

Hypertensive encephalopathy: BP lowering complicated by posterior circulation ischemic stroke

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In hypertensive encephalopathy (HTE), prompt reduction of blood pressure (BP) is essential to prevent permanent neurologic and other damages. Radiologically, HTE is characterized by white-matter edema affecting preferentially the occipital lobes and other posterior structures.¹ The clinical and radiologic manifestations of HTE usually resolve completely after correction of hypertension.^{1,2} We report two patients in whom neurologic deterioration occurred paradoxically with treatment of HTE.

Case reports. **Patient 1.** A previously healthy 36-year-old Filipino man presented with acute headache, confusion, bilateral visual loss, and BP of 260/130. There was no other focal neurologic deficit on admission. Retinal examination was unremarkable. Brain CT revealed white-matter edema at the occipital lobes. After 50 mg bolus of IV labetalol, BP was reduced with the lowest reading at 140/110. Two hours later, he developed acute pulmonary edema and generalized seizures. He was transferred to the Intensive Care Unit (ICU) and was ventilated under sedation. EKG showed no evidence of myocardial ischemia. His condition was stabilized, and he was extubated 40 hours later. Physical examination, however, showed left-sided cerebellar signs with ataxia and horizontal nystagmus. MRI performed on the same day showed T2W-hyperintense signals at left brainstem extending from medulla to pons, cerebellum, right thalamus, and bilateral occipital lobes (figure). The leukoencephalopathy initially shown on CT had resolved. He was discharged after 4 weeks of rehabilitation.

Patient 2. A 74-year-old Chinese man with hypertension and diabetes mellitus presented with headache and progressive visual blurring for 1 week. BP on admission was 215/100 despite use of metoprolol, nifedipine, and perindopril. He was fully alert with no focal neurologic deficit. Fundoscopy showed diabetic proliferative retinopathy. He was mildly anemic from a chronic esophageal polyp. CT brain revealed hypodense changes at the posterior subcortical white-matter. Oral metoprolol was increased from 50 to 75 mg twice daily. His BP was reduced with the lowest reading at 135/65. Eight hours afterward, he became drowsy with right upgoing plantar response. Systolic BP rose to about 180 mmHg after withholding the medications, but his neurologic status did not improve. CT brain showed acute pontine and midbrain infarctions bilaterally. Life support system was withheld because of his poor outlook. He continued to deteriorate and died of pneumonia 2 weeks later.

Discussion. Both patients had symptoms of HTE but no features of stroke on presentation. Although the initial management was not under an ICU setting, their BP was lowered to reasonable levels with appropriate treatment strategies. Onset of neurologic

deficits coincided with BP normalization. In Patient 1, seizures and hypoxia may be additional contributing factors.

The mechanism for posterior leukoencephalopathy in HTE is ill-defined. Diffusion-weighted MRI demonstrated that the radiologic changes represented vasogenic edema rather than tissue infarction.^{1,3} Autoregulation of cerebral circulation is mediated by adrenergic sympathetic innervations. Vasoconstriction in response to hypertension can protect the brain against its pressure transmission effects. However, acute upsurge of BP will overwhelm this autoregulatory mechanism, resulting in cerebral hyperperfusion. The hydrostatic pressure causes fluid extravasation and interstitial edema. The vertebrobasilar system is relatively devoid of sympathetic activation, making the posterior brain regions more susceptible to effects of HTE.

Posterior leukoencephalopathy can be complicated by hemorrhagic and, less commonly, ischemic stroke.^{1,4} The mechanism of ischemic stroke is probably hemodynamic rather than thrombotic. Increased posterior perfusion was demonstrated with SPECT and perfusion-weighted MRI.¹ Relative anterior hypoperfusion is also expected from the protective vasomotor response. However, a predominant posterior distribution of cerebral infarctions was found.⁴ One postulated mechanism is that vasogenic edema causes compromised tissue perfusion and infarction at the surrounding regions.⁴

In conditions where blood-brain barrier or cerebral autoregulation is breached, systemic pressure becomes an important determinant of cerebral perfusion. For instance, BP reduction during the acute phase of ischemic stroke increases the odd ratio for adverse outcome.⁵ We postulate that in our patients who had failure of autoregulation from HTE, abrupt BP lowering resulted in decompensation of pressure-dependent cerebral perfusion to precipitate ischemic stroke. Presence of vascular stenosis may further exaggerate this effect. Another study reported six cases of ischemic stroke following treatment of moderate hypertension.⁶ The brainstem was involved in three out of four patients whose initial presentation was not a cerebrovascular event. Patients with posterior circulation ischemic stroke and low BP on admission were also found to have poorer prognosis.⁷ These observations, together with ours, may suggest that the posterior circulation is also more prone to the hemodynamic effects of BP lowering in HTE.

In conclusion, while correction of BP is mandatory in hypertensive posterior leukoencephalopathy, ischemic stroke can be precipitated as a treatment-related complication.

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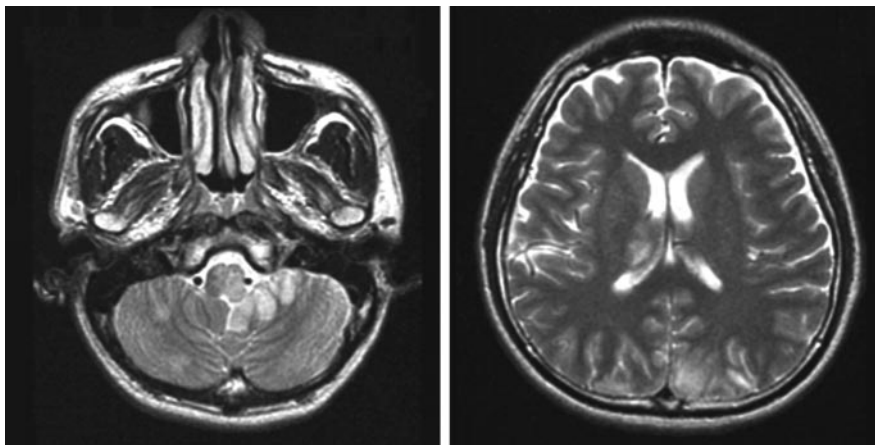


Figure. T2W-MRI of Patient 1 after onset of focal neurologic signs: (Left) Axial image showed hyperintense signal at left side of brainstem and cerebellum. A few smaller lesions were also present in the right cerebellar hemisphere. Flow void was seen in both vertebral arteries. (Right) The right thalamus and occipital lobes were also affected. Gray-matter involvement in the left occipital lobe indicates ischemic rather than hypertensive changes. The white-matter edema initially shown on CT had resolved.

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Tacrolimus leukoencephalopathy: A neuropathologic confirmation

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Tacrolimus leukoencephalopathy has well documented clinical and neuroradiologic features.¹ The latter suggest endothelial dysfunction as the underlying etiology.² Confirmatory neuropathologic data have been lacking.

Case reports. A 40-year-old woman with biopsy-proven acute rejection was admitted 3 weeks after an orthotopic liver transplant for alcoholic cirrhosis. Alanine aminotransferase was elevated at 226 IU/L (<50 IU/L). She also had elevated cholesterol levels (237–411 IU/L) and was hypertensive (approximately 160/90). Erythrocytes showed anisocytosis and poikilocytosis (spiculated, fragmented, and targets). Tacrolimus 4 mg BID had been started the day after transplantation.

The patient had 2 days of toxic tacrolimus levels of 25 ng/mL and 29 ng/mL (>20 ng/mL), followed 4 days later by new onset seizures and mental status changes (lethargy to agitation). BP just after the seizure was 172/104. The last reading prior to her seizure was 144/88. MRI revealed two large white matter lesions in the right frontal lobe without mass effect (figure 1A). There was minimal peripheral enhancement, as well as scattered white matter lesions in the frontal and parieto-occipital lobes bilaterally (figure 1B). Her condition continued to deteriorate over the next 2 days with increasing seizure activity culminating in unresponsiveness. Brain biopsy was performed to exclude a treatable infectious process. Her platelet count at this time was 329,000/ μ L (445,000/ μ L upon admission); her prothrombin time and partial thromboplastin time were normal. However, that same day bleeding at the biopsy site necessitated a craniotomy for evacuation of a hematoma. The patient remained unresponsive for the next few days, and she died 2 months after her admission as a result of transplant rejection and hemorrhagic necrosis of the entire right centrum semiovale.

Neuropathologic findings. The small biopsy sample consisted of abnormal white matter that had no evidence of infection even with an antibody to cytomegalovirus (DAKO Envision Plus System; DAKO, Carpinteria, CA; 1:100 with proteinase K pretreatment). There was a diffuse decrease in the staining of myelin with Luxol Fast Blue, but not with an antibody to myelin basic protein (Research Diagnostics, Flanders, NJ; Monoclonal, 1:300, no pretreatment), and without appreciable periodic acid-Schiff (PAS)- or CD68-positive macrophages (DAKO Envision Plus System; Monoclonal, 1:100) (figure 1C). A comparable decrease in Bodian stained axons was observed (figure 1D). Oligodendrocytes appeared to be numerically reduced but were not activated caspase-3-positive (R & D Systems, Minneapolis, MN; Polyclonal, 1:1000). A mild increase in glial fibrillary acidic protein-positive astrocytes (GFAP) (DAKO Envision Plus System; 1:1000 with proteinase K pretreatment) and CD68-positive microglia was noted. Several small veins were surrounded by PAS-positive material that was present within the vascular lumen (figure 1E). Another vessel showed a marked perivascular decrease in myelin and axonal staining with replacement by a pale PAS-positive background stain (figure 1F). That same vessel showed strongly positive intravascular and extravascular PAS-positive droplets, focal endothelial hyperplasia, and swelling with prominent nucleoli and fibrin transudation (figure 1G). The endothelium was immunoreactive

for tumor necrosis factor- α (Santa Cruz Biotechnology, Santa Cruz, CA; Monoclonal, 1:5) but not for interleukin-1 (Genzyme, Cambridge, MA; Polyclonal, 1:300).

Discussion. Tacrolimus leukoencephalopathy has been included within the reversible posterior leukoencephalopathy syndrome (RPLS), which is also caused by cyclosporin, eclampsia, malignant hypertension, renal failure, and drug-induced thrombotic thrombocytopenic purpura (TTP).¹ The most common clinical features include the sudden onset of seizures, headache, altered mental status, visual abnormalities, aphasia, and hemiparesis.¹

Neuroradiologic findings are most commonly located in white matter of the posterior cerebrum, but also in the white matter of the cerebellum, frontal lobes, and brainstem.¹ Radiologic imaging provides evidence of vasogenic edema and generalized cerebrovascular dysregulation.²

Neuropathologic confirmation of the neuroradiologic interpretations, however, has been lacking. Cortical and subcortical infarcts, areas of diffuse neuronal necrosis, coagulative necrosis including numerous macrophages, neutrophilic invasion of small cortical arteries and perivascular space, thrombi with perifocal edema³, and areas of “demyelination” with minimal reactive astrogliosis have been reported.⁴

Our patient had toxic levels of tacrolimus and neuropathologic evidence of endothelial damage with vasogenic edema in white matter in the absence of infarcts or demyelination. The myelin pallor in our patient and in a previous report does not constitute active demyelination (i.e., myelin breakdown with phagocytosis of myelin debris), and is more consistent with vasogenic edema as has been reported in HIV leukoencephalopathy.⁵

The precise etiology of tacrolimus leukoencephalopathy is not known. Tacrolimus toxicity has been implicated in cases of drug-induced thrombotic thrombocytopenic purpura (TTP); nephrotoxicity also has been reported in both animal and human studies. The precipitating event for both is most likely endothelial cell damage, which includes a microangiopathy with fibrinoid degeneration and endothelial swelling,⁶ comparable to that seen in our patient. Further evidence for endothelial dysfunction in our patient can be deduced from her erythrocytic abnormalities. Polymorphisms in the *ABCD1* gene that encodes the P glycoprotein transporter, a multidrug efflux pump acting to exclude tacrolimus from the brain, may render some patients genetically susceptible to the adverse neurologic effects of tacrolimus.⁷

One common precursor of RPLS is hypertension and hypocholesterolemia. The posterior circulation is purportedly more vulnerable to alterations in blood pressure because of its relative paucity of sympathetic innervation.³ In our patient, neither hypocholesterolemia nor the sympathetic innervation seem operative because at least some of the leukoencephalopathy and endothelial damage was located in the frontal lobe and she was hypercholesterolemic. The temporal linkage of her leukoencephalopathy to toxic drug levels suggests that tacrolimus was the main determinant for the endothelial lesions, but mild hypertension may have played a synergistic role in the genesis of the vasogenic edema. Additional references may be found on line at www.neurology.org.

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