

Tacrolimus-induced Akathisia in a Post-cardiac Transplant Patient: A Case Report

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ABSTRACT

Akathisia, a prevalent drug-induced movement disorder, is characterized by inner restlessness and an irresistible urge to move. It can occur after starting a new medication, increasing the dose, or switching to another medication. It is commonly associated with, but not limited to antipsychotic use. Tacrolimus (TAC), an immunosuppressant vital for preventing acute rejection post-solid organ transplantation, has been linked to various neurological side effects. Neurotoxic side effects of TAC may include headache, seizures, tremor, encephalopathy, and peripheral pain. This report details a case of TAC-induced akathisia in a post-cardiac transplant patient, emphasizing the need for heightened clinical suspicion and awareness of this underreported phenomenon. The patient's symptoms, including restlessness and an inability to sit still, were exacerbated by TAC, prompting a diagnosis and subsequent treatment for akathisia.

Drug-induced movement disorders encompass a spectrum of manifestations, with akathisia being a common yet frequently unrecognized condition.^{1,2} Akathisia is defined as a condition that causes an inner feeling of restlessness and the urge to move.² It can occur after starting a new medication, increasing the dose, or switching to another medication.¹ Unlike some movement disorders, which can be presented with external signs such as tremors, patients with akathisia describe a subjective sense of inner restlessness that may manifest as pacing or an inability to sit still, inner tension, anxiety, panic, irritability, discomfort, and sleeplessness. In severe cases, the thought processes of affected patients may become disorganized and their judgment impaired.¹⁻³ Also, impulsive behavior and/or suicidal ideation may be seen. However, some external manifestations like repetitive, purposeful, stereotypical, or suppressible movements can also be seen in some patients. For example, crossing and uncrossing the legs, rubbing the scalp or interior thighs, and rocking while sitting.²

Currently, akathisia is diagnosed solely by clinical observation and patient report, as there is

no confirmatory blood test, imaging assessment, or neurophysiological study available. The most commonly used assessment tool is the Barnes Akathisia Rating Scale, a four-item scale in which the subjective and objective components of the condition are rated separately and then combined.³

The management of akathisia includes cautiously reducing the medication dosage or switching to a medication with less potential to cause extrapyramidal symptoms; adding a beta-blocker (e.g., propranolol), an anticholinergic (e.g., benztropine), or, less commonly, a benzodiazepine (e.g., lorazepam) may be required to mitigate the symptoms, especially if discontinuation of the culprit drug is not an option.³⁻⁶

Tacrolimus (TAC) is an immunosuppressant in the class of calcineurin inhibitors that has been proven to prevent acute rejection after solid organ transplantation. Despite having dramatically improved survival after solid organ transplantation, TAC is associated with a number of neurological side effects, which have been demonstrated to have a significant impact on patients' quality of life. Neurotoxicity secondary to TAC may be due to low levels of vasoconstrictive cerebellar or

cerebral ischemia induced by the drug. Patients may present with different neurological and psychiatric manifestations. These symptoms can be mild, such as tremors, neuralgia, and peripheral neuropathy, or severe such as psychoses, hallucinations, cortical blindness, seizures, cerebellar ataxia, and motor weakness.^{7,8} Although akathisia is more common with antipsychotics, akathisia has also been reported with the antibiotic azithromycin, calcium channel blockers, lithium, and drugs often used for recreational purposes.⁹⁻¹¹ Interestingly, TAC-induced akathisia was reported in 1992 in a post-renal transplant patient by Bernstein et al.¹² We here report a case of TAC-induced akathisia in a post-cardiac transplant patient. Informed consent was obtained from the patient.

CASE REPORT

A 64-year-old female with a history of heart transplant, diabetes mellitus type II, and hypothyroidism experienced progressively severe symptoms of restlessness and an urge to move after initiating TAC therapy. The heart transplant was performed in September 2016 without immediate complications. She received TAC (1 mg BID for three days, then gradually increased up to 5 mg BID and adjusted the dose according to FK506), mycophenolate mofetil (1500 mg OD), and prednisolone (5 mg OD). In April 2020, she started having trembling legs when standing and a swaying upper body that improved with walking. The symptoms did not bother her initially. Her symptoms were progressive until they became severe enough to interfere with her daily activities, and she needed someone to be with her most of the time. In August 2022, she came to our clinic, where she was initially diagnosed with a functional disorder, as her physical examination, brain magnetic resonance imaging, and nerve conduction study/electromyography were normal, and there was no recent event or new medication. She described her symptoms as an inability to sit still with an urge to move. She also had intermittent postural tremors in the upper and lower limbs. She feels better when she is constantly moving, such as walking or fidgeting. She also suffered from chronic anxious thoughts that affected her sleep. She had no other neurological symptoms.

Examination showed a vitally stable woman with intact cognitive function and unremarkable

cranial nerve examination. Motor examination showed power 5/5 with normal tone and reflexes. All sensory modalities were also intact and cerebellar examination was unremarkable. She had a normal gait but could not perform a tandem gait, and had an impaired Romberg test.

Investigations were unremarkable except for elevated methylmalonic acid levels with normal B12. Nerve conduction study and electromyography revealed no evidence of peripheral neuropathy. Brain magnetic resonance imaging and magnetic resonance angiography were unremarkable.

At her first visit, she was not given any medications. At the next visit, she was treated with propranolol 10 mg daily for a week and then increased to 20 mg daily. A month later, she came to the clinic complaining of palpitations and worsening symptoms, at which point the propranolol was discontinued. She is now being treated with clonazepam 0.5 OD, with an increase in dose being considered at the next visit. She has regular follow-up visits at the movement disorders clinic.

DISCUSSION

TAC has been reported to cause neurotoxicity with different clinical manifestations. TAC-induced akathisia was reported in 1992 in a post-renal transplant case, and the patient improved to his baseline after receiving propranolol and haloperidol.¹² Our patient had a sense of restlessness, a feeling of discomfort sitting still with the urge to move, and felt better with continuous movements. Her symptoms and the temporal relationship with the onset of the new medication are typical of akathisia. In this patient, these symptoms began after starting TAC, and her symptoms were progressive and did not improve because we did not discontinue TAC and she could not tolerate propranolol. In addition, the possible causes and medications that could cause akathisia were reviewed and not found in her case. The lack of response to propranolol and its intolerance in our patient could be related to the heart transplant. The previously reported case and our case share common things, including akathisia and anxiety symptoms, which developed after the surgery. A prospective, cross-sectional study of 25 renal transplant recipients was conducted to determine whether akathisia occurred and/or was related to TAC plasma levels. They used Akathisia Rating Scales to detect drug-induced akathisia, and Hamilton Anxiety was used

to measure anxiety symptoms. The study showed that higher plasma TAC levels were associated with higher Hamilton Anxiety scores. Akathisia Rating Scale scores did not correlate with plasma TAC levels. They concluded that higher plasma TAC levels are more associated with features of anxiety than akathisia.¹³ TAC-induced akathisia, a case from 1992, occurred after renal transplantation, whereas in our patient it occurred after cardiac transplantation, which may suggest that TAC-induced akathisia and anxiety may not be related to drug clearance after renal transplantation.

This case highlights the importance of maintaining a high clinical suspicion for akathisia and remembering this when a patient presents with acute onset of restlessness in the setting of post-transplant surgery and a new immunosuppressant started. Akathisia is a treatable condition with a good prognosis if the condition is recognized and the drug causing it is discontinued. However, if the condition is left untreated, it has high morbidity and can even lead to suicidal ideation.¹⁴ Detecting the symptoms and initiating a treatment plan with the primary team will help the patient comply with treatment, trust treating physicians, and limit unnecessary investigations. Even though our patient's symptoms did not improve, mainly because she did not tolerate propranolol and we could not change her management plan at that time. It is also important to ask specifically about anxiety and akathisia symptoms. Akathisia's clinical picture may mimic anxiety as they share common features, and the symptoms can overlap. For example, patients with anxiety can present with restlessness and insomnia. Asking about symptoms specifically will help track if the akathisia worsens or if the patient develops anxiety too. It will guide the management, as each has a different approach. TAC-induced akathisia has been reported only by Bernstein et al,¹² and, to the best of our knowledge, ours is the second case.

TAC has significant clinical implications, given its growing popularity as an immunosuppressant. Knowing that TAC may cause akathisia, it is important to review patient medications prior to starting TAC and try to avoid other medications that are reported to cause akathisia to prevent drug-drug interactions.²

CONCLUSION

Akathisia may be common but underreported or unrecognized. This report raises awareness of this possibility. It will help prevent such adverse effects and their negative consequences on treatment adherence and healthcare costs. It will add valuable data to the existing literature. Further studies are needed to investigate the relationship between TAC and akathisia.

Disclosure

The authors declared no conflicts of interest.

REFERENCES

1. Duma SR, Fung VS. Drug-induced movement disorders. *Aust Prescr* 2019 Apr;42(2):56-61.
2. Owusu Aboagye G, Ankrah D. Drug-drug-induced akathisia: two case reports. *Case Rep Psychiatry* 2020 Apr 23;2020:9649483.
3. Lohr JB, Eidt CA, Alfaraj AA, Soliman MA. The clinical challenges of akathisia. *CNS Spectr* 2015 Dec;20 Suppl 1:1-14; quiz 15-6.
4. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989 May;154(5):672-676.
5. Iqbal N, Lambert T, Masand P. Akathisia: problem of history or concern of today. *CNS Spectr* 2007 Sep;12(9) (Suppl 14):1-13.
6. Kuniyoshi M, Arikawa K, Miura C, Inanaga K. Effect of clonazepam on tardive akathisia. *Hum Psychopharmacol Clin Exp* 1991 Mar;6(1):39-42.
7. Erro R, Bacchin R, Magrinelli F, Tomei P, Geroi C, Squintani G, et al. Tremor induced by Calcineurin inhibitor immunosuppression: a single-centre observational study in kidney transplanted patients. *J Neurol* 2018 Jul;265(7):1676-1683.
8. Wu Q, Marescaux C, Wolff V, Jeung MY, Kessler R, Lauer V, et al. Tacrolimus-associated posterior reversible encephalopathy syndrome after solid organ transplantation. *Eur Neurol* 2010;64(3):169-177.
9. Riesselman A, El-Mallakh RS. Akathisia with azithromycin. *Ann Pharmacother* 2015 May;49(5):609.
10. Sachdev P. The epidemiology of drug-induced akathisia: part I. Acute akathisia. *Schizophr Bull* 1995;21(3):431-449.
11. Asser A, Taba P. Psychostimulants and movement disorders. *Front Neurol* 2015 Apr;6:75.
12. Bernstein L, Daviss SR. Organic anxiety disorder with symptoms of akathisia in a patient treated with the immunosuppressant FK506. *Gen Hosp Psychiatry* 1992 May;14(3):210-211.
13. DiMartini AF, Trzepacz PT, Daviss SR. Prospective study of FK506 side effects: anxiety or akathisia? *Biol Psychiatry* 1996 Sep;40(5):407-411.
14. Patel J, Marwaha R. Akathisia. Treasure Island (FL): StatPearls Publishing; 2026 Jan. [cited 2023 Jul 18]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK519543/>.