



## **Hepatic Encephalopathy and Challenges in Elderly – An Updated Review**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

Hepatic encephalopathy, a type of brain disorder induced by hepatic dysfunction and portal system blood starvation. HE is the serious consequence of chronic liver disease that causes changes in individual behaviour, awareness, perception, activity performed. Depending on the severity, this split in two types: covert hepatic encephalopathy and overt hepatic encephalopathy. Most often utilised criteria for rating HE are the West Haven criteria (WHC). Septicaemia, GI hemorrhage, diuretic overdose, and dehydration, these risk factors are for the hepatic encephalopathy. The diagnosis is primarily clinical, but there are other possible causes for the altered state of mind. These patients have the poorer results, drop standard of living, and elevated hospital care utilization, inflicting financial and emotional load on caregivers. Other possible causes for the change in behavior consciousness should be ruled out, therefore the diagnosis is mainly clinical. Other possible causes for the altered mental state have been ruled out therefore the diagnosis is mainly clinical. The three major HE types are as follows: Acute liver failure leads to type A HE. Portosystemic bypass/shunting causes Type B HE. Cirrhosis-related HE of type C. Ammonia cannot be removed effectively due to liver dysfunction portosystemic collaterals. As a result, increased the level of NH<sub>3</sub> in blood plasma & breaches the BBB, resulting in brain damage edema. The patient's mental state, musculoskeletal system, and mood/behavior are all affected by the symptoms of HE. These symptoms might range in severity, but they can start highly light.

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## 1. INTRODUCTION

Hepatic Encephalopathy is a significant and lethal obstacle to hepatic failure. It is defined as a neuropsychiatric syndrome due to hepatic dysfunction and shunt of portosystemic blood. HE symptoms are progressive; their seriousness scale is from insignificant alteration in sleep pattern to last coma stage. It mainly influences the central nervous system, which effects individual frame of mind, behavior, skeletal muscle organization [1].

Three forms of HE have been stated as a result of the origin of disease: the first form is because of hepatic dysfunction, the second form is because of the result of portal system shunting wither hepatic failure, and third is in the patient with hepatic cirrhosis and portal system bypass [2]. Covert (CHE) and overt (OHE) HE are the two primary types based on severity (CHE). Covert has a crucial influence on individual living standards driving abilities; it is linked to an increase in hospitalizations and deaths. Similarly, OHE is linked to higher rates of hospitalization and dying, as well as a low standard of living [3]. Patients with MHE have minor cognitive, psychomotor abnormalities but no recognised clinical symptoms of HE [4].

Overt forms are estimated to occur in 30 percent of individual with hepatic cirrhosis. As a result of advanced liver disease, it is a difficult complication. About 20 percent to 60 percent of people with liver disease have minimal HE, which is characterized by more modest motor and cognitive abnormalities [4].

It is the neuropsychiatric consequence in relation to acute and chronic hepatic illness. HE is linked with considerable financial costs burden for patients and their caregivers. The consequences of HE go beyond the economic impact to include societal costs associated with patients' decreased standard of living and disability in daily work. Majority of danger of occurring HE points towards liver cirrhosis, and it is increased in recent years. Similarly rise in hospital protection load connected with is anticipated in future [5].

The frequently used grading for hepatic encephalopathy is WEST HAVEN CRITERIA (WHA). This criteria differentiates between four grades of HE. In grade I, lack of concentration and some individual behaviours observed by

their loved ones. In grade II, the most chief discovery is not oriented for O'clock. In grade III, individual daze, yet they give reaction for the stimulant. As well as individuals are not oriented to location, site & person & circumstances & show some unusual actions. Patients are in a coma at grade IV [2].

A fifth grade was added called subclinical or minimal encephalopathy [2]. some experts suggested that MHE and grade I HE together classified as "covert HE" that is opposite to "overt" HE which is under clinical grades of 2-4 [2]. When tested, CHE has been found in 30-80 percent of cirrhotics, whereas OHE has been found in up to 30-60 percent of cirrhosis patient [3].

Motor symptoms, the typical quality of HE other than altered sensorium, decision, attention, perception defect. Motor characteristics include extrapyramidal signs and cerebellar signs. This include reduction of facial expression, slow movements, involuntary shaking, impaired balance, rigidity, dysarthria, and flapping tremor. Flapping tremor is the specific sign of hepatic encephalopathy. The characteristics are neither surely related to a various forms of HE. Flapping tremors might be there in altered consciousness. Factors which might leads to hepatic encephalopathy are - Infection, Diuretics overdose, imbalance of electrolyte, Psychoactive drugs, Constipation, GI bleed, thirst [2].

## 2. DISCUSSION

### 2.1 Pathophysiology

The pathophysiology of HE involves increased levels of toxins in brain, with ammonium as its main agent ( $\text{NH}_3$ ). Current study state that ammonium is just one more agent of the multiple pathopathogenic factors that is involved in HE [6]. Pathophysiology is complex with many agents, which act alone or together to cause functional neurological impairment. These components includes ammonia, inflammatory cytokines, benzodiazepine like substances, and manganese [3].

Major events connected to the pathomechanism of HE in liver cirrhosis are:

1. Consequence of poison on cranium structure and function mechanism

2. Central nervous system ATP failure
3. Activity of inflammation,
4. Neurotransmitter Variation which cause inhibitory mechanism by GABA [7].

Cirrhosis patients have higher levels of ammonia in their blood and brain [7].

The content ammonium in cirrhotic patients can rise dramatically. This is due to a decrease in ammonium detoxification in the liver, as well as changes in metabolism in other organs like muscle, kidney, and intestine, which prevent ammonium from being effectively eliminated [6]. There is strong evidence linked to NH<sub>3</sub> that it is main part involved in the etiology of encephalopathy. Ammonia is produced by nitrogenous foods in the diet, bacterial metabolism and protein metabolism in the gut, and by the glutamine deamination in the small intestine via glutaminase enzyme. Ammonia cannot be removed efficiently in cirrhosis due to liver dysfunction, portosystemic collaterals, and sarcopenia, and as a result, ammonium cluster increases in plasma & breaches the blood-brain barrier (BBB), causing brain oedema [3]. Continued NH<sub>3</sub> exposure to the brain also causes additional physiological problems. Ammonia, for example, may bind to the GABA receptor complex on astrocytes, causing neurosteroids, which are GABA agonists. Other neurotransmitters, including serotonin, acetylcholine, glutamate, and monamines, implicated in the aetiology of HE [3].

Inflammation has a key role in the pathophysiology of HE. Cirrhosis is associated with liver tenderness and changes in the micro flora of the intestine, which is aggravated by infections, GI bleed, overweight. The production of -inflammatory cytokines is linked to proinflammatory environment, gut dysbiosis. The cytokines released are interleukin 1, IL6, tumor necrosis factor, they work together with ammonia and contribute in development of cerebral edema in HE [2]. In HE, pro-inflammatory signalling from the liver to the brain occurs, and human cerebrovascular endothelial cells exposed to TNF have enhanced ammonia transport capacity. Astroglial cells treated to a mixture of NH<sub>3</sub> and recombinant pro-inflammatory cytokines have higher levels of gene expression associated with HE [7].

The TCA cycle, is the important mechanism of metabolism included in support of brain energy demand, is inhibited by ammonia. In severe form

of HE in patient with liver cirrhosis there is elevated CSF lactate traces are included as the cycle slows down [7].

### 3. DIAGNOSIS

Diagnosis of HE yet need clinical expertise. Signs symptoms seen in patients of HE and the typical neurophysiological or neuropsychological findings are not specific. Therefore the identification of HE in every patient can be ruled out after excluding other likely etiology of brain disorder. At last, the treatment therapy response are the best measure to prove the diagnosis [2]. MHE is the mildest form of HE, affecting up to 80% of patients with cirrhosis of the liver. In an ideal world, every patient at risk for this condition would be tested for it because it is a significant health problem that, despite its mild manifestations, is linked to caregiver burden, increased risk of developing episodes of OHE, sleep disorders, falls, inability to drive, as a result it leads to poor quality of life [8].

Diagnosis can be made with psychometric tests and electrophysiological tests.

PHES (psychometric hepatic encephalopathy score): It includes battery of paper-pencil psychometric tests which is developed specifically for MHE. The subtests includes: NCT-A (number connection test A), NCT-B (number connection test B), LTT (line tracing test), SDT (serial dotting test), DST (digit symbol test). These tests lasts for about 15 minutes. The score is calculated as the sum of all the subtests' score, corrected for age and educational level. Total score < -4 points is suggestive for MHE. This test measures psychomotor speed, attention, set shifting, visual perception, visuomotor ability, visuospatial orientation, concentration and memory. This is recommended as the gold standard for MHE diagnosis because it covers the spectrum of cognitive alterations involved in HE, it is easy to administer and is expensive moreover, it has good prognostic value and validity since it can predict OHE development and survival. It is not sensitive to early neurological changes in a cirrhotic patient, the results are influenced by age and educational level. Some tests has learning effect.

#### 3.1 Diagnosis of Overt Hepatic Encephalopathy

An incident like electrolyte imbalance, gastrointestinal haemorrhage, or abrupt liver

injury can cause overt hepatic encephalopathy. Investigation of suspected initiating factors should be part of the first assessment. Furthermore, OHE must be distinguished from stroke or other types of neuralgic disruption that can appear to be OHE. Grades 2 to 3 of west haven criteria reflect severity of OHE manifestations. Presently no laboratory test is available to diagnose OHE. Although NH<sub>3</sub> plays a chief role in the pathogenesis of OHE but on individual basis serum ammonia level is not accurate in the diagnosis of OHE [9].

#### 4. CHALLENGES

Hepatic encephalopathy own significant impact upon patients' health-related quality of life (HRQOL), with clinical and psychosocial implications. HRQOL has been assessed in cirrhosis using generic and liver-specific instruments, with the majority of research finding that HE has a detrimental influence. Abnormalities in HRQOL include everyday functioning, sleep-wake cycle alterations, and work ability. Changes in the sleep-wake cycle have a significant impact on HRQOL, which is difficult to manage. The existence of HE, the aetiology of cirrhosis, and cognitive reserve all influence the personal effect of HRQOL. Patients with a higher cognitive reserve are better able to cope with HE and its effects on HRQOL than those with a lower cognitive reserve. Patients, as well as caregivers and relatives, are affected by HRQOL impairment. Caregivers of HE patients face a significant financial and psychological strain, which may have an impact on their own health and longevity [10].

##### 4.1 Burden for Patients and Caregivers

HE, unlike most other cirrhosis consequences, affects the entire family. The majority of carers for patients with HE are unpaid and are mainly family that are unprepared for this responsibility. High readmissions, decreasing cognitive performance with each HE episode, and a loss of independence characterise the patient's burden [10]. Patients who have frequent episodes of HE are frequently left with lifelong disability and low standard of living, putting a load on caregivers' and healthcare systems' resources. Patients have been demonstrated in a number of clinical studies shown that patient starts developing knowledge, skills, remembrance deficiencies. If overt OHE is resolved still reaction inhibition persists [9].

This adds to the medical, emotional, and financial burdens that HE places on these carers and their families. HE and Sleep Problems Sherlock et al. were the first to characterise so-called sleep-wake inversion, or the combination of restless evenings and extreme daytime sleepiness, as a marker of overt HE. There is also evidence that sleep disturbances deteriorate after the placement of transjugular intrahepatic portosystemic shunts and improve after starting ammonia-lowering therapy. These findings have led to the hypothesis that the pathophysiology of sleep-wake disruptions in cirrhotic patients is linked to that of HE, and that sleep and neuropsychiatric abnormalities are invariably associated in these patients [10].

#### 5. MANAGEMENT

The severity of HE determines how it is treated. Because 90% of HE patients will experience a precipitating incident, the inciting event must be addressed first. The following step should be to manage the patient's acute mental status alterations and get them back to normal. Finally, to prevent recurrence, supplementary components should be given. It has restricted medical therapy. Rifaximin and lactulose are two common medicines. Nutrition has a chief role in therapy of HE and the prevention of recurrence.

Nourishment – To continue healthy diets are crucial for HE individuals. PEM (protein energy deficiency) in individuals and is linked to bad results. Protein deficiency, recurrent body fluid removal via paracentesis, and anaemia caused by gastrointestinal haemorrhage are all potential causes. To avoid muscle loss, it is necessary to maintain an appropriate protein intake. Second big site for NH<sub>3</sub> metabolism is skeletal muscle, liver being the first. Astrocytes used glutamine synthase which produce glutamine by NH<sub>3</sub> and glutamate. Branched-chain amino acids are then used to make glutamate. This route is most likely the reason that HE patients have decreased serum branch chained amino acid concentrations. This adds to the medical, emotional, and financial burdens that HE places on these carers and their families. HE and Sleep Problems Sherlock et al. were the first to characterise so-called sleep-wake inversion, or the combination of restless evenings and extreme daytime sleepiness, as a marker of overt HE [10-19].

Lactulose and lactitol, nonabsorbable disaccharides, been the cornerstone therapy.

The use of these medications is advocated by (EASLD) direction. The most commonly prescribed medicine for HE is nonabsorbable disaccharides. When compared to antibiotics, nonabsorbable disaccharides showed a higher risk of no improvement.

Antibiotics- Neomycin, vancomycin, and metronidazole are utilized for treatment of HE in the past. However, because of its safety, rifaximin is a superior option used in treatment. Efficacy and tolerability are two important factors to consider. Furthermore, because rifaximin is nonabsorbable, it concentrates in the stomach, limiting its systemic effects.

Polyethylene glycol-It is usually used as it is secure and efficacious purgative.

Liver transplantation and artificial liver support In patients with end stage hepatic dysfunction, Daily dialysis of albumin improves portal pressure and HE and also decreases concentration of NH<sub>3</sub> bilirubin and creatinine in plasma.

## 6. CONCLUSION

Other probable causes of brain dysfunction must be distinguished from HE. There is strong proof that HE affects individual life, sleep-wake rhythms, and the balance of connections between the infected patient and their family, even in its lesser form. HE is a serious consequence of cirrhosis which is linked with high rate death and physical impairment. Hepatic encephalopathy is also linked to high health-care utilisation and negative caregiver effects. Anti-tb drug like rifampicin can be used alone or with lactulose to treat HE severity. Nutritional changes may also help to prevent HE recurrence.

Other alternatives for stubborn HE are splenorenal shunt embolization, phenylbutyrate, and unnatural support of liver, are still being researched.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Dellatore P, Cheung M, Mahpour NY, Tawadros A, Rustgi VK. Clinical Manifestations of Hepatic Encephalopathy. *Clin Liver Dis.* 2020;24(2):189–96.
2. Weissenborn K. Hepatic Encephalopathy: Definition, Clinical Grading and Diagnostic Principles. *Drugs.* 2019;79(Suppl 1):5–9.
3. Patidar KR, Bajaj JS. Covert and Overt Hepatic Encephalopathy: Diagnosis and Management. *Clin Gastroenterol Hepatol.* 2015;13(12):2048–61.
4. Dhiman RK, Chawla YK. Minimal hepatic encephalopathy. *Indian J Gastroenterol.* 2009;28(1):5–16.
5. Elsaid MI, Rustgi VK. Epidemiology of Hepatic Encephalopathy. *Clin Liver Dis.* 2020;24(2):157–74.
6. González-Regueiro JA, Higuera-de la Tijera MF, Moreno-Alcántar R, Torre A. Pathophysiology of hepatic encephalopathy and future treatment options. *Rev Gastroenterol Mex (Engl Ed).* 2019;84(2):195–203.
7. Butterworth RF. Hepatic Encephalopathy in Cirrhosis: Pathology and Pathophysiology. *Drugs.* 2019;79(Suppl 1):17–21.
8. Ridola L, Faccioli J, Nardelli S, Gioia S, Riggio O. Hepatic Encephalopathy: Diagnosis and Management. *J Transl Int Med.* 2020;8(4):210–9.
9. Suraweera D, Sundaram V, Saab S. Evaluation and Management of Hepatic Encephalopathy: Current Status and Future Directions. *Gut Liver.* 2016;10(4):509–19.
10. Montagnese S, Bajaj JS. Impact of Hepatic Encephalopathy in Cirrhosis on Quality-of-Life Issues. *Drugs.* 2019;79(Suppl 1):11–6.
11. Acharya, Sourya, Samarth Shukla, Amol Andhale, and Vidyashree Hulkoti. Hashimoto's Encephalopathy (HE) - Early Manifestation of Impending Thyroid Storm. *Journal of Evolution of Medical and Dental Sciences-Jemds.* 2020;9(30):2164–65. Available:<https://doi.org/10.14260/jemds/2020/471>.
12. Bhagvat, Aditya, Shilpa Abhay Gaidhane, Anusha Gupta, Nazli Khatib, and Priti Abhay Karabdhajane. "Scleroderma Renal Crisis Presenting as Posterior Reversible Encephalopathy Syndrome." *Journal of Evolution of Medical and Dental Sciences-Jemds.* 2020;9(52):4009–11.

- Available:<https://doi.org/10.14260/jemds/2020/876>.
13. Singh, Kirti, Sonakshi Singh, Neema Acharya, Sourya Acharya, and Samarth Shukla. Posterior Reversible Encephalopathy Syndrome Presenting as Atypical Eclampsia and Postpartum Status Epilepticus. *Medical Science*. 2020;24(103):1217–21.
  14. Agarwal, Himanshi, Anil Inamdar, S. A. Inamdar, and Sourya Acharya. Posterior Reversible Encephalopathy Syndrome in a Patient with Eclampsia. *Journal of Evolution of Medical and Dental Sciences-Jemds*. 2019;8(48):3643–45. Available:<https://doi.org/10.14260/jemds/2019/787>.
  15. Bhatia, Avni, Aditya Bhagwat, Sourya Acharya, Amol Bhawane, and Neema Acharya. Postpartum Haemolytic Uremic Syndrome (PHUS) with Posterior Reversible Encephalopathy Syndrome (PRES) Complicating Pregnancy: A Rare Case Report. *Journal of Clinical and Diagnostic Research*. 2019;13(4):OD1–3. Available:<https://doi.org/10.7860/JCDR/2019/40900.12748>.
  16. Singhal, Sonakshi, Amit Baheti, Kirti Singh, Sourya Acharya, and Neema Acharya. Cortical Blindness in Posterior Reversible Encephalopathy Syndrome in Postpartum Eclampsia. *Indian Journal of Medical Specialities*. 2019;10(4):229–30. Available:[https://doi.org/10.4103/INJMS.INJMS\\_123\\_19](https://doi.org/10.4103/INJMS.INJMS_123_19).
  17. Dehane MA, Shingode D, Patil M. Report on Steroid-Responsive Encephalopathy in a Case of Hashimoto's Thyroiditis. *Journal of Pharmaceutical Research International*. 2021;33(34A):1–6.
  18. Somani A, Gaidhane SA, Gaidhane PA, Khatib N, Acharya S. Posterior Reversible Encephalopathy Syndrome (PRES) in Haemolytic Anaemia - A Case Report. *Journal of Evolution of Medical and Dental Sciences-Jemds*. 2021;10(9):656–8.
  19. Sagar VVSS, Ghule A, Talwar D, Kumar S, Acharya S. Heavy Metal Encephalopathy Masquerading as Hepatic Encephalopathy - A Case Report. *Journal of Evolution of Medical and Dental Sciences-Jemds*. 2021;10(15):1088–90.

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