

## Identification of Precipitating Factors in Hepatic Encephalopathy Patients at Liaquat University Hospital Jamshoro

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**Abstract:** Hepatic Encephalopathy (HE) is an extra-hepatic complication of liver dysfunction manifested by neuropsychiatric features associated with acute or chronic liver disease, after exclusion of other known brain diseases. There are various factors which can precipitate HE. The purpose of this study was to identify precipitating factors of HE in liver cirrhosis patients at Liaquat University Hospital Jamshoro. It was a hospital-based descriptive study conducted from 1<sup>st</sup> January 2009 to 15<sup>th</sup> August 2009 at Liaquat University Hospital Jamshoro, Sind, Pakistan. During this study, 100 admitted patients manifesting symptoms and signs of HE associated with liver cirrhosis were enrolled. All patients were more than 12 years old and diagnosed as HE on history, comprehensive clinical examination and relevant laboratory investigations. The data has been collected on preformed proforma. The grades of HE and Child's Pugh Classification have also been noted in order to assess prognosis. Most 77(77%) patients were older than 40 years including 57(74%) males and 20(26%) females with M to F ratio of 2.85:1 in this group. Majority of patients 70(70%) were from rural areas of Sindh having poor socio-economic status. A large number of patients 72(72%) were in grade IV followed by 18(18%) in grade III encephalopathy. Anti- HCV has been found positive in 72(72%) of our patients. The most common precipitating factors of HE detected in our study were infections 53 (53%), GI bleeding 51(51%), constipation 49 (49%) and high protein diet 47(47%). Usage of cough- syrups, large- volume paracentesis, sedative and tranquilizer drugs were least common factors. 72(72%) of our patients have associated ascites, 12(12%) spontaneous bacterial peritonitis and 6 (6%) hepato- renal syndrome. Laboratory analysis revealed low hemoglobin in 61(61%), thrombocytopenia in 53(53%), leukocytosis in 73(73%), hypo-albuminemia in 52(52%), hypokalemia in 31(31%), hyponatremia in 27 (27%) and abnormal coagulation profile in 51(51%) of our cases. 65(65%) patients recovered completely and were discharged from the hospital, while 25(25%) expired. All expired patients were in Class C of Child's Pugh Classification. The overall in-hospital mortality was 25% in our study. This study concludes that infection, GI bleeding, constipation and high protein diet were the most common precipitating factors of HE in our patients. So there is a definite need of health education and proper counseling to liver cirrhosis patients.

**Key words:** Hepatic encephalopathy • Child's pugh classification • Liver cirrhosis • Porto-Systemic shunts • Precipitating factors

### INTRODUCTION

Cirrhosis of liver is a common cause of mortality amongst Pakistani population and frequent cause of admission to our hospitals [1]. However, in Pakistan and other developing countries where cost of health care has always been an issue, cirrhosis and its complications are

a major health problem and pose a big challenge to the health economy. Because of poverty, inadequate education, poor hygienic conditions and lack of counseling, the number of cirrhotic patients in our community are rapidly increasing.

Hepatic Encephalopathy (HE) is a neuropsychiatric syndrome occurring in patients with acute or chronic

liver dysfunction, after exclusion of other known brain diseases. It is functional in nature and potentially reversible and symptoms range from subtle personality changes to deep coma [2]. Cirrhosis of liver is becoming an epidemic in Pakistan due to very high prevalence of hepatitis C and B in our community [3]. As a result increasing number of patients come to hospitals with one or other complication of liver cirrhosis. Appearance of HE in any patients is indicative of poor prognosis [4]. About 30% of patients with cirrhosis usually die in hepatic coma [5]. HE can occur either due to acute liver failure or due to one or more precipitating factors in cirrhotic patients, or it could happen as a result of prolonged porto-systemic shunting leading to chronic portal-systemic encephalopathy [6]. Well recognized factors which tend to precipitate HE include gastro-intestinal bleeding, infections, constipation, azotemia, electrolyte imbalance and high protein diet [7]. Usage of drugs such as sedatives, tranquilizers, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), fulminant hepatic failure and large volume paracentesis have all been considered to precipitate encephalopathy in an otherwise stable cirrhotic patient [7,8].

The exact pathogenesis of HE is still unknown, however diminished hepatic reserve results in impaired ability of liver to detoxify nitrogenous compounds (e.g. ammonia, manganese, gamma aminobutyric acid (GABA), short-chain fatty acids, phenols, mercaptans and false- neurotransmitters such as tyramine, octopamine etc) that are absorbed from the bowel [9]. They gain access to systemic circulation as a result of poor hepatic function and/ or porto-systemic shunting of the blood. Furthermore, they also alter amino acid metabolism of neurons resulting in changes in neurotransmission and hence causing depressed cerebral function [10]. The survival of patients having chronic portal-systemic encephalopathy is better than those who develop HE acutely (100% vs 70%) [11]. However, prognosis in the later group can be improved if the precipitating factors are recognized early and managed accordingly [9].

Since chronic liver disease became a pandemic problem in Pakistan leading to cirrhosis and hepatic encephalopathy, this study has been conducted to find out frequency of various precipitating factors in HE and to assess disease severity according to Child-Pugh classification. Early diagnosis and treatment of precipitating factors will definitely reduce mortality rate in these patients. In addition, this study will provide a new forum of discussion about knowledge and protocol regarding medical workup of patients with HE.

## MATERIALS AND METHODS

We conducted a hospital-based non-interventional descriptive study on 100 patients admitted to medical wards of Liaquat University Hospital Jamshoro, Sind, Pakistan from 1<sup>st</sup> January 2009 to 15<sup>th</sup> August 2009. All patients who were aged 12 years or above, manifesting symptoms and signs of HE and associated liver cirrhosis either at presentation or during the course of hospital stay were included.

Liaquat University Hospital is the main tertiary care institute of Sind province. It has two buildings- one in Jamshoro and other in Hyderabad City. It has fifteen hundred beds and provides health cover for both rural as well as urban population of Sind.

A proforma has been designed and used for data collection. A detailed clinical history of the patients about fever, gastro-intestinal bleeding (i.e. hematemesis and or melenas), constipation, vomiting, diarrhea, high protein diet, any trauma or surgery and paracentesis. Drug history including use of diuretics, sedatives and tranquilizers, non-steroidal anti-inflammatory drugs (NSAIDs) and cough syrups was also inquired in detail. Past history of hospital admissions was also taken. All patients were carefully examined with special attention to fever, anemia, jaundice, dehydration, ascites and asterixis (flapping tremor of outstretched hands). Hepatic encephalopathy was diagnosed on clinical basis and graded according to the criteria as given in Table 1.

For each patient, all relevant investigations including complete blood count (CBC), random blood glucose level, liver function test (LFTs), serum electrolytes, serum albumin, coagulation profile, urine microscopy, blood urea, serum creatinine, HbsAg and anti-HCV (if not previously diagnosed and not a known case) and chest radiograph were done. An abdominal ultrasound was done to look for liver and spleen size, parenchymal echogenicity, portal vein diameter and ascites. In case of ascites, a diagnostic ascitic tap was also done to look for spontaneous bacterial peritonitis (SPB). The facility of testing serum ammonia was not available in our hospital's laboratory and in addition, raised serum ammonia not always indicates HE [12]. Any evidence for the presence of other co-existent complications of liver cirrhosis was also recorded and Child's Pugh Score [13] assessed for each patient based on parameters in Table 2.

All patients were followed for the duration of their stay in hospital and whether they survived or not at the end of their stay also recorded. A recent nomenclature

Table 1: Clinical Grades of hepatic encephalopathy

Grades	Description
I	Mild confusion, euphoria, anxiety or depression, reversed sleep rhythm, slurred speech
II	Drowsiness, lethargy, gross deficits in ability to perform mental tasks, relatively moderate confusion
III	Somnolent but rousable, severe confusion, inability to perform mental tasks
IV	Coma with (IVa) or without (IVb) response to painful stimuli

Table 2: Child Pugh score criteria

Parameters	Numerical Score		
	1	2	3
Ascites	None	Mild	Moderate/Severe
Encephalopathy	None	Mild	Moderate/Severe
Bilirubin (mg/dl)	<2	2-3	>3
Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time (seconds over normal)	<4	4-6	>6
Child Pugh Class	Total Numerical Score		
A	5-6		
B	7-9		
C	10-15		

has been proposed for categorizing HE [14]. Type A HE describes encephalopathy associated with acute liver failure. Type B HE describes encephalopathy associated with portal-systemic by-pass and no intrinsic hepatocellular disease. Type C HE describes encephalopathy associated with cirrhosis and portal hypertension or portal-systemic shunts. Type C hepatic encephalopathy is, in turn, subcategorized as episodic, persistent or minimal.

## RESULTS

A total of one hundred admitted patients including 72 (72%) males and 28 (28%) females, presenting or complicating to HE were studied. Majority of patients 70(70%) were from rural areas of Sindh having poor socio-economic status, while 30(30%) belonged to Hyderabad city and of middle class.

Most i.e. 77 (77%) patients were older than 40 years including 57(74%) males and 20 (26%) females with M to F ratio of 2.85:1 in these group. 20 (20%) patients were between 20-40 years old including 12(60%) males and 8(40%) females. Only 3(3%) patients, all of them males were less than 20 years. A large number of patients 72(72%) were in grade IV encephalopathy, 18(18%) in grade III, 5(5%) in grade II and another 5(5%) in grade I. The age and gender distribution in different grade of HE is shown in Table 3.

The most common precipitating factors of HE in our study were infections 53(53%), GI bleeding 51(51%), constipation 49(49%) and high protein diet 47(47%) patients. The frequency of other precipitating

factors involved in HE has been shown in Table 4. Out of one hundred patients of HE, 42(42%) patients had one factor, 36(36%) had two factors and 17(17%) had more than two precipitating factors, while no factor found in 5(5%) patients. Anti-HCV was detected in 72(72%) patients in which 57(57%) were known cases, while 15(15%) found during hospital admission. HBsAg was positive in 10(10%) patients in which 6 were known cases, while 4 diagnosed during hospitalization. About 10(10%) patients have found to be positive for three hepatitis B, C and D viruses, while 8(8%) were B, C and D negative. None of the patient had alcoholic liver disease in our study. 72(72%) of our patients have associated ascites, 12(12%) spontaneous bacterial peritonitis and 6(6%) had hepato-renal syndrome. When cirrhotic patients were grouped into Child's Pugh Classification, 72% of the patients were found to be in class C, 18% in class B and 10% in class A.

On laboratory analysis, complete blood count (CBC) shows low hemoglobin in 61(61%) and thrombocytopenia (platelet count <150,000/uL) in 53(53%) patients. However, leukocytosis (total leukocyte count >11,000/uL) has been found in 73(73%) of our patients. Electrolyte abnormalities showed hypokalemia in 31(31%) patients and hyponatremia in 27(27%) cases. Hypoglycemia was noted in 11(11%) of our patients. Hypoalbuminemia (serum albumin <3.0mg/dl) has been found in 52(52%) patients. Coagulation profile was abnormal in 51 (51%) patients having prothrombin time more than 4 seconds. In 23(23%) of our patients, blood urea and serum creatinine were found raised above normal limits.

Table 3: Age and Gender Distribution in Different Grade of Hepatic Encephalopathy (n=100)

Grades	No of patients and their percentages	No of patients according to age groups					
		<20 years		20-40 years		>40 years	
		Male	Female	Male	Female	Male	Female
IV	72(72%)	2	0	5	4	47	14
III	18(18%)	1	0	4	2	7	4
II	5(5%)	0	0	1	1	2	1
I	5(5%)	0	0	2	1	1	1

Table 4: Frequency of precipitating factors involved In patients of hepatic encephalopathy

S. No.	Precipitating factors	No of patients	Percentage
1	Infections	53	53%
2	GI bleeding	51	51%
3	Constipation	49	49%
4	High protein diet	47	47%
5	Hypokalemia	31	31%
6	Hyponatremia	27	27%
7	Hypoglycemia	11	11%
8	Diuretic therapy	7	7%
9	Miscellaneous Factor	5	5%
10	Trauma/Surgery	3	3%
11	Sedative and tranquilizer drugs	3	3%
12	Cough Syrup	2	2%
13	Paracentesis	2	2%

Out of one hundred patients with hepatic encephalopathy, 65(65%) recovered completely and were discharged from the hospital. About 7(7%) were insistent for discharge on request from the hospital, while 3 (3%) patients left hospital against medical advice. The remaining 25(25%) patients had expired in the wards-out of which 18 were males and 7 females. Out of 25 expired patients, 23 had grade IV while 2 were in grade III encephalopathy. All cirrhotic patients who expired were found to be in class C of Child's Pugh Classification.

The overall in- hospital mortality in our patients was 25% and mean time to come out of HE was 45.40 hours.

## DISCUSSION

Hepatic Encephalopathy (HE) is a major neuropsychiatric complication of cirrhosis indicating poor prognosis [15, 16] and is the commonest cause of death in cirrhotic patients [17]. HE is a diagnosis of exclusion [18] hence, it can be diagnosed after excluding metabolic disorders, infectious diseases, intra-cranial space-occupying lesions, intra-cranial vascular events, history of precipitating factors, knowledge of existing acute or chronic liver diseases and /or prior diagnosis of HE determined by history and specific investigations. A clearly defined precipitating factor is

usually identified in most patients with HE and the reversal or control of these factors is a key step in the management [19].

Infections, GI bleeding, constipation and high protein diet have been repeatedly demonstrated as important precipitating factors of HE [19], a fact also borne out by our study.

In this study, most patients belonged to rural areas of Sind province because of poverty, illiteracy, poor personal hygiene and improper counseling regarding the disease. We also found majority (77%) of patients more than forty years old which is quite similar to study by Durrani *et al.* [20] in the province of Baluchistan on chronic liver disease. There is a male dominancy in progression to advanced stages of chronic liver disease in our study, with same pattern to a retrospective study in Saudi Arabia by Al-Gindan [21]. Large number (72%) of our patients had hepatitis C virus infection which is the most common cause of liver cirrhosis in our country. On the other hand, alcohol is the main etiological factor of cirrhosis in Western countries [22]. Infections like spontaneous bacterial peritonitis (SPB), urinary tract infections (UTIs) and lower respiratory tract infections were the commonest present in 53% of our cases. This is in close similarity with the study done by Aisha [23] where infections account for 52% of cases.

However, infections have not been involved as precipitating factors of HE in the study of Faloon [24] because of better hygienic condition of patients and hospitals in the Western countries. GI bleeding was the second most common factor found in 51% of our patients which is less than the results of earlier studies [19, 25, 26]. Constipation was third most important factor involved in 49% of our cases which is slightly less than results of earlier published studies [19, 25]. However, it is quite similar to the study of Gomez *et al.* [27]. Constipation probably results from lack of consistent use of lactulose by our patients due to its cost or patients don't find it as a good laxative. High protein intake was another factor present in 47% of patients in our study which is less than the results of previous studies [19]. This is because most of our patients were unaware about dietary protein restrictions. Hypokalemia was found in 31% patients, which is consistent with the study of Hassanein *et al.* [28], while hyponatremia in 27% of our cases which is similar to the results of other studies [19, 29]. Electrolyte imbalance was mainly due to diarrhea, vomiting and/or diuretic therapy.

Hypoglycemia was seen in 11% of our patients. Out of which four (4%) patients have type 2 diabetes mellitus, who were already taking their anti-hyperglycemic drugs. The hypoglycemia can be prevented either by reducing the dose or stopping the drugs and by giving oral or parenteral glucose therapy. We found three (3%) patients who used sedative and tranquilizer drugs on self-prescription and went to HE, which is slightly similar to Mehboob [30]. All patients of HE should be properly counseled about use of sedative and tranquilizer drugs. In five (5%) of our patients, no precipitating factor was identified which is closer to study by Mehboob [30]. Hence such patients should have Doppler Ultrasonography for large spontaneous porto-systemic shunts, being treated by angiographic techniques. Sometimes an occult precipitating factor such as zinc deficiency should be kept in the mind [31]. We found leukocytosis in 73% of our patients supporting infection as a most common precipitant in our settings. Findings of low hemoglobin, thrombocytopenia and hypo-albuminemia in patients with HE correspond well with advanced stages of liver cirrhosis [32]. High urea and creatinine in large number of our patients highlight the fact that azotemia is an important pathogenic contributor to onset of HE [33]. The mortality rate of HE is high as shown by the study of Sargent and Fullwood [34], while in our study mortality rate was 25%. Patients who did expire were mostly in class C of Child's Pugh Classification and grade IV and III of HE.

Infact, complete recovery possible in HE especially if it is triggered by a reversible cause. Hence, our goal is to identify and manage specific precipitating factor and effective measures and steps should be taken especially in remote areas where there is lack of medical facilities.

## CONCLUSION

From this study, it is now concluded that various factors can precipitate HE but infections, GI bleeding, constipation and high protein diet were predominant. Hence, it is suggested that amelioration of HE can be associated with early and effective control of infections and better hygienic condition of government hospitals, emergency endoscopies with trained physicians to control GI bleeding, evacuation of the bowel with consistent use of lactulose and dietary protein restriction to cirrhotic patients.

HE occurred mainly in poor patients living in the rural areas of Sind province of Pakistan, so there is a definite need of health education and proper counseling to liver cirrhosis patients regarding the risk factors of HE. Furthermore, public awareness programs should be arranged regarding prevention against hepatitis C infection.

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