Posterior Reversible Encephalopathy Syndrome Following Cadaveric-Donor Kidney Transplantation; A Challenging Diagnosis

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A 19-year-old girl with haemolytic uraemic syndrome (HUS) and hypertension underwent a diseased donor kidney transplantation. She developed two episodes of generalised tonic-clonic convulsions on the second postoperative day. Posterior reversible encephalopathy syndrome (PRES) was diagnosed based on the history and imaging. PRES was likely as it is associated with factors which co-exist with chronic kidney disease. Perioperative MMF, tacrolimus and prednisolone were prescribed by the nephrologist. Her serum tacrolimus level was normal at the time of convulsions. Other causes of seizures such as hypoglycaemia, electrolyte abnormalities, infection and intracranial haemorrhages were excluded. Elevated blood pressure associated with severe visual impairment was noted during the second episode of convulsions. Clinical diagnosis was confirmed by magnetic resonance imaging (MRI). She had a complete recovery without residual neurological deficits. Her blood pressure was controlled at the time of discharge and she had a well-functioning graft. Timely detection and institution of early treatment led to a successful recovery.

Keywords: Posterior reversible encephalopathy syndrome, high blood pressure, haemolytic uraemic syndrome, kidney transplantation, Tacrolimus

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder characterized by visual disturbances, headache, seizures, vomiting, hypertension, and altered level of consciousness. Diagnosis is based on clinical presentation and imaging. With the availability of high-quality imaging modalities, PRES is reported more frequently.1 The pathophysiology of PRES is unclear. The commonest reason implicated is an inability of the posterior cerebral circulation to autoregulate in response to acute changes in blood pressure. Cerebral hyperperfusion with resultant disruption of the blood brain barrier results in vasogenic oedema, usually without infarction. In 70-90% of cases, vasogenic oedema is confined to the occipital and parietal regions of the cerebral hemispheres. Even though it is termed reversible, in some it can be permanent.2 Resistant hypertension secondary to chronic kidney disease, HUS, solid organ transplant and immunosuppressive therapy were the most likely contributory factors for development of PRES in this patient.

Case presentation

A 19-year-old girl weighing 30 kg and 146 cm in height (BMI- 14kg/m2) was worked-up for a renal transplantation. She was diagnosed with end stage renal failure (ESRF) for 3 years secondary to familial HUS. She was anuric and dialysis dependent for 2 ½ years. She was on maximum doses of three antihypertensive medication. Baseline serum creatinine was 5.3mg/dl. Echocardiography revealed moderate pulmonary hypertension with a pressure gradient of 60mmHg and TAPSE...
Immediate preoperative blood pressure was 170/90 mmHg (MAP - 120 mmHg). Left radial artery was cannulated under sedation and monitoring established. Anaesthesia was induced with 50 mcg of fentanyl, 50 mg of propofol and 30 mg of atracurium. Meropenem 500 mg was administered before the skin incision. She was intubated and ventilated with a tidal volume of 6 ml/kg ideal body weight, rate of 12/min with a PEEP of 5 mmHg. Ultrasound guided unilateral transversus abdominal plane block was performed with 20 ml of 0.25% bupivacaine in addition to 3 mg of morphine. Left internal jugular vein was cannulated under ultrasound guidance. Intraoperative MAP was maintained above 100 mmHg with an infusion of noradrenaline. One liter of Ringers lactate and 500 ml of 4% albumin was administered intraperatively. Methylprednisolone 500 mg was infused over 30 min before completing the venous anastomosis. 20% mannitol 0.5 g/kg and 30 mg of furosemide was administered prior to removal of the vascular clamps. Reperfusion period was uneventful. Total blood loss was 300 ml. She was extubated at the end of surgery. MAP was maintained above 90 mmHg without noradrenaline. She was transferred to the intensive care unit for observation. Intravenous fluids, tacrolimus 1.5 mg bd and prednisolone 20 mg once daily was prescribed as per the unit protocol.

She maintained a urine output of >1 ml/kg/hour. On postoperative day two, she developed sudden onset tonic-clonic seizures which resolved spontaneously within 30 seconds. Her blood pressure, capillary blood sugar and electrolytes were normal. Tacrolimus was withheld. Two hours later, she complained of visual impairment followed by convulsions and was treated with 2.5 mg of diazepam. During this episode her blood pressure was 180/110 mmHg. An infusion of labetalol was commenced. She had post-ictal drowsiness but was arousable, conscious and rational. She was prescribed amlodipine 2.5 mg twice daily, and prazosin 1 mg three times daily. Levetiracetam was prescribed by the neurologist. Serum tacrolimus level was subtherapeutic (1.4 mcg/L). Tacrolimus was re-commenced by the nephrologist once the seizures were controlled. Contrast-enhanced computer tomography brain was normal. Magnetic Resonant Imaging (MRI) of brain showed subtle focal changes in the gyri such as diffusion restriction in bilateral posterior parietal lobes (Figure 1). Grey-white differentiation was preserved. Magnetic Resonant Angiography (MRA) and Magnetic Resonant Venography (MRV) was normal. She recovered rapidly without residual neurological deficit. There was no evidence of infection and CRP was <6 ng/ml throughout her hospital stay. Therefore, lumbar puncture and EEG were not indicated.

**Figure 1. MRI showing low ADC (arrow in A) and corresponding high signal isotropic DWI (arrow in B) indicative of diffusion restriction (ADC- apparent diffusion coefficient, DWI- diffusion weighted imaging)**
Discussion
Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder characterized by visual disturbances, seizures, altered level of consciousness, headache, nausea and vomiting and unique patterns in brain imaging especially in diffusion-weighted MRI. It was first described by Hinchey et al in 1996 and is frequently diagnosed with the availability of modern imaging techniques. PRES following renal transplantation and immunosuppression is not uncommon. Globally 0.4% occur following solid organ transplantation. Incidence of PRES following liver transplantation is 0.59% vs post kidney transplantation 0.35%. There were no reported cases in Sri Lanka following cadaveric renal or liver transplant. This case posed a diagnostic dilemma.

PRES is associated with sudden increase in blood pressure. This was not evident in this patient following the first episode of convulsions. It is not uncommon among normotensive and hypertensive patients. Furthermore, it can be associated with HUS. Exact pathophysiology is unknown. Many theories have been postulated. Failure in cerebral autoregulation resulting in vasogenic oedema is an accepted theory. Posterior cerebral circulation is more vulnerable due to poor auto regulation and relative lack of sympathetic innervation. Sustained increase in MAP above 150-160 mmHg is beyond the auto regulatory range, which disrupts the regulatory mechanisms resulting in endothelial damage causing hyperperfusion. Patients with chronic high blood pressure are more prone to develop PRES. This patient had refractory hypertension on a background of HUS. Hypertension-hyperperfusion theory is further supported by clinical and radiological improvement of PRES following prompt treatment of high blood pressure. We believe this patient had a similar mechanism which resolved within minutes after commencement of antihypertensive medication.

Neuropeptide theory describes PRES induced by inflammatory mediators released during transplantation due to cerebral vasospasm, ischaemia and endothelial damage. Tacrolimus and cyclosporin are well-known to cause PRES. Despite subtoxic levels, endothelial damage can still be evident. Tacrolimus could have been a potential trigger despite sub therapeutic serum levels. Severe anaemia resulting in inadequate endothelial oxygenation can predispose to PRES. This patient had a pre-operative haemoglobin of 9.4g/dl and it was an unlikely contributory factor.

Symptoms can be acute or subacute and nonspecific. Varying degree of encephalopathy ranging from mild confusion to stupor and coma is reported in 28- 94%. In early course of the disease, seizures are common with an incidence of 74- 87%. Dull and diffuse headache occurs in 50% of patients and 39% of patients report visual disturbances. Papilledema can be appreciated in patients with hypertension. Aphasia, hemiparesis and opisthotonus are atypical and uncommon presentations.

There is no gold standard diagnostic test. Generalized and focal slowing in EEG are common patterns seen in PRES though not diagnostic. Neuroimaging includes CT, MRI and MRA. T2 weighted and FLAIR sequences on MRI are known to be more sensitive but was absent in this patient. The classic patterns show vasogenic edema involving parieto-occipital regions mostly involving the cortical and sub cortical areas of the brain. It is usually bilateral and symmetrical.

Management is mainly supportive. Early recognition and removal of precipitating factors is key. Control of blood pressure requires intravenous infusion of antihypertensive medication. Target should be a 25% reduction from the baseline. First line drugs include labetalol, nimodipine and nicardipine while hydralazine and sodium nitroprusside are considered second line therapy. Hypomagnesemia is a frequent occurrence in acute phase of PRES. Magnesium sulphate is beneficial when associated with eclampsia/ pre-eclampsia and hypomagnesemia. PRES following solid organ transplantation carries a mortality of 19%. Varying degree of functional impairment is seen in 44%. PRES of
hypertensive aetiology and multiple comorbidities are poor prognostic factors.  

**Conclusion**

PRES if diagnosed and treated early can have a benign course. A high index of suspicion is required especially in patients undergoing renal transplantation with multiple risk factors as highlighted in this case report. Identifying the high-risk patient preoperatively followed by perioperative control of blood pressure, ensuring normal blood biochemistry and close monitoring of serum tacrolimus levels can help diagnose this condition early and prevent fatal outcomes.

The authors declare no conflicts of interest.

**References**