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Precipitating Factors and Clinico-Endoscopic Study of Patients with Hepatic Encephalopathy Type C

Hepatik Ensefalopati Tip C Hastalarında Tetikleyici Faktörler ve Kliniko-Endoskopik Çalışma

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Abstract

Introduction: Hepatic encephalopathy (HE) is a decline in brain function as a result of severe liver disease and its inadequacy to remove toxins from the body. It is characterized by personality changes, intellectual impairment, and loss of consciousness. This study was conducted to determine the precipitating factors and endoscopic features of hepatic encephalopathy in patients with liver cirrhosis and evaluate the associated clinical features admitted in a tertiary hospital in Central India.

Material and Method: This hospital-based descriptive cross-sectional study was conducted from November 2016 to October 2018 on 102 patients with hepatic encephalopathy type C, aged above 18. All patients were carefully examined, relevant investigations performed, and data collected through pre-designed proforma. They were sent for statistical analysis where categorical outcomes were compared between study groups using the Chi-square test /Fisher's Exact test.

Results: The prevalence of HE was 19.6% in our study. In this study, we observed that constipation (26.5%), electrolyte imbalance (21.6%), renal failure (18.6%), and upper GI bleeding (18.6%) be among the leading precipitants for HE. Besides liver failure, the associated abnormalities in various factors like coagulation abnormalities, renal derangement, and changes in serum sodium levels can lead to the progression of HE to higher grades.

Conclusion: It is essential to identify the different factors like constipation, electrolyte imbalance, renal failure, and upper GI bleeding early in the course of cirrhosis to help prevent the development of HE.

Keywords: Brain, cirrhosis, hepatic encephalopathy, liver, precipitating factors

Öz

Giriş: Hepatik ensefalopati (HE), ağır karaciğer hastalığı ve vücuttan toksinleri atmakta yetersiz kalması sonucu beyin fonksiyonlarında azalmadır. Kişilik değişiklikleri, zihinsel bozulma ve bilinç kaybı ile karakterizedir. Bu çalışma, karaciğer sirozu olan hastalarda hepatik ensefalopatinin tetikleyici faktörlerini ve endoskopik özelliklerini belirlemek ve Orta Hindistan'da üçüncü basamak bir hastaneye kabul edilen ilişkili klinik özellikleri değerlendirmek için yapılmıştır.

Gereç ve Yöntem: Bu hastane bazlı tanımlayıcı kesitsel çalışma, Kasım 2016 ile Ekim 2018 tarihleri arasında, 18 yaş üstü hepatik ensefalopati tip C'li 102 hasta üzerinde yürütülmüştür. tasarlanmış proforma Kategorik sonuçların çalışma grupları arasında Ki kare testi/Fisher's Exact testi kullanılarak karşılaştırıldığı istatistiksel analiz için gönderildiler.

Bulgular: Çalışmamızda HE prevalansı %19,6 idi. Bu çalışmada HE için önde gelen presipitanlar arasında kabızlık (%26,5), elektrolit dengesizliği (%21,6), böbrek yetmezliği (%18,6) ve üst gastrointestinal kanama (%18,6) olduğunu gözlemledik. Karaciğer yetmezliğinin yanı sıra, pıhtılaşma anormallikleri, böbrek düzensizliği ve serum sodyum seviyelerindeki değişiklikler gibi çeşitli faktörlerdeki ilişkili anormallikler, HE'nin daha yüksek derecelere ilerlemesine neden olabilir.

Sonuç: Siroz seyrinde kabızlık, elektrolit dengesizliği, böbrek yetmezliği ve üst GİS kanaması gibi farklı faktörlerin HE gelişimini önlemeye yardımcı olması için erken dönemde belirlenmesi önemlidir.

Anahtar Kelimeler: Beyin, siroz, hepatik ensefalopati, karaciğer, çöktürücü faktörler

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INTRODUCTION

Hepatic encephalopathy is a challenging complication of advanced liver disease. It is a syndrome and is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction after excluding brain disease. It is characterized by personality changes, intellectual impairment, and a depressed level of consciousness.[1] Three types of HE are traditionally differentiated according to the underlying cause: Type A as an essential component of acute liver failure, type B as a consequence of portosystemic shunts in the absence of liver dysfunction, and type C in patients with liver cirrhosis and portosystemic bypass.[2] The current discussion concerns whether HE in patients with acute-on-chronic liver failure should be considered separately (type D). It is clinically, pathophysiologically, and prognostically distinct from types A–C. Hepatic encephalopathy occurs in approximately 30–45% of patients with cirrhosis and 10–50% of patients with trans jugular intrahepatic portosystemic shunt, while minimal hepatic encephalopathy affects approximately 20–60% of patients with liver disease.[3]

More than 40% of people with cirrhosis develop hepatic encephalopathy, classified under Type C.[4] More than half of those with cirrhosis and significant HE live less than a year. In those who can get a liver transplant, the risk of death is less than 30% over the subsequent five years.[5] A significant impairment is seen in social interaction, alertness, emotional behavior, sleep, home management, recreation, and past times. Hence it is said that hepatic encephalopathy affects health-related quality of life in cirrhosis patients. So, it is necessary to screen people with cirrhosis for minimal encephalopathy so that treatment can be started early to prevent the development of overt encephalopathy and further complications such as spontaneous bacterial peritonitis or esophageal varices. Further improvement of prognosis would be achieved by early recognition and management of precipitating factors.[6]

There is a lack of studies in India on the precipitating factors of hepatic encephalopathy. Hence, this study was carried out with the primary objective of estimating the prevalence and ascertaining the most common precipitating factor and their frequency in patients with hepatic encephalopathy Type C. They were previously diagnosed with liver cirrhosis and admitted to a tertiary care hospital in central India. The secondary objective was to evaluate the associated clinical features in such cases.

MATERIAL AND METHOD

Study populations

A cross-sectional, single-center, hospital-based, observational study was conducted on 521 consecutive cirrhotic patients who were admitted in the medicine inpatient and intensive care unit (ICU) setting of a tertiary care hospital in central India over two years between Nov 2016 and Oct 2018. Convenient sampling was followed, and the entire sampling frame was included in the study. Institutional Ethics Committee approval was obtained before commencement of the study and written informed consents were collected from the patients.

Patients above 18 years of age diagnosed with liver cirrhosis and hepatic encephalopathy were included in the study. Patients with acute fulminant hepatitis, extrahepatic portal hypertension, other metabolic encephalopathies, intracranial lesions, and those under antipsychotic medication were excluded from the study.

Demographic and clinical data: Patients who fulfilled the inclusion and exclusion criteria were enrolled in the study. All patient demographic data like age, sex, and clinical data like presenting symptoms, signs, blood pressure (BP), along with anthropometric data like height (cm), weight (kg), was obtained. Body mass index (kg/m²) was calculated using the standard formula.

Laboratory investigations: All the patients were investigated using complete hemogram, liver, and kidney function tests, coagulation markers like prothrombin time (PT), international normalized ratio (INR), chest X-ray, and ultrasonography of abdomen. Blood collection was done following all aseptic precautions, and all tests were done on standard laboratory instruments available at the hospital.

Ascitic fluid examination: Ascitic fluid tapping was done in all aseptic conditions as per standard procedure and was examined to rule out the presence of spontaneous bacterial peritonitis.

Endoscopy: All patients were subjected to the upper gastrointestinal (GI) endoscopy to identify the presence of varices. A single, experienced gastroenterologist performed all the endoscopic procedures in study patients.

Classification of HE: Patients with HE were classified as per West-Haven criteria as given below.

Grade 1: Trivial lack of awareness, euphoria or anxiety, shortened attention span and impaired performance of addition; Grade 2: Lethargy or apathy, minimal disorientation for time or place, subtle personality change, inappropriate behavior, and impaired performance of subtraction; Grade 3: Somnolence to semi-stupor, but responsive to verbal stimuli, confusion and gross disorientation and Grade 4: Coma (unresponsive to verbal or noxious stimuli).

Assessment of severity of cirrhosis: The severity of cirrhosis was assessed using the Child Turcotte-Pugh classification criteria.[7] The patients were divided into three groups depending on the severity:

Class A: 5 to 6 points (least severe liver disease)

Class B: 7 to 9 points (moderately severe liver disease)

Class C: 10 to 15 points (most severe liver disease)

Identification of precipitating factors for HE:

Operational definitions

The definitions adopted for confirming different risk factors in patients with cirrhosis were as below:[8]

Constipation: It was defined as straining, lumpy or hard stools, the sensation of incomplete evacuation, the sensation of anorectal blockage/obstruction during at least 25% of defecation with fewer than three defecations per week.

Upper GI bleeding: It was defined as the presence of hematemesis or melena secondary to oesophageal, gastric varices, peptic ulcer, Mallory Weiss tear, gastric erosions, esophagitis. Any bleeding source above ligament of Treitz.

Electrolyte abnormalities: These were defined as evidenced by hyponatremia (<135 mEq/L) or hypokalemia (<3 mEq/L).

Hepatorenal syndrome: It was defined in the presence of cirrhosis with ascites if serum creatinine level ≥ 1.5 mg/dL (133 µmol/L), no or insufficient improvement in serum creatinine level (remains≥ 1.5 mg/dL) 48 hours after diuretic withdrawal and adequate volume expansion with IV albumin, absence of shock, absence of intrinsic renal disease.

Dehydration: It was said to be present when a patient has loss of skin turgor, dry tongue, sunken eyeballs, and evidence of tachycardia and hypotension on clinical examination.

Superimposed liver injury: In the presence of alcoholic hepatitis, hepatitis A, E, or pre-existing hepatitis B or C with deranged liver enzymes.

Infection – SBP: It was defined as an infection of ascitic fluid in the absence of any intra-abdominal, surgically treatable source of infection.

Infection – UTI: It was defined as infections of the lower urinary tract (i.e., the urethra (urethritis) or the bladder (cystitis) with evidence of clinical features and/or presence of at least five pus cells or bacteria identified in urine on microscopy.

Infection – Pneumonia: It was defined as an acute infection of the lung parenchyma by one or co-infecting pathogens with clinical symptoms of cough and fever and/or evidence of consolidation on chest X-ray.

Ethics Statement: The study was approved by the Institutional Review Board and the Ethics Committee of the NKP Salve Institute of Medical Sciences and Research Centre (Date: 2016, Decision No: 17/2016). All participants agreed to and signed the informed consent before the study. Thus, the research has been conducted in compliance with the 1964 Declaration of Helsinki's ethical standards and subsequent amendments.

Statistical Methods

C-P Classification, MELD Score, CBC parameters and renal function parameters, and INR levels were considered as primary outcome variables. Demographic variables, clinical features, and clinical signs and complications were considered as secondary outcome variables. Hepatic encephalopathy (covert vs. overt) was considered as a primary explanatory variable. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. Univariate binary logistic regression analysis was performed to test the association between the explanatory variables and outcome variables. An unadjusted Odds ratio along with 95% CI is presented. P-value <0.05 was considered statistically significant. coGuide version V.1.0 was used for statistical analysis.[9]

RESULTS

A total of 102 subjects were included in the final analysis.

The mean age of the participants was 45.18±7.97 years, and the majority of the study participants were males 101(99.02%) Summary of habits, laboratory parameters (liver function test, creatinine, prothrombin time) of the participants were given (**Table 1**).

Table 1: Summary of personal habits and laboratory parameters (N=102)

Parameters	Summary
Personal habits	
Alcoholism	92 (90.20%)
Tobacco chewing	55 (53.90%)
Smoking	49 (48.0%)
HR	85.97±13.47
SBP	99.39±9.92
DBP	60.88±6.91
Hemoglobin (%)	8.86±1.23
Platelet	1.37±0.31
Serum Creatinine (Mg/Dl)	1.49±0.53
Serum Sodium (130 Meq/L),	133.43±5.34
Serum Potassium (Meq/L)	3.65±0.63
Total Bilirubin (Mg/Dl),	4.1±2.4
Serum Albumin (Mg/Dl),	2.34±0.3
Serum Globulin (Mg/Dl),	3.52±0.4
SGOT (IU)	83.02±24.84
SGPT (IU)	57.89±34.57
Prothrombin Time (Sec)	16.74±2.19
INR	1.66±0.23

UGI-Endoscopy was found to be normal for 30 subjects (29.41%). Out of the 72 (70.59%), subjects showed an abnormality, 25 (24.51%) had small oesophagal varices, 13 (12.75%) had large oesophagal varices, and 11 (10.78%) had oesophagal and gastric varices (**Table 2**). In the present study, the most common precipitating factor detected was constipation (26.5%), followed by electrolyte imbalance (21.6%) and renal failure (18.6%) (**Table 2**). In C P classification 22 (21.57%) subjects comes under class A, 62 (60.78%) comes under class B and 18 (17.65%) comes under class C. MELD score was < 20 for 18 (17.65%), score 21 to 25 for 45 (44.12%), score 26 to 30 for 29 (28.43%), score >30 for 10 (9.80%). 3 (2.94%) subjects comes under grade 0, 11 (10.78%) comes under grade 1, 45 (44.12%) comes under grade 2, 37 (36.27%) comes under grade 3, 6 (5.88%) comes under grade 4 West Haven Grade.

Table 2: Summary of baseline characteristics parameters (N=102 subjects)

Baseline characteristics	Frequency
Clinical features	
Yellow discoloration of eyes	71 (69.61%)
Abdominal distention	68 (66.67%)
Altered sleep	44 (43.14%)
Signs	
Pallor	98 (96.08%)
Icterus	79 (77.45%)
Ascites	71 (69.61%)
UGI-Endoscopy	
Normal	30 (29.41%)
Abnormal	72 (70.59%)
• Small esophageal varices	25 (24.51%)
• Large esophageal varices	13 (12.75%)
• Esophageal and gastric varices	11 (10.78%)
Number connection test (NCT) A and B	14 (13.7%)
Hepatic Encephalopathy	
Covert	14 (13.73%)
Overt	88 (86.27%)
Factors	
Constipation	27 (26.5%)
Electrolyte abnormalities	22 (21.6%)
Renal failure	19 (18.6%)
Upper GI bleeding	19 (18.6%)

Univariate logistic regression to assess the factors affecting Hepatic Encephalopathy (Overt) showed significant relation with C-P classification B (P value=0.004, OR= 6.54), C (P value=0.04, OR=9.71) taking Base line as classification A. Taking MELD score >= 30 as baseline, 21 to 25 (P value=0.01, OR=9.33), 26 to 30 (P value=0.04, OR= 5.78) showed significant relation with Hepatic Encephalopathy (Overt) (**Table 3**).

DISCUSSION

In this cross-sectional observational study, the patients with liver cirrhosis were screened, and the prevalence of hepatic encephalopathy was observed, which was found to be 19.6%. It has been reported that the prevalence of overt HE at the time of diagnosis of cirrhosis is 10–14% in general and 16–21% in those with decompensated cirrhosis. The cumulated numbers indicate that overt HE will occur in 30–40% of those with cirrhosis at some time during their clinical course.[10] A study by Romero-Gomez et al. reported the prevalence of overt HE to be 30% in patients with cirrhosis.[11] A study by Saunders et al. reported that HE was present in 12% of patients with decompensated cirrhosis.[12] Jepsen et al. reported that 11% of patients with cirrhosis developed HE over long-term follow-up.[13] Thus, our estimates are similar to the reported prevalence of HE. This suggests that at least 1 out of 5 patients with cirrhosis would develop HE during the clinical course.

There was a male preponderance with only a single female patient. Tariq et al., in their study, had reported that 53% of patients were males and 47% were females.[14] This contrasts with our observation. The gender difference is probably because most patients included in our study were alcoholics. Alcoholism was the most frequent etiology found in this study, followed by hepatitis B and hepatitis C. In India, alcoholism is more prevalent in males and less frequently seen in females. Heavy drinking has also been reported more in men than women.

Most of the patients had a classical presentation in the form of distension of the abdomen. At end-stage cirrhosis, ascites causes symptoms including abdominal distention, nausea and vomiting, early satiety, dyspnea, lower-extremity edema, and reduced mobility.[15]

Table 3: Univariate logistic regression analysis of factors associated with hepatic encephalopathy (overt) in study population (N=102)

Parameter	Hepatic Encephalopathy		Un adjusted odds ratio 95% CI	P value
	Covert(N=14)	Overt(N=88)		
Age	40.64± 6.23	45.90±8.01	1.095 (1.011-0.1.186)	0.026
Gender (Base line=Female)				
Male	13 (92.86%)	88 (100%)	0 (0-0)	1.000
Female	1 (7.14%)	0 (0%)		
C-P Classification (Baseline =A)				
A	8 (57.14%)	14 (15.91%)		
B	5 (35.71%)	57 (64.77%)	6.514 (1.846-22.990)	0.004
C	1 (7.14%)	17 (19.32%)	9.714 (1.081-87.313)	0.042
MELD Score (Base line = >30)				
≤20	4 (28.57%)	14 (15.91%)	2.333 (0.433-12.568)	0.324
21 To 25	3 (21.43%)	42 (47.73%)	9.333 (1.664-52.337)	0.011
26 To 30	3 (21.43%)	26 (29.55%)	5.778 (1.014-32.930)	0.048
>30	4 (28.57%)	6 (6.82%)		
Complications (Base line = No)				
Upper GI Bleeding	2 (14.29%)	17 (19.32%)	1.437 (0.294-7.029)	0.655
Coagulopathy (Base line = >1.5)				
(INR >1.5)	13 (92.86%)	74 (84.09%)	2.459 (0.297-20.340)	0.404
<1.49	1 (7.14%)	14 (15.91%)		

Most of the patients had a classical presentation in the form of distension of the abdomen. The distention of the abdomen is due to the development of the ascites in patients with cirrhosis. The presence of ascites is the hallmark of decompensated cirrhosis. Patients with cirrhosis are at risk of infections like spontaneous bacterial peritonitis. It has been observed that bacterial infections are common and account for major morbidity and mortality in cirrhosis. Patients with cirrhosis are immunocompromised and increased susceptibility to develop spontaneous bacterial infections, hospital-acquired infections, and a variety of infections from uncommon pathogens.[16] Thus, by assessing the symptomatology, it is possible to determine the severity of patients with cirrhosis.

We found that the percentage of patients in grades 1,2,3 and 4 of HE increased gradually from 9.7% to 83.3% in C-P class C, suggesting a significant association between severity of liver disease and progression of HE grades. This suggests that the severity of HE increases with an increase in severity of the cirrhosis as assessed by CP score. However, the MELD score varied between different grades of HE. Scores of 26 to 30 were seen in 50% of cases with grade 4 HE and were seen in a lower percentage of patients in lower grades of HE. A study by Sharma et al.[10] evaluated the patients with cirrhosis, of which 37%, 36%, and 27% were in C-P class A, B, and C, respectively. They observed that both CP score ($p=0.02$) and MELD score ($p<0.001$) were significantly greater in patients developing minimal HE than non-HE patients.[16] Gupta et al. also reported CP class (52.3%, 67.7%, and 92.3% in class A, B, and C, respectively), MELD score, and venous ammonia levels as predictors of minimal HE in cirrhosis patients.[17] When considering mortality outcomes in HE cases, a study from Udayakumar et al. observed no significant difference in the proportion of patients in CP class B and C or of MELD score in survivors and non-survivors.[18] Similarly, Sasidharan et al. reported patients in CP class C with a MELD score of >15 and serum bilirubin of 7.3 mg/dL were predictors of mortality in severe grades of HE.[19]

Constipation (26.5%) was the most common precipitating factor of HE, followed by electrolyte abnormalities (21.6%), renal failure (19.6%), and upper GI bleed (18.5%). Infection, which is one of the important precipitating factors, SBP and UTI were observed in 8.8% and 5.9% of patients. Most patients had two (57.8%) and three (24.5%) precipitating factors for HE. Thus, the evidence from various studies demonstrates that constipation, infections, electrolyte abnormalities, upper GI bleeding, renal failure, and dehydration as the most frequently encountered factors for the precipitation of HE. Therefore, every attempt should be made to prevent or reduce the occurrence of these complications in patients with cirrhosis.

In this study, INR levels between 1.5 to 2 were seen in 83.3% of patients in grade 4 HE, and level >2 was evident in 66.7% cases in grade 0. The overall distribution of the proportion of patients thus showed a statistically significant difference ($p<0.001$). Raised INR is suggestive of progressed liver disease, and this coagulation abnormality can be seen even in the absence of HE. Our finding is important in that patients in lower grades of HE, i.e., covert HE can also have coagulation abnormalities which should be identified and treated early. A study from Dhanunjaya et al. reported increasing levels of INR with increasing severity of liver disease, which suggests increased coagulation abnormalities. They observed a significant difference in D-dimer levels in increasing severity of the disease assessed by CP class. Thus, apart from coagulation defects, increased fibrinolytic activity could be one of the important factors responsible for the bleeding tendency in liver disease.[20] However, it is important to note that although traditionally, liver cirrhosis has been considered a disease with hypercoagulability state and increased bleeding tendency due to severe homeostatic disruption in liver disease, until recently, there is increasing awareness and evidence that cirrhotic patients are not completely protected from thrombotic events although they have an elevated international normalized ratio and auto anticoagulation.[21]

Though we did not observe any significant association of different grades of HE with factors like platelet count, sodium levels, bilirubin levels, creatinine levels, and serum albumin, these can contribute in various ways to the development and progression of HE. Nearly 25% of patients had small, and 12.8% of patients had large oesophageal varices. Most patients belonged to class B of the CTP classification. The varices are potential sources of upper GI bleeding. Upper GI bleeding is another important precipitating factor, and thus all the patients should be subjected to endoscopy to diagnose varices early and thus prevent HE. Upper GI bleeding is an established risk factor for the precipitation of HE.

We found that the distribution of GI bleeding did not vary significantly ($p=0.655$) in different grades of HE. Similarly, complications like SBP ($p=0.222$), HRS ($p=0.266$), and coagulopathy ($p=0.740$) did not differ significantly in grades of HE. Though the association was observed to be non-significant, the presence of these complications has been identified as precipitants for HE. A study from Romero-Gomez et al. observed that among 63 patients, 34 (53%) exhibited subclinical HE. 30% of them developed overt HE during follow-up.[11] Thus, the presence of complications like oesophageal varices should be looked after in patients with covert HE as it can predict progression to overt HE. This suggests that there is a complex association of different complications with each other, and more complications can result in adverse outcomes.

The limitations of our study were that it involved only a single-center and small sample size. The absence of data on etiology, lack of follow-up data like mortality rate and ICU admission were not assessed, which adds to the limitations. Data was not collected on specific infections except for SBP, UTI, and pulmonary infections. Further, large-scale, multicenter trials should be evaluated using robust clinical outcomes to validate our study.

CONCLUSION

Liver cirrhosis is an important sequela of chronic alcoholism, which is highly prevalent in India. Hepatic encephalopathy is one of the important complications of decompensated cirrhosis. The prevalence of HE was 19.6% in our study, which suggests that one out of five cirrhotic patients can develop HE. It has a very adverse effect on health-related quality of life. The majority of times, one or more precipitating factors are responsible for HE. In our study, we observed that constipation, electrolyte imbalance, renal failure, and upper GI bleeding be among the leading precipitants for HE. Thus, it is important to identify these factors early in the course of cirrhosis to help prevent the development of HE.

Abbreviations: CP-Child-Pugh, GI- Gastrointestinal, HE- Hepatic Encephalopathy, MELD- Model For End-Stage Liver Disease SBP- Systolic Blood Pressure, UTI- Urinary Tract Infection

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Institutional Review Board and the Ethics Committee of the NKP Salve Institute of Medical Sciences and Research Centre (Date: 2016, Decision No: 17/2016).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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