Progression of Neuropsychiatric Manifestations of Hepatic Encephalopathy: A Care Report

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Background

Hepatic encephalopathy (HE), a disturbance in central nervous system function due to hepatic insufficiency, exhibits a spectrum of neuropsychiatric abnormalities and neuromuscular signs. Affected individuals can exhibit symptoms ranging from mild neurocognitive impairment to delirium to coma. This complication is associated approximately 50% mortality within a year for severe cases. Despite this, the Model For End-Stage Liver Disease, or MELD score, which is used to stratify end-stage liver disease for transplant candidacy does not include hepatic encephalopathy. This aims to describe manifestations of HE to assist in recognition in patients with hepatic insufficiency.

Case Presentation

- D is a female in her 40s with a history of severe alcohol use and cirrhosis, and restrictive food intake resulting in chronic nutritional deficiencies
- Minimal known previous psychiatric treatment
- History of alcohol use disorder in multiple family members
- Highly educated employed prior to diagnosis of cirrhosis
- Over the course of about 6 months, the patient was seen over several encounters during multiple hospitalizations
- On multiple admission, D would admit to medication non-adherence for chronic cirrhosis treatment

	First Encounter	Second/Third Encounters	Fourth Encounter
Reason for admission	Bacteremia	Thrombocytopenia due to hepatic decompensation and hematuria	Altered mental status
Reason for psychiatric consult	Altered mental status	Altered mental status	Altered mental status
Mental Status Exam Pertinent Findings	Paranoid Ideation (responsive to reassurance)	paranoid ideation (not responsive to reassurance) and persecutory delusions	Bizarre behavior noted by nursing, soft speech , preservative on paranoid ideation
Cognitive Exam	Alert and oriented; able to perform on attention task; no defects in memory noted	Alert, disoriented to place, impairment on attention tasks and short term recall	Disorientation, decreased alertness, impairment on attention tasks,
Ammonia	25 (normal)	77-140 (elevated)	42 (mildly elevated)
Neuromuscular Exam	No tremor; No asterixis	No tremor	+Tremor; +asterixis
Head Imaging – CT	N/A	Neg for acute process	Neg for acute process
EEG	N/A	N/A	Generalized triphasic discharges, background slowing
Outcome	Encephalopathy attributed to infectious causes, improved with antibiotics	Lactulose increased; encephalopathy somewhat improved	Mental status improved with embolization of gonadal vein

Contributions to Pathogenesis

- Liver failure is associated with compromise of cerebral metabolism and alterations to neuroglia. Pathogenesis is incompletely understood – proposed contributions are discussed below

Hyperammonemia

- Colonic bacteria and mucosal enzymes digest proteins to release ammonia which enters the portal circulation of the liver and is converted to urea via the urea cycle
- In hepatic failure ammonia accumulates in circulation

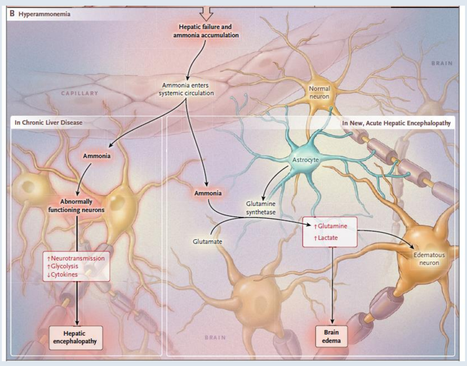

Figure 1: Potential pathway for hepatic encephalopathy via hyperammonemia; (Wijdicks, 2016)

- Hyperammonemia leads to cerebral edema (increased risk with levels >200 µmol)
- Ammonia is neurotoxic leading to decreased excitatory neurotransmission
- Ammonia causes inhibition
- of glucose (pyruvate) oxidation, stimulation of glycolysis, altered mitochondrial function, and impairment of key cellular transport systems

Neuroinflammation

- At high levels, ammonia can cross the blood-brain barrier
- astrocytic glutamine synthetase utilizes ammonia to produce glutamine (as shown in figure 1)
- Peripheral infection such as sepsis (a potential precipitating event) leads to cytokine release which enhance ammonia neurotoxicity
- Ischemic liver failure leads to a loss of expression of the glial fibrillary acidic protein (GFAP) gene in astrocytes and the extent of the loss of expression is correlated with the extent of hyperammonemia in animals
- Loss of GFAP expression was described in autopsied brain tissue samples from patients who died as a result primarily of brain herniation due to acute liver failure
- Microglial activation has also been reported in autopsied brain tissue from a patient with acute liver failure from viral hepatitis.

Manganese Toxicity

- Patients with long-standing cirrhosis have been found to have manganese toxicity (normally excreted by the hepatobiliary system) which appears as abnormalities in the globus pallidus on MRI

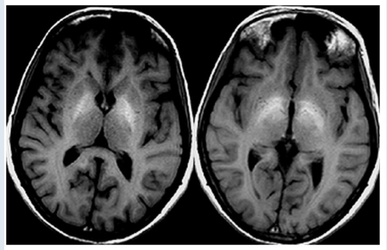

Figure 2: . Transverse T1-weighted MR images of the brain in a patient with chronic liver failure and parkinsonism – showing bilateral signal-intensity change involving globus pallidus and the anterior midbrain. (Rovira et al, 2008)

Other

- HE is associated with increased BBB permeability to gamma-aminobutyric acid (GABA)
- In a study with treatment with flumazenil, patients demonstrated both clinical and electroencephalographic improvement, though responses were unsustained
- Mercaptans, short fatty acid chains, have been implicated in HE and produce decreased glutaminergic synaptic function

Clinical Features

Precipitating Events: infections, gastrointestinal bleeding, constipation, diuretics, electrolyte imbalance

West Haven Criteria for Grading Hepatic Encephalopathy	
Grade	Features
0	No encephalopathy
1	Mild unawareness, euphoria or anxiety, shortened attention, impairment of calculation, sleep disturbances
2	Disorientation to time, inappropriate behavior, personality change, asterixis
3	Stupor, gross disorientation, bizarre behavior
4	Coma

Table 2 – adopted from Blei et al, 2001

- Neuromuscular manifestations can include myoclonus, asterixis, and focal neurological deficits
- Electroencephalography (EEG) findings:
  - dyssynchronization of fast activity, increased dysrhythmicity, more frequent delta activity, disorganization
  - Generalized, bilateral triphasic waves often associated with background slowing in grade 2-3 HE
- The practical use of EEG is to rule out epilepsy

Discussion

- In consideration of the pathophysiology, when examining the patient's multiple presentations, this case demonstrates a progression of neuropsychiatric sequelae of chronic hepatic insufficiency
- Initially precipitating factors for patient presentation were infection showing mild cognitive impairment which progressed to disorientation after multiple insults and chronic cirrhosis
- This patient likely had mild hepatic encephalopathy by her first encounter with psychiatry. By the fourth encounter, patient demonstrated overt grade 3 HE as defined by the West Haven criteria
- This patient returned to a functionally lower baseline after each hospitalization
- In retrospect, her difficulty with medication management may have been correlated with progression of encephalopathy which led to acute hepatic failure and furthered the severity of her encephalopathy
- This cycle has led to corrosion of this patient's overall condition while she continues to wait to become a candidate for transplant
- Treatment during each hospitalization was aimed at improving liver function
- The case outlines the importance of grading severity of hepatic encephalopathy during an evaluation of a patient with cirrhosis. With advancing knowledge in sequalae of cirrhosis, the case can help us discuss a model for detection and early treatment

Treatment

- Correction of precipitating factors
- Lactulose – change gut microbiome reducing ammonia production
- L-ornithine-L-aspartate – alternative substrate for urea cycle (if not responding to lactulose)
- Rifaximin (in addition to lactulose) for chronic cirrhosis – alters microbiome, shown to decrease frequency of hospitalizations
- If ammonia level 150-200 µmol – be vigilant in monitoring for cerebral edema and potential transfer to intensive care unit
- For patient with refractory HE - current literature supports the utility of shunt embolization of large portosystemic shunt (PS) in patients with HE associated with PS syndrome, more data required for specifics of PS-related HE
- Liver Transplantation

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