



# Posterior Reversible Encephalopathy and Cavernous Sinus Thrombosis in a Child with Nephrotic Syndrome using Cyclosporine; Causation or Coincidence?

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## Introduction

Cyclosporine A (CyA) is the initial immunosuppressive drug in SRNS [1]. Hypertension is a common side effect of CyA but PRES is rare [2]. CST is also rare in NS. Since CST and PRES might mimic each other, high index of suspicion and appropriate imaging is of vital importance for diagnosis and treatment which is different for each condition.

## Abstract

Cyclosporine A (CyA) is the initial immunosuppressive in Steroid Resistant Nephrotic Syndrome (SRNS). Hypertension is one of its adverse effects but Posterior Reversible Encephalopathy Syndrome (PRES) is rare. Nephrotic syndrome is a hypercoagulable state with thromboembolic events in 2-3% of the cases rarely involving cerebral vessels.

A 2.5-year-old girl using CyA (3mg/kg/day) for SRNS was brought with focal convulsions. She was hypertensive and edematous with normal renal functions. Magnetic resonance imaging revealed PRES and Cavernous Sinus Thrombosis (CST). Coexistence of these rare complications made us think that a causal link may exist. Although CyA is the prime suspect for PRES, its role in CST is vague. It might have been facilitatory for CST. Surprisingly a temporary remission was achieved probably with CyA but due to unpredictable metabolism and adverse events it could not be restarted. Pharmacogenetic differences might lead to CyA overdose in SRNS.

A causal link between the PRES and CST along with other thromboembolic risk factors in nephrotic patients might exist. But with only one case, the question of "causation or coincidence" still remains to be answered.

## Case

A 2.5-year-old girl diagnosed as SRNS with minimal change histopathology was prescribed CyA (3mg/kg/day) while tapering steroids. One week later, while taking 0.5mg/kg/day steroid, she was brought to emergency department with focal convulsions starting with headache. Her blood pressure was 150/100 mmHg (>95p), pulse rate 134/min, body temperature 36.5°C

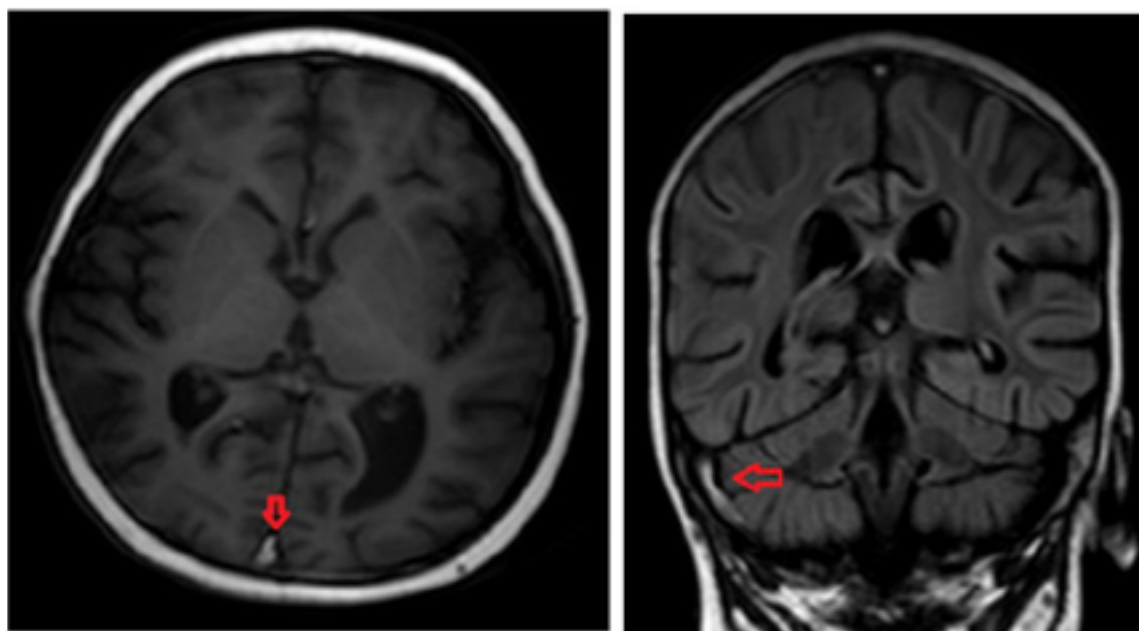


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and O<sub>2</sub> saturation 98%. She was normotensive with nonrevealing physical examination at outpatient visit 2 days ago but in this time she was hypertensive and edematous. Magnetic resonance imaging revealed PRES and CST (Figure 1 & 2). Thrombosis was detected in the superior sagittal sinus, at the level of sinus confluence and transverse sinus. Her coagulation tests and thrombosis panel (protein C, protein S, AT3 levels) were normal. Serum CyA level was very high (910ng/ml). CyA treatment was discontinued. Antihypertensive amlodipine (0.2mg/kg) was started. For CST, enoxaparin sodium (1 mg/kg/dose every 12 hours) and warfarin (0.2mg/kg/day) were started. Accidental overdose of CyA was excluded and PRES was attributed to CyA induced hypertension. Unexpectedly high serum level was probably secondary to pharmacogenetic differences of the patient for CyA metabolism. Because in the following week despite CyA was immediately discontinued, it was still detectable in serum at high levels. Surprisingly a temporary remission was achieved probably with CyA but due to unpredictable metabolism and adverse events, it could not be restarted. Levamisole was prescribed. She had no more seizures and headache following CyA discontinuation and her blood pressure returned to normal. Recovery of the thrombus was determined with control MRI and diffusion weighted MRI two months later.



**Figure 1:** Cranial MRI showing bilateral occipital hyperintensities on T1, suggestive of vasogenic edema



**Figure 2:** MRI T1A hyperintensity showing thrombosis of dural sinus

### Discussion

PRES is a clinical syndrome for which various conditions have been reported to be responsible. The underlying pathogenetic mechanism is thought to be disturbed cerebral autoregulation [3]. Radiographically, it is characterized by relatively symmetric, reversible T2 hyperintensities involving mainly occipital and parietal lobes. However it is now known that this description is more of a general rule, and asymmetric pictures involving the deep gray matter as well as the frontal and temporal lobes can be seen. The advent of diffusion weighted imaging helped clarify that the MRI changes are not due to ischemia or cytotoxic edema, but vasogenic edema. However, there are cases presenting with some degree of diffusion restriction, suggesting that ischemia can be a complication of PRES too [3,4].

Girigen *et al.* reported recurrent PRES in a young boy receiving PD [5]. He presented with headache and seizure, and the authors were concerned about an underlying infection. Initial blood pressure was 135/95 mmHg. A second episode of PRES occurred with a presenting blood pressure of 160/100 mmHg and no sign of underlying infection. With blood pressure and volume control, discontinuation of erythropoietin, and empirical antibiotic treatment at first presentation, seizures and visual symptoms recovered and initial radiologic findings were resolved in follow-up imaging one month after each episodes. As the boy was on PD for over a decade, the occurrence of PRES could not be linked to the initiation of dialysis. The development of PRES in this case, might have been secondary to endothelial dysfunction induced by infection [5,6]. The blood pressure of

our patient at the time of admission was 150/100mm/Hg. In nephritic patients PRES is an expected finding especially in hypervolemia [7]. However, in our patient, PRES developed in remission phase and this strengthened the idea that cyclosporine might have been the cause. CyA is a well known nephrotoxic agent but its neurotoxicity is rare and the mechanism is not clear. And also the severity of CyA related PRES has been reported to be independent from the blood level of the drug[8]. We describe a case with SRNS who developed Cy-A-associated neurotoxicity with unusual clinical presentation with PRES and CST. In one study, CyA level was <80ng/ml, and patients with nephrotic syndrome who were in remission were shown to develop PRES [7,8]. This thought us once again the complexity of the PRES formation mechanism. Therefore it is very difficult to decide what is the safe blood level of CyA.

CVT is an unusual condition, with few reports and case series described in the literature too, especially among children. Because of the highly variable clinical presentation and because the disease is relatively uncommon in pediatric patients, the diagnosis of CVT is difficult, delayed or missed in some cases. The low incidence contributes to our poor understanding of the source and pathophysiology of CVT in pediatric patients [7]. After the thrombolytic treatment, the patient's radiological and clinical complaints regressed in our patient. This was also confirmed PRES and CST coexistence in our patient.

Coexistence of PRES and CST which are relatively rare complications in our case made us think that a causal link may exist. Although CyA is the prime suspect for PRES, its role in CST is vague. It might have been facilitatory for CST.

### Conclusion

PRES and CST are two different conditions with similar clinical signs but their treatment protocols are totally different. Their coexistence is very rare but it is important to keep in mind and recognize the clinical entities. Pharmacogenetic differences might lead to CyA overdose in SRNS. A causal link between the PRES and CST along with other thromboembolic risk factors in nephrotic patients might exist, but with only one case, the question of "causation or coincidence" still remains to be answered.

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