조절되지 않는 신증후군 환아에서 대뇌 출혈 및 확산 강조 영상에서의 제한을 동반한 후두부 가역적 뇌병증 증후군 1예

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Posterior Reversible Encephalopathy Syndrome Accompanied by a Cerebral Hemorrhage and Restricted Diffusion in a Child with Uncontrolled Nephrotic Syndrome

Posterior reversible encephalopathy syndrome (PRES) is a rare clinico-radiological syndrome that is characterized by an acute onset of headache, vomiting, visual abnormalities, confusion, and/or seizures and is typically accompanied with edema of predominantly posterior portions of the cerebral hemispheres. Here, we report a case of PRES with cerebral hemorrhage that occurred in a female pediatric patient with uncontrolled nephrotic syndrome. The patient's magnetic resonance imaging (MRI) studies showed asymmetric white matter abnormalities, cerebral hemorrhage, and restricted diffusion. After controlling her hypertension and nephrotic syndrome, her neurologic symptoms improved, and follow-up MRI findings revealed interval resolving of the white matter lesions.

Key Words: Posterior reversible encephalopathy syndrome, Nephrotic syndrome, Cerebral hemorrhage, Diffusion magnetic resonance imaging

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Introduction

Posterior reversible encephalopathy syndrome (PRES) is a rare clinico-radiological syndrome of the central nervous system, which was first described by Hinchey et al in 1996¹. It is characterized by acute onset of headache, vomiting, visual abnormalities, confusion, and/or seizures, along with radiological findings of posterior white matter edema of the brain. PRES can occur in various clinical situations, including hypertension, renal diseases, immunosuppressant drug use, chemotherapy, or autoimmune diseases². The typical findings of radiologic images are bilaterally symmetrical vasogenic edema involving the white matters of both parieto-occipital regions. In some cases, atypical radiological findings have been reported, such as unusually distributed findings of cerebral edema and rarely, hemorrhage or infarction³. Here, we present a case of PRES with cerebral hemorrhage and restricted diffusion in a 7-year-old girl with uncontrolled nephrotic syndrome.

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Case report

A 7-year-old girl came to the emergency department with symptoms of visual disturbance, headache, fever, and mental change beginning the day before the visit. 1 year ago, she was diagnosed with nephrotic syndrome, and treated with prednisolone. Her disease was frequently relapsed, and cyclosporine A was added 5 months later. Her blood pressure (BP) was within normal range and no neurologic symptoms were observed. Due to her uncontrolled nephrotic syndrome, renal biopsy was done, showed minimal change disease (MCD).

3 months ago before the admission, her treatment was stopped at her parents' refusal, and until recently, she had been treated with alternative medicine. She had no history of other underlying diseases, recent head trauma, and no familial diseases including cardiovascular, renal, or autoimmune diseases.

She had a body temperature of 37.1°C, BP of 150/122 mmHg, pulse rate of 121/min, and respiratory rate of 30/min. Her mental status was drowsy, and her Glasgow coma scale score was 11. A neurological examination showed normal pupillary light reflex, but tests for the other cranial nerve and cerebellar function were not available because of non-cooperation. Motor and sensory

function was intact, and there was no pathologic responses such as rigidity, tremor, and Babinski sign. Her body weight was 43 kg on admission, which had been increased from 24 kg, previously checked 3 months ago. There was severe generalized edema of the whole body, including swelling of face, such that she could not open her eyes, and heavy ascites, such that she could not stand up.

Following laboratory evaluation, the test results were as follows: white blood cell (WBC) count of 17,890/mm³, hemoglobin of 8.1 g/dL, platelet count of 671,000/mm³, erythrocyte sedimentation rate (ESR) of 25 mm/hr. Her blood urea nitrogen was 35.8 mg/dL, creatinine 1.01 mg/dL, total protein 3.8 g/dL, albumin 1.2 g/dL, and total cholesterol 592 mg/dL. Her serum sodium was 132 mEq/L, potassium 4.3 mEq/L, calcium 7.4 mg/dL, phosphorus 5.8 mg/dL. In urine analysis, specific gravity was 1.026, red blood cell (RBC) count of more than 50 per high power field (HPF), WBC count of 10-19 per HPF, and protein/creatinine ratio was 13.5. Coagulation tests which including prothrombin time, activated partial thromboplastin time were within the normal range. Venous blood gas analysis demonstrated pH 6.97, HCO₃⁻ 8.7 mmol/L, base excess -23 mmol/L, and pCO₂ 38 mmHg.

Under the impression of uncontrolled nephrotic syndrome

Fig. 1. Brain MRI demonstrated a bilateral, asymmetric parieto-occipital high signal intensity lesion with cerebral hemorrhage in the left occipital lobe on T2-weighted images (A, B) and FLAIR (C, D) images with subcutaneous edema. DWI (E) and ADC map (F) showed increased signal intensities overall, but there is also a posterior diffusion restricted area in ADC map.

with acute kidney injury, hypertension, metabolic acidosis and sepsis, intravenous nicardipine (0.5 mcg/kg/min) and cefotaxime (75 mg/kg/day) were initiated. Intravenous albumin (0.5 mg/kg), continuous furosemide (0.05 mg/kg/hr), sodium bicarbonate and RBC transfusion were administered to correct fluid and metabolic imbalance. Total fluid intake was calculated based on insensible water loss, and fluid balance target per day was negative 2,000 mL/day.

On the second day of admission, her mental state and generalized edema demonstrated no improvement. Severe dyspnea due to pulmonary edema occurred, so endotracheal intubation was completed and mechanical ventilator care was started. Cerebral magnetic resonance imaging (MRI) T2/FLAIR (Fluid-attenuated inversion recovery) demonstrated a bilateral, asymmetric parieto-occipital high signal intensity lesions, involving the cortex and subcortical white matters. Furthermore, there were diffusion restriction areas in the parieto-occipital lobe on diffusion weighted images (DWI), and an internal hemorrhage in the left occipital lobe in T2 images, suggesting PRES with cerebral hemorrhage and restricted diffusion (Fig. 1). Her electroencephalogram was normal. There was no evidence of vein thrombosis or stenotic flow in neck ultrasonogram.

On the third day of hospitalization, her respiratory functions were recovered and she was extubated. BP dropped suddenly

lower to 75/57 mmHg, but normalized 1 hour after normal saline bolus injection and intravenous nicardipine was stopped. In follow up lab findings, metabolic acidosis improved and serum electrolytes were within normal range. On the fourth day of admission, hypertension occurred transiently up to 178/123

Fig. 3. MRA shows no vasculature anomaly or significant variations.

Fig. 2. Follow-up MRI shows interval resolving of the bilateral parieto-occipital lobe lesion and a newly developed subdural hemorrhage in the left cerebral convexity in T1 (A, B), T2-weighted images (C, D), and FLAIR (E, F) images. DWI (G) and ADC map (H) still present high signal intensities in the posterior portion of the brain.

mmHg, so intravenous nicardipine was started again.

On the fifth day of admission, her consciousness and vision were markedly improved and there was nothing grown in her blood, ascites, urine cultures. On the 18th day after admission, a follow-up MRI showed interval resolving of the bilateral parieto-occipital lobe lesion and a newly developed subdural hemorrhage in the left cerebral convexity (Fig. 2); her MR angiogram (MRA) demonstrated no vasculature anomaly or significant variations (Fig. 3). There were no newly generated neurologic symptoms. On the 57th hospital day, the patient was discharged with an alert mental state with incomplete remission of her underlying nephrotic syndrome. Last laboratory test results were as follows: WBC count of 16,170/mm³, hemoglobin of 10.2 g/dL, platelet count of 496,000/mm³. Her blood urea nitrogen was 14.2 mg/dL, creatinine 0.15 mg/dL, total protein 3.8 g/dL, albumin 2.1 g/dL, and total cholesterol 922 mg/dL. Her serum sodium was 135 mEq/L, potassium 4.2 mEq/L. Her urine protein/creatinine ratio right before discharge was 19.1, and she still showed mild edema and ascites. The last body weight was 27.5kg, which is 15.5kg less than the first. She visits the outpatient clinic and is taking prednisolone (36mg every other day), tacrolimus(0.5mg/kg/day), amiloride, amlodipine, and pravastatin. Follow-up MRI was not performed due to parental rejection.

Discussion

PRES, which was first described by Hinchey et al in 1996¹⁾, is characterized by headache, altered mental functioning, seizures, or loss of vision and is associated with edema of the predominantly posterior portions of the cerebral hemispheres. The pathophysiology of PRES is still unclear, but the failure of cerebral autoregulation by acute increase in cerebral blood flow or cerebral hypoperfusion, have been suggested⁴⁾. However, regardless of the exact causes, both theories lead to cerebral vasogenic edema due to the breakdown of the blood-brain barrier. PRES is known to be caused by hypertension, renal diseases, autoimmune diseases, chemotherapy, and use of immunosuppressant drugs in the pediatric population as well as in adults^{2,5)}. Our patient had uncontrolled nephrotic syndrome and high blood pressure, and the combined complexity of these medical conditions appears to have caused PRES. Interestingly, her initial mean arterial pressure (MAP) was 131 mmHg, which is inadequate to overcome the cerebral autoregulatory mechanism. The cerebral autoregulatory mechanism is reported to be disturbed when the MAP is greater than 170 mmHg⁶⁾.

However, there are several reports that nephrotic syndrome accompanying hypertension can lead to the development of PRES in children^{7,8)}. The presence of nephrotic syndrome may increase the risk of developing PRES due to low albumin levels, severe generalized edema, high vascular permeability, and unstable fluid balance⁸⁾.

In the diagnosis of PRES, brain MRI is the imaging study of choice. The classical findings of PRES are hyperintensity on T2-weighted and T2-weighted FLAIR images in the posterior parietal and occipital lobes³⁾, respectively. Because these findings on MR image can be also seen in cases of acute cerebral ischemia, diffusion weighted imaging (DWI), including quantification of the advanced diffusion co-efficient (ADC), should be performed⁹⁾. Both PRES and acute infarction show increased signals in DWI, but ADC can discriminate between cytotoxic and vasogenic edema. Vasogenic edema, which is thought to be the cause of PRES, appears hyperintense in ADC map; contralaterally, cytotoxic edema appears hypointense in ADC map¹⁰⁾. However, vasogenic edema may convulse to cytotoxic edema, and this can be shown as a diffusion restricted lesion. In our case, T2-weighted image and T2-weighted FLAIR image showed hyperintense signals. DWI displayed an increased signals, and ADC map simultaneously showed an increased signal lesion and a diffusion-restricted area in the posterior portion of brain. Such restricted diffusion has been described in some cases of PRES and is known to be potentially reversible; however, the risk of developing an irreversible brain injury remains possible¹¹⁾. Our patient currently has no clinical neurologic deficit, but further imaging follow-up is needed to check if there are any neurologic sequelae.

Her initial MRI scan showed intracerebral hemorrhage, and subsequent MRI scans revealed newly developed subdural hemorrhage (SDH). Brain hemorrhage is an uncommon finding in PRES, reportedly ranging from 5%²⁾ to 17%¹²⁾. Its pathology of hemorrhage is unknown, but cerebral hyperperfusion due to hypertension or post-ischemic reperfusion injury are suggested for the pathophysiology of PRES³⁾. In our case, the findings of restricted diffusion and clinical hypertension were found simultaneously, so both theories could be adjusted. New SDH was found on the follow-up MRI after markedly improved neurological state. Spontaneous SDH can occur in cases of severe intracerebral hypertension, intracerebral hypotension, vascular malformation or bleeding tendency, without any history of physical trauma. Our patient had fluctuating BP early on in the treatment, up to 178/123 mmHg and then lowered to 75/57 mmHg, and her MRA findings and coagulation test results were normal. She displayed an improved mental status without

neurological symptoms beginning on the third day after admission. So, the cause of SDH is assumed to be a fluctuation in BP, not PRES.

To our knowledge, PRES accompanied by cerebral hemorrhage in children has only been discussed in a few reports^{7,13}. We believe that this is the first PRES case involving both hemorrhage and diffusion restriction. Although PRES is known to be a reversible disease, this is not always true without early recognition and resolution of the underlying cause¹⁴.

During patient assessment, it is important to consider all of the possible underlying diseases and drugs and to control hypertension promptly. In this case, uncontrolled nephrotic syndrome with hypertension was the most suspected cause, and a possible infectious condition might have also contributed to the development of PRES. Our patient had two radiologic complications of PRES, cerebral hemorrhage and restricted diffusion, and thus, we wish to highlight management methods for severe case of PRES in pediatric patients with uncontrolled nephrotic syndrome. This case suggests more attention needs to be paid when neurologic signs develop in nephrotic syndrome patients to check for PRES and establish differential diagnosis through accurate imaging study.

요약

PRES는 두통, 구토, 시야 장애 혹은 경련을 동반하는 드문 증후군 경계의 증후군으로서, 일반적으로 뇌 자기공명 영상에서 양측 후두엽 백질의 대칭적인 부종 소견을 보인다. 저자들은 조절되지 않는 신증후군 환자에서 영상의학적 뇌출혈 및 확산영상의 제한 소견을 동반한 PRES를 경험하였기에 보고하는 바이다. 환자의 MRI에서는 양측 두정엽 및 후두엽의 비대칭적인 뇌백질 부종 및 대뇌 출혈, 확산 강조 영상에서의 제한 등 PRES의 비전형적인 소견이 관찰되었다. 고혈압 및 신증후군을 조절한 이후에 신경학적 증상과 함께 MRI의 병변이 호전되는 것을 확인하였다.

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