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A Study of the Factors Precipitating Hepatic Encephalopathy in Patients of Chronic Liver Disease Visiting A Tertiary Care Hospital

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ABSTRACT
Hepatic encephalopathy, a severe neuropsychiatric syndrome, is a frequent complication of chronic liver disease. Understanding the precipitating factors and outcomes can guide therapeutic strategies. This study aimed to identify the precipitating factors, underlying chronic liver diseases, severity and outcomes of hepatic encephalopathy. A cross-sectional hospital-based study was conducted at the Department of Medicine of Dr. Kiran C Patel Medical College and Research Institute, Bharuch, Gujarat, over a period of one year. The study comprised 100 patients with chronic liver disease who presented with or developed hepatic encephalopathy during their hospital stay. Alcoholic liver disease was the most common underlying chronic liver disease (54%). The most prevalent precipitating factor was gastrointestinal bleeding (18%). Sleep disturbance was reported by 52% of patients. According to the West haven grading system, 33% of patients presented with grade 3 hepatic encephalopathy and 23% were in grade 4. The mortality rate was 16%. Hepatic encephalopathy remains a severe complication of chronic liver disease with high mortality. Our findings emphasize the importance of early detection and intervention, particularly in managing precipitating factors, to improve outcomes.

INTRODUCTION

Hepatic encephalopathy (HE) is a severe neuropsychiatric syndrome observed in patients with chronic liver disease (CLD) and is a significant contributor to morbidity and mortality worldwide[1]. This complex disorder is characterized by a spectrum of symptoms that range from mild cognitive impairment to deep coma[2]. Over the past few decades, numerous studies have attempted to identify and understand the factors precipitating HE in CLD patients. However, the multifactorial etiology of HE complicates the identification of these precipitants, necessitating a comprehensive analysis of the current literature to delineate the primary triggers accurately.

The primary precipitants of HE in patients with CLD can broadly be categorized into metabolic, infectious and pharmacological factors. It is crucial to understand that while these factors might occur independently, their interplay often amplifies the detrimental neurological outcomes seen in HE[3].

Metabolic disturbances, particularly those related to nitrogen metabolism, have been significantly associated with HE onset. High levels of ammonia-a nitrogen-containing compound in the blood has been implicated in the pathophysiology of HE due to its neurotoxic effects[4]. Moreover, impairment in the urea cycle, which is responsible for ammonia detoxification, further exacerbates the accumulation of ammonia in patients with CLD[5].

Infections, especially spontaneous bacterial peritonitis, are another key precipitant of HE. It is suggested that the systemic inflammatory response elicited by the infection leads to an increase in the permeability of the blood-brain barrier, facilitating the entry of ammonia and other neurotoxic substances into the brain, thereby precipitating HE[6].

Pharmacological factors such as the use of psychoactive drugs and certain diuretics can trigger HE by exacerbating the aforementioned metabolic disturbances and altering the gut microbiota, which plays a critical role in ammonia metabolism[7].

This review intends to provide an exhaustive analysis of the factors precipitating HE in patients with CLD, thereby helping to improve patient management strategies and future therapeutic approaches for this devastating neurological disorder.

Aims and objectives of the study:

- **Objective 1:** To study the clinical profile of hepatic encephalopathy in patients of chronic liver disease
- **Objective 2:** To study the precipitating factors of hepatic encephalopathy in patients with chronic liver disease

MATERIALS AND METHODS

Study design and duration: This study was a hospital-based cross-sectional investigation carried out over a duration of one year from June 2021 to May 2022.

Study population: The study population comprised all diagnosed cases of Chronic Liver Disease that either presented with or developed Hepatic Encephalopathy during their hospital stay in the Department of Medicine at Dr. Kiran C Patel Medical College and Research Institute, Bharuch, Gujarat.

Diagnosis of chronic liver disease and hepatic encephalopathy: Patients were diagnosed with chronic liver disease based on an abdominal ultrasound revealing liver parenchymal changes with surface irregularity, +/-ascites, with or without portal hypertension.

For the diagnosis of hepatic encephalopathy, neuropsychometric tests (Pencil and paper tests) were employed to assess impairment in domains such as attention, processing speed and visuo-spatial functioning. These included the number connection test, digit symbol test, line tracing test and circle dotting test. Informed consent was acquired from patients or attendants before these assessments.

Sample size: The sample size was calculated using the equation:

$$N = \frac{Z^2 \times P \times (1 - P)}{d^2}$$

For the present study, prevalence was taken as 4.5%, based on a hospital-based study conducted at Dr. Kiran C Patel Medical College and Research Institute on the spectrum of complications of chronic liver disease. The precision was 4% and the calculated sample size was 100.

Inclusion and exclusion criteria: The study included patients aged 18 years or older, irrespective of sex, with clinical symptoms and signs of hepatic encephalopathy associated with chronic liver disease. Excluded were patients younger than 18 years, those with encephalopathy due to other known causes and cases of acute alcohol intoxication and alcohol withdrawal states.

Data collection tools, techniques and procedures: A detailed proforma was completed for each patient, including age, sex, hospital number, detailed history and clinical examination results. Laboratory parameters and necessary investigations were carried

out. Tools used included a clinical proforma and the West Haven criteria for grading of hepatic encephalopathy. Each patient's complete blood count, liver function test, renal function test, random blood sugar, serum electrolytes, serum albumin and coagulation profile were conducted. In patients with ascites, paracentesis was performed and the ascitic fluid was sent for culture and sensitivity.

Data analysis: All data were entered into Excel and statistical analyses were performed using standard statistical software. The study aimed to discern the factors precipitating hepatic encephalopathy in patients with chronic liver disease based on these data analyses.

RESULTS

Table 1 presents the demographic and clinical characteristics of 100 patients with hepatic encephalopathy. The age distribution showed that the highest proportion of patients 27% fell in the 40-49 age group, followed by the 30-39 and 50-59 age groups, both constituting 20% of the population. Patients aged 20-29 and 60-69 accounted for 15% each and the smallest proportion 9% were aged 70-79.

Regarding the sex of the patients, a significant majority 73% were male, while females accounted for 27%.

In terms of past medical history, 22% of the patients had a history of jaundice, while 19% had experienced symptoms similar to the presenting ones. Blood transfusion history was found in 17% of the patients and 12% had a history of abdominal surgeries. Less commonly, 11% of patients had a record of immunization, 10% had previous hospitalizations for similar complaints and 9% had a history of intake of hepatotoxic drugs.

The majority of the patients (84%) reported a mixed diet, while the remaining 16% followed a vegetarian diet. As for bowel and bladder habits, 57% of the patients had poor habits, while 43% reported good habits.

Table 2 presents the mean and standard deviation of various characteristics and clinical parameters of the patients. The mean age of the patients was 46 years with a standard deviation of 15 years. The mean duration of alcohol consumption was 7 years with a standard deviation of 2 years.

Among the laboratory findings, the mean hemoglobin (Hb) concentration was 10.96 g%, with a standard deviation of 4.05 g%. The mean total leukocyte count was approximately 6839.22 μL^{-1} of blood with a standard deviation of 2466.85. Patients had a mean random blood sugar level of 175.23 mg dL^{-1} and a standard deviation of 62.58.

Table 1: Demographic and clinical characteristics of patients with hepatic encephalopathy

Parameters	No.	Percentage
Age		
20-29	15	15.00
30-39	20	20.00
40-49	27	27.00
50-59	15	15.00
60-69	14	14.00
70-79	9	9.00
Sex		
Female	27	27.00
Male	73	73.00
Past history		
Abdominal surgeries	12	12.00
Blood transfusion	17	17.00
Immunization	11	11.00
Intake of hepatotoxic drugs	9	9.00
Jaundice in the past	22	22.00
Previous hospitalization for similar complaints	10	10.00
Similar ailments like presenting symptoms	19	19.00
Diet		
Mixed	84	84.00
Vegetarian	16	16.00
Bowel and bladder habits		
Good	43	43.00
Poor	57	57.00

Table 2: Mean and standard deviation of age, duration of alcohol consumption and clinical parameters of patients with hepatic encephalopathy

Parameters	Mean	Standard deviation
Age (years)	46.00	15.00
Duration of alcohol consumption (years)	7.00	2.00
Hb g (%)	10.96	4.05
Total count	6839.22	2466.85
Random blood sugar (mg dL^{-1})	175.23	62.58
Blood urea(mg dL^{-1})	14.56	8.87
Serum creatinine (mg dL^{-1})	1.32	0.53
Serum total bilirubin (mg dL^{-1})	2.70	0.88
Serum albumin	2.68	0.73
Albumin/globulin ratio	1.33	0.54
Serum globulin (g dL^{-1})	3.76	1.85
S.G.P.T	53.01	11.73
S.G.O.T	43.23	12.73
Serum alkaline phosphatase	163.71	61.06
PT-INR	13.30	2.76

The mean blood urea and serum creatinine levels were 14.56 mg dL^{-1} (SD = 8.87) and 1.32 mg dL^{-1} (SD = 0.53) respectively, providing insights into the renal function of the patients.

In terms of liver function tests, the mean serum total bilirubin was 2.7 mg dL^{-1} (SD = 0.88), mean serum albumin was 2.68 g dL^{-1} (SD = 0.73), the mean albumin/globulin ratio was 1.33 (SD = 0.54) and the mean serum globulin level was 3.76 g dL^{-1} (SD = 1.85). The mean levels of serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) were 53.01 U L^{-1} (SD = 11.73) and 43.23 U L^{-1} (SD = 12.73), respectively. The mean serum alkaline phosphatase level was 163.71 U L^{-1} (SD = 61.06).

The prothrombin time-international normalized ratio (PT-INR), an indicator of coagulation status, had a mean value of 13.3 (SD = 2.76). These values collectively provide an overview of the clinical status of the patients in the study.

Table 3 presents the variety of symptoms patients presented with upon their admission. The most frequent complaint was sleep disturbance, affecting

Table 3: Presenting complaints of patients with hepatic encephalopathy

Presenting complaints	Counts	Column N (%)
Altered sensorium	12	12
Black stool	26	26
Distension of abdomen	44	44
Fever	10	10
Hematemesis	14	14
Pain abdomen	28	28
Sleep disturbance	52	52
Swelling of lower limbs	50	50
Yellowish discoloration of eyes	19	19

Table 4: Precipitating factors of hepatic encephalopathy in patients with chronic liver disease

Precipitating factor	Counts	Column N (%)
Constipation	15	15
Dehydration	10	10
Drugs acting on CNS	3	3
Excessive dietary protein	9	9
Gastrointestinal bleeding	18	18
Hepatocellular carcinoma	2	2
Hypokalemia	8	8
Hyponatremia	9	9
Infection	12	12
Renal failure	10	10
Super imposed liver injury	3	3
Surgery	1	1

Table 5: Diagnosis of underlying liver disease in patients with hepatic encephalopathy

Diagnosis	Counts	Column N (%)
Alcoholic liver disease	54	54
Chronic viral hepatitis	13	13
Non-alcoholic fatty liver disease	21	21
Other	12	12

Table 6: West haven grading of hepatic encephalopathy among patients

West haven grade	Counts	Column N (%)
1	26	26
2	18	18
3	33	33
4	23	23

Table 7: Outcome of patients with hepatic encephalopathy

Outcome	Counts	Column N (%)
Discharged	84	84
Expired	16	16

52% of the patients. This was closely followed by swelling of lower limbs, reported by 50% of the patients.

The next prevalent symptom was abdominal distension, experienced by 44% of the patients, whereas 28% reported abdominal pain. A quarter of the patients 26% presented with black stools, indicative of possible upper gastrointestinal bleeding. Altered sensorium and yellowish discoloration of eyes, often indicating jaundice, were each reported by 19% of patients and 14% of the patients had hematemesis. Fever was the least common complaint, with only 10% of patients experiencing this symptom upon presentation.

These complaints mirror the wide-ranging and often overlapping symptomatology of hepatic encephalopathy, highlighting the need for comprehensive clinical evaluation in these patients.

Table 4 outlines the various precipitating factors that triggered hepatic encephalopathy in the study population. The most common precipitating factor was gastrointestinal bleeding, reported in 18% of the patients. This was followed by constipation and infections, both identified in 15 and 12% of the patients, respectively.

Dehydration and renal failure were each reported as precipitating factors in 10% of the patients, while excessive dietary protein and hyponatremia were identified in 9% of the patients. Hypokalemia was a trigger in 8% of the cases.

Less common precipitating factors included drugs acting on the central nervous system and superimposed liver injury, each accounting for 3% of the cases. Hepatocellular carcinoma and surgery were identified as the least common precipitating factors, seen in 2 and 1% of the patients, respectively.

These data illustrate the multitude of factors that can precipitate hepatic encephalopathy in patients with chronic liver disease, emphasizing the importance of comprehensive patient management to prevent and address these triggers.

Table 5 presents the underlying diagnoses of liver disease in the patients. The majority of the patients 54% were diagnosed with alcoholic liver disease (ALD), making it the most common cause of liver disease in this population.

Non-alcoholic fatty liver disease (NAFLD) was the second most common diagnosis, affecting 21% of the patients. Chronic viral hepatitis, including hepatitis B and C, was present in 13% of the patients.

Other less common diagnoses accounted for the remaining 12% of the cases. This diverse spectrum of diagnoses underscores the wide range of liver diseases that can lead to hepatic encephalopathy.

Table 6 displays the distribution of hepatic encephalopathy severity according to the West haven grading system.

The majority of patients (33%) were categorized into grade 3, representing severe hepatic encephalopathy. Patients falling into West haven grade 1, indicative of minimal hepatic encephalopathy, made up 26% of the population.

Meanwhile, grade 4, representing the most severe form of hepatic encephalopathy with coma, was observed in 23% of patients. The remaining 18% of patients were categorized into grade 2, indicating moderate hepatic encephalopathy.

This distribution indicates a significant proportion of patients present with severe forms of hepatic encephalopathy, emphasizing the importance of early recognition and management of this serious complication of chronic liver disease.

Table 7 depicts the outcomes for the patients in the study. A significant majority of patients 84% were discharged after successful treatment. However, the

condition proved fatal for 16% of the patients, highlighting the potential severity and risk of mortality associated with hepatic encephalopathy.

DISCUSSIONS

Our study provides valuable insights into the precipitating factors, underlying diagnoses and outcomes of hepatic encephalopathy in patients with chronic liver disease. Notably, our findings reflect a substantial degree of concordance with previous research, while also yielding novel observations that advance our understanding of this complex condition. In our cohort, the most common underlying diagnosis was alcoholic liver disease (ALD), accounting for 54% of cases. This aligns with global trends where alcohol abuse remains a significant contributor to liver disease and associated complications[8]. The prevalence of non-alcoholic fatty liver disease (NAFLD) at 21% also mirrors the rising incidence of this condition, propelled by the global epidemic of obesity and metabolic syndrome[9].

Gastrointestinal bleeding emerged as the most common precipitating factor of hepatic encephalopathy in our study (18% of cases), which is consistent with the literature. Studies have reported figures ranging from 10-25%[10,11], highlighting the critical role of gastrointestinal bleeding in triggering hepatic encephalopathy.

However, our findings contrast with some previous studies that identified infections and constipation as the most common precipitating factors[12]. These discrepancies may reflect geographical and population differences, emphasizing the need for region-specific data to guide the management of chronic liver disease patients.

One notable result was the high prevalence of sleep disturbance 52% among the presenting complaints of patients. Although, sleep disturbances have been recognized in the literature as a feature of hepatic encephalopathy[13], their prevalence in our study is significantly higher than previous reports. This discrepancy merits further research to elucidate the factors contributing to sleep disturbances in this patient population.

The West haven grading of hepatic encephalopathy in our study indicated a substantial proportion of patients (33%) were in grade 3 and 23% were in grade 4, the most severe stage of the condition. A study conducted by Patidar *et al.*[10] reported a lower prevalence of grade 3 and 4 encephalopathy (28 and 15%, respectively), indicating a potential discrepancy[10]. This might be due to regional differences or variation in the underlying liver diseases and their management.

Our study reported a mortality rate of 16%, similar to the figures reported by Sharma *et al.*[14] and slightly lower than the mortality rate of 18-20% reported in some Western studies[15]. This reflects the severe nature of hepatic encephalopathy and the urgent need for early recognition and intervention.

CONCLUSION

Our study underscores the diverse precipitating factors and varying severity of hepatic encephalopathy in patients with chronic liver disease. These findings align largely with the existing literature, indicating gastrointestinal bleeding as the most common precipitating factor and demonstrating high prevalence of severe hepatic encephalopathy grades. The outcome data confirms the serious nature of hepatic encephalopathy, with a significant proportion of patients succumbing to the condition. This study highlights the urgency of early detection, prevention and management of precipitating factors in patients with chronic liver disease to improve patient outcomes.

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