, it can involve atypical localizations such as frontal lobe, basal ganglia, thalamus, brainstem, and gray matter. Sudden increases in blood pressure and associated renal failure are probably the most frequently encountered etiologies in the literature. Recurrence of PRES is not common. In this article, we present recurrent atypical PRES in a hypertensive child with end-stage renal disease on a peritoneal dialysis program as a rare case and we discuss recurrence. Infections and sudden increase in blood pressure were observed as the causes of recurrent PRES in our patient.

The reversibility of PRES depends on immediate diagnosis and therapy; therefore, it should be kept in mind in the differential diagnosis of seizures or coma in chronic kidney disease patients.

Key words: posterior reversible encephalopathy, hypertension, end-stage renal disease, peritoneal dialysis, recurrent.

Posterior reversible encephalopathy syndrome (PRES) is a clinical and radiologic entity characterized by headache, seizures, visual changes, altered mental status, and focal neurologic signs. The first definition of PRES dates back to 1996 by Hinchey et al.[1] Various terms have been used to describe this syndrome including hypertensive encephalopathy, reversible occipitoparietal encephalopathy, reversible posterior cerebral edema, or reversible posterior leukoencephalopathy[2,3]. Sudden increases in blood pressure, renal failure, eclampsia, and immunosuppressive therapy have been reported to be the major causes of PRES[1-6]. Magnetic resonance imaging (MRI) typically demonstrates vasogenic edema in the posterior (parieto-occipital lobes) white matter. Atypical manifestations of PRES, in which the main lesions are discovered in regions other than parieto-occipital lobes, have been reported[2-5,7]. Information about recurrent PRES is limited; however, infections and hypertension are presumed to be the causes of the development of new lesions in patients with recurrent PRES[4,8,9].

We present recurrent and atypical PRES in a patient with hypertension and end-stage renal disease (ESRD) on a peritoneal dialysis program as a rare case.

Case Report

An 11-year-old boy with ESRD on a peritoneal dialysis program was admitted to the emergency department with complaints of severe headache, agitation and left localized tonic-clonic seizure. The patient had no earlier seizure or hypertension. He was initially diagnosed as chronic renal failure because of congenital dysplastic kidney and vesicoureteral reflux at the age of two months. His glomerular filtration rate was 10 ml/min per 1.73 m^2 and he also had anemia and metabolic acidosis. He was started on continuous peritoneal dialysis at the age of three months.

He was receiving calcitriol, calcium phosphate, sodium hydrogen, iron, and darbepoetin alpha at admission. His blood pressure was 135/95 mmHg (>95 p), and physical examination was normal except for dental abscess. Funduscopy

was also normal and revealed no sign of papilledema or hypertensive retinopathy.

In his laboratory findings, the white blood cell count was 9300/μl, hemoglobin was 11.6 g/dl, and blood urea nitrogen, creatinine, calcium, and phosphorus concentrations were 155, 7.9, 6.5, and 7.9 mg/dl, respectively. His electroencephalography showed the slow rhythm of the background in EEG and brain computerized tomography showed right parietal hypointensive areas. MRI revealed low signal intensity on T1-weighted images and high signal intensities on axial FLAIR and T2-weighted images involving the cortical and partially subcortical regions of the bilateral temporo-occipital lobes, prominent at the right frontal, nucleus caudatus and splenium of the corpus callosum (Figs. 1A-C).

On the first day of hospitalization, the patient showed drowsiness and left localized tonic-clonic seizure. Anticonvulsive, antihypertensive and anti-edema treatments were started and peritoneal dialysis cycles were increased as per hour. Darbepoetin alpha treatment was stopped. On the second day of hospitalization, his body temperature rose to 38.5°C; therefore, lumbar puncture was performed and found normal. Third generation cephalosporin and acyclovir treatments were started. On the third day of hospitalization, he developed loss of vision and left-sided hemiplegia, which recovered three days after the therapy was instituted. Control MRI was completely normal after a month (Figs. 1D-F). He was investigated for end-organ damage by cardiac echocardiogram and had evidence of left ventricular hypertrophy.

The patient was again admitted to the emergency department with loss of vision and headache three months after the first attack. His blood pressure was high (160/100 mmHg) and his physical examination including funduscopy was normal. Altered consciousness was followed by a generalized seizure. His blood urea nitrogen and creatinine concentrations were high, and other laboratory parameters were normal. Nifedipine and enalapril were given for hypertension. His seizures were difficultly controlled with phenytoin, valproic acid and midazolam therapies. As the findings suggested recurrent PRES, anti-edema and antibiotic therapies were given again. Left-sided hemiplegia and fever of unknown etiology developed on the second day of hospitalization and disappeared the next day. Glucose-based peritoneal dialysis solutions with an increased dose were used to provide more ultrafiltration. MRI revealed high signal intensities on axial FLAIR T2-weighted images in the right occipital and posterior parietal region (Figs. 2A-C) and MRI was found normal after one month (Figs. 2D-F).

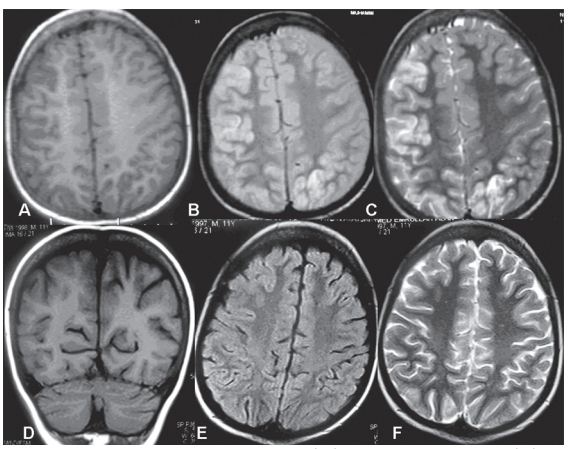

Figure 1. Axial T1-weighted **(A)**, proton density **(B)**, axial T2 **(C)**, coronal T1 **(D)**, axial FLAIR (E), and axial T2-weighted **(F)** MRI images revealed increased T2 signal at the cortical and subcortical region in the right frontoparietal and left occipital lobes (A-C). The lesions were completely resolved on follow-up MRI images obtained one month later on the initial exam (D-F).

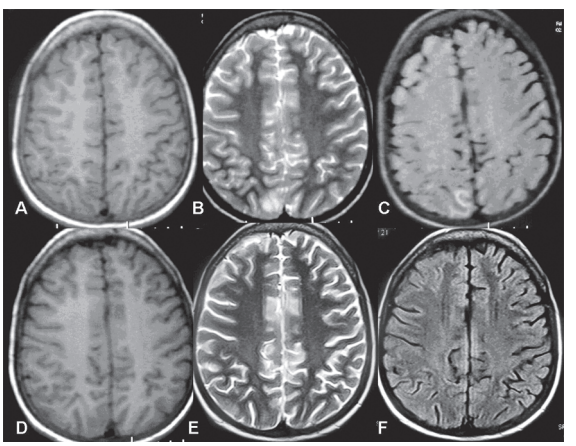

Figure 2. Initial axial T1-weighted **(A)**, T2-weighted **(B)**, and FLAIR **(C)** and follow-up axial T1-weighted **(D)**, T2-weighted **(E)**, and axial FLAIR **(F)** MRI show a focal cortical edema and hyperintensity on axial FLAIR T2-weighted images in the right occipital region (A-C). The lesion had disappeared on follow-up MRI (D-F).

Discussion

Posterior reversible encephalopathy syndrome clinically presents with seizures, severe headaches, cortical blindness and other visual abnormalities, altered mental status, and focal neurologic signs[1,2,4,5]. The cause of the PRES is multifactorial. Sudden increases in blood pressure and associated renal failure are probably the most frequently encountered etiologies in the literature[1,4]. Other reported causes of PRES include immunosuppressive (tacrolimus, cyclosporin A) and cytotoxic drugs, chemotherapeutic agents[2,6], oxybutynin, sickle cell disease, vasculitis (systemic lupus erythematosus [SLE], polyarteritis nodosa [PAN]), thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, porphyria, cryoglobulinemia, erythropoietin, hypercholesterolemia, hypomagnesemia[1], and hypercalcemia[10]. The main cause of PRES is acute elevation of blood pressure above the upper limit of cerebral blood flow autoregulation[6]. The uremia in ESRD has also been proposed as an independent triggering agent[4]. Patients with ESRD have a dysfunction in both vasopressor homeostasis and endothelial function related to elevations in lipoproteins, blood pressure, uremia, fluid overload, and drug therapies. Immunosuppressive and cytotoxic drugs may have a direct cytotoxic effect on vascular endothelial cells. Direct toxic effects on the vascular endothelium can cause damage to the blood-brain barrier[11]. Therapy with erythropoietin may contribute to hypertension and the development of hypertensive posterior leukoencephalopathy[12]. Erythropoietin administration, chronic renal failure, hypertension, and hypocalcemia were thought to contribute to the development of PRES in our patient's first attack. However, low-dose erythropoietin administration and normal blood calcium level during the second attack of PRES in our patient led us to suppose that chronic renal failure, infection and hypertension might trigger PRES.

Two main mechanisms have been suggested in the pathophysiology of PRES: first, cerebral vasospasm due to acutely increased blood pressure and second, loss of autoregulation. In the first hypothesis, it has been suggested that vasospasm contributes to ischemia and cytotoxic edema in regions of the arterial border zone. The second more recent hypothesis is supported by diffusion images suggesting that there is a temporary failure of autoregulatory capabilities of the cerebral vessels, leading to arteriolar vasodilatation, endothelial dysfunction and hyperperfusion, and breakdown of the blood-brain barrier, with red blood cell migration to the extravascular space from the intravascular space, producing vasogenic edema[4,6,9]. It occurs due to elevated blood pressure, which exceeds the autoregulatory capacity of the brain vasculature. PRES consists of reversible vasogenic edema in posterior circulation territories although conversion to irreversible cytotoxic edema has been described[2]. In our patient with ESRD, hypertension and darbepoetin therapy might have caused PRES due to dysfunction in both vasopressor homeostasis and endothelial dysfunction.

Magnetic resonance imaging findings are often very characteristic. The most common abnormality is edema involving the white matter in the posterior portion of the cerebral hemispheres, especially the bilateral parieto-occipital region[1,6]. The preferential involvement of the parietal and occipital lobes is thought to be related to the relatively poor sympathetic innervations of the posterior circulation[6]. The abnormalities affect primarily the white matter but the cortex is also involved[2]. The cerebral white matter is composed of myelinated-fiber tracts in a cellular matrix of glial cells, arterioles and capillaries, which make this region susceptible to the accumulation of fluid in the extracellular spaces[1]. Atypical manifestations of PRES in which the main lesions are discovered in regions other than parieto-occipital lobes, such as the frontal lobe, basal ganglia, thalamus, brainstem, and gray matter, are also reported[2-5,7]. The frontal, temporal lobe cortex and subcortical lesions and nucleus caudatus and thalamic involvements were the atypical lesions found in our patient, in contrast to the literature. Our patient with the typical findings of PRES had atypical manifestations according to MRI findings in his first attack but they were typical in the second attack.

When promptly recognized and treated, the symptoms and radiological and clinical abnormalities can completely resolve. However,

the lesions may not be reversible in all cases, and unrecognized patients can progress to ischemia and massive infarction with death[4]. This condition can cause neurological sequelae such as persistent brain damage and epilepsy, especially in those with hemorrhage on MRI arising from delays in diagnosis and therapy[9-13]. This syndrome should be recognized immediately and trigger agents can be discontinued to prevent long-term sequelae[11]. After symptomatic treatment of our patient, the clinical findings disappeared in one week and follow-up MRI was interpreted as normal after one month.

Of the limited cases of recurrent PRES in the literature, the underlying diseases were reported as SLE in two cases, sickle cell anemia in one case, bone marrow transplantation in one case[8], chronic hemodialysis related to ESRD in one case[9], and peritoneal dialysis related to ESRD in children[5]. We found only one published study in our country about recurrent and atypical PRES in a child with peritoneal dialysis[5]. In a large cohort study about PRES in children with renal disease, two of the 18 patients had recurrent PRES episodes, both of whom were anephric, one due to bilateral malignancies of the kidney and the other due to steroid-resistant nephrotic syndrome[4]. Five of the six episodes were due to hypertension and one case was triggered by catheter-related bacteremia[4]. In recurrent PRES, factors considered to trigger the development of new lesions were infection and hypertension[4,8,9]. Infections and sudden increase in blood pressure were observed as the causes of recurrent PRES in our patient.

When seizures and neurologic findings are seen in patients with ESRD, PRES should be considered, and MRI investigation and supporting therapy should be started immediately.

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