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Hepatic Encephalopathy

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Speakers Bureau: Salix, Clinical area: Hepatic Encephalopathy

Learning Objectives

The objectives of this learning activity:

- Describe current screening and diagnosis of Hepatic Encephalopathy (HE)
- Describe the currently available treatment modalities for HE
- Optimize treatment outcomes for patients with HE

Hepatic Encephalopathy (HE)

Defined as a brain dysfunction caused by liver insufficiency and/or portal-systemic blood shunting.

It manifests as a wide spectrum of neurological or psychiatric abnormalities, ranging from subclinical alterations, detectable only by neuropsychological or neurophysiological assessment, to coma.

May be precipitated by an event such as:

- Electrolyte imbalance
- Infection
- Gastrointestinal bleeding
- Drugs
- Acute liver injury

Pathogenesis

Accumulation of gut-derived toxins (e.g. ammonia), inflammation, and oxidative stress

- linked to microbial imbalance in the gut (i.e, dysbiosis)
- involve an impairment in the removal of gut-derived toxins, secondary to liver damage and portal systemic shunting, leading to accumulation of these toxins in systemic circulation
  - high blood levels, the gut-derived neurotoxins can penetrate the blood-brain barrier and alter brain function, thereby leading to clinical symptoms of HE
  - neurotoxins can lead to swelling in the brain, altered neurotransmission, and altered neurotransmitter function

HE SURVIVAL RATES

Following the diagnosis of HE, patients have significantly decreased survival rates, as low as 15% at 5 years

- Patients with grade 3 or 4 HE had a 90-day mortality rate of 24.4% compared with 6.8% in patients with grade 1 to 2 HE and 3.5% in patients with no HE
- This equates to a 66% increased risk of 90-day mortality among patients with more severe HE

1. Bustamante J et al. *J Hepatol.* 1999;30(5):890-895. 2. Jepsen P et al. *Hepatology.* 2010;51(5):1675-1682. 3. Ventura-Cots M et al. *Therap Adv Gastroenterol.* 2017;11:1-12. 4. Stewart CA et al. *Liver Transpl.* 2007;13(10):1366-1371. 5. Bajaj JS et al. *Clin Gastroenterol Hepatol*. 2017;15(4):565-574. 6. Cordoba A et al. *J Hepatol.* 2014;60(2):275-281. 7. Wong RJ et al. *Liver Transpl.* 2014;20(12):1454-1461.

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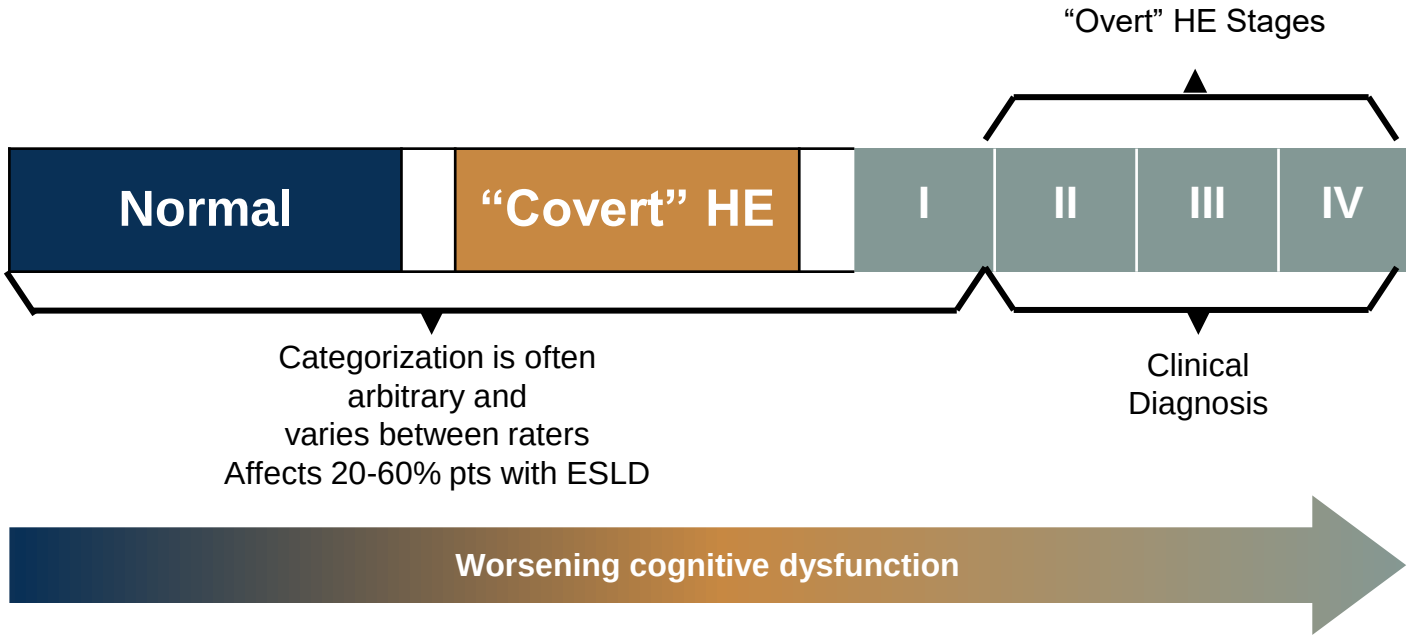
STAGES OF HE

Characterization of HE Stages



Bajaj JS, et al. *Hepatology*. 2009;50:2014-2021.

Covert HE

Minimal symptoms: abnormal results on psychometric or neurophysiological testing wo clinical manifestations (positive psychometric testing when standard neurological examination is completely normal)

Grade I: Changes in behavior, mild confusion, disordered sleep, slurred speech

- Impairment in cognitive capacity (decreased attention, reaction time, working memory,) mood changes, inappropriate behavior, somnolence, confusion, hypersomnia.
- Episodic, recurrent or persistent?
- Work performance, and driving related incidents
- Psychometric test: Reitan test, Stroop test among some used in clinical practice

Overt Hepatic Encephalopathy (OHE)

30% to 45% of cirrhotic patients; 10% to 50% of patients with TIPS

Signs and symptoms: Neuromuscular impairment usually seen on overt HE: bradykinesia, asterixis, slurred speech, ataxia, hyperactive deep tendon reflexes

Grade II: Lethargy, moderate confusion

Grade III: Marked confusion, incoherent speech, sleeping but arousable

Grade IV: Coma, unresponsive to pain

Hepatic Encephalopathy (HE)

Most common reason for hospitalization:

- Non-compliance

The impact of HE on both patients, their care givers, and society as a whole can be profound

PATIENT BURDEN

COGNITIVE DEFICITS

- Increased falls
- Difficulty driving
  - Specifically, in one driving study using driving instructors as evaluators, patients with overt HE or minimal HE (n=51) were less likely to be fit to drive compared with age-matched controls (n=48) with no HE
    (39% of patients with overt HE and 48% of patients with minimal HE were fit to drive vs 75% in the control group).
  - Cognitive defects and prolonged reaction times were the primary cause of driving problems in overt HE. Patients with minimal HE had problems related to attention deficits.
- Impairments in daily function
- Reduced quality of life as a result of cognitive dysfunction

HE and Healthcare Burden

Multiple factors contribute to high HE-related healthcare burden

- High hospitalization rates[1,2]
- Increased hospital length of stay[1]
- More frequent discharge to skilled nursing facilities[1]
- High readmission rates[2,3]

1. Stepanova M et al. *Clin Gastroenterol Hepatol.* 2012;10(9):1034-1041. 2. Agency for Healthcare Research and Quality. HCUP Nationwide Readmissions Database. 2013. https://www.hcup-us.ahrq.gov/nrdoverview.jsp. Accessed August 19, 2016. 3. Tapper EB et al. *Clin Gastroenterol Hepatol*. 2016;14(8):1181-1188.

Readmissions

- Hospital readmissions are a major healthcare burden[1]
  - Included as key quality measure for reimbursement[1,2]
- Readmission rates are high in patients with cirrhosis, with HE as a leading reason for repeated readmissions[1,3,4]

1. Bajaj JS et al. *Hepatol.* 2016;64(1):200-208. 2. Fontanarosa PB, McNutt RA. *JAMA.* 2013;309(4):398-400. 3. Tapper EB et al. *Clin Gastroenterol Hepatol*. 2016;14(8):1181-1188.
4. Seraj SM et al. *World J Gastroenterol*. 2017;23(37):6868-6876.

Goal of Treatment

The goal for many HE treatments is to remove the level of toxins, specifically ammonia, from systemic circulation

- Evidence-based guidelines developed by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (AASLD/EASL) recommended rifaximin as an add-on therapy to lactulose to reduce the risk of another overt HE recurrence after a patient experiences one or more recurrences while on lactulose alone.[2]
- A 2016 consensus statement on management of HE published in the *European Journal of Gastroenterology & Hepatology* supports the AASLD/EASL guidelines, highlighting that prompt initiation of effective management therapy for overt HE can reduce the duration of associated admissions and the risk of subsequent readmissions.[1]

Current Therapy Options for HE

- Lactulose:
  - lowers colonic PH, reduction in PH favors formation of non absorbable ammonium from ammonia, trapping ammonium in the colon, and reducing plasma ammonia concentrations.
- Rifaximin:
  - minimally absorbed, oral antimicrobial agent, has broad-spectrum activity against gram-positive and gram-negative aerobic and anaerobic enteric bacteria, and has a low risk of inducing bacterial resistance.

Current Therapy Options for HE

Agent	Drug Class	Indication
Lactulose[1]	Poorly absorbed disaccharide	• Decrease blood ammonia concentration • Prevention and treatment of portal-systemic encephalopathy
Rifaximin[2]	Non-aminoglycoside semi-synthetic, nonsystemic antibiotic	Reduction in risk of OHE recurrence in patients ≥18 years of age
Neomycin[3]	Aminoglycoside antibiotic	Not to be used, renal and ototoxic risk
Metronidazole[1]	Synthetic antiprotozoal and antibacterial agent	Not approved for HE
Vancomycin[1]	Aminoglycoside antibiotic	Not approved for HE

1. USNLM. DailyMed. Available at https://dailymed.nlm.nih.gov/dailymed. Accessed March 22, 2018;
2. Xifaxan (rifaximin) [prescribing information]. Valeant Pharmaceuticals North America LLC; Bridgewater, NJ; 2018;
3. Mullen KD, et al. *Semin Liver Dis*. 2007;27(Suppl 2):32-47.

Role of Ammonia Testing in HE

"Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with CLD. A normal value calls for diagnostic reevaluation (GRADE II-3, A, 1)."

Vilstrup H, et al. *Hepatology.* 2014;60:715-35.

Case Scenario

Lisa is a 50-yr-old female

HPI

- History of NASH Cirrhosis based on abdominal US about 4 years ago
- Noted melena one day prior to and hematemesis on the day of admission
- Her husband noted that she became confused on the way to the ED and became unresponsive at the hospital

Social History

- Used to drink heavily as a bartender when she was young
- Quit drinking and smoking 12 years ago
- Lives with husband

Case Scenario

- BP 108/54 mm Hg
- PR 116/min
- RR 16/min
- BMI 35 kg/m^2

PE

- Confused to time, person and place
- Anemic
- Anicteric
- Asterixis, tremor
- No ascites, not tender
- Trace edema
- Stool tarry and hemoccult (+)

Case Scenario

Medications

- Lisinopril
- Metformin
- Simvastatin
- Baby aspirin

Management

Initiation of care for patients with altered consciousness

- Thorough history taking with caregivers and PE
- Labs- CBC, CMP, PT/INR
- Drug screen/opioids or recent medications/OTC
- Infections (blood/urine cultures)
- Imaging – Head CT, CXR

Vilstrup H, et al. *Hepatology.* 2014;60:715-35.

Management

- Alternative causes of AMS should be sought and treated

E.g. diabetic ketoacidosis, drugs (benzodiazepines, neuroleptics, opioids), neuroinfections, GI bleed, renal failure, constipation, electrolyte disorders, intracranial bleeding and stroke

- Identification of precipitating factors and their correction
- Commencement of empirical HE treatment

Vilstrup H, et al. *Hepatology.* 2014;60:715-35.

Patient Case (cont.)

Hospital Course

- On admit day: She has an EGD with variceal banding and bleeding stopped
- Day 1: Mental status improved with lactulose (had 8 BM's), Lactulose dosage has to be reduced due to significant diarrhea.
- Day 2: Rifaximin 550 mg BID was started
- Day 3: Discharged to home. She was given prescription for Rifaximin and was instructed to follow up in one week after discharge with GI/Hep.

Patient Case (cont.)

Hospital Course

- Patient was re-admitted 9 days later due to recurrent grade III encephalopathy
- No melena or any signs of GI bleeding
- Per H&P: She is taking lactulose only as she was not able to pick up her rifaximin after discharge
  - She has not seen her GI/Hep or PCP yet

Patient Case (cont.)

Hospital Course during the second admission

Patient underwent work up for possible causes: labs (CBC,CMP,INR, infection work up with blood cultures/urine cultures, CT Head; CXR)

Admit day: The patient was empirically placed on lactulose and rifaximin; work up - negative

Day 2: Mental status improved to baseline and discharged

- Patient and caregiver was given education regarding the importance of compliance with rifaximin and lactulose
- Advise patient to follow up with GI/Hep

Prevention of Overt HE (OHE)

- Lactulose is recommended for prevention of recurrent episodes of HE after the initial episode (GRADE II-1, A, 1)
- Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second episode (GRADE I, A, 1)
- Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-TIPS HE (GRADE III, B, 1)
- 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 (GRADE III, C, 2)

AASLD. *Practice Guideline*. 2014.

Conclusions

- HE is an economic and social burden
  - Increased burden is realized not only by patients but also experienced by caregivers
- HE is an important cause of hospital readmission
  - To avoid the “revolving door”, treat after discharge
- Lactulose and rifaximin are important for secondary prophylaxis

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