HEPATIC ENCEPHALOPATHY AND MANAGEMENT CHALLENGES IN PALLIATIVE CARE

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Case

Mr. Z is a 68 year old male with end stage liver disease (ESLD) secondary to hepatitis C and alcoholism and lives in the community with his wife and 2 sons.

Mr. Z has many complications related to his ESLD including ascites, esophageal varices and hepatocellular carcinoma. Mr. Z was hospitalized 3 months ago for his first episode of an acute confusional state and was diagnosed with hepatic encephalopathy precipitated by an aspiration pneumonia and dehydration. Mr. Z also has a past medical history of hypertension, coronary artery disease, chronic lower back pain and depression. His current medication list includes aspirin 81mg once daily, furosemide 100mg once daily, spironolactone 40mg once daily, nadolol 40mg once daily, lactulose 30ml three times daily, hydromorphone contin 3mg twice daily, hydromorphone 0.5mg as a q4h prn and citalopram 20mg once daily. He is an ex-smoker and stopped consuming alcohol since his last hospitalization. He is not a liver transplant candidate.

Post-hospitalization, Mr. Z returned home at his baseline cognition however functionally, he declined and is currently at a PPS of 30% (Table 1). (1) The focus of his care is on comfort and no life prolongation - Mr. Z's wish is to remain home as his disease progresses. Palliative Home Services are involved to help support and manage symptoms for Mr. Z and his family.

Over the course of the last 3 days, Mr. Z experienced increasing lower abdominal and back pain requiring multiple breakthroughs of hydromorphone and he has become more confused, agitated and somnolent. He is inconsistent in taking his oral medications and his last bowel movement was 2 days ago despite Mrs. Z increasing the lactulose regimen from three to four times a day. Mrs. Z is now distressed over increasing symptom burden and care needs and is not coping well at home.

Introduction

Hepatic Encephalopathy (HE) is a common and distressing complication associated with chronic liver disease and is defined as a complex neuropsychiatric syndrome marked by personality changes, intellectual impairment, and an altered level of consciousness. The clinical manifestations of HE are varied and can range from subclinical alterations identified only on psychometric testing to coma. The pathophysiology of HE is not exactly defined but is most widely associated with hepatocyte loss, dysfunction and portosystemic shunting. These processes allow for nitrogenous substances to accumulate in the brain, ultimately adversely affecting brain function by altering neurotransmisions that affect consciousness and behavior. (2)

HE is a feature of decompensated liver disease and develops in 50% of patients with cirrhosis. (3) Once developed, hepatic encephalopathy is associated with increased morbidity and a 1-year mortality of 60%. (4) As a more common non-malignant disease to manage in the geriatric population, it is important for the clinician to appreciate the unique challenges that are associated with the management of HE in the palliative care setting as both symptom burden and goals of care need to be balanced in the context of a shortened and sometimes unpredictable prognosis.

Palliative Care Perspectives on the Diagnosis and Classification of Hepatic Encephalopathy

In the palliative care setting, the diagnosis and classification of Hepatic Encephalopathy (HE) remain important as both help in appreciating subsequent overall disease management.

A specific diagnostic marker of HE does not exist. Although many neurotoxins have been implicated, the most characterized neurotoxin associated with the pathogenesis of HE is serum ammonia. However, an elevated serum ammonia is not required to make the diagnosis of HE and does not aid in staging or prognosticating. (5) If a patient with HE has an elevated serum ammonia level, it does not exclude co-existent medical conditions that may explain abnormal mental status. HE thus remains a diagnosis of exclusion and this should be thoughtfully communicated in the palliative care setting, especially if burdensome investigations are not part of the patient's overall goal of care.

HE resulting from cirrhosis is classified according to the severity of clinical manifestations,

time course and precipitating factors.(6) The West Haven Criteria (WHC) is the gold standard for staging the clinical severity of HE and ranges from stage I to IV (Table 2). Stage I or minimal HE describes patients with no clinical symptoms but subtle findings on neurophysiological and neuropsychometric testing - these patients present with unique challenges, one of which is the implication for fitness to drive. The guidelines from the International Society for Hepatic Encephalopathy (ISHEN) and Nitrogen Metabolism have combined the terms minimal HE and grade 1 encephalopathy and changed the name to *covert hepatic encephalopathy* to describe these patients. (7) *Overt HE,* which is the focus of this review, is used to describe patients who demonstrate disorientation or asterixis, encompassing patients within stages 2-4 of the WHC. HE is subcategorized as being episodic, recurrent, or persistent. Episodic hepatic encephalopathy is further subdivided based on whether it developed spontaneously or whether a single or multiple precipitants were identified and persistent hepatic encephalopathy is subdivided based on its severity (mild, severe, or treatment-dependent).

Palliative Care Perspectives on the Management of Hepatic Encephalopathy

Anticipating and managing precipitating causes, reducing gut-derived nitrogenous products, and instituting concurrent supportive care are the cornerstone of management of HE.

The most common precipitants of HE in end stage liver disease include infections, gastrointestinal bleeding, electrolytes disorders, hypovolemia, constipation, and psychotropic medications.(5) Multiple precipitants to any one episode of HE may coexist and the symptoms of HE are thought to be mostly reversible if the precipitant(s) are identified and managed – this may not necessarily be the case though in a palliative care setting. Unique to palliative care is that it may be challenging to identify and manage possible precipitants of HE if certain investigations and interventions are not within a patient's goals of care. Even if possible precipitant(s) are identified, care to further avoid those precipitants, either individually or collectively, may not be possible especially if the main goal of care is comfort. This concept needs to be carefully explained to patients and their caregivers, ideally in advance of any crisis. With or without the search for and management of precipitating factors in the palliative care setting, measures to reduce the nitrogenous load from the gut must be implemented with the understanding that the symptoms can be managed, without the identification and reversal of the precipitant(s).

Traditionally, non-absorbable disaccharides such as lactulose and lactitol, are considered first-line in the management of HE. (5) Non-absorbable disaccharides work by reducing gut pH, and by interfering with the uptake of glutamine in the gut thus reducing both the synthesis and absorption of ammonia. The more common of the non-absorbable disaccharides, lactulose, is typically dosed at 15-45 mL every 8-12 hours, and titrated up with the aim of having 2-3 soft stools per day.(5) Common side effects include bloating, abdominal cramps, and diarrhea. Poor patient compliance with an oral lactulose regimen in patients receiving palliative care needs to be considered. As well, attention must also be taken to avoid diarrhea and possible subsequent perianal skin irritation, dehydration, hyponatremia and worsening of HE while titrating lactulose. If the patient is on an oral lactulose regimen and develops an altered mental status, discussions regarding the risk and management of aspiration need to be discussed. Circumstance may arise where a patient is not able to safely swallow oral lactulose – in such cases, lactulose can be administered via NG or as a rectal enema (300 ml in 1 L of water retained for 1 hour with the patient in the Trendelenburg position).

The administration of empiric lactulose may be associated with improvement in mental status within 24-48 h of initiation if the precipitant(s) to HE are concomitantly being addressed. If there is a lack of response to lactulose by 72 h of treatment, other possibilities need to be explored including other causes of encephalopathy and precipitating factors that may have been missed or inadequately managed.(7) Patients and their caregivers need to be educated about the use of lactulose and warned about side effects of aggressive use and a possible lack of response.

As a second-line, various antibiotics have been used in managing HE by decreasing the intestinal load gut bacteria that produce ammonia. Antibiotics are traditionally considered for patients who cannot tolerate or who respond poorly to disaccharide monotherapy. (8) Antibiotics such as neomycin and metronidazole are no longer widely used due to limited evidence on efficacy and risks of nephrotoxicity, ototoxicity and peripheral neurotoxicity respectively.(5) Rifaximin is a gut-specific, semisynthetic, nonabsorbable oral antibiotic, offering minimal systemic absorption and few side effects. It is dosed at 550mg twice daily by mouth. When added to lactulose, rifaximin has been shown to reduce the risk of recurrence of HE from 46% to 21%. (9)

High-animal protein dietary intake has been implicated in the past as worsening serum ammonia levels, precipitating and worsening the symptoms of HE. As a strategy to maintain low serum ammonia levels, patients with cirrhosis and HE were often protein-restricted – this practice is no longer advocated as protein restriction does not improve HE and may be harmful considering many patients receiving palliative care with end-stage cirrhosis have protein-calorie malnutrition. (10) Daily protein intake should be 1.2-1.5 g/kg/day (5).

Symptom control issues at the end of life

It is prudent to anticipate multiple symptoms in patients with hepatic encephalopathy in the context of end stage liver disease and palliative care. As the disease naturally progresses, patients may experience multiple distressing symptoms that undoubtedly affect quality of life. Medications classes such as opioids, anticholinergics, benzodiazepines and neuroleptics, should be used with caution, but may not be totally avoidable if the patient's goals are for comfort.

Opioids and their metabolites may contribute to a worsening of symptoms of HE, but the clinician must keep in mind that under treated pain may increase confusion in the patient with HE. The severity of pain and goals of care should guide opioid use. If pain is an active issue for any given patient with HE, there are many strategies that may help in trying to achieve adequate pain control while minimizing the risk for precipitating or worsening symptoms of HE. Some strategies include switching from long-acting opioid preparations to a q4h around the clock schedule and monitoring breakthrough use, enabling the clinician to titrate the opioid more carefully. If some cases, a 10-25% reduction in total daily dosing or opioid rotation using equianalgesic dosing and a 25-50% reduction for incomplete cross-tolerance may be helpful. Because of the risk of metabolite accumulation and risk of neurotoxicity with morphine, especially in the context of compromised renal function, hydromorphone and fentanyl are better alternatives.(11)

If present, agitation in patients with HE may resolve with the above-mentioned approaches. Medications that depress central nervous system function, especially benzodiazepines, should be avoided or used with caution as they can worsen symptoms of HE.(12)

Case Re-visited

The Palliative Care team visited with Mr. Z the following day. When seen, Mr. Z was disoriented and restless. His vitals included a pulse of 110, a blood pressure of 103/80, a temperature of 38.5C, a respiratory rate of 26 and an O2 sat of 90% on room air. Mr. Z was audibly congested. He had dry mucous membranes and Mrs. Z had noted that he was voiding less. Mr. Z had significant ascites and his abdomen was generally tender to touch.

Goals of care, symptom burden and prognosis were all re-visited. Of prime importance was the known desire for Mr. Z to die comfortably at home and to avoid further investigations or interventions. Mr. Z was diagnosed with a recurrence of HE with likely several precipitants, including dehydration, constipation and suspected spontaneous bacterial peritonitis. The increased use of opioids was likely another contributing factor.

Carefully discussed was the fact that not all precipitants may be identified or reversed and in light of Mr. Z's previously stated goals of care, hydration and empiric antibiotics were not initiated. Mr. Z's hydromorphone contin was discontinued and sub-cutaneous hydromorphone was started at a reduced dose of 0.3mg scheduled q4h around the clock. Mr. Z was given a fleet enema which produced a large bowel movement. Lactulose enemas were ordered TID as Mr. Z was too somnolent to take oral lactulose. For his agitation, a low dose of haldol at 0.25mg sc q8h scheduled and q4h prn was started. Glycopyrolate at 0.4mg sc q4h prn was also ordered for terminal respiratory secretions. Mr. Z's symptoms of pain and agitation improved but despite these changes, he became more somnolent. All his medications by mouth were stopped other than furosemide which was switched to the sub-cutaneous route. Mrs. Z was counselled for what expect over the ensuing days. Mr. Z died peacefully at home the next day.

Conclusion

Hepatic encephalopathy is a common complication of end stage liver disease that can occur simultaneously with other complications of ESLD and in the elderly, within the context of multiple co-morbidities. Once developed, it signals a poor prognosis for patients receiving palliative care. Although thought to be reversible, for patients whose primary goals of care are for comfort, the precipitants and overall management of HE may prove to be challenging as medication classes required to provide symptom control may precipitate or worsen hepatic encephalopathy. Guided by the patient's goals of care, families should be counselled about what to expect in terms of symptom burden, management strategies and prognosis.

Table 1: Palliative Performance Scale (PPSv2) version 2 (1)

PPS Level	Ambulation	Activity & Evidence of Disease	Self-Care	Intake	Conscious Level
100%	Full	Normal activity & work No evidence of disease	Full	Normal	Full
90%	Full	Normal activity & work Some evidence of disease	Full	Normal	Full
80%	Full	Normal activity & Effort Some evidence of disease	Full	Normal or reduced	Full
70%	Reduced	Unable Normal Job/Work Significant disease	Full	Normal or reduced	Full
60%	Reduced	Unable hobby/house work Significant disease	Occasional assistance necessary	Normal or reduced	Full or Confusion
50%	Mainly Sit/Lie	Unable to do any work Extensive disease	Considerable assistance required	Normal or reduced	Full or Confusion
40%	Mainly in Bed	Unable to do most activity Extensive disease	Mainly assistance	Normal or reduced	Full or Drowsy +/- Confusion
30%	Totally Bed Bound	Unable to do any activity Extensive disease	Total Care	Normal or reduced	Full or Drowsy +/- Confusion
20%	Totally Bed Bound	Unable to do any activity Extensive disease	Total Care	Minimal to sips	Full or Drowsy +/- Confusion
10%	Totally Bed Bound	Unable to do any activity Extensive disease	Total Care	Mouth care only	Drowsy or Coma +/- Confusion
0%	Death	-	-	-	-

Table 2: The West Haven criteria of altered mental state in HE (7)

Stage	Description
Stage 0	• Lack of detectable changes in personality or behavior
Stage 1	• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm
Stage 2	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis
Stage 3	• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior
Stage 4	• Coma

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Date of Acceptance: 12th Sept., 2015
Plagiarism Check Date: 19th Sept., 2015
Peer Reviewed by Three editors blindly: 29th Sept., 2015
Reviewer's Comment Send to author: 27th Sept., 2015
Comment Incorporated and Revert by Author: 10th October l, 2015
Send For CRC: 12th October, 2015
Conflict of Interest: Authors of a Paper had no conflict neither financially nor academically
Citation: Giulia-Anna Perri, Houman Khosravani. Hepatic Encephalopathy and Management Challenges in Palliative Care. Annals of Geriatric Education and Medical Sciences" Volume-2, Issue-1, Jan-June, 2015 www.agems.in