Management of Recurrent HE

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Disclosures

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Carla Molliner, PA-C

Advisory Board:

- Bausch Health (formerly Valeant Pharmaceuticals)
Overview

• Case study

• Hepatic encephalopathy (HE)
  a. definition and diagnosis
  b. pathogenesis and precipitant

• Management
  a. current
  b. recurrent

• Summary
52 yo M with NASH, Alcohol use disorder, Cirrhosis presents to the hospital with confusion.

His wife report that he has increased somnolence and unable to communicate.

Noted to have asterixis on exam.

The primary team admits the patient and consults hepatology team.
Hepatic Encephalopathy

- Wide spectrum of reversible neurological or psychiatric abnormalities in advanced chronic liver disease patients
- After exclusion of neurologic and or metabolic etiologies.
- It ranges from covert to overt hepatic encephalopathy.
Epidemiology of HE

- Can occur in 30-40% of Cirrhotic patients
- 10-50% in patients with transjugular intrahepatic portosystemic shunt (TIPS)
- Prognosis of these patients is poor
- Mortality ranges 15-25%

Clinical Findings Associated With HE

<table>
<thead>
<tr>
<th>ISHEN Classification</th>
<th>West Haven Grade</th>
<th>Neurological changes</th>
<th>Asterixis</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVERT</td>
<td>Minimal</td>
<td>Abnormal results on neuropsychological testing No clinical manifestations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Decrease attention span, altered sleep rhythm</td>
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<tr>
<td>OVERT</td>
<td>2</td>
<td>Lethargy, disoriented, mod confusion, obvious personality changes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Somnolence, confused, bizarre, muscular rigidity</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Coma</td>
<td></td>
</tr>
</tbody>
</table>

# Overall Classification of HE

<table>
<thead>
<tr>
<th>Type</th>
<th>Grade</th>
<th>Time Course</th>
<th>Presence of precipitating factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Minimal I</td>
<td>Covert</td>
<td>Spontaneous</td>
</tr>
<tr>
<td>B</td>
<td>II</td>
<td>Episodic</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>III</td>
<td>Recurrent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Persistent</td>
<td>Precipitated (specify)</td>
</tr>
</tbody>
</table>

Diagnosis of HE

- Based on clinical examination and clinical decision.
- Asterixis or "flapping tremor" early – middle stages of HE. Is not pathognomonic of HE, since can be observed in other diseases, i.e., uremia.
- Gold standard for staging severity is the West Haven criteria.
- Exclusion of other etiologies for a patient with altered mental status is warranted.
Pathogenesis

• Complex entity with multiple components resulting in functional impairment of neuronal cells, none of which are well understood:
  – Ammonia (NH₃)
  – Inflammatory cytokines
  – Benzodiazepine like compounds
  – Manganese
  – Altered gut microbiota
Pathogenesis

GI TRACT

Toxic
Cannot be excreted

UREA CYCLE

Non-toxic
Easily excreted in urine

KIDNEY

ammonia

ammonia

ammonia

Urea
Ammonia Levels in HE

Ammonia Levels Do Not Guide Clinical Management of Patients With Hepatic Encephalopathy Caused by Cirrhosis

Mona Haj, MD¹ and Don C. Rockey, MD¹

INTRODUCTION: Ammonia appears to play a major role in the pathophysiology of hepatic encephalopathy (HE), but its role in guiding management is unclear. We aimed to understand the impact of ammonia levels on inpatient HE management, hypothesizing that patients with elevated ammonia levels would receive more aggressive lactulose therapy than patients with normal ammonia or no ammonia level drawn.

METHODS: We examined patients with cirrhosis older than 18 years admitted for management of HE from 2005 to 2015. We additionally used propensity matching to control for confounding by the severity of underlying disease. Patients with an ammonia level taken at time of HE diagnosis were further separated into those with normal or elevated ammonia levels. The primary endpoint was the total lactulose (mL) amount (or dose) given in the first 48 hours of HE management.

RESULTS: One thousand two hundred two admissions with HE were identified. Ammonia levels were drawn in 551 (46%) patients; 328 patients (60%) had an abnormal ammonia level (>72 µmol/L). There were no significant differences in the Child-Pugh score, MELD, or Charlson Comorbidity Index in those with and without ammonia levels drawn. The average total lactulose dose over 48 hours was 167 and 171 mL in the no ammonia vs ammonia groups, respectively (P = 0.42). The average lactulose dose in patients with an elevated ammonia level was 161 mL, identical to the lactulose dose in patients with a normal ammonia level. There was no correlation between lactulose dose and ammonia level (R² = 0.0026).

DISCUSSION: Inpatient management of HE with lactulose was not influenced by either the presence or level of ammonia level, suggesting that ammonia levels do not guide therapy in clinical practice.

Precipitating Factor for HE

- GI hemorrhage
- Hypokalemia
- Azotemia
- Constipation
- Infection
- ↑ Ammonia production
- Systemic alkalosis
- ↑ Diffusion of ammonia across BBB
- Progressive parenchymal damage
- Dehydration
- Anemia
- Arterial hypotension
- Arterial hypoxemia
- Hepatoma
- Shunts
- ↓ Toxin metabolism
- Activation of central GABA-benzodiazepine receptors
- Benzodiazepines
- CNS = blood brain barrier
- CNS = central nervous system
- GABA = γ-aminobutyric acid
- GI = gastrointestinal
- HE = hepatic encephalopathy
The Basics of Hepatic Encephalopathy

• A – Airway
  – Protect the airway

• B – Brain, Bleeding, Blood
  – Infection work up
  – Upper GI endoscopy
  – Head CT

• C – Catharsis
  – Bowel movements

Treatment Goals for HE

- Provide supportive care
- Correct the precipitant cause
- Reduce nitrogenous load from the gut
- Nutritional support
- Assessment of long-term therapy
  - Role of liver transplantation
Current Therapies for HE

- Non-absorbable disaccharides
  - Lactulose
- Non-absorbable antibiotics
  - Rifaximin
- Ammonia scavengers (clinical trials ongoing)
  - Bind ammonia in the gut
- Manipulation of the splanchnic circulation, splenorenal shunt
  - IR interventions
Lactulose

- Metabolized by the bacteria flora to short chain fatty acids
- Lowering the pH in the colon
- Causes osmotic diarrhea
- Nitrogen in the feces
- Ammonia levels
- Considered the treatment of choice for HE
- 30-45 ml, 3x/day, titrate to achieve 3 soft stools per day
Rifaximin

• Oral minimally absorbed antibiotic, < 0.4%
• Effective add-on therapy for prevention of overt HE recurrence.
• Contributed to restoring gut microflora imbalance
• Reduce ammonia production by eliminating ammonia producing colonic bacteria
• Approval 550 mg twice a day
• Granted for reduction in risk of HE recurrence
Rifaximin vs Placebo

A Time to First Breakthrough HE Episode (Primary End Point)

Hazard ratio with rifaximin, 0.42 (95% CI, 0.28-0.64)

P<0.001

Refractory/Recurrence HE

- Persistent encephalopathy despite appropriate medical treatment.
  - Portosystemic Shunt(s): “flow phenomenon”
    - Need cross sectional imaging
    - If MELD score (< 15), and shunt > 8 mm diameter, then coil embolization with IR
    - Can worsen portal hypertension
  - TIPS related refractory hepatic encephalopathy (TRHE)
    - occurs if portosystemic gradient is reduced > 60%
    - Shunt diameter reduction

# Summary of Available Therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
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<tbody>
<tr>
<td><strong>First-line therapy</strong></td>
<td></td>
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<tr>
<td>Nonabsorbable disaccharides</td>
<td>Promotes conversions of NH$_3$ to NH$_4^+$ in the colon, osmotic laxative, prebiotic</td>
</tr>
<tr>
<td>Nonabsorbable antibiotics (Rifaximin)</td>
<td>Alters gut microbiota Eliminates ammonia-producing colonic bacteria</td>
</tr>
<tr>
<td><strong>Adjunctive therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>Enhances urea formation from ammonia to amino acids</td>
</tr>
<tr>
<td>BCAAS</td>
<td>Reduces ammonia from circulation by converting to glutamine</td>
</tr>
<tr>
<td>Embolization of large portosystemic shunts</td>
<td>Decreases systemic shunting of ammonia</td>
</tr>
</tbody>
</table>

BCAAS, branched chain amino acids; NH$_3$, ammonia, NH$_4^+$, ammonium.
Implications of HE

- Caregiver fatigue
- Compliance with medicine
- Patients living alone
- Driving/working
- Recurrence of HE
Take Away Points

• Standard therapy:
  – Neurocognition can be reversible with lactulose +/- rifaximin while treating the underlying precipitants

• Recurrent/refractory or persistent HE
  – Look for spontaneous shunts
    • Embolization for MELD < 15
    • Liver transplant referral

• Malnutrition and loss of muscle mass, is a risk factor for development of HE
  – Energy intake of 35-40 kcal/kg/day, protein intake 1.2-1.5 g/kg/day. Late night snack, unless risk for aspiration