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Case Report

A Case of Posterior Reversible Encephalopathy Syndrome in a Girl with Nephrotic Syndrome

Min Ji Kim[1], M.D., Hoyeon Hwang[1], M.D., Yu Jin Jung[1], M.D., Jung Hyun Lee[1], M.D., Jae Sun Park[1], M.D. Kyung Soon Jeong[2], M.D.

[1]Department of Pediatrics, [2]Department of Radiology, Kosin University College of Medicine, Busan, Korea

A 12-year-old girl with nephrotic syndrome was admitted to Kosin University Gospel Hospital because of progressive generalized edema and weight gain for the last one month. From the eighth day of admission, she developed headache and generalized tonic seizures. Magnetic resonance imaging (MRI) of the brain showed multiple T2-high signal intensity lesions in the bilateral posterior parieto-occipital cortex and subcortical white matter. The convulsions responded to anticonvulsant and antihypertensive drugs but recurred again until she developed massive diuresis and became normotensive. Follow-up brain MRI 5 days later showed complete resolution of the previous abnormal lesions. The cause of Posterior Reversible Encephalopathy Syndrome (PRES) in our case remains unclear. Blood pressure has been only moderately elevated when the patient became symptomatic. Here, we report a case of minimal change nephrotic syndrome complicated by PRES with a literature review.

Key Words: Hypertension, Nephrotic syndrome, Posterior leukoencephalopathy syndrome Introduction

Posterior reversible encephalopathy syndrome (PRES) is a relatively new clinicoradiological entity of heterogenic etiologies that was described as reversible posterior leukoencephalopathy syndrome in 1996.[1] Since then, there have been various reports of PRES in a variety of clinical settings. The classic neuro-imaging findings in PRES patients include edema involving the white matter in the posterior portions of the cerebral hemispheres, especially bilaterally in the parieto-occipital regions. Though there are several case reports of PRES in a patient with minimal change disease, the exact incidence of the PRES developing in mimimal change nephrotic diseases remains obscure. If imaging studies were not used, some of the patients with PRES could not be noticed when their symptoms are subtle or milder. According to the study by Prasad et al,[2] there was no case having minimal change nephrotic syndrome (MCNS) among 19 children with MRI confirmed PRES. There are several reports of PRES developed in Korean children during the cancer treatment or cyclosporine therapy,[3,4] however, repots of PRES in MCNS is uncommon.

CASE REPORT

A 12-year-old girl was admitted to ward from the emergency room because of progressive generalized edema and severe weight gain during the last month. The patient's weight at admission was 64 kg, which had been increased from the 50 kg (75-90 percentile) prior to her illness, and her height was 157 cm (75-90 percentile). On admission, her vital signs were as follows; body temperature 37.7℃, pulse 76 beats/min, respirations 20/min, and blood pressure (BP) 130/80

Corresponding Author: Jae Sun Park, Department of Pediatrics, Kosin University Gospel Hospital, 34 Amnam-dong, Seo-gu, Busan 602-702, Korea
TEL: 051) 990-6230 FAX: 051) 990-3005 E-mail: pjs@ns.kosinmed.or.kr

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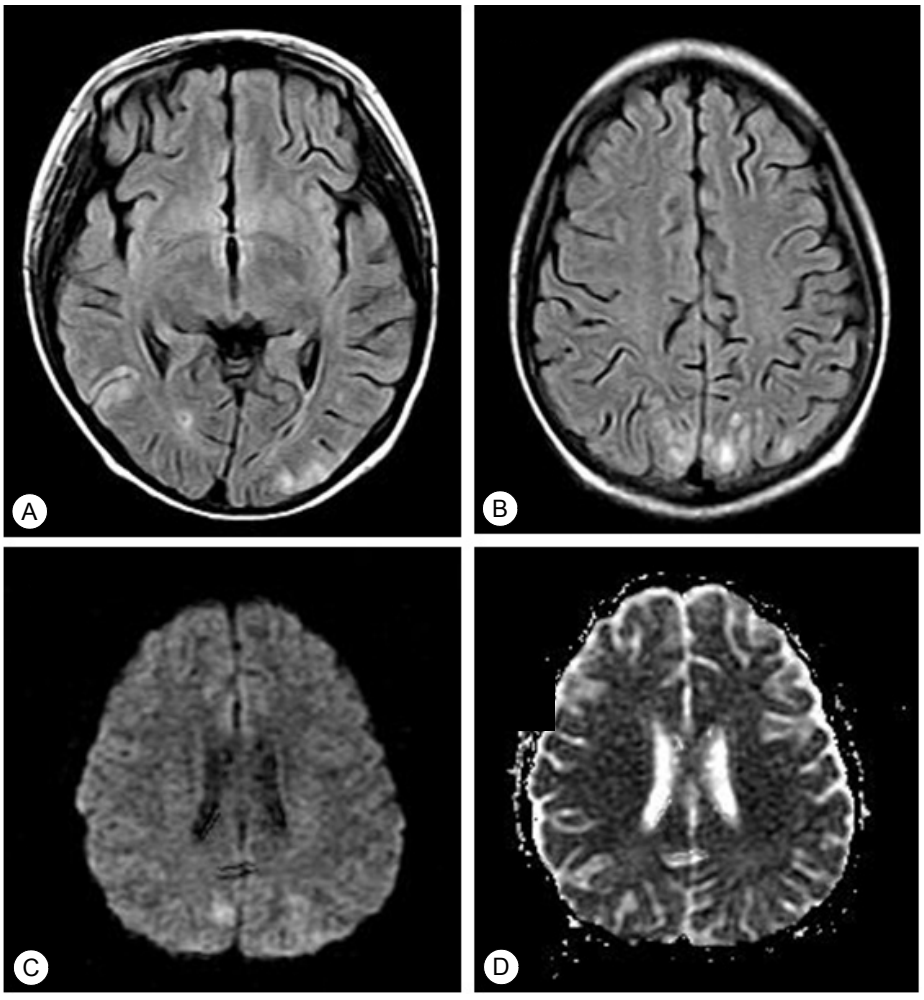

Fig. 1. Fluid attenuated inversion recovery brain magnetic resonance imaging (MRI) showed multifocal cortical and subcortical hyperintense lesions at the bilateral posterior parietal and occipital lobes (A, B). Axial diffusion- weighted MRI (C) showed bright signal intensities on the same area with no change in apparent diffusion coefficient (D).

mmHg. Laboratory test results on the first day were as follows: white blood cell count 6,700/mm^3 with 69% neutrophils and 24% lymphocytes, hemoglobin 9.4 g/L, platelet count 265,000/mm^3, ESR 41 mm/hr, blood urea nitrogen 59 mg/dL, creatinine 3.8 mg/dL, total protein 3.2 g/dL, albumin 2.0 g/dL, total cholesterol 571 mg/dL, triglyceride 672 mg/dL, serum complement 3 69.8 mg/dL (reference range, 82-170 mg/dL), urine SG 1.025, urine protein 3+, urine RBC 11-15/HPF, and 24-hour urine protein excretion more than 2 g/day in a specimen of 700 mL. Her serum sodium was 136 mEq/L, potassium 3.8 mEq/L, calcium 6.9 mg/dL, phosphorus 6.1 mg/dL, magnesium 2.6 mg/dL, HBsAg negative, and anti-HBs positive. Chest x-ray showed bilateral effusions with dominant left side. An ultrasonogram of the kidney showed increased echo texture without abnormal mass or stone.

Under the diagnosis of nephrotic syndrome with acute renal failure, prednisolone (60 mg/day/ divided 4 times) was initiated from the first day with daily use of 100 mL of 20% albumin and furosemide (40 mg/day divided 2 times). On the 8th, 9th and 11th day of admission, she developed multiple generalized tonic seizures and her BP were in the range of

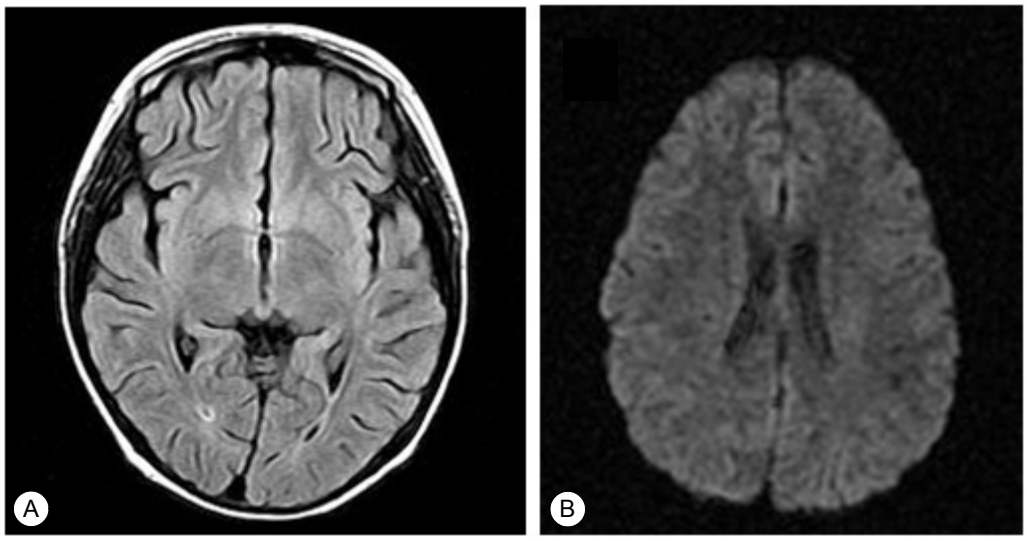

Fig. 2. Follow up fluid attenuated inversion recovery magnetic resonance imaging (MRI) 5 days later showed resolution of the previous lesions (A), and on diffusion-weighted MRI (B).

130-140/80-100 mmHg. Intravenous diazepam and oral angiotensin converting enzyme inhibitor (enalarpril) were administered during each episode with response. On the 9th hospital day, her 24-hr urine output increased up to 1,200 mL and serum creatinine normalized to 0.92 mg/dL. The serum concentrations of protein and albumin, however, remained at low levels of 3.7 g/dL and 2.1 g/dL, respectively. Brain MRI performed on the 12th hospital day demonstrated multifocal cortical and subcortical hyperintense signals in the bilateral posterior parietal and occipital lobes on T2 weighted FLAIR magnetic resonance imaging, suggestive of PRES (Fig. 1). Enalarpril was administered 30 mg/day until hypertension was resolved and maintained 5 mg /day for several weeks. The patient was usually responded to questions and alert after and between the seizures. Her blood pressure continued to be equal or lower than 110/70 mmHg after the 20th hospital day. Follow-up MR images five days later (on the 17th hospital day) revealed complete resolution of the lesions (Fig. 2). Ultrasonogram of the carotid arteries showed no stenotic flow. Clinical course of the patient around the development and resolution of PRES was shown with regard to changes of body weight, blood pressure and urine output. Some of the clinical indices around the time of the seizures and PRES were depicted (Fig. 3).

From the 17th hospital day, her clinical course was stabilized with improvement of edema and absence of seizure. Her laboratory findings at the time of 1 month therapy were as follows; blood urea nitrogen 5.8 mg/dL, creatinine 0.68 mg/dL, total protein 6.7 g/dL, albumin 3.9 g/dL, total cholesterol 419 mg/dL, and complement 3,156 mg/dL. Spot urine protein showed 3 to 2+ for the first two months but became 1+ or trace thereafter.

Because of her mildly decreased initial serum complement 3 (69.8 mg/dL), though normalized later, percutaneous kidney biopsy was done on the 21th hospital day. Biopsy showed 12 glomeruli, none of which had global sclerosis or an increase in the mesangial matrix. Immunofluorescence study of four glomeruli stained with antisera for IgG, IgA, IgM, C3,

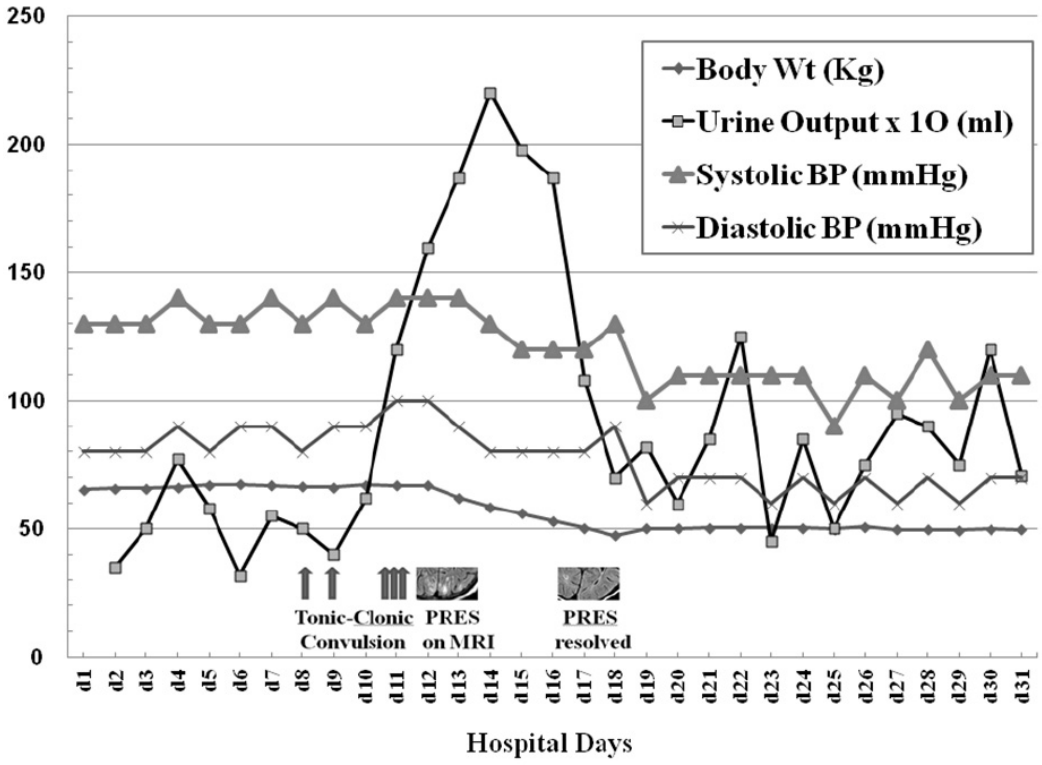

Fig. 3. Changes of body weight, blood pressure, and urine output of the patient before and after the event of posterior reversible encephalopathy syndrome (PRES). Cerebral hemodynamic changes related to nephrotic state appears to be involved in the development and resolution of PRES.

C4, and fibrinogen showed no deposits. Electron microscopy results were normal except for a few effacements of the foot processes of the glomerular visceral epithelial cells (podocytes) between 5 to 10 %. These findings were compatible with a minimal change disease. After one month of full dose of prednisolone and succeeding four months of alternate day therapy of prednisolone with low dose of enalapril (5 mg daily), she could be off all drugs for the next 15 months with no sign of the disease.

DISCUSSION

In 1996, Hinchey et al. initially described a clinico-radiological syndrome characterized by bilateral, reversible, symmetric and vasogenic edema, attributable to a variety of different etiologies.[1] While, the term "posterior reversible encephalopathy syndrome (PRES)" has been most commonly used, "hyperperfusion encephalopathy" and "brain capillary leak syndrome" are also used. The term, PRES, describes a potentially reversible imaging appearance and symptomatology that presents in patients with nephrotic syndrome, lupus nephritis, hypertension, eclampsia, immunosuppressive drugs, cytotoxic chemotherapy for hematologic malignancies, Henoch-Schönlein purpura, and hemolytic uremic syndrome.[3-7] The most common clinical symptoms are seizures, headaches and visual disturbances such as blurred vision and cortical blindness. Other common symptoms are altered alertness, vomiting, mental abnormalities including confusion, diminished spontaneity, and speech disorders.[6,7]

The pathophysiology of PRES is unclear. However,

failure in cerebral autoregulation has been suggested.[5] Normal autoregulation maintains constant cerebral blood flow over the range of systemic BP by arteriolar constriction and dilatation. If an acute increase in blood pressure overrides the autoregulation of cerebral mean arterial pressure, this may lead to vasodilatation and brain hyperperfusion. Another mechanism proposed is a direct toxic effect on the endothelial cells of the cerebral vasculature that results in endothelial dysfunction. This may occur in normotensive individuals with nontoxic levels of the drugs. Whether the pathophysiologic mechanism of the PRES is autoregulation disorder or direct toxic endothelial damage, the end result is breakdown of the blood brain barrier, and the diffusion of plasma proteins and cells into the extracellular space, and subsequent cerebral edema. A combination of acute hypertension and endothelial damage results in hydrostatic edema, a type of vasogenic edema, characterized by forced leakage of serum through capillary walls and into the brain interstitium.[8]

The exact cause of seizures and PRES in our case remains unknown. But, factors related to nephrotic state, such as severe generalized edema, use of steroid and hypertension, all these might have been served for a development of PRES. It has been suggested that associated intracranial hemorrhage is present in approximately 5% to 17% of cases of PRES. Considering the normal brain CT findings, the rapid improvement in clinical symptoms, MRI with angiographic images, and normal carotid artery ultrasonogram, the underlying causes of the present case appear to be brain edema rather than parenchymal hemorrhage.

The most characteristic imaging pattern in PRES is the presence of edema involving the white matter in the posterior portions of both cerebral hemispheres, especially in the parieto-occipital regions. The predilection sites are followed by the frontal lobes, the inferior temporal occipital junctions and the cerebellum, in a relatively symmetric pattern, sparing the calcarine and paramedian parts of the occipital lobes.[5,9] Although the abnormality primarily affects the subcortical white matter, the cortex and the basal ganglia may also be involved. In our case, multiple lesions were seen along the posterior parietal, occipital cortex and subcortical white matter, which is typical, but focal lesions seen around the calcarine and paramedian occipital lobe appeared to be somewhat uncommon findings. MRI with contrast and diffusion-weighted magnetic images (DWIs) usually helps to differentiate cytotoxic edema (e.g., stroke) from vasogenic edema (e.g., PRES). Regions with cytotoxic edema show diffusion coefficients that are restricted (true restricted diffusion) compared with those of white matter, whereas regions with vasogenic edema demonstrate apparent diffusion coefficients (ADCs) that are increased compared with those of normal white matter.[9] In our case, bright signal intensities are seen on diffusion-weighted images, with no definite decrease in ADC. This finding is suggestive of vasogenic edema probably due to cerebovascular autoregulatory dysfunction.

As PRES presents in diverse clinical settings, it is important to recognize the characteristics of PRES, and to manage the inciting conditions. All the patients with risk factors of PRES, such as nephrotic syndrome, hypertension and renal dysfunction should be suspected of being affected with PRES if they experience a sudden episode of neurological symptoms. BP should be controlled with anti-hypertensive agents. The goal of a mean arterial BP between 105

and 125 mmHg has been proposed.[10] Our case, in which the patient's blood pressure continued to be mildly high and convulsions lasted in spite of diuretics and anticonvulsants, cast the doubt that whether more intensive treatment of hypertension even with mild degree might have been effective for a prevention of the PRES. Although this condition is usually transient and completely reversible, ischemic injury and irreversible damage have been reported.[2,4] Delayed diagnosis and treatment may lead to white matter edema that can evolve into cerebral infarction, hemorrhage, leukomalacia or sequelae such as focal epilepsy and cognitive impairment in children. A better understanding of this syndrome may allow management of associated problems in prompt and appropriate ways.

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