A Review of Hepatic Encephalopathy

2017 edition
What is yellow and flaps?
Goals of this presentation

- Review the possible mechanisms of the pathogenesis of hepatic encephalopathy
- Review the clinical manifestations of hepatic encephalopathy
- Understand how to make a diagnosis of encephalopathy
- Understand the treatment strategies of hepatic encephalopathy
Impaired brain function occurring in liver failure encompassing a spectrum of clinical features from multiple chemical, neurochemical, neurodegenerative, and structural etiologies
Pathogenesis

- Can be multi-factorial due to chemical, cerebral edema, impaired blood flow, atrophy, toxic metabolite, and impairment of neurotransmitter factors

- Several metabolic factors implicated

- Difficult to separate out the different factors clinically

- There is no single, “correct” hypothesis – multiple mechanisms have been proposed with various support, but a multi-factorial concept is currently favored overall
Pathogenesis

- Cerebral edema is implicated in late state encephalopathy, especially with coma.

- Increases in intracellular osmolarity secondary to metabolites has been suggested as one cause of cerebral edema.

- Impaired blood flow from shunting and systemic hypotension is also related to late stage encephalopathy, as well as decreased oxygen delivery.

- Several metabolic and neurotransmitter pathways have been identified as well.
Ammonia hypothesis

- Ammonia is highly implicated in HE
- Gut derived from glutamine and catabolism of ingested protein and secreted urea by gut flora
- H. pylori may be a source with urea digestion, but connection is poorly described
Ammonia hypothesis

- Liver responsible for ammonia clearance from portal system before it hits systemic circulation by converting ammonia back to glutamine.

- Liver disease can cause both porto-systemic shunting and decreased metabolism due to hepatocyte dysfunction.

- **Arterial** ammonia levels are elevated in ~90% of patients with hepatic encephalopathy.
Ammonia hypothesis

\[ \text{NH}_4^+ \rightleftharpoons \text{NH}_3 + \text{H}^+ \]

OR

Ammonium \rightleftharpoons \text{Ammonia} + \text{hydrogen ion}
Ammonia hypothesis

- Interferes with CNS function at multiple sites
- Toxicity can be potentiated by other toxins, including mercaptananes and short chain fatty acids
- Also affects amino acid transport, increasing the uptake of some amino acids, including tryptophan, tyrosine, and phenylalanine, which can affect dopamine, norepinephrine, and serotonin synthesis
Can precipitate cerebral edema in astrocytes due to mitochondrial metabolism converting ammonia into glutamine.

Glutamine in astrocytes has been shown to potentiate mitochondrial oxidative injury by free radical formation.

Ammonia has also been shown to cause oxidative injury in mRNA and rRNA in rat and mouse models.
Effects on astrocytes
Neurotransmitters

- GABA-A/benzodiazapene receptors implicated
- Progesterone-derived neurosteroids implicated
- Catecholamines, serotonin, histamine, and melatonin also implicated
GABA hypothesis

- Causes increased sensitivity to benzodiazepenes, both endogenous and exogenous
- May be related to an astrocyte translocator protein leading to increased cholesterol uptake, upregulation of neurosteroids leading to modulation of the GABA-A receptor system
Nitric oxide

- Increase in intracellular osmolarity in astrocytes leading to edema, including involvement of activation of NMDA receptors (N-methyl-D-aspartate)
- NMDA receptors increase Nitric Oxide formation through up-regulation of Nitric Oxide synthetase, leading to vasodilation, which leads to increased cerebral free water accumulation leading to hyperemia
Effects on astrocytes

Colquhoun, Steven, Connelly, Caroline. Acutely Failing Liver 2nd ed 11/1/99
Other proposed factors

- Increased permeability of blood-brain barrier to amino acids by unknown mechanism
- Altered CNS glucose utilization
- Generation of glutamine related free radicals
- Oxindole (tryptophan metabolite) accumulation
Precipitating factors

- Drugs
- Vascular
- Ammonia altering factors
- Dehydration
- Gut flora alteration
- Malignancy
Precipitating factors

- Drugs:
  - Benzodiazepenes – implicated in GABA
  - Narcotics – mu receptors
  - Alcohol
  - Any drug affecting electrolytes
  - Anticholinergic/antihistamines
Precipitating factors

- Vascular
  - Portal vein thrombus
  - Hepatic vein thrombus
  - Portosystemic shunting (physiologic/anatomic)
  - Portosystemic shunting – iatrogenic – TIPS
    (makes ascites better, but encephalopathy worse!)
Precipitating factors

- Ammonia production/absorption
  - Dietary protein – leads to increased nitrogen load
  - GI bleed – protein digestion from hemoglobin
  - Infection
  - Constipation – decreased GI ammonia excretion
  - Electrolyte disturbances, acidosis, alkalosis (affect REDOX reaction between ammonia/ammonium)
  - Potassium disturbances can profoundly alter the REDOX balance of ammonia/ammonium ions by pushing the reaction more towards ammonia, which can cross cell membranes, especially in alkalosis
Precipitating factors

- Dehydration
  - Vomiting
  - Diarrhea
  - Diuretics
  - Large volume paracentesis
  - Hypovolemia is one of the leading precipitants of acute hepatic encephalopathy
Precipitating factors

- Hepatocellular carcinoma - consider checking an alpha-fetoprotein

- Alterations in gut bacteria – can cause altered ammonia metabolism in gut
  - Antibiotics
  - Constipation and bacterial overgrowth
Classifications

- 3 types recognized based on underlying cause
- Clinically, we see type C most commonly in the hospital

- Type A: hepatic encephalopathy occurring in the setting of acute liver failure
- Type B: hepatic encephalopathy occurring in the setting of portal-systemic bypass with no intrinsic hepatocellular disease
- Type C: hepatic encephalopathy occurring in the setting of cirrhosis with portal hypertension or systemic shunting
Clinical manifestations

- 4 stages of hepatic encephalopathy, graded from 1-4
- 4 major symptom complexes associated, each with its own staging:
  - Level of consciousness
  - Intellectual function
  - Personality/behavior
  - Neuromuscular disturbance
Clinical manifestations

Evolution of encephalopathy

Taken from Uptodate.com – Ferenci, Peter. Clinical Manifestations and Diagnosis of Hepatic Encephalopathy. 10/08
Clinical manifestations

- Stages of Hepatic Encephalopathy

Taken from Uptodate.com – Ferenci, Peter. Clinical Manifestations and Diagnosis of Hepatic Encephalopathy. 10/08
Level of consciousness

- Stage 0 – Normal
- Stage 1 – Hypersomnia, insomnia, or altered sleep pattern
- Stage 2 – Slow response, lethargy
- Stage 3 – Disorientation, somnolence, confusion
- Stage 4 – Semi-stupor to stupor, coma
Intellectual function

- Stage 0 – normal
- Stage 1 – Subtle impairment of computations
- Stage 2 – Decreased attention span, loss of time sensitivity
- Stage 3 – Loss of orientation to place, inability to process or compute
- Stage 4 – Loss of orientation to self
Personality/behavior

- Stage 0 – normal
- Stage 1 – Euphoria or depression, exaggerated behavior
- Stage 2 – Irritability, talkative, decreased inhibition
- Stage 3 – Overt personality change, anxiety, apathy, bizarre behavior
- Stage 4 – Paranoid, anger, rage
Neuromuscular

- Stage 0 – normal
- Stage 1 – Muscular incoordination
- Stage 2 – Impaired handwriting, asterixis, slurred speech
- Stage 3 – Hypoactive reflexes, ataxia, hyperactive reflexes, nystagmus
- Stage 4 – Babinski clonus, rigidity, dilated pupils, coma
Ask about symptoms

- Insomnia
- Trouble with math/bills (computational abnormalities)
- Alterations in mood
- Neurologic changes
- GI bleeding
- Signs/symptoms of infection
Bowel habits are crucial to determine
Look for compliance with meds, especially lactulose
Dietary compliance
Physical Exam

- Look for stigma of chronic liver disease if hepatic disease status is unknown and hepatic encephalopathy is expected

- Neuro exam
  - Asterixis – hands (late stage I, early stage II, tends to be gone by stage IV) and tongue
  - Bradykinesia
  - DTR abnormalities (hypo/hyper)
  - Focal neuro deficits
  - Decerebrate posturing in extreme cases (Stage IV)
Laboratory analysis

- Order a CBC to look for leukocytosis suggesting infection or anemia suggesting a GI bleed
- BMP to look for electrolyte or acid/base disturbance
- LFTs to look for marked change in liver function that may suggest acute thrombus
If a patient with hepatic encephalopathy has ascites that can be accessed by paracentesis, obtaining a diagnostic paracentesis is ESSENTIAL!!!! to evaluate for the presence of SBP, a common precipitating factor!
What about the ammonia level

- Does an ammonia level help the clinical diagnosis of hepatic encephalopathy?

- Does following ammonia levels help determine the course of hepatic encephalopathy?
Not really.

- The hepatology community mostly feels that venous ammonia does not provide any additional clinical information that cannot be obtained from a history and physical. There are certain situations it might be helpful, though...(you have to wait 3 slides)

- Unless you believe Case Western University, who seems to be the only place putting out positive data and recommendations to check/follow venous ammonia levels in conjunction with arterial levels. Refer to Ong JP et.al Correlation between ammonia levels and the severity of hepatic encephalopathy. Am J Med 2003 Feb 15; 114(3):188-93
Why ammonia stinks

- Hepatic encephalopathy is a clinical diagnosis, and ammonia is not part of the diagnostic criteria.
- Venous ammonia is unreliable, because it is inconsistent and affected by multiple physiologic factors.
- Arterial ammonia may be more reliable, but requires an arterial stick and still required rapid transport on ice to the lab. Partial pressure of NH₃ would be the gold standard, but is only really used in research.
Things that affect venous ammonia values

- Reye’s syndrome
- GI bleeding
- Renal disease
- Proteus infection
- Ureterosigmoidostomy
- Shock
- Exertion
- Tobacco smoking
- Genetic urea cycle defects
- ANY portosystemic shunting
- TPN
- Multiple drugs including narcotics and diuretics and salicylates
- Ethanol
- Fist clenching during phlebotomy
- Tourniquet
Times ammonia might be helpful

- A sedated patient on a vent, where sedation precludes good analysis of the patient's neurologic status.
- Situations where there are other potential etiologies of mental status change (meds, alcohol withdrawal, etc).
- Obtaining a baseline ammonia may help direct ammonia-reducing strategies in patients with sub-clinical hepatic encephalopathy.
CT useful to evaluate for other causes of mental status changes – not always indicated, should be driven by a good neurologic exam and history. It is NOT cost effective to get a CT on every hepatic encephalopathy patient.

MR spectroscopy – evaluates metabolites of brain, great for research but not so much for clinical purposes.

CXR helpful to evaluate for infiltrates.

Abdominal ultrasound can help evaluate for ascites that may suggest SBP - and, if you don’t feel comfortable performing a paracentesis, your friendly radiologists can help!
Minimal (formerly subclinical) hepatic encephalopathy

- Represents low grade, pre-staging encephalopathy
- Seen in some, but not all patients with cirrhosis
- Difficult to detect clinically
- May be correlated with quality of life markers, as well as driving safety
- Consider testing in advanced patients (especially transplant listed) who are still driving
Testing for minimal encephalopathy

- Neuropsychiatric testing – accurate, but poorly available and expensive – eg Number Connection Test
- Hepatic encephalopathy specific psychometric testing – specialized training required
- EEG – may pick up low grade cases, but not reliable at minimal levels
- Visual evoked potentials
- Visual critical flicker frequency
- 3-nitrotyrosine testing sensitive and specific for minimal hepatic encephalopathy
Check an ammonia level – if it is high, try lactulose. See if their quality of life/sense of well-being improves.

Thanks Rupa!
Treatment - General

- Always make sure the underlying cause/trigger is being addressed, especially hypovolemia and uremia
- Treat any infections – DO NOT MISS SBP!
- Avoid heavy protein diets – efficacy of protein restriction is equivocal
- Treat GI bleeding
- Avoidance of trigger medications
- Correct electrolyte disturbances and dehydration
- Correct hypoxia
- Treat vascular occlusion if present
Grade I requires either close outpatient monitoring or brief hospital observation.

Grade II generally requires hospitalization.

Grade III-IV definitely requires hospitalization, often in the ICU.

In Grade III-IV, intubation for airway protection may be indicated.
Treatment - lactulose

- Synthetic disaccharide
- Improves symptoms, but no documented effect on mortality
- Titrate to 2-3 soft BM/day
- Can be given PO or in enema
- Normal PO dose 45-90 grams/day
- 70-80% likelihood of patient response
Treatment - lactulose

Mechanism:
- Lowers enteric pH, trapping ammonia in ammonium ion (NH₄⁺) form which does not get absorbed
- Affects ammonia bacterial absorption
- Affects colonic flora, displacing urease-producing bacteria
- Increases fecal nitrogen excretion due to increased stool volume
- Reduces short chain fatty acid formation
- Cures constipation
Rifaximin is better than placebo
Combined therapy with lactulose and rifaximin led to improved resolution of HE (76% vs 44%) and lower mortality rates (24% vs 49%) in hospitalized patients (randomized trial data)
Does appear to improve quality of life, especially for minimal change patients
Similar to lactulose efficacy wise as monotherapy
Seems to reduce recurrence rates in patients with chronic cirrhosis
Generally beneficial, might reduce mortality (based on meta-analysis of 19 trials)
Neomycin, metronidazole, vancomycin, have been shown to be questionably effective.

Strong evidence lacking for neomycin and metronidazole.

Proposed mechanism of gut flora changes.

Can cause side effects, toxicities, can cause bacterial overgrowth syndromes.

Should only be used as second line therapies if disaccharides have failed for over 48 hours.
Treatment – branched chain amino acids

- Treatment with BCAA to correct amino acid imbalances
- Not standard of care
- Conflicting study data on meta-analysis (one study shows increased mortality, one decreased)
Theoretically helpful under GABA-A hypothesis
In trials, seems to only help people who would likely have a good prognosis anyway
Not routine part of therapy
May be useful in benzodiazepene intoxication leading to hepatic encephalopathy, but watch closely for acute benzodiazepene withdrawal
Ornithine-aspartate

- Not available in US
- Limited trials
- Shifts ammonia to glutamine
- Might be useful in chronic cirrhosis, does not appear to help in acute hepatic failure
Acarbose – keeps polysaccharides in gut, still in early phases – not much progress since 2005

Probiotics - still in early phase trials, mostly in India. No recommendations yet

Sodium benzoate – mechanism is to waste nitrogen in urine - no placebo controlled trials yet, nor much progress since the early 90’s

Other neurotransmitter therapies are in research phases, including melatonin

Polyethylene glycol (PEG) as a cathartic to reduce constipation
Zinc – might help with zinc deficient patients, but no good data

Naltrexone studied in rat models as being possibly helpful

NMDA antagonists (memantine) being studied
Prognosis

- Variable, depends on the level of underlying hepatic impairment and subtype (acute hepatic failure vs cirrhosis)
- Hepatic Encephalopathy development in liver disease does predict increased mortality rate, but it is very variable based on type
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