Case Report

Posterior Reversible Encephalopathy in Nephrotic Syndrome: Case Report

Madiha Nooreen1,2, Zeenath Unnissa1, Shafia Fatima1, Uzma Khan1, Zeba Fatima1, Mazhar Uddin Ali Khan2
1Department of Pharmacy Practice, Deccan School of Pharmacy, Hyderabad, Telangana, INDIA.
2Department of Orthopedics, Deccan College of Medical Sciences, Hyderabad, Telangana, INDIA.

ABSTRACT
Posterior Reversible Encephalopathy Syndrome is a potentially life-threatening complication of nephrotic syndrome in pediatric patients. It is characterized by the presence of vasogenic edema in the parietal and occipital region of the brain that leads to the acute and sudden onset of unconsciousness, epileptic episodes, headache and visual disturbances. Multiple factors can predispose an individual with nephrotic syndrome to PRES such as uncontrolled hypertension, administration of drugs (cyclosporine, tacrolimus), reduced serum albumin levels, anasarca, disturbed body fluid status and renal insufficiency. PRES in pediatric patients with the nephrotic syndrome has been rarely reported. Here, we report a case of a 13-year-old boy with nephrotic syndrome who was presented with cellulitis in left knee and developed acute proteinuria and review of literature on PRES occurrence in nephrotic syndrome.

Key words: Posterior reversible encephalopathy syndrome, Nephrotic syndrome, Pediatric, Tacrolimus, Calcineurin inhibitor.

Correspondence
Ms. Madiha Nooreen, Pharm.D, Deccan School of Pharmacy, Nampally, Hyderabad, Telangana, INDIA.
Email: madihanoooreen94@gmail.com
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INTRODUCTION
Immunosuppressive agents such as cyclophosphamide and cyclosporine have been widely used in steroid-dependent nephrotic syndrome (SDNS) and steroid-resistant nephrotic syndrome (SRNS).1-2 But the introduction of tacrolimus has been groundbreaking as it has higher immunosuppressive activity and causes lesser adverse drug reactions compared to cyclosporin.3-4 But it is known to induce neurological complications ranging from milder symptoms of tremors, myalgia, sleep disturbances, mood changes to more serious such as altered mental status, seizures, visual disturbances, encephalopathy and even coma.4-5 This neurological phenomenon is commonly referred as Posterior Reversible Encephalopathy Syndrome.5 It is well documented in solid organ transplant patients. However, very few case studies have been published regarding the PRES in nephrotic syndrome patients.

Here we report a case of a 13-year-old male patient with mesangio proliferative glomerulonephritis, a nephrotic syndrome. The patient was on steroid therapy but the relapse was deteriorating his renal performance consistently as he additionally developed cellulitis. He was prescribed tacrolimus for severe nephrotic proteinuria. After receiving tacrolimus for 2 days the patient developed posterior reversible encephalopathy syndrome.

CASE STUDY
A 13-year-old male patient was admitted to the orthopedic ward of a tertiary care hospital i.e., Owaisi Group of Hospitals, Hyderabad, after he slipped and developed swelling, pain, and tenderness in his left ankle. The patient was presented with the acute soft tissue injury and cellulitis in left ankle. He was a known case of mesangioproliferative glomerulonephritis and nephrotic syndrome. The patient was on Omnocord (prednisolone) 60mg/day. His vitals on the day of admission were stable but his BP was 130/100 mmHg. He was started on injection tramadol, cefepime, and rabeprazole. He then developed fever, chills, lower back pain and frothy urine. His urinary spot test revealed 430mg/dl of urine protein (increased), 40 mg/dl of urine creatinine and 10.75 serum protein: creatinine ratio (increased). Urinalysis reported pale yellow, slightly turbid acidic appearance with 5-6/HPF of pus cells, 6-7/HPF of epithelial cells and traces of albumin. The complement component test for C3 showed increased levels 338.33 mg/dl and C4 levels were within normal limits. The patient was diagnosed with severe nephrotic proteinuria. The patient was put on tablet takfa (tacrolimus) 1mg once a day.

On day 2, the patient developed pitting edema in the left ankle. He was started on tablet linezolid 600mg BD and was advised foot elevation. His serum CRP level was 48mg/L, suggesting the possibility of an infection. The microbiological test isolated MRSA organism. Additionally, he had complaints of a mild headache.

On day 3, the patient had 4 episodes of generalized tonic-clonic seizures each lasting for not more than 2 minutes. On his first seizure episode, injection levetiracetam along with phenytoin was administered immediately. Physical examination was done after his first seizure episode revealed that the patient was restless, not obeying commands, had a 98.6°F temperature, 140/70 mmHg of BP, pulse rate of 99/min and no neck stiffness and spontaneous movement of all limbs. The fourth seizure activity subsided after the administration of injection midazolam. After fourth seizure activity, the patient was drowsy, arousable, irritable, and restless and was responding to pain stimuli. He had GCS score of 4, V4, M4. Brain CT scan showed symmetrical parietal-occipital white matter hypodensities. The patient was suspected to have tacrolimus induced parietal reversible encephalopathy syndrome. Thus, tablet tacrolimus was withdrawn.
On day 4, serum tacrolimus drug levels were found to be 12ng/mL. He also had decreased hemoglobin levels 8g/dl. The patient was maintained on following medications: injection Piperacillin/Tazobactam 4.5mg TID, injection levetiracetam 500mg BD, injection phenytoin 100mg BD, tab. Enalapril 2.5mg OD, tab. Linezolid 600mg BD, tab. Prednisolone 30mg BD, syrup dexorance and syrup grilinctus. No fresh seizure episode was reported.

Subsequent to tacrolimus withdrawal and hypertension management, seizure activity was subsided. On day 10, the patient had complaints of a dry cough which was suspected to be due to ACE inhibitor, Enalapril. The patient was then put on tablet laciactalone (Furosemide and spironolactone) and nebulizer budesonide was administered. In the next few days, he showed rapid improvement.

**DISCUSSION**

Nephrotic syndrome or nephrosis is usually observed in children between the age group of 3-5 years. Nephrotic syndrome can lead to proteinuria, hypoalbuminemia, hyperlipidemia, and edema. Steroid therapy is considered to be most effective in inducing the remission state-that can be achieved within two weeks. Steroid therapy has the risk of causing following adverse effects of steroid-resistant and steroid dependant nephritic syndrome: avascular necrosis, myopathy, cataract, newly developed diabetes, and psychiatric disturbances. The management of idiopathic steroid-resistant nephrotic syndrome aims at inducing complete or partial remission of proteinuria. According to a study conducted by International Study of Kidney Diseases in Children, oral cyclophosphamide has no significant effect in SRNS. Smaller studies demonstrated that approximately 40-60% of patients with SRNS responded to intravenous pulse cyclophosphamide. Cyclophosphamide has the potential for causing severe dose-related adverse effects such as bone marrow suppression, gonadal toxicity, hemorrhagic cystitis, increased risk of infections and malignancies. The conflicting results reported on its effectiveness in pediatric nephrotic syndrome and its serious adverse effects underlines the need for more number of larger studies.

Cyclosporin is considered as an effective immunosuppressive agent and its indication in SRNS and SDNS is well established. It has the remission rate of 85%. However, its use is limited as it is expensive, can cause serious adverse effects such as nephrotoxicity, intestinal fibrosis etc. Thcough cyclophosphamide and cyclosporine have high remission rate, they are reported to have a high relapse and resistant rate as well.

Tacrolimus, a calcineurin inhibitor has been widely used in various immune-mediated disorders as it exhibits more potent cytokine suppression and lesser potential to cause nephrotoxicity compared to cyclosporin. It binds to an immunophilin, FK506 binding protein (FKBP) which interferes with the Tc, cells transcription as well as its growth and proliferation. It is considered as a favorable alternative to cyclosporin as it has high remission and low relapse rate. However, due to adverse effects such as renal toxicity and neurotoxic effects tacrolimus needs to be administered with utmost care. Neurological complications can range from milder signs such as tremors, paraesthesias and myalgia to severe signs- encephalopathy, seizures and coma. Such complication has been more commonly reported in patients with the solid organ transplant, especially when the serum drug concentration was more than that of the therapeutic range of 10-15 ng/mL. As tacrolimus is a narrow therapeutic range drug, achieving and maintain the therapeutic blood levels of the drug is a therapeutic challenge. When the blood level of the drug is more than that of the therapeutic window, patients are at higher risk of adverse drug effects.

Neurotoxicity due to tacrolimus in nephrotic patients has been less frequently reported in the literature. In 1996 Hinchey et al. reported Posterior Reversible Encephalopathy Syndrome (PRES) in 15 patients, about 7 patients were receiving immunosuppressive therapy after transplantation or as a treatment for aplastic anemia. It is a clinic-neuroradiological syndrome characterized by a headache, altered alertness and behavior ranging from drowsiness to stupor, seizures, vomiting, mental abnormalities including confusion and diminished spontaneity and speech, and abnormalities of visual perception. The song et al. reported that approximately 89.3% of the patients who developed calcineurin inhibitor-associated PRES recovered completely whereas about 10.7% of the recovered patients had irreversible neurological consequences. In patients with nephrotic syndrome, administration of calcineurin inhibitors like cyclosporine or tacrolimus, uncontrolled hypertension due to the administration of methylprednisolone or prednisolone, renal insufficiency and neurotoxicity of CNIs can contribute to developing PRES. Nephrotic syndrome itself has been reported to be a risk factor for PRES.

The pathophysiology of drug-induced PRES is unclear. However, various hypotheses have been proposed. The “Hyperperfusion Theory” is the most popular which describes that severe hypertension temporarily interferes with the myogenic and neurogenic autoregulation system that leads to cerebral vasodilation which helps in the extravasation of the blood and fluids in the brain parenchymal tissue causing “vasogenic cerebral edema”. The “Hyperperfusion Theory” suggested that the vasospasm along with the hyperperfusion of the brain tissue and presumed ischemia leads to the PRES development. Increased endothelial activation and movement of leucocytes in the blood vessels causes an elevation in the vasoconstriction which leads to hyperperfusion of various organs including the brain. Tacrolimus compared to other CNIs causes relatively higher urinary magnesium wasting resulting in hypomagnesemia. Due to this, higher incidences of renal impairment or nephrotoxicity have been reported among the patients who receive tacrolimus. Thus, it can conclude that wide range of unrelated triggering factors is involved in PRES which when combined follow a common pathway, possibly alteration in the cerebral autoregulation. Hypertension or drug associated PRES can be managed by dose reduction, switching medication or discontinuation of the offending drug, vigorous blood pressure control and administration of seizure controlling drugs as required. Some patients suffer from irreversible life-threatening neurological damage even after reducing the dose or withdrawing the offending drug. Patients usually recover from PRES within few days. This suggests that the serum drug levels of immunosuppressants may not be related to the neurotoxicity.

In the present case, hypertension was one of the predisposing factors but the involvement of tacrolimus was not fully established as the serum drug levels were within the recommended limits. Most of the PRES cases recover within few days to weeks. But, poor seizure and hypertension management can lead to long-term neurological consequences or death. Early identification and aggressive management of PRES is crucial for better prognosis of the patients.

**CONCLUSION**

The present paper underlines that the steroid-resistant nephritic syndrome especially when presented along with hypertension can predispose an individual to PRES. The physician needs to be aware of a possible life-threatening complication that can be reversed when identified early. The mechanism involved in PRES has not been well understood. This makes its detection and prevention in early stages difficult. Delayed diagnosis can have a lasting neurological impact on patients.
CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES