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**Case Report** **OPEN ACCESS**

# Posterior reversible encephalopathy syndrome: A conundrum of nephrotic syndrome complication

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**ABSTRACT**

Nephrotic syndrome is a kidney disease with proteinuria, hypoalbuminemia, and edema. One rare, potentially life-threatening complication of nephrotic syndrome is posterior reversible encephalopathy syndrome (PRES). Sudden episodes of neurological symptoms such as headache, confusion, seizures, or focal neurological deficits with radiological findings of white matter abnormalities in the parietal and occipital lobes characterize it. Multiple factors predispose an individual with nephrotic syndrome to PRES, such as uncontrolled hypertension, reduced serum albumin levels, administration of drugs (cyclosporine, tacrolimus), anasarca, disturbed body fluid status and renal insufficiency. Here, we report a case of PRES in a seven-year-old girl with nephrotic syndrome who presented with high blood pressure while admitted to the ward. Her neurological symptom rapidly recovered after the control of hypertension. Recurrence of acute severe hypertension, nephrotic state (edema/hypoalbuminemia), and renal insufficiency may lead to recurrent PRES. Thus, early treatment of trigger factors, especially of hypertension, is vital to reduce the episodes of PRES.

**Keywords:** nephrotic syndrome, posterior leukoencephalopathy syndrome, posterior reversible encephalopathy syndrome, PRES

## INTRODUCTION

Nephrotic syndrome is a glomerular disease that is characterized by massive proteinuria, hypoalbuminemia, edema and hypercholesterolemia [1]. Nephrotic syndrome can affect any age. Nephrotic syndrome affects many people of different ages but is first diagnosed in children between 2 and 4 years old [2]. Boys are affected more than girls [2]. The most common cause of nephrotic syndrome in children is minimal change disease [3]. Meanwhile the most common cause of nephrotic syndrome in white adults is due to membranous nephropathy, and the common cause of nephrotic syndrome in African populations is focal segmental glomerulosclerosis [3]. Complications of nephrotic syndrome can be divided into disease-associated and treatment-related [4]. The most commonly reported neurological complication is cerebral thromboembolism, which is posterior reversible encephalopathy syndrome [5]. Posterior reversible encephalopathy syndrome is a rare disorder of the central nervous system that can develop in hypertension, one of the complications of nephrotic syndrome in children. Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiographic syndrome of various etiologies, first described in a 1996 case series [6]. It is characterized by headache, seizure, confusion, or focal neurology deficits. Hypertension is found in 70%-80% of patients with PRES [7]. Hypertension, renal disease, immunosuppression, and chemotherapy of malignancies are triggers for PRES [8].

## CASE PRESENTATION

A 7-year-old girl with underlying idiopathic nephrotic syndrome for six months presented with abdominal pain and fever for one day, preceded by four days of facial puffiness. She described it as vague abdominal pain with gradual onset, radiating to the back on and off. It was associated with fever for one day, but there was no documented temperature at home. She was warm to the touch but did not take any medication at home. Her grandmother noticed the facial puffiness at home four days prior to the admission, but the grandmother did not do a dipstick urine test because she lost the kit. She was brought to paediatric clinic and was admitted to the general ward for relapsed nephrotic syndrome.

Her blood pressure remained normotensive for one week, but she still has facial puffiness with positive urine protein and balanced fluid turnover. Because of the positive, balanced fluid turnover, she was planned for fluid restriction of 1L/day until the dry weight was achieved. However, on day 7 of admission, her blood pressure was persistently higher than the 99th centile (range from 140-155/100-111 mmHg). Red code was alerted in the ward when suddenly she developed an abrupt drop in a Glasgow coma scale with the episode of staring

blankly, not responding to verbal stimuli, jaw clenching, jerkiness of left upper and lower limb, and urinary incontinence.

On examination, she was unresponsive with the Glasgow coma scale of 3, pupils 2 mm/2 mm sluggish, oxygen saturation of 67% under room air, and blood pressure 128/90 mmHg. She was then intubated for airway protection. The fitting was resolved. She was then loaded with intravenous levetiracetam 1000 mg (40 mg/kg) over 30 minutes, then started on maintenance intravenous levetiracetam 500 mg (20 mg/kg) BD in the pediatric intensive care unit. Laboratory findings showed raised blood urea nitrogen of 5.4 µmol/L, serum creatinine of 59 µmol/L with an abrupt increase of 51% in serum creatinine from the baseline (See **Tables 1**-**5** in **Appendix**). The fitting was resolved.

Subsequently, contrast-enhanced computed tomography brain proceeded on the same day. The impression given was a small area of hypodensity at the bilateral parietal lobe, mainly involving the subcortical region, and no enhancement post-contrast. In view of the clinical history of persistently high blood pressure, changes may suggest posterior reversible encephalopathy syndrome. There was no evidence of cerebral venous sinus thrombosis or intracranial hemorrhage.

Her blood pressure was managed with an intravenous infusion of labetalol and stopped the next day when the systolic blood pressure reached at 110-120 mmHg. She was extubated on day 9 of admission. The blood pressure in the intensive care unit ward was 95th to 99th centile. She was started with tab Nefidipine 7.25 mg TDS, oral Levetiracetam 500 mg BD (20mg/kg/dose) for at least six weeks, syrup Paracetamol 380 mg PRN and tab Prednisolone 60 mg OD. She recovered fully after normalization of blood pressure and was transferred to the general ward on day 11. She was discharged well with no residual symptoms on day 14. Subsequently, she was seen a week after being discharged on day 21 of induction. She was well and achieved remission five days after and completed the entire course of the steroid regime.

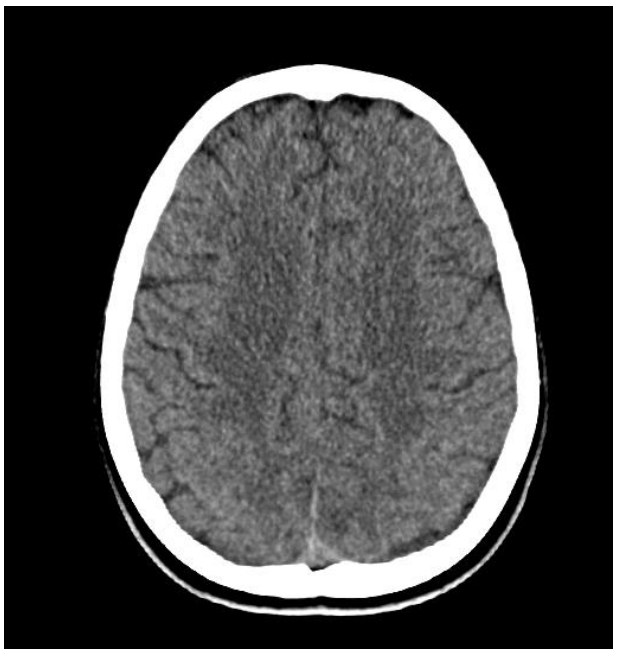

**Figure 1.** Axial view non-contrasted CT Brain (reprinted with permission of the patient)

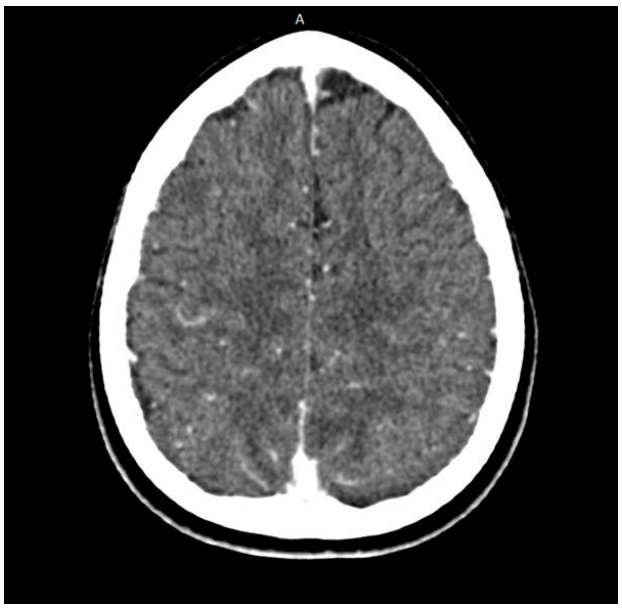


**Figure 2.** Axial view contrasted CT Brain (reprinted with permission of the patient)

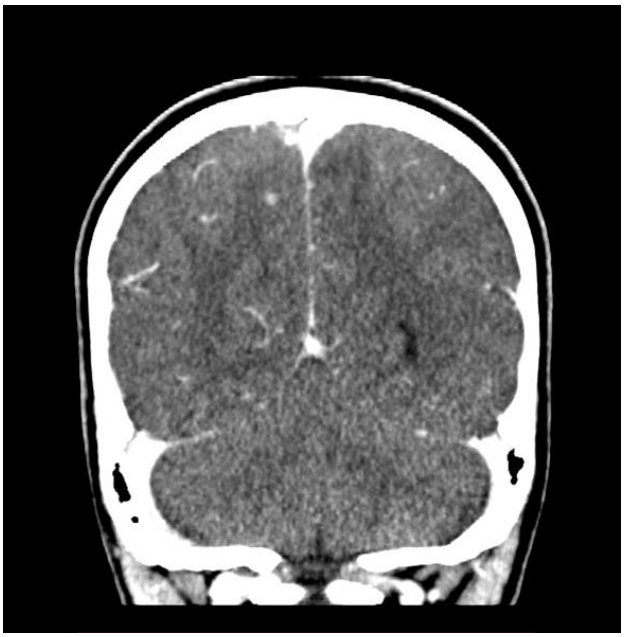

**Figure 3.** Coronal view contrasted CT Brain (reprinted with permission of the patient)

A small area of hypodensity is seen at the bilateral parietal lobe (more prominent on the left side), near the vertex and mainly involves the subcortical white matter region seen on axial non-contrasted (**Figure 1**) axial contrasted (**Figure 2**) and coronal contrasted (**Figure 3**) CT brain.

## DISCUSSION

Posterior Reversible Encephalopathy Syndrome in nephrotic syndrome is a syndrome of clinico-radiological that is characterized by seizures, altered mental status, headache and visual loss [9]. It is characterized by vasogenic edema and its white matter that affects the posterior occipital and the brain's parietal lobes on a predominant basis. The key pathophysiological process of PRES was identified as

vasogenic edema, which denotes fluid extravasation from intracerebral capillaries [6]. Meanwhile, hypertension may also induce vasogenic edema due to autoregulation failure of the cerebral blood flow [10]. Other factors seen in the nephrotic state could induce vasogenic edema due to decreased intravascular oncotic pressure, increased permeability of intracerebral capillaries and fluid overload [6]. The factors that devote to the pathogenesis of PRES were uncontrolled hypertension (100%), severe hypoproteinemia (9%), persistent hypocalcemia (9%), hemolytic uremic syndrome (36%), cyclosporine toxicity (9%), lupus nephritis (9%), high hematocrit (9%), and pulse methylprednisolone (9%) [8]. The nephrotic state itself is a predisposing factor for PRES; consequently, low serum albumin levels, moderate to severe generalized oedema, that induce vasogenic oedema due to decreased intravascular oncotic pressure, increased permeability of intracerebral capillaries and fluid overload [5]. However, the exact mechanism of PRES in peadiatric cases remains obscure. The incidence of PRES in children with nephrotic syndrome is about 2-7 per 100,000 [8].

Negligence in the treatment of PRES will result in life-threatening complications such as severe cerebral hemorrhage, cerebellar herniation and refractory status epilepticus [11]. Thus, early treatment is needed to prevent such complications.

The differential diagnosis in PRES can be varied. Venous sinus thrombosis, subdural or intracerebral hemorrhage, infective encephalitis, meningitis, particularly herpes simplex encephalitis, posterior circulation stroke, basilar artery thrombosis also can present like PRES [12].

PRES in children is known to have favourable outcome if the triggering factors are identified and treated promptly. The rapid-onset symptoms and radiologic features usually fully resolve within days to weeks, although some may take longer [12].

Pertaining to this case, the cause of PRES is uncontrolled hypertension. She was started with tab nifedipine 7.25 mg TDS to control hypertension and oral levetiracetam for at least six weeks to reduce the risk of seizure. Since discharge from the ward, the blood pressure was normalized and fit-free until now.

## CONCLUSION

The treatment aims of nephrotic syndrome are to ensure patient safety and prevent complications. Despite the nonspecific nature of neurological symptoms, hypertension should be a red flag to alert the pediatrician. Unlike in adults, hypertension in children is always ignored and often been counterfeited by the pediatrician because they always think that hypertension is due to child's agitation and other factors, such as seizures related to autonomic functions. Pediatricians need to be more cautious in handling a child with uncontrolled hypertension in nephrotic syndrome as they are more prone to developing PRES. Thus, as PRES is avoidable, early recognition of nephrotic syndrome, good adherence to treatment and proper management can be done in order to avoid such complications.

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**Ethical statement:** Informed consent was obtained from the patient to publish this case report and accompanying images. Any personally identifiable information about the patient has been removed.

**Declaration of interest:** No conflict of interest is declared by authors.

**Data sharing statement:** Data supporting the findings and conclusions are available upon request from the corresponding author.

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# APPENDIX

## Laboratory Investigations

**Table 1.** Urine FEME

| Parameter | 5/1/2021 | 6/1/2021 | 7/1/2021 | 8/1/2021 | 9/1/2021 | 10/1/2021 | 11/1/2021 | 12/1/2021 | 13/1/2021 | 14/1/2021 | 15/1/2021 | 16/1/2021 | 17/1/2021 | 18/1/2021 | 19/1/2021 | 20/1/2021 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Urine protein | 44+ | 33+ | 44+ | 33+ | 44+ | 44+ | 33+ | 44+ | 44+ | 44+ | 44+ | 22+ | 22+ | 22+ | 33+ | 33+ |

Interpretation: The UFEME urine protein range from 2+ to 4+. This means nephrotic range proteinuria is between 100 mg/dl to 2000 mg/dl or more.

**Table 2.** Full blood count

| Parameter | 5/1/2021 | 13/1/2021 | 16/1/2021 | 18/1/2021 | Reference Range |
|---|---|---|---|---|---|
| Hb | 14.1 | 10.5 | 8.8 | 11.7 | 11.5-16g/dL |
| MCV | 80.4 | 80.9 | 73.6 | 81.2 | 76-96fL |
| MCH | 27.4 | 27.1 | 24.1 | 28.5 | 27-32pg |
| Platelet | 386 | 551 | 408 | 501 | 150-400x10^9/L |
| WBC | 21.4 | 17.9 | 16.9 | 18.1 | 4-11 x 10^9/L |
| Neutrophil % | 73.1 | 70.6 | 65.8 | 70.2 | 40-75 |
| Lymphocyte % | 22.6 | 20.5 | 20.3 | 23.7 | 20-45 |

Interpretation: The full blood count shows hemoglobin and leucocytosis in reducing trend.

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| Lymphocyte % | 22.6 | 20.5 | 20.3 | 23.7 | 20-45 |

Interpretation: The full blood count shows hemoglobin and leucocytosis in reducing trend.

**Table 3.** Renal function test

| Parameter | 5/1/2021 | 11/1/2021 | 14/1/2021 | 15/1/2021 | 16/1/2021 | 18/1/2021 | Reference Range |
|---|---|---|---|---|---|---|---|
| Urea | 3.3 | 5.4 | 4.9 | 4.9 | 3.1 | 4.3 | 2.5-6.0 |
| Sodium | 132 | 140 | 147 | 140 | 143 | 139 | 138-145 |
| Potassium | 4.5 | 4.7 | 3.5 | 3.1 | 4.0 | 5.4 | 3.4-4.7 |
| Chloride | 102 | 111 | 103 | 107 | 109 | 102 | 98-107 |
| Creatinine | 39 | 55 | 59 | 43 | 49 | 44 | 36-60 |

Interpretation: Renal function test is normal.

**Table 4.** Liver function test

| Parameter | 5/1/2021 | 6/1/2021 | 10/1/2021 | 13/1/2021 | 16/1/2021 | 18/1/2021 | Reference Range |
|---|---|---|---|---|---|---|---|
| Total Protein | 38 | 35 | 32 | 60 | 53 | 61 | 60-80G/L |
| Albumin | <4 | 10 | 9 | 33 | 18 | 27 | 38-54 |
| Globulin | 21 | 25 | 24 | 27 | 35 | 31 | 20-39 |
| ALP | 149 | 89 | 96 | 104 | 87 | 196 | <500U/L |
| AST | 21 | 18 | 23 | 19 | 22 | 30 | 5-34U/L |
| ALT | 8.3 | 6.1 | 9.7 | 17.5 | 19.5 | 21 | 5-37U/L |
| Total Bilirubin | 1.9 | 10.4 | 7.4 | 5.1 | 1.9 | 15 | 5-20umol/L |
| Calcium | 1.67 | 1.75 | 1.86 | 2.04 | 2.21 | 2.32 | 2.2-2.7 umol/L |
| Magnesium | 0.94 | N/A | N/A | 0.89 | N/A | 0.75 | 0.7-0.95 umol/L |
| Phosphate | 2.12 | N/A | N/A | 3.06 | N/A | 1.46 | 0.74-1.52 mmol/L |

Interpretation: Liver function test shows hypoalbuminaemia and hypocalcemia.

**Table 5.** AutoImmune screening

| Parameter | 14/01/2021 | Interpretation |
|---|---|---|
| ANA | Negative | No autoantibodies present |
| ASOT | Negative | No recent strep infection |
| C3 | 1.19 | Normal complement levels |
| C4 | 0.25 | Normal complement levels |
| CRP | 13.9 | Normal level. |