Diagnosing and Managing Hepatic Encephalopathy

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Patient DC

• 60 year old male with history of cirrhosis secondary to alcohol use
• Presented with alcoholic hepatitis, jaundice and ascites 18 months ago.
• Alcohol abstinence since then.
• Fluid overload resolved with diuretics (spironolactone 100 mg daily and furosemide 40 mg daily)
Patient DC

- Patient was well until 1 days prior to presentation when he developed lethargy and slurred speech.
- Symptoms worsened until he became disoriented and his family brought him for evaluation
- No fevers, GI bleeding, edema, increased abd girth or alcohol recidivism
Patient DC

- Examination revealed a well appearing male oriented to name only with no evidence of head trauma
- + asterixis
- Labs reveal a platelet count of 68K. Otherwise the CBC and liver panel (including bilirubin) were WNL. INR 1.1. Electrolytes reveal a serum Na 129 and a Cr of 1.8 (baseline 0.9)
- What do you suspect?
Patient DC

- Patient was hospitalized and hydrated with IV albumin and administered lactulose 2 tbsp tid
- Diuretics were discontinued
- Mentation and electrolytes rapidly normalized
- Rifaximin 550 mg bid was added.
- Diuretics were not restarted. The patient was discharged on lactulose and rifaximim.
Patient DC

• Questions
  • What are common precipitating factors of acute overt HE?
  • Is serum NH3 level an important diagnostic strategy in a patient with this presentation?
  • How do you treat acute overt HE?
  • What is an appropriate strategy to prevent recurrence of HE?
Your liver is an amazing factory which is involved in many tasks your body needs:

- Helps in digestion through the production of bile.
- Provides storage for essential nutrients such as iron, vitamins and minerals.
- Stores energy by stockpiling carbohydrates, glucose and fats.
- Metabolizes what you ingest such as drugs and medications.
- Detoxifies ingested substances such as alcohol, chemicals.
- Makes proteins that you need to stay healthy and grow.
- Makes clotting factors that stop bleeding.
What Happens to the Liver When It’s Injured?

• The liver responds to injury by replacing damaged tissue with scar tissue
• What is cirrhosis?
  • Permanent scarring of the liver; hard scar tissue replaces soft healthy tissue
  • Cirrhosis does not identify either the cause of the damage or tell us about the function of the liver
  • People may have cirrhosis, still appear healthy and not know they have liver damage
Stages of Chronic Liver Disease

Causes of Chronic Liver Disease

• HCV and NASH are the most common causes of cirrhosis in the US\(^1\)

• HCV and NASH are growing in prevalence therefore cirrhosis rates are increasing\(^2,3\)

HBV = Hepatitis B; HCV = Hepatitis C; NASH = Nonalcoholic steatohepatitis; NAFLD = Nonalcoholic Fatty Liver Disease

US Hospital Discharges Due to Cirrhosis Are Increasing

Number of Discharges With Cirrhosis*

Year  Number of Discharges
2004  403,665
2005  411,029
2006  436,901
2007  444,883
2008  459,496
2009  498,181
2010  526,096
2011  576,573

10% increase

*ICD-9-CM diagnosis codes 571.2, 571.5, 571.6; all listed diagnoses.

Cirrhosis: Symptoms and Signs

- Anorexia, weight loss
- Weakness, fatigue
- Muscle loss, cramps
- Nausea
- Vague (RUQ) abdominal pain
- Pruritus
- Easy bruising, epistaxis
- GI bleeding
- Confusion, sleep disturbance
- Amenorrhea or irregular menses

- Spider angiomata
- Palmar erythema
- Gynecomastia, testicular atrophy
- Abdominal distention, edema
- Parotid hypertrophy
- Dupuytren’s contractures
- Clubbing, leukonychia
- Jaundice, icterus
- Splenomegaly
- Asterixis, fetor hepaticus
- Cachexia
Focus Will Be Hepatic Encephalopathy

Cirrhosis

Portal hypertension

Liver insufficiency

Hepatopulmonary syndrome
Portopulmonary hypertension
Variceal hemorrhage
Ascites, Hydrothorax
SBP
Hepatorenal syndrome

Encephalopathy

“Coagulopathy”
Jaundice
Hypoalbuminemia
What is Hepatic Encephalopathy (HE)?

- Reversible syndrome of impaired brain function seen in patients with advanced liver disease
- Mechanism:
  - Damaged liver can’t remove toxins from blood, e.g., ammonia
    - Reduced number of liver cells to do the job of toxin removal
    - Shunting of blood from the gut around the damaged liver allows toxins to enter the bloodstream
  - Toxins build up and get into brain causing temporary worsening of brain function resulting in HE
What Can Trigger HE?

• Non-compliance
• Infections
• Constipation
• Dehydration
• Bleeding from stomach, intestines, or esophagus
• Medications that affect your nervous system:
  • Sleeping pills
  • Antidepressants
  • Pain medications

• Kidney problems
• An alcohol binge
• Surgery
• Having a portosystemic shunt:
  • Tube placed in your liver (TIPS)
  • Surgical procedure to reroute blood flow and relieve high blood pressure in veins in/around liver (portal HTN)
Where Do Ammonia and Other Toxins Come From?

- GI tract is primary source
  - Produced by cells in small intestine and bacteria in colon
- Enters the circulation via the portal vein
  - The portal vein takes all the blood coming from the gut and routes it to the liver before it goes out to the rest of the body
  - Intact liver cells clear almost all ammonia and other toxins

http://www.webmd.com/digestive-disorders/digestive-diseases-portal#1
How is HE Diagnosed?

• There is no specific “HE test.”

• Diagnosis is based on a combination of three things:
  • Patient symptoms
  • Patient medical history
    • Caregivers at medical visit helpful
  • A thorough clinical exam
    • Alternative causes of AMS should be sought and treated (e.g. DKA, drugs, neuro infections, electrolyte disorders, intracranial bleeding and stroke
Mental Symptoms of HE

Mild to moderate symptoms
• Short attention span
• Mild confusion
• Forgetfulness
• Mood swings
• Personality changes
• Inappropriate behavior
• Difficulty doing basic math

More severe symptoms
• Marked confusion
• Severe anxiety or fearfulness
• Disorientation regarding time/place
• Coma
Physical Symptoms of HE

Mild to moderate symptoms

• Change in sleep patterns
• Difficulty writing or doing small hand movements
• Breath that smells musty or sweet
• Slurred speech

More severe symptoms

• Extreme sleepiness
• Slowed or sluggish movement
• Shaking of hands or arms (called “flapping” or asterixis)
• Jumbled speech that can’t be understood
• Coma
Characterization of HE Stages

Categorization is often arbitrary and varies between raters.

“Overt” HE Stages

Clinical Diagnosis

Worsening cognitive dysfunction

Why It’s Important to Treat HE

- Patients with confusion and poor function are at increased risk of falls and infections.
- Patients with HE require more hospitalizations and are at increased risk for death.
- Caregivers of patients with confusion have a greater burden resulting in increased stress and loss of work.
- Treatment has been shown to decrease both caregiver burden and hospitalizations in patients.
Treatment Overview

Treatment varies depending upon a number of factors including the precipitating cause, or triggering event as well the severity of symptoms.

Therapies may include:

• Medications to treat infection
• Hydration
• Procedure to control bleeding
• Stopping medications that triggered episode
# FDA Approved Treatment Options for HE

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action¹</th>
<th>Potential Adverse Effects</th>
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<tbody>
<tr>
<td>Lactulose</td>
<td>• Decreases blood ammonia concentration - Promotes elimination of NH₃ - Fermentation by bacteria acidify colon and prevent absorption - Reduces urease-producing bacteria</td>
<td>Overuse can lead to aspiration, dehydration, hypernatremia, and severe perianal skin irritation; overuse can even precipitate HE²</td>
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<tr>
<td>15-30ml PO BID/TID</td>
<td></td>
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<td>Titrate to 2-3 soft BMs/day</td>
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<td>Rifaximin</td>
<td>• Decreases blood ammonia concentration - Broad spectrum antibiotic; results in a change in bowel flora - May cause downregulation of intestinal glutaminase activity</td>
<td>Diarrhea (due to overgrowth of C diff) peripheral edema, nausea, dizziness, fatigue, and ascites³</td>
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<tr>
<td>550mg PO BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neomycin</td>
<td>• Decreases blood ammonia concentration - Inhibits intestinal glutaminase. Use limited. • Should not be used in clinical practice</td>
<td>Risk of C diff Risk of ototoxicity and nephrotoxicity with long-term treatment due to some systemic absorption</td>
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Prevention of Overt HE (OHE)

- Goal of treatment is to minimize symptoms, improve overall quality of life and prevent hospitalizations.
- Lactulose is recommended for prevention of recurrent episodes of HE after the initial episode.
- Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second episode.
- Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-TIPS HE.
- Under circumstances where the precipitating factors have been well controlled (i.e., infections and VB) or liver function or nutritional status improved, prophylactic therapy may be discontinued.
Conclusion

• Hepatic encephalopathy is a key sign of end-stage liver disease.
• HE is readily treatable and active interventions can decrease hospital admission rates.
• Rifaximin, combined with lactulose, is a common care option for HE management in the community.
• Familiarize yourself with guidelines for its diagnosis, classification, and treatment.