Challenges in the Diagnosis and Management of Hepatic Encephalopathy

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Disclosures

I have received speaking/consulting fees from Intercept and Lupin pharmaceuticals
CANMEDS Objectives

- Scholar
- Health Advocate
Objectives

1. To review the diagnostic criteria/categorization of overt and covert hepatic encephalopathy
2. To understand the pathophysiology of hepatic encephalopathy
3. To discuss the management of overt hepatic encephalopathy
Hepatic encephalopathy - definition

- Spectrum of neuropsychiatric abnormalities
  - seen in patients with liver dysfunction
  - after exclusion of other known brain disease

- Categorized into three broad groups
  - type A: acute liver failure
  - type B: bypass shunts
  - type C: cirrhosis

HE results in increased mortality

Bustamante et al, J Hepatol 1999
Mortality is Independent of Liver function

![Graph showing cumulative incidence of mortality over time with different outcomes and p-values](image_url)

Romero-Gomez et al, J Hepatol 2015
Diagnosis - Categorical approach

Stage 0
- No abnormality detected

Stage I
- Euphoria or anxiety
- Shortened attention span
- Lethargy or apathy

Stage II
- Disorientation to time
- Inappropriate behavior/personality change
- Somnolence to semi-stupor

Stage III
- Confused
- Gross disorientation
- Bizarre behavior

Stage IV
- Coma

Minimal Hepatic Encephalopathy

- HE without an obvious clinical profile
- Diagnosed only by specialized cognitive testing
- Occurs in 30-70% of patients with cirrhosis

Overt vs. Covert Encephalopathy

- **Overt hepatic encephalopathy**
  - clinical diagnosis (altered mental status, asterixis)

- **Covert hepatic encephalopathy**
  - encompasses minimal or subclinical hepatic encephalopathy and stage I encephalopathy
  - requires specialize cognitive testing
Diagnosis – Continuous approach

Cordoba J. J Hep 2011; Bajaj. APT 2009.
Overall Classification of HE: Four Axes

<table>
<thead>
<tr>
<th>Type</th>
<th>Grade</th>
<th>Time Course</th>
<th>Presence of precipitating factor</th>
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<tbody>
<tr>
<td>A (Acute Liver Failure)</td>
<td>Minimal</td>
<td>Episodic (no further HE for ≥ 6 months)</td>
<td>Precipitated (specific factor found)</td>
</tr>
<tr>
<td></td>
<td>Covert</td>
<td>Recurrent (further episode within 6 mths)</td>
<td>Spontaneous (no precipitating factor found)</td>
</tr>
<tr>
<td>B (porto-systemic Bypass or shunt without cirrhosis)</td>
<td>1</td>
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<td>4</td>
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<tr>
<td>C (Cirrhosis)</td>
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</table>
Should I use ammonia levels to diagnose HE?

- Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value
- If normal – diagnosis of HE is in question
- Logistic challenges to accurately measure blood ammonia
  - Venous, arterial blood, or plasma ammonia
Should I screen for covert HE?
Covert HE is not minimal

• It is associated with increased progression to Overt HE
• It is associated with poor Health-related Quality of Life
• Individuals are high risk for traffic violations and accidents
• It is an independent predictor for death and hospitalizations

• Diagnosis is dependent on specialized psychometric testing
• No clear treatment guidelines if diagnosed
• Could consider trial of therapy if QOL impacted

Pathogenesis – Ammonia hypothesis
Neuro-Morphological Changes in HE
Management

Inflammation
  - Intracranial Pressure
  - Swelling
  - Cerebral Blood Flow

Glutamine Neuron
  - NH₃
  - Glutamate

Oligodendrocyte

Astrocyte
Ammonia

Fermentation
  - Lactulose converted to Volatile Fatty Acids by bacteria

Lactulose
  - VFA: volatile fatty acids

Colonic bacteria
  - NH₃: Ammonia
  - NH₄⁺: Ammonium

Lupin pharmaceuticals
Inhibit ammonia production
- Disaccharides
- Antibiotics
- Probiotics
Management

Metabolic ammonia removal:
- Ornithine-aspartate
- Glycerol phenylbutyrate

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Increase skeletal muscle mass?

Glutamate
Acyl-Phosphate intermediate
Glutamine
False Neurotransmitter Hypothesis

↑AAA
Excessive entry of AAA within the brain

↓BCAA

Formation of false neurotransmitters
False Neurotransmitter Hypothesis

- Excessive entry of BCAA within the brain
- Formation of false neurotransmitters

BCAA supplementation

- ↑ BCAA
- ↓ BCAA
Treatment of Overt encephalopathy

Exclusion of alternative neurological disorders
1. Medical history + physical exam: presence of headache, focal neurological signs, meningeal signs
2. Basic analysis: glycemia, PCO₂
3. Toxics in blood or urine: benzodiacepines (consider flumazenil if suspicious), alcohol...
4. Assess B1 deficit in blood (or give thiamine if suspicion)
5. Neuroimaging (CT, MR) if any abnormality in 1 or coma (unless rapid improvement).
6. EEG if suspicion of seizures or non-convulsive status.

Cirrhosis + acute change in mental state

Search of precipitating factors
1. Medical history + physical exam: explore signs of gastrointestinal bleeding, constipation, dehydration, infection (fever, localized signs)
2. Basic analysis: Hemoglobin, leukocytes, creatinine, Na, K, pH,
3. Leukocytes in urine and ascites (if present)
4. X-rays (thorax and abdomen).
5. Cultures of blood, urine, ascites or other body fluids (if abnormal)

Liver function and portal-systemic circulation
1. Medical history+physical exam: signs of complications of cirrhosis
2. Blood test: bilirubin, albumin, prothrombin, AST, ALT
3. Imaging of liver and portal-systemic circulation: CT, MR...

Cordoba et al., J Hep 2011
Treatment of Overt encephalopathy

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Cirrhosis + acute change in mental state

- Infections
- GI bleeding
- Diuretic overdose
- Electrolyte disorder
- Constipation
- Unidentified

Liver evaluation

1. Medical history and physical exam: symptoms of cirrhosis
2. Blood tests: liver function test, bilirubin, albumin, CT
3. Imaging of liver and portal-systemic circulation: CT, MR...

Infections

1. Medical history and physical exam: fever, localized signs
2. Blood tests: complete blood count, CRP, glucose, Na, K, pH,
3. Cultures of blood, urine, CSF
4. X-ray of chest
5. Ultrasound of liver and kidneys (if abnormal)

GI bleeding

1. Medical history and physical exam: history of bleeding, anemia
2. Blood tests: complete blood count, hemoglobin, platelets, 
3. Upper endoscopy
4. Imaging of abdomen: CT, MRI

Diuretic overdose

1. Medical history and physical exam: history of diuretic use
2. Blood tests: electrolytes, creatinine, urine output
3. Imaging of abdomen: CT, MRI

Electrolyte disorder

1. Medical history and physical exam: symptoms of electrolyte imbalance
2. Blood tests: electrolytes, glucose, creatinine, BUN
3. Imaging of abdomen: CT, MRI

Constipation

1. Medical history and physical exam: history of constipation
2. Blood tests: complete blood count, electrolytes
3. Imaging of abdomen: CT, MRI

Unidentified

1. Medical history and physical exam: symptoms of undetermined cause
2. Blood tests: complete blood count, liver function test, bilirubin
3. Imaging of abdomen: CT, MRI

Cordoba et al., J Hep 2011
Do I need to restrict protein intake?

- 1.2 g/kg/day protein
- immediately
- gradual increase
- No difference in groups

Cordoba et al., J Hep 2004
Treatment of acute episode of OHE

- Lack of randomized, controlled studies
  - Mostly circumstantial observations

**Lactulose – 1st line therapy**
- Rifaximin
- Other antibiotics
- BCAAs
- LOLA
- Probiotics
- Laxatives (Polyethylene glycol)

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  - Other antibiotics
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  - Probiotics
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- Higher proportion of complete reversal of HE (76% vs. 50.8%, p<0.004)
- Improved 10 day mortality (49.1% vs 23.8%, p<0.05)
- More infections in lactulose + placebo group
Treatment of acute episode of OHE

- Lack of randomized, controlled studies
  - Mostly circumstantial observations

- Lactulose – 1st line therapy
  - Rifaximin
  - Laxatives (Polyethylene glycol)
    - 3 doses lactulose/24 hrs. vs. 4L PEG/24 hrs
    - No lactulose in preceding 7 days
    - Did not include subjects on rifaximin

Secondary Prophylaxis - Lactulose

Recurrent HE in 46.8% (placebo) vs. 19.6% (lactulose)
Secondary Prophylaxis - Rifaximin

- Subjects with 2 prior overt HE episodes
- Recurrent HE in 22% Lactulose + Rifaximin vs. 46% Lactulose + Placebo

Hazard ratio with rifaximin, 0.42 (95% CI, 0.28–0.64) P<0.001
Promising Treatments

• Branched-chain amino acids
• Probiotics/Fecal microbiota transplantation
• Shunt embolization
Branched chain amino acids


Hepatic encephalopathy

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<td>6.40 (1.58, 26.00)</td>
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<tr>
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<td>2.27 (1.39, 3.70)</td>
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<tr>
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Mortality

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Branched chain amino acids

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Vs. placebo

?Treatment of protein-energy malnutrition vs. HE

Probiotics

• Microbial dysbiosis is thought to contribute to HE
• Studies show a relative dearth of short-chain fatty acid-producing enrichment of pathogenic *Enterobacteriaceae*
• Probiotics 3 capsules/day
  • 112.5 billion lyophilized bacteria/capsule
  • *Lactobacillus, Bifidobacterium, Strep salivarius* subsp. *Thermophiles*
  • Fewer episodes of HE in the probiotic arms (45.4%), compared to placebo (64.1%)
• VSL #3 may prevent emergence of HE, re-hospitalizations

Fecal Microbiota Transplantation

- Case report in 1 recipient with grade I-II HE on lactulose only
- Improvement in psychometric testing, ammonia level, HRQOL with FMT but reverted to baseline when FMT stopped
Fecal Microbiota Transplantation

• Open-label, randomized clinical trial of 20 patients (FMT vs. SOC)
  • Recurrent HE on SOC

• 5 days of broad-spectrum antibiotic pretreatment, then single FMT enema from the same donor
  • Followed for 5 months

• Primary endpoint was safety
  • FMT 20% vs. SOC 80% serious adverse events (none FMT-related)

• Secondary endpoint development of HE
  • FMT 0 vs. SOC 50%

• Increased diversity and beneficial taxa

Bajaj et al., Hepatology 2017.
Shunt embolization for medically refractory hepatic encephalopathy

Lynn et al, Liver Transpl 2016
Transplantation

- Indicated in individuals with recurrent HE
- May not resolve completely post-transplantation
- N=7 (13%) persistent mild cognitive impairment
Driving

• Local laws may differ on mandatory reporting
  • Overt HE should be reported
  • No guideline recommendations re. covert HE

• Inform the patient and their family
Conclusions

• Overt HE is a clinical diagnosis
  • Ammonia levels not required to make diagnosis

• Initial management
  • Precipitating factors!
  • No need for protein restriction
  • Lactulose +/- rifaximin +/- PEG

• After 1\textsuperscript{st} episode: lactulose therapy
• After 2\textsuperscript{nd} episode: addition of rifaximin
• Consider liver transplant evaluation