Two Cases With Developing Neurologic Complications After Liver Transplant

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Abstract
The widespread use of immunosuppressive agents has significantly increased the rates of successful solid-organ and stem cell transplants, especially with liver and kidney. Cyclosporine and tacrolimus are most commonly used for this purpose. Although these agents have different mechanisms of action, both have various adverse effects, including nausea, vomiting, headache, hypertension, nephrotoxicity, and rarely epileptic seizures. In our first case, a patient presented with epileptic seizures and hemiparesis after a liver transplant, and posterior reversible encephalopathy syndrome related to cyclosporine toxicity was considered. Once cyclosporine levels in the blood decreased, the patient had both clinical and radiologic improvements.

In our second case, a patient presented with delirium after a liver transplant. Again, when cyclosporine levels in the blood decreased, the patient showed improvement in clinical findings. Neurologic complications may develop after liver transplant, and these complications are encountered most frequently within the first postoperative month. Neurologic complications are multifactorial; insufficient graft function, intracranial bleeding, cerebral infarcts, infections, and immunosuppressive drug toxicity (tacrolimus and cyclosporine) may be considered among these factors. As shown in our presented cases, most neurologic complications can be successfully treated by correcting the underlying factor.

Key words: Neurotoxicity, Transplant, Tacrolimus, Cyclosporine

Introduction
The widespread use of immunosuppressive agents has significantly increased the rates of successful solid-organ and stem cell transplants, especially with liver and kidney. Cyclosporine and tacrolimus are the commonly used agents for this purpose. Since the introduction of cyclosporine in the early 1980s, survival rates have increased to nearly 80%. Even when calcitonin inhibitory levels are normal, serum creatine levels may increase if the patient has a loss of volume. It is expressed in the patient’s total body fluid section. Another laboratory finding when a calcitonin inhibitor is elevated is hypercalcemia. Both cyclosporine and tacrolimus may cause rhabdomyolysis, which is as concerning as toxicity. Over the past decade, tacrolimus, another calcineurin inhibitor, has been shown to be as effective as cyclosporine for preventing allograft rejection; although both of these immunosuppressive agents have different mechanisms of action, both have adverse effects, including nausea, vomiting, headache, hypertension, nephrotoxicity, and rarely epileptic seizures. Central nervous system toxicity has been reported with both drugs, with the rate of neurologic complications after liver transplant of between 10% and 47%.

Case 1
Three weeks after receiving a liver transplant from a live donor, a 60-year-old woman presented with epileptic seizures, which had occurred 3 times, and sudden muscle weakness on her left side. Her neurologic examination revealed grade 4/5 left hemiparesis, which included her face, and a positive Babinski response, also on her left side. The patient had no previous history of epilepsy. Blood analyses showed a cyclosporine level of 670 ng/mL (normal range, 50-200 ng/mL) and a tacrolimus
level of 24 ng/mL (normal range, 5-20 ng/mL). Electroencephalogram results showed right parieto-occipital sharp wave activity (Figure 1A), and levetiracetam at 500 mg per day was prescribed. Brain magnetic resonance imaging showed an intensity increase in the bilateral basal ganglia and a contrast-enhanced lesion at the right parieto-occipital region (Figure 1B). These complications were considered to be related to her medications, with diminished complications after medications were decreased. At last follow-up, her neurologic examination revealed mild hemiparesis of the left upper and lower extremities, and she was seizure free.

Case 2

Ten days after liver transplant from a live female donor, a 64-year-old woman was admitted with delirium, convulsions, and hand tremors. Her neurologic examination was normal except for dysarthria. Blood analyses showed a cyclosporine level of 757 ng/mL (normal range, 50-200 ng/mL) and a tacrolimus level of 16 ng/mL (normal range, 5-20 ng/mL). Brain magnetic resonance imaging showed bilateral subdural effusions and intensity increases in the corpus striatum and brainstem (Figure 2A). Electroencephalogram results revealed diffuse slow wave activity (Figure 2B). After cyclosporine treatment was stopped, the patient no longer had delirium and dysarthria, with no abnormalities shown on a follow-up electroencephalogram (Figure 2C).

Discussion

In a study by Ghaus and associates, neurologic complications were evaluated in 65 pediatric liver transplant recipients. Two patients developed epileptic
seizures, and 7 patients developed encephalopathy. Brain magnetic resonance imaging showed hemorrhage and hyperintense lesions in the bilateral basal ganglia. The reported incidence of neurologic complications varies for different transplant centers. Mueller and associates reported a rate of approximately 21% after liver transplant, whereas Vogt and colleagues reported a rate of 42%. Over a 3-year period, Saner and associates recorded a rate of neurologic complications of 24.7% in transplant patients. Diffuse encephalopathy is considered to be the most common neurologic complication after liver transplant, with Adams and associates reporting an encephalopathy rate of 76%. Similar results were presented by Moreno and associates, who reported an encephalopathy rate of 73%. These results are similar to the finding in our previous study of 72.1%. However, one recently published article reported an encephalopathy rate of only 12.2%. The second most reported neurologic complication after transplant is seizures. In a liver transplant series, the incidence ranged from 0% to over 40% for patients who needed retransplants. In other series, 11.6% of transplant recipients developed seizures. Another study reported a seizure rate of only 1.6%. Solid-organ transplant patients who receive cyclosporine may present with headaches, dizziness, visual disturbances, and seizures. Magnetic resonance imaging often shows areas of hyperintensity when displayed with T2 weighting and fluid-attenuated inversion recovery contrast in the subcortical white matter of the posterior temporal, parietal, and occipital lobes. Overlying cortical gray matter may occasionally be involved. The frontal lobes also may be involved. This condition is termed “posterior reversible encephalopathy syndrome.” The most commonly encountered causes of posterior reversible encephalopathy syndrome are hypertensive encephalopathy, eclampsia, cyclosporine neurotoxicity, and a postictal state after seizure. In our first patient, posterior reversible encephalopathy syndrome related to cyclosporine toxicity was considered, as the patient presented with epileptic seizures and hemiparesis. After blood levels of cyclosporine decreased, both clinical and radiologic improvements were observed. Our second patient presented with delirium. As with the first patient, once cyclosporine levels had declined in the blood, the patient’s complications regressed. In the second patient, hyperintense lesions, detected in basal ganglia by brain magnetic resonance imaging, were thought to be related to the existing liver disease.

Neurologic complications may develop after liver transplant, with these complications most frequently encountered within the first postoperative month. Neurologic complications are multifactorial, with insufficient graft function, intracranial bleeding, cerebral infarcts, infections, and immunosuppressive drug toxicity (tacrolimus and cyclosporine) considered among these factors. As in our patients, most neurologic complications can be successfully treated by correcting the underlying factor.

References