Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 5 Issue 7 July 2022

Clinical Review

Hepatic Encephalopathy: A Comprehensive Review

Wani Mubashir[1], Mehraj Sharik[1], Wani Ahad[2], Shafi Aamir[3]* and Ifrah Riaz[3]

[1]Junior Resident, Department of General Medicine, Sheri Kashmir Institute of Medical Sciences Medical College Bemina Srinagar, Jammu and Kashmir, India

[2]Assistant Professor, Department of General Medicine, Sheri Kashmir Institute of Medical Sciences Medical College Bemina Srinagar, Jammu and Kashmir, India

[3]Registrar, Department of General Medicine, Sheri Kashmir Institute of Medical Sciences Medical College Bemina Srinagar, Jammu and Kashmir, India

***Corresponding Author:** Shafi Aamir, Registrar, Department of General Medicine, Sheri Kashmir Institute of Medical Sciences Medical College Bemina Srinagar, Jammu and Kashmir, India.

DOI: 10.31080/ASGIS.2022.05.0449

Received: June 01, 2022

Published: June 21, 2022

Abstract

Hepatic encephalopathy is a reversible disorder seen in patients with advanced cirrhosis. It is manifested by wide spectrum of neurological and psychiatric abnormalities which occur due to accumulation of toxic substances specially ammonia in the brain. The common triggers include constipation GI bleeding infection, TIPS etc. it is seen in 30 to 45% of patients with cirrhosis. Presence of liver disease together with factoring out other causes of altered mental status is essential for diagnosis of HE. Management includes proper identification and treatment of underlying cause of underlying cause. Antibiotics like rifaximin, metronidazole are often given empirically to take care of infections. In addition osmotic laxatives, L-ornithine and L-aspartate (LOLA) are also used to decrease the levels of ammonia. Feacal microbiota transplant is gaining significant progress in the management of refractory hepatic encephalopathy.

Keywords: Hepatic Encephalopathy; Ammonia; Liver

Introduction

Liver transplantation is considered to reverse the HE according to the studies. In patients with advanced liver dysfunction, HE can cause neuropsychiatric abnormalities from the neurotoxic substances accumulation in the brain.

Patients typically present with altered mental status, personality changes and a decreased level of consciousness. An inverted sleep-wake pattern can be seen in the early stages wherein patients are found to be awake during the night and sleeping throughout the day and patients typically are in lethargic state. In late stages, hepatic encephalopathy may eventually lead to hepatic coma or coma hepaticum followed by death [1-3]. HE greatly affects the quality of life together with the morbidity and mortality causing economic affliction on the patients.

Etiology

Renal failure, Gastrointestinal bleeding, Constipation, Infections, Medication non-compliance, Excessive dietary protein in-

take, Dehydration, electrolyte imbalance and Trans jugular intrahepatic portosystemic shunt (TIPS) all are known to be the factors responsible for precipitating HE in patients with chronic liver disease [4,5].

Classification

According to national guidelines, HE is classified based on the underlying cause, the severity of the disease, duration of the disease, and the presence or absence of precipitating factors [6].

- Based on the underlying cause of HE and as per World health congress of Gastroenterology criteria Hepatic encephalopathy can be Type A (acute) seen in acute liver failure, Type B(bypass) in patients with Porto-systemic bypass with no hepatocellular disease, and Type C(cirrhosis) in patients with cirrhosis with portal hypertension or systemic shunting. Type C being the most common presents with signs of liver failure like ascites, spider telangiectasias, jaundice and palmar erythema [7].
- Classification according to the severity of HE is depicted in the following table

WHC Grade	ISHEN	HESA	CHESS	Clinical Features
Unimpaired				No encephalopathy at all, no history of HE
Minimal	Covert	Grade O	0-1	Alteration in psychomotor speed/executive functions. No evidence of clinical/mental status changes.
Grade I		Grade I	0-3	Anxiety, attention span deficit, impaired simple mathematical skills, altered sleep pattern, unaware of deficits.
Grade II	Overt	Grade II	1-6	Lethargy, not oriented to time, personality changes, buzzare behavior, dyspraxia, asterexis
Grade III		Grade III	3-6	Somnolence, semistupor, responsive to stimulus, increasing confussion and disorientation.
Grade IV		Grade IV	9	Coma

Table 1: Classification criteria for hepatic encephalopathy.

WHC: West Haven Criteria; ISHEN: International Society of Hepatic Encephalopathy and Nitrogen Metabolism; CHESS: Clinical Hepatic Encephalopathy Staging Scale; HESA: The Hepatic Encephalopathy Scaling Algorithm

Commonly used criteria include West Haven Criteria (WHC) and the International Society for Hepatic Encephalopathy (ISHEN) criteria [6]. Other grading systems, such as Clinical HE Staging Scale (CHESS) and HE Scoring Algorithm (HESA) were developed to grade patients according to the severity of HE [25].

- According to the timing/duration of disease HE can be episodic, recurrent (less than 6 months), or persistent (presenting with altered behaviour always with recurrent HE) [6].
- Triggering factors include infections, gastrointestinal bleeding, diuresis, electrolyte abnormalities, and constipation. HE can be resolved in 90% of patients by aggressively treating risk factors [6].

Pathophysiology

The neurotoxicity of ammonia in the brain, either due to increased production or impaired excretion is the most well understood pathophysiology leading to the HE [8].

The two main sites of ammonia production are the small intestine about 50% and the kidneys about 40%. In the gastrointestinal system, urease producing bacteria degrade dietary protein to ammonia together with the breakdown of glutamine by enterocyte glutaminase. In kidneys, the proximal tubular cells generate ammonia from glutamine and bicarbonate is produced as a by-product. Various mechanisms can alter the production of ammonia at these sites like bleeding from gastrointestines, hypovolaemia, over-diuresis, hypokalaemic state, acidosis, and increased pro-

tein intake [8]. The urea cycle (Krebs-Henseleit cycle) in the liver converts ammonia into water-soluble urea, from there elimination from the body occurs through intestines and the urine. Due to hepatocellular damage liver's ability to detoxify ammonia is reduced, subsequently levels increase within the systemic circulation [9]. Increased levels of ammonia in the systemic circulation can cause neuronal damage/dysfunction. Ammonia and glutamate are converted into glutamine-by-glutamine synthetase in astrocytes, leading to increase in cerebral volume by osmosis, thereby increasing the risk of cerebral edema [10]. In addition, in the mitochondria of the astrocyte's ammonia is formed from glutamine which in turn leads to oxidative damage [11].

Evaluation

In the early stages, patients may only report disturbances in their sleep-wake cycle [12]. Personality changes among the patients develop subsequently. With time patients can present with cognitive impairment such as disorientation, memory impairment, slurred speech, confusion, and eventually coma if the disease is left untreated [13,14]. HE can also affect the musculoskeletal system. Patients also reported to have coordination problems, such as changes in their handwriting, in patients with minimal HE [6].

Patient should thoroughly evaluated followed by classification of the symptoms according to the West-Haven Criteria. Differentiating between the presence of asterexis and tremulousness associated with alcohol withdrawal or abuse is important for diagnosis of exclusion [15-17]. Elevated blood ammonia levels are often seen in patients with hepatic encephalopathy. Monitoring of patients should be done by assessing the clinical improvement or deterioration of a patient undergoing treatment rather than serial arterial blood ammonia measurements.

No definitive test or imaging modality is available to accurately diagnose and assess the severity of HE. Current guidelines recommend the use of an EEG (sensitivity 57-100% and specificity 41-88%) other neurophysiological tests (psychometric testing of attention as well as working memory and psychomotor speed) to diagnose HE after excluding other causes [6,18].

Treatment

Laxative is the first line of therapy for HE with aim to prevent ammonia absorption through non-absorbable disaccharides. They are potent laxatives as well as alter the intestinal microbiome to non-urease-producing bacteria thereby reducing ammonia production [19,20]. Lactulose also lowers the pH of the colon, leading to the conversion of ammonia to the ammonium ion causing impaired absorption of ammonia. Excess ammonia from the colon can be removed using enemas and polyethylene glycol and are proven to be useful [21,22].

Antimicrobials against gut flora producing ammonia are also used to treat HE. Rifaximin is one such drug that is effective in reducing hospital admissions and the frequency of recurrent episodes [19,23]. Faecal microbiota transplant (FMT) is a promising treatment for patients with refractory HE.

Restriction of protein is not recommended as normal protein intake levels do not exacerbate or cause HE instead Protein restriction can be harmful already in those patients with reduced skeletal muscle mass [19].

Other treatment options include LOLA (L-ornithine and L-aspartate) which increases the production of urea by increasing the use of Ammonia in the urea cycle, and underlying zinc deficiency common in cirrhotic patients also needs to be addressed.

Prognosis

Hepatic encephalopathy carries a poor prognosis. Around 40% of patients die within 12 months. Given high mortality, MDT (multidisciplinary team) that closely monitors and manages the patient is important to improve the quality of life. The patient should be referred to a liver transplant surgeon to determine his or her eligibility as early as possible after the diagnosis has been made. There is an increased mortality (three times more than single episode of HE) in patients with recurrent overt HE after calculating MELD score, ascites, albumin, indication for TIPS, and age [24]. Numerous studies have demonstrated that neuroinflammation and neuronal cell death are characteristic of HE and recurrence of which can lead to permanent damage which is irreversible. Post-liver transplantation neurological complications can persist [26].

Conclusion

The prognosis in patients with hepatic encephalopathy is poor irrespective of treatment. The existing treatments are to ease symptoms and improve the quality of life. One of the most impor-

tant indicator of worsening cirrhosis is the HE with increased mortality and morbidity of patients with cirrhosis. To improve clinical outcomes in patients with HE further studies are ongoing with hope to improve the mortality and morbidity in patients with HE.

Acknowledgement

Dedicated to medical students.

Source of Funding

Nil.

Conflict of Interest

Authors declare no conflict of interest exists.

Bibliography

1. European Association for the Study of the Liver. "EASL Clinical Practice Guidelines on nutrition in chronic liver disease". *Journal of Hepatology* 70.1 (2019): 172-193.
2. Tajiri K and Shimizu Y. "Branched-chain amino acids in liver diseases". *Translational Gastroenterology and Hepatology* 3 (2018): 47.
3. Acharya C and Bajaj JS. "Altered Microbiome in Patients with Cirrhosis and Complications". *Clinical Gastroenterology and Hepatology* 17.2 (2019): 307-321.
4. Kibrit J., *et al*. "Clinical Assessment and Management of Portal Hypertension". *Seminars in Interventional Radiology* 35.3 (2018): 153-159.
5. Fiati Kenston SS., *et al*. "Mechanistic insight, diagnosis, and treatment of ammonia-induced hepatic encephalopathy". *Journal of Gastroenterology and Hepatology* 34.1 (2019): 31-39.
6. Vilstrup H., *et al*. "Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver". *Hepatology* 60.2 (2014): 715-735
7. Mumtaz K., *et al*. "Precipitating factors and the outcome of hepatic encephalopathy in liver cirrhosis". *Journal of College of Physicians and Surgeons Pakistan* 20.8 (2010): 514-518
8. Jaffe A., *et al*. "Pathophysiology of hepatic encephalopathy". *Clinical Liver Disease* 24.2 (2020): 175-188.
9. Weiner ID., *et al*. "Urea and ammonia metabolism and the control of renal nitrogen excretion". *Clinical Journal of the American Society of Nephrology* 10.8 (2015): 1444-1458.
10. Poveda MJ., *et al*. "Brain edema dynamics in patients with overt hepatic encephalopathy: a magnetic resonance imaging study". *Neuroimage* 52.2 (2010): 481-487.
11. Dasarathy S., *et al*. "Ammonia toxicity: from head to toe?" *Metabolic Brain Disease* 32.2 (2017): 529-538.
12. Córdoba J., *et al*. "High prevalence of sleep disturbance in cirrhosis". *Hepatology* 27.2 (1998): 339-345.
13. Weissenborn K. "Diagnosis of encephalopathy". *Digestion* 59.2 (1998): 22-24.
14. Wiltfang J., *et al*. "Psychiatric aspects of portal-systemic encephalopathy". *Metabolic Brain Disease* 13.4 (1998): 379-389.
15. Nardelli S., *et al*. "Management of Hepatic Encephalopathy Not Responsive to First-Line Treatments". *Current Treatment Options in Gastroenterology* 16.2 (2018): 253-259.
16. Kornerup LS., *et al*. "Update on the Therapeutic Management of Hepatic Encephalopathy". *Current Gastroenterology Reports* 20.5 (2018): 21.
17. Amodio P. "Hepatic encephalopathy: Diagnosis and management". *Liver International* 38.6 (2018): 966-975.
18. Karanfilian BV., *et al*. "Laboratory abnormalities of hepatic encephalopathy". *Clinical Liver Disease* 24.2 (2020): 197-208.
19. Wijdicks EF. "Hepatic encephalopathy". *The New England Journal of Medicine* 375.17 (2016): 1660-1670.
20. Nielsen K., *et al*. "Liver collagen in cirrhosis correlates with portal hypertension and liver dysfunction". *APMIS* 122.12 (2014): 1213-1222.
21. Mahpour NY., *et al*. "Pharmacologic management of hepatic encephalopathy". *Clinical Liver Disease* 24.2 (2020): 231-242.
22. Riggio O., *et al*. "Effect of lactitol and lactulose administration on the fecal flora in cirrhotic patients". *Journal of Clinical Gastroenterology* 12.4 (1990): 433-436.

23. Bass NM., *et al*. "Rifaximin treatment in hepatic encephalopathy". *The New England Journal of Medicine* 362.12 (2010): 1071-1081.

24. Zuo L., *et al*. "Early-recurrent overt hepatic encephalopathy is associated with reduced survival in cirrhotic patients after transjugular intrahepatic portosystemic shunt creation". *Journal of Vascular and Interventional Radiology* 30.2 (2019): 148-153.

25. Hassanein TI., *et al*. "Introduction to the hepatic encephalopathy scoring algorithm (HESA)". *Digestive Diseases and Sciences* 53.2 (2008): 529-538.

26. Garcia-Martinez R., *et al*. "Hepatic encephalopathy is associated with posttransplant cognitive function and brain volume". *Liver Transplant* 17 (2011): 38-46.