Case Report
Posterior reversible encephalopathy syndrome in a child with steroid-resistant nephrotic syndrome: a case report and review of literature

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Abstract: Posterior reversible encephalopathy syndrome (PRES) is a rare and serious syndrome of central nervous system that can develop in both adults and children. It is characterized by acute onset of headache, confusion, seizures or focal neurological deficits along with radiological findings of white matter abnormalities in the parietal and occipital lobes. In the past ten years, this syndrome has been described mainly in adults, rare in children. Here, we report a case of PRES presenting in a 12-year-old girl with steroid-resistant nephrotic syndrome. Her neurological symptom was rapidly recovered after control of hypertension without discontinuation of cyclosporine A.

Keywords: Posterior reversible encephalopathy syndrome, steroid-resistant nephrotic syndrome, hypertension, cyclosporine A, children

Introduction
Posterior reversible encephalopathy syndrome, a rare disorder of central nervous system, was first described by Hinchey in 1996 [1]. It was defined as a variable combination of consciousness impairment, seizure activity, headaches, vomiting, visual abnormalities (hemianopsia or cortical blindness) and focal neurological signs, which was associated with neuroimaging abnormalities characterized by partially or completely reversible subcortical vasogenic edema in the posterior white matter [1-6]. PRES can develop in association with a vast array of clinical conditions including autoimmune diseases (such as SLE or Wegener granulomatosis), systemic infections, pre-eclampsia, hypertension, organ transplantation, malignancies, chemotherapy, and immunosuppression (especially with calcineurin inhibitors) [2, 4, 6]. Here, we present a case of PRES in a 12-year-old girl with steroid-resistant nephrotic syndrome.

Case report
A 12-year-old Chinese girl presented with oliguria, severe generalized body edema, proteinuria of 150.2 mg/kg/24 hr, low serum albumin of 9 g/L, high serum cholesterol of 13.2 mmol/L and initial arterial blood pressure of 95/81 mmHg. She was found to have steroid-resistant nephrotic syndrome and kidney biopsy revealed mild mesangial hypercellularity with moderate tubulointerstitial lesions (Figure 1). The girl was treated with steroids and cyclosporine A. On day twenty-one of hospitalization (thirteen days after the initiation of cyclosporine A therapy at a dose of 100 mg twice a day (5.7 mg/kg/day)), while her symptoms were improving, the child developed sudden headache, temporal blindness and generalized tonic clonic convulsion followed by unconsciousness. The blood pressure was 132/97 mmHg, pulse 150 beats per minute and temperature 36.8°C. Neurological examination showed normal cranial nerve function, equal and symmetric deep tendon reflexes. Muscle strength was 3/5 in bilateral upper and lower extremities.

On laboratory evaluation, the child had no evidence of infection. She had massive urinary protein excretion of 150 mg/kg/24 hr, low serum albumin of 18.3 g/L, normal serum urea of 3.44 mmol/L, normal serum creatinine of 34
μmol/L and normal serum electrolytes levels. A non-contrast computed tomography was done on the day of the seizures, and it showed symmetrical hypodensities in parieto-occipital regions of cerebral hemispheres (Figure 2). Two days after seizures, magnetic resonance imaging T2 showed hyperintense signal in the parieto-occipital regions, and axial FLAIR images and DWI revealed bilateral cortical and subcortical white matter edema in parieto-occipital lobes (Figure 3). The child was treated with antihypertensive medications (amiodipine besylate and fosinopril), anti-seizure medication (levetiracetam), diuretic, steroids and immunosuppressant (cyclosporin A), thereafter she got no seizure and regained full consciousness and vision 5 days later. Her blood pressure was kept at 90/63 mmHg and urinary protein excretion gradually decreased. Follow-up MRI 13 days after seizures demonstrated partial resolution of the initial cerebral lesions (Figure 4). She got complete remission of nephrotic syndrome after two months treatment of cyclosporin A.

**Discussion**

PRES was first described by Hinchey et al in 1996. Over the past decade, with advance in neuroimaging techniques, PRES has been shown to be associated with Henoch-Schönlein purpura, post streptococcal glomerulonephritis, hemolytic uremic syndrome, hypertension, Addison’s disease, ganglioneuroma, acute lymphoblastic leukemia, intrabdominal neurogenic tumors, porphyria, bone marrow transplant and steroids in children [7-10]. Clinical features of PRES are typically characterized by headache, vomiting, visual disturbances, confusion, altered sensorium, and seizure. This nephrotic case presented with headache, seizures, blindness, confusion and hypertension, with cyclosporin A treatment. It was similar to previous descriptions in the literature.

The exact pathophysiological mechanism of PRES remains unclear. Three hypotheses have been suggested, which include: first, after exposure to causative agent (such as severe hypertension), autoregulation mechanism of...
intracranial pressure fails, leading to vasogenic edema; second, after exposure to causative agent (such as mild-to-moderate hypertension), cerebral vasoconstriction and hypoperfusion cause vasogenic brain edema and ischemia; third, endothelial injury with disruption of the blood-brain barrier leads to fluid and protein transudation in the brain [4, 5, 11]. It's speculated that, in this case, sudden elevations in blood pressure, severe hypoalbuminaemia and cyclosporine A administration may be the candidate causes of PRES.

PRES can be diagnosed according to typical clinical manifestation and neurological image examination. Patients are generally presented with headache, vomiting, visual perception abnormalities and seizures, and radiologically characterized by symmetric distribution of patchy or globe-like lesions in the white matter of the parietal and occipital lobes. CT scan, which is usually easier to perform first, shows multiple hypodensities in the cortico-subcortical areas, which is different from acute infarct or hemorrhage. On magnetic resonance imaging, T1-weighted hypointense, T2-weighted hyperintense and T2-weighted FLAIR hyperintense areas are bilaterally revealed in the occipital and parietal lobes, which can partially or completely resolved on follow-up scans. In general, vasogenic edema is considered to account for the pathophysiology of PRES, but the presence of cytotoxic oedema is the main prognostic factor for the condition as it may signify irreversible brain injury. DWI sequence can be helpful in differentiating between cytotoxic edema and vasogenic edema. In our case, T2-weighted imaging, axial FLAIR imaging and diffusion weighted imaging showed hyperintense signal in the parieto-occipital areas that were partially resolved at 13 days after therapy. DWI hyperintense suggested the patient may have irreversible brain injury.

PRES must be managed carefully, the pathogenic factors should be clarified if possible since remove of etiologies is very important for the successful treatment. In hypertension-
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related and drug-induced PRES, effective management includes prompt withdrawal of offending agent, aggressive control of blood pressure, timely anti-convulsion. Controversy still exists whether immunosuppression should be continued in the treatment of PRES with steroid-resistant nephrotic syndrome. In our case, hypertension was undoubtedly an important cause, but we were uncertain whether cyclosporine A also played a pathogenic role. Considering that extreme hypoalbuminemia may worsen brain edema, and patient could not get remission of nephrotic syndrome without powerful immunosuppression treatment, we continued cyclosporine A and steroid treatment along with prompt anti-hypertension and anti-seizure, and finally the patient got remission of not only PRES but also nephrotic syndrome. It suggests that immunosuppressive agents can be cautiously administrated in steroid-resistant nephrotic patients with PRES. Most PRES cases were fully reversible in a matter of days to weeks, with timely treatment. However, prolonged seizures and hypertension may result in death or permanent neurological disability [12-14]. Therefore, prompt recognition and timely rational management is important to prevent irreversible neurological deficits.

Conclusion

Through our case report and a review of the literature, we wish to highlight that steroid-resistant nephrotic syndrome especially along with hypertension should be considered risk factors for developing PRES in children. An awareness of this observation is crucial for timely diagnosis and treatment, and therefore minimizing the risk of permanent neurologic deficits. Moreover, our case suggests that immunosuppressive agents might be cautiously used in steroid-resistant nephrotic syndrome with PRES when patients present with severe edema and extreme hypoalbuminemia.

Disclosure of conflict of interest

None.

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