Stanford MEDICINE School of Medicine

Department of Psychiatry and Behavioral Sciences

Delayed-Onset Psychosis After Lung Transplant Secondary to Tacrolimus Neurotoxicity: A Case Report and Systematic Review

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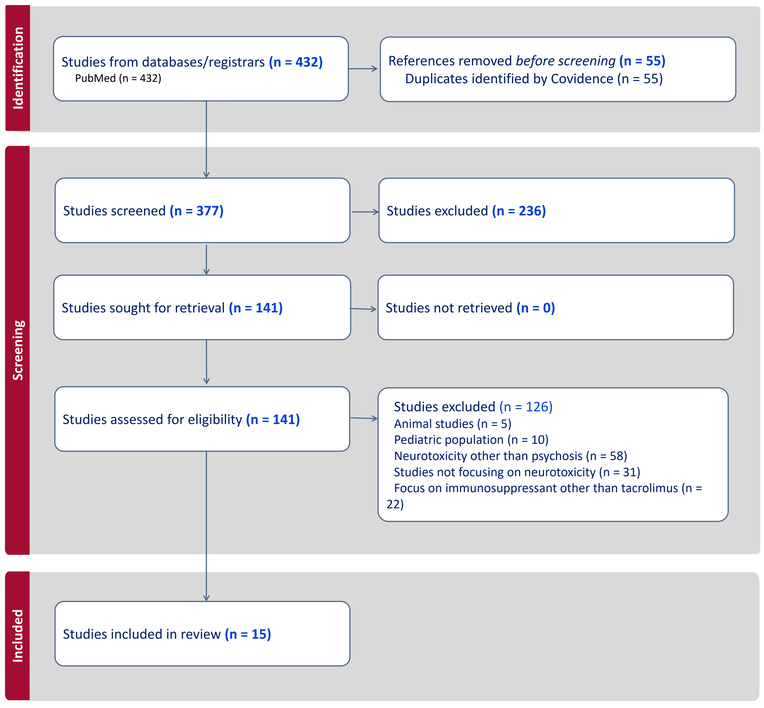
Background

- Tacrolimus, a calcineurin inhibitor (CNI), is the most common immunosuppressant used after transplantation due to benefits in prevention of organ rejection.
- It can result in moderate-to-severe neurotoxicity in up to 32% of patients.
- Signs of neurotoxicity can vary from mild (tremor or headache) to severe (posterior reversible encephalopathy syndrome (PRES) or psychosis.
- ***Tacrolimus-induced psychosis*** is a severe form of neurotoxicity involving a spectrum of auditory or visual hallucinations, delusions, or mania.
- We sought to systematically review all cases of tacrolimus-induced or associated psychosis using PRISMA guidelines (see below).

PRISMA Diagram



Results

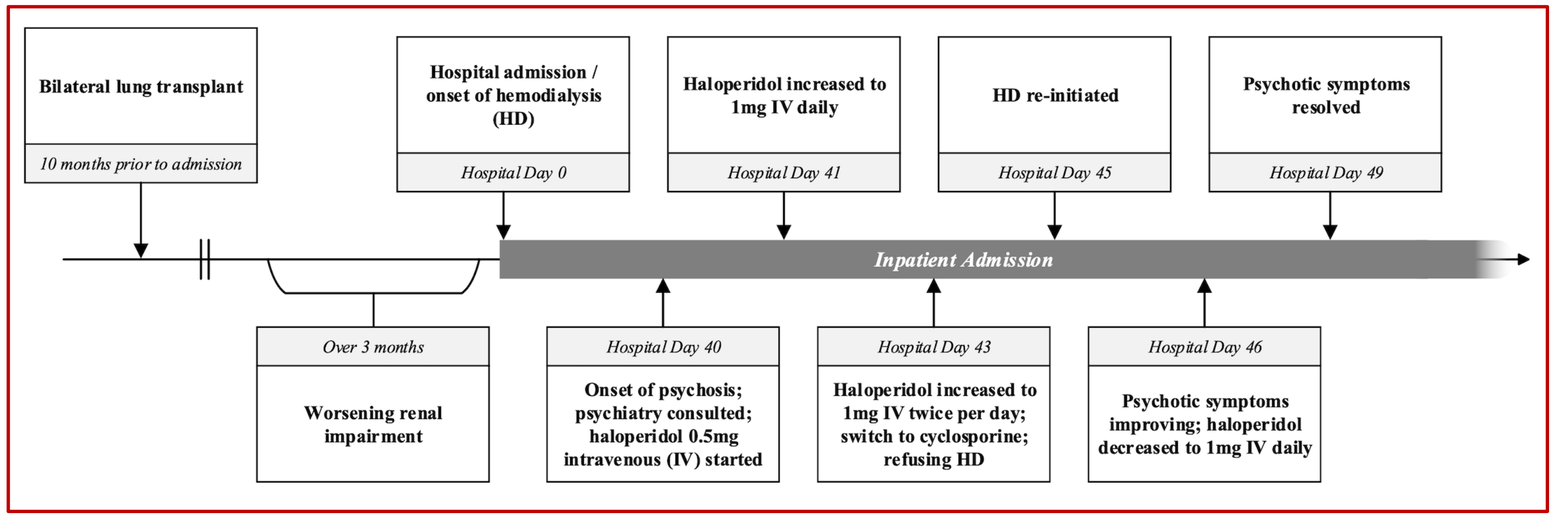
- Our review produced 15 articles yielding 39 total cases of psychosis associated with tacrolimus use. Majority (12) were case reports.
- The average age was 50.8 years, 11 of whom were female (28%).
- Of the 39 cases, 29 were liver transplants, 9 were kidney transplants, one was a pancreas transplant, and one was a hematopoietic cell transplantation.
- The average time of onset of psychotic symptoms after transplantation was ***8.7 months*** (standard deviation of 31.4 months).

Case Presentation

A 62-year-old male with advanced fibrotic interstitial lung disease receives a bilateral lung transplant. Psychiatry consulted for change in personality, refusal of interventions/medications, and focus on controlling room temperature.

Mental Status Exam: Fixed delusion that room temperature was too cold; paranoia about staff adjusting temperature, attempting to "kill him"; no evidence of delirium – fully oriented, attention/arousal intact, no fluctuations.
Medical History*:* Cognitive impairment (~3 years), progressive renal failure (ESRD), no psychiatric history.

Objective Findings: MRI Brain with no radiographic evidence of PRES; periventricular and white matter hyperintensities; mild global volume loss; tacrolimus level 4.4 to 8.7; GFR 17 (on dialysis).



Discussion

Pathophysiology

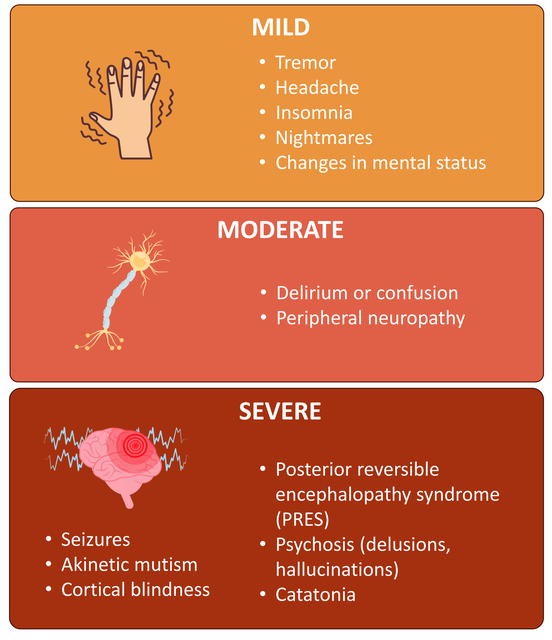
- Tacrolimus is a calcineurin inhibitor.
- It can lead to ***toxicity to glial cells and oligodendrocytes*** through increased glutamate release and possible gamma-aminobutyric acid (GABA) reduction.

Risk Factors for Neurotoxicity

- Blood brain barrier disruption (e.g., HTN, infection, hepatic. encephalopathy, renal failure)
- Tacrolimus levels (not always).
- Underlying CNS function.

Management Strategies

- Dose reduction, if supratherapeutic.
- Switch to alternate immunosuppressant regimen (e.g., cyclosporine).
  - This may not be feasible, especially during the ***first year*** where acute rejection is a top concern.
  - Tacrolimus is associated with ***lower risk*** of acute rejection compared to cyclosporine (28.1% versus 37.5%).
  - An alternative agent, such as sirolimus (an mTOR inhibitor) could be considered; however, regimens without a CNI are associated with ***higher rejection rates*** than those that include a CNI.
  - mTOR inhibitors impair wound healing and must be avoided ***for several months*** after the surgery.
- No specific psychopharmacologic guidelines available – antipsychotics, benzodiazepines, and mood stabilizers used with varying effect.
- We could consider ***haloperidol*** as an initial strategy – used in delirium post-transplant, not anticholinergic, routes of administration, potent D2-antagonism.



Symptoms of Tacrolimus-Induced Neurotoxicity

Conclusions

- Tacrolimus-induced psychosis is a unique form of neurotoxicity without alteration of attention or sensorium (as compared to delirium).
- Development of neurotoxicity (and psychosis specifically) can occur at any stage post-transplant and may be independent of tacrolimus serum level.
- Psychopharmacologic management may help disrupt behavioral symptoms while definitive strategies are coordinated by transplant team.

For complete references including access to the now published systematic review, please use this QR code.