Early tacrolimus administration induced encephalopathy in a renal transplanted patient; a case report

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ABSTRACT
Neurotoxicity due to CNI (calcineurin inhibitors; cyclosporine or tacrolimus) is common after organ transplantation and associated with significant morbidity and mortality. Early identification of drug induced neurotoxicity in transplanted patients is important. We report a 45 year-old-woman who had undergone kidney transplantation and after 24 hours while she suffered from blurred vision and severe headache that did not respond to analgesic drugs. She was administered tacrolimus, prednisone, mycophenolate and anti-thymocyte globulin. Neurologic examination revealed subjective homonymous hemianopia without focal deficit. Other laboratory tests and brain magnetic resonance imaging (MRI) were normal. There was not any evidence of infections, metabolic and neoplastic diseases. Diagnosis of posterior reversible encephalopathy syndrome (PRES) was made by clinical finding. Tacrolimus was withdrawn 2 days after administration and replaced by cyclosporine. Clinical symptoms were resolved 4 days after discontinuation of tacrolimus.

Implication for health policy/practice/research/medical education:
Tacrolimus induced neurotoxicity and its neurologic manifestation is an important issue and should be considered in organ transplanted patients even for those who recently initiated the treatment.


Introduction
Neurotoxicity due to CNI (calcineurin inhibitor; cyclosporine or tacrolimus) is common after organ transplantation and associated with significant morbidity and mortality. The frequency of CNI neurotoxicity among solid organ transplant (SOT) is 20% to 40% (1). In some studies incidence rate of CNI-induced neurotoxicity in SOT reported from 7% up to 32% (2,3). The incidence of posterior reversible encephalopathy syndrome (PRES) occurs in about 0.5% of SOT recipients (4). Early identification of drug induced neurotoxicity in transplanted patients is important. We report a patient who presented with early neurotoxicity (24 hours) after initiation of tacrolimus.

Case Presentation
A 45 year-old-woman who had undergone kidney transplantation and after 24 hours, complained blurred vision and severe headache that did not respond to analgesic drugs. The patient’s blood pressure was elevated 160/90 mm Hg. She was administered tacrolimus, prednisone, mycophenolate, anti-thymocyte globulin. Neurologic examination revealed subjective homonymous hemianopia without focal deficit. Tacrolimus trough levels was 8.1 ng/mL (therapeutic level 5-15 ng/mL), that was within target range. Other laboratory tests and brain magnetic resonance imaging (MRI) were normal. There was not any evidence of infections, metabolic and neoplastic diseases. Diagnosis of PRES was made by clinical finding. Tacrolimus was withdrawn 2 days after administration and replaced by cyclosporine. Clinical symptoms were resolved 4 days after discontinuation of tacrolimus.

Discussion
Some clinical features of PRES include headache, altered mental state, confusion, visual disturbance and focal neurological deficits which accompanied by some findings on brain imaging (5). However, in our patient, absence of characteristic finding of leukoencephalopathy on MRI did not exclude diagnosis of tacrolimus induced PRES. Treatment and prognosis PRES are highly dependent on its early recognition. Adjusting the dosage or discontinuation of medications which are known or suspected to be cause PRES can prevent neurological deficit.

Tacrolimus is an immunosuppressive drug of calcineurin inhibitors which is effective in preventing acute rejection.
in organ transplant but neurotoxicity and nephrotoxicity are major side effects. Neurotoxicity consists of mild symptoms including tremor and peripheral neuropathy. Severe symptoms are psychosis, hallucination, cortical blindness, seizure and PRES syndrome. PRES is the most severe symptom of CNI toxicity (6). Risk factors for development of CNI neurotoxicity consist of using methylprednisolone and cyclophosphamide, hypertension, fluid overload, hypocholesterolemia, hypomagnesemia and hyponatremia (7). Diagnose of PRES should be considered in the setting of acute neurological symptom in patients with renal failure, blood pressure fluctuation and use of cytotoxic drugs (5). PRES is manifested by convulsion, headache, visual alterations, coma, paresis, hemianopsia, changes in mental status and focal neurological deficit (8). Pathological studies have shown extracellular edema with endothelial damage (9). Brain imaging studies usually revealed vasogenic edema predominantly involving the bilateral parieto-occipital region (1). MRI is the gold standard imaging technique in this syndrome (6). Fluid attenuated inversion recovery (FLAIR) is the optional sequence to identify the leukoencephalopathy (9). Characteristic of radiological findings include bilateral regions of subcortical vasogenic edema that resolved within days or weeks (5). Onset time of CNI associated PRES is varied among studies. The median time to onset was 17.6 days after kidney transplantation (1). Time of PRES was markedly different between liver and kidney transplantation. PRES developed early in patients who had undergone liver transplant (11 to 68 days), however, it developed later in patient undergone kidney transplantation (14 to 120 months) (4). In one case series, time of tacrolimus neurotoxicity ranged from 3 to 234 days after allogeneic hematopoietic stem transplant recipients (10). In a study, a trend toward an earlier occurrence of PRES in transplant recipients receiving cyclosporine than those receiving tacrolimus (median time 12 versus 26 days) ($P = 0.07$) was detected (1). In our patient symptoms of PRES presented 24 hours after administration of tacrolimus and this short time has not been reported in kidney transplanted patient. Signs of neurotoxicity may occur even at therapeutic trough level of tacrolimus (1,10), in our patient the tacrolimus level was within the therapeutic range.

It is important to be mindful of certain diagnosis consideration when the possibility of tacrolimus neurotoxicity is high. Absence of characteristic leukoencephalopathy on MRI cannot exclude the possibility of tacrolimus neurotoxicity (9). Early diagnosis is critical for PRES although many patients have mild symptoms and signs as well as a reversible course. If PRES is not recognized and treated early, it can lead to severe and life threatening condition (1).

**Conclusion**

Tacrolimus neurotoxicity should be considered as an important cause of neurologic manifestation in transplanted patients even for those who recently initiated the treatment.

**Authors’ contribution**

All authors contributed to write the manuscript. All authors read, revised, and approved the final manuscript.

**Conflicts of interest**

The authors declare no conflict of interest.

**Ethical consideration**

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