# PRECIPITATING FACTORS OF HEPATIC ENCEPHALOPATHY: EXPERIENCE AT PAKISTAN INSTITUTE OF MEDICAL SCIENCES ISLAMABAD.

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**Background:** Hepatic encephalopathy is an extra hepatic complication of impaired liver function and is manifested as neuropsychiatric signs and symptoms associated with acute or chronic liver disease in the absence of other neurological disorders. There are numerous factors of hepatic encephalopathy. The main objective of this study was to analyse the precipitating factors of hepatic encephalopathy in cases seen in Pakistan Institute of Medical Sciences Islamabad. **Methods:** Fifty admitted patients with acute or chronic liver diseases complicating to hepatic encephalopathy were probed into for precipitating factors, based on history, clinical examination and laboratory methods from September 2005 to December 2005. The associated biochemical laboratory data analysis and prognostic stratification through Child's Pugh classification was also done. **Results:** Infection (44%), gastrointestinal bleeding (38%) and constipation (38%), stood out as the most common factors. Usage of drugs with ammonium salts, tranquilizers and large volume paracentesis were least common factors. Most patients were in grade III (52%), and grade IV (22%), of hepatic encephalopathy. Other common associations were ascites (64%), Child's class C (62%), hyponatremia (50%), low haemoglobin (70%), hepatitis C (62%), and high mortality rate (30%). **Conclusion:** Infection, gastrointestinal bleeding and constipation being the most important precipitating factors must be prevented and hospital funds, medicines and human efforts should lay emphasis, on these factors to decrease the incidence of hepatic encephalopathy. This also includes effective control measures against rising cases of hepatitis C, as it is the leading cause of liver cirrhosis in Pakistan.

**Key Words:** Hepatic Encephalopathy, Liver cirrhosis, precipitating factors.

## INTRODUCTION

Liver diseases affect millions of people worldwide each day. However, in the developing countries where cost of health care has always been an issue, long lasting diseases such as liver cirrhosis and its complications are a major health problem and pose a big challenge to the health economy. Because of poverty, poor hygienic conditions, inadequate education and lack of counselling, the number of cirrhotic patients is increasing and most of them are admitted to medical wards with different complications.

The syndrome of hepatic encephalopathy (HE) describes all neuropsychiatric symptoms occurring in patients with acute or chronic liver diseases (CLD) in the absence of other neurological disorders.[1] About 30% of patients with cirrhosis die in hepatic coma.[2] Cirrhosis liver (CL) is becoming an epidemic in Pakistan due to a very high prevalence of hepatitis B and C in our community.[3] As a result increasing number of patients come with one or the other complication of cirrhosis liver. Appearance of HE in any patient is indicative of poor prognosis.[4]

HE can occur either due to acute liver failure or due to one or more precipitating factors in a cirrhotic patient, or it could happen as a result of prolonged portal systemic shunting resulting in a chronic portal systemic encephalopathy.[5] Survival of patients having chronic portal systemic encephalopathy is better than those who develop HE acutely (100% vs. 70%).[6] However prognosis in the later group can be improved if the precipitating factors are recognized early and managed accordingly.[7] Common precipitating factors include gastrointestinal bleeding , infection, azotemia, constipation, electrolyte imbalance [8] and high protein diet. Usage of drugs such as sedatives,[9] tranquilizers, analgesics and diuretics, fulminant hepatic injury, large volume paracentesis have all been considered to precipitate encephalopathy in an otherwise stable cirrhotic patient. Exact pathogenic mechanism involved is unknown till date, however the basic processes are failure of hepatic clearance of gut derived substances such as ammonia, free fatty acids, mercaptans etc., either through hepatocellular failure or shunting, and altered amino acid metabolism, both of which result in changes in cerebral transmission causing depressed cerebral function.[10]

This study was aimed at ascertaining the common precipitating factors and their frequency in patients presenting with HE. Other objectives were to analyse the commonly associated biochemical laboratory findings in such patients, to stratify these patients according to Child's classification of CLD, the outcome, and the aetiological factors involved.

## PATIENTS AND METHODS

A hospital based non-interventional descriptive study was carried out on 50 patients in Medical Unit III of Pakistan Institute of Medical Sciences Islamabad from September 2005 to December 2005. All patients who were aged 13 years or above manifesting signs and symptoms of HE either at presentation or during the course of hospital stay were studied. This also included patients with acute fulminant hepatitis or known liver cirrhosis developing HE.

For data collection, a questionnaire was developed. A detailed clinical history of the patient was taken regarding the present and past illnesses. Questions were asked about gastrointestinal bleeding, including hemetemesis and malena, constipation, fever, high protein diet, paracentesis and any trauma or surgery. Use of any sedatives, tranquilizers, analgesics and cough syrups was also inquired in detail.

All patients were carefully examined with special attention to jaundice, anaemia, fever, asterixes, and ascites. Encephalopathy was graded according to the clinical criteria as given in Table 1.

**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. |

For each patient full blood count, liver function tests, renal function tests, random blood sugar, serum electrolytes, serum albumin and coagulation profile were carried out. An abdominal ultrasound was done to look for liver and splenic size, parenchymal echogenicity, portal vein diameter, and ascites. In case of ascites, an ascitic tap was also done to look for spontaneous bacterial peritonitis. Any evidence of the presence of other co-existent complications of cirrhosis liver was also recorded and Child's score was assessed for each patient based on parameters in table 2.

**Table 2: Child Pugh scoring criteria**

| Parameters | Numerical score | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascites | none | slight | moderate to severe |
| Encephalopathy | none | slight to moderate | moderate to severe |
| Serum bilirubin (mg/dl) | <2 | 2-3 | >3 |
| Albumin (gm/dl) | >3.5 | 2.8-3.5 | <2.8 |
| Prothrombin Time (sec) | 1-3 | 4-6 | >6 |

| Total numerical score | | Child Pugh Class |
|---|---|---|
| 5-6 | -- | A |
| 7-9 | -- | B |
| 10-15 | -- | C |

All patients were followed for the duration of their stay in hospital and whether they survived or died at the end of the stay was also recorded.

## RESULTS

A total of 50 admitted patients, including 25 (50%), male and 25(50%) females, presenting or complicating into hepatic encephalopathy were studied. Majority i.e. 43(86%) patients were older than 40 years including 24 (56%) males and 19 (44%) females in this group. Six (12%) patients were between 20 and 40 years old, all of them were females. Only one patient (2%), a male, was less than 20 years.

The age and gender distribution in different clinical presentation grades of patients with HE is given in Table 3.

**Table 3: Age and gender distribution in different clinical presentation grades of patients with HE**

| Grades | No. & % | No. of patients acc. to age groups | | | | | |
|---|---|---|---|---|---|---|---|
| | | <20 years | | 20-40 yrs | | >40 yrs | |
| | | M | F | M | F | M | F |
| **I** | 4 (8%) | 0 | 0 | 0 | 0 | 2 | 2 |
| **II** | 9 (18%) | 0 | 0 | 0 | 2 | 4 | 3 |
| **III** | 26 (52%) | 1 | 0 | 0 | 3 | 12 | 10 |
| **IV** | 11 (22%) | 0 | 0 | 0 | 1 | 6 | 4 |

The precipitating factors of HE most commonly found in our patients were infection (44%), GI bleeding (38%) and constipation (38%) (Figure 1).

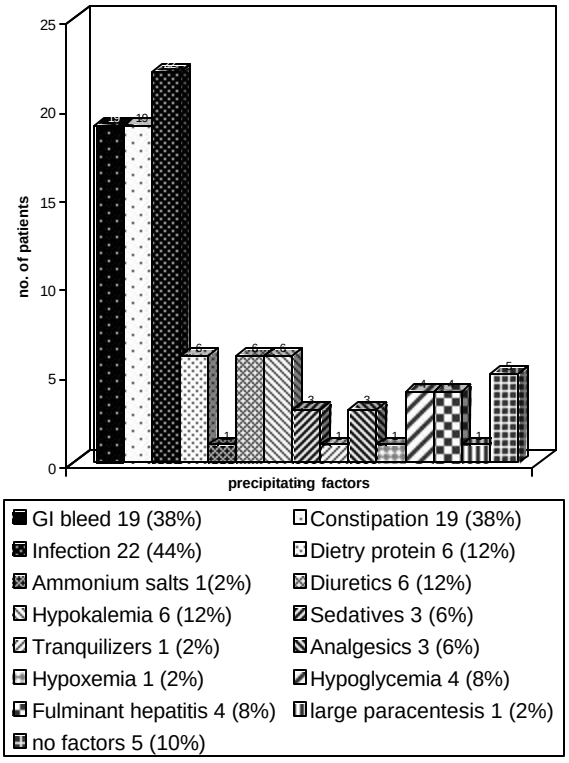


**Figure 1: Graph for precipitating factors**

Out of a total of fifty patients of HE, no factors could be found in 5 (10%) patients, 18 (36%) patients had one factor; fifteen (30%) had two factors, while 12 (24%) patients had more than two precipitating factors.

HBsAg was found solely positive in 4 (8%), HCV antibodies were found positive alone in 31 (62%) patients, 2 (4%) patients had both B and C positive, while 13 (26%) had neither B nor C.

When cirrhotic patients were grouped into Child Pugh classification, 62% of the patients were found to be in Class C, as shown in Table 4.

**Table 4: Frequency according to Child's classification and associated age and gender distribution.**

| Child's Class | No. (50) | % | No. of patients acc. to age groups | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | <20 yrs | | 20-40 yrs | | >40 yrs | |
| | | | M | F | M | F | M | M |
| A | 1 | 4% | 0 | 0 | 0 | 0 | 1 | 0 |
| B | 14 | 28% | 0 | 0 | 0 | 2 | 5 | 7 |
| C | 31 | 62% | 0 | 0 | 0 | 4 | 17 | 10 |
| Non cirrhotics | 4 | 8% | 1 | 0 | 0 | 0 | 1 | 2 |

32 (64%) patients have associated ascites, 5 (10%) had spontaneous bacterial peritonitis, 4 (8%) patients had hepatorenal syndrome, while in 1 (2%) patient hepatopulmonary syndrome was diagnosed.

In the analysis of the laboratory findings, hyponatremia, hypokalemia, hypoglycaemia and low haemoglobin were found in 25 (50%), 6 (12%), 4 (8%), and 35 (70%) patients respectively. In 35 (70%) patients blood urea was found high while creatinine was above normal limits in 31 (62%) patients. Hypoalbuminemia (serum albumin <3.3 g/dl) was found in 43 (86%) patients. Leukocytosis (total leukocyte count >11000/μL) was a feature in the laboratory data of 20 (40%) patients. The rest of the patients had either normal or low TLC count. Coagulation profile was abnormal in a fraction of patient with 22 (44%) patients having Prothrombin time >5 seconds. However thrombocytopenia (platelet count <150,000/μL) was a consistent finding in 36 (72%) patients.

Out of all the 50 patients 15 (30%) died including 6 males and 9 females. 2 of them had acute fulminant hepatitis, 4 patients were in HE grade 3 and 9 patients were in grade 4. All cirrhotic patients who expired were found to be in Class C of Child's classification.

## DISCUSSION

Hepatic Encephalopathy has never been less than an unsolved mystery for physicians and researchers around the globe. Since the time of Hippocrates it has been difficult to diagnose and manage any patient of hepatic encephalopathy. Although the exact pathogenic mechanism is yet to be determined, modern research has proved time and again that identifying and removing precipitating factors is still the key step in the overall management.[11]

In our study that was conducted on 50 patients, majority (86%) of patients were more than forty years old. Durrani [12] had a similar finding in the province of Balochistan. Slight male dominance in progression to advanced stages of chronic liver disease was found in our patients. Al-Gindan [13] also reported the same pattern in a study in Saudi Arabia. The increasing concern regarding hepatitis C virus becoming an epidemic and an important cause of liver cirrhosis in Pakistan is justified yet again in this study as 62% of our patients were tested positive for antiHCV antibody screening. Hepatitis B was an uncommon cause of cirrhosis in our study. This is in complete harmony with the study done by Alam [14] in the province of N.W.F.P.. A probable explanation could also be that most of our patients were at end stage cirrhosis in which hepatitis C is the commonest cause here. This is in contrast to studies done in industrialized nations of the west, which show alcohol as the main aetiological factor.[15]

Infection, gastrointestinal bleeding and constipation have been repeatedly demonstrated as important precipitating factors of HE,[16, 17] a fact also borne out by our study. The findings of the frequencies of different precipitating factors in different national and international studies are given in Table 5.

**Table 5: Comparison of the studies of different precipitating factors**

| Studies | GI bleed (%) | Constipation (%) | Infection (%) | Abnormal $K^+$ (%) | Large prot. diet (%) |
|---|---|---|---|---|---|
| Conn [18] | 18 | 3 | 4 | 9 | 9 |
| Faloon [19] | 33 | 6 | --- | 18 | --- |
| Souheil [20] | 18 | 3 | 3 | 11 | 9 |
| Bustamante[21] | 36 | 10 | 41 | 60 | --- |
| Alam [14] | 22 | 32 | 24 | 18 | 4 |
| Shaikh [22] | 56 | 52 | 15 | 70 | -- |
| Aisha [23] | 76 | 36 | 52 | --- | --- |
| Hameed [24] | 56 | 52 | 28 | 68 | 52 |
| Khurram [25] | 31 | 33 | 11 | 7 | 13 |
| Present study | 38 | 38 | 44 | 12 | 12 |

It can be assessed from the above table that our findings match those studies done locally. This is especially true for the province of Punjab where Aisha[23] and Khurram[25] reveal gastrointestinal bleeding, infection and constipation as the main factors. Studies done by Shaikh [22] and Hameed [24] show electrolyte imbalance ranked at the top. Three out of four foreign studies however reveal infection as a less common cause abroad, which is understandably due to better hygienic conditions of the patients and hospitals in the western countries.

In 10 % patients, no precipitating factors could be found. In such patients exploration should include Doppler Ultrasonography to search for large spontaneous portosystemic shunts which can be confirmed and treated with angiographic techniques.[26] Occult precipitating factors such as zinc deficiency should also be sought.[27]

50% of our patients had hyponatremia and 12% were hypokalemic. This was due to the fact that most of them were on diuretics and there was associated diarrhoea or vomiting contributing to the electrolyte disturbances. Findings of low haemoglobin, thrombocytopenia and hypoalbuminemia correspond well with advanced stages of cirrhosis.[28] Raised total leukocyte count in 40% of patients, supports infection as a common precipitant in our settings. High urea and creatinine in majority of our patients highlight the fact that azotemia is an important pathogenic contributor to the onset of HE.[29]

The mortality rate in our patients was 30%, which is precisely what Sheila Sherlock [6] reported. Patients who did expire were mostly in Class C of Child's classification and grade 3 or 4 of hepatic coma.

## CONCLUSION

Infection, gastrointestinal bleeding, constipation and electrolyte disturbances are the most common factors of HE in Pakistan. Priority should be given to these factors in terms of hospital funds, medicines and human efforts. Caution must be exercised in putting cirrhotic patients on diuretics. Early and effective infection control measures and better hygienic conditions in government hospitals are needed to be maintained. Consistent use of lactulose and fibre should be encouraged to prevent constipation. More and more endoscopic facilities should be made available nationwide for prompt control of gastrointestinal bleeding, and most importantly, a more committed effort is the need of the hour to control increasing incidence of hepatitis C. Only then we stand any chance of combating cirrhosis and even worse hepatic encephalopathy.

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