Altered Mental Status after Orthotopic Liver Transplant

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University of Michigan Department of Anesthesiology
Outline

- Case scenario
  - Preoperative history
  - Intraoperative management
  - Postoperative course
- Neurologic complications in setting of liver transplant
- Relevance/Implications
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• Case scenario
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Case Scenario

63 y.o. F, ASA 4E, who presented for orthotopic liver transplant
Preoperative History

Nov 2014  Diagnosis with cirrhosis secondary to alpha-1 antitrypsin deficiency
Mar 2015  First encounter at UMHS
Nov 2015  Referral to transplant surgery
Jan 2016  Transplant workup initiated
Mar 2016  MELD 27; listed for transplant
April 2016  Admitted from clinic due to hepatic encephalopathy
May 12, 2016  Orthotopic Liver Transplant
Preoperative History

Other medical history: hypertension, hypothyroidism
Surgical history: cholecystectomy, tonsillectomy, TAH-BSO
Medications: HCTZ/losartan, thyroid supplement
Intraoperative Course

Induction
Division of hepatic artery
Reperfusion
Anhepatic phase
Intraoperative Course

Coagulopathy

- 28 u pRBC
- 25 u FFP
- 4 five-pack Plts
- 3 u Cryoprecipitate

EBL = 11L
Intraoperative Course

Induction

Anhepatic phase

Division of hepatic artery

Reperfusion

Anhepatic phase
# Intraoperative Course

<table>
<thead>
<tr>
<th>Blood Gas Source</th>
<th>14:00</th>
<th>15:00</th>
<th>16:00</th>
<th>17:00</th>
<th>18:00</th>
<th>19:00</th>
<th>20:00</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>Arterial</td>
<td>Arterial</td>
<td>Arterial</td>
<td>Arterial</td>
<td>Arterial</td>
<td>Arterial</td>
<td>Arterial</td>
</tr>
<tr>
<td>pH</td>
<td>7.33</td>
<td>7.28</td>
<td>7.27</td>
<td>7.33</td>
<td>7.38</td>
<td>7.43</td>
<td>7.46</td>
</tr>
<tr>
<td>pCO2</td>
<td>40</td>
<td>41</td>
<td>42</td>
<td>40</td>
<td>40</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td>pO2</td>
<td>157</td>
<td>250</td>
<td>244</td>
<td>253</td>
<td>168</td>
<td>210</td>
<td>216</td>
</tr>
<tr>
<td>Na</td>
<td>131</td>
<td>134</td>
<td>136</td>
<td>138</td>
<td>139</td>
<td>141</td>
<td>139</td>
</tr>
<tr>
<td>K</td>
<td>3.4</td>
<td>3.5</td>
<td>3.7</td>
<td>3.7</td>
<td>4.6</td>
<td>4</td>
<td>3.8</td>
</tr>
<tr>
<td>Ca</td>
<td>1.18</td>
<td>0.93</td>
<td>1.51</td>
<td>1.02</td>
<td>1.29</td>
<td>1.4</td>
<td>1.57</td>
</tr>
<tr>
<td>Glu</td>
<td>98</td>
<td>134</td>
<td>157</td>
<td>195</td>
<td>252</td>
<td>243</td>
<td>231</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.6</td>
<td>2</td>
<td>3</td>
<td>6.4</td>
<td>6.1</td>
<td>5.8</td>
<td>3.6</td>
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<tr>
<td>Blood Gas Hct</td>
<td>27</td>
<td>17</td>
<td>23</td>
<td>16</td>
<td>24</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>O2 Sat</td>
<td>99</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>99</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Postoperative Course

POD 1  Extubated
POD 3  Concern for worsening mental status: Responsive but confused
POD 4  Mild tremors noted
POD 7  Continued mental decline, increased severity of tremors; Neurology consulted
POD 8  MRI performed
Outline

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  • Postoperative course
• Neurologic complications in setting of liver transplant
• Relevance/Implications
Perioperative Neurological Complications in Liver Transplant

Neurologic complications in 30-60% of solid organ transplant recipients

Table 1: Organ-specific posttransplant neurologic complications

<table>
<thead>
<tr>
<th>Organ</th>
<th>Neurologic complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Central pontine myelinolysis, Hepatic encephalopathy, Brachial plexopathy</td>
</tr>
<tr>
<td>Kidney</td>
<td>Diabetic neuropathy (<em>may get better after transplantation</em>), Atherothrombotic stroke (late posttransplant), Uremic encephalopathy, Femoral neuropathy</td>
</tr>
<tr>
<td>Heart</td>
<td>Cardioembolic stroke (early posttransplant)</td>
</tr>
<tr>
<td>Lung</td>
<td>Phrenic neuropathy</td>
</tr>
</tbody>
</table>

Avila, Curr Neurol Neurosci Rep. 2015
Perioperative Neurological Complications in Liver Transplant

- **Procedural Complications**
- **Complications of Immunosuppression**
  - Opportunistic Infections
  - Neurotoxicity of Immunosuppressants
- **Other Complications**
  - Seizures
  - Metabolic Disturbances
  - Cerebrovascular Complications
  - Malignancy
Procedural Complications

Intraoperative brain ischemia
Residual anesthetic effect
Perioperative Neurological Complications in Liver Transplant

• Procedural Complications
• **Complications of Immunosuppression**
  • Opportunistic Infections
  • Neurotoxicity of Immunosuppressants
• Other Complications
  • Seizures
  • Metabolic Disturbances
  • Cerebrovascular Complications
  • Malignancy
Complications of Immunosuppression

Opportunistic Infection

– Prevalence: 1-2%
– Diagnosis may be delayed because of diminished ability to mount inflammatory response
– Viral, fungal, protozoal, bacterial

Avila, Curr Neurol Neurosci Rep. 2015
Complications of Immunosuppression

Toxoplasmosis
# Drug-Related Toxicity

## Table 2: Common drug-related toxicity in transplant recipients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antirejection medications</strong></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus, cyclosporine</td>
<td>Tremor, headache, encephalopathy, seizures, PRES</td>
</tr>
<tr>
<td>Sirolimus, everolimus</td>
<td>Tremor, headache, depression, <em>PRES</em> (rare)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Mood disorders, psychosis, myopathy, tremor, <em>epidural lipomatosis</em> (rare)</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Headache, dizziness</td>
</tr>
<tr>
<td>Antithymocyte globulins</td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td>Muromonab (OKT3)</td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td><strong>Other medications</strong></td>
<td></td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Encephalopathy, seizures</td>
</tr>
<tr>
<td>Triazole antifungals</td>
<td>Painful neuropathy</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Sedation</td>
</tr>
<tr>
<td>Statins, colchicine</td>
<td>Rhabdomyolysis</td>
</tr>
</tbody>
</table>

Drug-Related Toxicity

PRES: Posterior Reversible Encephalopathy Syndrome
Perioperative Neurological Complications in Liver Transplant

• Procedural Complications
• Complications of Immunosuppression
  • Opportunistic Infections
  • Neurotoxicity of Immunosuppressants
• Other Complications
  • Seizures
  • Metabolic Disturbances
  • Cerebrovascular Complications
  • Malignancy
Metabolic Disturbances and Encephalopathy

- Hepatic encephalopathy
  - Pretransplant hepatic encephalopathy associated with greater risk of perioperative complications
- Electrolyte disturbances
  - Wernicke’s encephalopathy
  - Central Pontine Myelinolysis
- Glucose disturbances
Diagnostic Workup

Blood cultures, urine culture negative
Head CT (x2): no acute intracranial pathology
TSH: normal
Ammonia: normal
EEG long-term monitoring: no seizures; mild-moderate encephalopathy
Diagnostic Workup
## Sodium Trend

<table>
<thead>
<tr>
<th>Time</th>
<th>Sodium (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/11</td>
<td>127</td>
</tr>
<tr>
<td>5/12 (preop)</td>
<td>134</td>
</tr>
<tr>
<td>5/12 (intraop, start)</td>
<td>131</td>
</tr>
<tr>
<td>5/12 (intraop, last)</td>
<td>139</td>
</tr>
<tr>
<td>5/12 (postop)</td>
<td>146</td>
</tr>
</tbody>
</table>
Central Pontine Myelinolysis

Background and Epidemiology
Pathophysicsology
Images
Clinical Course
Treatment
Prognosis
Central Pontine Myelinolysis

A Hitherto Undescribed Disease Occurring in Alcoholic and Malnourished Patients

RAYMOND D. ADAMS, M.D.; MAURICE VICTOR, M.D., and ELLIOTT L. MANCALL, M.D., Boston
CPM: Background & Epidemiology

First described in liver transplantation in 1978

1-2% of liver transplant patients

Osmotic Demyelination Syndrome

– Extrapontine involvement (basal ganglia, thalamus, etc)

– ~60% of liver transplant patients with CPM

Crivellin, Transplantation. 2015
Singh, European Journal of Neurology. 2004
CPM: Background & Epidemiology

Predisposing factors in liver failure

- Malnutrition
- Alcohol abuse
- Chronic hyponatremia
- Depletion of myoinositol
- Negative nitrogen balance
- Decreased glycogen reserve

Campos, Transplantation Proceedings. 2011
Crivellin, Transplantation. 2015
CPM: Pathophysiology

Acute Hyponatremia

- Cell Swelling
  - AQP 4
  - Water entry from area of low osmolality to intracellular area of higher osmolality

Chronic Hyponatremia

- Restoration of cell volume
  - Na-K-ATPase
  - Organic solute transporter
  - Removal of inorganic and organic solutes and water from cell

King, *The American Journal of the Medical Sciences*. 2010
CPM: Pathophysiology

Cell chronically adapted to hyponatremia

Rapid correction of hyponatremia

1. Breakdown of blood-brain barrier
2. Exposure of glial cells to cytokines, complement
3. Axonal shear injury
4. Cellular ATP depletion
5. Induction of apoptosis

Osmotic Demyelination

King, *The American Journal of the Medical Sciences*. 2010
CPM: Pathophysiology
CPM: Images
CPM: Images

King, *The American Journal of the Medical Sciences*. 2010
King, The American Journal of the Medical Sciences. 2010
CPM: Clinical Course

48 hours
- confusion, drowsiness, stupor
- dysarthria, dysphagia
- seizures

~7-10 days: Flaccid paralysis, locked-in syndrome

Depending on location of involvement: Parkinsonism, dystonia, postural limb tremor
CPM: Treatment

Supportive
CPM: Treatment

Suggested Rate of Na Improvement

Martin, *Clinical Liver Disease*. 2004
CPM: Prognosis

All CPM patients
- 20-30% mortality
- Of survivors, 50% recovery to Rankin $\leq 1$

Liver transplant population
- 40-50% mortality
- Of survivors, 40% recovery to Rankin $\leq 1$

Lesion location, MRI-based estimation of volume not predictive of prognosis

Postoperative course, revisited

POD 1  Extubated
POD 3  Concern for worsening mental status
POD 4  Mild tremors noted
POD 7  Continued worsening of symptoms
POD 8  MRI performed
POD 10 Blinking, no tracking with eyes, no response to commands
POD 12 Nearly tetraplegic
Clinical Course
Outline

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Relevance/Implications

- MELD scoring change
- Intraoperative Management
- Fluid and Electrolyte Management
- Na increase in liver transplant
- Postoperative Management
- Future direction
A Model to Predict Poor Survival in Patients Undergoing Transjugular Intrahepatic Portosystemic Shunts

Michael Malinchoc,1 Patrick S. Kamath,1 Fredric D. Gordon,2 Craig J. Peine,3 Jeffrey Rank,4 and Pieter C. J. ter Borg5

MELD Score = 0.957 \times \log_e(\text{creatinine mg/dL})
+ 0.378 \times \log_e(\text{bilirubin mg/dL})
+ 1.120 \times \log_e(\text{INR})
+ 0.643^1

Multiply the score by 10 and round to the nearest whole number.
MELD-Na

Hyponatremia associated with mortality independent of MELD score
Increases predictive accuracy

\[ \text{MELD-Na} = \text{MELD} + 1.32 \times (137-\text{Na}) - [0.033 \times \text{MELD} \times (137-\text{Na})] \]
MELD-Na

We will see an increase in liver transplant patients with hyponatremia
Intraoperative Management

Decrease sodium administration
  – Judicious administration of sodium-containing products

Increase free water administration
# Fluid and Electrolyte Management

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Sodium Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% Sodium Chloride</td>
<td>154 mEq/L</td>
</tr>
<tr>
<td>0.45% Sodium Chloride</td>
<td>77 mEq/L</td>
</tr>
<tr>
<td>Sodium Bicarbonate (8.4%)</td>
<td>1 mEq/mL = 1000 mEq/L</td>
</tr>
<tr>
<td>FFP</td>
<td>172 mEq/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>130-160 mEq/L</td>
</tr>
<tr>
<td>D5W</td>
<td>0 mEq/L</td>
</tr>
<tr>
<td>THAM</td>
<td>0 mEq/L</td>
</tr>
</tbody>
</table>

The image shows the chemical structure of sodium bicarbonate. The molecular formula of sodium bicarbonate is $\text{Na}_2\text{CO}_3$. The molecule consists of two sodium ions ($\text{Na}^+$) and one bicarbonate ion ($\text{HCO}_3^-$).
Fluid and Electrolyte Management

THAM

- Alternate to sodium bicarbonate as treatment of metabolic acidosis
- $pK_a = 8.07$; buffer 7.5-9
- Not available any more
Fluid and Electrolyte Management

Low sodium solutions
- VIP carrier
- Belmont priming solution
Fluid and Electrolyte Management

Targeted blood product transfusion

pRBC Cellsaver
Intraoperative Sodium Increase in Liver Transplant

UM data from last six years

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Na &gt;135</th>
<th>Na &lt;135</th>
<th>Na &lt;130</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>512</td>
<td>351</td>
<td>161</td>
<td>46</td>
</tr>
<tr>
<td>Mean Na rise</td>
<td>2.7</td>
<td>2.0</td>
<td>4.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Standard Dev</td>
<td>3.6</td>
<td>3.3</td>
<td>3.9</td>
<td>4.2</td>
</tr>
<tr>
<td>25%</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>50%</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>75%</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>7.7</td>
</tr>
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</table>
Intraoperative Sodium Increase in Liver Transplant

UM data from last six years

<table>
<thead>
<tr>
<th>Increase in Sodium (mEq/L)</th>
<th>Count</th>
</tr>
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<tbody>
<tr>
<td>8</td>
<td>20</td>
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<tr>
<td>9</td>
<td>13</td>
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<tr>
<td>10</td>
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<tr>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>17</td>
<td>1</td>
</tr>
</tbody>
</table>
Postoperative Management

Vigilance with high risk patients
Appropriate correction of sodium with free water administration
Case Conclusion: Three Months Later

Moderate care unit, awaiting LTAC placement

Barely communicative with nodding head yes/no, with only a 50% accuracy rate

Trach dependent

Movement: standing with assist

Pressure ulcers
Case Conclusion: Six Months Later

10/7/2016: Transfer to inpatient rehabilitation center
- Requires patient to be medically stable
- Be able to participate in 3 hours of PT

11/18: Discharge home
Case Conclusion: Clinical Sequelae

Neuro/Psych: paranoia, delirium, generalized anxiety disorder
CV: dilated cardiomyopathy
Pulm: trach-dependent for five months
GI: severe malnutrition, ~100 lb loss
Renal: Stage III CKD
MSK: impaired mobility requiring moderate to maximal, ADL
Case Conclusion:
One Year Later

Significant improvement following discharge
- Walk 200ft
- Recumbent bike for 20 minutes
- Daily exercise

Gaining more independence IADL, ADL
Follow-up MRI
Take-Home Points

Differential for altered mental status in the post-transplant patient is extensive.

Central Pontine Myelinolysis has an incidence of 1-2% in liver transplant patients with a combined morbidity-mortality rate of 77%.

Treatment for CPM is supportive; best measures are preventative with emphasis on slow correction of hyponatremia.

We must have increased awareness of the effect of the fluids we give intraoperatively and be judicious in their administration.
Questions/Discussion
References


