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Original Research Paper

General Medicine

CLINICAL PROFILE of PATIENTS WITH HEPATIC ENCEPHALOPATHY IN CIRRHOSIS OF LIVER

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ABSTRACT

Introduction- Hepatic encephalopathy (HE) is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of other known causes of brain disease. In India hepatic encephalopathy is considered as indicator of poor prognosis in patients of cirrhosis of liver with 1 year survival in just 42% patients and 3 year survival in 23% of patients.

Aim and Objective- Study clinical profile for adverse outcome in patients of hepatic encephalopathy due to cirrhosis of liver.

Methods and Methodology- This was a cohort type of study done for a period of 2 years from September 2016 to September 2018 on a study population of 130 patients. Cirrhosis of liver was confirmed by ultrasound of liver.

Results - Study included 130 patients of HE secondary to cirrhosis of liver, 82% were males, 44% and 45 % of patients were in grade 2 and grade 3 of West Haven criteria respectively. Icterus, ascites and asterexis were present in almost 65% patients. Cirrhosis was associated with alcohol dependence among 75% of patients followed by NAFLD in 6.15% of patients. Other unknown causes were among 19(14.62%) patients. In our study lactulose was found as the leading treatment modality in 73.84% of patients.

Conclusion- Most of the patients were in grade III of HE, alcohol was the most common etiology of cirrhosis, icterus was the most common sign of liver cell failure, most common drug used was lactulose.

KEYWORDS :

INTRODUCTION

Hepatic encephalopathy (HE) describes a wide range of neuropsychiatric abnormalities which are the result of hepatic insufficiency or portosystemic shunting. Hepatic encephalopathy can be broadly classified into overt hepatic encephalopathy (in which neurologic and neuropsychiatric abnormalities are detected using bedside examinations and bedside tests) or minimal hepatic encephalopathy (where mental status is normal and neurologic examination is normal in conjunction with abnormalities on psychometric testing).(1–3)

Overt hepatic encephalopathy will occur in 30 to 40% of patients suffering from cirrhosis of liver and incidence rate of hepatic encephalopathy is as high as 30-50% in patients who undergo transjugular intrahepatic portosystemic shunting whereas 60% of patients suffering from cirrhosis are likely to develop minimal hepatic encephalopathy(3,4). Very poor prognosis and reduced survival are the two basic outcomes after the onset of hepatic encephalopathy in patients of cirrhosis of liver.

Although some of the precise details about the cause of hepatic encephalopathy remains unknown but a general consensus has been achieved regarding raised levels of ammonia and its central role in the disease by acting as a neurotoxin that results in astrocyte swelling.(1)

Cirrhosis and chronic liver disease was found to be the 10th leading cause of death for men and the 12th for women in the United States in 2001, killing about 27,000 people each year(7). In India in patients with cirrhosis, hepatic encephalopathy is often considered an indicator of poor prognosis, with 1 and 3-year survival after its first occurrence being 42% and 23% respectively in the absence of liver transplantation(8). Also the cost for cirrhosis in terms of human suffering, hospital costs and lost productivity is very high.

Moreover the etiology of cirrhosis of liver and precipitating factors of hepatic encephalopathy is by far not very well documented in literature currently available for central India.
Aim of the study is to study clinical profile and risk factors for adverse outcome in patients of hepatic encephalopathy due to cirrhosis of liver.

Objectives were to study the severity and precipitating factors of hepatic encephalopathy in patients with cirrhosis of liver, to study association of prognostic indicators (CTP score and MELD score) and Mortality and morbidity among patients with hepatic encephalopathy in cirrhosis of liver at 90 days, to study etiology of cirrhosis of liver, to find out risk factors associated with adverse outcome in patients of hepatic encephalopathy due to cirrhosis of liver, to identify the treatment protocol in patients with hepatic encephalopathy in cirrhosis of liver.

METHODOLOGY

All patients of cirrhosis of liver admitted in medicine ward and ICU of Acharya Vinoba Bhave Rural Hospital sawangi (meghe) were considered for the study. It was a cohort type of study. The study was conducted for 2 years from September 2016 to September 2018. Inclusion criteria for the study were the persons who have been diagnosed with CIRRHOSIS OF LIVER (confirmed by ULTRASOUND) and,

Patients showing any one signs of hepatic encephalopathy such as-

- Flapping tremors(tremor of the hand when wrist is extended called asterixis) or abnormal movements
- Drowsiness or severe confusion
- Strange behaviour or severe personality changes
- Slowed or sluggish movement
- Coma: unconscious and unresponsive

Exclusion criteria for the study was setup which included the patients who presented with acute fulminant hepatitis and non cirrhotic portal hypertension/ TIPS or surgical portosystemic shunts, patients who had CNS manifestations (e.g. prior CVE, dementia) or intake of toxins (e.g. benzodiazepines) that would make the neurological examination difficult, and patients who had terminal disease (e.g. advanced hepatocarcinoma)

A structured questionnaire was used for data collection. Detailed demographic data like name, age, sex, hospital registration no, address and occupation. Detailed history of patients alcohol intoxication assessed by CAGE scoring, hepatitis B and hepatitis C examination was done, where viral etiology was considered superior to history of alcohol due to its severity, patients were evaluated according to west haven criteria, they were also examined for signs of liver cell failure,

lab investigations including liver and kidney function tests, coagulation profile, and serum ammonia and lastly treatment protocol of these patients were documented.

DEFINITIONS

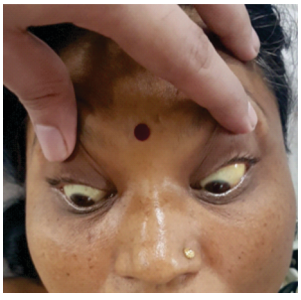
- **Cirrhosis-** cirrhosis of liver can be defined as chronic liver injury leading to fibrous bands formation which surround the regenerative nodules whose development can be acknowledged on histological basis which eventually leads to conditions like portal hypertension and end stage liver disease.(104)
- **Hepatic encephalopathy-** It is defined as a range of neuropsychiatric manifestations in subjects with hepatic dysfunction, after exclusion of neurological cause (106,107)

Grading for hepatic encephalopathy was done as follows: West Haven criteria(2)

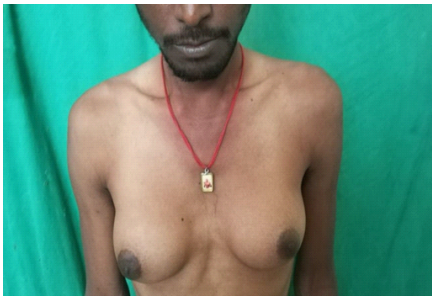
These criteria are based on severity

- Grade 0. Normal
- Grade I. Mild impairment: sleep alterations, subtly impaired intellectual function, heightened irritability, metabolic tremor, and impaired muscular coordination
- Grade II. Moderate impairment: lethargy, grossly impaired intellectual function, disorientation to time, inappropriate or bizarre behaviour, slurred speech, hypoactive reflexes, ataxia
- Grade III. Severe impairment: somnolence, confusion, disorientation, paranoia or anger, clonus
- Grade IV. Coma: unconsciousness, dilated pupils
- Jaundice -as per history given by the patient, history of yellowish discoloration of the eyes and urine was taken for the same.

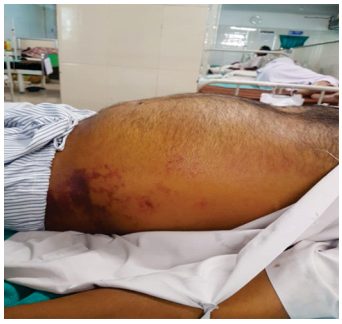
Jaundice can be defined as serum bilirubin levels of more than 2.5 to 3 mg/dl along with a clinical picture of yellowish skin and sclera or both.(119)



- Gynecomastia- appears due to benign proliferation of male glandular breast tissue(104)
- With increase in size of the MAMMARY glands by >0.5 cms associated with tenderness around it.

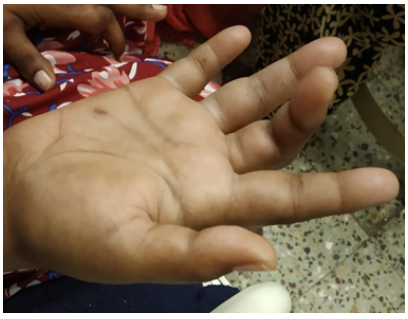


- Ascites- free fluid in peritoneal cavity, clinically evident when more than or equal to 1.5 lits(104) by examination manoeuvres like shifting dullness(vol. of ascitic fluid >1000 ml), horse shoe dullness(at least 500ml of fluid volume is required) and fluid thrill(massive ascites) or by ultrasound examination showing free fluid in abdominal sac(fluid less than 500ml can also be detected).



- Testicular atrophy- also called hypogonadism due to direct effect of alcohol or iron in case of hemochromatosis (104).

- **Asterixis-** asynchronous flapping movement of dorsiflexed hands(104)
- **Dupuytrens contracture-** fibrosis and contraction of the palmar fascia(104)



OBSERVATION AND RESULTS

Table 1: Baseline characteristics of study population

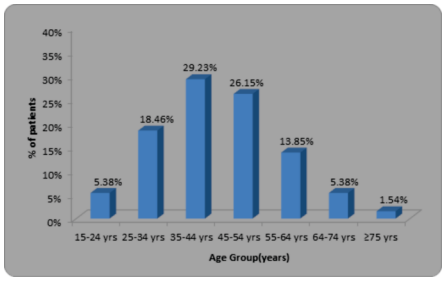
Baseline characteristics	No of patients Mean±SD(n=130)	Percentage (%) Range
Mean Age(yrs)	43.99 ± 13.08	15-85 yrs
Gender		
Male	107	82.31
Female	23	17.69
History of alcohol		
Yes	92	70.77
No	38	29.23
Clinical Investigations		
Sr. Ammonia	116.73±67.36	50-412
HE Grading		
Grade I	11	8.46
Grade II	57	43.85
Grade III	61	46.92
Grade IV	1	0.77

The Table no I show baseline characteristics of our study population. In our study of 130 patients, mean age of cirrhotic patients was 43.99 years and ranged from 15 to 80 years in which 107 patients were male and 23 patients were female.

Out of 130 patients 92 patients gave positive history of alcohol whereas 38 patients had no prior history of alcohol intake.

Serum ammonia values of all 130 patients were analyzed and the mean value was found to be 116.73 with values ranging from 50 to 412.

According to west haven criteria for hepatic encephalopathy on admission out of 130 subjects 11 were found to be in grade I, 57 patients were found to be in grade II, 61 patients came under grade III of the criteria whereas only 1 patient was found to be under grade IV.



Graph 1: Age wise distribution of patients

Table 2: Distribution of patients according to clinical signs of liver failure

Clinical Signs	No of patients(n=130)	Percentage(%)
Icterus	86	66.15
Male pattern baldness	27	20.77
Foetor Hepaticus	54	41.54
Spider Naevi	23	17.69
Gynecomastia	50	38.46
Ascites	86	66.15
Testicular Atrophy	6	4.62
Purpura	9	6.92
Echymotic Patches	57	43.85
Leuconychia	1	0.77
Paper money skin	5	3.85
Asterexis	85	65.38
Dupuytren's Contracture	11	8.46

In Table no 2 according to our study in population of 130 patients 66.15% of persons had icterus , 66.15% of persons had ascites,65.38% of persons had asterixis, echymotic patches were present in 43.85% of persons, foetor hepaticus was present in 41.54% of patients, gynaecomastia was present in 38.46% of patients, male pattern baldness was present in 20.77% of patients, spider naevi was present in 17.69% of patients, dupuytren's contracture was present in 8.46% of patients, purpura was present in 6.92% of patients, testicular atrophy was present in 4.62% of patients, paper money skin was present in 3.85% of patients and leuconychia was present in 0.77% of patients.

Hence in our study population icterus, ascites and asterexis were 3 leading signs of liver cell failure present in almost 65% of patients followed by echymotic patches, foetor hepaticus and gynaecomastia.

Table 3: Distribution of patients according to the treatment protocol in the patients of hepatic encephalopathy

Treatment	No. of patients	Percentage (%)
Lactulose	96	73.84
l-ornithine-l-aspartate	46	35.38
Cefotaxim	51	39.23
Mannitol	47	36.15
Rifaximin	81	62.30

In table no 3 lactulose was used as treatment modality in 96(73.84%) persons, l-ornithine-l-aspartate was used in 46(35.38%) patients, cefotaxim was used in 53(39.23%) persons, mannitol was used in 47(36.15) persons and rifaximin was used for treating 81(62.30%) patients of hepatic encephalopathy in our study population.

Hence lactulose and rifaximin were the two most common treatment modalities used in our study setup followed by cefotaxim and mannitol.

Distribution of patients according to etiology of cirrhosis of liver

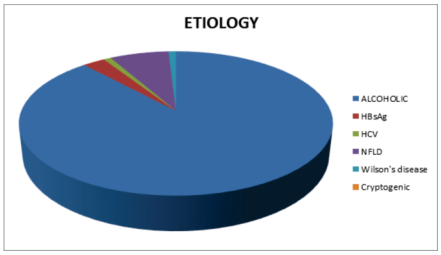


Table no 4.

Etiology	No of patients	Male	Female	ϰ2-value
Alcoholic	98(75.38%)	97(74.62%)	1(0.77%)	75.99,p=0.0001,S
HBsAg	3(2.31%)	2(1.54%)	1(0.77%)	
HCV	1(0.77%)	1(0.77%)	0(0%)	
NFLD	8(6.15%)	5(3.85%)	3(2.31%)	
Wilson's Disease	1(0.77%)	0(0%)	1(0.77%)	
Cryptogenic	19(14.62%)	2(1.54%)	17(13.08%)	78.39,p=0.0001,S
Total	130(100%)	107(82.34%)	23(17.69%)	

This table no 4 reports the distribution of patients according to etiology of cirrhosis of liver. In our study population of 130 patients 98 patients were found to be alcoholic which was significantly higher in males(97 persons) than in females(1 person) (p=0.0001 S). HBsAg status was positive in 3 persons 2 were male and 1 was a female. According to our study HCV was found positive in 1 person- a male. NFLD status was positive in 8 persons 5 were male persons and 3 female. Wilson's disease was found to be positive in 1 female patient which was significantly higher (p=0.030 S) than in male patients. 19 persons suffered from cryptogenic cirrhosis and was significantly higher in females (17 persons) than in males (2 persons) (p=0.0001 S)

Table 5: Laboratory parameters of all patients with cirrhosis of liver

	N	Minimum	Maximum	Mean	Std. Deviation
Total Bilirubin	130	0.57	10.52	3.66	2.77
Conjugated Bilirubin	130	0.14	7.20	1.71	1.65
Unconjugated Bilirubin	130	0.16	5.40	1.94	1.34
Total Protein	130	3.60	8.80	6.49	0.98
Sr. Albumin	130	1.20	4.80	2.87	0.70
Sr. Globulin	130	1.80	6.40	3.62	0.91
Sr. Urea	130	20.00	166.00	41.69	32.48
Sr. Creatinine	130	0.44	8.84	1.28	1.05
Sr. Sodium	130	124.00	154.00	137.13	5.00
Sr. Potassium	130	2.20	6.39	4.10	0.65
Prothrombin Time	130	11.30	41.00	18.72	5.25
INR	130	1.00	3.28	1.54	0.39
AP TT	130	29.10	70.30	37.41	7.54
Sr. Ammonia	130	50.00	412.00	116.73	67.36

Table no VIII shows laboratory parameters of all the patients with cirrhosis of liver. In our study population of 130 patients minimum value of serum bilirubin was 0.57 and 10.52 was the maximum value with a mean of 3.66 .Conjugated bilirubin ranged from 0.14 to 7.20 with a mean value of 1.71 and unconjugated bilirubin ranged from 0.16 to 5.40 with a mean value of 1.94. Minimum value of total protein in our study was 3.60 and maximum value was 8.80 with mean value of 6.49. Serum albumin ranged from 1.20 to 4.80 with mean value of 2.87, also serum globulin was analyzed with minimum value and maximum value of 1.80 and 6.40 respectively with the mean value of 3.62 .In our study population minimum and maximum value of serum urea were 20 and 166 respectively with the mean value of 41.69. Serum creatinine values ranged

from 0.44 to 8.44 in 130 study subjects with a mean value of 1.28. Minimum value of serum sodium in our population was found to be 124 and maximum value was 154 and with the mean of 137.13. Serum potassium values were documented where the minimum value was 2.20 and maximum was 6.39 with the mean of 4.10. Prothrombin time was also studied in 130 patients where the minimum value was found to be 11.30 and maximum value of 41.00 with a mean value of 18.72. In our population INR ranged from 1 to 3.28 with mean value of 1.54. APTT values recorded in our study ranged from 29.10 to 70.30 with a mean value of 37.41. Serum ammonia was analyzed with minimum value of 50 and maximum value was 412 with a mean value of 116.73.

DISCUSSION-

The present Cohort study titled "Clinical profile for adverse outcomes in patients with Hepatic Encephalopathy in Cirrhosis of Liver" was carried out in Department of Medicine, Jawaharlal Nehru Medical College and associated Acharya Vinoba Bhave rural hospital, Sawangi (Meghe), Wardha over a period of 2 years from September 2016 to September 2018.

The study was conducted to determine clinical profile of a patient suffering with Hepatic Encephalopathy in Cirrhosis of liver. The components studied were signs of liver cell failure, etiology of cirrhosis, treatment used among these patients.

Our study included 130 patients of HE secondary to cirrhosis of liver.

The mean age of study population was 44 years, and most of them were males i.e. 82% of total patients and 44% and 45 % of patients were in grade 2 and grade 3 of West Haven criteria of HE respectively.

Cirrhosis of liver was associated with alcohol dependence in 70% of patients. In current study population icterus, ascites and asterexis were 3 leading signs of liver cell failure present in almost 65% of patients followed by ecchymotic patches, foetor hepaticas and gynaecomastia.

Cirrhosis was associated with alcohol dependence among 98 (75%) patients followed by NAFLD in 8 (6.15%) patients, Hepatitis B in 3(2.31%) patients and hepatitis C in 1(0.77%) patient only. Other unknown causes were among 19(14.62%) patients.

In our study population of 130 patients, 82.31% of patients were male and 17.69% were females and the mean age of our study was 44 years. Over all patients were of younger age group i.e. in 4th decade affected with HE. This can have significant effect on family economy as well as on social stability.

In the study by **Intekhab Alam et al**(86), 50 patients were enrolled with 64% males and 36% were females and the mean age of 48 years. In the study by **Ijaz U H Taseer et al**(94) 80% were male and 20% were female out of 50 patients included in the study with mean age 47.45 years. These findings were similar to our results.

Newer insights into the pathogenesis of HE has led to newer approaches in its management, though these are yet to be widely applied particularly in the resource poor nations(123), documentation of its profile including precipitating factors will go a long way in formulating rational strategies in its management including prophylaxis in view of the reported poor outcome.

The patients in this study were nursed in the open ward and this was largely due to financial constraints. In our setting, usually healthcare costs are borne by the patients and payment often has to be made before some facilities are made available for use. Management in an intensive care unit as well as employment of the newer therapeutic measures may have improved the outcome.

In our study lactulose was used as treatment modality in 73.84% of patients and the 2nd most common drug used in treatment of HE is Rifaximin in 62.30% of patients.

In a study by **F Qazi et al**(90) done at Aga Khan university stated that lactulose is the most commonly prescribed agent to relieve constipation in patients with chronic liver disease.

Etiology of cirrhosis is one of the important parameters involved in progression of the disease as it can help in identifying and removing the cause of disease.

In our study total 130 patients were studied of which 75.38% of patients were found to be alcoholic. Followed by NFLD, present in 6.15% of patients which was the 2nd most common cause of cirrhosis of liver in our patients. 14.62% of patients were attributed to causes which were unknown or could not be diagnosed. Male predominance was seen in patients suffering from alcoholic cirrhosis of liver whereas females were predominantly present in the group where the diagnosis could not be made and the cause remained unknown (cryptogenic) for cirrhosis of liver.

Comparison of different national and international studies in view of etiology (values in %)

Etiology	**CA ONYEKWERE et al** (95)(nigeria)	**MOHAN et al** (88)(manipal)	**AHMAD et al** (91)(Pakistan)	Our study
Alcoholic	48	76.4	-	75.38
HBV	48	7.9	44	2.31
HCV	2	4.2	32	0.77
NFLD	-	-	-	6.15
Cryptogenic	-	9.1	-	14.62
Wilson's disease	-	0.9	-	0.77

Our findings when compared with studies done in different countries show that alcoholism is clearly the leading cause of cirrhosis of liver and hence awareness among people towards alcohol abstinence can significantly alter the course of cirrhosis in our study setup. These findings were contrary to the ones done in countries like Pakistan where HCV infection was the leading cause of cirrhosis of liver. On the other hand, in the western world alcoholism is the main cause of liver cirrhosis where there is definite male preponderance to the extent of 77:33, making it the 4th commonest cause of death in males in USA.(124).

Lab parameters	No. of patients (n=130)
Total Bilirubin (>2.5)	69
Sr. Albumin (<3)	73
Sr. Urea (>40)	35
Sr. Creatinine (>1.5)	26
Sr. Sodium (<136)	17
Sr. Potassium (<3)	12
Prothrombin Time (>13)	114
INR (>1.2)	105
Sr. Ammonia (>90)	75

These parameters were helpful in identifying the different precipitating factors responsible for worsening the course of disease, hyperbilirubinemia, hypoalbuminaemia, deranged renal profile(hepatorenal syndrome), hypokalemia, hyponatremia, deranged coagulation profile and hyperammonemia are the most common findings.

It is very clear from the above findings that almost 2/3rd of the patients have coagulopathy, more than half of the study population have hyper ammonemia, hypoalbuminemia and hyperbilirubinemia. Patients with cirrhosis have variety of haematological, vascular and other defects that increase their morbidity and mortality rates, in majority of the patients PT was prolonged and serum albumin levels were low. PT may be prolonged due to failure to absorb fat soluble Vitamin K or due to failure of synthesis of prothrombin and other liver derived factors, prolonged PT is a relatively late manifestation of liver disease clearly indicating the advancement of liver cirrhosis in our patients by the time of their presentation in the hospital, findings of our study were consistent with those of **Maqsood et al(85)** where 86% of the patients had hypoalbuminemia and 44% of the patients suffered with coagulopathy.

Findings of hypoalbuminemia correspond well with advanced stages of cirrhosis. High urea and creatinine in majority of our patients highlight the fact that azotemia is an important pathogenic contributor to the onset of HE.

Limitation of the study were-

Due to high costs of imaging patients in this study, we did not have brain computerized tomographic scan (CT scan) to exclude primary neurological disease, however most of these patients had pre existing liver disease.

The intake of protein in diet could not be assessed as precipitating factor in our study due to lack of guidance regarding nutritional supplements for the patient or unavailability of a nutritionist, which acted as a limitation for our study.

Liver biopsy could not be done to confirm the histological diagnosis of the patients of cirrhosis of liver, due to lack of technical requirements and reluctance of patients and their relatives toward such procedure.

Poor follow up compliance of the patients was a huge limitation in our study setup, due to illiterate and negligent behavior of the patients during the follow up period, this is the same reason associated with poor compliance of the patients towards medications and their routine hospital visits.

CONCLUSION-

In present study alcohol was found to be the leading cause of cirrhosis of liver followed by NFLD.

In our study most common clinical feature associated were icterus, ascites , asterexis , and echymotic patches .

Our study showed that most commonly used treatment for hepatic encephalopathy is lactulose and rifaximin.