PEARLS

- Tacrolimus is an immunosuppressive agent that inhibits the activity of calcineurin. Neurologic adverse effects are varied and manifest irrespective of tacrolimus levels. These can include minor headaches and tremor to more severe seizures, cortical blindness, and coma.
- Tacrolimus-associated brainstem neurotoxicity is a rarely documented phenomenon that should be considered in the differential diagnosis of isolated brainstem T2 fluid-attenuated inversion recovery (FLAIR) hyperintensities on MRI, in addition to infectious, autoimmune, and neoplastic/paraneoplastic etiologies of rhombencephalitis (RE).

CASE REPORT A 52-year-old man with hepatitis C–induced cirrhosis underwent cadaveric liver transplant in July 2014. Postoperative immunosuppression included tacrolimus, mycophenolate mofetil, and prednisone. He presented 3 months later with 2 weeks of intermittent headaches, diplopia mostly with down gaze, and gait unsteadiness. He reported no constitutional symptoms. He was normotensive at 136/73 mm Hg. Pertinent findings on neurologic examination were sustained gaze-evoked direction beatings (figure, A) without corresponding diffusion-weighted imaging abnormality. Cerebral hemispheres were normal. Basic laboratory studies including sodium levels were unremarkable. He underwent extensive negative evaluation for etiologies of RE: negative erythrocyte sedimentation rate, C-reactive protein, HIV, galactomannan, 1,3-β-D-glucan, cryptococcus, and TB spot. CSF had one white blood cell, total protein 101 mg/dL, and negative Gram stain, bacterial and fungal culture, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, human herpesvirus 6, JC virus, and oligoclonal bands. Immunoglobulin G index was normal. A chest x-ray was negative. Brain PET scan revealed no abnormalities of FDG-PET uptake. Based on few reports in the literature of tacrolimus-induced neurotoxicity,1–5 we hypothesized that this was the potential culprit and changed to cyclosporine. Tacrolimus levels were therapeutic throughout his hospitalization (6.3–9.0 ng/mL). Two-week and 6-week follow-up MRI scans revealed reversal of imaging findings (figure, B and C), coincident with resolution of his neurologic complaints. Six months later, he continued without abnormal findings on neurologic examination or repeat MRI.

DISCUSSION RE is an inflammatory disorder of the hindbrain, involving the brainstem with or without cerebellum.6 Etiologies of RE are broadly categorized as infectious, autoimmune, and neoplastic/paraneoplastic. The most common etiologies in each category are as follows: listeria, enterovirus, and herpes simplex virus; multiple sclerosis and Behçet disease; and paraneoplastic syndromes associated with anti-Yo and anti-Tr antibodies, respectively.6 Rarer causes include JC virus, CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids), lymphoma, and subacute sclerosing panencephalitis. Clinical characteristics, CSF, and radiologic findings help guide the initial approach to diagnosis and management. Our patient had no fever, other constitutional symptoms, systemic disease, or CSF pleocytosis. Bickerstaff brainstem encephalitis, a GQ1b antibody–associated syndrome in the continuum of the Miller Fisher variant of Guillain-Barré syndrome, can share similarities of clinical and radiographic presentation with our patient.
In searching for potential causes of our patient’s constellation, we encountered reports of tacrolimus-associated brainstem neurotoxicity.\textsuperscript{1–5} Tacrolimus is an immunosuppressive agent that inhibits calcineurin phosphatase activity and T lymphocyte activation.\textsuperscript{7} Neurologic adverse effects range from tremors and headaches to cortical blindness and status epilepticus.\textsuperscript{8} These adverse effects manifest irrespective of tacrolimus levels.

Clinical findings of tacrolimus neurotoxicity are well described, but reports of neuroimaging correlates are rare. In one study of 7 patients with tacrolimus neurotoxicity,\textsuperscript{9} the posterior frontal and parietal lobes were involved in 6, the occipital lobe in 4. The predilection for parietal and occipital lobe injury has been well documented, sometimes accompanied by the clinical picture of posterior reversible leukoencephalopathy syndrome. The absence of a consistent clinical or radiographic correlate makes identification of tacrolimus neurotoxicity a diagnostic challenge, particularly when serum levels are not supratherapeutic. In a prospective study of 14 patients with tacrolimus neurotoxicity, 5 had white matter abnormalities on brain MRI, one had putaminal hemorrhage, and 8 were normal.\textsuperscript{10} We found only 5 prior reports describing tacrolimus neurotoxicity presenting as a pontine predominant lesion with hyperintense signal on T2-weighted MRI,\textsuperscript{1}–\textsuperscript{5} and in these cases, the clinical presentations varied widely.

Proposed mechanisms of tacrolimus neurotoxicity include cytotoxic edema after prolonged drug exposure, direct endothelial damage causing vasoconstriction, and inhibition of the expression of drug-efflux pumps.\textsuperscript{7} With documentation of posterior leukoencephalopathy, others have postulated hypertension to be a common pathway. The neuropathology of tacrolimus-related neurotoxicity includes demyelination, and endothelial damage with vasogenic edema in white matter in the absence of infarction and demyelination.\textsuperscript{11} Pontine involvement is thought to reflect a brainstem variant of posterior reversible leukoencephalopathy syndrome, or central pontine myelinolysis, a suggestion bolstered by autopsy results showing the incidence of central pontine myelinolysis after liver transplantation to be as high as 17\%.\textsuperscript{3}

Whatever the mechanisms leading to tacrolimus neurotoxicity, it is important that clinicians recognize tacrolimus as a potential cause of RE with isolated brainstem T2 FLAIR hyperintensity on MRI. In a retrospective observational study of 97 cases of RE, the etiology of 31 cases was ultimately not determined.\textsuperscript{6} Recognition that tacrolimus-related neurotoxicity is in the differential diagnosis of RE is therefore essential in ensuring prompt withdrawal of the offending agent and reversal of the neurologic and imaging manifestations.

**AUTHOR CONTRIBUTIONS**

Dr. Saadi: study concept and design, acquisition of data, analysis and interpretation. Dr. Schmahmann: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision.

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**REFERENCES**

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