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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

Definition 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

$NH_4^+ \Leftrightarrow NH_3 + H^+$

OR

Ammonium ⇔ Ammonia + hydrogen ion

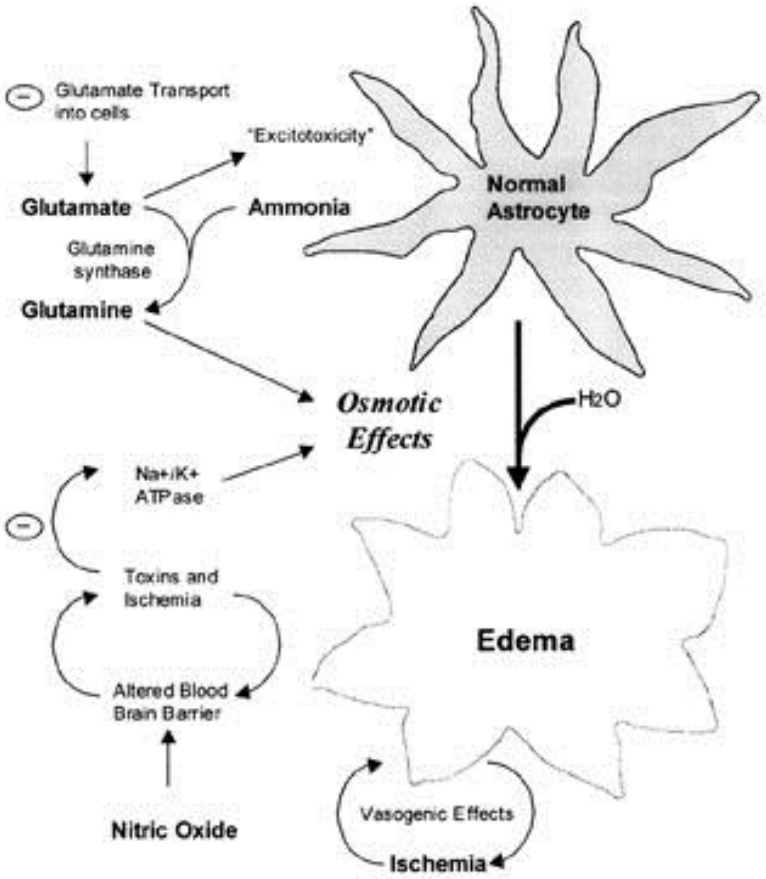
Ammonia hypothesis

- Interferes with CNS function at multiple sites
- Toxicity can be potentiated by other toxins, including mercaptanes 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

Ammonia hypothesis

- 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



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Neurotransmitters

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

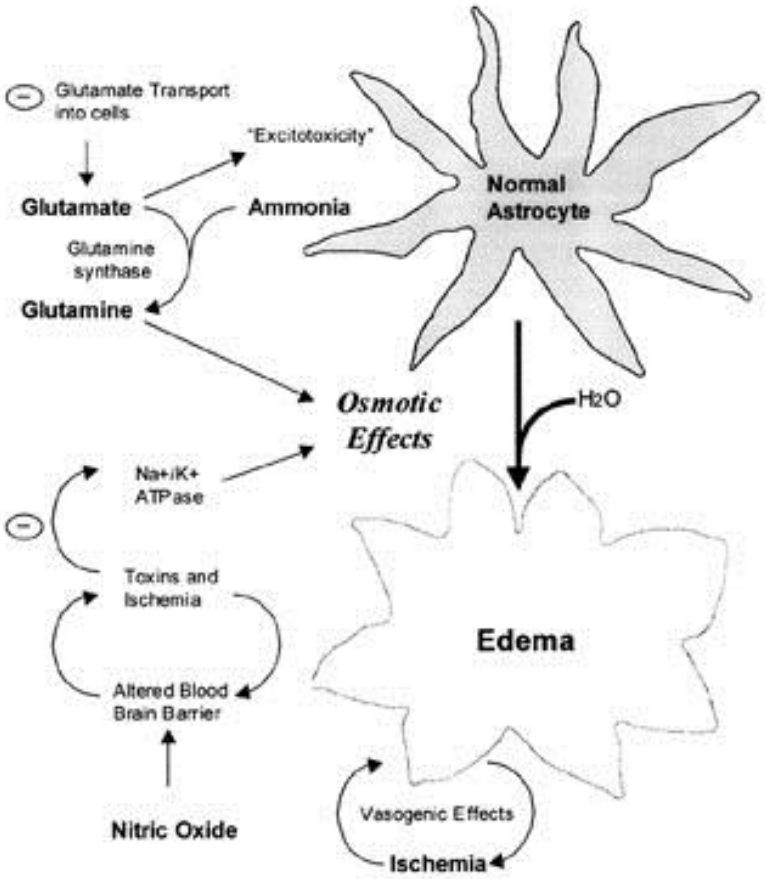
GABA hypothesis

- 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



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Other proposed factors

- Increased permeability of blood-brain barrier to amino acids by unknowm 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

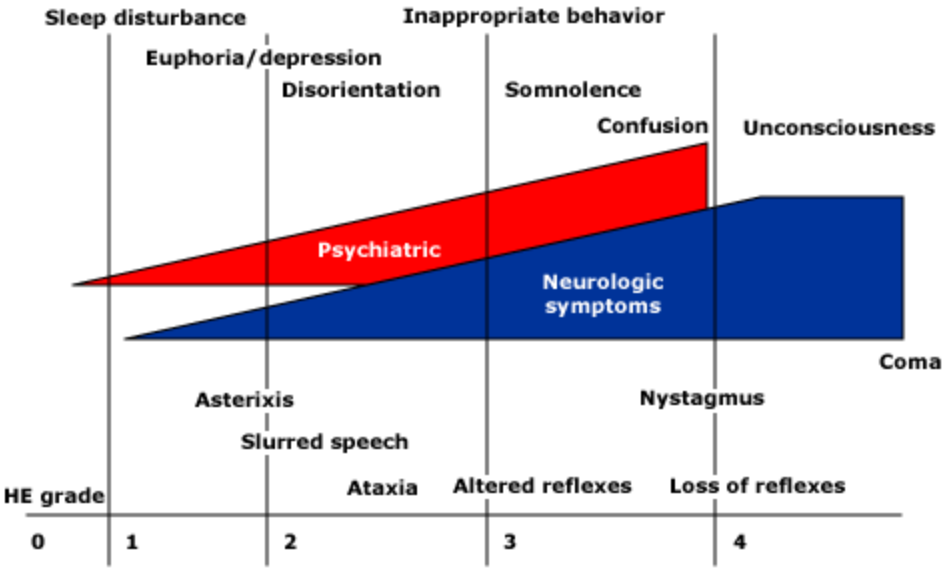
  - Type A: hepatic encephalopathy occurring in the setting of acute liver failure
  - Type B: hepatic encephalopathy occurring in the setting of portal-systemic bypass with no intrinsic hepatocellular disease
  - Type C: hepatic encephalopathy occurring in the setting of cirrhosis with portal hypertension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

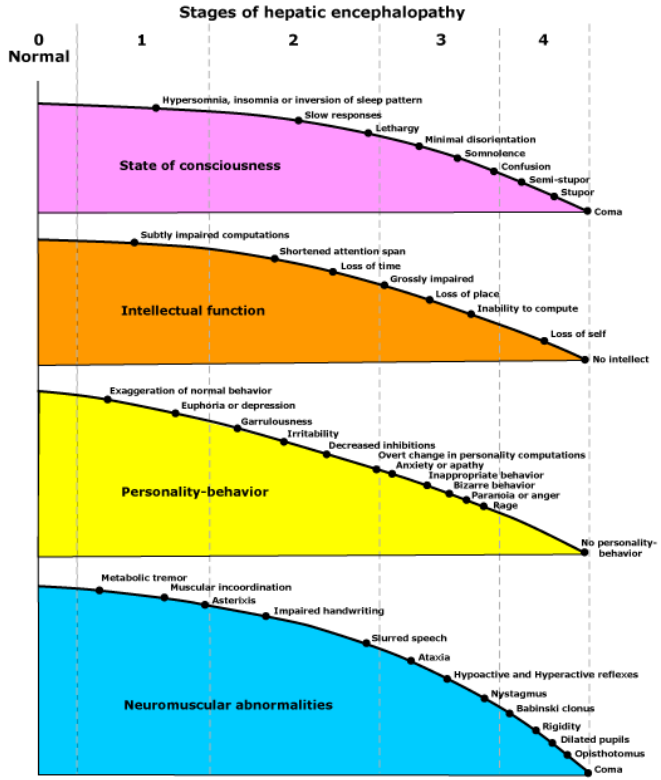
Evolution of encephalopathy



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

Clinical manifestations

- Stages of Hepatic Encephalopathy



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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, decresed inhibition
- Stage 3 – Overt personality change, anxiety, apathy, bizarre behavior
- Stage 4 – Paranioa, 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

History

- Ask about symptoms
  - Insomnia
  - Trouble with math/bills (computational abnormalities)
  - Alterations in mood
  - Neurologic changes
  - GI bleeding
  - Signs/symptoms of infection

History

- 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

Procedures

- 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?

The answer is…….

- 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 serverity 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 NH_3 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
- Tourniqet

Times ammonia might be helpful

- A sedated patient on a vent, where sedation precludes good analysis of the patients neurologic status
- Situations where there are other potential etiologies of mental status change (meds, alcohol withdrawl, etc)
- Obtaining a baseline ammonia may help direct ammonia-reducing strategies in patients with sub-clinical hepatic encephalopathy

Imaging

- 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

Cheaper testing for minimal 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

Treatment - General

- 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% likelyhood of patient response

Treatment - lactulose

- Mechanism:
  - Lowers enteric pH, trapping ammonia in ammonium ion (NH_4+) 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

Treatment - rifaxamin

- Rifaxamin 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)

Treatment –antibiotics (not rifaximin)

- 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)

Treatment - Flumazenil

- 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 withdrawl

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

Treatment – up and coming

- 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

Treatment – up and coming

- 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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