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Case Report

TACROLIMUS-INDUCED TREMORS AMONG POST-RENAL TRANSPLANT PATIENTS: A CASE SERIES

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ABSTRACT

Triple immunosuppression in renal transplant has drastically changed the outcome of graft survival. However, concern always remains among the physicians because of adverse effects produced due to triple immunosuppression. Calcineurin inhibitors are associated with wide range of side effects. Hence, we report a case series of tremors associated with tacrolimus among renal transplant patients in a tertiary care hospital in southern India.

Keywords: Tacrolimus, Tremors, Neurological complications, Renal transplant, Triple immunosuppression.

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INTRODUCTION

Over past two decades, renal transplantation has become the treatment of choice for end-stage renal disease, and it had become a reality with the introduction of triple immunosuppressive therapy. In renal transplant, survival has increased mainly due to proper perioperative care as well treatment with antirejection drugs [1]. The aim of the therapy is to prevent graft rejection, and as renal transplant patients require lifelong immunosuppression, the side effect of immunosuppression is always a problem to combat. Infection being one of the major side effects due to lowering of immunity, neurological toxicity with calcineurin inhibitors has always been a great challenge to face and it ranges from seizures, leukoencephalopathy, coma, but it has always been more in patients with lung and liver transplantation when compared to renal transplant recipients [2]. Hence, we report a case series of two such cases of tremors associated with tacrolimus (TAC) in post-renal transplant patients.

CASE REPORTS

Case 1

A 43-year-old male patient after his renal transplantation for stage 5 chronic kidney disease due to adult polycystic kidney disease was started on TAC 5 mg, mycophenolate mofetil 500 mg, wysolone 20 mg, valganciclovir 450 mg, and co-trimoxazole single strength (80/400 mg). On day 10, the patient's TAC level was 10.63 ng/ml. Induction therapy was not given to this patient. The dose was reduced to 4 mg. On the 37th day, post-transplant patient came with complaints of tremors on both hands. On day 37, TAC level was found to be 9.83 ng/ml. Other neurological causes were ruled out, and neurological investigations were normal. His vitals were normal, but he had elevated blood pressure. Hence, it was confirmed to be TAC toxicity, and dose of TAC was maintained at 4 mg. Tremors reduced finally. His final TAC level was 9.83 ng/ml after his last visit (Table 1).

Case 2

A 55-year-old male patient diagnosed of diabetic nephropathy along with ischemic heart disease and hypertension underwent renal transplant in the month of December 2016. The patient was given induction therapy before transplant with antithymocyte globulin 100 mg. Post-transplant, he was started with triple suppression with TAC 7.5 mg, mycophenolate mofetil 500 mg, wysolone 20 mg along with valganciclovir and co-trimoxazole single strength tablet. On day 5, after triple immunosuppression, his TAC levels were 14.83 ng/ml following which the dose of TAC was reduced to 7 mg. On day 17, he came with complaints of tremors on both hands and so, the dose of TAC was further reduced to 6.5 mg. Other neurological causes of tremors were ruled out, and it was confirmed to be a case of TAC-induced tremors. On repeat follow-up on day 26, the patient was fine, and his tremors disappeared. His TAC level was found to be 12.11 ng/ml (Table 2).

DISCUSSION

Renal transplantation being the cornerstone in the treatment of end-stage renal disease over past few decades, it became very successful after the advent of triple immunosuppression therapy. Triple immunosuppression consists of a calcineurin inhibitor either TAC or cyclosporine, an antiproliferative agent like azathioprine or mycophenolate mofetil, and steroids like prednisolone. Induction therapy may or may not be given. The main goal of immunosuppression is to prevent graft failure due to cell-medicated immunity. However, triple immunosuppression being a double-edged sword, side effects due to these drug regimens have always been a difficult task for health-care professionals to combat. Some of the known side effects include nephrotoxicity, infections, bone marrow suppression, new onset diabetes after transplant, hypertension, weight gain, dyslipidemia,

Table 1: Case 1 - correlation of tacrolimus levels and dose with tremors post-renal transplant

Tacrolimus levels (ng/ml)	Tacrolimus dose (mg)	Tremors
On day 10-10.63	5	Absent
On day 37-9.83	4	Present
On day 50 (last reading) - 9.83	4	Absent

Table 2: Case 2 - correlation of tacrolimus levels and dose with tremors post-renal transplant

Tacrolimus levels (ng/ml)	Tacrolimus dose (mg)	Tremors
On day 5-14.83	7.5	Absent
On day 17-12.43	7	Present
On day 26 (last reading) - 12.11	6.5	Absent

Table 3: Adverse drug assessment

Naranjo's scale	Probable
Hartwig's scale	Mild severity
Thornton's scale	Not preventable

and neurotoxicities in various cases [2]. Neurological toxicity ranges from tremors, seizures, leukoencephalopathies, and coma in rare cases. However, evidence says neurological side effects with calcineurin inhibitors are more in patients who undergo liver and lung transplantation when compared to renal transplant recipients [3]. There are few case reports associated with neurological side effects with calcineurin inhibitors post-renal transplantation [4,5]. The mechanism by which calcineurin inhibitors cause tremors is by binding to calcineurin-binding proteins in central and peripheral nervous system and thereby increasing the sympathetic activity. This leads to tremors, and evidence also says beta-blocking drugs such as propanol are used in the treatment of physiological tremors caused by TAC [6].

In both of our patients, TAC was found to be the causative agent after ruling out other neurological causes and other drug-induced side effects. Causality assessment was done using Naranjo's scale, and probable causal relationship was established [7]. Severity assessment and preventability assessment were done using Hartwig's scale [8] and Thornton's scale [9], respectively, and it was found to be mild-severe and not preventable (Table 3). No treatment was given to these patients, and tremors disappeared on the reduction of TAC dose.

CONCLUSION

Since triple immunosuppression is the backbone in renal transplant patients, TAC being one among the vital drugs used, adverse drug monitoring for TAC toxicity should be of profound concern for the treating physicians. Hence, it is prudent enough to monitor TAC level in serum and balance the TAC dose accordingly to prevent adverse effects and also avoid graft rejection.

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