

Reminder of important clinical lesson

Posterior reversible encephalopathy syndrome: the importance of early diagnosis

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Summary

A 14-year-old boy was submitted to cardiac transplant due to a dilated cardiomyopathy. On the fourth day of immunosuppression (corticosteroids, mycophenolate mofetil and tacrolimus), he developed right focal seizures and drowsiness. Blood pressure was in the normal range and laboratory findings in cerebral spinal fluid and blood were unremarkable, with drugs in non-toxic levels. The EEG showed a slow background rhythm more pronounced on the right and a seizure onset in the right occipital region. MRI revealed a diffuse hyperintense subcortical white-matter lesion on fluid attenuated inversion recovery, with lesser involvement of left temporal–occipital region. There was no enhancement with gadolinium and MRI diffusion-weighted imaging was consistent with vasogenic oedema. Tacrolimus was stopped with regression of MRI abnormalities and clinical recovery. Posterior reversible encephalopathy associated with tacrolimus is a rare but potentially serious complication of solid organ transplants. A prompt diagnosis and correct treatment is essential to avoid irreversible brain damage.

BACKGROUND

Posterior reversible encephalopathy syndrome (PRES) is a newly recognised brain disorder, first codified as a single name syndrome by Hinchey *et al.*¹ Classically characterised by extensive and symmetric white-matter abnormalities suggestive of vasogenic oedema in the posterior regions of the cerebral hemispheres, it may also commonly involve other cerebral areas (frontal and temporal lobes) as well as cerebellum, brain stem and the basal ganglia. The clinical findings tend to evolve rapidly and are usually diverse. The typical clinical features include seizures, headache, nausea, vomiting, altered mental status, visual disturbance and focal neurological deficits.^{2–6} PRES is often associated with abrupt increase in blood pressure, autoimmune disorders, renal disease and cytotoxic or immunosuppressive therapy. We present a case of PRES caused by tacrolimus. In doing so, we want to highlight the differential diagnosis and possible aetiopathogenesis underlying this condition. We also want to stress the importance of neuroimaging in the establishment of a prompt diagnosis and correct treatment. Finally we intend to discuss the possible relation between tacrolimus doses and use of concomitant drugs in the development of PRES.

CASE PRESENTATION

A 14-year-old boy with chronic heart failure and pulmonary hypertension due to a post viral dilated cardiomyopathy was admitted to our hospital in September 2008 for a cardiac transplant. After surgery he received prednisone, mycophenolate mofetil and tacrolimus for initial immunosuppression. At that time itraconazole, mycostatin and cefuroxime were also administered as prophylaxes against opportunistic infection.

The course was uneventful for 1 week, but on day 8 after surgery and day 4 after immunosuppression, he

became lethargic and sleepy. The neurological examination showed a decreased level of consciousness with a left extensor plantar response. On the next day he started focal seizures with secondary generalisation. He experienced multiple episodes of eye deviation to the left and clonic movements of the left limbs followed by a generalised tonic–clonic seizure. Blood pressure remained within normal range values.

INVESTIGATIONS

Laboratory findings including ionogram, liver and renal functions were normal. Cerebral spinal fluid (CSF) examination was unremarkable (glucose 79 mg/dl; white blood cells 1.0/mm³; proteins 53 mg/dl) with negative PCR analysis for John Cunningham virus and serology for *Herpes simplex* 1 and 2. Plasma levels of tacrolimus were always maintained within the therapeutic range (5.7–15.3 ng/ml) (normal values 5–20 ng/ml).

On the brain CT scan, we could see a linear image of hyperdensity on the left precentral sulcus with a subcortical hypodensity on the inferior frontal gyros (figure 1).

A conventional 1.5 tesla-MRI was performed 5 days after presentation. It revealed an asymmetric and discrete cortical–subcortical signal increase on fluid attenuated inversion recovery (FLAIR)-weighted images, in the left precentral and postcentral gyros, frontal poles and parietal lobes, with no paramagnetic enhancement (figure 2).

The EEG performed after the first seizure showed an asymmetric background, slower on the right hemisphere. Multiple seizures were recorded, all beginning on the right occipital lobe.

Seven days after, the EEG showed slow activity mainly in the posterior regions and bilateral occipital epileptic activity.

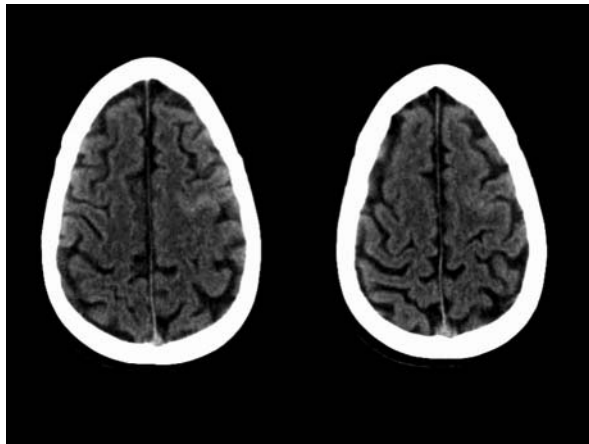


Figure 1 CT imaging demonstrates hyperdensity in the left precentral sulcus and surrounding discrete hypodensity.

The MRI performed at that time, revealed diffuse and extensive hyperintense subcortical white-matter lesions on FLAIR-weighted images, spanning both hemispheres, with lesser involvement of temporal and occipital left lobes and

extension to frontal poles. There was no enhancement after administration of gadolinium, and MRI diffusion-weighted imaging (DWI) was consistent in establishing that they represented vasogenic oedema (figure 3).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included various acute neurological conditions such as stroke, cerebral venous thrombosis, encephalitis and progressive multifocal leucoencephalopathy (PML). CSF examination helped us to exclude an infection, namely encephalitis or PML. A vascular aetiology was also ruled out by brain MRI and DWI (no restriction in water molecules diffusion). These imaging studies allowed us to understand the vasogenic and not ischaemic nature of the white-matter lesions.

TREATMENT

Tacrolimus was discontinued and cyclosporine and azathioprine were introduced. Two days after tacrolimus withdrawal, the boy was no longer stuporous, although he remained mildly confused and with visual hallucinations. A 1.5 tesla-MRI was performed 20 days after tacrolimus withdrawal. It showed an almost complete regression of signal changes (figure 4). The symptoms

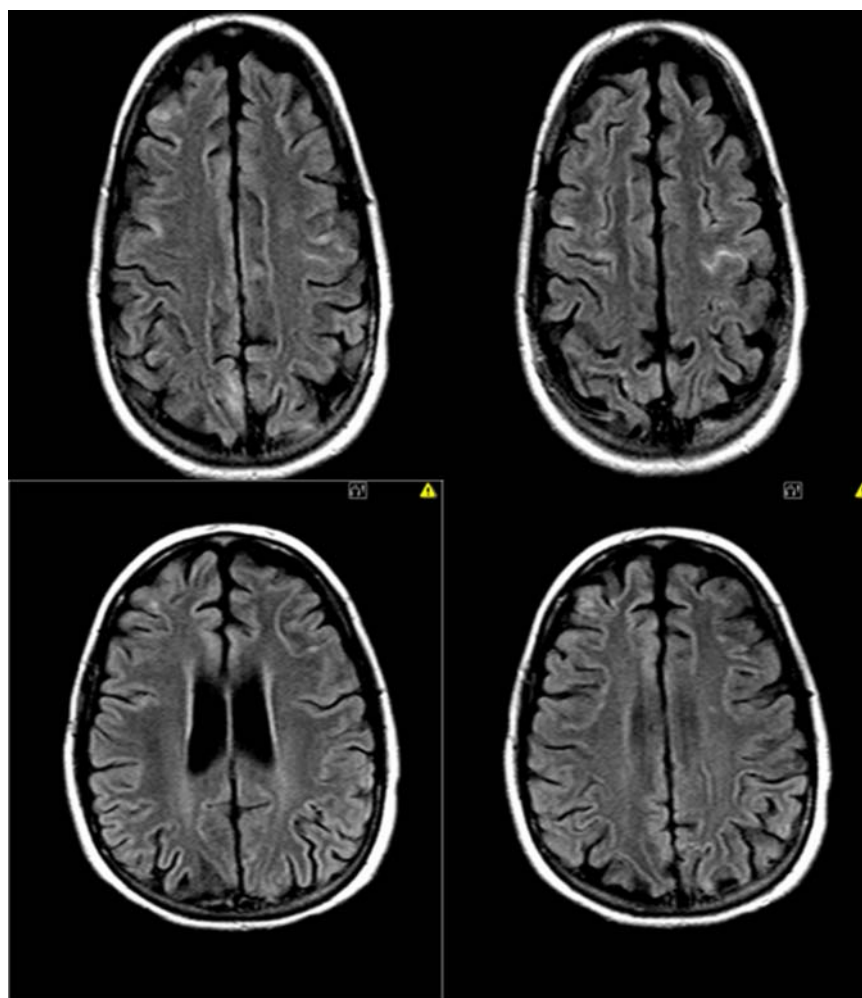


Figure 2 Brain MRI imaging (fluid attenuated inversion recovery sequence), demonstrates hyperintense, linear, cortical-subcortical lesions, in the parietal and frontal lobes, with frontal pole extension.

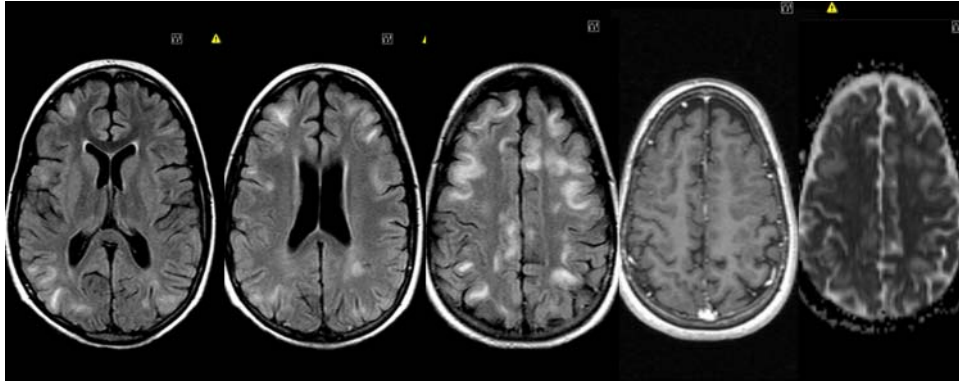


Figure 3 Brain MRI imaging (fluid attenuated inversion recovery, diffusion-weighted imaging and postcontrast T1-weighted images), demonstrates extensive vasogenic oedema, with subcortical white-matter hyperintense lesions, affecting on both sides, the occipital, parietal and frontal lobes. It seemed to be present at the vascular anastomotic border zones. There is no restricted diffusion, and no enhancement after gadolinium.

gradually cleared and 30 days after admission, the neurological examination had no abnormalities. He was then discharged in a good clinical condition.

OUTCOME AND FOLLOW-UP

One month after discharge he visited our outpatient clinic. He was seizure-free, with no complaints and with a normal neurological examination. The EEG performed at that time showed a normal background activity with scarce bilateral temporo-occipital delta waves.

In a second visit, the boy complained of poorer performance at school. A neuropsychological assessment was done and a multifocal and mild cognitive impairment associated with a left frontal and right hippocampal dysfunction was revealed. An EEG was repeated 5 months after discharge and the initial slow activity was no longer

perceived, but some occipital spikes were identified. The 1.5 tesla-MRI was performed 6 months after admission and showed a complete resolution of the former white-matter signal changes (figure 5).

DISCUSSION

Although the disorders that can predispose to PRES are multiple and well identified (box1), the precise mechanisms underlying this condition are not clearly known. Some hypotheses have been postulated, but the issue is still controversial.⁷ One hypothesis, favoured by the majority of the authors, is the hypertension–hyperperfusion theory. According to this theory, a rapid rise in blood pressure may lead to loss of normal brain blood flow autoregulation. This disturbance would promote dilatation of cerebral arterioles, opening up of endothelial tight junctions and cerebral oedema by leakage of plasma into extracellular space.⁸

Alternatively, others have proposed that PRES would result from vasospasm secondary to sudden and severe rise in blood pressure. The subsequent ischaemic damage would induce cytotoxic oedema followed by extracellular oedema. Although angiographic and single-photon

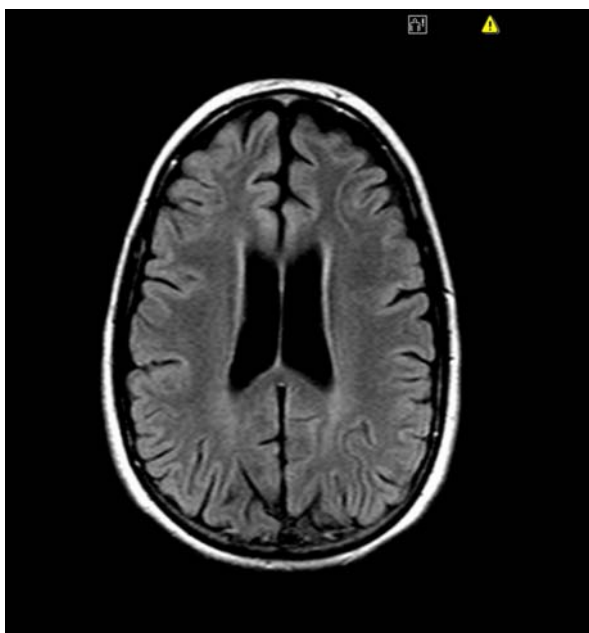


Figure 4 Brain MRI imaging (fluid attenuated inversion recovery), showed almost complete resolution of the vasogenic oedema.

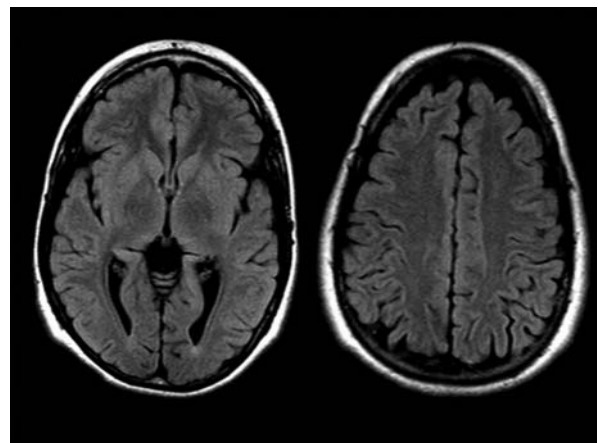


Figure 5 Normal brain MRI imaging (fluid attenuated inversion recovery).

Box1 Conditions associated with posterior reversible encephalopathy syndrome

1. Uncontrolled essential hypertension
2. Secondary hypertension
 - ▶ Renal failure with hypertension
 - ▶ Acute glomerulonephritis
3. Toxemia of pregnancy (eclampsia/pre-eclampsia)
4. Infection/sepsis
5. Post-transplantation
 - ▶ Allogeneic bone marrow transplantation
 - ▶ Solid organ transplantation
6. Drugs
 - ▶ Ciclosporin
 - ▶ Tacrolimus
 - ▶ Interferon- α
 - ▶ Fludarabine
 - ▶ Cisplatin
 - ▶ Gemcitabine
 - ▶ Ifosfamide
 - ▶ Intravenous immunoglobulins
 - ▶ Erythropoietin
7. Auto-immune disease
 - ▶ Systemic lupus erythematosus
 - ▶ Wegener's
 - ▶ Polyarteritis nodosa
 - ▶ Scleroderma
 - ▶ Behçet's syndrome
8. Others
 - ▶ Thrombotic–thrombocytopenic purpura
 - ▶ Haemolytic uraemic syndrome
 - ▶ AIDS
 - ▶ Acute intermittent porphyria
 - ▶ Hyponatraemia, hypomagnesaemia, hypercalcaemia

emission CT studies performed during the symptomatic period were consistent with vasospasm, the uncommon infarction seen in this syndrome does not favour a relevant cerebral ischaemia.⁹

In basal conditions the sympathetic nervous system preserves cerebral blood flow by modifying vascular tone if sudden change of blood pressure occurs. The anterior cerebral circulation is controlled in part by adrenergic sympathetic nerve supply from superior cervical ganglion along the carotid arteries, whereas posterior circulation depends on the sympathetic chain via vertebrobasilar arteries. The sympathetic nerve supply of the posterior circulation is rather deficient when compared with the anterior one. Consequently, a poor autoregulation of blood flow occurs in the posterior regions with a predominance of oedema in these areas.

However, a moderate-to-severe hypertension is encountered in only 70–80% of patients with PRES.^{7–10} Is not uncommon that patients with PRES and eclampsia/pre-eclampsia, allogeneic bone marrow transplantation, infection/sepsis or immune suppression therapy have normal or minimally elevated blood pressure that does not reach the level of cerebral autoregulation failure. It seems that an endothelial dysfunction must be implicated in PRES, especially in cases without hypertension.¹¹ Concerning

immunosuppressive agents such as tacrolimus, a probable direct toxic effect on neurons with axonal swelling and a direct capillary endothelial injury causing a blood-barrier breakdown may explain the clinical and radiological findings. Seizures associated with PRES may also increase lactate levels and serum CO₂ with a subsequent increase in vascular permeability.¹²

The not uncommon association between autoimmune disorders and PRES also supports a possible inflammatory underlying mechanism. Inflammatory cytokines induced by activated monocytes and lymphocytes could provoke endothelial dysfunction with subsequent fluid and protein leakage to the interstitium.³

In PRES, brain MRI imaging typically demonstrates focal or confluent regions of symmetric vasogenic oedema, most commonly in the parietal and occipital lobes.^{13–16} Confluence of the lesions may develop as the extent of the oedema increases. The PRES imaging pattern tends to reflect the watershed nature of this condition. Three hemispheric pattern variants can be usually identified: a holohemispheric, a superior frontal sulcal and a dominant parietal–occipital. There are incomplete expressions (partial or asymmetric) of the three primary variants. These patterns reflect the junctional expression between distal hemispheric branches of major cerebral arteries (anterior, middle and posterior cerebral arteries).^{10–17}

The MRI presentation of the disease, in our patient, strengthens the holohemispheric watershed pattern of PRES.

Of note, a low proportion of patients show a cytotoxic oedema component instead of vasogenic oedema. The analysis of albumin levels of 28 patients with classical PRES showed that patients with vasogenic oedema had significantly decreased serum albumin levels compared with those with cytotoxic oedema, suggesting that low serum albumin levels may be involved in the development of vasogenic oedema in PRES.¹⁸

A prompt diagnosis and treatment are crucial as an adequate intervention usually leads to complete recover within hours (12–24 h) to days.⁵ Nevertheless, imaging findings may persist for weeks, even when a clinical improvement is achieved earlier. A late recognition and/or incorrect treatment can cause irreversible brain damage and even death. A delayed correction of the causative agent or removal of the offending drug can induce prolonged brain ischaemia and infarction. Ischaemic changes on DWI/apparent diffusion coefficient and involvement of large brain areas are predictors of poor prognosis. In case of hypertension, the aim should be to decrease mean blood pressure by 20% within the first hour or to obtain normal mean arterial blood pressure between 105 and 125 mm Hg.^{12–19} Intravenous labetalol is preferred by many physicians for its short duration of action. Calcium channel blockers can also be an effective option as they reduce arterial muscle contractility, inhibiting arterial vasospasm.¹⁹

It is known that the incidence of tacrolimus-induced PRES is nearly 1.6%, with an onset approximately 61 days after the initiation of the immunosuppressive drug.²⁰ Interestingly, in our case the onset of PRES occurred much earlier, only 4 days after tacrolimus introduction, with serum levels always within the therapeutic range. We question ourselves if this reflects an individual susceptibility to the development of PRES or if it may

be related to the effect of multiple drugs since our patient was on several medications that are known to be potentially associated with PRES. Previous reports of PRES related to tacrolimus have noted that this kind of neurotoxicity is not uncommonly seen with non-toxic levels.²¹ Of note, in series of a paediatric population with kidney transplantation or end-stage renal disease that developed PRES, all children under calcineurin inhibitors presented drug levels within therapeutic range.²² In our view, this should raise the possibility of children being more susceptible to develop neurotoxic side effects with lower doses of tacrolimus. It is important remember that PRES may not be necessarily the same for children as for adults. Risk factors for its occurrence in the younger population might be different and should be further investigated.

Learning points

- ▶ Posterior reversible encephalopathy syndrome (PRES) can complicate a large number of medical conditions, such as immunosuppressive therapy.
- ▶ Clinical features include headache, nausea, vomiting, seizures, confusion, visual disturbance and focal neurological deficits.
- ▶ Gold standard imaging study is brain MRI that usually shows bilateral and subcortical diffusion-weighted imaging and apparent diffusion coefficient maps should always be performed when the possibility of PRES is raised in order to confirm the typical vasogenic oedema seen in this condition.
- ▶ The aetiopathogenesis is not fully understood yet. Vasogenic oedema, vasospasm and direct toxic effect are some possible implicated mechanisms.
- ▶ A prompt diagnosis and treatment are essential, as a permanent damage can be expected in a delayed correction of the causative condition or removal of the offending drug.

Competing interest None.

Patient consent Obtained.

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