

Frequency of Different Precipitating Factors of Hepatic Encephalopathy in Patients with Cirrhosis of Liver Based on Child Class

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ABSTRACT

Objective: To determine the frequency of precipitating factors of Hepatic Encephalopathy in Patients with Cirrhosis of Liver based on Child class.

Study Design: Descriptive study.

Setup: Medical Unit of Fauji Foundation Hospital (FFH) Rawalpindi.

Duration of study: Duration of study was 06 months after the approval of synopsis i.e 1st November, 2010 to 31st April, 2011.

Methods: Patients with Cirrhosis of liver who were aged 13 years or above; of either gender with signs and symptoms of hepatic encephalopathy were enrolled in the study. Precipitating factors were determined by detailed history, examination and laboratory investigations. Patients presenting with fever were evaluated through detailed systemic examination, blood complete picture for leucocytosis, ascitic fluid routine examination in patients with ascites. Cirrhotic patients were classified into Group A, B and C according to Child Pugh classification.

Results: Out of 148 patients, 129 (87.16%) were females. Hepatitis C was the cause of cirrhosis in 135 (90.54%). Child class C was found in 67(45.27%) of patients while 63(42.6%) had Child class B. On presentation 39.9 % of the patients were in Grade 1, while 31.9%, 16.9% and 12.2% were in grade 2, grade 3, and grade 4 respectively. The most common precipitating factors of hepatic encephalopathy, were constipation 51 (34.5%), infection 44(29.7%) and upper GI bleed 41(27.7%). The most common precipitant of Hepatic encephalopathy in Child class C was infection, while in class B and A, most common precipitating factor was GI bleed and constipation, respectively. Constipation had a important role in precipitation of Hepatic encephalopathy in all Child classes.

Conclusion: The study concluded that the most common precipitating factors of hepatic encephalopathy are constipation, infection and gastrointestinal bleed. Infection is the leading precipitating factor of hepatic encephalopathy in Child Class C

Keywords: Hepatic Encephalopathy, Child Pugh Classes, Liver Cirrhosis

Introduction

Liver Cirrhosis and its complications are a major health problem affecting millions of people world wide and in Pakistan. 3% of the world population has been infected with Hepatitis C virus. It is estimated that 10 million people of

Pakistan are living with Hepatitis C infection.¹ Liver Cirrhosis is becoming an epidemic in Pakistan due to a very high prevalence of Hepatitis B and Hepatitis C in our community.² The increasing concern regarding Hepatitis C virus becoming

an epidemic and an important cause of Liver Cirrhosis in Pakistan.³

In Europe, the prevalence of HCV antibodies has been reported to be ranging from 1% to 1.4%.⁴ HCV currently infects an estimated 2-3 million people in United States and 175 million people globally.⁴ With regard to incidence, most of the available data are from cross sectional studies of the selected high risk groups. Specifically, the incidence per 100 persons among drug users was reported to be 6.4 in Baltimore⁵, 6.2 in Italy⁶, and 11.7 in Switzerland⁷. Data referring to general population or to countries with different anti HCV prevalence rates are scarce, although studies show that the annual number of the newly acquired infections world wide has decreased from approximately 180000 in the mid 1980s to 28000 in 1995, and the major factors contributing to this decrease have been accurate screening of blood products and the active modification of risk factors.⁸

Many cases of cryptogenic cirrhosis appear to have resulted from non alcoholic fatty liver disease (NAFLD). Fat builds up in the liver and eventually causes scar tissue. When cases of cryptogenic cirrhosis were reviewed, many patients had one or more of the classical risk factors for NAFLD i.e. Obesity, diabetes mellitus, coronary artery disease, hypertriglyceridemia and treatment with corticosteroid medications. Biopsy is needed for diagnosis. It is postulated that steatosis may regress in some patients as hepatic fibrosis progresses, making the histological diagnosis of NAFLD difficult.⁹

Hepatic encephalopathy is a syndrome observed in patients with cirrhosis, characterized by personality changes, intellectual impairment and a depressed level of consciousness.^{3,10} It occurs as an acute or chronic, progressive disorder that is associated with chronic liver disease. Both forms may result in irreversible coma and death. Approximately 80% (8 out of 10 patients) die if they go into coma. Recovery and risk of the recurrence vary from patient to patient.^{11,12,13,14} Treatment of hepatic encephalopathy is mostly directed towards the cause or precipitating factors. Commonly reported precipitating factors are infections 44%, gastrointestinal bleeding 38% and constipation 38%.² When cirrhotic patients were grouped into child pugh classification, 62% patients were in class C and 28% were in class B.²

Patients with hepatic encephalopathy are predisposed to develop problems with their quality of life.¹⁵ Hepatic encephalopathy affects attention, working memory, response

time and driving skills. In majority of the patients with hepatic encephalopathy, a clearly defined precipitating factor usually is identified, and the reversal and control of these factors is a key step in the management. Only few studies have been done in Pakistan to identify the precipitating cause of hepatic encephalopathy and none of these studies have mentioned precipitating factors in different severities of cirrhosis (child class).

The study would help to identify the causative factors, leading to proper health education, early recognition and targeted treatment which would decrease the morbidity and mortality in such patients.

Methodology

The study was conducted in the three medical wards, emergency and intensive care unit of Fauji Foundation Hospital Rawalpindi.

Duration of study was 06 months after the approval of synopsis i.e 1st November, 2010 to 31st April, 2011

The study population consisted of 148 patients who were enrolled in the study if they met the inclusion criteria.

Data Collection Procedure: Patients with cirrhosis of liver those aged 13 years or above of either gender with signs and symptoms of hepatic encephalopathy were enrolled in the study. Informed consent was taken from the patients who were conscious and from the attendants of those patients who were unable to give the consent. Patients with cirrhosis were received by the same observer in emergency to avoid the observer bias. Acute fulminant hepatitis, Non Cirrhotic Portal Hypertension, Presence of other neurological disorders (stroke, meningitis, encephalitis), Patient with acute or chronic renal failure were excluded from the study.

Hepatic encephalopathy was diagnosed based Stages of encephalopathy (see Annexure-A) whereas Child Pugh Class according to Child Pugh Grading System was explained (see Annexure-B).

Precipitating factors like Constipation defined by Less than 2 stools in 24 hours². Gastrointestinal bleed: history of haematemesis or maelena and Infection defined as raised total leukocyte count of more than $11 \times 10^9/l$ ².³. Polymorphonuclear cells (PMNs) $>250/mcL$ on ascitic fluid examination^{2,3}

Precipitating factors were determined by detailed history, examination and laboratory investigations. History included questions regarding gastrointestinal bleed,

constipation, fever, diarrhea and intake of drugs (benzodiazepines, opiates, hypnotics, diuretics). Examination was performed for severity of ascites and grades of hepatic encephalopathy and to identify the source of infection.

Investigations included hepatitis serology (for Hepatitis B and C by Elisa), serum bilirubin, serum albumin, prothrombin time, serum electrolytes, serum urea, creatinine and blood complete picture. All these investigations were performed in the pathology department of Fauji Foundation hospital.

Patients presenting with fever were evaluated through detailed systemic examination, blood complete picture for leucocytosis, ascitic fluid routine examination in patients with ascites. Cirrhotic patients were classified into Group A, B and C according to Child Pugh classification. The data was entered in the worksheet specially prepared for the study using the Statistical Package for Social Sciences version 16.0. Mean +/- SD calculated for quantitative variables such as age, serum bilirubin, prothrombin time, and serum albumin. Frequency and percentages presented for qualitative variables like gender, grades of hepatic encephalopathy and different precipitating factors. A separate table was made showing descriptive statistics of above mentioned variables in each child class.

Results

Mean age was 59.97 ± 9.42 . Only 12.84% of our study population was male. Majority of study population was female i.e. 87.16% of patients. with 90.54 % was HCV positive. Only 4.05% were found to be HBV positive. In 5.41% of total study population we neither found HCV nor HBV. We assessed the severity of cirrhosis on the basis of Child Pugh score in our study population. 45.27% of total patients were found to be in Child Class C, 42.57% in Child Class B and only 12.16 % in Child Class A. Patients with Hepatic Encephalopathy were assessed and graded by clinical assessment. Most of the patients were in Hepatic Encephalopathy Grade 1, i.e 39.86%. Second most common was grade 2 i.e. 31.08%. 16.89% patients were in grade 3, and only 12.16% patients of total study population in Grade 4 as shown in Table No. 01.

Serum bilirubin was found significantly high in patients with child class C i.e. $55 \pm 12 \mu\text{mol/l}$ as compared with child class A where serum bilirubin is almost normal i.e. $14 \pm 4 \mu\text{mol/l}$ while in child class B it was moderately raised i.e. $24 \pm 6 \mu\text{mol/l}$.

Table No 1 Results of study	
Characteristics	Patients evaluated n=148
Demographic Characteristics	
Age mean (years)	59.97 ± 9.42
Gender: Males	19 (12.84%)
Females	129 (87.16%)
Hepatitis serology	
HCV positive	90.54s%
HBV positive	4.05%
HCV and HBV negative	5.54%
Child class	
Child class A	18(12.16%)
Child class B	63(42.57%)
Child class C	67(45.27%)
Grades of hepatic encephalopathy	
Grade 1	59(39.86%)
Grade 2	46(31.08%)
Grade 3	25(16.89%)
Grade 4	18(12.16%)
Precipitating factors of hepatic encephalopathy in total study population	
Infection	44 (29.7%)
GI bleed	41 (27.7%)
Constipation	51 (34.5 %)
Diarrhea	4 (2.7%)
Drugs	1 (0.7%)
No cause found	4 (2.7%)
Others	3 (2.0%)
Total	148 (100.0%)

Serum albumin decreased with severity of disease i.e. $38 \pm 4 \text{mg/dl}$, $29 \pm 5 \text{mg/dl}$ and $23 \pm 4 \text{mg/dl}$ in Child Class A, B and C respectively. Likewise another synthetic liver function, prothrombin time was normal in Child Class A i.e. 98% of patients in Child class A had normal PT. In Child Class B it was prolonged (4-6sec) in 50% of the patients. While in Child Class C, Prothrombin time was significantly prolonged i.e.51% of the patients in child class C had prolonged PT of more than 6 seconds as shown in Table. No. 02

In our study, the leading precipitating factor for hepatic encephalopathy was constipation i.e. 34.5% followed by

Infection and Upper GI bleed, 29.73% and 27.70% respectively. Less common causes were diarrhea in only 2.7%, drugs in 0.7% of total study population. In only 4% of patients no precipitating cause was found.

The most common precipitating factor of Hepatic encephalopathy in Child class A was Constipation. In Child Class B, Gastrointestinal bleed was the leading precipitating factor. The most common precipitating factor in Child Class C was infection. Out of 67 (45.27%) patients in Child class C, in 27 (40.29%) patients, precipitating factor was infection followed by constipation i.e. 21 (31%).

In Child Class B, Out of 63 (42.56% patients of total patients) GI bleed was responsible precipitating factor in 23 (36.50%) patients followed by constipation and infection in 20 (31%) & 15 (23%) patients respectively.

Constipation is Commonest precipitating factor of hepatic encephalopathy in each Child Class as shown in Table. No. 03

Lab Investigations	Child Pugh Score		
	A	B	C
Serum Bilirubin ($\mu\text{mol/l}$) (mean \pm SD)	14 \pm 4	24 \pm 6	55 \pm 12
Serum Albumin (g/l) (mean \pm SD)	38 \pm 4	29 \pm 5	23 \pm 4
Prothrombin Time	98%	30%	15%
0-4sec	2%	50%	34%
4-6sec	0%	20%	51%
>6 sec			

Identified precipitating factor	Severity of Cirrhosis (Child Pugh score)			Total
	Child Class A	Child Class B	Child Class C	
Infection	2	15	27	44
GI bleed	5	23	13	41
Constipation	10	20	21	51
Diarrhea	0	2	2	4
Drugs	0	1	0	1
no cause found	0	1	3	4
Others	1	1	1	3
Total	18	63	67	148

Discussion

Hepatic encephalopathy is the most common complication of liver Cirrhosis and patients with Hepatic Encephalopathy are predisposed to develop problems with their quality of life⁴. Identification of the precipitating factor is important because it would help to identify the causative factor and in targeted treatment⁸. In majority of the patients a clearly defined precipitating factor is identified and the reversal or control of that factor is the important step of management of patients with hepatic encephalopathy. In my study, I analyzed the possible important precipitating factors that can precipitate hepatic encephalopathy and the most common factors in different severities of cirrhosis (Child Class) Out of 148 patients 128 (87.16%) patients were female and 20 (12.84%) were male. Mumtaz¹⁶ shows that 62% of the study population were males

In my study, it seems that it is almost exclusively a disease of females but the reason is that in our hospital we mainly treat the families of retired army personals. Majority of the patients were in the age group of 30-80 years. Mean age was 59 years, while study done by Alam³ in N.W.F.P most of the patients were in age group 40-50 years. There was a wide range of age among the study population. Out of 148 patients 90.54% were HCV positive and only 4.05% were HBV positive. 5.41% of total study population was both B&C negative. Studies done in Pakistan suggest that HCV is the leading cause of cirrhosis in Pakistan.^{1, 2, 3} Mumtaz¹⁶ also found in his study that HCV was the cause of cirrhosis in 70% of the patients. Hepatitis C is increasing dangerously as the cause of cirrhosis in our country as compared to the western world where alcoholism is the main cause of cirrhosis and where there is definite male preponderance to the extent of 77:33. Faloon¹⁹ found that, it is the 4th commonest cause of death in USA. In my study I did not find any patient with both HCV & HBV positive. In Child Class C, serum albumin was low and it indicates the severity of cirrhosis, as serum bilirubin is the synthetic function of liver. Similarly prothrombin time was prolonged significantly in Child Class C due to the same reason. Serum bilirubin increased with the severity of cirrhosis. These are all parameters of Child Classification and indicate advanced liver disease. Maqsood² found in his study that 62% of the total selected patients were in Child Class C, 28% in Class B and 4% in child class A. My study shows that 45.27% of the patients were in class C, while 42.57% of patients were in class B and only 12.2% in Child Class A. The percentage

was almost the same in both class B&C. I have included not only admitted patients but also patients seen in emergency as well. Kumar¹⁷ conducted a study in Hyderabad. Results show that 80 % of total patients were in Grade IV, 9% in Grade III, 6% in Grade II, and 5% in Grade I. In my study, only 12.16% were in grade IV, 31.08% were in Grade II. Almost 40% of total patients were in grade I and 16.89% were in grade III. Most of the population in my study was in grade I and II and the outcome was excellent in grade I&II as compared to grade III&IV.

Similarly lesser the grade of hepatic encephalopathy, shorter was the stay in hospital. In local studies, the most common precipitating factors of Hepatic Encephalopathy were infection, constipation, and upper GI bleed. Tariq¹⁸ published almost the similar results where constipation and the infection were the leading precipitating factors i.e. 30% each, followed by GI bleed (29%). Maqsood² shows that infection 44%, gastrointestinal bleed 38% and constipation 38% stood out as the most common precipitating factors. In my study constipation stood as the leading precipitating factor in total study population i.e. 34.5%. Other common precipitating factors were Infection and gastrointestinal bleed, 29.7% and 27.7% respectively. These results are close to the earlier published statistics as stated above. But I have found in my study that the most common precipitating factor is constipation instead of infection in total study population but infection is leading precipitating factor in Child Class C. International data suggests that constipation is not the commonest precipitating factor. Faloon¹⁹, Souheil²⁰ and Conn²¹ reported constipation in 6%, 3% and 3% of their cases respectively. But my study and local literatures reveal that constipation is a key factor in precipitation of hepatic encephalopathy. Infection is the second commonest precipitating factor of Hepatic encephalopathy in total study population, leading precipitant in Child class C and in other local studies¹⁶. International data shows Souheil²⁰ found infections responsible in only 3% of cases and Conn²¹ found infection responsible in only 4% of cases. Increased total leukocyte count (TLC) suggested infection. Commonly found infections were urinary tract infection, respiratory tract infection and spontaneous bacterial peritonitis. High frequency of infection in our country is probably because of unhygienic conditions and poor nutritional status.

Gastrointestinal bleed is another common precipitating factor found in my study. i.e. acute variceal bleed presented as Hemetemesis, maelena or both. Results are almost similar to the local studies.

Less common precipitating factors identified in my study were diarrhea only in 4(4.7%) and drugs (benzodiazepines) only in 1(0.7%) in whole study population. very small fraction of patients (1.9%) had electrolyte imbalance, vomiting, hyperglycemia. No cause was found in only 4 (1.9%) of patients as compared to a study by Mumtaz¹⁶ where in 12% of patients no precipitant was noted.

None of the studies have mentioned the precipitating factor in different severities of cirrhosis (child class). In my study I have analyzed different precipitating factors in different child class so that we can predict precipitating factor in a better way and similarly to find out that which factor is more common in which class.

According to my statistics infection is the most common precipitating factor in Child class C. Out of 67(45.27%) patients in Child class C, in 27(40.29%) patients, precipitating factor was infection followed by constipation i.e. 21(31%). It is probably because of nutritional status, malnourishment, and unhygienic conditions.

GI bleed is the leading precipitant in Child Class B. Out of 63(42.56% patients of total patients) GI bleed was responsible precipitating factor in 23(36.50%) patients followed by constipation and infection in 20(31%) & 15(23%) patients respectively. While in child Class A constipation was the leading factor. One very important finding in this study is that constipation has significant role in the precipitation of hepatic encephalopathy in all Child Pugh Classes and hence affecting the quality of life and cost effectiveness in medical wards. That is probably because of dietary patterns, social taboos, poor compliance with lactulose, poor health education and inadequate understanding of the disease among patients and their attendants.

Conclusion

Most of the patients with Hepatic Encephalopathy had an identifiable precipitating factor. Constipation, Infection and upper GI bleed were the most frequent precipitating factors. Infection is most significantly frequent precipitating factor in Child Class C. Constipation is the commonest precipitating factor in all child class. Prevention of constipation by laxatives, proper dietary advice, adherence to the treatment

and proper health education needs to be given importance. Likewise prompt control of infection, and use of prophylactic antibiotics for infection, prophylactic use of β blockade, variceal banding for GI bleed and more importantly proper counseling are the measures that can improve the quality of life of the patients and can ultimately decrease the burden of admissions in medical wards.

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