

Neurological Complications after Renal Transplantation: A Retrospective Clinical Study

Nilgün CENGİZ¹, Zelal ADIBELLİ², Yarkın Kamil YAKUPOĞLU³, Hande TÜRKER¹

¹Department of Neurology, Ondokuz Mayıs University, Faculty of Medicine, Samsun, Turkey

²Department of Nephrology, Atatürk State Hospital, Antalya, Turkey

³Department of Urology, Ondokuz Mayıs University, Faculty of Medicine, Samsun, Turkey

ABSTRACT

Introduction: The aim of this study was to evaluate the incidence and types of neurological complications (NCs) and associated factors in renal transplantation (RT) patients.

Methods: Three hundred and forty-four patients who had RT performed at our institution between January 2005 and July 2014 were retrospectively evaluated.

Results: File records of the patients revealed 19 who experienced a total of 22 episodes of NCs, of whom three had more than one episode. The mean age of 19 patients included in the study, of whom eight were female, was 37.52±13.08 (range, 18–65) years. NCs were classified into central or peripheral depending on the location of involvement of the central nervous system (CNS). CNS involvement was found in 16 (84.2%) of the 19 patients. Tremor (36.8%) was the most common CNS complication in these patients. Encephalopathy, generalized tonic-clonic seizures, and status epilepticus were

observed in two patients (10.5%). Delirium and dementia were observed in one patient (5.2%). Headache was experienced by one patient, and agitated depression was observed in one patient. Six patients (26.3%) had the peripheral nervous system involvement. One patient had the numbness of hands with normal electromyography findings, and four patients had polyneuropathy. In one patient, lumbar plexopathy was observed. Seventeen of the 22 NCs were considered to be caused by immunosuppressive agents. Each incidence of amyloidosis, infection, septic emboli, and hypoglycemia caused a neurological episode. The etiology of one episode was unknown.

Conclusion: Different neurological disorders can be seen after RT, and most of them are caused by immunosuppressive drugs. NCs seen after RT can be treated by decreasing the dose or changing the immunosuppressive drug.

Keywords: Encephalopathy, neurological complications, renal transplantation, renal failure

INTRODUCTION

Neurological complications (NCs) after transplantation are still a major problem and cause significant mortality and morbidity, despite improvements in organ preservation, surgical techniques, and immunosuppressive treatment. These complications may be caused by an underlying primary disorder, particularly diabetes mellitus, owing to renal failure, neurotoxicity of immunosuppressive drugs or surgical procedures, or their combination (1,2,3,4,5). These complications may involve the central or peripheral nervous system (PNS). NCs after renal transplantation (RT) were described in the previous studies, but their electrophysiological findings were not evaluated. The aim of this study was to evaluate the types of NC and their electrophysiological findings in RT patients. Besides, treatment methods of NC after RT were also investigated under the light of the English literature.

METHODS

In this study, 344 patients who had RT performed at the Ondokuz Mayıs University Hospital between January 2005 and July 2014 were retrospectively evaluated. All patients were administered tacrolimus, mycophenolate mofetil, and prednisolone with induction treatment initially comprising basiliximab or antithymocyte globulin. In case of tacrolimus toxicity, it was switched to cyclosporine or sirolimus.

File records of the patients revealed 19 cases having 22 episodes of NC, of which three cases had more than one episode. Electroneuromyography (EMG) was performed on six patients with signs of polyneuropathy, and electroencephalography (EEG) was performed on six other patients.

Descriptive statistics regarding age, gender, and frequency of NCs were analyzed. NCs were classified as central or peripheral. This study was performed according to the tenets of the Declaration of Helsinki.



Correspondence Address: Dr. Nilgün Cengiz, Ondokuz Mayıs Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, Samsun, Türkiye
E-mail: drnilcen@yahoo.com

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RESULTS

A total of 22 episodes of NC was identified in 19 patients (8 females, 11 males), three of whom had more than one episode. The mean age of the 19 patients enrolled in the study was 37.52 ± 13.08 (range, 18–65) years. The demographic data of the patients and their NCs are summarized in Table 1. Central nervous system involvement was found in 16 (84.2%) patients. Seven (36.8%) of the 19 patients had tremors. Generalized tonic-clonic status epilepticus, tonic-clonic seizures, and encephalopathy were observed in two (10.5%) cases. One had delirium and dementia (5.2%), one had agitated depression (5.2%), and one had headache (5.2%).

Polyneuropathy appeared after encephalopathy in one of the three patients who had multiple episodes of NCs. Other two patients had tremor and agitated depression or polyneuropathy.

Seven of the 22 (31.8%) episodes of NCs were tremor. Six of the seven patients with tremor were using tacrolimus, and one patient was using cyclosporine. All of these patients had bilateral postural hand tremor; in advanced cases, additional kinetic tremor was observed. However, none of them had resting tremor. Three patients (No.1, 2, 6) had tremor prior to

RT, but it did not affect their daily lives. Tremor of these patients increased after RT to a degree that it prevented eating. In the other four patients, tremor emerged after RT. Three of the seven patients had tremors in the limbs, and one of these patients also had lower-extremity neuropathy.

Two of the 22 episodes of NCs (9.0%) were generalized tonic-clonic status epilepticus, and two (9.0%) were generalized tonic-clonic seizures. All four patients were taking tacrolimus. They are still under the antiepileptic drug treatment. One (4.5%) of the 22 episodes of NCs was diagnosed as agitated depression and responded immediately to a change in medication from tacrolimus to sirolimus. Delirium occurred in one patient because of infection, and the patient recovered after antibiotic treatment; one patient had a migraine-type headache with a history of 2 weeks that was relieved with beta-blocker therapy.

Six patients (26.3%) had a PNS involvement; one case had numbness of hands but normal EMG. Four patients were diagnosed with polyneuropathy according to clinical and electrophysiological findings, three of whom had polyneuropathy caused by immunosuppressive drugs (cyclosporine, two patients; tacrolimus, one patient) and one had polyneuropathy caused

Table 1. The demographic data of patients and their neurological complications

Patient	Age (years) Sex	Development of NCs	Type of NC(s)	Symptoms	Indication for RT	Cause(s) of NC(s)	Diagnostic tools used		
							EMG	EEG	MRI
1	40/M	Before RT	Tremor	Hand tremor	Glomerulonephritis	Tacrolimus	-	-	-
2	32/F	Before RT	Tremor	Hand tremor	Polycystosis	Tacrolimus	-	-	-
3	33/M	15 days	Tremor	Hand and Leg tremor	Chronic renal failure	Tacrolimus	-	-	-
4	56/M	15 days	Tremor	Hand and Leg tremor	Polycystosis	Tacrolimus	-	-	-
		15 days	Polyneuropathy	Leg weakness and sensory disturbances	Polycystosis	Tacrolimus	+	-	-
5	37/F	15 days	Tremor	Hand and Leg tremor	UTI	Tacrolimus	-	-	-
6	35/M	Before RT	Tremor	Hand tremor	Unknown	Cyclosporine	-	-	-
7	23/F	1 week	Tremor	Hand tremor	Hypertension	Tacrolimus	-	-	-
		4 months	Depression	Depression	Hypertension	Tacrolimus	-	-	-
8	32/F	1.5 months	Encephalopathy	Confusion	Unknown	Tacrolimus	-	+	+
		2 months	Polyneuropathy	Weakness in limbs	Unknown	Cyclosporine	+	-	-
9	65/M	7 months	Dementia Delirium	Delirium	Hypertension	Infection	-	+	-
10	55/M	4 years	Lumbar radiculopathy	Unilateral thigh pain	Diabetes mellitus and hypertension	Unknown	+	-	-
11	18/M	5 years	Polyneuropathy	Unilateral thigh pain and leg weakness	Amyloidosis and FMF	Amyloidosis	+	-	-
12	36/M	4 years	Polyneuropathy	Sensory ataxia	Unknown	Cyclosporine	+	-	-
13	48/M	4 months	Sensory disturbance	Hand numbness	Bilateral nephrolithotomy	Tacrolimus	+	-	-
14	26/M	2 years	Seizure	GTC seizure	Polycystosis	Tacrolimus	-	+	+
15	42/F	5 years	Status epilepticus	GTC seizures	Diabetes mellitus	Hypoglycemia	-	+	-
16	36/M	4 years	Status epilepticus	GTC seizures	Nephritis	Tacrolimus	-	+	-
17	23/F	6 years	Headache	Headache	Unknown	Tacrolimus	-	-	-
18	22/F	10 days	Seizure	GTC seizure	Bilateral renal atrophy	Septic emboli	-	+	-
19	54/F	4 days	Encephalopathy	Confusion GTC seizures	Unknown	Tacrolimus	-	+	+

RT: renal transplantation; EEG: electroencephalography; EMG: electroneuromyography; MRI: brain magnetic resonance imaging; NCs: neurological complications; UTI: urinary tract infection; PNP: polyneuropathy; FMF: familial Mediterranean fever

by amyloidosis. In the other patient with lumbar plexopathy, the cause is being investigated.

Sensory ataxia and progressive sensory polyneuropathy were observed in one patient (No.12) who received cyclosporine for 4 years. Neurological examination revealed deep sensory impairment, normal somatosensory evoked potentials (SEP) and cervical MRI, and low vitamin B12 and ferritin levels; however, even after the correction of these parameters, progression in clinical and EMG findings was observed. The administration of cyclosporine, which was considered as the cause of polyneuropathy, was discontinued. There was improvement in symptoms after the discontinuation of cyclosporine.

In another patient (No.8) with acute axonal mixed polyneuropathy, cyclosporine level was very high, i.e., 1138 (100–400) ng/dL. When the concentration of the drug in the blood decreased to 213 ng/dL, the patient's symptoms almost completely disappeared.

Another cachectic patient who had meralgia paresthetica and severe sensory symptoms (No.11) was considered to have polyneuropathy because of amyloidosis. The patient was administered codeine for severe pain in one thigh. This patient, who also had autonomic gastrointestinal symptoms (diarrhea) and pituitary deficiency, had the most severe clinical symptoms of all the patients and died from cardiac arrest.

Fourteen of 22 NC were considered to be caused by the immunosuppressant tacrolimus and three were caused by cyclosporine. Amyloidosis, infection, septic emboli, and hypoglycemia were other causes of NCs. In one patient, the etiology was unknown.

DISCUSSION

Our study evaluated NCs after RT. There are few studies on this issue in the literature; neurological signs and symptoms after RT, such as encephalopathy, the PNS involvement, tremor and headache, have been reported (1,2,3,4,5).

Tremor is one of the most common neurological symptoms after RT, and different incidence rates of tremor have been reported (4). Yardimci et al. (5) reported a tremor rate of 11.1%. whereas in our study, it was 36.8%, which is much higher. In a multi-center study conducted in Europe, 448 RT patients were randomly selected. In their immunosuppressive therapy, they were receiving either cyclosporine (n=145) or tacrolimus (n=303) (6). The incidence of tremor in patients receiving tacrolimus (34.7%) was higher than that in patients receiving cyclosporine (11.7%) ($p<.001$). In another study, 412 patients were receiving either tacrolimus (n=205) or cyclosporine (n=207) for immunosuppression. In that study, the incidence of tremor in patients who received tacrolimus (54.1%) was higher than that in patients who received cyclosporine (33.8%) ($p<.001$) (7).

The mechanism by which tacrolimus causes tremor is not fully understood; however, there has been a study indicating that the level of calcineurin inhibitors (CNI) is associated with the tremor (8). Calcineurin inhibition by cyclosporine and tacrolimus alters sympathetic outflow, which may play a role in the mediation of tremor (9).

Diffuse encephalopathy is diagnosed with mental illness, generalized tonic-clonic status, seizures, or encephalopathic EEG and normal cranial MRI findings. Posterior leukoencephalopathy syndrome (PLES) is a reversible encephalopathy, which partially affects the cerebral cortex, and the sym-

metric involvement of posterior regions has been commonly reported. PLES is clinically characterized by altered mental status, seizures, and frequent visual disturbances, and it is generally reported in patients who receive immunosuppressive drugs after transplantation (10,11,12,13,14). In our study, the sudden onset of drowsiness, diffuse delta and theta waves in EEG, and a suicide attempt in one patient suggested diffuse encephalopathy. The absence of clinical hypertension, blurred vision, or headache and other focal neurological findings also indicated diffuse encephalopathy. However, a limitation of unilateral diffusion in the right cerebellum in the cranial MRI of the patient suggested PLES. In the study by Kastrup et al. (10), there was not only unilateral cerebellar involvement but also additional cerebral lesions in all of the 50 patients with PLES. The clinical condition and EEG improved after tacrolimus was switched to cyclosporine in one of our patient with a normal tacrolimus level. However, she developed acute axonal polyneuropathy after cyclosporine treatment. PNP findings that occurred while receiving cyclosporine improved when the dosage was reduced. There was axonal involvement in both the central nervous system (CNS) gray matter and the PNS of the patient, suggesting it was not a demyelinating process but a direct attack on neurons. In this patient, the toxic effects appeared in response to two CNI (cyclosporine and tacrolimus). In our opinion, the monitoring of drug levels is very important and medication should not be changed in polyneuropathies, which can improve by the reduction of drug doses.

We assert that the neuropathic symptoms of this patient resulted from dose-dependent toxic effects of the cyclosporine because the patient had been using the same drug for 5 years.

One patient with both CNS and neuropathy was reported in the literature; however, the involvement of both systems was observed while the patient was taking tacrolimus and inadvertently had an overdose of the drug (11).

Cyclosporine and tacrolimus (CNI) are known to be a substrate of cytochrome P450 (CYP) 3A5 and P-glycoprotein (P-gp), which are encoded by CYP3A5 gene and ATP-binding cassette subfamily B member 1 (ABCB1) gene, also known as multidrug-resistant gene 1 (MDR1), respectively (15,16,17,18). Yanagimachi et al. (19) showed an association between CNI-related neurotoxicity and gene polymorphism in the ABCB1 and CYP3A5 genes in patients with hematopoietic stem cell transplantation. These gene polymorphisms may explain the reason for CNS side-effect patterns in some patients. However, we did not search gene polymorphism in our study population; two of our patients with severe encephalopathy may have had gene polymorphism. CYP3A5 gene polymorphism results in the inhibition of the metabolism of two different CNIs and may cause encephalopathy and polyneuropathy.

In our study, the other tacrolimus-induced the CNS involvement was agitated depression, which was switched to sirolimus. Headache was recorded in 56% of the patients in another study, but it was 5.2% in our study (5).

There are usually case reports regarding PNP after RT, and femoral neuropathy is the most common type of neuropathy (20,21,22,23,24,25,26,27). However, there was no femoral neuropathy in our patients.

In the literature, cyclosporine-induced axonal sensory and sensorimotor polyneuropathy after RT have been reported in two patients (21,22). In our study, cyclosporine-induced sensorimotor axonal polyneuropathy was diagnosed by EMG and clinical findings in two patients. Although cyclospo-

rine-induced axonal neuropathies are very rare, Guillain–Barre Syndrome (GBS) was reported in one patient and CIDP was reported in another patient after transplantation (23,24).

Bhagavati et al. (25) reported that two patients developed tacrolimus-induced polyneuropathy after RT; one had block with axonal neuropathy in the left ulnar nerve and the other had demyelinating neuropathy. Another demyelinating polyneuropathy was reported in one patient who received tacrolimus after RT by Echaniz-Laguna (24). In one of our patients who developed tacrolimus-induced neuropathy, there were axonal and demyelinating (mixed-type) neuropathy findings. These findings appeared while the patient was receiving therapeutic doses of tacrolimus. Tacrolimus may have increased his polyneuropathic symptoms because this patient had undergone dialysis for many years and had neuropathic symptoms before RT.

Uremic neuropathies are generally reported to be sensorimotor and axonal (28). In the literature, the symptoms of uremic neuropathy are reported to resolve after RT (29,30), while in our patients, these symptoms emerged or progressed after RT despite modification or reduction of the dosage of medications.

This is a retrospective study. Because the patients were followed up for 1–9 years at our center, this facilitated the close monitoring of clinical and electrophysiological responses of patients to the modifications in medication. Different neurological disorders can be seen after RT, and most of them are caused by immunosuppressive drugs and can be treated by decreasing the dose or switching the immunosuppressive drugs.

Prospective studies, which focus on the assessment of neurological complication of patients who undergo RT, can help to achieve better patient outcomes.

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REFERENCES

- Ponticelli C, Campise MR. Neurological complications in kidney transplant recipients. *J Nephrol* 2005; 18:521-528.
- Bruno A, Adams HP Jr. Neurologic problems in renal transplant recipients. *Neurol Clin* 1988; 6:305-325.
- Lee JM, Raps EC. Neurologic complications of transplantation. *Neurol Clin* 1998; 16:21-33. [\[CrossRef\]](#)
- Ce P, Koskderelioglu A, Coban G, Gedizlioglu M, Nart A, Uslu A. Neurologic complications of renal transplant. *Exp Clin Transplant* 2012; 10:243-246. [\[CrossRef\]](#)
- Yardimci N, Colak T, Sevmis S, Benli S, Zileli T, Haberal M. Neurologic complications after renal transplant. *Exp Clin Transplant* 2008; 6:224-228.
- Mayer AD, Dmitrewski J, Squifflet JP, Besse T, Grabensee B, Klein B, Eigler FV, Heemann U, Pichlmayr R, Behrend M, Vanrenterghem Y, Donck J, van Hooff J, Christiaans M, Morales JM, Andres A, Johnson RW, Short C, Buchholz B, Rehmert N, Land W, Schleibner S, Forsythe JL, Talbot D, Pohanka E. Multicenter randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection: a report of the European Tacrolimus Multicenter Renal Study Group. *Transplantation* 1997; 64:436-443. [\[CrossRef\]](#)
- Neylan JF, Sullivan EM, Steinwald B, Goss TF. Assessment of the frequency and costs of posttransplantation hospitalizations in patients receiving tacrolimus versus cyclosporine. *Am J Kidney Dis* 1998; 32:770-777. [\[CrossRef\]](#)
- Veroux P, Veroux M, Puliatti C, Morale W, Cappello D, Valvo M, Macarone M. Tacrolimus-induced neurotoxicity in kidney transplant recipients. *Transplant Proc* 2002; 34:3188-3190. [\[CrossRef\]](#)
- Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. *Transpl Int* 2000; 13:313-326. [\[CrossRef\]](#)
- Kastrup O, Schlamann M, Moeninghoff C, Forsting M, Goerick S. Posterior Reversible Encephalopathy Syndrome: The Spectrum of MR Imaging Patterns. *Clin Neuroradiol* 2014 Feb 20.
- Wu G, Weng FL, Balaraman V. Tacrolimus-induced encephalopathy and polyneuropathy in a renal transplant recipient. *BMJ Case Rep* 2013; 2013.
- Cadavid-Aljure D, Caicedo-Paredes A, Meza JC, Granados-Sánchez AM, Posada-Chávez JG, Mesa-Ramírez L, Schweineberg-López J. Tacrolimus associated to posterior reversible atypical encephalopathy syndrome and brain haemorrhage in renal transplant recipient. *Nefrologia* 2012; 32:861-863.
- Chegouchi M, Hanna MG, Neild GH. Progressive neurological disease induced by tacrolimus in a renal transplant recipient: case presentation. *BMC Nephrol* 2006; 7:7. [\[CrossRef\]](#)
- Kastrup O, Gerwig M, Frings M, Diener HC. Posterior reversible encephalopathy syndrome (PRES):electroencephalographic findings and seizure patterns. *J Neurol* 2012; 259:1383-1389. [\[CrossRef\]](#)
- Fredericks S, Holt DW, MacPhee IA. The pharmacogenetics of immunosuppression for organ transplantation: a route to individualization of drug administration. *Am J Pharmacogenomics* 2003; 3:291-301. [\[CrossRef\]](#)
- Mourad M, Wallemacq P, De Meyer M, Malaise J, De Pauw L, Eddour DC, Goffin E, Lerut J, Haufroid V. Biotransformation enzymes and drug transporters pharmacogenetics in relation to immunosuppressive drugs: impact on pharmacokinetics and clinical outcome. *Transplantation* 2008; 85:19-24. [\[CrossRef\]](#)
- Eichelbaum M, Fromm MF, Schwab M. Clinical aspects of the MDRI (ABCB1) gene polymorphism. *Ther Drug Monit* 2004; 26:180-185. [\[CrossRef\]](#)
- Yamauchi A, Ieiri I, Kataoka Y, Tanabe M, Nishizaki T, Oishi R, Higuchi S, Otsubo K, Sugimachi K. Neurotoxicity induced by tacrolimus after liver transplantation: relation to genetic polymorphisms of the ABCB1 (MDRI) gene. *Transplantation* 2002; 74:571-572. [\[CrossRef\]](#)
- Yanagimachi M, Naruto T, Tanoshima R, Kato H, Yokosuka T, Kajiwara R, Fujii H, Tanaka F, Goto H, Yagihashi T, Kosaki K, Yokota S. Influence of CYP3A5 and ABCB1 gene polymorphisms on calcineurin inhibitor-related neurotoxicity after hematopoietic stem cell transplantation. *Clin Transplant* 2010; 24:855-861. [\[CrossRef\]](#)
- Junaid I, Kwan JT, Lord RH. Femoral neuropathy in renal transplantation. *Transplantation* 1993; 56:240-241. [\[CrossRef\]](#)
- Sayin R, Soyoral YU, Erkoc R. Polyneuropathy due to cyclosporine A in patients with renal transplantation: a case report. *Ren Fail* 2011; 33:528-530. [\[CrossRef\]](#)
- Etemadi J, Shoja MM, Ghabili K, Talebi M, Namdar H, Mirnour R. Multiple etiologies of axonal sensory motor polyneuropathy in a renal transplant recipient: a case report. *J Med Case Rep* 2011; 5:530. [\[CrossRef\]](#)
- Falk JA, Cordova FC, Popescu A, Tatarian G, Criner GJ. Treatment of Guillain-Barré syndrome induced by cyclosporine in a lung transplant patient. *J Heart Lung Transplant* 2006; 25:140-141. [\[CrossRef\]](#)
- Echaniz-Laguna A, Anheim M, Wolf P, Kessler R, Massard G, Mohr M, Moulin B, Braun-Parvez L, Jaeck D, Tranchant C. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in patients with solid organ transplantation: a clinical, neurophysiological and neuropathological study of 4 cases. *Rev Neurol (Paris)* 2005; 161:1213-1220. [\[CrossRef\]](#)
- Bhagavati S, Maccabee P, Muntean E, Sumrani NB. Chronic sensorimotor polyneuropathy associated with tacrolimus immunosuppression in renal transplant patients: case reports. *Transplant Proc* 2007; 39:3465-3467. [\[CrossRef\]](#)
- Patel MK, Rashed A, Mesraoua B, Khaddash S, Romeh SA. Cyclosporine neurotoxicity presenting as an unilateral foot drop in a renal transplant patient. *Nephron* 1991; 58:116. [\[CrossRef\]](#)

27. Bulsara KR, Baron PW, Tuttle-Newhall JE, Clavien PA, Morgenlander J. Guillain-Barre Syndrome in organ and bone marrow transplant patients *Transplantation* 2001; 71:1169-1172. **[CrossRef]**
28. Raskin NH. Neurological aspects of renal failure. Aminoff MJ, ed. *Neurology and general medicine*. 2. Ed. New York Churchill Livingstone 1989; 231-246.
29. Ho DT, Rodig NM, Kim HB, Lidov HG, Shapiro FD, Raju GP, Kang PB. Rapid reversal of uremic neuropathy following renal transplantation in an adolescent. *Pediatr Transplant* 2012; 16:E296-E300. **[CrossRef]**
30. Bolton CF. Electrophysiologic changes in uremic neuropathy after successful renal transplantation. *Neurology* 1976; 26:152-161. **[CrossRef]**