Case Report

DOI: 10.7860/JCDR/2026/82170.22396

Psychiatry/Mental Health Section

Drug-induced Neuropsychiatric Syndrome in a Liver Transplant Recipient: A Case Report

KETAKI LADI[1], AKSHAY NAIK[2], ARCHANA NARENDRA JAVADEKAR[3]

ABSTRACT

In postliver transplant patients, numerous factors may lead to the presentation of neuropsychiatric symptoms. These may include pre-existing hepatic encephalopathy, metabolic disturbances, adverse drug reactions, and complex drug-drug interactions. Differentiating among these potential causes is often challenging for the treating team. However, it is crucial because distinguishing between them directly impacts treatment choices and patient outcomes. The present case report discusses a young 24-year-old female who developed acute psychiatric disturbances in the early postoperative period following a liver transplant. Her presentation was characterised by agitation, disorganised behaviour, and confusion. This raised questions about whether the patient was experiencing post-transplant delirium or primary drug-induced neurotoxicity. Laboratory evaluations revealed elevated serum tacrolimus levels at the time of symptom onset. The patient was concurrently receiving high-dose corticosteroids as part of her immunosuppression and antifungal therapy with fluconazole, a potent inhibitor of Cytochrome P450 3A4 (CYP3A4). This is known to reduce tacrolimus metabolism and increase circulating drug concentrations. The patient's symptoms showed marked improvement following timely pharmacological adjustments, including modifications to her immunosuppressive and antifungal regimens. This underscores the reversibility of these manifestations when identified early. Therefore, the present case highlights how the use of tacrolimus, corticosteroids, and fluconazole may synergistically precipitate neuropsychiatric complications. It emphasises the need for close monitoring of immunosuppressant levels, regular reviews of concomitant medications, a high index of suspicion for drug-drug interactions, and a multi-disciplinary team effort in postliver transplant patients exhibiting acute neuropsychiatric syndromes.

Keywords: Corticosteroids, Fluconazole, Neurotoxicity syndromes, Tacrolimus

CASE REPORT

A 24-year-old female was referred in March 2025 for fitness as part of the pre-liver transplant workup. She had reportedly experienced decompensated chronic liver disease since 2019 and underwent esophageal variceal binding in 2022 elsewhere. She had no history of psychiatric illness.

On Mental Status Examination (MSE), the patient was conscious, alert, and oriented to time, place, and person. Other MSE findings were unremarkable, and she was given clearance for surgery. In May 2025, she was brought to the hospital in altered sensorium, having experienced three episodes of vomiting since the previous day. She was diagnosed with grade 2 hepatic encephalopathy with decompensated chronic liver disease of autoimmune etiology, portal hypertension, coagulopathy, and right-sided hydrothorax [1]. For acute stabilisation, she underwent multiple transfusions, pleural tapping, and correction of hyperammonemia (serum ammonia level of 343 µg/dL). She was started on oral methylprednisolone 10 mg daily for 20 days preoperatively.

Nearly a month after her hospital stay, she underwent a deceased donor liver transplant. She received preoperative methylprednisolone 500 mg intravenously on the day of surgery. Postoperatively, she remained in the Intensive Care Unit (ICU) for 15 days and received tacrolimus, high-dose intravenous methylprednisolone, and intravenous fluconazole.

On postoperative day 3, the transplant team noted that she spoke irrelevantly and was irritable. For this, she was given a single dose of 0.25 mg injectable haloperidol {2.5 mg haloperidol diluted in 4 mL Normal Saline (NS)} intravenously. On day 6, increased irritability, irrelevant speech, and disorganised behaviour were observed. Her serum tacrolimus level was found to be 18.70 ng/mL (therapeutic range 5-15 ng/mL) [2]. Subsequently, tacrolimus was withheld, and injectable fluconazole was stopped. Injectable anidulafungin 100 mg Once Daily (OD) intravenously was then initiated as an antifungal agent for the patient. A reduction in her symptoms of irritability was noted by the team. Tacrolimus was re-initiated on day 8 at a dose of 1.5 mg orally after her serum levels normalised. However, the re-initiation of tacrolimus led to a worsening of symptoms. A psychiatric referral was sought on day 9 for restlessness, irritability, spitting at staff, and repeating words and phrases she heard.

During the psychiatric evaluation, physical examination findings revealed a moderately built young female sitting up in a propped-up position with increased motor activity. Her bulbar conjunctiva showed icterus. In the MSE, she was uncooperative, and rapport could not be established. Eye contact was briefly made but was lost later. She was alert; however, her orientation could not be assessed. During the interview, she exhibited echolalia that hampered progress. Her judgment was impaired, and insight was absent, preventing further MSE administration. A provisional diagnosis of tacrolimus-induced neurotoxicity, with differentials of steroid-induced mania and postoperative delirium, was considered. A primary psychiatric disorder was not contemplated due to the underlying medical condition. She was initiated on tablet amisulpride 25 mg orally once at night.

On day 10, she was re-evaluated and showed improvement from the previous day. During her MSE, she made eye contact, and rapport was easily established. She was alert and oriented to time, place, and person. Echolalia was present to a lesser extent than the day before, but her behaviour exhibited child-like regression. She reported her mood as happy. Her affect was expansive, and lability was observed as she became tearful during conversation while remaining preoccupied with thoughts of discharge. Her judgment was intact, and insight was graded at 3. No changes to the differentials or treatment were made during this review.

On day 13, based on the interview, her MSE revealed an intact sensorium with increased speech output, expansive affect, and improved mood, which she reported as happier than usual. No grandiose content was noted, although lability persisted. Since she had been out of delirium for four days, but her symptoms persisted, postoperative delirium was ruled out. The dose of amisulpride was increased to 50 mg. She was later shifted to the ward on day 15 as her condition stabilised.

By day 17, her oral intake had improved, and ambulation was achieved with chest physiotherapy and spirometry. During the psychiatric evaluation, no complaints were reported by the caregivers, and the patient's MSE was within normal limits. A final diagnosis of secondary neurocognitive syndrome due to a medication or substance (tacrolimus-induced) was established as per International Classification of Diseases, 11th revision (ICD-11). At discharge (day 18), she was vitally stable and symptomatically improved, with regular bowel movements. She was advised to continue tablet amisulpride 50 mg once at night along with immunosuppressants and to follow up after five days. Amisulpride 50 mg was withdrawn during a subsequent hospital visit as the patient exhibited no further behavioural abnormalities.

DISCUSSION

Neuropsychiatric manifestations associated with liver transplant can arise due to pre-transplant hepatic encephalopathy, direct neurotoxic effects of immunosuppressants, or drug-drug interactions among various pharmacotherapeutic agents [3-5]. This may lead to a complex presentation and pose a diagnostic dilemma for the treating team. Studies have shown that hepatic encephalopathy prior to liver transplant strongly predicts postoperative cognitive impairment, neurological conditions such as delirium, overall hospital stay, and recovery [3,4].

Tacrolimus, a calcineurin inhibitor, is a mainstay in post-transplant immunosuppression; however, patients are prone to dose-dependent neurotoxicity due to its narrow therapeutic index. A retrospective study by Varghese J et al., involving 32 liver transplant recipients found that trough levels of 5 to <8 ng/mL were least likely to be associated with neurotoxicity and acute cellular rejection. The risk of adverse effects rises if concentrations exceed 11 ng/mL [6]. Tacrolimus toxicity can manifest as tremors, confusion, agitation, psychosis, difficulties in articulating speech, and, rarely, manic symptoms, catatonia, or even Posterior Reversible Encephalopathy Syndrome (PRES) [7,8].

The pathophysiological disturbances responsible for the acute abnormalities include vasogenic edema due to fluid extravasation, while prolonged exposure results in cytotoxic edema leading to severe vasoconstriction and ischemia [9]. In this case, the development of psychiatric symptoms coincided temporally with elevated serum tacrolimus levels (18.7 ng/mL). The symptoms also subsided as serum levels dropped later. Jin B et al., (2021) reported a case of tacrolimus-induced mania postliver transplantation despite normal serum tacrolimus levels [10]. Similarly, Tatreau JR et al., reported two cases of early post-transplant catatonia with normal tacrolimus levels that improved with lorazepam and a switch to cyclosporine due to suspected tacrolimus neurotoxicity [11].

A systematic review by Belur P et al., (2025) highlighted the lack of a clear relationship between tacrolimus levels and the onset of symptoms but stated that the temporal relationship, rapid response to dose adjustments, or discontinuation, implicates tacrolimus in an underlying role [12]. The present study, however, did not account for other drugs administered to such patients that could affect tacrolimus levels and contribute to the risk. While corticosteroids have been well documented to induce neuropsychiatric symptoms-including mania, psychosis, and mood lability-the relationship appears to be dose-dependent and idiosyncratic [13]. This patient had been on methylprednisolone preoperatively but without psychiatric symptoms. Post-transplant, she received a tapering intravenous regimen: 500 mg on day 1, then 250 mg, 125 mg, 80 mg, and 60 mg over subsequent days. Symptoms emerged after the completion of this course, coinciding with elevated tacrolimus levels on day 6.

Glucocorticoids promote tacrolimus metabolism by inducing CYP3A4 enzymes; therefore, sudden tapering of steroids could have led to a rise in tacrolimus levels [14].

It is also important to note the role of fluconazole, a known CYP3A4 inhibitor, and its co-administration with tacrolimus. This could have led to decreased metabolism and elevated serum tacrolimus concentrations [15,16]. From day 6 onward, the patient was switched over to anidulafungin, an antifungal that does not significantly inhibit Cytochrome P450 (CYP) enzymes. Hence, it can be stated that steroid tapering (reducing CYP3A4 induction) and concomitant fluconazole (CYP3A4 inhibition) likely raised tacrolimus levels, precipitating neurotoxicity.

Psychiatric evaluation revealed neuropsychiatric features atypical of classic delirium or primary mania, highlighting the need to consider medication-induced syndromes in the differential diagnosis. The resolution of symptoms with the withdrawal of tacrolimus, temporary use of low-dose amisulpride, and eventual tapering off of antipsychotics prior to discharge further supports a reversible, iatrogenic etiology.

CONCLUSION(S)

This case emphasises the importance of close therapeutic drug monitoring and awareness of potential drug-drug interactions in the post-transplant period. Neuropsychiatric symptoms in such patients require a high index of suspicion and an interdisciplinary approach involving hepatologists, transplant surgeons, pharmacists, and psychiatrists. Early identification and management can prevent the escalation of symptoms and reduce the length of hospital stay.

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PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Psychiatry, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune, Maharashtra, India.
2. Assistant Professor, Department of Psychiatry, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune, Maharashtra, India.
3. Professor, Department of Psychiatry, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Akshay Naik,
Assistant Professor, Department of Psychiatry, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune-411018, Maharashtra, India.
E-mail: drakshaynaik@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 25, 2025
- Manual Googling: Sep 02, 2025
- iThenticate Software: Sep 11, 2025 (5%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jul 19, 2025**
Date of Peer Review: **Aug 06, 2025**
Date of Acceptance: **Sep 13, 2025**
Date of Publishing: **Feb 01, 2026**