

Original Article

Precipitating Factors of Hepatic Encephalopathy in Patients with Cirrhosis of Liver in a Tertiary Care Center of Nepal

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ABSTRACT

Introduction: Chronic liver disease is a common disease presenting in hospitals of Nepal. A large number of cirrhotics present with hepatic encephalopathy. Various precipitating factors are present which precipitate hepatic encephalopathy. This study was intended to identify the precipitating factors of hepatic encephalopathy and to assess whether identifiable precipitating factors of encephalopathy is present.

Materials and Methods: This was hospital based observational cross-sectional study conducted at Department of Medicine, Manipal Teaching Hospital, Pokhara. A total of 80 patients were included. The precipitating factors for encephalopathy were documented along with grading. SPSS was used for data analysis.

Results: The mean age of the patients was 54.725 ± 11.33 years. There were 55 males (68.8%) and 25 (31.3%) females in the study. All the patients (100%) had significant amount of alcohol consumption. It was found that hepatic encephalopathy was more severe in higher Child-Pugh class as compared to a lower one. At least 1 precipitating factor was identified in 81% patients. The common precipitating factors were increased protein intake, bleeding, infection, diarrhea and constipation.

Conclusions: We conclude that there are different factors which play a key role in precipitating hepatic encephalopathy, high protein diet, constipation, bleeding and infections being predominant. A minor change in dietary habit, regular follow up and timely visit to the health care facility may result in the identification of these common precipitating factors like infections, constipation and diarrhea.

Keywords: Chronic liver disease; Cirrhosis; Hepatic encephalopathy

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INTRODUCTION

Chronic liver disease (CLD) and cirrhosis affect more than 5.5 million people in the United States and hundreds of millions all over the world.¹ Hepatic encephalopathy (HE) is a syndrome observed in patients with cirrhosis. It is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of other known causes of brain disease.² It is characterized by personality changes, intellectual impairment and a depressed level of consciousness. An important prerequisite for the syndrome is diversion of portal blood into the systemic circulation through portosystemic collateral vessels.³ HE may develop in patients without cirrhosis who have undergone portocaval shunt surgery. The development of HE is explained, to some extent, by the effect of neurotoxic substances, which occur in patients with cirrhosis and portal hypertension. Abnormalities in glutamatergic, serotonergic, gaminobutyric acid-ergic (GABA-ergic) and catecholamine pathways have been described in experimental HE.⁴ Ammonia is a key factor in the pathogenesis of HE. About 30% of patients with cirrhosis die due to HE.⁵

Perhaps the most common predisposing factor is gastrointestinal bleeding (GIB), which leads to an increase in the production of ammonia and other nitrogenous substances in the gut.⁶ GIB contributes approximately 15-20 grams of proteins per 100 ml of the blood and is responsible for 18-34% of cases of portosystemic encephalopathy.⁷ Excess dietary, especially animal protein intake may also precipitate HE through the same mechanism.⁸ The effects of a mainly vegetable protein diet were compared with an animal protein diet in eight patients with cirrhosis and chronic permanent encephalopathy, under optimum lactulose therapy. After a run-in period, patients were fed two equi-caloric, equi-nitrogenous diets for 7 days (71 g total proteins). Other common factors are vomiting, diarrhea, over-diuresis or very large paracentesis. Systemic alkalosis causes an increase in the amount of nonionic ammonia (NH₃) relative to ammonium ions (NH₄⁺).⁹ Only nonionic ammonia readily crosses the blood-brain barrier and accumulates in the central nervous system. Hypokalemia also directly stimulates renal ammonia production. Drugs like narcotics, tranquilizers, sedatives and diuretics can also cause hepatic encephalopathy.⁹ Various infections such as urinary tract infection (UTI), chest infection and spontaneous bacterial peritonitis (SBP) are frequent causes of morbidity in cirrhosis, including the development of HE.¹⁰ Usually related to portosystemic shunts and with no exogenous precipitating factors. Bacterial infections are frequent causes of morbidity in cirrhosis, including the development of HE in its acute form, but there are no reports of its role in chronic forms of HE. **METHODOLOGY:** We studied 168 episodes of hepatic encephalopathy in 111 patients with cirrhosis who were admitted to hospital during the last four years. Clinical staging was used for the diagnosis of acute and chronic HE, complemented by number connection tests and EEG. In chronic HE the diagnostic criteria were intolerance to animal proteins and a continuous need for medications and/or special diets. Alcohol was the etiology of cirrhosis in 81.1% of patients, hepatitis B or C virus in 12.6% and various factors in 6.3%. The male/female ratio was 3:1 and mean age was 53 years. **RESULTS:** Twenty patients (18%.) Moreover, constipation, surgery and super imposed acute liver disease may also lead to the onset of HE.⁹ Studies have indicated that overt HE affects 30 to 45% of patients with cirrhosis and a higher percentage may be affected by minimal degree of encephalopathy.¹¹

This study was intended to identify the precipitating factors of hepatic encephalopathy in patients with cirrhosis and to assess whether identifiable precipitating factors of HE is present in patients with CLD.

MATERIALS AND METHODS

This was hospital based, descriptive, observational, cross-sectional study conducted at Department of Medicine, Manipal Teaching Hospital, Pokhara, Nepal from March 2013 to March 2014 for a duration of one year. This study was conducted after obtaining ethical approval from Manipal College of Medical Sciences, Ethical Committee. Consecutive sampling technique was used and 80 patients were included in the study. Informed consent was obtained from all the study participants or attendants before enrollment. A total of 80 patients aged 18 years and above meeting the inclusion criteria were enrolled in the study. History and detailed clinical examination was performed as per the working Performa. HE was diagnosed after excluding metabolic disorders, infectious diseases, intracranial vascular events and intracranial space occupying lesion (SOL). Knowledge of existing acute or chronic liver disease, the history of precipitating factors and/or prior diagnosis of HE determined by history, clinical examination and relevant specific investigations. The inclusion criteria included patients admitted with HE in medicine department irrespective of sex, race and ethnic group and age more than 18 years. Patients failing to provide informed consent, presence of diagnosis other than HE that explained the neuropsychiatric manifestation at the time of admission, presence of space occupying lesion, hemorrhage, or other radiological abnormalities in the CT scan of head and presence of metabolic abnormalities like hypoglycemia, hyperglycemia, hyponatremia, hypernatremia were excluded from the study. The following precipitating factors were especially looked for which included increased protein diet, bowel habit either constipation or diarrhea, vomiting that can give rise to electrolyte disturbances, GIB, fever, leukocytosis indicating infections especially UTI, SBP and pneumonia, hypokalemia, hyponatremia, use of sedative or therapeutic paracentesis.

The routine and relevant investigations were carried like, full blood count, urine examination, blood urea and creatinine, blood glucose, chest radiograph, serum electrolytes, serum albumin, coagulation profile, ultrasound of abdomen, liver function test (LFT), HbsAg and Anti-HCV (if not previously diagnosed and not a known case).

The HE was graded according to the West Haven Criteria.¹² USG abdomen was done to assess for liver size, parenchymal echogenicity, portal vein diameter, spleen size and for the detection of ascites. In the presence of ascites, diagnostic ascitic tapping was also performed to look for the evidence of any SBP. Classification of the severity of the disease was classified according to the Child-Pugh classification.

The patients diagnosed as the case of HE were then admitted and details of the history, physical examination, and investigations were evaluated and entered in the working Performa. The detailed evaluation was done to find the precipitating factors for HE in

the individual patients among the well-established precipitating factors. The patients were then started with appropriate treatment and the clinical improvement was noted.

Data obtained were entered in Microsoft Excel and statistical analysis was done by SPSS version 20 (SPSS Inc, Chicago USA). Baseline characteristics were represented using appropriate descriptive statistics. Descriptive statistics such as percentage, mean, standard deviation and inferential statistics was also applied to identify relation between two variables at 5% level of significance.

RESULTS

A total of 80 patients with CLD presenting in HE meeting the inclusion criteria were included in this study. The mean age of the patients was 54.725 ± 11.33 years with age ranging from 25 to 80 years. There were 55 males (68.8%) and 25 (31.3%) females in the study. All the patients (100%) had significant amount of alcohol consumption, while total of 3 patients (3.75%) were hepatitis C positive and 1 (1.25%) was hepatitis B positive. Among alcohol consuming patients, the commonest type of alcohol consumed was homemade local alcohol in 92% of the patients, while only 8% drank other brands like Beer, Brandy and Whisky. The average duration of alcohol consumption in the population was 27.6 years with maximum of 55 years and minimum of 15 years of alcohol consumption. The average duration of alcohol consumption among males was 27.23 years before the development of cirrhosis while that in females was 28.45 years.

On reviewing the grades of HE, 3 (3.8%) had grade 0 or covert HE while 47 (58.8%) had grade I, 18 (22.5%) had grade II, 9 (11.3%) had grade III and 3 (3.8%) had grade IV HE. Majority of the patients were in CTP class C (73.75%).

On reviewing the HE grading, it was found that HE was more severe in higher CTP class as compared to a lower one which is shown in Table 1.

Table 1: Comparison between grades of Hepatic Encephalopathy and Child-Turcotte-Pugh class at the time of presentation

	Child-Turcotte-Pugh Class			Total Number
	A	B	C	
	0	2	1	3
	1	8	39	47
HE Grading	2	4	13	18
	3	0	5	9
	4	0	1	3
Total	4	17	59	80

Out of 80 patients enrolled in the study, 22(18 males and 4 females) had the history of increase in protein intake, 18(14 males and 4 females) patients had GIB, 16(12 males and 4 females) had constipation, 12(10 males and 2 females) had hypokalemia, 9(6 males and 3 females) had UTI, 3(1 male and 2 females) had SBP and 1 (male) had history of surgery prior to the development of HE (Table 2).

Table 2: Precipitating factors for hepatic encephalopathy

Precipitating factors	Number	Percentage (%)
Fever	15	18.8
GI bleeding	18	22.5
Constipation	16	20.0
Diarrhea/vomiting	15	18.8
Trauma/surgery	1	1.3
Increased protein diet	22	27.5

Out of 80 patients enrolled in the study group, 67 patients (46 males and 21 females) had icterus, 30 patients (21 males and 9 females) had limb edema, 26 patients (21 males and 5 females) had pallor, 5 patients (4 males and 1 female) had parotid swelling, 3 patients (2 males and 1 female) had spider nevi and 1 patient (female) had dupuytren contracture. On reviewing the precipitating factors for HE, it was absent in 15 patients (19%) whereas at least one precipitating factor was present in remaining patients (81%, n=65).

DISCUSSION

This study was conducted to assess the precipitating factors of HE in patients with CLD. In majority of the patients with HE, a clearly defined precipitating factor usually is identified, and the reversal or control of these factors is a key step in the management. In our study that was conducted on 80 patients of CLD presenting with HE, all possible important factors which could be responsible for precipitation or aggravation of HE were looked for and analyzed.

Hepatic encephalopathy is a diagnosis of exclusion hence; such tool was used in our study to detect hepatic encephalopathy. Evidence exists that serum ammonia has low sensitivity in hepatic encephalopathy and is not always raised in HE therefore, it is not a good screening tool.¹³ an ambulatory and continuous monitoring of wrist motor activity fitted to study sleep/wake patterns in hepatic encephalopathy (HE)

In this study, there were more male patients (68%) than female patients (31.3%) which is similar to the study done by Awad Ali et al.¹⁴ This is despite of the fact that females are more prone to develop alcoholic liver disease.¹⁵ This may just be the manifestation of the gender bias in our society as evidenced by a study done by Bikram Pradhan et al. where ALD were seen more in male population as compared to females as opposed to the scientific background of development of ALD in females than males.¹⁶ some studies have shown a beverage-specific effect. In the present study, we aim to study the effects of locally brewed alcoholic beverages on the development of liver disease. Patients and methods: This cross-sectional study was conducted at the internal medicine department of a university hospital in Nepal. All patients classified as having either alcohol abuse or alcohol dependence by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition were evaluated for the presence of ALD. Results: A total of 1,500 patients were screened, of which, 447 patients had ALD. Chronic liver disease (CLD) The mean age of the patients in our study was 54.725 ± 11.33 years with age range from 25 to 80 years which was as comparable to various other studies on the topic, like in the study by Mahmoud A. Ashoor.¹⁷

In this study, only 3 patients (3.8%) belonged to grade 0 or covert HE, whereas more than half of the population i.e. 47 patients (58.8%) had grade I while, 18 patients (22.5%) had grade II, 9 patients (11.3%) had grade III and 3 patients (3.8%) had grade IV HE which is in contrast to the study by Atif Sitwat Hayat et al. in which most of the patients i.e. 72%, belonged to grade IV HE.¹⁸ This shows that most patients have health services seeking behavior only after having significant symptoms.

In this study, 4 patients (5%) were in CTP class A while 17 patients (21.25%) were in CTP class B and the majority 59 patients (73.75%) were in CTP class C. This finding is similar to the study done by R Maskey et al. in which sixty percent of young cirrhotics and 52% of adult cirrhotics were in CTP grade C at the time of presentation.¹⁹ This reveals that with more deterioration of liver function the incidence of HE increases accordingly. Each of the 80 patients (100%) had history of significant alcohol consumption, while only total of 3 patients (3.75%) were hepatitis C positive and 1 (1.25%) was hepatitis B positive. This was similar to two studies which were the study by R Maskey et al. in which 90 out of 105 patients were having alcohol related cirrhosis.¹⁹ This depicts the etiological causes of CLD in our society.

In our study, the commonest type of alcohol consumption was locally brewed alcohol (92%), while 8% drank other brands like Beer, Brandy and Whisky which is similar to the study done by Bikram Pradhan in which most of the patients consumed homemade locally brewed alcohol and the study by SR Niraula which observed local raksi was the most common type of alcohol used.^{16,20} Some studies have shown a beverage-specific effect. In the present study, we aim to study the effects of locally brewed alcoholic beverages on the development of liver disease. Patients and methods: This cross-sectional study was conducted at the internal medicine department of a university hospital in Nepal. All patients classified as having either alcohol abuse or alcohol dependence by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition were evaluated for the presence of ALD. Results: A total of 1,500 patients were screened, of which, 447 patients had ALD. Chronic liver disease (CLD) Due to the open supply of home brewed alcohol in community, people get more used to drinking local alcohol thus resulting in high consumption of it.

In this study, no precipitating factor of HE was observed in 18.75% of the patients, 47.5% of the patients had one of the precipitating factors while 33.75% had more than 1 precipitating factors of HE which is similar to the study done by Hakim Ali Abro et al.²¹ Increased protein intake (27.5%), gastrointestinal bleeding (22.5%), constipation (20%), hypokalemia (15%) and infections (15%) were the common precipitating factors detected in this study. On the other hand, infections remained the most common precipitating factors in most other similar studies like studies by Atif Sitwat Hayat et al.¹⁸ Infections (SBP and UTI) were less common in our study as a factor for precipitation of infections.

The commonest precipitating factor in this study was found to be high consumption of protein diet. This reflected the tradition of consuming a high protein diet in some days as compared regular good consumption as per daily requirement. This could be one important area for good patient counselling in improving the diet plan of the patients. Constipation was an important precipitating factor of HE in our study (20%) which is similar to the study of M. Ashooret al.¹⁴ Thus, it is imperative to properly counsel regarding two to three good bowel movements daily along with consumption of lactulose. By counselling about a good diet, regular consumption of prescribed medications and early recognition of hepatic encephalopathy will result in lesser morbidity and decrease in health care costs of cirrhotic patients.

CONCLUSIONS

From this study, we can conclude that there are different factors which play a key role in precipitating HE. Among these factors, high protein diet, constipation, GIB and infections, are predominant. There is a definite need for health education and proper counseling in patients who are diagnosed as liver cirrhosis in relation to HE as minor changes in dietary habit, regular follow up and timely visit to the health care facility may result in the identification of these common precipitating factors like infections, constipation and diarrhea. These precipitating factors could be treated resulting in lower incidence of HE. Simple use of laxatives can prevent HE in vast majority of patients. Lastly education about the harmful effects of alcohol and dreadful complications can help in decreasing the prevalence of alcoholic liver disease.

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