HEPATIC ENCEPHALOPATHY: CLINICAL AND LABORATORY ADVANCES

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Hepatic Encephalopathy in Chronic Liver Disease

- Neuropsychiatric Syndrome
- Personality changes, sleep disorders
- Attention deficit, motor incoordination
- Asterixis
- Stupor
- Coma
Hepatic Encephalopathy in Chronic Liver Disease

- Impact on quality of life
- Precipitating factors
  - Protein load
  - Gastrointestinal bleed
  - Sedatives
  - Hypoglycemia
  - Infection
Hepatic Encephalopathy Post-TIPS

- New or worsening encephalopathy in ~50% of cases
- Predictors
  - Prior encephalopathy
  - Non-alcoholic etiology
  - Hypoalbuminemia
  - Patient age
Recent Progress in the Pathophysiology of Hepatic Encephalopathy

1. Neuropathology
2. Neuroimaging
   - Positron Emission Tomography (PET)
   - Magnetic Resonance Imaging (MRI)
3. Spectroscopy
4. Molecular Biology
5. Implications for New Therapeutic Strategies
   - GABA modulation (neurosteroids)
Images of the Brain in Liver Failure

1. Neuropathology

2. Neuroimaging
   - Positron Emission Tomography (PET)
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Neuroimaging in Liver Failure

- POSITRON EMISSION TOMOGRAPHY (PET)
  - $^{18}$F-DEOXYGLUCOSE
  - $^{13}$N-NH$_3$
Local Cerebral Glucose Utilization (LCGU) using $^{18}$F-Deoxyglucose (PET)
Correlation Between Decreased LCGU and Impaired Psychometric Test Performance in Cirrhotic Patients with Mild HE

Anterior cingulate cortex
Neuroimaging in Liver Failure

- POSITRON EMISSION TOMOGRAPHY (PET)
  - $^{18}$F-DEOXYGLUCOSE
  - $^{13}$N-NH$_3$
PET Images of Brain using $^{13}$NH$_3$ in a Patient With Mild HE

[Normal Patient]

[CBF, CMRA, PS Images]

[JCBFM, 11: 337-341, 1991]
### PET Imaging Studies: Data

<table>
<thead>
<tr>
<th></th>
<th>Controls (5)</th>
<th>Patients (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial NH(_3) (mM)</td>
<td>0.03±0.007</td>
<td>0.062±0.02*</td>
</tr>
<tr>
<td>CMR/NH(_3)</td>
<td>0.35±0.15</td>
<td>0.91±0.36*</td>
</tr>
<tr>
<td>BBB transfer (NH(_3)) (ml/g/min)</td>
<td>0.13±0.03</td>
<td>0.22±0.07*</td>
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*p<0.01

*JCBFM, 11: 337-341, 1991*
Neuroimaging in Liver Failure

- POSITRON EMISSION TOMOGRAPHY (PET)
  - $^{18}\text{F}$-DEOXYGLUCOSE
  - $^{13}\text{N}$-NH$_3$
- MAGNETIC RESONANCE IMAGING (MRI)
Magnetic Resonance Imaging in Chronic Liver Failure

Note: Bilateral $T_1$-weighted signal hyperintensities in globus pallidus of patient (P) compared to control (C)
Manganese

- 98% cleared by liver, excreted in the bile
- Accumulates in globus pallidus following chronic intoxication
- Causes Alzheimer type II astrocytosis
Selective Increase of Brain Manganese in Globus Pallidus of HE Patients
Toxins Normally Removed by Hepatobiliary System Which Accumulate in Brain in Chronic Liver Failure

- Ammonia
- Manganese
Ammonia removal by brain

. No urea cycle

. Glutamine synthetase major system involved

Glutamate → Glutamine

\[ \text{NH}_3 \quad \text{ATP} \quad \text{GS} \]

. GS uniquely ASTROCYTIC
IMAGES OF THE BRAIN IN LIVER FAILURE

1. Neuropathology
2. Neuroimaging
   - Positron Emission Tomography (PET)
   - Magnetic Resonance Imaging (MRI)
3. Spectroscopy
4. Molecular Biology
5. Implications for New Therapeutic Strategies
   - GABA modulation (neurosteroids)
   - Hypothermia
Increased brain glutamine correlates with severity of encephalopathy in chronic liver failure: results of $^1$H-MRS studies

Images of the Brain in Liver Failure

1. Neuropathology
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   - Positron Emission Tomography (PET)
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4. Molecular Biology
5. Implications for New Therapeutic Strategies
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Altered Transcripts following Portacaval Anastomosis in Rat Cerebral Cortex

[J Neurosci Res 68(6), 2002]
Chronic Liver Failure Results in Increased Gene Expression in Brain

- Peripheral-type benzodiazepine receptor (PTBR)
- Nitric oxide synthase (nNOS isoform)
- Monoamine oxidase (MAO-A isoform)
Allopregnanolone is a Potent Inhibitory Neurosteroid with GABA-Agonist Properties
Increased Brain Concentrations of Allopregnanolone in Patients With HE
Treatment of Hepatic Encephalopathy in Chronic Liver Disease

1. Treatment of precipitating factor
2. No protein restriction (maintain 1-2g/kg/day)
3. Ammonia-lowering strategies
   - Aimed at residual liver (L-ornithine L-aspartate)
   - Aimed at the gut (Lactulose, antibiotics)
   - Aimed at the muscle (L-ornithine L-aspartate)
   - Aimed at the brain (none yet)
Treatment of Hepatic Encephalopathy in Chronic Liver Disease

4. Neuropharmacology

- Benzodiazepine Receptor Antagonists (Flumazenil) effective in Bz-induced encephalopathy, otherwise only in small sub-group

- Dopamine agonists (L-DOPA, Bromociptine). No clear effects in controlled clinical trials; may improve motor dysfunction.

- Use of opioid receptor antagonists, serotonin reuptake inhibitors, non-sedative antihistaminics suggested from animal studies but no translational research in this area.
Pathogenesis of Hepatic Encephalopathy: Take Home Message

- Neuropsychiatric Disorder
- High Impact on Quality of Life
- Precipitating Factor in >80% of cases
- Occurs in ~50% of TIPS cases
- Results from altered function of brain ASTROCYTES
- Brain regional selectivity (anterior cingulate cortex)
- Neurotoxins
  - Ammonia (throughout brain)
  - Manganese (globus pallidus)
- Altered expression of GENES coding for key brain proteins
Treatment of Hepatic Encephalopathy: Take Home Message

- Treat precipitating Factor
- Maintain protein at 1-2 g/kg/day
- Lower circulating ammonia
  - Lactulose, antibiotics (gut)
  - L-ornithine L-aspartate (muscle, liver)
- Neuropharmacology
  - Flumazenil (if Bz precipitation component of encephalopathy)
  - Limited translational research in this area
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