ICU Care of Patients with Hepatic Encephalopathy

Nae-Yun Heo

Department of Gastroenterology
Inje University College of Medicine Haeundae Paik Hospital
Contents

• Pathogenesis and diagnosis of HE
• Grading of HE
• Indication of ICU management of HE
• General intensive care for HE
• HE in acute liver failure
Complications of Liver Cirrhosis

- Cirrhosis
  - Portal HTN
    - Variceal hemorrhage
    - Ascites
      - HRS
      - SBP
    - Hepatic Encephalopathy
  - Liver insufficiency
    - Jaundice
Incidence of HE in cirrhosis

- Of 63 patients with cirrhosis, 53% exhibited subclinical HE, and 30% developed overt HE during follow-up (mean $4.8 \pm 0.7$ yr).

- The incidence of Post-TIPS encephalopathy within 1 year was 23~30%.
  - Somberg et al. Am J Gastroenterol 1995
  - Sanyal et al. Hepatology 1994
Survival of patients with HE in cirrhosis

111 patients in cirrhosis
- Zero-time: 1st episode of HE
- Endpoint: death, LT, or f/u loss

- 42% at 1yr
- 27% at 2yr
- 23% at 3yr

Bustamante J. J Hepatol 1999;30:890-895
Pathogenesis of HE

- NH₃ production:
  - Bacteria
  - Enterocyte

- NH₃ + Glutamate

- Porto-systemic shunting

- Liver dysfunction

- Astrocyte swelling

- Impairment of neurotransmission (GABA, serotonin, glutamate, CA)

- Urea

- Glutamate

- Glutamine
Classification

• Type A: HE occurring in acute liver failure

• Type B: HE occurring in porto-systemic bypass without intrinsic hepatocellular disease

• Type C: HE occurring in cirrhosis with portal HTN or systemic shunting
A typical case of type C HE

- 56/F
- HBeAg (-) CHB
- LC, Child C
- h/o Esophageal variceal bleeding
- P/Ex: spider angioma (+)
- Constipation (+)
- Confusion, Tremor
Flapping tremor
Clinical Manifestations

• **Cognitive deficit**
  – Sleep disturbance
  – Impairments in attention, reaction time, and working memory
  – Mood changes (euphoria, depression)
  – Disorientation (time/place/person)
  – Inappropriate behavior
  – Somnolence, confusion, unconsciousness
Clinical Manifestations

- Impaired neuromuscular function
  - Bradycardia
  - Asterixis
  - Slurred speech
  - Ataxia
  - Hyperactive deep tendon reflexes
  - Nystagmus
  - Focal neurologic deficits such as hemiplegia (rare)
Clinical Manifestations

• Laboratory abnormalities
  – Elevated serum ammonia
  – Abnormal LFT
  – Electrolyte disturbance such as hypoNa
Clinical Manifestations

- **Ammonia**
  - Usually elevated in HE
  - Elevated in other than HE (alcohol, GI bleeding, valproic acid etc.)
  - Variable level according to sampling method
  - $>2 \times \text{UNL}$ of ammonia is associated with HE

Limited in sensitivity and specificity in diagnosing HE
Diagnosis

• A history and physical exam
• Exclusion of other causes of mental status changes
• Evaluation for predisposing factors of HE
Differential Diagnosis for HE

- Brain hemorrhage or infarction
- Meningitis or encephalitis
- Toxic encephalopathy
- Alcohol (acute intoxication, withdrawal syndrome, Wernicke encephalopathy)
- Drugs (Psychotropics, morphine, amphetamine)
- Metabolic (hypoxia, hypercapnia, hypoglycemia, ketoacidosis, etc)

Predisposing Factors for HE

- GI bleeding
- Infection (SBP, pneumonia, UTI, etc)
- Constipation
- Protein over intake
- Dehydration
- Renal insufficiency
- HypoNa, HypoK
- Benzodiazepine
- Acute hepatic insufficiency
Grading of Severity

• Important for decision making in management
• To triage the patients (general ward or ICU)
• For prediction of prognosis
• For monitoring of treatment response
## West Haven scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Consciousness</th>
<th>Intellect and Behavior</th>
<th>Neurologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal examination</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If impaired psychomotor testing, then MHE</td>
</tr>
<tr>
<td>1</td>
<td>Mild lack of awareness</td>
<td>Shortened attention span Impaired addition or subtraction</td>
<td>Mild asterixis or tremor</td>
</tr>
<tr>
<td>2</td>
<td>Lethargic</td>
<td>Disoriented</td>
<td>Obvious asterixis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inappropriate behavior</td>
<td>Slurred speech</td>
</tr>
<tr>
<td>3</td>
<td>Somnolent, but arousable</td>
<td>Gross disorientation Bizzare behavior</td>
<td>Muscular rigidity and clonus Hyperreflexia</td>
</tr>
<tr>
<td>4</td>
<td>Coma</td>
<td>Coma</td>
<td>Decerebrate posturing</td>
</tr>
</tbody>
</table>

Hepatic Encephalopathy Scoring Algorithm (HESA)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>○ No eyes opening ○ No verbal/voice response ○ No reaction to simple commendings</td>
</tr>
</tbody>
</table>

All applicable → Grade 4; otherwise continue examination

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>○ Somnolence ○ Confusion ○ Disoriented to place ○ Bizarre Behavior/Anger/Rage ○ Clonus/Rigidity/Nystagmus/Babinsky ○ Mental Control = 0</td>
</tr>
</tbody>
</table>

3 or more applicable → Grade 3; otherwise continue examination

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>○ Lethargy ○ Loss of time ○ Slurred speech ○ Hyperactive Reflexes ○ Inappropriate Behavior ○ Slow Responses ○ Amnesia of recent events ○ Anxiety ○ Impaired Simple Computations</td>
</tr>
</tbody>
</table>

2 or more ○ and 3 or more □ applicable → Grade 2; otherwise continue examination

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>○ Sleep Disorder/Impaired Sleep Pattern ○ Tremor ○ Impaired Complex computations ○ Shortened attention span ○ Impaired Construction ability ○ Euphoria or Depression</td>
</tr>
</tbody>
</table>

4 or more applicable → Grade 1; otherwise Grade 0

Indication of ICU care in HE

• The patients with HE Gr 3 or 4 should be transferred to ICU to protect airway

• The patients with HE Gr 2 (i.e. disorientation) should be admitted to the hospital to evaluate potentially serious precipitating factors
Algorithm for In-Patient HE Management

Patients with possible overt HE

Confirm that it is HE: Yes

Search for precipitating factor

Precipitating factors found

Precipitating factors Not found

Treatment for precipitating factors

Admit to ICU for Gr ≥3 HE Specific HE therapy with lactulose or rifaximin

No HE: other causes of altered mental status

Bajaj JS. Review article: the modern management of hepatic encephalopathy. Aliment Pharmacol Ther 2010;31:537-547
General Supportive Care in ICU

• Adequate nutrition
  + Correction of dehydration/electrolyte disturbance

• Securing the safety of the patient
Adequate Nutrition

- ESPEN Guidelines for liver cirrhosis (2009)
  - Start PN immediately in malnourished cirrhotic patients, who cannot be fed sufficiently either orally or enterally.
  - Give iv glucose (2-3 g/kg/day) when fasting > 12hrs
  - Give PN when the fasting > 72 hrs.
  - Consider PN in patients with unprotected airways and encephalopathy when cough and swallow reflexes are compromised.
Adequate Nutrition

- **ESPEN Guidelines for liver cirrhosis (2009)**
  - Energy:
    - Provide energy to cover $1.3 \times$ basal metabolic rate
    - Give glucose to cover 50-60% of non-protein energy requirements
  - Amino acids
    - Provide **AA at 1.2-1.5 g/kg/day** (cf. 0.8-1.2 g/kg/day in acute liver failure)
    - In HE Gr III or IV, consider the use of solution **rich in BCAA and low in AAA, methionine and tryptophan**
  - Micro-nutrition: vitamin (esp. B1 in alcoholics), minerals (Pi, K, Mg) replacement
  - Glucose monitoring
Safety of Patient

• Disorientation, agitation, irritability
  – High risk of fall down for the patient
  – Possible harm to care-giver

• Managements
  – Judicious restraints
  – Pharmacologic treatment (haloperidol is a safer option than benzodiazepine)
## Correction of Precipitating Causes in ICU

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relevant Tests/Exams</th>
<th>Treatment/Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variceal bleeding</td>
<td>Upper GI endoscopy, CBC, liver function tests</td>
<td>Blood transfusion, endoscopic therapy, terlipressin</td>
</tr>
<tr>
<td>Infection</td>
<td>CBC, chest X-ray, urinalysis, stool blood test, blood cultures</td>
<td>Broad-spectrum antibiotics, surgical debridement, Flumazenil injection</td>
</tr>
<tr>
<td>Constipation</td>
<td>History of constipation, abdominal X-ray, stool analysis</td>
<td>Gradual GI decompression, bowel resection, laxatives</td>
</tr>
<tr>
<td>Hyperproteinemia</td>
<td>BUN/Cr</td>
<td>Albumin supplementation, diuretics, gastrostomy for nutrition</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Serum sodium level, water restriction test</td>
<td>Oral hydration, diuretics, saline infusion, hemodialysis</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Serum potassium level, electrolyte repletion test</td>
<td>Oral potassium restriction, hemodialysis</td>
</tr>
<tr>
<td>Benzodiazepine overdose</td>
<td>History of use, serum benzodiazepine level</td>
<td>Discontinuation, Flumazenil injection</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>Liver function tests, prothrombin time test</td>
<td>Supportive care, liver transplantation, dialysis</td>
</tr>
</tbody>
</table>

Correction of Precipitating Causes in ICU

- **Acute GI bleeding**
  - Low threshold for intubation
  - Endoscopic hemostasis
  - Adequate transfusion (Target Hb level >7.0 d/L)
  - Prophylactic antibiotics

- **Sepsis**
  - Complete work-up for infection (diagnostic paracentesis, blood/urine culture, CXR)
  - Septic shock management if hypotension
  - Early empirical antibiotics

Bajaj JS. Review article: the modern management of hepatic encephalopathy. Aliment Pharmacol Ther 2010;31:537-547
Lowering Blood Ammonia

- **Lactulose**
  - Laxative effect
  - ↓ colonic pH & ↓ mucosal uptake of glutamine in the gut → ↓ synthesis and absorption of NH$_3$
  - Oral or rectal route
  - Overtreatment can induce dehydration, hypoNa, thus worsening HE

Lowering Blood Ammonia

- **Rifaximin**
  - A minimally absorbed oral antibiotics
  - Similar efficacy to lactulose
  - Few adverse effects
  - 550 mg bid or 400 mg tid
  - Alone or add-on lactulose

Lowering Blood Ammonia

• **Ornithine-aspartate**
  - NH$_3$ removal via urea cycle and glutamine synthesis
  - Effective in mild HE
  - No evidence of effectiveness in severe HE
  - No effect in acute liver failure

Bridging to Liver Transplantation

• High mortality in HE

Post TIPS HE
Gr 3 vs. Gr 0~2
OR =3.7

Hospitalized patients in cirrhosis with HE
Gr 2-3 vs. Gr 1
OR=3.9

Bridging to Liver Transplantation

• KONOS status

– Status 1: 18세 이상의 전격성 간부전증
만성 간질환 없이 간질환의 증상이 나타난 후 8 주 이내에 급성 전격성 간부전증이 발생하고 뚜렷한 간성혼수가 동반된 경우
Bridging to Liver Transplantation

• KONOS status

  - Status 2A: 만성 간부전증, CTP score ≥ 10이고, 다음 중 한 가지 이상에 해당
    • 치료에 반응하지 않는 활동성 정맥류 출혈
    • 간신증후군
    • 난치성 복수/간흉수증
    • 내과적 치료에 반응하지 않는 stage III나 IV인 뇌질환 (encephalopathy)
Acute liver failure

• Classification of HE
  – Type A: HE occurring in acute liver failure
  – Type B: HE occurring in porto-systemic bypass without intrinsic hepatocellular disease
  – Type C: HE occurring in cirrhosis with portal HTN or systemic shunting
Acute liver failure

• Definition
  ✓ Acute onset of liver damage in patients without underlying liver disease
  ✓ PT prolongation & acute onset of HE

• Pathogenesis of HE
  ✓ ↑NH$_3$ → ↑Glutamine in astrocyte
    → brain edema

Acute liver failure

- Causes of deaths in patients with acute liver failure

ICU care of Acute liver failure

- Cerebral edema
- Infection
- Coagulopathy
- Hemodynamics/Renal failure
- Metabolic concerns
ICU care of Acute liver failure

• Cerebral edema

Gr I/II HE
  Consider transfer to LT center
  Brain CT
  Antibiotics
  Lactulose, possibly helpful

Gr III/IV HE
  Intubation
  Elevate head of bed
  ICP monitoring
  Seizure control
  Mannitol
  Hypertonic saline (target Na 145-155 mmol/L)
  Hyperventilation

Lee WM et al. Hepatology 2011
ICU care of Acute liver failure

• Cerebral edema

Gr I/II HE
  Consider transfer to LT center
  Brain CT
  Antibiotics
  Lactulose, possibly helpful

Gr III/IV HE
  Intubation
  Elevate head of bed
  ICP monitoring
  Seizure control
  Mannitol
  Hypertonic saline (target Na 145-155 mmol/L)
  Hyperventilation

Lee WM et al. Hepatology 2011
Lactulose in Acute Liver Failure

- A multicenter retrospective cohort study in USA
  - 70 lactulose vs. 47 no lactulose in ALF
  - Final outcome was the same (LT 33% vs. 29%; death 25% vs. 24%; discharge from hospital 43% vs. 46%)
  - Median survival time 15 days vs. 7 days

- Concerns
  - Dehydration, electrolyte imbalance
  - Increasing ICP during enema

Survival of Acute liver failure: LT or non-LT

- 1 year survival of acute liver failure
Summary

• The patients of HE should be evaluated for other causes of altered mental status and precipitating factors.

• The patients with HE Gr III-IV should be considered for ICU care for airway protection.

• Most of patients with HE could be reversible via correction of precipitating factors and NH₃ lowering therapy.

• LT should be considered in case refractory to medical therapy.

• HE in acute liver failure should be considered for ICP control and emergency LT.
Thank you for your attention!