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Elucidating the mechanism of posterior reversible encephalopathy syndrome – A case of transient blindness after central venous catheterization

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Abstract

Introduction—Posterior reversible encephalopathy syndrome (PRES) is a condition characterized by reversible symptoms including headache, visual disturbances, focal neurological deficits, altered mentation, and seizures. It has been associated with circumstances that may affect the cerebrovascular system, such as hypertension, eclampsia, and immunosuppression with calcineurin inhibitors. The underlying etiology of PRES has remained unclear; however, cerebrovascular autoregulatory dysfunction, hyperperfusion and endothelial activation have been implicated.

Case Report—We describe a case of a young lung transplant patient, who presented with headache, acute binocular blindness and seizure immediately after infusion of saline through a peripherally inserted central catheter (PICC) line which inadvertently terminated cephalad in the left internal jugular vein, near the jugular foramen. Subsequent brain MRI revealed vasogenic edematous lesions in a pattern consistent with posterior reversible encephalopathy syndrome - a diagnosis supported by his constellation of symptoms, history of lung transplantation on tacrolimus immunosuppression, and relative hypertension.

Conclusion—This is the first reported case describing the development of PRES following the insertion of a PICC line. The development of PRES in a typical high-risk patient immediately after cerebral venous outflow obstruction implicates the role of the cerebral venous system and provides potential insight into the mechanism of this disorder that remains of unclear pathogenesis.

Keywords

Posterior reversible encephalopathy syndrome; organ transplantation; tacrolimus; peripherally inserted central catheter; seizure

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Case Report

A 31-year-old male with cystic fibrosis, two years status post his second bilateral lung transplantation was admitted to the medical service for salvage therapy with alemtuzumab for presumed bronchiectasis obliterans syndrome. Prior to PICC line placement, the patient was in his usual state of health. Immediately upon flushing the inserted line with approximately 5 to 10 cc of saline, the patient had a strange feeling in his neck, became nauseated and vomited. After the episode of emesis, he experienced a transient subjective loss of consciousness followed by complete visual loss upon awakening. Subsequently, he began to experience a severe bilateral frontal headache without photophobia or phonophobia. A chest x-ray taken at the time of line placement showed the PICC tip inadvertently terminating cephalad, in the left internal jugular vein as opposed to the intended right atrial target. The PICC line was subsequently repositioned.

Vital signs taken shortly after the incident occurred showed a blood pressure of 157/92 mm Hg and a heart rate of 77 beats per minute. His blood pressure on clinic visits prior to this admission ranged from 110–130/60–70 mm Hg; however, his blood pressure on this admission just prior to PICC line placement was 152/83 mm Hg. His neurological examination was significant for very limited vision with inability to discern the number of fingers held inches from his face, throughout both visual fields. There was no blink to threat bilaterally and no saccades were noted with an optokinetic nystagmus strip. Fundoscopic examination did not reveal any retinal pathology; formal dilated eye examination by ophthalmology was also unrevealing. The remaining general and neurological examination was unremarkable.

Initial contrast enhanced magnetic resonance imaging (MRI) of the brain and orbits, done within 1 hour after the onset did not reveal any intracranial pathology (Figure 1). Magnetic resonance angiogram (MRA) and magnetic resonance venogram (MRV) did not show any evidence of thrombosis or occlusion. His serum and cerebrospinal fluid (CSF) evaluation was within normal limits except for a serum magnesium level of 1.2 mEq/L.

The following morning, the patient stated that his vision was improving. Repeat bedside examination showed a complete right homonymous hemianopsia with preserved perception of light and gross movement in his left visual field. Shortly after examination in the morning, the patient had a generalized tonic-clonic seizure that lasted several seconds. The patient was treated with lorazepam and levetiracetam, and then a phenytoin load. Repeat MRI (Figure 2) showed restricted diffusion with subtle T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity in the left occipital lobe cortex consistent with PRES. Continuous electroencephalogram (EEG) monitoring showed persistent bi-occipital epileptic discharges with left sided predominance, consistent with status epilepticus. The EEG normalized with antiepileptic medications and aggressive blood pressure lowering to a goal systolic blood pressure less than 140 mm Hg. The patient's vision gradually recovered and within 24 hours he had returned to baseline.

Prior to discharge, a transcranial doppler (TCD) vasomotor reactivity study showed vasomotor hyporeactivity in the left middle cerebral artery (59%) and right middle cerebral artery (63%), indicating impaired cerebrovascular reserve. On follow-up visits, the patient did not report any further visual symptoms, focal neurological deficits or seizures.

Discussion

With the sudden onset of our patient's symptoms after vascular manipulation, we were initially most concerned for an ischemic event; however, detailed MRI did not show any evidence of this. Furthermore, MRA and MRV did not reveal any arterial or venous

occlusions. Dilated fundoscopic examination by ophthalmology did not reveal any retinal pathology and MRI images with thin cuts through the orbits with and without contrast did not show any optic nerve abnormalities. Furthermore, the prolonged duration of symptoms with complete resolution shortly after treatment of blood pressure and seizures would argue against an ischemic etiology. With the second MRI showing diffusion-weighted imaging (DWI) changes suggestive of PRES, we also considered the possibility that these changes may have been secondary to the seizure activity. However, the seizures were bilateral on the EEG, yet the DWI changes were ipsilateral to the left PICC line insertion, and correlated with the patient's complaints of right hemianopsia. Taken together with the clinical picture, it is more likely that the seizures were secondary, as part of the clinical syndrome of PRES, rather than the causative agent. Thus, in this lung transplant patient on tacrolimus immunosuppression with relative hypertension who presented with headache, nausea, seizure, and reversible focal neurological deficit, PRES remains the only unifying diagnosis.

Due to his organ transplant status and use of immunosuppression, our patient was at increased risk for the development of PRES. In the setting of organ transplantation the use of calcineurin inhibitors such as cyclosporine and tacrolimus have been associated with PRES through several possible mechanisms.^{1, 2, 3, 4} Calcineurin inhibitors may increase release of the vasoconstrictor endothelin-1, and inhibit endothelial production of nitric oxide, resulting in systemic vasoconstriction and hypertension.^{5, 6, 7} There may be further vasoconstriction and endothelial injury secondary to release of inflammatory cytokines seen with tacrolimus administration⁸. In addition, nephrotoxic effects on the glomerular endothelium may cause magnesium wasting, leading to further vascular autoregulatory dysfunction through loss of the competitive antagonism of calcium.^{9, 10} Our patient had relatively elevated blood pressure and low magnesium measured on the morning of the incident (1.2 mEq/L). The cerebrovascular autoregulatory dysfunction seen on TCD further supports tacrolimus toxicity. Taken together, this combination of factors lead to a predisposition for PRES through vascular autoregulatory impairment from tacrolimus toxicity.

In addition to the patient's underlying predisposition for PRES, the event was finally triggered by a clear vascular insult – the infusion of saline flush into the internal jugular vein, which supports the involvement of the venous system in the development of PRES. PRES itself is a vascular process resulting in sudden development of edema due to fluid shifts in the brain. Angiographic studies have shown areas of constriction and dilation; in addition to decreased cerebral blood flow in areas of PRES associated edema.^(11, 12, 13) Brubaker et al considered that venous greater than arterial vasoconstriction could potentially increase capillary hydrostatic pressure and thus result in vasogenic edema through increased downstream resistance.¹³ Venous hypertension leading to blood brain barrier permeability has been demonstrated. In a study by Mayhan and Heistad,¹⁴ increasing cerebral venous pressure by occluding the superior vena cava in rats caused disruption of the blood brain barrier. Similarly, by placement of the central venous catheter terminating near the jugular foramen, and further injection of saline cephalad into a major cerebral venous outflow tract would have added to the cerebral venous volume and thus increased the cerebral venous pressure in our patient. This resulted in immediate disruption of the blood brain barrier leading to vasogenic edema directly upstream from the inserted line.

At baseline our patient had already shown signs of tacrolimus toxicity with elevated blood pressure and low serum magnesium. Furthermore, the TCD vasomotor reactivity study showed decreased vasomotor reactivity, implicating an impaired compensation to varying vascular pressure. The inadvertent cephalad termination of the central venous catheter in the internal jugular vein and further injection of saline may have mechanically increased cerebral venous pressure, which precipitated the development of PRES in this high-risk

patient. Thus, this case supports the potential involvement of the cerebral venous system in the etiology of PRES.

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Figure 1. DWI (A) and FLAIR (B) images acquired within 3 hours of onset of symptoms. A comprehensive MRI protocol was utilized, including MRA, MRV, DWI, ADC, GRE, T2, T1, T1 post contrast, and thin cuts through the orbits, yet no abnormalities were demonstrated.

Figure 2.

MRI after the patient's generalized tonic clonic episode showed an area of hyperintensity in the left occipital lobe cortex on DWI (A). There is a corresponding decreased signal on ADC map and subtle hyperintensity on FLAIR images (B). Given the clinical setting, these findings are highly suggestive of PRES.

Figure 3.

EEG acquired shortly after the patient's generalized tonic-clonic seizure reveals continuous bilateral occipital epileptiform discharges with left-sided predominance.