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TACROLIMUS INDUCED REVERSIBLE ENCEPHALOPATHY: A CASE REPORT

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ABSTRACT

Tacrolimus is a novel immunosuppressant used to prevent graft rejection after allogenic organ transplantation. Serious neurological complications of tacrolimus are rare. We present a lady who developed confusion, paresthesiae and visual hallucinations while on tacrolimus following a renal transplant.Her tacrolimus level was high and she improved on stopping the drug. This case highlights the reversible encephalopathy induced by tacrolimus.

Key Words: Encephalopathy, Tacrolimus

INTRODUCTION

Tacrolimus is widely used in allogenic organ transplantation, particularly renal transplant. Though relatively safe,it is known to cause nephrotoxicity, hypertension and diabetes and is associated with an increased risk of malignancy. Neurological complications of tacrolimus are uncommon and usually mild. Tremors and paresthesiae have been described with its use. Severe neurological symptoms like Posterior reversible encephalopathy syndrome (PRES) and encephalopathy can occur, but are uncommon. Here we describe one patient in whom tacrolimus induced encephalopathy was diagnosed at the earliest suspicion and just by stopping tacrolimus her symptoms remitted. Hereby we want to stress on the fact that early suspicion and reversibility of encephalopathy in an encephalopathic patient on tacrolimus can help us manage patient without invasive investigations like lumbar puncture.

CASE REPORT

A 55 year old lady with hypertension presented with headache, confusion, irrelevant talk, visual hallucinations and severe paresthesiae in lower limbs and upper limbs of a few days duration.She had undergone a renal transplant four years ago and was on tacrolimus for immunosuppression. She had no fever, vomiting or seizures. Her vital parameters were normal. Coarse tremors of her hands were present and plantars were extensor.There was no focal motor or sensory deficit.Meningeal signs were absent.

Her blood investigations including complete blood count, blood sugar, blood gas analysis, bicarbonate, liver function tests, electrolytes,calcium and thyroid profile were all normal. Her creatinine was 2.6mg/dl. Her HIV ELISA was nonreactive. Electrocardiogram and chest x ray were normal. Her serum magnesium and cholesterol levels were low (0.8mg/dl and 65mg/dl respectively).Her serum tacrolimus level was high at 29ng/ml(normal 4-5ng/ml). MRI of the brain showed diffuse and focal chronic ischaemicchanges (figure 1).

A provisional diagnosis oftacrolimus induced encephalopathy was made. Tacrolimus was stopped and she received magnesium replacement along with supportive treatment. Over the next 24 hours she became more alert, her paresthesiaereduced and visual hallucinations disappeared. After 3 days she showed a near complete recovery. Tacrolimus was restarted at a lower dose and she was discharged.

DISCUSSION

Tacrolimus is a novel immunosuppressant drug widely used in allogenic organ transplantation.Like cyclosporine, it is a calcineurin inhibitor, suppressing IL 2 production by T-cells1. However, it is about 100 times more potent than cyclosporine.

Common adverse effects of tacrolimusinclude hypertension, diabetes,hirsutism, gum hyperplasia, alopecia anddiarrhea. It is also associated with an increased risk of skin cancer. Neurologic side-effects are usually mild. They occur in 40-60% patients and include headache, paresthesiae, tremors, photophobia and sleepdisturbances Major neurologic complications

are rare and include confusion, expressive dysphasia[8], seizures, cortical blindness[7], encephalopathy, visual hallucinations and coma. It can also cause a posterior reversible encephalopathy syndrome[3].

Tacrolimus decreases endothelial cell viability and increases vascular permeability, which is consistent with impaired function of the blood-brain barrier[5]. Tacrolimusattaches to myelin which is rich in lipids, permitting FK506 to exert a direct toxic effect. Tacrolimus is selectively toxic for cultured glial cells. However, the mechanism of demyelination is undetermined. This is the probable mechanism underlying tacrolimus neurotoxicity.The encephalopathy associated with it is multifactorial in origin. Contributory factors include changes in brain intracellular urea concentration, fluid overload, high blood levels of tacrolimus, and inadequate blood pressure control. In our patient, high tacrolimus blood level was the likely cause of her encephalopathy. However, neurotoxicity may not always correlate with high tacrolimus level and may occur even at therapeutic plasma level. Some factors such ashypocholesterolaemia or hypomagnesaemia may predispose to encephalopathy.

Typical MRI findings intacrolimus toxicity include high signal intensities mainly in the subcortical white matter of the posterior parietal and occipital lobes in T2-weighted and FLAIR sequences[2]. Involvement of gray matter, frontal lobes, thalamus, brainstem, and cerebellum as well as restricted diffusion on DWI can also occur uncommonly. MRAngiography may show moderate to severe vessel irregularity consistent with vasoconstriction and vasodilation[4].

Tacrolimusencephalopathy must be differentiated from CNS infections, metabolic and autoimmune disorders, drugs and toxins, hypertensive encephalopathy and paraneoplastic syndromes. The first step in management is to stop tacrolimus and start an alternative immunosuppressant. Elevated blood pressure must be controlled with appropriate antihypertensive drugs. Nicardipine is particularly useful. Correction of electrolytes particularly hypomagnesaemia is important. Tacrolimus may be restarted later on if it is deemed necessary,

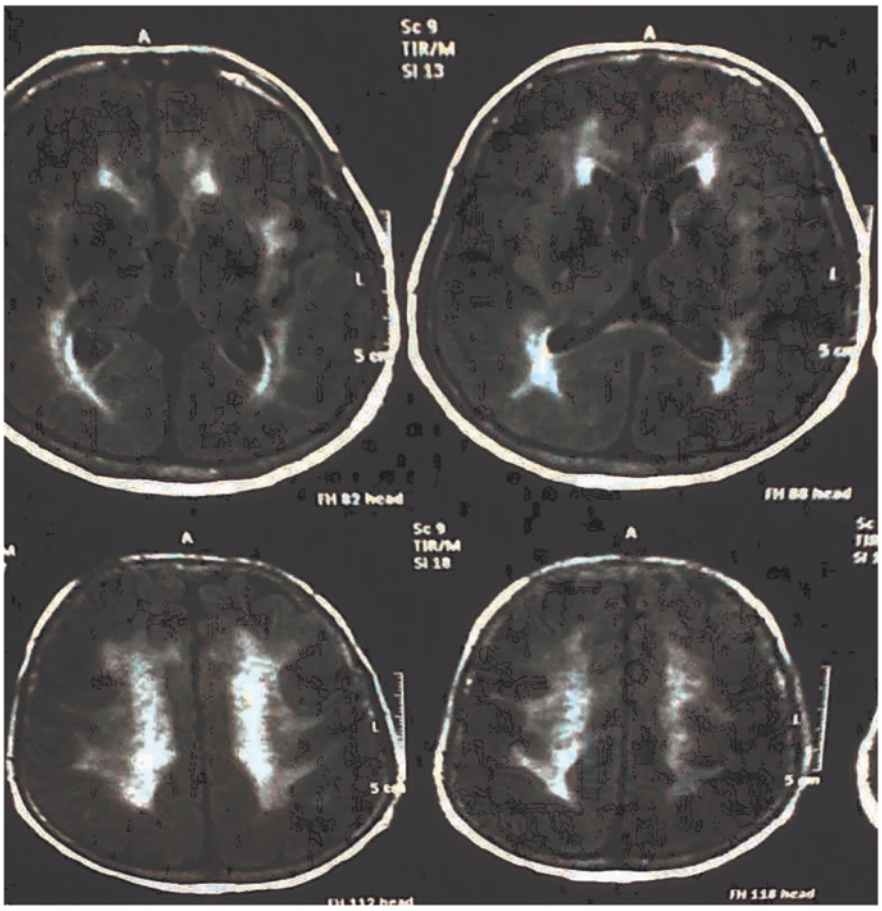

Figure 1:MRI Brain: Diffuse confluent and focal discrete FLAIRhyperintense areas in the bilateral periventricular regions,coronaradiata, cenrtumsemiovale and external capsule suggestive of chronic ischaemic changes.

CONCLUSION

This case illustrates that tacrolimus encephalopathy is a reversible cause of encephalopathy in patients who are receiving it. Tacrolimus drug level can confirm the diagnosis and simply stopping the drug may lead to reversal of symptoms.Very few cases of encephalopathy due to tacrolimus toxicity have been reported. A prompt diagnosis can lead to a rapid recovery and prevent morbidity and a drain on financial resources.

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