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Case Report

Acute schizophrenia-like psychotic disorder associated with immunosuppressive agent use three years after renal transplantation: a case report

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ABSTRACT

Tacrolimus is a potent immunosuppressive agent used to prevent graft-versus-host disease after organ transplantation. Though a beneficial drug that contributes in the post-transplant life of patients, it comes with various side effects including, though rarely, psychiatric manifestations such as psychosis. Reported here is the case of a 21 year old lady with no prior psychiatry history with apparent tacrolimus-induced schizophrenia-like psychosis. Withdrawal of the immunosuppressant led her to full recovery from the mental problem. To the best of my knowledge, there are only few reports that describe psychosis induced by tacrolimus but none of such reports is from Nigeria, a country with increasing demand for kidney transplant. Clinicians are reminded to regularly watch out for mental status changes in post-transplant patients as early identification of any aberration with immediate reduction of the dosage or substitution of the drug would save both the patient and the already emotionally and financially-stressed family from further distress.

Keywords: Tacrolimus, Psychosis, Post-transplant

INTRODUCTION

In Nigeria in recent years, the prevalence of end-stage renal disease has been on the increase. End-stage renal disease is a general health problem because of its high prevalence, changing pattern of aetiology, and complex and expensive modalities of treatment usually required.[1] The definitive treatment of choice in end-stage renal disease is kidney transplant as it is a treatment option that gives patients the chance to return to a satisfactory quality of life.[2] However, transplantation and life-long immunosuppressant treatments are at times not without some prices one of which is immunosuppressant-related psychosis.[3]

Tacrolimus (Prograf®), a calcineurin-inhibitor, is considered one of the mainstays of post-transplant immunosuppression drugs used to prevent graft-host disease after organ transplantation.[4] Discovered in 1984, it is a macrolide lactone extracted from *Streptomyces tsukubaensis* as an alternative to cyclosporine.[5] Tacrolimus has a narrow therapeutic window with wide inter-individual variability in pharmacokinetics and clearance.[6]

According to the manufacturers, it has some common side effects such as headache, hyperglycemia, hyperkalemia, increased blood urea nitrogen, increased serum creatinine, and delirium, among others with psychiatric manifestations occurring rarely. Its therapeutic ranges in kidney transplanted patients should be 10–15 ng/ml in the first 6months of treatment; 8–12 ng/ml in the following six months; and 5–10 ng/ml as maintenance therapy after 1 year.[7]

There seem to have been several reports of mild neurological side effects (such as tremors, paresthesias, headache, and myalgia) following the use of tacrolimus.[8] Only few cases of severe psychiatric side effects have been reported and none of these cases was reported from Nigeria, the increasing rate of kidney transplant among Nigerians notwithstanding.

CASE REPORT

We present a 21 year old undergraduate who was brought to our hospital in July 2016. The complaints were sudden change in behaviour (mainly irritability and talking out of context), strong belief that her classmates knew her unspoken thoughts, and hearing of voices of unseen persons running commentary over her.

Three days prior to presentation, she was reported to have suddenly become irritable and very unco-operative with family members that she even hit her younger brother on the head with a rod, an action that appeared strange to the family. Later that day, she left the house to a near-by secondary school where she was seen to be moving from one classroom to the other. A teacher who identified her took her home. She could remember finding herself in the school compound but could not remember how she moved from her house (about five kilometers away) to the school. She had poor sleep for few days earlier.

She strongly believed that people, especially her classmates, knew her unspoken thoughts. She reported hearing voices of unseen persons in clear consciousness discussing her in third person as well as running commentary over whatever she did. The onset of her problem was dated to about two weeks prior to presentation.

She had never used any psychoactive substance and had not had any behavioural abnormalities in the past. None of her family members had also met the criteria for a psychiatric diagnosis.

Her father had systemic hypertension which was under control before he died a year earlier. Patient was diagnosed to have systemic hypertension at the age of 15 and by 17 she developed end-stage kidney failure and had renal transplant outside the country in 2013 when she was 18 years old. Since after the surgery, she had been on some maintenance drugs including tacrolimus, mycophenolate mofetil, and prednisolone. Her blood drug levels were checked periodically and adjustments on the dosage of the tacrolimus in particular made accordingly. However, this routine investigation is expensive and the family could no longer cope with it following the father's death in early 2016. She continued the medication without checking for the trough concentration.

Her haematologic and biochemical panels including renal function tests, cerebrospinal fluid analysis, and urine examination were all within the normal ranges. The magnetic resonance imaging (MRI) of the brain and electroencephalography showed no abnormalities. Her blood tacrolimus level on presentation was 20 ng/ml.

A diagnosis of acute schizophrenia-like psychotic disorder (ICD-10, F23.2) was made. She was admitted. The dose of tacrolimus was gradually tailed down over a week after which she started having doubts in her abnormal thoughts and the frequency of auditory hallucination reduced. She was commenced on oral risperidole 2 mg daily but her condition remained almost the same for the next one week, though her sleep improved. She was then switched over to cyclosporine while the tacrolimus was completely withdrawn. Within the following two weeks all symptoms had disappeared. She was then discharged after a period of one month admission. Her risperidone was tailed off over the next one month. She had remained stable for over a year, completed her degree programme, and is currently undergoing the one year compulsory national youth service.

DISCUSSION

Tacrolimus has a narrow therapeutic index which needs blood concentration monitoring. Approximately one third (10-59%) of transplant recipients experience neurologic side effects including encephalopathy, seizures, confusion, optic neuropathy, dysarthria, headaches, tremors, and sleep disturbances while psychosis and delirium are listed as rare adverse effects in the manufacturer's package insert.[4,9,10] Various tacrolimus-associated behavioural abnormalities have been reported: catatonia or akinetic mutism, paranoid and fugue-like states, psychotic symptoms, and mania.[7,11-14] To our knowledge, it does appear that there has not been any earlier report of tacrolimus-induced schizophrenia-like disorder.

The mechanisms of these psychiatric adverse effects are extremely complex, unpredictable, and usually severe.[15] Calcineurin inhibitors have regulatory effects on both dopaminergic and the N-methyl-D-aspartate receptor (also known as the NMDA receptor or NMDAR) systems. Glutamate/NMDA excitatory system inhibition caused by tacrolimus as well as its central serotonergic effects could explain the drug-induced psychosis.[13,16] Some researchers have also highlighted its mechanism of action to be fulfilled through the binding with the cytoplasmic protein macrophilin 12 and the consequent inhibition of calcium-dependent phosphatase calcineurin, which is followed by the blockade of the transcription factor NF-AT.[17]

Intravenous administration, presence of hypo-cholesterolemia, hypomagnesemia, previous cerebro-vascular disease, hypertension, central nervous system ischemia-reperfusion injury or hepatic encephalopathy, have been noted to be risk factors to neuropsychiatric

disorders in high plasma levels of the calcineurin inhibitors.[15]

The patient presented had no family or personal history of mental disorder prior to and even over three years after the surgery but she developed psychosis following elevated plasma level of tacrolimus. Similar reports are in the literature. High tacrolimus blood concentrations have been reported to be correlated with nephrotoxicity and anxiety in renal transplantation.[18,19] Corruble and colleagues also reported a case of a 44 yr old man with no psychiatric history who developed hallucinations and delusion associated with elevated trough tacrolimus whole-blood concentrations. The administration of olanzapine and eventual total withdrawal of the immunosuppressant led to his restoration of full mental stability.[13]

Tacrolimus neurotoxic adverse effects has been correlated with trough concentration with concentration of 5 to <8 ng/ml being associated with least overall toxicity, neurotoxicity, and acute cellular rejection.[20]

The psychiatric treatment of mental disorders in individuals with organ transplant is important because psychotic disorders can reduce treatment compliance, which is crucial in the post-transplant period, and indirectly cause tissue rejection.[21] Renal experts practising in centres without psychiatrists are encouraged to refer such patients to other facilities where the services of psychiatrists are available.

This patient also had prednisolone in her regimen. Although the patient did not use high-dose corticosteroids, the use of low dose prednisolone for a long time might serve as a risk factor for the occurrence of psychotic symptoms during the tacrolimus overdose.

She developed psychosis three years post-transplant. A Turkish report had it that a 26 year old man developed psychotic features four years after he had kidney transplant.[15] It does appear that the toxic effect could be shortly after transplant or much longer, especially with increased plasma level of the drug. Whichever time it occurs, the experience in the case presented here shows that dose reduction, and preferably total substitution where possible leads to complete recovery from the psychiatric sequel.

Strength

Our patient developed psychosis when the level of tacrolimus mistakenly got elevated above the normal range. With the use of an atypical antipsychotic and reduction of the dosage, the psychosis subsided but did not stop completely until the tacrolimus was completely replaced. The temporal relationship between symptom relief on reduction of tacrolimus dose and complete symptom disappearance with tacrolimus stoppage strongly supports that the psychosis was *ab initio* induced by the tacrolimus.

Limitation

The information received regarding past and family history of mental illness was as provided by the patient and her family member. We practice in an environment where stigma against mental illness is still very high that people are often reluctant to admit positive history of mental illnesses.

CONCLUSION

Immunosuppressive agents are commonly used to prevent graft rejection and cause graft survival for the purpose of the extension of the patient's post-transplant life. These agents, especially calcineurin inhibitors like tacrolimus have been associated with a range of neurobehavioural side effects, including overt psychotic symptoms, especially when the plasma level is higher than normal. Medication withdrawal, dose reduction, or antipsychotic medication may be helpful in addressing the psychiatric symptoms. Physicians should consistently educate patients about these potentially severe psychiatric side effects and encourage early reporting because early identification and prompt action will save a lot. Most importantly, the diagnosis should not be missed as the remedy is simple and failure to diagnose accurately may result in unnecessary brain biopsy, as well as irreversible injury.

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