Differentiation of hepatic encephalopathy from delirium tremens: A case series and review

Spandana Devabhaktuni, Prajakta Patkar, V. Pooja, Sana Dhamija, Nishtha Gupta, Suprakash Chaudhury, Daniel Saldanha

Department of Psychiatry, Dr. D. Y. Patil Medical College, Dr. D. Y. Patil Vidyapeeth, Pune, Maharashtra, India

Address for correspondence: Dr. Suprakash Chaudhury, Department of Psychiatry, Dr. D.Y. Patil Medical College, Dr. D. Y. Patil Vidyapeeth, Pimpri, Pune, Maharashtra, India. E-mail: suprakashch@gmail.com

Received: 21 February 2021
Revised: 18 April 2021
Accepted: 03 June 2021
Published: 22 October 2021

Hepatic encephalopathy (HE) is an important and potentially life threatening complication in alcoholic patients with decompensated liver function that develop even as they continue drinking. Delirium tremens, on the other hand, is an acute condition resulting from alcohol abstinence in a person dependent on alcohol, making it a life threatening diagnosis that requires intensive care and successful management of the withdrawal. Often in medical wards, these two conditions are mistaken and so is the management plan confused with each other. Making the right diagnosis early on during the hospital course is extremely important in these critical conditions so as to make an appropriate schedule for treatment and a better outcome for the same. A case series of patients who presented with a diagnostic dilemma is reported. Clinical examinations, diagnostic tools to measure the levels of ammonia and liver function tests and hemogram, West Haven criteria and Child–Pugh grading, and clinical scales of these patients are reported. Increased levels of ammonia were present in all the cases. The subtle similarities in the presentation of the two conditions often make it confusing for the clinician to distinguish between them. Using a simple test of measuring ammonia levels in the blood helps in such situations. The detection of raised levels of ammonia in cases of chronic liver disease helps in not just the diagnosis but also is an important prognostic indicator for development of HE.

Keywords: Chronic alcoholic liver disease, delirium tremens, hepatic encephalopathy

The prevalence of alcohol dependence syndrome is 7% and 0.4% in males and females in the age group of 15 and above, whereas in India, a higher trend in 12-month prevalence estimates of alcohol use disorder, i.e. 9.1% and 0.5% in males and females, respectively, is reported. A total of nearly 1.4 lakh deaths have been attributed to liver cirrhosis in both the sexes in the year 2016.[1]

Alcohol-induced liver disease spectrum includes several clinical illnesses ranging from fatty liver to hepatic inflammation and necrosis to progressive fibrosis (alcoholic cirrhosis). Sustained alcohol consumption increases susceptibility to other liver pathologies such as virus-related chronic hepatitis and hepatocellular carcinoma. Several primary and secondary factors are implicated in the complex pathophysiology of alcohol hepatotoxicity. It is postulated that these factors interact leading to the worsening of liver function in patients who continue to consume alcohol. Primary factors include genetic background and its complex interrelationship with direct ethanol hepatotoxicity and alcohol-induced metabolic and immunological changes. Secondary cofactors also promote the development of alcohol liver disease including nutritional deficiency and hepatotoxic comorbid conditions.
Excessive consumption of alcohol resulting in a dependence pattern is associated with several complications affecting nearly all the major systems in the human body. In chronic alcoholism, liver functions are severely affected, sometimes leading to portosystemic shunting. When a patient dependent on alcohol abruptly abstains from consuming alcohol, for whatever reason, he puts himself at the risk of developing a severe withdrawal state known as delirium tremens. Delirium tremens develops in 5% of patients with alcohol dependence and has a mortality rate of 10%–20%. If left untreated, it is a life-threatening condition that requires intensive care and successful management of the withdrawal. In contrast, hepatic encephalopathy (HE) is another important and potentially life-threatening complication in cases of alcoholic patients with decompensated liver function and can develop HE even as they continue drinking.[2]

### ASSESSMENT OF DELIRIUM

Delirium is an acute, fluctuating disturbance of consciousness, arousal, cognition, and perception. Despite the high prevalence in palliative care, delirium is often under-recognized and misdiagnosed leading to prolonged hospital stay; escalating health-care costs; and increased mortality, morbidity, and human suffering. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, defines delirium as a disturbance of attention and awareness that develops over a short period of time with fluctuations in consciousness through the day and associated with cognitive disturbances. Depending on the levels of arousal and motor activity, the term “hypoalert/hypoactive” was distinguished from “hyperalert/hyperactive” and these were regarded as two distinct subtypes of delirium.[3] Contemporary phenomenology identifies three subtypes of delirium: hyperactive, hypoactive, and the mixed form.[4] The most frequently encountered subtype is the mixed form, occurring 52% of the time in patients diagnosed with delirium. The mixed form involves the characteristics of both hypoactive and hyperactive delirium. Often the agitated, hyperactive periods are recognized whereas the more withdrawn, hypoactive features are missed or perceived to indicate an improvement.[4] These assumptions delay or preclude appropriate therapy, and for this reason, the mixed type of delirium is believed to have the worst prognosis.[3]

The clinical diagnosis of delirium is based on bedside observations and the evaluation of key features.[3] Clinical features of delirium include acute onset and fluctuating course; disturbance of consciousness, arousal, and awareness; attention disturbances; disorientation; cognitive disturbances including memory impairment and executive dysfunction; perceptual disturbances; disorganized thinking; delusions; psychomotor disturbances; sleep-wakefulness cycle disturbances; and neurological signs—asterixis, frontal release signs, and myoclonus.

### HEPATIC ENCEPHALOPATHY

Deleterious effects of chronic alcohol consumption are not limited to liver cells but also affect the functioning of distant organs such as the brain. One such fatal brain disorder is known as HE and it occurs in nearly 40% of patients with cirrhosis in its overt form. The risk of developing a milder form of HE or covert HE rests at 20%–80% in patients with cirrhosis.[5] Nearly 10%–15% of patients with alcohol dependence disorder develop cirrhosis, and the 5-year survival rate for patients with late-stage cirrhosis who continue to drink is 35%.[7]

HE is defined as brain dysfunction caused by liver dysfunction and/or portosystemic shunting resulting in diffuse disturbances of brain dysfunction that range from subclinical alterations to coma.[6]

### PATHOGENESIS

Although several hypotheses were made about HE, its pathogenesis is not entirely understood, impeding advances in its diagnosis and therapy. Worsening of the cirrhotic state leading to HE follows a variable course depending on the presence/absence of precipitating factors. The role of portosystemic venous blood shunting, a sequela of cirrhosis, can lead to the development of neurotoxicity as the liver cannot effectively remove the toxins. The rise in neurotoxins and inflammatory mediators results in low-grade brain edema which leads to a plethora of neuropsychiatric sequelae. Among the neurotoxins implicated in the pathogenesis of HE, the role of ammonia and glutamine is most often suggested. Furthermore, the part of inflammatory mediators such as cytokines, certain amino acids, and manganese cannot be ignored.[12-14]

### Ammonia hypothesis

In the absence of liver disease, ammonia generated from the dietary nitrogenous compounds from the gut is
effectively converted into urea and eliminated from the body. In the setting of liver dysfunction, hepatocytes lose the ability to detoxify the blood ammonia, and in the case of portosystemic shunting, the blood is not delivered to the hepatocytes. This sequence of events leads to the accumulation of large amounts of ammonia in the blood causing it to cross the blood–brain barrier.

Role of astrocytes and glutamine
As the brain is devoid of urea cycle, it metabolizes ammonia to glutamine via glutamine synthase, an enzyme present only in astrocytes. As glutamine generated via this mechanism is osmotically active, it causes swelling of astrocytes leading to the development of brain edema. The accumulation of water in the astrocytes induces changes in the cells which are characteristic of type II astrocytosis. Glutamine’s additional action on N-methyl-D-aspartate and gamma-aminobutyric acid receptors on the mitochondria leads to oxidative stress which further impedes the protein synthesis occurring in the cell. This state generates reactive nitrogen and oxide radicals causing the release of inflammatory mediators such as interleukins 1 and 6 and tumor necrosis factor which lead to further damage of the integrity of the neurons.

Role of manganese
Manganese deposits in the caudate nucleus and globus pallidus on magnetic resonance imaging (MRI) of patients of cirrhosis were reported in several cases presenting with extrapyramidal symptoms. Some studies observed the disappearance of these deposits once the HE resolved. The hepatobiliary system is implicated in the elimination of manganese, and a rise in the levels of the same is observed in individuals with hepatic dysfunction. As the levels in the blood increase, manganese crosses the blood–brain barrier and gets deposited in the basal ganglia. Autopsy of brain tissue from alcoholic cirrhotic patients who died from complications of HE revealed up to seven times more manganese in the globus pallidus compared with normal levels.

Changes in the blood–brain barrier
Astrocytes also maintain the selective permeability of blood–brain barrier. Disruptions to this in the setting of HE leads to abnormal diffusion of molecules out of astrocytes. One such molecule implicated is zinc; its role in gene transcription and synaptic plasticity is affected due to accumulation in the astrocytes leading to its deficiency.

CLASSIFICATION

HE is classified according to four factors:

1. According to the underlying disease:
   a. Type A due to ALF
   b. Type B due predominantly to portosystemic bypass or shunting
   c. Type C due to cirrhosis
   d. Type D due to disorders of the urea cycle.

2. According to the severity of manifestations:

The manifestations of HE are observed as a continuum from mild sequelae affecting the consciousness to severe forms including states of stupor and coma. West Haven is one such criterion which is used for establishing the severity of HE and takes into account the consciousness, behavior, and intellectual function of the patient. It is limited by the poorly established operative definitions and vague
symptoms, especially seen in stages 1 and 2. The other scales used in the assessment of manifestations of HE include Glasgow Coma Scale. Clinical HE Staging Scale and HE Scaling Algorithm which includes well-defined criteria and combines these criteria with psychometric tests.\[23,24\]

3. According to time course of HE:
   a. Episodic
   b. Recurrent HE denotes bouts occurring with a time interval of 6 months
   c. Persistent HE denotes a pattern of behavioral alterations that are always present interspersed with relapses of overt HE.

4. According to the existence of precipitating factors:
   a. Nonprecipitated
   b. Precipitated.

Precipitating factors
Most patients presenting with symptoms of HE in chronic liver disease have at least one and in some cases more than one precipitating factor.\[11\] Successful treatment of HE, especially in the background of precipitating factors, requires prompt identification and treatment of these underlying abnormalities. Conditions that can lead to the development of HE are: ALF; renal failure, gastrointestinal bleeding, infection, constipation, lactulose nonadherence, dehydration, electrolyte imbalances – hypokalemia, hyponatremia, metabolic alkalosis excess dietary protein, benzodiazepines, opioids.\[16,26\]

**ASSESSMENT AND DIAGNOSIS OF HEPATIC ENCEPHALOPATHY**

Owing to the vague nature of the symptoms seen in the early stages of HE, clinicians must be vigilant when assessing individuals displaying changes in behavior and mental status in the setting of delirium and liver dysfunction. A thorough history evaluating the individuals functioning may reveal personality changes, declining performance at work, poor social interaction, and in some cases, recent road traffic accidents.\[26,27\]

The diagnosis of mild forms of HE can be done with the use of neuropsychological testing because symptoms such as mild confusion, decreased executive function, and forgetfulness seen in the early stages may be difficult to discern clinically.

Typically, in the subclinical cases, communication skills remain unaffected, but testing can reveal deficits in attention and concentration, memory (working), fine motor skills, and visuospatial abilities.\[28\] Some tests for minimal HE are the Psychometric HE Score (PHES), the Portosystemic Encephalopathy (PSE) Syndrome Test, the Cognitive Drug Research Ltd Assessment System, the Repeatable Battery for the Assessment of Neurological Status, the Critical Flicker Test, and the Inhibitory Control Test.\[30\] The PHES combines serial dotting test, line-tracing test, digit symbol test, and number-connection or finger-connection test. Impairment in at least three of the four subtests yields an abnormal syndrome test. The PSE syndrome test has been validated for use in various countries including India.\[29\] Neurophysiologic tests include electroencephalography and auditory or visual event-related P300 (evoked potential) testing.\[30\]

**THE DIFFERENTIATION OF DELIRIUM TREMENS FROM IMPENDING HEPATIC COMA**

The importance of differentiating these two conditions lies in the field of therapy, for what is appropriate therapy for one condition may be lethal for the other.

Treatment by tranquillizers and sedatives may precipitate terminal hepatic coma in the patient in whom coma is only impending. Even small doses may be lethal. Hydration therapy required for delirium tremens may also be fatal to the patient with impending hepatic coma. A high protein diet for supposed delirium tremens may precipitate a patient with impending hepatic coma into terminal coma. On the other hand, purging and a protein-free diet, appropriate for impending hepatic coma, may be disastrous for the patient with delirium tremens. It is therefore vital to the patient’s welfare that the physician be able to distinguish between delirium tremens and impending hepatic coma. It is also important to recognize that both conditions may exist simultaneously.\[31\]

A misdiagnosis can lead to devastating consequences as the treatment regimens are entirely different.

Apart from alcohol withdrawal, there are other conditions which could present with a similar picture of HE. As the treatment guidelines vary for each condition, it is imperative to arrive at the appropriate diagnosis before treatment ensues.\[32\]

Conditions other than alcohol withdrawal that mimic HE were as follows: Wernicke–Korsakoff syndrome; hypoglycemia; diabetic ketoacidosis; endocrine abnormalities – hypothyroidism, Addison’s disease, and hypopituitarism; meningitis; encephalitis; abuse of benzodiazepines and opioids; electrolyte imbalances; brain tumors; cerebrovascular incidents; subdural hematoma; and dementia.

The following case histories highlight the importance in early diagnosis of these two divergent conditions [Table 2].
Case 1
A 42-year-old male with a history of dependency on undistilled alcohol was brought to the psychiatry emergency department (OPD) with complaints of altered sleep pattern and sleep disturbances for 4 days. He worked in a mechanic shop until a few months back, but as he was being listless and performing poorly, he was dismissed from his job. His wife reported his alcohol consumption increased post that event, and he refused to visit a physician for complaints of constipation which later led to the development of hemorrhoids. General physical examination revealed a person moderately nourished, conscious, not oriented to time, place, person. On general physical examination, pallor, icterus, and bilateral mild pedal edema were noted. His blood reports revealed a total bilirubin of 1.5, INR 1.65, and serum ammonia level of 174 µmol/L. His blood reports revealed a total bilirubin of 2.3 mg/dL, international normalized ratio (INR) 1.72, aspartate aminotransferase 90 U/L, alkaline phosphatase 140 U/L, and serum ammonia 168 µmol/L. The patient's ultrasound of the abdomen revealed alcoholic steatosis.

Case 2
A 45-year-old male patient presented to the emergency department (OPD) with complaints of irrelevant talks, restlessness, and sleep disturbances for 4 days. He worked in a mechanic shop until a few months back, but as he was being listless and performing poorly, he was dismissed from his job. His wife reported his alcohol consumption increased post that event, and he refused to visit a physician for complaints of constipation which later led to the development of hemorrhoids. On admission, his alcohol consumption increased post that event, and he refused to visit a physician for complaints of constipation which later led to the development of hemorrhoids. General physical examination revealed a person moderately nourished, conscious, not oriented to time, place, person. On general physical examination, pallor, icterus, and bilateral mild pedal edema were noted. His blood reports revealed a total bilirubin of 1.5, INR 1.65, and serum ammonia level of 174 µmol/L. His blood reports revealed a total bilirubin of 2.3 mg/dL, international normalized ratio (INR) 1.72, aspartate aminotransferase 90 U/L, alkaline phosphatase 140 U/L, and serum ammonia 168 µmol/L. The patient's ultrasound of the abdomen revealed alcoholic steatosis.

Case 3
A 56-year-old male patient presented to the emergency department (OPD) with complaints of irrelevant talks, restlessness, and sleep disturbances for 4 days. He worked in a mechanic shop until a few months back, but as he was being listless and performing poorly, he was dismissed from his job. His wife reported his alcohol consumption increased post that event, and he refused to visit a physician for complaints of constipation which later led to the development of hemorrhoids. General physical examination revealed a person moderately nourished, conscious, not oriented to time, place, person. On general physical examination, pallor, icterus, and bilateral mild pedal edema were noted. His blood reports revealed a total bilirubin of 1.5, INR 1.65, and serum ammonia level of 174 µmol/L. His blood reports revealed a total bilirubin of 2.3 mg/dL, international normalized ratio (INR) 1.72, aspartate aminotransferase 90 U/L, alkaline phosphatase 140 U/L, and serum ammonia 168 µmol/L. The patient's ultrasound of the abdomen revealed alcoholic steatosis.
Case 4
A 62-year-old male, driver by occupation, currently unemployed, was brought to the psychiatry OPD with complaints of restlessness, fearfulness, and disturbed sleep for 2 days. The patient is diagnosed with alcohol dependence disorder and had a history of several admissions in the past for detoxification. On further evaluation, the history of several road traffic accidents in the past 6 months is noted, with the most recent a few days back. The patient also reports a history of several episodes of melana and hematemesis in the past few months. On general physical examination, the patient appeared poorly nourished with pallor and icterus. At the time of examination, the patient was conscious, oriented to time, place, and person, and appeared anxious. His blood work revealed a total bilirubin of 5.84, INR 1.70, and a serum ammonia level of 174. Previous blood work revealed deranged liver function tests, and the ultrasound report suggested alcoholic steatosis.

DISCUSSION
The timely diagnosis and appropriate treatment of HE is of significant clinical relevance, especially in the setting of chronic alcoholism.

The individuals described in the case series presented to a tertiary care center situated in an urban area. All the patients were male and belonged to a lower socioeconomic class and drank undistilled alcohol for an average of 20 years. At the time of admission, none were employed and were dependent on their family members for economic support. Except for one patient (case 2), all the patients first presented to the psychiatry OPD with symptoms as described in the case vignettes. All displayed neuropsychiatric symptoms and a thorough history of alcohol intake and the recent evolution of symptoms were recorded. A general, physical, and mental status examination was conducted to further determine the nature of illness. The above evaluation led to the suspicion of a coexisting severe liver pathology as evidenced by the presence of constipation, jaundice, a history of hematemesis, or melena.

All the patients had a history of long-standing alcohol consumption which led to several physical complications in the past. All individuals had a history of eye-opener pattern and continued to drink despite significant economic repercussions. The oldest patient in the series, a 62-year-old male, had a history of road traffic accident when he was not under the influence of alcohol which raises the suspicion of declining motor skills often observed in patients with covert HE.

The preliminary clinical impression was confirmed with timely laboratory assessments and the results of which confirmed the presence of moderate to severe liver damage. Ultrasound was done for three patients, and all of them had irreversible changes in liver parenchyma, verifying the presence of chronic liver pathology.

A key biomarker used to assess the probable presence of HE was ammonia, which was significantly raised in all the patients. Two independent psychiatrists assessed the patients according to the West Haven criteria for HE. Two patients were assigned Grade 3 and the rest as Grade 2 level of impairment. Child–Pugh scoring was assessed using the laboratory values and the presence of signs of HE. Patients were found to have significant levels of liver impairment.

Although raised levels of ammonia being a predictor of severity and prognosis have been heavily debated, several studies found it to be useful in clinical practice to assess for the presence or impending HE in patients with chronic liver disease.[33,34]

Based on a study of patients with ALF, Bhatia et al.[35] concluded that ammonia levels of 124 μmol/l or more are predictive of subsequent development of severe complications and mortality. This was supported by Hu et al.[36] from China who measured ammonia levels in patients with acute-on-chronic liver failure and predicted raised ammonia levels to be an important prognostic factor.

Limitations
Sample size was limited; neuropsychological tests and MRI scans were not done in the case series. Inclusion of these will strengthen observations in future studies.

CONCLUSION
Detection of raised levels of ammonia in cases of HE is an important prognostic indicator for timely intervention and should help us to deal with the cases at the first available opportunity.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.
REFERENCES

1. World Health Organization. Global status report on alcohol and health 2018. Geneva: World Health Organization; 2018.

2. Connn HO. Hepatic encephalopathy. In: Schiff L, Schiff ER, editors. Diseases of the Liver. 7th ed. Philadelphia, PA: Lippicott; 1993. p. 1036-1060.

3. Stagno D, Gibson C, Breitbart W. The delirium subtypes: A review of prevalence, phenomenology, pathophysiology, and treatment response. Palliat Support Care 2004;2:171-9.

4. Kuebler KK, Heidrich DE, Vena C, English N. Delirium, confusion, and agitation. In: Ferrell BR, Coyle N, editors. Textbook of Palliative Nursing. 2nd ed. New York: Oxford University Press; 2006. p. 401-42.

5. Casarett DJ, Inouye SK. Diagnosis and management of delirium near the end of life. Ann Intern Med 2001;135:32-40.

6. American Association for the Study of Liver Diseases. Diagnosis and management of hepatic encephalopathy. Hepatology 2010;51:15-25.

7. Bajaj JS, Wade JB, Sanyal AJ. Spectrum of neurocognitive impairment in cirrhosis: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol 2014;61:642-59.

8. Mann RE, Smart RG, Govoni R. The epidemiology of alcoholic liver disease. Alcohol Res Health 2003;27:209-19.

9. Prakash R, Mullen KD. Mechanism, diagnosis and treatment response. Palliat Support Care 2004;2:171-9.

10. Ferenci P, Lockwood A, Mullen KD, Tarter R, Weissenborn K, et al. Performance of the hepatic encephalopathy scoring algorithm in a clinical trial of patients with cirrhosis and severe hepatic encephalopathy. Hepatology 2009;50:1392-400.

11. American Association for the Study of Liver Diseases. Diagnosis and management of hepatic encephalopathy. Hepatology 2010;51:15-25.

12. Pantham G, Mullen KD. Practical issues in the management of hepatic encephalopathy. Gastroenterol Hepatol (N Y) 2017;13:659-65.

13. Norenberg MD, Jayakumar AR, Rama Rao KV, Panickar KS. New concepts in the mechanism of ammonia-induced astrocyte swelling. Metab Brain Dis 2007;22:219-34.

14. Hüsingsser D, Görg B. Interaction of oxidative stress, astrocyte swelling and cerebral ammonia toxicity. Curr Opin Clin Nutr Metab Care 2010;13:87-92.

15. Romero-Gómez M, Ramos-Guerrero R, Grande L, de Terán LC, Corpas R, Camacho I, et al. Intestinal glutaminase activity is increased in liver cirrhosis and correlates with minimal hepatic encephalopathy. J Hepatol 2004;41:49-54.

16. Wolf DC. eMedicine. Hepatic Encephalopathy; 2011. Available from: http://emedicine.medscape.com/article/186101-print. [Last accessed on 2021 Feb 08].

17. Llansola M, Rodrigo R, Monfort P, Montoliu C, Kosenko E, Cauli O, et al. NDMA receptors in hyperammonemia and hepatic encephalopathy. Metab Brain Dis 2007;22:321-35.

18. Montoliu C, Piedrafita B, Serra MA, del Olmo JA, Urios A, Rodrigo JM, et al. IL-6 and IL-18 in blood may discriminate cirrhotic patients with and without minimal hepatic encephalopathy. J Clin Gastroenterol 2009;43:272-9.

19. Cauli O, Rodrigo R, Llansola M, Montoliu C, Monfort P, Piedrafita B, et al. Glutamatergic and gabergic neurotransmission and neuronal circuits in hepatic encephalopathy. Metab Brain Dis 2009;24:69-80.

20. Krieger D, Krieger S, Jansen O, Gass P, Theilmann L, Lichtnecker H. Manganese and chronic hepatic encephalopathy. Lancet 1995;345:735.

21. Butterworth RF, Spahr L, Fontaine S, Layrargues GP. Manganese toxicity, dopaminergic dysfunction and hepatic encephalopathy. Metab Brain Dis 1995;10:259-67.

22. Butterworth RF, Spahr L, de Terán LC, Corpas R, Camacho I, et al. Intestinal glutaminase activity is increased in liver cirrhosis and correlates with minimal hepatic encephalopathy. Metab Brain Dis 2007;22:321-35.