Neurologic Complications After Renal Transplant

Nilgul Yardimci,[1] Turan Colak,[2] Sinasi Sevmis,[2] Sibel Benli,[1] Turgut Zileli,[1] Mehmet Haberal[2]

Abstract

Objectives: **Neurologic complications are a significant cause of morbidity and mortality in patients who undergo transplants. We sought to evaluate the nature and incidence of neurologic complications in patients undergoing a renal transplant.**

Patients and Methods: **Between January 2005 and December 2007, 132 adults (35 women, 97 men; mean age, 34.32 ± 0.90 years) underwent a renal transplant at our institution. Associated comorbid medical conditions, presenting neurologic symptoms, and type of immunosuppression were obtained from patients' medical records.**

Results: **Major indications for renal transplant were hypertensive nephropathy (14.4%), vesicoureteral reflux (11.4%), and idiopathic causes (21.2%). Mean follow-up was 17.26 ± 0.89 months (range, 2 weeks to 40 months). Twenty neurologic complications were found in 18 patients (6 women, 12 men; mean age, 33.83 ± 2.37 years). Presenting symptoms included posterior leukoencephalopathy syndrome, 1 (5.6%); cephalgia, 10 (55.6%); cerebral infarcts, 2 (11.1%); seizure, 3 (16.7%); tremor, 2 (11.1%); encephalopathy, 1 (5.6%); and sinus thrombosis, 1 (5.6%). Immunosuppressive agents were the primary cause of 16 of the 20 neurologic complications. Effectiveness and complications of cyclosporine were screened for a total of 1858.50 months, tacrolimus for 853.50 months, and sirolimus for 620 months; 50.2% of the neurologic complications appeared during the first 3 months after transplant; the blood level of immunosuppressive medications did not need to be higher than normal in every case.**

Discussion: **In addition to cyclosporine and tacrolimus, we suggest (for the first time) sirolimus as a cause of neurocomplications after renal transplant.**

Key words: *Immunosuppressive agents, Sirolimus, Neurologic symptoms, Morbidity*

Organ transplant traces its origins to a landmark operation by Murray in Boston in 1954 in which an identical twin received a donated sibling kidney (1). Since that seminal procedure, advances in tissue matching, improvements in surgical technique, and new and more-powerful immunosuppressive agents have increased the number and types of transplants that can be done. Advances in immunology and transplant technique have allowed longer survival for transplant recipients, but this has resulted in the emergence of several neurologic problems.

The kidney is the most frequently transplanted organ with more than 10000 transplants occurring per year worldwide. Since that historic operation, kidney transplants have developed into the best-accepted therapy for most causes of end-stage renal failure. The 1-year survival rate is close to 100%, with an 85% to 95% graft survival rate (2). However, despite these advances, neurologic complications after renal transplants occur approximately 30% of the time (3, 4).

Several characteristics of renal transplant patients make overall complication rates in these persons different from those of other organ transplant recipients. Many renal transplant patients have some degree of vascular compromise either as a result of their underlying disease (eg, hypertension, diabetes) or because of emboli associated with underlying

From the Departments of [1]Neurology and [2]General Surgery, Baskent University Faculty of Medicine, Ankara, Turkey

Address reprint requests to: *Nilgul Yardimci, Baskent University Faculty of Medicine, Department of Neurology, Fevzi Cakmak Cad 10. Sok No:45, Bahcelievler, Ankara, 06490 Turkey*
***Phone**: +90 312 2126868 **Fax:** +90 312 2237333 **E-mail:** ntuncel@yahoo.com*

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atherosclerosis or heart disease (5). After transplant, neurologic complications may develop secondary to the transplant itself, the immunosuppressive agent, or a previously known organ parenchymal failure.

Patients and Methods

The medical reports of 132 renal transplant recipients who had been operated on between January 2005 and December 2007 were analyzed retrospectively for presence of neurologic complications. The cutoff time for follow-up was June 2008. Male and female patients, 18 years of age or older, who had received a kidney transplant (first or second transplant) qualified for inclusion in the study. Thirty-five kidney recipients were women and 97 were men. We reviewed 142 episodes of renal transplant in 132 patients (10 patients were retransplanted). The causes of end-stage renal disease in all of the patients and the total dialysis time before transplant were assessed.

Significant medical histories other than chronic renal disease for these patients also were evaluated. We analyzed 20 episodes of neurologic complications in 18 patients (2 patients had 2 different episodes of neurologic complications). The type and incidence of neurologic complications, the type of immunosuppressive medication used, and the onset of symptoms were evaluated.

Results

We evaluated 132 patients who had undergone a renal transplant. Ninety-seven of the recipients (73.5%) were men and 35 (26.5%) were women (M:F=2.77:1). The mean age of the recipients was 34.32 ± 0.90 years (range, 18-66 years). One hundred forty-two transplants were done; 10 patients had a retransplant. Among these 142 transplants, 36 grafts (25%) were taken from a deceased donor, and 106 (75%) were obtained from a living donor (deceased:living donor=1:3).

The most common renal diseases leading to renal transplant were hypertension (19 patients, 14.4%), vesicoureteral reflux (15 patients, 11.4%), and glomerulonephritis (membranoproliferative, 7 patients [5.3%]; mesangioproliferative, 6 patients [4.5%], and focal segmental glomerulosclerosis, 10 patients [7.6%]). In 28 patients (21.2%), the cause of end-stage renal disease was unknown. The mean duration of renal disease before renal transplant was 63.11 ± 5.74 months (range, 1-444 months); of these, 115 had received dialysis for a mean of 35.57 ± 3.24 months (range, 1-156 months). Thirty-five patients (26.5%) had received continuous ambulatory peritoneal dialysis for a mean of 24.68 ± 3.6 months (range, 1-84 months; total, 863.96 months); 89 patients (67.4%) had undergone hemodialysis for a mean of 36.26 ± 3.70 months (range, 1-144 months; total, 3227.72 months). Seventeen patients had not received any type of dialysis. At the time of transplant, 103 patients (78%) had hypertension, and 21 (15.9%) had hyperlipidemia. The mean follow-up was 17.26 ± 0.89 months (range, 2 weeks to 40 months; total, 2279.50 months).

Neurologic complications were observed in 18 patients (13.6%; mean age, 33.83 ± 2.37 years; range, 20-59 years). Those 18 individuals experienced a total of 20 episodes of neurologic complications (2 separate episodes in 2 of the patients). The observed 20 neurologic complications were classified as follows: headache (10 episodes; 55.6%), seizure (3 episodes; 16.7%), cerebral infarcts (2 episodes; 11.1%), tremor (2 episodes; 11.1%), encephalopathy (1 episode; 5.6%), sinus thrombosis (1 episode; 5.6%), and posterior leukoencephalopathy syndrome (1 episode, 5.6%). Immunosuppressive agents were the primary cause of 16 of the 20 episodes of neurologic complications. Encephalopathy due to hyponatremia (1 patient), sinus thrombosis (1 patient), and stroke (2 patients) were the other causes of neurologic complications.

Of the 10 episodes with headache, 7 patients had been receiving cyclosporine for a mean of 6.04 ± 2.99 months (range, 2 days to 23 months), 2 patients had been receiving sirolimus for a mean of 10.5 ± 6.5 months (range, 4-17 months), and 1 patient had been receiving tacrolimus for 7 months. When cyclosporine blood levels of these patients with headache were analyzed, cyclosporine concentrations were within normal limits in 4 patients, and they were higher than normal in 3 patients. Tacrolimus and sirolimus blood concentrations all were within normal limits in the other patients with headache.

We observed seizures in 3 patients, each of whom had been receiving cyclosporine, tacrolimus, or sirolimus. None of the patients had seizures before the transplant. The first patient had a seizure during the first month after transplant, and the blood concentration of cyclosporine was 305 ng/mL. The second patient had been taking tacrolimus for 1

month; the blood level at the time seizure occurred was 19 ng/mL. The third patient had been taking sirolimus for 3 months; the concentration at the time of the symptom was 17 ng/mL. At the time of the seizure, there were no electrolyte disturbances or clinical events that could precipitate seizures. Functioning of the kidneys was within normal limits. Plasma sodium and magnesium concentrations were within normal ranges. None of these patients had a fever, and none was on any other medication that could cause a convulsion. The results of brain magnetic resonance imaging scans all were normal, with no evidence of a mass lesion.

Tremor developed in 2 patients who had been taking cyclosporine for a mean of 0.62 ± 0.37 months (range, 1 week to 1 month). The cyclosporine blood concentration was within normal limits in 1 patient and higher than normal in the other. However, tremor was so severe in these patients, that cyclosporine had to be switched to another calcineurin inhibitor. One patient developed posterior leukoencephalopathy syndrome after taking tacrolimus for 11 months (blood concentration, 5.5 ng/mL). The patient clinically presented with altered mental functioning and seizures associated with symmetrical, posterior, hemispheric edema, which was apparend on cranial magnetic resonance imaging.

We observed encephalopathy due to hyponatremia (118 mmol/L) in 1 patient. Cerebrovascular infarcts were present in 2 patients, and a sinus thrombosis was observed in 1 patient.

Discussion

Several characteristics of renal transplant patients make overall complication rates in these persons different from those of other organ transplant recipients. Neurologic complications are frequent (range, 30%-60%) in renal transplant recipients and may largely contribute to morbidity and mortality (3, 4, 6). Posttransplant neurologic complications may be categorized as due to immunosuppressive medications, stroke, infection, neuropathies, and malignancies. Several complications are directly caused by the neurotoxicity of immunosuppressive agents. Calcineurin inhibitors may cause symptoms such as tremor and paresthesia, or more severe symptoms such as disabling pain syndrome and leukoencephalopathy.

Posttransplant headache is a recognized complication of organ transplant, both in the form of a de novo headache or worsening of a known migraine (7, 8, 9). Given their vasoactive properties, immunosuppressive agents like cyclosporine and tacrolimus are thought to play a role; however, the exact mechanisms by which immunosuppressive agents induce or exacerbate headache are unknown. Commonly considered a minor problem, post-transplant headache is seldom thought of as becoming intense and disabling; however, the symptom is disabling and significantly lowers the quality of life (8, 9). In our study, headache was the most frequent neurologic complication occurring in 55.6% of patients. Among 10 patients with headache (7.6%; mean length of onset, 8.23 ± 2.62 months, range, 0.07-23 months), 7 received cyclosporine, 2 received sirolimus, and 1 received tacrolimus. The patients developed headache while taking tacrolimus for a mean of 7 months, sirolimus for a mean of 10.5 months, and cyclosporine for a mean of 5.75 months. In only 3 of the patients taking cyclosporine, the level of the drug in the serum was higher than the therapeutic range.

Seizure occurs frequently in transplant recipients, manifesting in 6% to 36% of patients (10, 11). The most common causes of seizures in the transplant population include drug toxicity (especially cyclosporine and tacrolimus), metabolic de-rangements (especially hypomagnesemia), and hypoxic-ischemic injury (12). Less common causes of seizures are strokes and infections. Cyclosporine is epileptogenic (13) and causes seizures in 2% to 6% of patients receiving it (14, 15, 16). Tacrolimus is the cause of seizure in 5.6% to 11.6% of the patients who have one (17). We evaluated seizures in 3 patients (2.3%), each of whom had been receiving cyclosporine, tacrolimus, or sirolimus. None of the patients had a seizure before transplant.

Many renal transplant patients have some degree of vascular compromise, either as a result of their underlying disease (hypertension, diabetes) or because of emboli associated with underlying atherosclerosis or heart disease (5). The most common posttransplant neurologic complications in this patient population are cerebrovascular events; these occur in approximately 9% of all renal transplant patients (4, 6, 18). We assessed infarcts in 2 patients (1.5%). Stroke may occur in about 8% of renal transplant patients (19).

An increased risk of venous thromboembolism also has been demonstrated after renal transplant. Commonly reported sites have been deep vein thrombosis, pulmonary thromboembolism, and vascular thrombosis involving the graft. Cerebral venous thrombosis has not been reported thus far. We assessed transverse sinus thrombosis in 1 patient (0.8%).

Tremor is another common complication, which is frequently seen after transplant; sometimes present in up to 40% of patients (16). Tremor is mostly the consequence of immunosuppressive treatment. The most pronounced neurotoxic effect is induced by the calcineurin inhibitors, tacrolimus and cyclosporine. The spectrum of neurologic disturbances caused by calcineurin inhibitors ranges from mild symptoms such as paraesthesia, tremor, headache, or flushing, to severe changes that can cause a lethal outcome. In our study, we evaluated 2 patients (1.5%) with tremor while taking cyclosporine. To control tremor, the drug must be switched to another calcineurin inhibitor. In fact, tremor in most of the recipients is the result of immunosuppressive agents. However, if severity of the tremor is not significant and does not worsen the patient's quality of life, there is a tendency to ignore the symptom (because survival of the graft is the ultimate goal in immunosuppressive therapy). In the current study, we observed only 2 tremors; however, these were severe enough to warrant a change in the immunosuppressive protocol. The slight tremor in the other recipients probably had been underestimated in the patients' records.

Posterior leukoencephalopathy syndrome is most commonly seen in patients with hypertensive encephalopathy, eclampsia, renal failure, or use of immunosuppressive agents (20). In the transplant population, posterior leukoencephalopathy syndrome is a well-known complication of immunosuppressive therapy with cyclosporine and tacrolimus (20). In the current study, we observed 1 patient (0.8%) with posterior leukoencephalopathy syndrome. *Posterior leukoencephalopathy syndrome* is a term first used by Hinchey and associates (20) to describe a group of disorders that present clinically with headache, seizures, visual disturbances, and altered mental function associated with symmetrical posterior hemispheric edema. The cause of posterior leukoencephalopathy syndrome is not fully understood but is believed to be due to a breakdown in cerebral autoregulation that results in leakage of fluid into the interstitium, which is detected as vasogenic edema (21).

Encephalopathy is a severe adverse effect of cyclosporine and tacrolimus, occurring in approximately 5% of patients taking the drugs. These patients may present with a decreased level of consciousness, headache, dysarthria, depression, mania, cortical blindness, visual hallucinations, and seizures (22). The syndrome is usually found in patients with elevated blood calcineurin inhibitor levels; however, other factors, such as hypocholesterolemia, hypomagnesemia, hyponatremia, high-dose steroids, hypertension, and uremia may be involved as well. We observed encephalopathy due to hyponatremia in 1 patient (0.8%); the encephalopathy resolved after the hyponatremia ameliorated.

In the current study, we did not evaluate any malignancies or central nervous system infections that are other frequent causes of neurologic complications in transplant recipients.

Despite advances in organ transplant technology, neurologic complications remain a significant cause of morbidity and mortality. Improved surgical techniques and perioperative care have reduced the rates of mortality and morbidity of many organ transplant procedures to acceptable levels. The major challenge for the future is to develop agents and strategies for management that can effect selective tolerance to the donated organ without paralyzing the immune system. Some of the neurologic complications of a renal transplant are due to the underlying disease for which the transplant was performed. On the other hand, neurotoxicity can be a serious complication due to drug-specific toxicity of immunosuppressive therapy after renal transplant. Cyclosporine and tacrolimus are immunosuppressive agents that have been well studied for their adverse effects, including their neurologic complications. However, there is a paucity of data regarding the neurocomplications of sirolimus at this time.

In this study, we examined the potential neurologic adverse effects of sirolimus. The other important issue is that the blood concentration of a particular immunosuppressive agent at the time of neurologic symptoms is not the only factor leading to neurocomplications; simply taking the immunosuppressive agent, itself, is the most important factor.

Follow-up of recipients for neurologic complications is important and may lead to changes in the immunosuppressive protocol. Because more than half of the neurologic symptoms occur during the first 3 months after a transplant, careful follow-up, including monitoring for any neurologic symptoms, by a neurologist familiar with complications of an organ transplant can significantly contribute to the effectiveness of the transplant team.

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