Hepatic Encephalopathy

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Hepatic encephalopathy reflects a spectrum of neuro-psychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known brain disease

Ferencz et al Working Group on Hepatic Encephalopathy Hepatology 2002
Pathogenic Mechanisms in HE

- Glutamate & NH$_3$
- Glutamine
- Astrocyte Swelling
- Proinflammatory Cytokines
- Nitric Oxide & Oxidative Stress
- Increased brain water, deterioration in neuropsychological function & hepatic encephalopathy


Microbiome in cirrhosis is different from controls

Adapted from Bajaj JS et al AJP 2012, Chen et al Hepatol 2011
Microbiome in cirrhosis is different from controls

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th></th>
<th>Cirrhosis</th>
<th></th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SE</td>
<td></td>
<td>Mean</td>
<td>SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erysipelotrichaceae</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
<td>2.02</td>
<td>0.70</td>
<td></td>
<td>0.0009</td>
</tr>
<tr>
<td>Clostridium Incertae sedis XIV</td>
<td>7.35</td>
<td>1.59</td>
<td></td>
<td>1.08</td>
<td>0.18</td>
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<td>0.0009</td>
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<tr>
<td>Lachnospiraceae</td>
<td>23.44</td>
<td>2.24</td>
<td></td>
<td>10.40</td>
<td>2.60</td>
<td></td>
<td>0.0009</td>
</tr>
<tr>
<td>Ruminococcaceae</td>
<td>17.72</td>
<td>1.89</td>
<td></td>
<td>6.75</td>
<td>1.28</td>
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<tr>
<td>Enterobacteriaceae</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
<td>7.60</td>
<td>2.89</td>
<td></td>
<td>0.001</td>
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<tr>
<td>Fusobacteriaceae</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
<td>1.80</td>
<td>1.06</td>
<td></td>
<td>0.0059</td>
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<tr>
<td>Methylococaceae</td>
<td>0.89</td>
<td>0.34</td>
<td></td>
<td>2.76</td>
<td>0.73</td>
<td></td>
<td>0.032</td>
</tr>
</tbody>
</table>

A

B

Nomenclature of Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>HE Type</th>
<th>Nomenclature</th>
<th>Subcategory</th>
<th>Subdivisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>HE associated with cirrhosis and PHTN / or portosystemic shunts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Episodic HE</td>
<td>Precipitated Spontaneous Recurrent</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Persistent HE</td>
<td>Mild Severe Treatment-dep.</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Minimal HE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
West Haven Criteria

Stage 0: No detectable personality changes.

Stage 1: Trivial lack of awareness. Impaired attention span. Altered sleep, euphoria or depression.


Stage 4: Coma

Spectrum of neuro-cognitive impairment in cirrhosis (SONIC)

Overt HE Stages

Unimpaired Covert HE

Worsening cognitive function

Bajaj et al Hepatology 2009

Spectrum of neuro-cognitive impairment in cirrhosis (SONIC)

Unimpaired Covert HE

Worsening cognitive function

Bajaj JS et al ISHEN Consensus Statement Aliment Pharmacol Ther 2011
### Unimpaired, Covert and Overt HE

<table>
<thead>
<tr>
<th></th>
<th>Unimpaired</th>
<th>Covert HE</th>
<th>Overt HE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental status</td>
<td>Not impaired</td>
<td>Not impaired</td>
<td>From disorientation through coma</td>
</tr>
<tr>
<td>Specialised tests</td>
<td>Not impaired</td>
<td>Impaired</td>
<td>Not specifically required but will be abnormal</td>
</tr>
<tr>
<td>(according to local expertise)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asterixis</td>
<td>None</td>
<td>None</td>
<td>Present (except in coma)</td>
</tr>
</tbody>
</table>

*Source: Bajaj JS et al ISHEN Consensus Statement Aliment Pharmacol Ther 2011*

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### Minimal/Covert hepatic encephalopathy

- Affects **30-84%** of individuals tested
- No recognizable symptoms or signs of overt hepatic encephalopathy (OHE) on history or physical exam
- Exclusion of other causes of altered mentation, including drugs and medications
- **By definition, cannot be diagnosed by clinical examination and needs specialized testing**

*Source: Ferenci 2002, Ortiz 2002*
Cognitive function in daily life

<table>
<thead>
<tr>
<th>Domain</th>
<th>Need in daily life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working memory</td>
<td>Remember things from minute-to-minute to do daily tasks</td>
</tr>
<tr>
<td>Inhibitory control</td>
<td>Inhibit responses when not accurate</td>
</tr>
<tr>
<td>Problem solving</td>
<td>Problem solving and planning</td>
</tr>
<tr>
<td>Reaction time</td>
<td>Responses in driving and work</td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>Driving, machinery operation</td>
</tr>
<tr>
<td>Immediate Memory</td>
<td>Remember things over a few minutes</td>
</tr>
<tr>
<td>Visuo-motor coordination</td>
<td>Navigation, driving, working, drawing and designing</td>
</tr>
<tr>
<td>Language</td>
<td>Speech, Comprehension</td>
</tr>
<tr>
<td>Delayed Memory</td>
<td>Remembering the distant past</td>
</tr>
</tbody>
</table>

Cognitive dysfunction in HE

**Domains affected**
- Attention
- Visuo-motor coordination
- Psychomotor speed
- Working memory
- Response inhibition

**Domains not affected**
- Language skills
- Delayed memory
- Overall verbal and non-verbal intelligence

Amodio et al 2005, Ferenci et al 2002
Weissenborn et al 2001, Tarter 1984
Methods for Detecting Covert HE

<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>Automated tests (ICT, critical flicker frequency)</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
</tr>
</tbody>
</table>

Adapted from Mullen KD et al. Semin Liver Dis. 2007
Recommendations for testing

- Psychometric Hepatic Encephalopathy Score (PHES)
- For the US: Impairment in 2 of 4 tests below
  - Number connection test-A, Number connection test-B, Digit Symbol and Block Design tests
- ICT: has been used in limited centers

- Field is in evolution and an ideal test and combination is still needed.

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Why should we test for Minimal/Covert HE?

- Is it associated with poor outcomes?
- Can we treat it?
Covert HE is associated with Poor Quality of Life

<table>
<thead>
<tr>
<th>Study</th>
<th>Instrument used</th>
<th>Poor QOL?</th>
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</thead>
<tbody>
<tr>
<td>Groeneweg 1998</td>
<td>Sickness Impact Profile</td>
<td>Yes</td>
</tr>
<tr>
<td>Schomerus 2001</td>
<td>Sickness Impact Profile</td>
<td>Yes</td>
</tr>
<tr>
<td>Bao 2007</td>
<td>Chronic liver disease Q, SF-36</td>
<td>Yes</td>
</tr>
<tr>
<td>Prasad 2007</td>
<td>Sickness Impact Profile</td>
<td>Yes</td>
</tr>
<tr>
<td>Zhou 2009</td>
<td>Chinese adaptation of QOL</td>
<td>Yes</td>
</tr>
<tr>
<td>Les 2010</td>
<td>Chronic liver disease Q, SF-36</td>
<td>Yes</td>
</tr>
<tr>
<td>Sidhu 2010</td>
<td>Sickness Impact Profile</td>
<td>Yes</td>
</tr>
<tr>
<td>Wunsch 2011</td>
<td>Chronic liver disease Q, SF-36</td>
<td>No</td>
</tr>
<tr>
<td>Bajaj 2011</td>
<td>PROMIS tools and Sickness Impact Profile</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Covert HE predicts overt HE development

- Romero-G 2007: 3.3% no MHE, 45% MHE
- Saxena 2002: 5.7% no MHE, 59% MHE
- Das 2001: 6% no MHE, 23% MHE
- Romero-G 2001: 10% no MHE, 47% MHE
- Hartmann 2000: 8% no MHE, 56% MHE
Employment is affected by MHE

Schomerus and Hamster Metab Brain Dis 2001

MHE is associated with falls

Roman et al Am J Gastroenterol 2010
Driving Capability

- Several competing inputs that have to be balanced while driving
- Medical impairments only affect them partially.
- Decisions while operating a car are made on a
  - strategic,
  - tactical and
  - operational level.
- Tests can be
  - Simulation
  - On-road driving tests
  - Analysis of driving offenses


Bajaj et al Hepatology 2008
Results of on-road tests

Crashes in patients with MHE

N = 167

Period of analysis of official driving record: 12 months

History of crashes:
Abnormal ICT: 17%
Normal ICT: 3%

Future driving offenses

P=0.03

P=0.01

Bajaj et al. Hepatology 2009
Driving Capability

- Difficulties in on-road driving tests (44-100% considered “unsafe”)
- Difficulties in simulator performance
  - Problems with crashes
  - Navigation issues resulting in patients “getting lost”
- Increased risk of traffic offenses, both within the prior year and prospectively with poor ICT performance
- MHE patients also have poor insight into their driving skill impairments

MHE is associated with poor outcomes

- Increased progression to overt HE
- Adverse effect on employment
- Poor quality of life
- Higher risk of falls
- Increased risk of traffic accidents

However, can we treat it?
<table>
<thead>
<tr>
<th>Author</th>
<th>Agent</th>
<th>Duration</th>
<th>Improved MHE?</th>
<th>Testing of clinically relevant outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watanabe</td>
<td>Lactulose</td>
<td>8 weeks</td>
<td>Yes</td>
<td>_</td>
</tr>
<tr>
<td>Li</td>
<td>Probiotic</td>
<td>24 weeks</td>
<td>Yes</td>
<td>_</td>
</tr>
<tr>
<td>Horsmans</td>
<td>Lactulose</td>
<td>2 weeks</td>
<td>Yes</td>
<td>_</td>
</tr>
<tr>
<td>Prasad</td>
<td>Lactulose</td>
<td>90 days</td>
<td>Yes</td>
<td>Improved quality of life</td>
</tr>
<tr>
<td>Morgan</td>
<td>Rifaximin</td>
<td>8 weeks</td>
<td>Yes</td>
<td>_</td>
</tr>
<tr>
<td>Bajaj</td>
<td>Yogurt</td>
<td>60 days</td>
<td>Yes</td>
<td>Trend: reduced OHE</td>
</tr>
<tr>
<td>Liu</td>
<td>Synbiotic</td>
<td>60 days</td>
<td>Yes</td>
<td>CTP improvement</td>
</tr>
<tr>
<td>Malguanera</td>
<td>Probiotic</td>
<td>90 days</td>
<td>Yes</td>
<td>_</td>
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<tr>
<td>Sidhu</td>
<td>Rifaximin</td>
<td>90 days</td>
<td>Yes</td>
<td>Improved quality of life</td>
</tr>
<tr>
<td>Bajaj</td>
<td>Rifaximin</td>
<td>60 days</td>
<td>Yes</td>
<td>Improved driving</td>
</tr>
</tbody>
</table>

**Quality of life improves in MHE after lactulose therapy**

![Graph showing quality of life improvements](image)
Rifaximin improves cognition and quality of life

- A significantly higher rate of MHE reversal was seen in the rifaximin group
- The mean total SIP (QOL) score also improved significantly in rifaximin group but not in the placebo ($P=0.82$).

Rifaximin improves driving simulator performance

$P=0.013$
Barriers to treating minimal/covert HE

- Current diagnostic methods are in evolution
- Affected patients do not think they have a problem; therefore adherence may be an issue.
- Most current trials are of short duration
- Clinically relevant outcomes have not been studied rigorously.
Summary and future: Minimal/covert hepatic encephalopathy

• Treatment trials have provided ample proof of concept that psychometric and neuro-physiologic tests improve after therapy

• Prospective, long-term trials are required to study clinically relevant outcomes such as
  » Development of overt HE
  » Confirmation of QOL measures
  » Overall survival
  » Driving capability

Spectrum of neuro-cognitive impairment in cirrhosis

Disorientation  Coma

Overt Hepatic Encephalopathy
Case 1

• 58 yo man with alcoholic cirrhosis was brought in due to dizziness, left hand numbness and “not feeling himself”.
• No seizures, headaches or bleeding.
• Four variceal bleeding episodes in the last 3 years; currently on propranolol.
• BP=121/75, P=72, Stupor but no asterixis
• Hgb: 6.4 (reduction from 11.0 one month ago), Platelet count: 23, Creatinine: 1.6, Ammonia: 57.
• Heme-positive stools noted; no blood in rectum

Admitted to the ICU for HE with GI bleeding

Case 1

• Was started on lactulose and GI consulted
• On exam 4 hours later, patient was alert, oriented X 3 without focal deficits and bleeding
• Of note, his LDH and reticulocyte counts were high.
• EGD was not performed; instead a peripheral smear evaluation was requested.
All that is altered is not HE: Clues against HE

- New focal deficits
- Excitatory motor activity, especially seizures
- Current/recent alcohol use
- Current/recent illegal drug use
- Other situations in which HE is unlikely
Altered mental status: it's not always HE

- Intracranial hematomas
- Drug intoxication
- Alcohol withdrawal
- Severe sepsis
- Thyroid dysfunction
- Hypoglycemia
- Hyperglycemia
- Encephalitis
- Uremia
- Hypoxia
- Hyper-capnia

*Most entities can be diagnosed by brain imaging or laboratory tests.
*Severe sepsis can cause encephalopathy or precipitate HE.

Adapted from Mullen KD. Semin Liver Dis. 2007

Overt HE reduces survival

Survival estimates of hospitalized patients according to grade of HE

Bustamante et al J Hepatol 1999, Stewart et al Liver Transpl 2007
Case 2

- 68 yo man with cirrhosis brought by family for 4 days of confusion
- Two weeks after UTI (currently on ciprofloxacin)
- Variceal bleeding 1 year ago with HE; not on HE Rx
- Patient went to the ER at an outside hospital
- Physical exam: Stupor, arousable with verbal stimuli, non-comprehensible speech
- Temp 98.5 F, BP 98/60, HR 60, SpO2: 99%
- Asterixis without focal deficits and symmetric reflexes

Case 2

- Patient underwent lab testing
  - CBC unremarkable (platelet count 68000)
  - Na 126, Creatinine 1mg/dl
  - MELD 24
  - Ammonia: 129
- CT head performed: mild volume loss
- Urine and Chest x-ray: normal
- Blood and urinary cultures: negative
Serum ammonia levels and hepatic encephalopathy

Kramer, Hepatology 31:1, 2000

Venous ammonia levels and hepatic encephalopathy

Ong, American Journal of Medicine, 114:3, 2003
Arterial ammonia levels and hepatic encephalopathy

Ong, American Journal of Medicine, 114:3, 2003
**Algorithm for In-Patient HE Management**

1. **Patient with possible overt HE**
2. **Confirm that it is HE: Yes**
3. **Search for precipitating factor**
   - **Precipitating factors found**
     - Treatment directed to the precipitating factor
   - **Precipitating factors not found**
     - Admit to ICU for grade 3 HE
     - Specific HE therapy with lactulose or rifaximin
     - Can consider metronidazole or zinc

**General Principles of Management of Overt HE**

- Acute or chronic HE is reversible in the majority of patients
- A precipitating cause rather than worsening of hepatocellular function can be identified in an episode of HE
- Management of the precipitating events typically leads to prompt improvement in HE
- Clinicians should simultaneously identify and resolve precipitating events while instituting pharmacologic therapy for HE
Overt HE: Precipitating Factors

- Gastrointestinal bleeding
- Infection
- Sedative drugs
- Hyponatremia
- Non-adherence
- Dehydration

- Fluid restriction
- Diuretics
- Vomiting or diarrhea

Treatment Options for Overt HE

- Reduction in the nitrogenous load arising from the gut (lactulose, antibiotics)
- Drugs that affect neurotransmission (flumazenil, bromocriptine)
- Manipulation of the splanchnic circulation (occlusion of portal-systemic collaterals)

Adapted from Blei AT et al. Am J Gastroenterol. 2001
Treatment goals in overt HE

• **Acute HE episode**
  – Treatment of precipitating factors
  – Improvement in mental status
  – Evaluation for liver transplant

• **Episodic HE outpatient**
  – Improve daily functioning
  – Prevention of recurrent episodes of HE
  – Evaluation for liver transplant

Overt HE prevention during variceal bleed

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lactulose group (n = 35)</th>
<th>Non-lactulose group (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic encephalopathy (n)</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Death (n)</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Hospital stay in days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with HE</td>
<td>11.8 ± 1.4</td>
<td>10.4 ± 2.3</td>
</tr>
<tr>
<td>Patients without HE</td>
<td>7.1 ± 2.0</td>
<td>7.5 ± 1.3</td>
</tr>
<tr>
<td>P*</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Lactulose therapy prevented overt HE development in patients admitted with variceal bleeding compared to those randomized to no therapy

Sharma et al J Gastroenterol Hepatol 2011
Patient was admitted to the floor

Careful hydration was provided, diuretics were stopped and lactulose was initiated at the dose of 30 ml every 4 hours.

Repeat sodium increased but the patient remained in stupor

Prolonged encephalopathy

Undiagnosed precipitating factor?

Hidden predisposing condition?

Advanced liver failure?

Persistent HE may be associated with shunts

Embolization of these shunts can improve the course of HE
Patient’s CT

Hidden prostatic abscess

Cirrhosis and clinical symptoms or signs of overt HE

- Identify and correct precipitating factors
- Rule out other causes
- Assess vital signs and volume status
- Evaluate for GI bleed, infection and metabolic abnormalities
- Eliminate sedatives or tranquilizers
- Administer intravenous (IV) fluids; correct electrolyte abnormalities

Adapted from Mullen KD et al. Semin Liver 2007 and Garcia-Tsao et al Am J Gastro 2009
Grade 1 to 2\(^a\) HE
- Initiate oral lactulose therapy
- If lactulose is not tolerated or ineffective, consider therapy with a short course of rifaximin

Grade 2\(^a\) to 4 HE
- Admit patient to hospital
- Provide supportive care
- Initiate therapy with lactulose (enema ± enteral)
- If lactulose is not tolerated or not effective, consider rifaximin or other antibiotics

Consider referral or evaluation for transplant

Adapted from Mullen KD et al. Semin Liver 2007 and Garcia-Tsao et al Am J Gastro 2009

Treatment goals in overt HE

- **Episodic HE outpatient**
  - Improve daily functioning
  - Prevention of recurrent episodes of HE
  - Evaluation for liver transplant

- **Acute HE episode**
  - Treatment of precipitating factors
  - Improvement in mental status
  - Evaluation for liver transplant
Protein restriction does not help in overt HE

There were no statistical differences between the low-protein diet (white boxes) and the normal protein diet (gray boxes).

Cordoba et al 2004 J Hepatol

Treatment of Overt HE: Lactulose

Sharma et al Gastro 2009
Adverse effect management
Patient education
Therapy titration
Counseling of family members

HE recurrence as a function of lactulose adherence

46% recurred due to problems with lactulose

Bajaj et al Alimentary Pharmacol Ther 20
Breakthrough HE Episodes* Over 6 Months: Rifaximin vs. Placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifaximin 550 mg bid (n=140)</td>
<td>22%</td>
</tr>
<tr>
<td>Placebo (n=159)</td>
<td>46%</td>
</tr>
</tbody>
</table>

\[ p < 0.0001 \]

*Patients who had \( \geq 2 \) episodes of HE within 6 months prior to screening and who were in remission at trial start

Summary

- Not all altered mental status in cirrhosis is HE
- Diagnosis of HE is largely exclusionary but brain imaging and ammonia levels are often not required
- Therapy of HE episode should concentrate on investigating and treating precipitating factors.
- Goals of HE therapy depend on the acuity of the presentation.
- Rifaximin and lactulose can prevent relapse of HE as an outpatient.

Bass N et al. NEJM 2010
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