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Foot drop in a renal transplant recipient A case report and review of literature

DINESH KUMAR THANIKACHALAM
Department of Nephrology,
MADRAS MEDICAL COLLEGE AND GOVERNMENT GENERAL HOSPITAL

Abstract :

Tacrolimus is a potent immunosuppressive agent used in solid organ transplantation.it acts by inhibiting calcineurin phosphatase and inhibits T-lymphocyte activation. Neurotoxicity is a potentially serious toxic effect of tacrolimus which often is under-recognised. Neurotoxicity ranges from tremors and insomnia to seizures and encephalopathy.We describe a 46 yr-old male renal transplant recipient who developed right foot drop after 6 months of renal transplantation due to tacrolimus toxicity which improved after tacrolimus dose reduction.

Keyword : Foot drop, Tacrolimus, PRES

INTRODUCTION:

Calcineurin inhibitors (CNIs) are the mainstay of immunosuppression in renal transplantation. Compared to cyclosporine (CsA), tacrolimus (TAC) is associated with lower rate of biopsy proven acute rejection episodes,better long-term allograft survival and more favorable cosmetic side effect profile . Long-term administration of tacrolimus has been associated with adverse effects such as nephrotoxicity, neurotoxicity, electrolyte abnormalities, and glucose intolerance .Recently significant neurotoxicity has been reported with the use of calcineurin inhibitors which is more often with TAC.

CASE REPORT:

A 46 yrs old male patient, non diabetic with chronic kidney disease-stage V of unknown etiology was on hemodialysis for 2 years. He underwent deceased donor renal transplant in October 2011.His immediate post transplantation period was uneventful except for non-dialysis requiring delayed graft function.He was discharged on day 12 with serum creatinine of 1.3 mg/dl. His immunosuppression include TAC 6mg, mycophenolate mofetil 1500 mg and prednisolone 30mg per day.He was on cotrimoxazole prophylaxis.TAC trough levels were 6.7 ng/ml on day 5 and 7.2 ng/ml on day 35 respectively (done by chemiluminescent microparticle immunoassay).His follow up creatinine was0.8mg/dl. After 6 months, he developed acute onset right sided foot drop

figure 1a) with no other motor weakness or sensory loss in the lower limbs.There was no history of trauma, backache and addictions. His blood pressure was 110/70 mm Hg. Nervous system examination was normal except for right foot drop (power 1/5) and tremors.No peripheral nerve thickening was noted.Urine analysis revealed trace proteinuria.Complete hemogram, serum electrolytes, calcium phosphorus, liver function tests and serum lipid profile were normal. Serum creatinine was 1.3 mg/dl (baseline value - 0.8 mg/dl).X rays and Ultrasonagram of knee and hip to rule-out local pathology were normal.Viral markers were negative.Magnetic resonance imaging (MRI) spine with brain screening was normal except for minimal disc bulge at the level of L1-2. Nerve conduction study revealed reduced distal motor response amplitude in right peroneal nerve consistent with axonopathy. TAC trough level was 9.2ng/ml. Foot drop improved within 3 days (power-4/5) after TAC dose was reduced to 4 mg/d (figure 1 b).His creatinine value also returned to baseline.

DISCUSSION:

Around 10 - 28% of patients who are treated with CNIs develop neurotoxicity [1].CNI induced neurotoxicity include mild symptoms (20 – 40%)in the form of tremors, headache, insomnia, photophobia, paresthesias, rarely peripheral neuropathy and major complications, such as confusion,seizures,cortical blindness,posterior reversible encephalopathy syndrome(PRES) and coma that occur in 5% to 8% of patients. It can be early (< 2months) or late (> 2 months).Risk factors include previous seizures/ cerebrovascular disease, hypertension, cholesterol levels <100 mg/dL, use of intravenous methylprednisolone, hypomagnesemia, high CNI levels, and aluminium overload [2]. As CNIs are highly lipophilic, hypocholesterolemia causes increased percent of unbound drug and increased diffusion across the blood-brain barrier, resulting in increased uptake in the brain. No absolute relationship between the serum CNI levels and the occurrence or severity of neurologic symptoms is noted, but high levels are often found. Neurologic improvement occurs on dose reduction or discontinuation of drug. Two-third of patients improves by 48 hours. As neurotoxicity is reported in patients with therapeutic levels of CNI without any risk factors [common especially with CsA], possibility of idiosyncrasy has also been implicated.CNIs cause magnesium depletion that lower the seizure threshold, and treatment with magnesium may improve symptoms. Genetic polymorphisms of ABCB1, CYP3A5 and MDR1 are observed in CNI induced neurotoxicity.Major neurological toxicities occur early with obseved median of 10–13 days,often within 3 months,more common after liver and lung transplantation and with TAC rather than CsA.PRES[3] (Posterior reversible leukoencephalopathy syndrome/reversible posterior cerebral edema syndrome) was initially described in 1996. The pathogenesis proposed are cerebral vasospasm / ischemia and consequent cytotoxic oedema which is supported by angiographic evidence of diffuse or focal vasospasm and by infarctions, loss of auto regulation with passive dilatation of the cerebral arterioles and enhanced release of endothelin (potent vasoconstrictor) causing microvascular damage .Cerebral vasculopathy has been proposed due to location of lesion at watershed zones and high co-existence of neurological symptoms with bone marrow-associated thrombo

microangiopathy[4] .Correlation between neurotoxic events and intracerebral concentration of TAC suggests a direct neurotoxic effect of the drug.Singh and colleagues[5] showed the presenting features of CNI induced PRES as seizures(74%),altered mental status (50%),and visual abnormalities (28%).Multifocal low attenuation of white matter in CT and increased signal intensities in both parieto-occipital lobes on T2weighted MRI are the predominant radiological findings[6].The differential diagnosis include hypertensive encephalopathy, Cytomegalovirus encephalitis,cerebral fungal infections,demyelinating disease,electrolyte disorders, (hyponatremia, hypercalcemia or hypocalcemia) and neoplasms.The pathogenesis of neurotoxicity involving the peripheral nerves is unclear. CNI may cause an inflammatory neuropathy by altering T-cell subsets, dysimmune neuropathy by enhancing or failing to inhibit T activation in response to peripheral myelin and disturbances in vasculature resulting in ischemia.Jain *et al* [7] *reported a renal transplant patient who developed left common peroneal nerve* palsy due to tacrolimus toxicity that recovered with switching over to CsA.Masri *et al*[8]*described a case of pediatric renal transplant recipient who developed right brachial neuritis considered to be a neurotoxic manifestation of TAC.Cyclosporine has also been implicated in the development of unilateral* foot drop in a renal transplant patient [9].In our patient we ruled out all other possible cause of foot drop and near complete recovery was seen after TAC dose reduction. The Naranjo Probability score was 4 in our patient that suggest TAC as a definite cause of foot drop[10]. (Naranjo developed simple, reliable questionnaire to identify the probability of a drug causing adverse reaction. A score of more than 3 out of 10 is suggestive of a drug causing reaction).

CONCLUSION:

In conclusion,tacrolimus is a rare but potential cause of unilateral common peroneal axonopathy in a renal transplant recipient. CNI neurotoxicity is under-recognised with varied presentation. The onset can be late, severe and irreversible.Though often occur with high serum drug level, can occur at therapeutic levels also.Early recognition and prompt treatment with dose reduction or replacing the drug can avert the serious potentially irreversible adverse effect.

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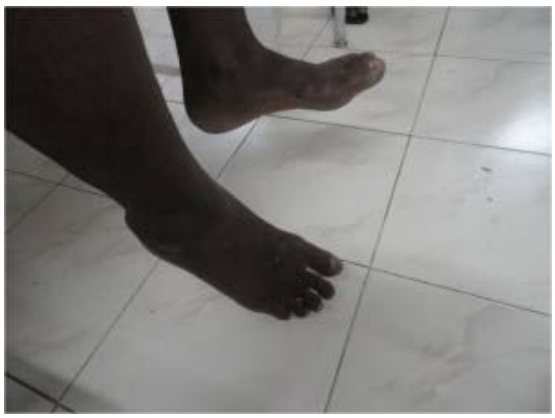

figure 1a

figure 1b