Neuropsychiatric Complications in the Liver Transplant Recipient: Recognition and Management

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With respect to the following presentation, there has been no relevant (direct or indirect) financial relationship between Dr. Weinrieb and any for-profit company in the past 24 months which could be considered a conflict of interest.
Introduction

1. 20%-30% of liver transplant recipients suffer neuropsychiatric complications early in the post-operative course.

2. Calcineurin inhibitors Tacrolimus (FK-506, Prograf) and Cyclosporine (Neoral) are causatively linked.

3. Diagnosis can be difficult.

4. Management is not evidence based.
Journey Into the Mind of a (Liver)Transplant Psychiatrist: A Case Based Presentation
Case Example*

PSM service consulted by liver transplant team to evaluate a 54 y/o man with “anxiety and fear of swallowing” 7 days after successful transplant of a deceased donor liver

* (O’Donnell et al. Gen Hosp Psy 07)
Case: History and Examination

Findings

• Past Psychiatric History: none
• Symptoms on initial evaluation:
  a. Psychomotor slowing
  b. Poverty of speech with response latency of > 60 seconds
  c. Alert, fully oriented with no abnormality of attention, concentration, working memory, comprehension or writing fluency
  d. No focal neurological signs
a. Laryngoscopy revealed no swallowing abnormalities

b. Medications:
   - Tacrolimus, mycophenolate, prednisone, furosemide, ranitidine, antimicrobials

c. Laboratory Values:
   - Trough Tac level 5.4 ug/L (toxic > 20)
   - Creatinine 1.1mg/dl, BUN 61 mg/dl
   - Expected mildly elevated serum transaminases
Initial Differential Diagnosis of Dysphagia, Catatonia

1. Delirium
2. Psychosis, NOS
3. Seizure activity
4. Central Pontine Myelinolysis (CPM)
5. Posterior Reversible Leukoencephalopathy Syndrome (PRES, PLES, RPLS)
6. Akinetic, Catatonic Mutism
Interpretation of Findings: Moving Toward a Treatment Plan

1. **Evaluate for Delirium**
   - Rapid onset of symptoms +
   - Fluctuation or disturbance -/+ of attention
   - Apparent medical causes +
Interpretation of Findings: Moving Toward a Treatment Plan

2. Psychosis, NOS
   - Delusions (paranoia) +
   - History of pre-txp depression -
     or psychosis
   - Mutism -/+
3. **Seizure activity**
   - Absence, focal motor signs or sterotypies
   - EEG results not obtained +/-
4. **Central Pontine Myelinolysis**

- Rapid correction of hyponatremia -
5. **PRES**
   - Posterior Reversible Encephalopathy Syndrome
   - Affects 1%-6% of liver transplant recipients
Posterior Reversible Encephalopathy Syndrome: Diagnostic Associations

- Hypertension
- Eclampsia
- Autoimmune diseases (Lupus, Thrombocytopenic Thrombotic Pupura, Hemolytic Uremic Syndrome)
- Renal impairment
- Immunosuppression
<table>
<thead>
<tr>
<th>Symptom</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Abrupt onset of symptoms</td>
<td>+</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-</td>
</tr>
<tr>
<td>Confusion</td>
<td>-/+</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>-</td>
</tr>
<tr>
<td>Headache and nausea/vomiting</td>
<td>-</td>
</tr>
<tr>
<td>Seizures (multiple tonic-clonic, occas. status epilepticus)</td>
<td>-</td>
</tr>
<tr>
<td>Cortical blindness (visual field defect, visual neglect)</td>
<td>-</td>
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</tbody>
</table>
PRES: Possible Pathogenesis

- Sudden increases in BP results in compensatory cerebral vasoconstriction and limits cerebral hyperperfusion (autoregulation), usually within first few weeks up to 90 days post-transplant
- Hypertension and/or immunos may cause failure of cerebral autoregulation
- Vasodilation, endothelial damage and blood-brain barrier breach
- **Vasogenic white matter edema and hypertensive encephalopathy**
Posterior Reversible Encephalopathy Syndrome: Diagnostic Imaging

- MRI more sensitive than CT
- Typical bilateral white matter edema in posterior brain regions (occipital) because there is less sympathetic innervation
- A study* of 9 pts described one patient with classical clinical signs, but MRI abnormalities in frontal lobes only
- Edema also seen in parietal, temporal and frontal lobes, midbrain, pons, thalamus, cerebellum

*Tungkasaereerak, J. Med. Assoc Thai, 08
Typical PRES Lesions are T2-hyperintense and Located in Posterior Brain Regions

MRI (FLAIR)  CT
PRES can resolve rapidly once the causal insult is removed.
Interpretation of Findings

5. PRES?
   - **Pro**: abrupt onset, confusion
   - **Con**: no HTN, no seizures, no blindness, CT normal (but MRI not done)
   - Keep looking…………

6. Tacrolimus associated akinetic mutism and dysphagia
Tacrolimus Associated Akinetic Mutism and Dysphagia

- No obvious neurological impairment or evidence of delirium, seizures, CPM or PRES
- Onset of symptoms were abrupt and occurred early in post-operative course
- No speaking or swallowing problems over post-operative days 1-5
- No prior psychiatric history
- Most lab values and studies were normal
Management of Symptoms

1. Lorazepam, 1mg IV given

**Results:**
- In < 60 minutes, pt. regained normal psychomotor activity
- Mild dysarthria
- Said he felt “terrified that people were calling him to take back his liver”
Management of Symptoms

2. Recommended Lorazepam, 1mg q. 4 hours, prn signs of catatonia and Haloperidol, .5mg IV q. 12 hours standing order

*Results:*
- Haldol given, not Lorazepam
- In 24 hours; catatonic, responding only to sternal rub, but eyes tracked and responded to threat
Management of Symptoms, Cont’d

3. Gave Lorazepam, 1mg IV again

**Results:**
- In < 30 minutes, pt. regained normal psychomotor activity, fluent, spontaneous speech

4. Lorazepam, .5mg IV q. 12 hours and Haloperidol, .5mg IV q. 12 hours standing order

**Results:**
- Asymptomatic X 5 days
- Discharged to home on oral Lorazepam and Haldol
- Meds tapered over three weeks with no neuropsychiatric symptom recurrence
Conclusions

• Typical management of neuropsychiatric disorders ass’ed w. calcineurin inhibitors involves stopping offending immunos and switching to another such as Cyclosporine (Neoral) or Sirolimus (Rapamune)

• Symptom abatement can takes weeks to months

• Risks of switching include rejection

• Risk of Rapamune is wound dehiscence if started within 6-8 weeks of transplant
Summary

1. The first reported case of management of catatonia in liver transplant recipients was reported in 1993. The patient responded to IV lorazepam.

2. Including ours, there are now 9 cases reported in the literature; all responding to benzodiazepines +/- neuroleptic.

3. Each case report says it’s the first or second case ever reported!

4. Early recognition is critical since catatonia can be fatal and can occur with normal blood levels of immunosuppressants.

5. The risks of treating the symptoms without switching immunos are unclear, but may be reasonable.