Hyperammonemia in Patients with Brain Injury

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Disclosure

- No industry relationships to disclose...
Main goals of rehab of patients with Brain Injury

- Prevent/reduce secondary complications (emotional/cognitive/functional impairment)
- Identify/treat/remove exacerbating factors
- Ex: -Infectious/endocrine/metabolic disturbances
  - Neurotoxic/sedating medications
Background

- Hyperammonemiania (HA) is an established cause of neurotoxicity (Shawcross et al, 2012; Butterworth 2011)

- Difficult to distinguish from sequelae of brain injury (BI)
  - Fatigue (Wilkinson et al, 2011)
  - Memory/processing speed (Ortiz et al, 2006; Butterworth 2011)
  - Balance and coordination (Butz et al, 2010)

- Treatable condition

- To date no studies investigating HA in BI
Sources of ammonia

- Ammonia: normal protein byproduct

**Production**
1. Gut (main source)
2. Skeletal muscle
3. Kidney

**Breakdown**
1. Liver (main source)
2. Kidney/Muscle/Brain (limited)

Clay et al, 2007
Causes of Hyperammonemia

Excess Production

Decreased Breakdown
Potential causes of Hyperammonemia in BI

**Excess production**

1. **Protein load to gut:**
   - Constipation
   - Protein rich food

2. **Muscle breakdown:** (Laish et al, 2011; Tomita et al, 2011)
   - Trauma/Atrophy/Starvation
   - Steroids
   - Seizures

3. **Neurogenic bladder with urease-producing bacteria** (Drayna et al, 1981)

**Decrease breakdown**

1. **Liver disease:** (Clay et al, 2007)
   - Substance abuse
   - Hepatotoxic/antiepileptic meds (Dreifuss et al, 1987)
   - Infection
   - Urea cycle disorders

2. **Metabolic alkalosis** (NH4 → NH3)
   - Vomiting
   - Hypoxia
   - Tube feeding
Ammonia: role of blood brain barrier

• Hyperammonemia **alone** is not enough to result in neurocognitive changes.

• HA **and** a disrupted BBB together make BI susceptible to neurocognitive effects of HA

• TBI ➔ impaired BBB ➔ vulnerable to even mild HA
Ammonia: role of blood brain barrier

Studies describing the role of the BBB:

- **Wilkinson et al, 2011**
  - Healthy subjects with intact BBB → no cognitive impairments following IV infusions of high levels of ammonia.

- **Lockwood et al, 1991**
  - In chronic liver disease, PET scan showed patients with cognitive impairments had ↑BBB permeability even at low peripheral ammonia levels.

- **Shlosberg et al, 2010**
  - BBB disruption occurs following TBI
Ammonia as neurotoxin

Direct Neuronal Damage

Increased Glutamine in Astrocytes

Neurotransmitter Disruption/Increase GABA tone

Astrocyte swelling/Cell Death

(Panickar et al, 2009) (Butterworth, 2011)
Study Objectives

- Pilot study to identify frequency of HA, a known neurotoxin, in patients with brain injury

- Identify certain readily identifiable factors via chart review associated with HA in patients with brain injury
  - PMH of liver disease
  - Hepatotoxic medication
  - Elevated liver enzymes
Methods

➢ Retrospective chart and lab review

➢ Approved by Institutional IRB

➢ Patients with ammonia levels drawn between 8 month period (August 1, 2011 - March 31, 2012)

➢ Hyperammonemia defined as:
  › Normal ammonia: \( \leq 32\mu\text{mol/L} \)
  › Hyperammonemia: \( > 32\mu\text{mol/L} \)
Inclusion criteria:
- Ages 18-89
- Inpatient acute rehabilitation
- Diagnosis of brain injury was operationally defined as: stroke, traumatic and non-traumatic
- Ammonia test performed
Methods

- Exclusion criteria:
  - Age < 18 or > 89 years old
  - Without diagnosis of brain injury
  - Ammonia testing not performed
  - Presence of other neurological disorders
Analysis

- Percentages to assess frequency of HA in patients with brain injury
- Pearson’s chi square analysis to determine if the frequency of demographic and clinical factors looked at was significantly greater in patients with HA than those with normal ammonia
- Odds ratio analysis to assess likelihood of having HA
Results

- 167 charts were initially identified
  - 16 were excluded for age > 89 years old
  - 18 were excluded for PMH of neurologic disease other than brain injury

- 133 charts met research criteria and were reviewed

- 22.6% (30 out of 133) found to have hyperammonemia
<table>
<thead>
<tr>
<th>Feature</th>
<th>High Ammonia</th>
<th>Normal Ammonia</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean + SD)</strong></td>
<td>50.6 ± 17.8</td>
<td>55.6 ± 18.9</td>
<td>p = .2</td>
</tr>
<tr>
<td><strong>Gender</strong> (percentage)</td>
<td>Male 66.7</td>
<td>Male 50.5</td>
<td>p = .118</td>
</tr>
<tr>
<td></td>
<td>Female 33.3</td>
<td>Female 49.5</td>
<td></td>
</tr>
<tr>
<td><strong>Admission FIM Total</strong></td>
<td>35.0 (38.3 ± 19.1)</td>
<td>30.0 (35.9 ± 19.7)</td>
<td>p = .482</td>
</tr>
<tr>
<td><strong>Admission FIM Motor</strong></td>
<td>19.0 (24.0 ± 12.4)</td>
<td>15.0 (22.5 ± 12.9)</td>
<td>p = .559</td>
</tr>
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<td><strong>Admission FIM Cognitive</strong></td>
<td>12.5 (14.3 ± 7.9)</td>
<td>11.0 (13.3 ± 7.8)</td>
<td>p = .625</td>
</tr>
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<td><strong>Days since admission</strong> (mean + SD)</td>
<td>2.7 ± 2.5</td>
<td>3.6 ± 5.3</td>
<td>p = .38</td>
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Results

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<tr>
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<tr>
<td>History of Liver Disease</td>
<td>0</td>
<td>4 (3.9%)</td>
</tr>
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<td>Hepatotoxic medication</td>
<td>8 (26.7%)</td>
<td>24 (23.3%)</td>
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<tr>
<td>Elevated LFTs</td>
<td>23 (76.7%)</td>
<td>52 (50.5%)</td>
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- Chi square analysis: **No significant group difference** with either history of liver disease or use of hepatotoxic medications
# Results

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- Chi square analysis:

**Significant group difference** was seen with regards to elevated liver function tests (LFTs) \( \chi^2 = 6.48, p = .01 \)
## Results

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<tr>
<td>CVA</td>
<td>2 (6.7%)</td>
<td>14 (13.6%)</td>
</tr>
<tr>
<td>TBI</td>
<td>21 (70%)</td>
<td>39 (37.9%)</td>
</tr>
<tr>
<td>NTBI</td>
<td>7 (23.3%)</td>
<td>50 (48.5%)</td>
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</table>
Majority of cases with normal ammonia levels were found in NTBI patients \( (p<.001) \)
Hyperammonemia

- Majority of cases of hyperammonemia were found in patients with TBI (p<.001)
Odds ratio analysis: individuals with traumatic brain injury 3.83 times more likely to have hyperammonemia (p < 0.001)
Discussion

- Pilot study shows increased frequency (22.6%) of HA in patients with brain injuries.
- Of pts with BI, TBI patients nearly 4X more likely to have HA and accounted for 70% of total cases of HA.
- Although likely multifactorial, some degree of liver dysfunction contributes to significant number of cases of HA in BI.
  (Statistically signif. association with elevated LFT’s)
Limitation of Study

- Pilot study
- Retrospective chart review
  - Only looked at factors pertaining to liver, other factors to be considered
- Convenience sample
  - no specific indications for screening
- Small sample size
Future Direction

- Prospective studies
  - Larger sample size to determine frequency/prevalence in TBI population
  - Assess rehab outcomes in TBI population with HA and normal ammonia levels
  - Assess impact of treatment of HA on neurocognitive function/rehab outcomes
  - Identify other factors associated with HA (Gut/Kidney/Muscle/Meds)
  - Develop guidelines for screening
The first study looking at HA, a known cause of neurotoxicity, in patients with BI

Pilot study shows increased frequency of HA in patients with TBI

TBI population particularly vulnerable to neurotoxic effects of HA (disruption of BBB/pre-existing neuronal damage)

Warrants further studies to assess impact of HA on rehab outcomes in TBI patients
Thank you

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Steven Kirshblum, MD
Neil Jasey, MD
Questions???
References


References


