Hepatic Encephalopathy in Cirrhosis: a Disorder of Glial-Neuronal Signalling

Prof. Roger F. Butterworth, Ph.D., D.Sc.

Classification of hepatic encephalopathy (HE)

- Type A: associated with acute liver failure
- Type B: associated with portosystemic bypass with no intrinsic hepatocellular disease
- Type C: associated with cirrhosis and portal hypertension

Hepatic encephalopathy in cirrhosis

- Neuropsychiatric syndrome
- Personality changes, sleep disorders
- Attention deficit, motor incoordination
- Asterixis
- Stupor
- Coma
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Hepatic encephalopathy in cirrhosis (2)
- Major impact on quality of life
- Precipitating factors
  - Protein load
  - Gastrointestinal bleed
  - Sedatives
  - Hypoglycemia
  - Infection

Transjugular intrahepatic portosystemic shunt (TIPS)
- Treatment of portal hypertension in cirrhosis
- Prevention of gastro-intestinal bleeding
- Effectively a liver bypass
- Artificial channel to link in-flow (portal vein) and out-flow (hepatic vein) in cirrhosis

Hepatic encephalopathy post-TIPS
- New or worsening encephalopathy in ~50% of cases
- Predictors
  - Prior encephalopathy
  - Non-alcoholic etiology
  - Hypoalbuminemia
  - Patient age

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Survival in TIPS patients as a function of grade of HE

- Survival decreases as grade of HE increases.
- Grade HE=0 shows the highest survival rate.

Neuropathology of HE in chronic liver failure

- Normal astrocytes (N)
- Alzheimer type 2 astrocytosis (ALZ)

Pathogenesis of HE in cirrhosis: Neuroimaging

- Magnetic resonance imaging (MRI)
- Positron emission tomography (PET)
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T1-weighted MRI due to manganese deposition in basal ganglia of cirrhotic patients

C (control) P (patient(s))

Manganese (μg/g dry WT)

C P

Globus pallidus

Cirrhosis-related Parkinsonism: MRI findings

• Burkhard et al., Arch Neurol 60: 521-528, 2003
• Extensive hyperintensities involving both substantia nigra and globus pallidus

Cirrhosis-related Parkinsonism

• Burkhard et al., Arch Neurol 60: 521-528, 2003
• 22% of 51 cirrhotic patients screened prior to LT showed moderate to severe Parkinsonism
  • Chronic
  • Rapidly progressive over months
  • Symmetric akinetic-rigid syndrome
  • Postural (but not resting) tremor
  • Early postural and gait impairment
• Attributed to manganese deposition in basal ganglia

2 patients treated with L-DOPA: both showed improvement
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Pathogenesis of HE in cirrhosis:  
Neuroimaging

• Magnetic resonance imaging (MRI)  
• Positron emission tomography (PET)

Positron emission tomography (PET)  
studies in cirrhosis

• Fluorodeoxyglucose

Fluorodeoxyglucose-PET showing  
deactivation of anterior cingulate cortex  
correlation with abnormal NCT-B test

Anterior cingulate cortex

Lockwood et al., Metab Brain Dis., 2002

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NCT-B test

Positron emission tomography (PET) studies in cirrhosis

- Fluorodeoxyglucose
- $^{13}$N-ammonia

$^{13}$NH$_3$ PET images of brain in a cirrhotic patient with mild HE

<table>
<thead>
<tr>
<th></th>
<th>CBF</th>
<th>CMRA</th>
<th>PS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patient</td>
<td></td>
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<tr>
<td>Arterial NH$_3$ (mM)</td>
<td>0.03±0.007</td>
<td>0.06±0.02</td>
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<tr>
<td>CMR/NH$_3$</td>
<td>0.35±0.15</td>
<td>0.91±0.36*</td>
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<tr>
<td>BBB transfer (NH$_3$) (ml/g/min)</td>
<td>0.13±0.03</td>
<td>0.22±0.07*</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.01

Lockwood, J Cerebr Blood Flow & Metab., 2007

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Neuroinflammation and hepatic encephalopathy in cirrhosis

Systemic inflammatory response syndrome (SIRS) in cirrhosis
- Functionally immunosuppressed
- Impaired host defenses
- Increased TNFα, IL-1β
- Multiple cells involved (monocytes, neutrophils, lymphocytes, Kupffer cells)

Circulating TNFα in cirrhotic patients with grades 0-4 hepatic encephalopathy

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Serum TNFα as a function of improvement of HE grade in cirrhosis

![Graph showing serum TNFα levels as a function of HE grade improvement](image)


Microglial activation in BDL model of biliary cirrhosis

- D’Mello et al., *J Neurosci*, 2009

Translocator protein and hepatic encephalopathy in cirrhosis
Translocator protein

• Mitochondrial location, particularly in astrocytes and microglia
• Catalyzes cholesterol transport across mitochondrial membrane
• Activated by both ammonia and manganese

Translocator protein complex

End-stage liver failure results in increased expression of IBP, a key subunit of translocator protein
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Increased translocator protein ([3H]-PK11195) sites in human HE brain

PET imaging using the translocator protein ligand 11C-PK11195 indicative of microglial activation

Translocator protein activation by ammonia or manganese leads to increased synthesis of neurosteroids

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Modulatory site for neurosteroids on the GABA-A receptor
- Gated Cl⁻ channel
- Mediates fast inhibitory neurotransmission
- GABA recognition site
- Several modulator sites:
  - Barbiturates
  - Benzodiazepines
  - Neurosteroids (allopregnanolone)

GABA-A receptor activation by neurosteroids: glial-neuronal signalling

Concentrations of allopregnanolone are increased in autopsied brain tissue from cirrhotic patients who died in hepatic coma

Ahboucha et al., Ann Neurol., 2005
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Prevention and treatment of HE in cirrhosis

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Prevention and treatment of HE in cirrhosis (2)

- Treatment of precipitating factors:
  - Dietary protein overload
  - Gastrointestinal haemorrhage
  - Infection
  - Constipation
  - Dehydration
  - Hypokalemia
  - Hypoglycemia
  - Hypoxia
  - Sedative drugs (benzodiazepines)

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Prevention and treatment of HE in cirrhosis (3)

- Nutrition
  - Start with 40 g protein per day, increase gradually every 3-5 days to 1-2 g/kg/day
  - Care(f) to avoid a negative nitrogen balance, do not reduce below 40 g/day
  - Benefit of vegetable versus animal protein

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Prevention and treatment of HE in cirrhosis (4)

- Non-metabolizable disaccharides
  - Inhibit ammonia-producing bacteria (lower colonic pH)
  - Displacement of urease-containing bacteria
  - Cathartic effect
  - Lactulose ($\beta$-galactosidofructose)
    - Introduced 35 years ago
    - No adequate controlled clinical trials but still treatment of choice
    - Doses 45-90 g/day; Titrate to 2/3 soft stools/day
  - Lactitol ($\beta$-galactosidosorbitol)
    - As effective as lactulose
    - Fewer side effects
    - Less expensive

Prevention and treatment of HE in cirrhosis (5)

- Antibiotics
  - Reduce bacterial ammonia production in the colon
  - Neomycin, paromomycin (aminoglycosides)
  - Aminoglycosides are ototoxic/nephrotoxic; limit use to 1 month
  - Metronidazole, vancomycin; Use limited by adverse events
  - Rifaximin; Non-absorbable antibiotic, high efficacy, minimal adverse events

L-ornithine L-aspartate (LOLA) lowers circulating ammonia and improves NCT scores in cirrhotic patients

Fasting ammonia

NCT-A

Kircheis et al., Hepatology, 1997
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Summary: therapies based on improvement of inter-organ trafficking of ammonia in HE

- L-OA
- Lactulose, rifaximin

Prevention and treatment of HE in cirrhosis

- Flumazenil
  - Central benzodiazepine receptor antagonist
  - No intrinsic actions – counteracts effects of benzodiazepines
  - Short half-life (1-2h in cirrhotic patients)
  - Controlled trials show small positive effect, may be primarily due to action on circulating pharmaceutical benzodiazepines

Flumazenil in HE: results of a meta-analysis

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<tr>
<th>Study</th>
<th>Number (% of HE)</th>
<th>Placebo</th>
<th>T2</th>
<th>T1</th>
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<th>Placebo</th>
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Favours Flumazenil, Placebo
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Prevention and treatment of HE in cirrhosis

- Emerging new therapeutic approaches:
  - Liver assist devices (cultured hepatocytes, activated charcoal, albumin)
  - Probiotics
  - L-DOPA (may improve Parkinsonian symptoms)

Take home messages

1. HE in cirrhosis associated with cognitive, motor and psychiatric symptoms
   - High prevalence post-TIPS
   - Major impact on quality of life
2. Both global and focal changes of brain metabolism occur in cirrhosis
   - Ammonia accumulation throughout the brain
   - Manganese accumulation in globus pallidus (MR signal hyperintensities)
   - Anatomy of attention deficit in cirrhosis – anterior cingulate cortex

Take home messages (cont’d)

3. Neuroglial changes in cirrhosis:
   - Alzheimer type II astrocytosis
   - Microglial activation, neuroinflammation
   - Induction of translocator protein (astrocytes and microglia) by ammonia and manganese, neurosteroid production
4. Treatment options for HE in cirrhosis:
   - Treat precipitating factor
   - Maintain protein at 1-2g/kg/day
   - Lower circulating ammonia
     - Lactulose, antibiotics (gut)
     - L-ornithine L-aspartate (muscle, liver)
   - Probiotics
5. Neuropharmacology
   - Flumazenil (for E-precipitated component of encephalopathy)
   - L-DOPA, bromocriptine (cirrhosis-related Parkinsonism)
   - Limited translational research in this area

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