

A STUDY OF THE CLINICAL PROFILE OF CIRRHOSIS OF LIVER AND ANALYSIS OF PRECIPITATING FACTORS IN HEPATIC ENCEPHALOPATHY

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ABSTRACT: BACKGROUND AND OBJECTIVES: Liver cirrhosis and its complications are a major health problem in the developing countries where cost of health care is high. The syndrome of hepatic encephalopathy (HE) can occur either due to acute liver failure or due to one or more precipitating factors in a cirrhotic patient. Survival of patients having chronic portal systemic encephalopathy is better than those who develop HE acutely. However prognosis in the later group can be improved if the precipitating factors are recognized early and managed accordingly. The present study was done to analyze the precipitating factors of hepatic encephalopathy and the final outcome. **METHODS:** The study included a total of 200 patients (173 males & 27 females) presenting as cirrhosis with hepatic encephalopathy at Sri Ramachandra Medical College from November 2011 to November 2012. All lab parameters, coagulation profile and abdominal ultrasound were done. Abdominal paracentesis was done and Child Pugh score calculated. **RESULTS:** Alcoholic cirrhosis was the most common etiology and gastrointestinal bleed was the most common presentation. 58% patients were in Child Pugh C group. GI bleed was the most common precipitating factor followed by infection and hyponatremia. 80% patients recovered with treatment and 15 % died.

KEYWORDS: Cirrhosis liver, Hepatic encephalopathy, Gastrointestinal bleed.

INTRODUCTION: Chronic liver disease and cirrhosis results in 26000-35000 deaths each year in India. Many patient die from the disease in the fifth or sixth decade of the life. Each year 2000 additional deaths are attributed to Fulminant Hepatic Failure (FHF). Alcoholic liver disease is still the predominant cause of cirrhosis in India, with chronic hepatitis B & C close second. Because of poverty, poor hygienic conditions, inadequate education and lack of counseling, the number of cirrhotic patients is increasing and most of them are admitted to medical wards with different complications.

Hepatic encephalopathy is a common and dreaded complication of cirrhosis liver. The syndrome of hepatic encephalopathy (HE)⁽¹⁾ describes all neuropsychiatric symptoms occurring in patients with acute or chronic liver diseases (CLD) in the absence of other neurological disorders. About 30% of patients with cirrhosis die in hepatic coma.⁽²⁾ Appearance of HE in any patient is indicative of poor prognosis. 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.⁽³⁾

Survival of patients having chronic portal systemic encephalopathy is better than those who develop HE acutely (100% vs. 70%).⁽⁴⁾ However prognosis in the latter group can be improved if the precipitating factors are recognized early and managed accordingly.⁽⁵⁾ Common precipitating factors include gastrointestinal bleeding, infection, azotemia, constipation, electrolyte imbalance and high protein diet.

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Usage of drugs such as sedatives, 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.⁽⁶⁾

The terminology of hepatic encephalopathy remained poorly defined for decades. One major problem was the lack of definition of what constituted acute versus chronic HE. Many physicians assumed acute HE was a term used for the fast onset of a bout of alteration in consciousness in patients with underlying cirrhosis. Others thought acute HE was seen only in patients with acute liver failure. Chronic HE caused even more confusion because it was proposed by some to signify any bout of HE in patients with chronic liver disease, whereas others thought it denoted a protracted (Length of time specified) period of loss of consciousness.

This confusion was solved, to a significant extent, by the report of the HE Consensus Group at the World Congress of Gastroenterology in Vienna in 1998. This report led to an entirely new multi-axial definition for the terminology of HE. (Fig.1)

Fig. 1: Multi-axial classification of HE. This classification system was introduced by the HE Consensus Group at the world Congress of Gastroenterology meet in Vienna 1998.

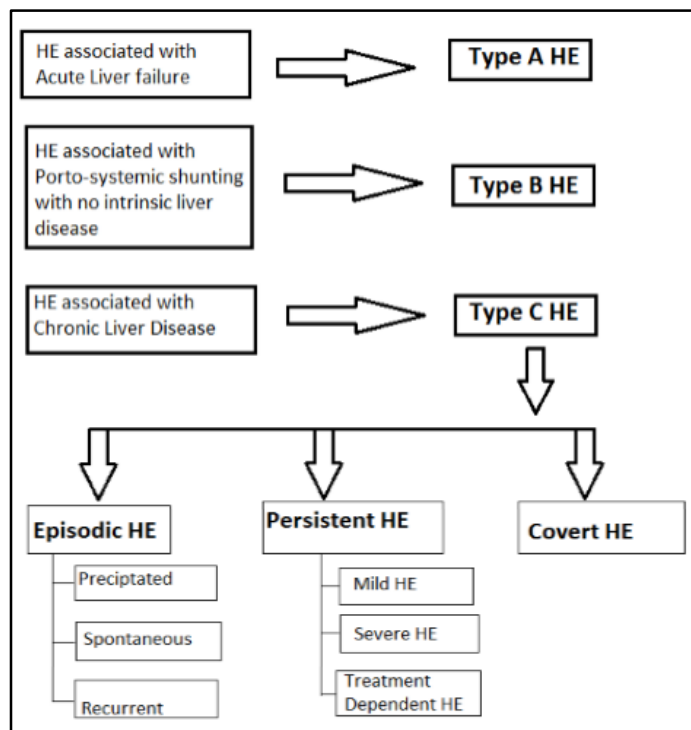


Fig. 1

As noted, three broad types of HE were defined. Type A signified the HE associated with acute liver failure. Type B was designated to represent the rare form of HE associated with portosystemic bypass in the absence of any intrinsic liver disease. Finally type C HE referred to the encephalopathy

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associated with chronic liver disease, which is primarily cirrhosis. Under the categories of type B & C HE, there are further terms subdividing HE into episodic, persistent and subtle form called minimal HE.

As it turned out, the recommendation of the term minimal HE, along with acceptable diagnostic criteria for this form of HE, had a major impact on the field of HE. Multiple articles have appeared using this terminology and diagnostic criteria.⁽⁷⁾ Minimal HE is now known to be associated with the reduction in quality of life, reduced driving skills, reduced ability to hold certain kinds of employment,^(8,9) and most importantly, predicts the subsequent onset of overt HE.⁽¹⁰⁾ Such has been the impact of these findings that consideration is being given to treat patients with minimal HE before overt HE has ever occurred.

The spectrum of neurocognitive impairment in cirrhosis (SONIC) is a term coined by Bajaj & colleagues,⁽¹¹⁾ to describe the prevailing status of the brain function in patients with cirrhosis (Fig.2).

Fig. 2: Spectrum of neurocognitive impairments in cirrhosis.

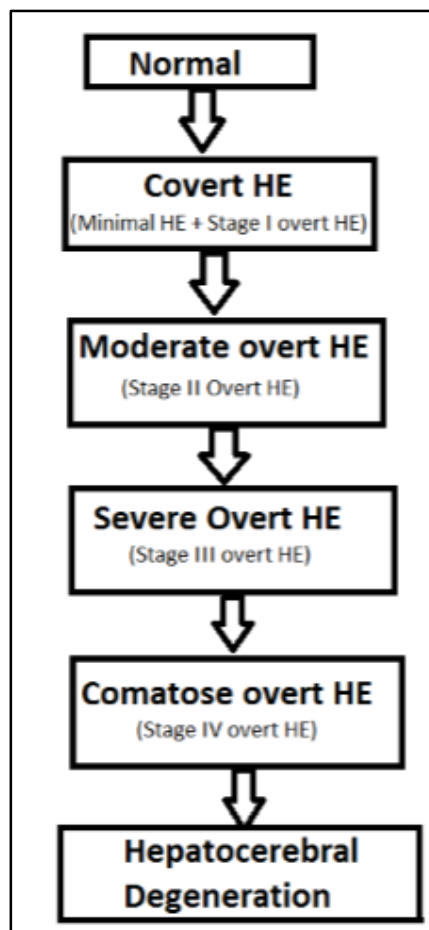


Fig. 2

This concept views the spectrum as a continuum rather than discrete, separate entities. Conventionally, it is stated that patients with prior bouts of overt HE should not be classified as minimal or covert HE. With the advent of SONIC & widespread psychometric testing of patients with

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cirrhosis, it is more likely to encounter patients who have covert HE with or without prior bouts of overt HE.

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

MATERIAL AND METHODS: This study was a prospective and descriptive study conducted in the Department of Medicine and Gastroenterology, Sri Ramachandra medical college & Hospital, Chennai from November 2011 to November 2012.

Patients with cirrhosis of liver, belonging to either sex, age above 18 years, and evidence of hepatic encephalopathy excluding minimal hepatic encephalopathy were included in the study. Patients with psychiatric disorders or on treatment for psychiatric disorders, those with altered sensorium due to metabolic disease or head injury, acute alcoholic intoxication and alcoholic withdrawal states were excluded from the study.

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 hematemesis and melena, constipation, vomiting, diarrhoea, oliguria, fever, bleeding manifestation, high protein diet, paracentesis and any trauma or surgery. Personal history about alcohol consumption was noted in along with smoking and intravenous drug abuse. Use of any sedatives, diuretics, tranquilizers, analgesics and cough syrups was also inquired in detail. All patients were carefully examined with special attention to jaundice, anaemia, fever, asterixis, hydration and pedal edema. Detailed abdominal and neurological examination was done on all patients. Encephalopathy was graded according to the clinical criteria as given in Table 1.

Grade	Neurologic manifestations
0	No alterations in consciousness, intellectual function, personality, or behavior
1	Trivial lack of awareness, euphoria or anxiety, shortened attention span, impaired performance of addition
2	Lethargy or apathy, minimal disorientation for time or place, subtle personality change, inappropriate behavior, impaired performance of subtraction
3	Somnolence to semistupor but responsive to verbal stimuli, confusion, gross disorientation
4	Coma; no response to verbal or noxious stimuli

Table 1: Grades of Hepatic Encephalopathy according to West Haven scale

For each patient full blood count, liver function tests, renal function tests, 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 patients with ascites, an ascitic tap was 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.

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Clinical variable	1 point	2 point	3 point
Encephalopathy	None	Stage 1-2	Stage 3-4
Bilirubin (mg/dl)	<2	2-3	>3
Albumin (G/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time Seconds prolonged or INR	< 4 sec <1.7	4-6 seconds 1.7-2.3	>6 sec >2.3
Ascites	None	Slight	Moderate to severe

Table 2: Child-Turcot-Pugh classification

All patients were followed for the duration of their stay in hospital and the outcome was recorded.

RESULTS: The study population included a total of 200 patients, 173 males (86%) & 27 (14%) female patients, presenting as cirrhosis with hepatic encephalopathy. Most of the patients were aged > 40years (86%) and 14% were less than 40 years. Gender wise and age wise distribution is given in the following chart.

The most common etiology of cirrhosis in the study population was alcohol (63.5%), followed by Hepatitis B viral infection (18%).

Etiology	Frequency
Alcohol	137
HBV related	36
HCV related	12
Cryptogenic and others	15

Table 3: Presenting complaints and their frequency

Presenting complaint	Frequency
GI Bleed	86
Fever	57
Diarrhoea	2
Constipation	1

Table 4: Most common presenting complaint was gastrointestinal bleed

Most common physical presentation was Ascites followed by icterus and pedal edema. Other presenting features are given in the figure below.

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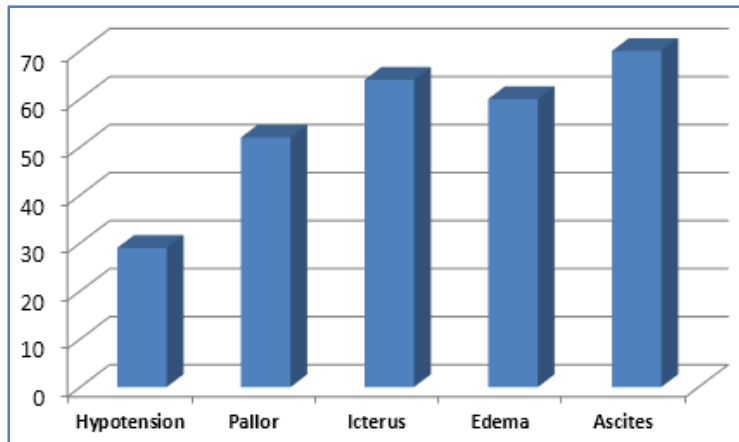


Fig. 3: Clinical Presentation

Anemia was the commonest laboratory abnormality detected and it correlated with the number of individuals presenting with GI bleed. Other laboratory abnormalities are given in the table below (Table 5)

Variables	Numbers
Anemia	126
Leucopenia	58
Thrombocytopenia	77
Hypernatremia	51
Hypokalemia	24
Pre-Renal ARF	49

Table 5: Lab abnormality

When patients were grouped into Child Pugh classification, 58% of the patients were found to be in Class C, 41.5 % of patients in Class B, 1.5% of patient in class A, as shown in Table 6

CPC Stage	%
A	1.5
B	41.5
C	58

Table 6: Child Pugh classification

The following table (Table 7) shows the grade of hepatic encephalopathy with which the study population presented.

HE grade	%
1	44
2	35
3	20
4	1

Table 7: Grade of HE with which the patients presented

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The precipitating factors found in these patients were GI bleed, fever followed by hypernatremia. Out of 200 patients, cause of hepatic encephalopathy was not established in 8 cases (4%) as represented in Table 8.

Precipitating factor	No. of Patients (%)
GI Bleed	86(43%)
Fever	57(28.5%)
Hyponatremia	51(25.5%)
Hypovolemia	29(14.5%)
Hypokalemia	24(12%)
Renal disease	20(10%)
Alkalosis	8(4%)
Surgery	3(1.5%)
Diarrhoea	2(1%)
Constipation	1(0.5%)
No causes	8(4%)

Table 8: Precipitating factors of Hepatic Encephalopathy

Out of the 200 patients 80% recovered (161), 15% of the patients died and the outcome was not known in 9 patients who went against medical advice. Anemia, elevated bilirubin along with liver enzymes were strong predictors of mortality. Among the patients who died 9 patients were HBsAg positive, 4 patients were HCV positive and associated infection was more common among this group of patients.

DISCUSSION: In our study that was conducted on 200 patients, majority (86%) of patients were more than forty years old. Male dominance in progression to advanced stages of chronic liver disease was found in our patients. Al-Gindan⁽¹²⁾ also reported the same pattern in a study in Saudi Arabia. Alcoholism was the most common cause of Cirrhosis liver in this study. 137(68.5%) person were alcoholic, compared to 63(31.5%) nonalcoholic. This is in conjunction with the studies done in industrialized nations of the west, Conn,⁽¹³⁾ and Faloon,⁽¹⁴⁾ which showed alcohol as the main aetiological factor.

Infection and gastrointestinal bleeding and have been repeatedly demonstrated as important precipitating factors of HE. Studies done by Shaikh,⁽¹⁵⁾ show electrolyte imbalance as the major precipitating factor. The findings of the frequencies of different precipitating factors in different national and international studies are given in Table 9.

Study	GI Bleed	Infection	Hypo-Natremia	Hypo-Kalemia	Constipation	Diarrhea
Faloon	33 %	-	-	18%	6%	-
Conn	18%	4%	-	9%	3%	12%
Shaik	56%	15%	20%	70%	52%	22%
Souheil	18%	3%	-	11%	3%	-
Alam	22%	24%	24%	18%	32%	-
Khurram	31%	11%	33%	-	33%	-
Present study	43%	28.5%	25.5%	12%	0.5%	1%

Table 9: Comparison between various studies

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It can be assessed from the table that our findings match those studies done in this sub-continent,^(16,17) but studies from western countries reveal infection as a less common cause, which is understandably due to better hygienic condition of the patients and environment in the western countries.

25.5% of our patients had hyponatremia and 12% were hypokalemic. This was due to the fact that most of them were on diuretics and associated diarrhoea or vomiting contributing to the electrolyte disturbances. Findings of low haemoglobin, thrombocytopenia and hypoalbuminemia correspond well with advanced stages of cirrhosis.⁽¹⁸⁾ Raised total leukocyte count in 40% of patients supports infection as a common precipitant in our setting. Raised urea and creatinine was seen in 28% of patients, highlighting the fact that azotemia is an important pathogenic contributor to the onset of hepatic encephalopathy.

In 7% 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.⁽¹⁹⁾ Occult precipitating factors such as zinc deficiency should also be sought.⁽²⁰⁾ These patients need thorough work-up but cost & logistics is a major factor in a resource limited setting.

The mortality rate in our patients was 15%, which is almost half of what was reported by Sheila Sherlock and those who expired were mostly in Class C of Child's classification with grade 3 or 4 of hepatic coma.

CONCLUSION: Gastrointestinal bleeding, infection, electrolyte disturbances, renal diseases are the most common factors of hepatic encephalopathy in this study. Early identification and prompt treatment is necessary for a favorable outcome. Most importantly, a committed effort is the need of the hour to control the menace of alcoholism which is becoming prevalent in our society and measures should be taken to control increasing incidence of hepatitis B. Only then we stand any chance of combating cirrhosis and even worse hepatic encephalopathy.

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