HEPATIC ENCEPHALOPATHY (HE) AND NUTRITIONAL SUPPORT

Jin-Woo Lee, MD, PhD.
Division of Hepatology
Inha University Hospital
Contents

1. Definition and causes of HE
2. Diagnosis and treatment of HE
3. Malnutrition in liver cirrhosis
4. Nutritional supports for HE
DEFINITION AND CAUSES
OF HEPATIC ENCEPHALOPATHY
What is hepatic encephalopathy?

- Potentially reversible neuropsychiatric abnormalities of acute and chronic liver disease
  - personality changes,
  - intellectual impairment,
  - depressed level of consciousness
- Main cause of hospital admission
## Classification of HE

<table>
<thead>
<tr>
<th>Type</th>
<th>Nomenclature</th>
<th>Subcategory</th>
<th>Subdivisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Encephalopathy associated with <em>Acute liver failure</em></td>
<td>Episodic HE</td>
<td>Precipitated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spontaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recurrent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment-dependent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Persistent HE</td>
<td>Persistent HE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment-dependent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimal HE</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Encephalopathy associated with <em>portal-systemic Bypass</em> and no intrinsic hepatocellular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Encephalopathy associated with <em>Cirrhosis</em> and portal hypertension/or systemic shunts</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overt</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HE**, hepatic encephalopathy
Type of hepatic encephalopathy

- **Episodic HE**
  - Clinical detection level
  - Day to month
  - HE grade (Westhaven criteria)

- **Persistent HE**
  - Clinical detection level
  - Day to month
  - HE grade (Westhaven criteria)

- **Minimal HE**
  - Clinical detection level
  - Day to month
  - HE grade (Westhaven criteria)
Minimal HE vs Overt HE

- **Minimal HE:**
  - Normal mental and neurological status
  - Abnormal specific psychometric test
  - Increased risk of progression to overt HE, poor QOL

- **Overt HE:**
  - Syndrome of neurological and neuropsychiatric abnormalities
  - Based on clinical diagnosis
Clinical problem

- No warning sign & require hospitalization
- Deficits in working memory, attention, and response inhibition
  - increase with the number and severity of episodes of OHE.
  - cause chronic neurologic injury, not readily reversible

1- and 3-year of survival rates of severe HE
  - less than 50% and less than 25% respectively

*J Hepatol 2010;52(Suppl 1):S66.*

*J Crit Care 2009;24:364–70.*
Significant burden of HE

- Burden on patients, their families, and health care resources

- Previous episode: ass. w/
  - 87.5% unemployment versus 19% ($P = .00001$)
  - lower financial status
  - higher caregiver burden

Pathogenesis Theories: Unknown?

- **Ammonia**: most widely spread & best supported
  - Increased Permeability of Blood-Brain Barrier
- False neurotransmitters and Changes in receptors
  - GABA
  - Altered BCAA/AAA ratio
  - Serotonin
- **Endogenous Neurotoxins**
  - Mercaptans, Phenols, Short-medium fatty acids
- **Other**
  - Zinc deficiency
  - Manganese deposits
Liver Cycle
Where? Periportal cells of liver—some kidney

Dietary Protein and Protein Breakdown

\[ \text{Glutamine}^{(NN)} \]

\[ \text{Glutamine Synthetase} \]

\[ \text{ADP} \]

\[ \text{ATP} \]

\[ \text{NH}_3 \]

\[ \text{Glutamate}^{(N)} \]

\[ \alpha\text{-ketoacids (i.e. oxaloacetate or pyruvate)} \]

\[ \text{A.A. Pool (i.e. aspartate or alanine)} \]

\[ \text{Transamination RXN} \]

\[ \text{Transaminase} \]

\[ \text{\alpha\text{-Ketoglutarate}} \]

Liver

\[ \text{Glutamate}^{(N)} \]

\[ \text{Glutamine}^{(NN)} \]

\[ \text{Ammonia Trap} \]

\[ \text{Glutamine Synthetase (Every Cell)} \]

\[ \text{NH}_3 \]

\[ \text{Glutamate}^{(N)} \]

\[ \text{Liver} \]

\[ \text{Glutamate Dehydrogenase (+) Leu} \]

\[ \text{CAP Synthase} \]

\[ \text{NAD}^+ \]

\[ \text{NADH} \]

\[ \text{\alpha\text{-Ketoglutarate} + NADH} \]

\[ \text{CAP} \]

\[ \text{Glutaminase} \]

\[ (+) \text{ NAG} \]

\[ \text{NH}_3 \]

\[ \text{HCO}_3^- \]

\[ \text{CO}_2 + \text{H}_2\text{O} \]

\[ \text{Ornithine} \]

\[ \text{Orotic Acid}^{(N)} \]

\[ \text{OAA} \]

\[ \text{Glu} \]

\[ \text{\alpha\text{-keto-Glu}} \]

\[ \text{Asp} \]

\[ \text{Citrulline}^{(N)} \]

\[ \text{Urea}^{(NN)} \]

\[ \text{Arginase} \]

\[ \text{Arginase (NN)} \]

\[ \text{Arginino succinate lyase} \]

\[ \text{Arginino succinate synthase} \]

\[ \text{Aspartate}^{(N)} \]

\[ \text{Citrulline}^{(N)} \]

\[ \text{Fumarate} \]

\[ \text{O.T.C (X-linked gene)} \]

\[ \text{Acetyl CoA} \]

\[ \text{Glutamate}^{(N)} \]

\[ \text{NAG Synthase (+) Arg} \]

\[ \text{(-) propionylCoA} \]

\[ \text{(low K}_m\text{)} \]

\[ \text{(High K}_m\text{)} \]

\[ \text{Camire, Sept. 2005} \]
Inter-organ trafficking of ammonia

Urea cycle in Liver

Gln pathway in Muscle

정상 간

대상성 간경변

Normal

Cirrhosis wellnourished
Gln pathway in Brain

비대상성 간경변

Cirrhosis malnourished

HE+++ → Brain

Urea → Liver

NH₃ → GUT

Muscle → Glutamine → Kidney

NH₃

NH₃

NH₃

SHUNTS

urea

colonic flora

DIET

gnase

GLU

GLU

GLN

urea
Direct Neurotoxic by Ammonia?

- Increased permeability: easily crosses BBB
- Increased NH$_3$ = increased glutamate
  - $\alpha$-ketoglutarate + NH$_3$ + NADH $\rightarrow$ glutamate + NAD
  - glutamate + NH$_3$ + ATP $\rightarrow$ glutamine + ADP + Pi
- Increased glutamine formation
  - As $\alpha$-ketoglutarate is depleted, TCA cycle activity halted.
  - Glutamate (need for neural tissue): ↓
  - Irreparable cell damage & neural cell death
Increased permeability of BBB

- Astrocyte volume: by intracellular glutamin.
  - Organic osmolyte

- Glutamine levels in the brain
  - volume of fluid within astrocytes (cerebral edema)

- Neurological impairment
  - N=Normal Astrocytes
  - A=Alzheimer type II astrocytes
  - Pale, enlarged nuclei
  - characteristic of HE

Alcohol Research and Health. 2003;27,3: 240-246.
Treatment of MHE w/ LOLA: Potential Novel Mechanism of Action

- Single arm study of a 4-week LOLA treatment in MHE
  - 21 patients with cirrhosis w/ MHE (as defined by PHES)
  - Psychometric improvement: correlated w/ visual cortex activation

- However, No loco-regional changes in brain
  - suggests that a mechanism other than reversible cerebral edema may explain...

  
  \[ \text{Excessive glutamine enters the astrocytic mitochondria:} \]
  \[ \text{glutaminase} \quad \text{glutamine} \rightarrow \text{glutamate} + \text{ammonia} \]

  - This triggers a mitochondrial damage and GABA synthesis.

  \[ \text{Gastroenterology & Hepatology. 2011;7,6, suppl. 9 EASL abstract} \]
Pathogenesis Theories: Changes In Neurotransmitters and Receptors

- Gamma-Aminobutyric Acid (GABA)
- BCAA-Ammonia Connection
  - NH$_3$ detoxification in muscle glutamine synthesis
Multifactorial pathogenesis

- **Exact cause**: unknown

- **Consensus**
  - *Elevated level of* ammonia: *Dominant role*
    - Astrocyte swelling and brain edema
    - Mitochondrial damage
DIAGNOSIS AND TREATMENT OF HEPATIC ENCEPHALOPATHY
Clinical Diagnostic Criteria & Grading

- HE grade more accurately
  - more timely in early stage & prevention
- Several systems, but... subjective & not reproducible
  - Categorically into different stages
  - inter-observer variability in diagnosing low grade HE

West-Haven classification

Hepatic Encephalopathy Scoring Algorithm (HESA)

Clinical Hepatic Encephalopathy Scoring System (CHESS)

## West-Haven Criteria (Conn score) of HE

<table>
<thead>
<tr>
<th>Grade</th>
<th>Consciousness</th>
<th>Intellect and Behavior</th>
<th>Neurologic Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal examination; 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; slurred speech</td>
</tr>
<tr>
<td>2</td>
<td>Lethargic</td>
<td>Disoriented; inappropriate behavior</td>
<td>Obvious asterixis; slurred speech</td>
</tr>
<tr>
<td>3</td>
<td>Somnolent but arousable</td>
<td>Gross disorientation; bizarre behavior</td>
<td>Muscular rigidity &amp; clonus; hyperreflexia</td>
</tr>
<tr>
<td>4</td>
<td>Coma</td>
<td>Coma</td>
<td>Decerebrate posturing</td>
</tr>
</tbody>
</table>

- Terms used for defining each grade
  - Imprecise
  - Dependent on clinician judgment
- Not sensitive for differentiating milder severities of HE

Spectrum of neurological impairment (SONIC): MHE leads to OHE

MHE: Alert mental state, but

Cognitive domain Impairment

abnormalities in attention, problem solving, executive functioning, psychomotor speed, visuo-spatial co-ordination

Simple clinical diagnosis

Worsening cognitive function
### Hepatic Encephalopathy Scoring Algorithm (HESA)

<table>
<thead>
<tr>
<th>HE Grade</th>
<th>Clinical Assessments</th>
<th>Neuropsychological Assessments</th>
<th>HE Grade Determination</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>No Eyes Open</td>
<td>Not Applicable</td>
<td>All 3 indicators present</td>
</tr>
<tr>
<td>III</td>
<td>Somnolence</td>
<td>Mental Control = 0(^1)(^4)</td>
<td>At least 3 indicators present, either clinical or neuropsychological</td>
</tr>
<tr>
<td>II</td>
<td>Lethargy</td>
<td>Slow Responses(^1)(^4)</td>
<td>At least 2 clinical and 3 neuropsychological indicators present</td>
</tr>
<tr>
<td>I</td>
<td>Sleep Disorder</td>
<td>Complex Computations(^1)(^9)</td>
<td>At least 4 indicators present, either clinical or neuropsychological</td>
</tr>
</tbody>
</table>

**Discrepant ratings:** 22 cases in 7 pts, more severe using HESA in 15 cases, more severe using WHC

**HESA**
- valuable to detect minimal HE
- Some grade 0 patients impaired on many grade 1 indicators even though not meet the full criteria
  - indicate minimal HE
  - need close monitoring & early intervention
- Further validation of the HESA

**Hassanein et al, Dig Dis Sci, 2008**
Proposed modification of West-Haven classification

- Proposed to combine *minimal HE* and *Stage I overt HE* (W-H) to be called "Covert HE"
- Prevent inter-observer variation
Diagnosis of MHE

PHES performance: influenced by age & education

- Expected results in cirrhotics need to be adjusted for these factors
- Consider bias due to learning effect

Stable cirrhotics: Grade 0 of West Haven criteria and MMSE score ≥ 24

Administer any of the following:
At least two of the following: NCT-A, NCT-B (or FCT-A), BD or DS; or PHES; or CFF; or ICT

Normal scores

Abnormal scores

Diagnosis of MHE established

Initiate therapy with lactulose

Rescreening every 6-12 months

Dhiman et al. J. Gastroenterol Hepatol 2010;25:1029-1041
Number connection test – A, B
Block design test
Digit symbol test
# Diagnostic methods for MHE

<table>
<thead>
<tr>
<th>Methods</th>
<th>Expense</th>
<th>Time</th>
<th>Validated</th>
<th>Predicting outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formal psychological assessment</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Neurophysiologic tests (EEG)</td>
<td>+++</td>
<td>++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Short Batteries (Block design tests, PHES)</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Computerized tests (ICT, CFF)</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
</tr>
</tbody>
</table>

Difficulty in HE Diagnosis

- No single standard test !!!
  - Measuring serum ammonia which always debated
  - Studies have shown that both venous and arterial ammonia correlate well with severity of HE
  - not routinely recommended for the diagnosis of HE, as a normal ammonia level in the setting of HE would not preclude treatment
Initial approach for overt HE

- Deterioration in mental status
  - Look for other causes of mental status changes
  - Identify & correct precipitating factors of HE

- Out-patient management after an episode
  - Prevention of recurrent episodes
  - Need effective, well-tolerated & safe long-term Tx
<table>
<thead>
<tr>
<th>Precipitating factor</th>
<th>Tests</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal bleeding</td>
<td>Endoscopy, complete blood count, digital rectal examination, stool blood test</td>
<td>Transfusion, bleeding treatment, vasoactive drugs</td>
</tr>
<tr>
<td>Infection</td>
<td>Complete blood count, chest X-ray, urine analysis, culture, diagnostic paracentesis</td>
<td>Broad-spectrum antibiotics</td>
</tr>
<tr>
<td>Constipation</td>
<td>History taking, abdomen X-ray</td>
<td>Enema or drug therapy</td>
</tr>
<tr>
<td>Protein intake</td>
<td>History taking</td>
<td>Limiting protein intake</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Skin elasticity, blood pressure, pulse rate, blood urea nitrogen, Creatinine</td>
<td>Stop diuretics or reduction, fluid therapy</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Blood urea nitrogen, Creatinine</td>
<td>Stop diuretics or reduction, albumin, fluid therapy</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Serum sodium concentration</td>
<td>Restriction water consumption, diuretics dose adjustment or stop</td>
</tr>
<tr>
<td>hypokalemia</td>
<td>Serum potassium concentration</td>
<td>Diuretics dose adjustment or stop</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>History taking</td>
<td>Stop drug, consideration flumazenil</td>
</tr>
<tr>
<td>Acute liver dysfunction</td>
<td>Liver function test</td>
<td>Conservation treatment</td>
</tr>
</tbody>
</table>
Treatment of HE

- Firstly, non-absorbable disaccharides:
  - lactulose, lactitiol
  - 15~45 mL, orally 2~4 times/day
  - for loose stool defecation, 2~3 times a day

- Rifaximin
  - Limited absorption by the intestine
  - Broad spectrum antibiotics affect urea-producing bacteria
  - Dosage: maximum dose of 550 mg BID/day
US treatment option for HE

Lactulose (FDA approved 1976)
Neomycin (FDA approved 1970)
Metronidazole and Vancomycin (not approved)

Rifaximin (FDA approved 2010):

\textit{For reduction in risk of overt HE}

- Neomycin & Metronidazole: \textit{currently not recommended}

A/E: intestinal malabsorption, nephrotoxicity, and ototoxicity
A/E: neurotoxicity of metronidazole
## Rifaximin vs Placebo studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All rifaximin-treated patients (n=392)</th>
<th>Randomized controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rifaximin (n=140)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo (n=159)</td>
</tr>
<tr>
<td>Mean age</td>
<td>57 years</td>
<td>56 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>57 years</td>
</tr>
<tr>
<td>Gender</td>
<td>59% male</td>
<td>54% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td>67% male</td>
</tr>
<tr>
<td>Race</td>
<td>90% white</td>
<td>84% white</td>
</tr>
<tr>
<td></td>
<td></td>
<td>87% white</td>
</tr>
<tr>
<td>Geographic distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>84%</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>16%</td>
<td>28%</td>
</tr>
<tr>
<td>Russia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26%</td>
</tr>
<tr>
<td>Mean duration of remission prior to study entry</td>
<td>96 days</td>
<td>69 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>73 days</td>
</tr>
<tr>
<td>Number of HE episodes in past 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>71%</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td>29%</td>
<td>31%</td>
</tr>
<tr>
<td>&gt;2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>Conn score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>64%</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>33%</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Mean MELD score</td>
<td>12.8 points</td>
<td>13.1 points</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.7 points</td>
</tr>
<tr>
<td>Lactulose use</td>
<td>89%</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>91%</td>
</tr>
</tbody>
</table>

*Bass NM et al. NEJM 2010;362, Gastroenterology & Hepatology. 2011;7,6, suppl. 9 EASL abstract*
Rifaximin Reduced the relapse episode of HE compared to Placebo

- 58% reduction in the risk of HE breakthrough event compared to placebo
- Significant reduction in rates of hospitalization due to any cause
- Lower adverse event rate

Mean duration of drug exposure among rifaximin-treated patients was 476 days

Bass NM et al. NEJM 2010;362, Gastroenterology & Hepatology. 2011;7,6, suppl. 9 EASL abstract
Indication of Rifaximin in HE

- Meta-analysis comparing rifaximin vs non-absorbable disaccharides showed no significant difference.  
  
  *Eur J Gastroenterol Hepatol* 2008; **20**: 1064-1070.

- Recent meta-analysis: 12 RCT
  - rifaximin vs conventional oral agents
  - comparable in regard to clinical efficacy for HE
  - fewer side effects

- Rifaximin should be considered as
  - Second-line in the treatment of HE patients who fail disaccharide therapy
  - First-line in those intolerant of disaccharides.

Treatment of HE: L-ornithine-L-aspartate (LOLA)

- metabolize ammonia to urea and glutamine
  - By stimulating hepatic urea cycle activity
  - By promoting glutamine synthesis

- Intravenous form: more effective than oral form
  - iv route avoids the transamination in the intestinal mucosa

- Maximal recommended infusion dose: 5 g/h
Treatment of HE: other medications

- Branched-Chain Amino Acids (BCAA)
- Zinc
- Levodopa & Bromocriptine
- Sodium benzoate
  - non-urea cycle pathway
  - ammonia removal
- Flumazenil
- Probiotics
MALNUTRITION IN LIVER CIRRHOSIS
Malnutrition in ESLD

- Early and typical aspect of cirrhosis
  - poor prognosis and complications

- Severity and disease etiology (higher in alcoholics)
  - Mortality doubled in cirrhotic patients with malnutrition (35% vs 16%)
  - Complications more frequent than in well-nourished (44% vs 24%)
  - Usually more of a clinical problem than HE itself
## Metabolic alteration in ESLD

<table>
<thead>
<tr>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased catabolism</td>
<td>Decreased hepatic &amp; skeletal muscle glycogen synthesis</td>
<td>Increased lipolysis</td>
</tr>
<tr>
<td>Increased utilization of BCAAs</td>
<td>Increased gluconeogenesis</td>
<td>Enhanced turnover &amp; oxidation of fatty acids</td>
</tr>
<tr>
<td>Decreased Ureagenesis</td>
<td>Glucose intolerance &amp; insulin resistance</td>
<td>Increased Ketogenesis</td>
</tr>
</tbody>
</table>
Factors Contributing to Malnutrition in Cirrhosis

1. Diminished nutrient intake
2. Hypermetabolic state
3. Inadequate synthesis or absorption of nutrients
1. Causes of diminished intake

- Loss of appetite
- Alcohol-induced anorexia
- Impaired gastric accommodation
- Impaired expansion capacity of the stomach due to ascites
2. Hypermetabolic state

- Liver damage
- Proinflammatory cytokine
- Energy expenditure, protein catabolism
3. inadequate synthesis or absorption of nutrients

- Inadequate synthesis of various protein
- Diminished storage capacity of cirrhotic liver
- Impaired absorption of nutrients due to portal hypertension
Nutritional assessment in ESLD

- Anthropometric parameters
  - not affected by the presence of ascites or peripheral edema
    1. Mid-arm circumference (MAC)
    2. Mid-arm muscle circumference (MAMC)
    3. Triceps skin fold thickness (TST)
      - below the 5th percentile in 18–74 years or the 10th percentile in over 74 years
    4. Hand-grip examination by dynamometer
    5. BMI + mid-arm muscle circumference (MAMC)

- BMI cutoff value depending on ascites
  - Reliable, but not standardized indicator of malnutrition

<table>
<thead>
<tr>
<th>Malnutrition</th>
<th>No ascites</th>
<th>Mild ascites</th>
<th>Tense ascites</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>&lt;22</td>
<td>&lt;23</td>
<td>&lt;25</td>
</tr>
</tbody>
</table>

NUTRITIONAL SUPPORTS FOR HEPATIC ENCEPHALOPATHY
Altered Nutritional status potentially affects brain function in cirrhosis

- Hyperammonemia
- Zinc deficiency
- Decreased levels of selenium
- Increased blood manganese level
- L-Carnitine deficiency
- Vitamin B1 deficiency
Nutritional recommendations for the management of HE in cirrhosis

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>35–40 kcal/kg/day</td>
</tr>
<tr>
<td>Protein</td>
<td>1.2–1.5 g/kg of body weight/day*</td>
</tr>
<tr>
<td>BCAA</td>
<td>In severely protein-intolerant patients</td>
</tr>
<tr>
<td>Antioxidant and vitamins</td>
<td>Multivitamin supplements</td>
</tr>
<tr>
<td>Probiotics, prebiotics</td>
<td>Increasing use for ammonia-lowering and anti-inflammatory actions</td>
</tr>
</tbody>
</table>

*In severely protein intolerant patients, protein may be reduced for short periods of time, particularly in grade III-IV hepatic encephalopathy.

Historical treatment theories: Protein restriction

- Studies in early 1950’s showed cirrhotic pts given “nitrogenous substances” developed hepatic “precoma”
- Led to introduction of protein restriction
  - Began with 20-40g protein/day
  - Upper limit of 0.8-1.0 g/kg
  - Was thought sufficient to achieve positive nitrogen balance
- Lack of valid evidence
  - Efficacy of restriction never proven within controlled trial
Dispelling the Myth

- Objective: To test safety of normal-protein diets
- Randomized, controlled trial in 20 cirrhotic patients with HE
  - 10 patients subjected to protein restriction, followed by progressive increments
    - No protein first 3 days, increasing q3days until 1.2g/kg daily for last 2 days
  - 10 patients followed normal protein diet (1.2g/kg)
  - Both groups received equal calories

- Results
  - On days 2 and 14:
    - Similar protein synthesis among both groups
    - Protein breakdown higher in low-protein group

- Conclusion
  - No significant differences in course of HE
  - Greater protein breakdown in protein-restricted subjects

Cordoba et al. J Hepatol 2004; 41: 38-43
Low protein diet to be avoided

- Severe HE (grades III or IV)
  - Transient protein restriction (0.5~1.2g/kg/day)
- Chronic protein restriction must be avoided
- High protein diets: generally well tolerated
- Adequate protein diet in malnutrition:
  - between 1.2 - 1.5g/kg/day
  - Sustained improvement in mental status
- Preserve lean body mass (skeletal muscle) for NH₃ removal
Vegetable proteins

- Potentially better tolerated than animal proteins in ESLD
  - higher content of BCAAs
  - rapid intestinal transit due to high dietary fiber
  - Low allergic reaction

- Daily intake of 30–40 g vegetable protein is effective
Branched Chain Amino Acids (BCAA)

**Valine**
- consumed by skeletal muscles for ammonia metabolism and energy generation

**Leucine**
- Metabolized in muscle & brain, not in liver
  - promote protein synthesis
  - suppress protein catabolism
  - substrates for gluconeogenesis

**Isoleucine**
- regulate protein synthesis & keep the skeletal muscles
Branched-chain amino acids (BCAAs)

- Use of BCAAs: established almost 25 years ago in cirrhosis
- Recent Cochrane review in 2012
  - oral BCAAs have been helpful in the resolution of HE
  - However, survival was not affected by BCAAs
- Late evening snack of BCAAs: substrates for protein synthesis
  - Daytime BCAAs: used primarily as calories
  - Nocturnal BCAAs maybe preferentially used for proteinsynthesis
- Noncompliance due to unpalatability & expensive costs

Liver cirrhosis

Insulin resistance

Hyperinsulinemia

Resistant hyperglycemia

Hypoglycemia

40~50% of all patients suffer from insulin-resistant DM

Diminished glycogen storage capacity

Impaired glucose uptake from the skeletal muscles

Recommendation:
Multiple meals (4~6 meals) containing food rich in carbohydrates
Nutrition : Fat

- high-fat diet + impaired hepatic VLDL release
  - increased hepatic fat storage
  - suffering liver cannot tolerate an excess fat inflow
Conclusions

- Our understanding of pathogenesis is improving, but much work remains.
- Link between liver and brain still only partially understood.
- Risk factors for HE, esp. in HCC:
  - Opioid pain control, malnutrition, GI bleeding
Thank You for your attention!

Comments ?
Questions ?