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Recurrent posterior reversible encephalopathy syndrome in a patient with focal segmental glomerulosclerosis: A case report

Nathasha Vihangi Luke, Sumudu Sajeewa Wickramasinghe, Udaya K. Ranawaka

ABSTRACT

Introduction: Posterior reversible encephalopathy syndrome (PRES) is a rare clinical syndrome of which the aetiology and pathogenesis still remain unknown. We present a rare case of recurrent PRES in a patient with adult onset nephrotic syndrome due to focal segmental glomerulosclerosis (FSGS).

Case Report: A 30-year-old Asian female with FSGS on renal biopsy developed two episodes of PRES with residual neurological deficits without significant hypertension. Both these episodes were preceded by initiation of treatment with calcineurin inhibitors for persistent proteinuria. She was subsequently started on mycophenolate mofetil without further recurrences of PRES.

Conclusion: Although PRES is well recognized, this case has a combination of several unusual features that merit special attention. Recurrent PRES, and its association with focal segmental glomerulosclerosis, are extremely rare. Furthermore, development of PRES without significant hypertension and persistent neurological sequelae are rare findings. The association between FSGS and PRES has been previously noted but to our knowledge this is the first case of recurrent PRES in a patient with FSGS.

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Keywords: Focal segmental glomerulosclerosis, Nephrotic syndrome, Posterior reversible encephalopathy syndrome, Recurrences

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INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological entity that was first described by Hinchey et al. in 1996 [1]. It is a syndrome with a wide array of clinical features including headache, vomiting, visual disturbances and focal neurological deficits. It characteristically affects the posterior white matter, with reversible changes in most instances, but

can cause irreversible damage leading to permanent disability or death in some cases [2].

The pathophysiology of PRES is not exactly known. One hypothesis suggests impaired cerebral autoregulation as the pathophysiological basis. Cerebral autoregulation maintains cerebral blood flow at a constant level when the mean arterial pressure (MAP) is between 60–120 mmHg, despite changes in systemic blood pressure. However, autoregulation is impaired when MAP exceeds 120 mmHg, which results in increased cerebral blood flow leading to vasogenic edema [3]. Another theory focuses on cytotoxicity as the mechanism of PRES, particularly in relation to PRES syndromes associated with causes other than hypertension. Immune system (T-cell) activation leads to endothelial cell activation with release of various mediators such as histamine, free radicals, nitric oxide, bradykinin and arachidonic acid which results in cerebral edema [3].

Cytotoxic therapy is the best known causative factor for PRES, with hypertension being the second most common cause. The other known causes for PRES include sepsis, preeclampsia and autoimmune diseases [3].

CASE REPORT

We present a case of 30-year-old female who was on follow-up for adult onset nephrotic syndrome for seven years. A histological diagnosis of focal segmental glomerulosclerosis (FSGS) had been made on renal biopsy. She had persistent proteinuria despite high dose corticosteroids and immunosuppressants.

Three years ago, the patient was started on cyclosporine which was continued for one year and subsequently withdrawn due to failure to resolve proteinuria. She did not have any notable adverse effects during this period. Following the withdrawal of cyclosporine, she was started on methylprednisolone pulse therapy and subsequently on mycophenolate mofetil (MMF) with no significant improvement of proteinuria. She was then re-started on cyclosporine. Within two weeks of its reintroduction, she developed recurrent frontal headaches. She was admitted to a regional hospital with severe headache, blood pressure of 130/90 mmHg and no significant findings on neurological examination, and was discharged the following day. She was readmitted a week later after developing six generalized tonic clonic convulsions within six hours. She continued to have recurrent seizures after hospitalization, and was intubated and ventilated in the intensive care unit. Her blood pressure on admission was 160/100 mmHg, and a non-contrast CT scan of the done showed cerebral edema. Her hematological and biochemical investigations did not reveal significant abnormalities on admission. A follow-up CT scan three days later, showed asymmetrical hypodensities in both occipital and posterior parietal lobes with cerebral edema. The diagnosis of PRES was made on clinical and radiographic findings. She had a prolonged ICU stay with ventilatory and hemodynamic support. She was treated with broad spectrum intravenous antibiotics for a hospital acquired urinary tract infection, and seizures were managed with a short course of phenytoin sodium.

Cyclosporine was withheld and she was continued on oral prednisolone. Her condition gradually improved but she had persistent bilateral lower limb weakness and impaired visual acuity. She was transferred to a specialized hospital for rehabilitation after a prolonged hospital stay of two months.

At the rehabilitation hospital, she was started on tacrolimus, and on the fifth day she again developed recurrent generalized tonic-clonic seizures. She was then transferred to our hospital, a tertiary care centre.

On admission to the emergency unit, the patient was drowsy, with a GCS of 11/15. She was afebrile, and pupils were equal and reactive. She had quadrihyperreflexia and bilateral extensor plantar responses without neck stiffness. Her blood pressure on admission was 160/90 mmHg, and pulse rate was 110/min. She had significant lower limb and facial edema, but did not have features of heart failure. An urgent non-contrast CT scan of brain showed hypodensities involving both occipital lobes and posterior parietal lobes. Seizures were treated with phenytoin and sodium valproate. She was commenced on broad spectrum intravenous antibiotics. An MRI scan of brain, done on the second day, showed asymmetrical hyperintense signals in both occipital and posterior parietal lobes on T2 and fluid-attenuated inversion recovery (FLAIR) sequences, suggestive of chronic and sub-acute infarctions due to recurrent PRES (Figure 1).

By the second day seizures had completely resolved and her GCS was 15/15. Investigations revealed gross proteinuria with low serum albumin consistent with ongoing nephrotic syndrome, and she was started on oral prednisolone 1 mg/kg/day. Serum creatinine was normal and septic screen was negative. Anticonvulsants were gradually tailed off.

Following the second episode of PRES, she complained of deterioration of her vision. Her visual acuity was 6/36 in the right eye and 6/60 in the left eye, with normal perimetry. Visual symptoms gradually improved over the next two weeks.

She was started on mycophenolate mofetil two weeks later and steroids were gradually tailed off. She did not develop recurrent neurological symptoms following the introduction of mycophenolate mofetil. She was re-transferred to the rehabilitation hospital for long-term follow-up.

DISCUSSION

Characteristic findings in neuroimaging in PRES include regions of bilateral subcortical vasogenic edema, commonly involving parieto-occipital regions. The

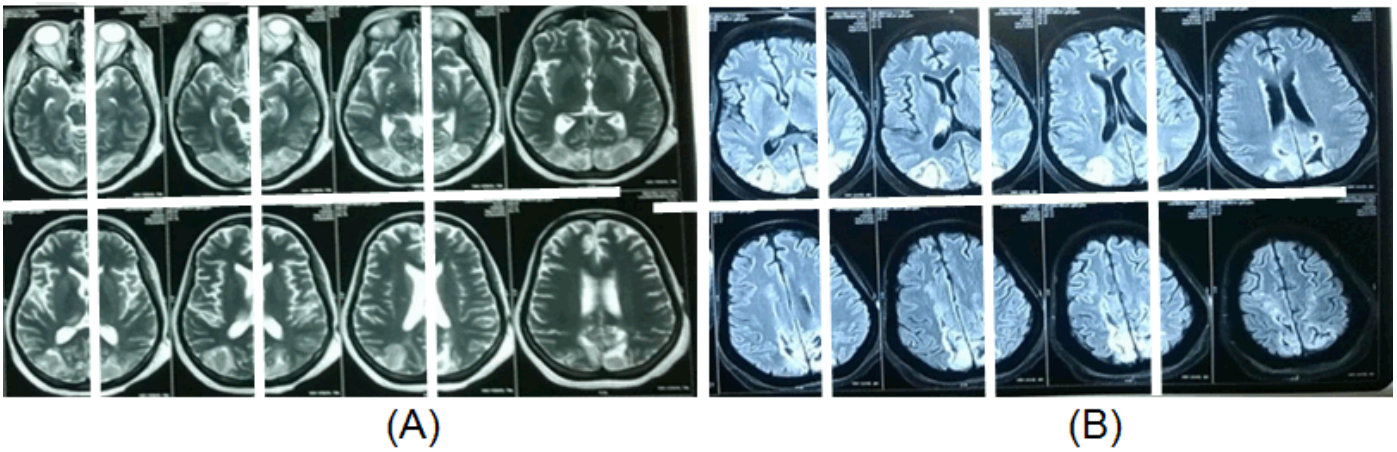

Figure 1: Asymmetrical hyperintense signals in both occipital and posterior parietal lobes on magnetic resonance imaging scan (A) T2-weighted sequences, (B) Fluid-attenuated inversion recovery (FLAIR) sequences.

calcarine and paramedian occipital lobe structures are generally preserved, which distinguishes PRES from bilateral cerebral infarctions. Other regions that can be affected by PRES include frontal lobes, brain stem, cerebellum and basal ganglia [1]. Other radiological findings which are compatible with diagnosis of PRES include hemorrhage, restricted diffusion, contrast enhancement and vasoconstriction [2].

Cyclosporine was the likely cause for the first episode of PRES in this patient, and the second episode was probably triggered by tacrolimus. Both these agents are calcineurin inhibitors which are associated with variable neurotoxic adverse effects including PRES [4].

Calcineurin inhibition by cyclosporine and tacrolimus alters sympathetic outflow, which can potentially give rise to neurotoxic effects and hypertension. Neurotoxic adverse events of calcineurin inhibitors can be reversed in most patients by drug discontinuation or dose reduction. However, irreversible neurotoxic effects or fatal events can occur in some patients [4].

Only some cases of recurrent PRES have been reported. It is considered to be more common in patients with uncontrolled hypertension compared with normotensives [2]. In a study of 28 cases of PRES, four patients had recurrences of which the etiology was primary hypertension [5]. In one study of 38 occurrences of PRES, 53% had previously diagnosed hypertension and the mean systolic blood pressure at the time of development of PRES was 187 mmHg (ranging between 80–240 mmHg) [6]. In our patient, the admission blood pressure was lower than what is usually considered to lead to PRES.

The role of FSGS in the pathogenesis of PRES is unclear. In our literature survey, we were able to identify only four patients with PRES and FSGS [7–9]. All these cases were associated with other well-known etiological factors for PRES such as hypertension and use of immunosuppressive drugs. To the best of our knowledge, this is the first case of recurrent PRES associated with FSGS.

Steroid resistant nephrotic syndrome is usually treated with immunosuppressive drugs, and the development of PRES in such patients poses a challenge in management. Our patient was treated with MMF after the second episode of PRES with no recurrence and improvement of proteinuria. There had been previous case reports where calcineurin inhibitor induced PRES were subsequently treated with MMF with no significant adverse outcomes [8].

A temporal relationship between starting immunosuppressive therapy and development of PRES is not always evident. In a previous study, symptoms occurred between six days and five years after commencement of treatment with cyclosporine [10]. In our patient, both episodes of PRES occurred within a short period of starting immunosuppressive therapy (first episode after two weeks and second episode after five days).

This patient had residual neurological deficits. Most patients with PRES recover uneventfully. In a case series of 16 patients with cyclosporine induced PRES, one person died in the acute phase of intracranial hemorrhage and one had long-term neurological deficits, while 14 made a complete recovery [10].

CONCLUSION

There have been some cases where occurrence of posterior reversible encephalopathy syndrome (PRES) with focal segmental glomerulosclerosis (FSGS) has been described. However, this is the first case to our knowledge where recurrent PRES is associated with FSGS. Other known etiologies such as calcineurin inhibitors too may have contributed to the pathophysiology in this patient.

The role of FSGS as a primary etiological factor for PRES is not clear but warrants further evaluation.

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Author Contributions
Nathasha Vihangi Luke – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Sumudu Sajeewa Wickramasinghe – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Udaya K. Ranawaka – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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