Management of Immunosuppressant-Induced Psychosis Across the Lifespan

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Disclosure: Avneet Soin, MD

With respect to the following presentation, in the 24 months prior to this declaration there has been no financial relationship of any kind between the party listed above and any ACCME-defined ineligible company which could be considered a conflict of interest.
Learning Objectives

• Discuss a case of suspected immunosuppressant-induced psychosis and the use of LAI antipsychotics

• Review the current understanding of the pathophysiology of psychosis secondary to immunosuppressants, as well as management recommendations

• Propose additional considerations in management including the use of LAI antipsychotics and the involvement of interdisciplinary teams
Clinical Case

• 60F, married, domiciled with 2 adult children, PPH of unspecified psychosis since 2012, multiple psych admissions and ED visits, no recent OP psychiatric treatment, history of poor medication adherence (previously on Abilify), PMH ESRD s/p renal transplant in 2010 on chronic immunosuppressants.

• HPI: BIB EMS activated by daughter 2/2 worsening psychosis (AH, paranoia, persecutory delusions) leading to wandering from home.

• Meds: tacrolimus 1.5mg PO BID, mycophenolate 500mg PO BID, prednisone 5mg PO daily - patient reported adherence, confirmed by daughter

• Positive findings on MSE: Avoidant eye contact, guarded, paranoid/persecutory ideation, internally preoccupied, poor insight into psychiatric history (good insight into renal history)
Clinical Case

- **Labs**: Basic labs (including B12, TSH) within normal limits, Utox negative, HIV negative, syphilis negative. **Tacrolimus level was not obtained.**
- **Ddx**: Primary psychotic disorder vs. substance-induced psychotic disorder
- **Hospital Course**: Restarted Abilify up to 20mg TDD and received Abilify Aristada 882mg q28d
  - Pt continued to have poor insight, but with reduction in AH and good behavioral control
  - OP nephrologist was unaware of the psychogenic risks of various immunosuppressants, and recommended keeping regimen unchanged.
  - Patient was discharged to OP care with HHA services.
- **Discharge Dx**: Substance-induced psychotic disorder secondary to immunosuppressants
Common Culprits

• Immunosuppressant-induced psychosis:
  • Glucocorticoids (prednisone)
  • Calcineurin Inhibitors (tacrolimus, cyclosporine)

• Other immunosuppressive and immunomodulatory agents have been implicated in development of neuropsychiatric symptoms:
  • Mycophenolate mofetil (CellCept)
  • Macrolides (immunomodulatory, not immunosuppressive)
Glucocorticoid-induced Psychosis

• Steroid-Induced Psychosis
  • Administration of exogenous corticosteroids → stress on HPA axis → decreased CRH/ACTH via negative feedback → hippocampal dysfunction due to altered metabolic needs
  • Corticosteroids may additionally induce tyrosine hydroxylase, which is the rate limiting enzyme involved in catecholamine production, potentially causing increased levels of dopamine
  • CYP3A4 inhibition may increase concentrations

Glucocorticoid-induced Psychosis

• Incidence
  • ~5% of patients treated with glucocorticoids

• Time course
  • Symptom onset is usually early in treatment course (within a few days to a few weeks), but can occur years after

• Risk factors
  • Prednisone-equivalent doses >20 mg/day over prolonged period (months)
    • Dosage does not correlate to type, duration, or onset of psychotic symptoms
  • Systemic use (oral) > inhaled or topical
  • Autoimmune disorders
  • Female sex (even when excluding patients with autoimmune diseases like SLE, RA)
  • Other considerations: history of primary psychotic illness, previous episode of steroid-induced psychosis, hepatic or renal dysfunction
Immunosuppressants: Calcineurin Inhibitors

- Calcineurin: complex of phosphates with multiple subunits
  - APCs interact with T-cells → increased Ca → activates calcineurin → T-cell and cytokine production
- Calcineurin inhibitors decrease activation for genes for IL-2, TNF-alpha, IL-3, IL-4, CD40L, granulocyte-macrophage colony-stimulating factor, interferon-gamma
- Different chemical structure, overall similar MOA
  - Tacrolimus may have similar effects as cyclosporine at lower concentrations
- Tacrolimus
  - Inhibits CYP3A4
  - Indications: prophylaxis of post-transplant organ rejection, autoimmune diseases, topical use for atopic dermatitis
- Cyclosporine
  - Inhibits CYP3A4 and P-glycoprotein
  - Indications: solid organ transplant immunosuppression, autoimmune diseases, ALS, nephrotic syndrome

Calcineurin Inhibitors and Psychosis

• Calcineurin is downstream of the NMDA activation pathway and modulates dopamine pathway.

• PPP3CC, a calcineurin-related gene, has been identified as a potential schizophrenia susceptibility gene\(^{12}\)
  • Codes for calcineurin gamma subunit

[PPP3CC image]

https://www.genecards.org/loci-bin/carddisp.pl?gene=PPP3CC
Calcineurin Inhibitors and Psychosis

- Incidence
  - Unclear due to limited data in literature

- Risk factors
  - Supratherapeutic levels, but can also occur in normal levels
  - Liver transplant recipients > other solid organ transplants
  - Hyponatremia
  - Pre-transplant hepatic encephalopathy

- Time course
  - Symptom onset is usually within 1 month from initiation but can occur years into treatment
Management: Current Recommendations

- If possible, taper/discontinue agent or switch to a different agent with lower risk of psychotic symptoms\(^2\). Other special considerations:

- **Glucocorticoids**
  - If chronic use, slow taper to prevent adrenal insufficiency (due to chronic HPA axis suppression) and exacerbation of primary medical condition\(^{16}\)
  - Long term use may lead to more persistent effects
  - Can consider whether a lower potency glucocorticoid would be an appropriate alternative

- **Calcineurin inhibitors**
  - Evaluate level (true trough) and adjust as necessary with primary team\(^{11}\)
  - Case studies and prior studies suggest that tacrolimus may be more neurotoxic than cyclosporine\(^{13, 14}\)

<table>
<thead>
<tr>
<th>Steroids</th>
<th>Half-life (minutes)</th>
<th>Duration of action (hours)</th>
<th>Glucocorticoid potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>80</td>
<td>8–12</td>
<td>1.0</td>
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<tr>
<td>(cortisol)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cortisone</td>
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<td>8–12</td>
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<tr>
<td>Prednisone</td>
<td>60</td>
<td>12–36</td>
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<tr>
<td>Prednisolone</td>
<td>200</td>
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<tr>
<td>Methylprednisolone</td>
<td>200</td>
<td>12–36</td>
<td>5.0</td>
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<td>Triamcinolone</td>
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<tr>
<td>Betamethasone</td>
<td>300</td>
<td>36–72</td>
<td>25.0</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>300</td>
<td>36–72</td>
<td>30.0</td>
</tr>
</tbody>
</table>

Management: Current Recommendations

• If immunosuppressant regimen cannot be altered or symptoms persist after dose reduction, treat symptoms with antipsychotics. Selection of antipsychotic mimics selection for tx of primary psychosis.

• Special Considerations:
  • Renal/hepatic function
  • Calcineurin inhibitors
    • Antipsychotics with high affinity for D2 receptors (risperidone, paliperidone) are favored for calcineurin inhibitor-induced psychosis\(^{11}\)
  • Glucocorticoids
    • Limited data favoring selection of atypical antipsychotics\(^2\)
    • ECT and psychotic depression
  • Psychotic symptoms usually improve or resolve within a few weeks of antipsychotic initiation
    • Some studies have found up to 10% of patients can have persistent psychotic symptoms for >6 weeks, especially after long-term use at high doses\(^{15}\)
Management: Current Recommendations

• Lithium$^{22, 23}$
  • Very few case reports regarding preventative use in glucocorticoid-induced psychosis/mania$^4$
  • Risk of use in patients with impaired renal function (SLE)

• Valproic Acid
  • Old case reports regarding preventative use for glucocorticoid-induced psychosis$^{24}$
  • One case report showed success when combined with risperidone$^{25}$
  • Rapid reversal of steroid-induced mania$^{26}$
Long-Acting Injectables

- Adherence is a particularly important consideration for patients with complex medical histories requiring long-term immunosuppressive treatment
- Limited research on the use of LAI antipsychotics in immunosuppressant-induced psychosis
- LAIs are useful in optimizing adherence to psychotropics and immunosuppressants by simplifying the overall medication regimen
  - Supporting studies in patients with both primary psychotic and primary mood disorders\textsuperscript{18, 20, 21}
- Room for further exploration in chronic immunosuppressant-induced psychosis
  - When picking LAIs, consider co-morbidities, interactions, and metabolism. Atypicals such as risperidone, paliperidone, aripiprazole often favored

\textsuperscript{18} https://www.educationaldoseillustrator.com/ce1m/podcasts/podcast212controller/
\textsuperscript{20} description
Interdisciplinary Teams and Adherence

• Inpatient:
  • Clear role for collaborative care in the hospital, given the potential of treatment interactions and unintended adverse effects of immunosuppressives
    • Transplant evaluations
Interdisciplinary Teams and Adherence

• Outpatient:
  • Multidisciplinary team, including physicians from multiple specialties, nurses, pharmacists, social workers can be valuable
    • Psychosocial support: “Case reports and small studies suggest that poor psychosocial supports appears to be one of the most predictive variables for poor [renal] graft outcomes”
  • Hypertension Study from Union Hospital in China
  • Secondary analysis of the international BRIGHT study
Areas for Future Research

• Longitudinal studies of the efficacy of LAIs in management of immunosuppressant-induced psychosis
• Specific psychiatric risks associated with individual immunosuppressants
• Preventative measures for immunosuppressive-induced psychosis
• Possible pro-active role for CL with immunosuppressant use
References