Hepatic Encephalopathy, Hepatic Myelopathy, and Acquired Hepato-Cerebral Degeneration

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2012
Hepatic Encephalopathy
Definition & Pathogenesis

• Reversible neuro-psychiatric manifestation of severe liver dysfunction.
  – One-year survival 40%.

• Decreased hepatic clearance of ammonia derived from:
  – 1) kidney,
  – 2) urease activity of gastro-intestinal bacteria, and
  – 3) deamination of glutamine in small bowel.

• Increased Gut-derived neuro-mediators:
  – 1) benzodiazepine-like substances,
  – 2) neurotoxic short- and medium-chain fatty acids,
  – 3) phenols and,
  – 4) mercaptans.
Types (by Cause)

• **Type A:** Acute Liver Failure

• **Type B:** Large Spontaneous or Post-traumatic Portal-Systemic By-pass (normal liver)
  – Uretero-Sigmoid anastomosis.

• **Type C:** Cirrhosis; Portal HTN or Shunt

• Hepatic Myelopathy: Symmetrical demyelination of lateral corticospinal tracts
Sub-Categories of Cirrhotic Hepatic Encephalopathy

• **Minimal or Covert:**
  – Detected only by psycho-metric testing.
  – Impairs concentration and ability to drive.

• **Overt Episodic:**
  – Clinically apparent (stages 1 to 4)
  – Usually precipitated after a triggering event.
  – May be spontaneous and recurrent

• **Chronic Persistent:**
  – H.E. fluctuating from “mild” to “severe”
  – Usually without apparent trigger;
  – May be treatment dependent.
  – Very rare.
## Current Terminology for the Classification of HE

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Subcategory</th>
<th>Subdivision</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Encephalopathy associated with acute liver failure</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>B</td>
<td>Encephalopathy with portosystemic bypass and no intrinsic hepatocellular disease</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
| C    | Encephalopathy associated with cirrhosis or portal hypertension/portosystemic shunts | • Episodic HE  
• Persistent HE  
• Minimal | • Precipitated  
• Spontaneous  
• Recurrent  
• Mild  
• Severe  
• Treatment dependent |

Neurologic Manifestations of OHE

Common
- Confusion or coma
- Asterixis
- Loss of fine motor skills
- Hyper-reflexia
- Cognitive deficits detected by special testing
- Slow speech

Less Common
- Babinski sign
- Slow, monotonous speech
- Extrapyramidal-type movement disorders
- Clonus
- Decerebrate posturing
- Decorticate posturing
- Hyperventilation
- Seizures

*Seizures seen primarily in type A HE.
## West Haven Criteria

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (minimal)</td>
<td>• No detectable changes in behavior or personality¹</td>
</tr>
<tr>
<td>1</td>
<td>• Euphoria or anxiety²</td>
</tr>
<tr>
<td></td>
<td>• Impaired performance of addition²</td>
</tr>
<tr>
<td></td>
<td>• Shortened attention span²</td>
</tr>
<tr>
<td></td>
<td>• Trivial lack of awareness²</td>
</tr>
<tr>
<td>2</td>
<td>• Minimal disorientation to time or place²</td>
</tr>
<tr>
<td></td>
<td>• Inappropriate behavior²</td>
</tr>
<tr>
<td></td>
<td>• Impaired performance of subtraction²</td>
</tr>
<tr>
<td></td>
<td>• Lethargy or apathy²</td>
</tr>
<tr>
<td></td>
<td>• Subtle personality change²</td>
</tr>
<tr>
<td>3</td>
<td>• Confusion²</td>
</tr>
<tr>
<td></td>
<td>• Gross disorientation²</td>
</tr>
<tr>
<td></td>
<td>• Somnolence to semistupor (may respond to verbal stimuli)²</td>
</tr>
<tr>
<td>4</td>
<td>• Coma (no response to verbal or noxious stimuli)²</td>
</tr>
</tbody>
</table>

HE = hepatic encephalopathy.

Precipitating Factors

- Constipation
- Gastrointestinal bleed
- Infection
- Overdiuresis
- Azotemia & dehydration
- Hypokalemia
- Hypo- or hypernatremia

- Sedative or opiate
- Hepatic injury (toxic, viral, HCC)
- Portal vein thrombosis
- Excessive protein intake.
- TIPSS
- Non-compliance with H.E. therapy
Multiple Factors Can Lead to HE Breakthrough

- GI hemorrhage
- Hypokalemia
- Azotemia
- Constipation
- Excess dietary protein
- Infection

\[ \uparrow \text{Diffusion of ammonia across BBB} \]

- Systemic alkalosis

- Progressive parenchymal damage
  - Dehydration
  - Anemia
  - Arterial hypotension
  - Arterial hypoxemia
  - Hepatoma
  - Shunts

\[ \downarrow \text{Toxin metabolism} \]

- Psychoactive drugs

\[ \downarrow \text{CNS depression} \]

- Benzodiazepines

\[ \uparrow \text{Ammonia production} \]

- Activation of central GABA-benzodiazepine receptors

Benzodiazepines

- BBB = blood brain barrier
- CNS = central nervous system; GABA = \( \gamma \)-aminobutyric acid
- GI = gastrointestinal
- HE = hepatic encephalopathy
Differential Diagnosis

- Intracranial lesion
  - bleed,
  - tumor,
  - infarct,
  - abscess

- CNS infection

- Metabolic
  - Hyper- or hypo-glycemia,
  - uremia,
  - acidosis,
  - electrolyte disorder

- Neuro-psych disorder

- Alcohol-related
  - Intoxication,
  - withdrawal,
  - Wernicke, Korsakoff

- Drug
  - sedative,
  - psychoactive,
  - heavy metal

- Post-ictal
Hospital Discharges Associated with HE
Increased by 21% in 2010

HE = hepatic encephalopathy; ICD = International Classification of Diseases.

*Data calculated using ICD-9-CM codes 291.2 (alcoholic dementia, not elsewhere classified), 348.30 (encephalopathy, not otherwise specified), and 572.2 (hepatic coma). †Includes all listed discharge diagnoses.

Greater Than 50% Increase in Cost
HE Discharge Since 2004

Cost per HE patient discharge*†

<table>
<thead>
<tr>
<th>Year</th>
<th>Cost per HE patient discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>$22,511</td>
</tr>
<tr>
<td>2005</td>
<td>$25,415</td>
</tr>
<tr>
<td>2006</td>
<td>$26,541</td>
</tr>
<tr>
<td>2007</td>
<td>$29,065</td>
</tr>
<tr>
<td>2008</td>
<td>$32,764</td>
</tr>
<tr>
<td>2009</td>
<td>$35,242</td>
</tr>
<tr>
<td>2010</td>
<td>$37,598</td>
</tr>
</tbody>
</table>

HE = hepatic encephalopathy; ICD = International Classification of Diseases.
*Data calculated using ICD-9-CM codes 291.2 (alcoholic dementia, not elsewhere classified), 348.30 (encephalopathy, not otherwise specified), and 572.2 (hepatic coma). †Includes all listed discharge diagnoses.

Poor QoL and Prognosis in Patients With HE

- HE significantly diminishes physical and mental QoL\(^1\)
  - Patient may be disabled from driving, employment, and independent care\(^2\)
- <50% survival at 1 year after diagnosis of HE and <25% survival at 3 years\(^3\)
  - For patients with severe HE who are hospitalized in intensive care, 1-year survival rate is <50%\(^4\)

HE = hepatic encephalopathy; QoL = quality of life.

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HE = hepatic encephalopathy; QoL = quality of life.

Cognitive Deficits in Patients With a History of Overt HE

• 226 patients with cirrhosis and a history of overt HE, MHE,* or no HE underwent psychometric evaluation
  – 54 had prior overt HE†
  – 120 had MHE
  – 52 had normal psychometric test results

• Patients with a history of overt HE performed significantly worse than normal patients with cirrhosis ($P \leq 0.001$) and had impaired learning on the ICT

ICT = inhibitory control test; HE = hepatic encephalopathy; MHE = minimal HE.
*Patients had an impairment of 2 standard deviations from normal on 2 of the 4 following: number connection tests A or B, block design test, or digit symbol test. †Patients adherent on lactulose therapy.
History of Overt HE May Cause Learning Deficit

Inappropriate responses (i.e., ICT lures), n

<table>
<thead>
<tr>
<th></th>
<th>First set of tests</th>
<th>Second set of tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n=52)*</td>
<td>3.4</td>
<td>2.1</td>
</tr>
<tr>
<td>MHE (n=120)</td>
<td>7.2 (P=0.0001)</td>
<td>5.7</td>
</tr>
<tr>
<td>History of OHE (n=54)</td>
<td>6.8 (P=0.24)</td>
<td>6.3</td>
</tr>
</tbody>
</table>

HE = hepatic encephalopathy; ICT = inhibitory control test; MHE = minimal HE; OHE = overt HE.

*Patients with cirrhosis with normal cognitive function.

Treatment Goals for Patients with HE

• Investigate precipitating factors that may have led to an HE event
  – Precipitating factors may include GI bleed, sepsis, and dehydration
  – In a large clinical trial, 80% of HE events at baseline were considered spontaneous

• After ruling out precipitating factors, chronic management of HE should be initiated
  – The prevention of further episodes of HE is an important goal in the treatment of patients with liver disease
  – After an episode of OHE, prophylactic therapy with lactulose or rifaximin is recommended for an indefinite period of time or until liver transplantation

Mechanism of Action of Therapies for HE

- **Lactulose:** (also sorbitol, fiber, and acarbose) inhibit intestinal ammonia production by a number of mechanisms:
  - Conversion of unabsorbed sugar to lactic acid results in acidification of the gut lumen. This favors conversion of $\text{NH}_4^+$ to $\text{NH}_3$ and the passage of $\text{NH}_3$ from tissues into the lumen.
  - Gut acidification inhibits ammoniagenic coliform bacteria, leading to increased levels of nonammoniagenic lactobacilli.
  - Unabsorbed works as a cathartic, reducing colonic bacterial load.
- **Antibiotics:** such as rifaximin, neomycin, metronidazole, oral vancomycin, paromomycin, and oral quinolones, decrease the colonic concentration of ammoniagenic bacteria.
- **Zn:** improves hyperammonemia by increasing the activity of ornithine transcarbamylase, an enzyme in the urea cycle.
Mechanism of Action of Therapies for HE

- **Sodium benzoate**: interacts with glycine to form hippurate. The renal excretion of hippurate results in the loss of ammonia ions.
- **Sodium phenylbutyrate** is converted to phenylacetate. Phenylacetate, reacts with glutamine to form phenylacetylglutamine, which is subsequently excreted in the urine, with loss of ammonia ions.
- **L carnitine**: is unclear if improves blood ammonia levels or if works centrally by decreasing brain ammonia uptake.
- **LOLA** is a stable salt of l-ornithine and l-aspartate:
  - L-ornithine stimulates the urea cycle, with resulting loss of ammonia.
  - Both l-ornithine and l-aspartate are substrates for glutamate transaminase. Their administration increases glutamate levels. Ammonia is subsequently used in the conversion of glutamate to glutamine by glutamine synthetase.
Treatment of Hepatic Encephalopathy

- **Reduction of Ammonia load:**
  - Lactulose p.o. to give 3-4 BM/day or retention enema (300 ml + 700 ml water) TID
  - Rifaximin 550 mg BID, p.o.
  - Neomycin 4-6 grams/day p.o.
  - Metronidazole 250 mg TID, p.o.
  - Others: arginine benzoate, sodium benzoate (Ammonul), L-carnitine 990 mg TID, sodium phenylbutyrate (Buphenyl), Acarbose, fiber, sorbitol, LOLA (L-ornithine and L-aspartate)
Treatment of Hepatic Encephalopathy

• **Nutritional Management:**
  - Early nutrition to cover calorie needs and 1-1.5 g protein/kg/day.
  - In Chronic Persistent PSE: branched-chain aminoacids enriched formula (Nutra-Hep)
  - Zn 50 mg QD or BID.

• **Manipulation of Splanchnic Circulation:**
  - Radiology-guided occlusion of shunts.
  - Reduction of TIPS with hourglass-shaped expanded polytetrafluoroethylene (ePTFE) stent-graft.
Treatment of Hepatic Encephalopathy

- **Drugs affecting Neurotransmission:**
  - Flumazenil: used more often in Acute Liver Failure in person without chronic benzodiazepine use.
  - Bromocryptine: may improve extra-pyramidal signs.
64% of Patients Did Not Receive Treatment for their HE Outside the Hospital in 2011

Percent of Patients with HE Untreated & Treated as OP

- Untreated: 36%
- Treated: 64%

Walters Kluwer 2012
ICD-9 Code: 572.2 Hepatic Encephalopathy
Xifaxan 550 Reduced the Risk of Breakthrough HE Episode* by 58% vs Placebo

Patients without HE breakthrough, %

Days post-randomization

HR = 0.42 (95% CI, 0.28-0.64) (58% Risk Reduction)

P<0.001

Xifaxan 550 mg b.i.d.
(n=140)

Placebo
(n=159)

b.i.d. = twice daily; CI = confidence interval; HE = hepatic encephalopathy; HR = hazard ratio.

*HE breakthrough defined as increase in Conn score to ≥2 or, if baseline Conn = 0, an increase of 1 each in Conn score and asterix grade.

Xifaxan 550 Reduced the Risk of HE-Related Hospitalization by 50% vs Placebo

Patients with no HE-related hospitalization, %

Days post-randomization

HR = 0.50 (95% CI, 0.29-0.87) (50% Risk Reduction)  
\( P=0.01 \)

Xifaxan 550 mg b.i.d. (n=140)  
86 (14% Hosp)

Placebo (n=159)  
77 (23% Hosp)

b.i.d. = twice daily; CI = confidence interval; HE = hepatic encephalopathy; HR = hazard ratio.
Minimal or Covert Hepatic Encephalopathy
Minimal Hepatic Encephalopathy

- Cirrhotic patients
  - Without clinical signs of encephalopathy
  - Perform worse in psychometric tests when compared with healthy controls
- Affects an estimated 60% (50% to 80%)* of patients with cirrhosis
- Cerebral dysfunction has a major impact on patients’ daily living
- No consensus on diagnostic criteria or diagnostic tests has been established

*depends on mode of diagnosis

Mullen KD. *Aliment Pharmacol Ther.* 2006;25(suppl 1):11-16.
# Diagnostic Methods for Detecting Minimal HE

<table>
<thead>
<tr>
<th>Methods</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formal neuropsychologic assessment</td>
<td>Established and well-recognized clinical significance</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time consuming</td>
</tr>
</tbody>
</table>
| Short neuropsychologic batteries | • Easy to administer in office setting  
• Inexpensive  
• Rapid results  
• High sensitivity for discerning minimal HE from other encephalopathies | Test often copyrighted  
• Limited access                                      |
| Computerized tests (CFF, ICT, reaction times, etc.) | • Easy to apply                                                                                           | Limited data on diagnostic significance  
• Require standardization                                     |
| Neurophysiologic tests (EEG, spectral EEG, P300) | • Allows for objective repeat testing                                                                       | Equipment  
• Limited data on diagnostic significance |

CFF, critical flicker frequency; ICT, inhibitory control test; EEG, electroencephalography; P300, auditory event-related evoked potential.


- Number connection test A (NCT-A)
- Number connection test B (NCT-B)
- Digit symbol test (DST)
- Serial-dotting test (SDOT)
- Line-tracing test (LTT)
- Figure connection test
- Block design test

The Porto-systemic Encephalopathy (PSE) Syndrome Test

*PSE psychometric test is not currently available in the United States.

Recommendations for MHE Testing

- Alternatives to psychometric hepatic encephalopathy score (PHES) in the United States
  - Impairment in 2 of 4 tests below
    - Number connection test-A
    - Number connection test-B
    - Digit Symbol
    - Block Design tests of the Wechsler’s Adult Intelligence Scale-III (Psychological Corp, San Antonio, TX)
  - Above tests need psychological expertise to order, administer, and interpret

Bajaj JS et al Gastroenterol 2008 135(5):1591-1600
Test Studied in the U.S. for MHE

Inhibitory Control Test

- A computerized test of attention and response inhibition which consists of lures and targets.
- Does not need a psychologist for administering or interpretation.
- Can be administered by a medical assistant within 15 minutes.
- ICT has a high sensitivity and specificity for MHE diagnosis and predicting overt HE.

Bajaj JS et al Gastroenterol 2008;135(5):1591-1600
Inhibitory Control Test

- ICT has good reliability between 2 administrations
- ICT also has external validity, i.e. gets worse after TIPS and gets better after therapy
- ICT performance has been correlated with driving simulator performance.
- Available on the Chronic Liver Disease Foundation website (www.hecme.tv) for download with detailed instructions.

Bajaj JS et al Gastroenterol 2008;135(5):1591-1600
Probiotic Yogurt in the treatment of MHE
Bajaj JS et al. Am J Gastroenterol 2008;103:1707-1715

• Subjects: 25 nonalcoholic MHE cirrhotics (defined by a standard psychometric battery); 84% were Child A

• Groups: randomized with unblinded allocation to receive for 60 days in 2:1 ratio
  – A: probiotic yogurt (N: 18) (CC’s Jersey Crème Yogurt 6 oz BID; with proven culture stability)
  – B: no treatment (no Rx) (N: 7).

• Measurements: Quality of life (short form [SF]-36), adherence, venous ammonia, model of end-stage liver disease (MELD) scores, and inflammatory markers (tumor necrosis factor [TNF]-α, interleukin [IL]-6).

• Outcomes:
  – MHE reversal using blinded scoring,
  – OHE development, and
  – Adherence.
Probiotic Yogurt in the treatment of MHE
Bajaj JS et al. Am J Gastroenterol 2008;103:1707-1715

• RESULTS:
  – A significantly higher percentage of yogurt patients reversed MHE compared to no Rx patients (71% vs 0%, $P = 0.003$, intention-to-treat).
  – Yogurt patients demonstrated a significant improvement in number connection test-A (NCT-A), block design test (BDT), and digit symbol test (DST) compared to baseline/no Rx group.
  – Overt HE: developed in 25% of no Rx versus 0% of yogurt patients.
  – Adherence: Eighty-eight percent of yogurt patients.
  – No adverse effects or change in covariates were observed.
  – All patients who completed the yogurt arm were agreeable to continue yogurt for 6 months if needed.
CC’s Jersey Crème Yogurt
6 oz BID
Treatment of MHE

• 160 cirrhotics with MHE were randomized in 4 groups of 40 patients to receive for 3 months:
  – Group A: no therapy,
  – Group B: lactulose 30–60 ml b.i.d.,
  – Group C: probiotics of 110 billion colony-forming units b.i.d. or
  – Group D: L-ornithine-L-aspartate 6 g t.i.d. (LOLA).

• Parameters:
  – health-related quality of life (HRQoL) improvement, and
  – progression to overt hepatic encephalopathy.

• RESULTS:
  – A) Using neuropsychological assessment, recovery of MHE was seen in groups: A = 10%, B = 48%, C = 35% and D = 35% (P = 0.006).
  – There was no significant difference in recovery from MHE or changes in ammonia levels when comparing lactulose to either probiotics or LOLA.
  – B) Nine (6%) developed overt PSE.
Treatment of MHE
(Bajaj JS et al. Gastroenterology 2011; 140:478–487; e1).

• 42 cirrhotics with MHE at baseline were randomized to 8 weeks of rifaximin \((n = 21)\) or placebo \((n = 21)\) and tested in a driving simulator.

• RESULTS:
  – A) Rifaximin group showed improvement in avoiding total driving errors \((76 \text{ vs. } 31\%; P = 0.013)\), speeding \((81 \text{ vs. } 33\%; P = 0.005)\), and illegal turns \((62 \text{ vs. } 19\%; P = 0.01)\) compared to those given placebo; however,
  – B) The number of collisions were not significantly different between groups.
  – C) In rifaximin group, the cognitive performance improved \((91 \text{ vs. } 61\%; P = 0.01)\) compared to placebo group.
Hepatic Myelopathy

• **Symptoms:**
  – Subacute bilateral lower extremity weakness,
  – Puppet-like walk or inability to walk in setting of cirrhosis or porto-caval shunt.
  – Upper extremity involvement is very rare.
  – Disorder is progressive and irreversible.

• **Signs:** Spastic paraparesis, hyperreflexia, extensor plantar response, and no sensory level (Zieve 1960).

• **Pathogenesis:** Symmetrical demyelination of lateral corticospinal tracts, occasionally with axonal loss.
Hepatic Myelopathy

• Imagen:
  – a) Brain MRI: may show FLAIR in subcortical white matter,
  – b) MRI of spine with contrast, or CT myelogram: No evidence of compression. MRI may show FLAIR in subcortical spinal tracts.

• Central motor conduction time (CMCT): abnormal in lower lumbar spine, and normal in upper cervical spine.

• Treatment: Closure of shunt or liver transplantation.
Acquired (non-Wilsonian) hepatocerebral degeneration (AHCD)

- Clinico-pathological syndrome of brain dysfunction associated with a variety of liver diseases. (Victor et al. in 1965).
- **Clinical features:** dementia, dysarthria, ataxia of gait, intention tremor and choreoathetosis.
- **Evolution:** chronic and largely irreversible syndrome.
- **Pathogenesis:** poorly understood; may be damage accumulated from multiple episodes of hepatic encephalopathy
- **Neuropathological findings:** diffuse but patchy cortical necrosis, diffuse proliferation of Alzheimer type II glial cells and uneven neuronal loss in the cerebral cortex, basal ganglia and cerebellum.
- **MRI:** T1-weighted images hyperintensities in the globus pallidus, and 75% have extrapallidal involvement.