

# Posterior reversible encephalopathy syndrome and hemorrhage associated with tacrolimus in a pediatric heart transplantation recipient

Loar RW, Patterson MC, O'Leary PW, Driscoll DJ, Johnson JN. Posterior reversible encephalopathy syndrome and hemorrhage associated with tacrolimus in a pediatric heart transplantation recipient.

**Abstract:** Posterior reversible encephalopathy syndrome (PRES) is a disorder characterized by gray and white matter abnormalities in the temporal, parietal, and occipital lobes of the brain. Its etiology has been attributed to renal failure, immunosuppressive drugs such as cyclosporine and tacrolimus, and other potential entities leading to acute hypertension. Clinical findings include headaches, altered mental status, seizures, visual changes, and focal neurologic deficits. We report the case of a child who developed PRES with intracerebral and subarachnoid hemorrhages associated with tacrolimus exposure 10 days after heart transplantation for restrictive cardiomyopathy. The patient initially presented with complex partial seizures, headache, agitation, and hypertension. Head MRI was suggestive of PRES along with intracerebral and subarachnoid hemorrhages. Tacrolimus was discontinued and blood pressure was controlled. The patient's encephalopathy resolved, but he has had ongoing neurologic symptoms secondary to hemorrhage. Generally, PRES is less common in children than in the adult population and is a rare complication of calcineurin inhibitors (CNI). Presentation with secondary hemorrhage also can occur. In children receiving CNIs presenting with new neurologic symptoms, PRES should be considered as prompt discontinuation of the offending agent can induce resolution of symptoms. Children can develop hemorrhage in the context of PRES, leading to increased morbidity.

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PRES is a clinical and radiological condition characterized by headaches, altered mental status, seizures, visual changes, and focal neurologic deficits (1–4). Characteristic neuroimaging findings include widespread vasogenic subcortical edema, predominantly in the parietal and occipital lobes (1, 2). Since its initial description, several causes have been implicated. PRES has been linked to eclampsia, hypertensive emergency, renal failure, and chemotherapeutic and immunosuppressive

medications (3, 4). It is treated by strict blood pressure control and decreasing the dose or removal of the offending medication. The natural history is reversible, with typical resolution of encephalopathy and neurologic deficits within two months (3).

PRES most frequently occurs in pediatric patients with hematologic, neoplastic, renal, and autoimmune diseases (5–7). More rarely, PRES presents after solid organ transplantation, typically associated with CNIs used for immunosuppression (8–11). PRES secondary to CNIs after heart transplantation in children has been reported rarely (11), with more cases reported in the adult literature (12, 13). We report a case of a child who developed PRES with secondary

Abbreviations: ATG, anti-thymocyte globulin; CNI, calcineurin inhibitor; ICH, intracerebral hemorrhage; POD, post-operative day; PRES, posterior reversible encephalopathy syndrome; SAH, subarachnoid hemorrhage.

intracerebral (ICH) and subarachnoid hemorrhages (SAH) associated with tacrolimus exposure after heart transplantation.

### Case report

A 10-yr-old boy, weighing 28 kilograms, had orthotopic heart transplantation for restrictive cardiomyopathy. The operation was uncomplicated, and the donor heart was thought to be of appropriate size. Initial immunosuppressive therapy consisted of methylprednisolone (10 mg/kg per dose) and ATG.

Tacrolimus (0.04 mg/kg/day) was initiated on the seventh POD, aiming for drug concentrations of 8–12 ng/mL. This typically is initiated earlier in our program, but the patient had transient renal dysfunction that delayed initiation. Prednisone wean was started on POD 6 at 1 mg/kg/day and had reached 0.8 mg/kg/day at the time of presentation. Azathioprine (100 mg daily, 3.6 mg/kg/day) was added to his immunosuppressive therapy as well. He was slow to awaken after weaning of sedative medications, most likely due to slowed hepatic clearance as transaminases were elevated. The cause of the elevated transaminases was postulated to be due to hypotension that required significant pressor support after transplantation. Due to his hepatic dysfunction and the potential for coagulopathy, a head CT was obtained to exclude hemorrhage. The scan did not demonstrate any appreciable hemorrhage, mass, or ischemia. Over the course of the next few days, the patient became more awake and oriented.

On POD 10, the patient complained of headache that responded to analgesic medication. He was agitated, restless, and had difficulty sleeping later that night. The following day, the patient continued to be agitated with headaches and was hypertensive to 159/112 mmHg. Nitroprusside and labetalol infusions were started for blood pressure control. That evening, he had two complex partial seizures with secondary generalization, characterized by head posturing to the right followed by tonic stiffening and clonic shaking of all extremities. Intravenous lorazepam and levetiracetam were given.

A head CT (Fig. 1) revealed an acute left parasagittal parieto-occipital lobe ICH with an associated SAH that extended into the left frontoparietal lobe and anterior right lateral frontal lobe. The patient was not receiving anticoagulants, and there was no evidence of a coagulopathy as his PTT that day was 27 and the INR was 1.3. Head MRI (Fig. 2) was performed subsequently and was remarkable for

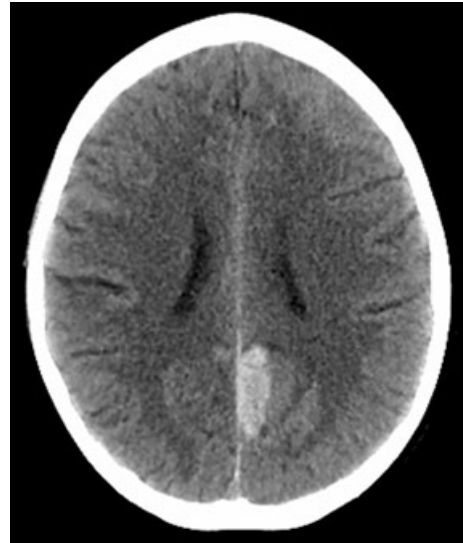


Fig. 1. CT head, acute left parasagittal parieto-occipital lobe ICH.

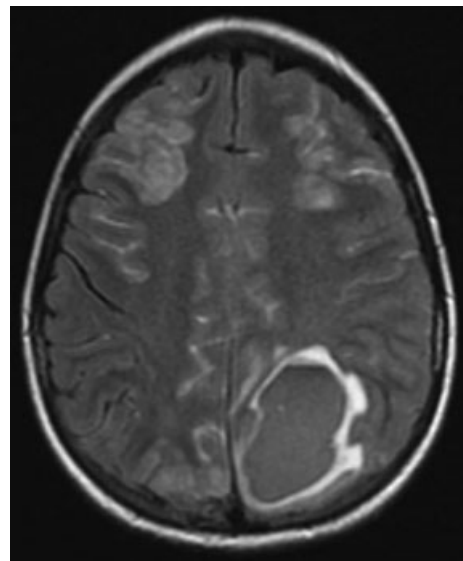


Fig. 2. MRI FLAIR image, extensive cortical and subcortical vasogenic edema involving the frontal and parieto-occipital lobes. ICH at left parasagittal-parietal lobe.

cortical and subcortical T2 hyperintensity in all cerebral lobes and the cerebellum, suggestive of PRES. The MRI also showed an interval increase in the size of the ICH, when compared with the previous CT.

Two days later, the patient continued to exhibit confusion and had difficulties with speech. He had reduced movement of his right lower extremity. He also had spells that were suspicious for ongoing seizure activity. An electroencephalogram showed severe diffuse non-specific slow waves with diminished amplitudes, consistent

with the diagnosis of PRES. Repeat head CT and MRI were performed, demonstrating interval expansion of the ICH. The hemorrhage was emergently evacuated, and an external ventricular drain was placed.

The patient's diagnosis of PRES was attributed to tacrolimus exposure. The range of drug levels from initiation of tacrolimus to presentation of PRES was 8.4–14.2 ng/mL. The dose of tacrolimus was decreased immediately, aiming to maintain serum concentrations in the low-normal range (8–10 ng/mL). Alternative drugs like cyclosporine and sirolimus were suboptimal choices for immunosuppression in the immediate time frame given the similar risk of PRES with cyclosporine and poor wound healing with sirolimus. On POD 14, the primary immunosuppressive therapy was changed to intermittent ATG with prednisone and azathioprine. With gradual improvement in his language and motor deficits, as well as having no further seizure activity, cyclosporine was initiated on POD 24. At most recent follow-up four months after transplantation, the patient has residual difficulties with speech, right-sided hemiparesis, and homonymous hemianopia. His allograft has demonstrated excellent function without any episodes of diagnosed rejection.

### **Discussion**

PRES has been reported increasingly over the last decade, in which time the list of causes of PRES has expanded. One cause is treatment with a CNI. A minority of reported CNI-induced PRES cases in children have involved patients who had solid organ transplantation (8–11).

Our patient demonstrated the characteristic clinical findings of altered mental status, hypertension, headache, and complex partial seizures. His initial presentation occurred 10 days after cardiac transplantation and three days after initiation of tacrolimus. Neuroimaging showed classic findings of vasogenic edema in all cerebral lobes and cerebellum. In addition, there was an expanding ICH with an associated SAH, both of which were thought to be secondary to PRES.

The underlying mechanism of PRES remains unclear. Currently, there are two opposing hypotheses regarding cerebral blood flow. One theory refers to cerebral hyperperfusion as the underlying pathophysiologic mechanism (14). This theory suggests that systemic hypertension leads to transient disruption of cerebral autoregulation, leading to cerebral vasodilation and ultimate capillary leak. This theory is most recent

and popular, likely because the majority of patients experience acute hypertension at presentation. However, this theory does not account for those patients who are normotensive at presentation (15). In addition, the severity of brain edema in PRES does not correlate with the degree of hypertension (15, 16).

In contrast, the original theory refers to vasoconstriction and hypoperfusion leading to ischemic injury and subsequent vasogenic edema (14). This phenomenon is thought to be due to endothelial injury and dysfunction, followed by altered intrinsic vascular tone. Imaging studies have demonstrated that the vasogenic edema seen in PRES presents in a watershed distribution, which is consistent with an ischemic process (17). Vasospasm and hypoperfusion have also been shown with imaging of PRES lesions (18).

A case series in children with PRES revealed that 28% developed hemorrhage, 17% of whom had an ICH and 11% of whom had minute hemorrhages (19). In adult studies, hemorrhage has been reported in as many as 15% with the use of conventional MRI (20, 21). Recently, more advanced imaging modalities have revealed that up to 65% of adult patients with PRES have associated hemorrhage, due in large part to the detection of microhemorrhages (22). The underlying pathophysiology of hemorrhage in PRES is purely speculative at this time. One adult case series revealed the prevalence of underlying coagulopathy or bleeding diathesis to be as high as 85% (23). This same case series also revealed a much more variable clinical outcome with persistence of neurologic deficits in those patients with hemorrhage.

The suggested role of tacrolimus in the neurotoxicity seen in PRES is that of a vasculopathy. CNIs may cause direct endothelial cell injury with alteration of the blood–brain barrier and the release of vasoconstrictors such as endothelin and thromboxane, which lead to vasospasm (15). The release of these vasoconstrictive agents is thought to be a key step in the hypoperfusion theory, as it may lead to vasospasm and ischemic injury (14). Investigators in other studies have implicated CNIs to induce apoptosis in brain endothelial cells (24, 25). Furthermore, neuropathologic confirmation of tacrolimus-induced encephalopathy has been made with evidence of endothelial damage and vasogenic edema (26).

### **Conclusion**

We describe a 10-yr-old boy with classic findings of PRES, both clinically and radiologically. The secondary ICH with associated SAH is an inter-

esting finding, given the lack of an underlying coagulopathy or bleeding diathesis. While likely multifactorial, exposure to tacrolimus was likely an important risk factor for development of PRES in this case. The diagnosis of PRES should be considered in pediatric patients presenting with new neurologic deficits when receiving tacrolimus, as removal of the offending agent leads to remission of neurotoxicity. Hemorrhage can occur in children with PRES without overt evidence of coagulopathy and is likely an indicator of increased morbidity thereafter.

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