CONTROVERSY: AMMONIA, TO MEASURE IT OR NOT?

Dr Marika Rudler
Brain-Liver Pitié-Salpêtrière (B-LIPS)
Clinical case (1)

- 31-year-old Asian man with Child-Pugh B hepatitis C cirrhosis
- Hospitalized for variceal bleeding
  - Transfusion/somatostatin/ceftriaxone
  - Band ligation/beta-blockers
- Transferred to liver unit on day 25
Clinical case (2)

- No bleeding
- Jaundice/mild ascites
- Confusion, insomnia, decreased alterness=0
- Asterixis=0
- PT=55%, INR=1.7, BiliT=70 μmol/L, creat=90μmol/L, albumin=29g/L
- Child-Pugh C10/MELD 18
- Evaluation for liver transplant
  - Ammonia level was measured as part of the routine transplant evaluation
## Laboratory test results

<table>
<thead>
<tr>
<th>Test</th>
<th>Day 1 (Hospital Admission)</th>
<th>Day 25 (Transfer to Liver Unit)</th>
<th>Day 38</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count, $\times 10^3/\mu$L</td>
<td>60.42</td>
<td>15.45</td>
<td>14.68</td>
<td>4.16-9.95</td>
</tr>
<tr>
<td>Hemoglobin, $g/dL$</td>
<td>10.9</td>
<td>9.9</td>
<td>8.1</td>
<td>13.5-17.1</td>
</tr>
<tr>
<td>Platelet count, $\times 10^3/\mu$L</td>
<td>70</td>
<td>319</td>
<td>123</td>
<td>143-398</td>
</tr>
<tr>
<td>Creatinine, $mg/dL$</td>
<td>1.0</td>
<td>1.6</td>
<td>0.9</td>
<td>0.5-1.3</td>
</tr>
<tr>
<td>Serum ammonia, $\mu g/dL$</td>
<td>NA</td>
<td>55</td>
<td>221</td>
<td>39-90</td>
</tr>
<tr>
<td>Total bilirubin, $mg/dL$</td>
<td>6.2</td>
<td>10.9</td>
<td>3.3</td>
<td>0.2-1.1</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>1215</td>
<td>34</td>
<td>33</td>
<td>7-36</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>1364</td>
<td>28</td>
<td>17</td>
<td>4-45</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>82</td>
<td>114</td>
<td>144</td>
<td>31-103</td>
</tr>
<tr>
<td>Total protein, $g/dL$</td>
<td>3.4</td>
<td>5.2</td>
<td>6.0</td>
<td>6.2-8.6</td>
</tr>
<tr>
<td>Serum albumin, $g/dL$</td>
<td>2.2</td>
<td>2.6</td>
<td>2.3</td>
<td>3.7-5.1</td>
</tr>
<tr>
<td>INR</td>
<td>1.9</td>
<td>1.2</td>
<td>1.2</td>
<td>0.8-1.2</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio; NA, not applicable.
How do you interpret these test results?

• A: The patient has hepatic encephalopathy (HE) and should be treated
• B: The patient has subclinical HE and should be treated
• C: The patient is at high risk for developing HE and should be prophylactically treated
• D: The patient does not have HE so no treatment is necessary
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Dosing serum ammonia

✓ Several conditions influence blood ammonia: cigarette smoking, physical activity

✓ Collection: arterial or venous blood, cooling after collection (ice), immediate centrifugation (<15 min after collection), storage at 4°C (stable concentration for 60 min)

Blanco-Vela et al. Ann Hepatol 2011
Urea cycle

1. Carbamyl Phosphate Synthetase
   - NH₄⁺
   - Carbamyl Phosphate

2. Ornithine Transcarbamylase
   - Ornithine
   - Citrulline
   - Argininosuccinate

3. Argininosuccinic Synthetase
   - Aspartate
   - Argininosuccinate

4. Arginase
   - Arginine
   - Urea
   - Fumarate
Physiopathology of HE: It is at least related to ammonia

\[
\text{NH}_3 + \text{Glutamate} \rightarrow \text{Glutamine}
\]

Astrocytic swelling

Glutamine \(\rightarrow\) NH4 + Glutamate
Glutamate \(\rightarrow\) NH4 + αCétoglutarate

Urea cycle

NH3 + Glutamate \(\rightarrow\) Glutamine

Astrocytic swelling
Cause of hyper ammonia

- Urea cycle disorders
- Urinary tract infection
- Renal disease
- Chemotherapy
- Valproic acid
- Urine output
- Glutamine synthetase
- Sarcopenia
  - Physical exercise

Ferency, UpToDate 2014
Even when blood samples are correctly obtained...many aetiologies for elevated ammonia...
Should we measure ammonia in cirrhosis?

3 issues

Does elevated ammonia mean HE?
Does normal ammonia rule out HE?

Does ammonia correlate with prognosis?

Is it predictive of HE after procedure at risk of developing HE (TIPS)?
Evaluation of plasma ammonia levels in patients with acute liver failure and chronic liver disease and its correlation with the severity of hepatic encephalopathy and clinical features of raised intracranial tension

Arun Kundra, Anil Jain, Alok Banga, Girish Bajaj, Premasish Kar*

Pearson's correlation coefficient ($r$) at $p<0.05$: ALF=0.91; CLD=0.30

...However, among patients with CLD, the proportion of patients with PAL more than upper limit of normal range is not significantly different between those with or without HE
Physiopathology of HE: It is at least related to ammonia

\[ \text{NH}_3 + \text{Glutamate} \rightarrow \text{Glutamine} \]

Astrocytic edema

\[ \text{Glutamine} \rightarrow \text{NH}_4 + \text{Glutamate} \]
\[ \text{Glutamate} \rightarrow \text{NH}_4 + \alpha \text{Cétoglutarate} \]

Urea cycle

NH\text{3} + \text{Glutamate} → Glutamine

Astrocytic edema
Spectroscopy

Cr: cerebral metabolism
Cho: membrane metabolism
Lac: glycolysis
ml: glial inflammation
NAA: neuronal suffuring or death
Glu/Gln=Glx
No correlation between Glx and NH3

23 patients Ammonia MRS No correlation NH3

Rudler, DDW 2016
### NH3: neurological prognosis in cirrhosis?

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>58 ±13</td>
</tr>
<tr>
<td>Male gender</td>
<td>74</td>
</tr>
<tr>
<td>Cause of cirrhosis (%)</td>
<td>70/26/4%</td>
</tr>
<tr>
<td>Alcohol/Virus/other</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh (%)</td>
<td>9/31/60%</td>
</tr>
<tr>
<td>A/B/C</td>
<td></td>
</tr>
<tr>
<td>MELD score</td>
<td>21 ±9</td>
</tr>
<tr>
<td>Ammonia µmol/l</td>
<td>99 ±57</td>
</tr>
<tr>
<td>Elevated ammonia (%)</td>
<td>64%</td>
</tr>
<tr>
<td>Patent HE (%)</td>
<td>69%</td>
</tr>
<tr>
<td>HE as a cause for hospitalisation (%)</td>
<td>27%</td>
</tr>
<tr>
<td>Medications for HE before admission (%)</td>
<td>17%</td>
</tr>
</tbody>
</table>

*Tripon, SRLF 2016*
✓ Ammonia correlates with neurological evaluation.

West-Haven score

Glasgow score

$p<0.0001$
34 patients worsened neurological presentation after admission. Ammonia at admission was significantly higher: 128 (95%CI: 108-147) vs 87 (95%CI: 64-110), p=0.007.

In multivariate analysis, neurological worsening was associated with:

- MELD score (p=0.01)
- Ammonia at admission (p=0.02)

If we had tried to normalize ammonia in those patients, what would have been the evolution?
Normal ammonia does not rule out the diagnosis of HE in case of neuropsychological manifestations in chronic liver disease.

Elevated ammonia does not diagnose HE in case of neuropsychological manifestations in chronic liver Disease.

No good correlation with neurological prognosis.

No data regarding cut-off, PPV, NPV in the literature.
What are alternative diagnostic approaches?
EEG: typical patterns in HE (triphasic waves slow activity)

EEG: helps for differential diagnosis of NC status epilepticus
Example of two EEG recording showing an electrical generalized seizure (A) or an HE (B). Their main characteristics are summarized in the right boxes. The dotted line indicates the auditory stimulation.

**SE pattern:**
- Sharp and polysharp waves
- Generalized or partial
- Rapid rhythmic activity
- No reactivity to stimulations

**HE pattern:**
- Fluctuating triphasic waves
- Predominantly anterior
- Slow activity (2-3Hz)
- Reactivity to stimulation
  (Inconstant in severe HE; not seen in this example)
Electroencephalogram variability in patients with cirrhosis associates with the presence and severity of hepatic encephalopathy

Søren Schou Olesen¹,* , Mikkel Gram¹, Clive Douglas Jackson², Edwin Halliday³, Thomas Holm Sandberg¹, Asbjørn Mohr Drewes¹,⁴, Marsha Yvonne Morgan³

222 pts
Gradual loss of the alpha rhythm
Replacement with Theta and delta Activity
The decrease in “variability “ correlates with HE

Diagnostic utility?
Cr: cerebral metabolism  
Cho: membrane metabolism  
Lac: glycolysis  
ml: glial inflammation  
NAA: neuronal suffering or death

3 classical patterns
- decrease myoinositol (ml)  
- decrease choline (Cho)  
- increase glutamate/glutamin (Glx)
How to predict HE after TIPS?

Pierre Berlioux, Marie Angèle Robic, Hélène Poirson, Sophie Métivier, Philippe Otal, Carine Barret, Frédéric Lopez, Jean Marie Péron, Jean Pierre Vinel, and Christophe Bureau
Significant decrease in FA before TIPS in patients who will develop HE after TIPS

Incinate fasciculus
Incinate fasciculus
Cingulate gyrus
Body of corpus callosum
External capsule
Occipito frontal fasciculus

* p<0.05

Absence of dev of HE
Dev of HE

Rudler DDW 2016
Ammonia does not help for the diagnosis of HE
Ammonia may predict neurological evolution in the ICU
Ammonia does not predict HE after TIPS
Our patient...

As a result of the ammonia findings, he received lactulose, which caused him considerable discomfort and frustration, without clinical benefit or improvement to his serum ammonia levels. The treatment was discontinued.

He never developed HE..
Thank you!