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Original research article

A STUDY ON CLINICAL PROFILE OF PATIENTS WITH HEPATIC ENCEPHALOPATHY IN A TERTIARY CARE TEACHING HOSPITAL

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Abstract

Background: Hepatic encephalopathy (HE) refers to a broad spectrum of neuropsychiatric disorders caused by hepatic insufficiency or portosystemic shunting. HE can be divided into two types: overt HE (in which neurologic and neuropsychiatric abnormalities are recognized by bedside examinations and tests) and minimal HE (in which mental status is normal, the neurologic examination is normal, and psychometric testing is abnormal).

Objectives:

1. To study in detail epidemiology, incidence, morbidity and mortality associated with hepatic encephalopathy in patients admitted medical wards.
2. To know the various etiologies for hepatic encephalopathy.
3. To evaluate different prognostic indicators in hepatic encephalopathy.
4. To determine any possible preventive measures.

Material & Methods:

Study Design: Hospital-based, cross-sectional study.

Study area: The study was conducted in the Department of General Medicine and Gastroenterology, from April 2022 to March 2023, in Vydehi Institute of Medical Sciences. The study was carried out on 50 patients with hepatic encephalopathy admitted to medical wards.

Sample size: The study consisted of a total of 50 subjects.

Sampling Technique: Simple Random technique. On admission, a detailed history was noted and a thorough clinical examination was done. For data collection, a questionnaire was developed. History of previous episodes of jaundice, blood

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transfusions, IV abuse, drug intake, and alcoholism concerning the type, duration, amount & frequency was elicited. History regarding alteration in sleep pattern & neurological symptoms were enquired into. A complete history regarding precipitating events of hepatic encephalopathy like GI bleeding, high protein intake & overzealous use of diuretics, or vigorous paracentesis was noted.

Results: In the present study, altered sensorium ranging from drowsiness to coma was seen at presentation in 48 (96%) patients, the other two developed hepatic encephalopathy during hospital stay. About 74% of patients had jaundice at the time of presentation. Twenty-three (46%) patients complained of decreased urine output at presentation. Fever was documented in 16 (32%) of patients. Although only 5 patients complained of distention of the abdomen, ascites were clinically documented in 10 (20%) patients.

Conclusion: From this study, it was concluded that in most of the cases, different factors play a key role in precipitating hepatic encephalopathy which is a common phenomenon in patients with liver disease. Infections, upper GI bleeding, constipation, and electrolyte imbalance were the most common precipitating factors.

Keywords: Hepatic encephalopathy, upper GI bleed, chronic liver failure

Introduction

Hepatic encephalopathy (HE) refers to a broad spectrum of neuropsychiatric disorders caused by hepatic insufficiency or portosystemic shunting. He can be divided into two types: overt HE (in which neurologic and neuropsychiatric abnormalities are recognized by bedside examinations and tests) and minimal HE (in which mental status is normal, the neurologic examination is normal, and psychometric testing is abnormal) [1-3].

Overt HE occurs in 30%-40% of patients with liver cirrhosis, and the incidence rate of HE is as high as 30%-50% in patients who have transjugular intrahepatic portosystemic shunting (TIPS), although 60% of people with cirrhosis are likely to develop mild HE. [3,4] After the development of HE in individuals with liver cirrhosis, the two main consequences are a very poor prognosis and shortened survival.

Although some facts about the origin of HE are unknown, a consensus has been reached regarding elevated amounts of ammonia and its important function in the disease by acting as a neurotoxin, causing astrocyte enlargement [1]. In India, HE is frequently used as a sign of a bad prognosis in cirrhosis patients, with 1-and 3-year survival rates of 42% and 23%, respectively, in the absence of liver transplantation [5]. Furthermore, the cost of cirrhosis in terms of human misery, hospitalization, and lost productivity is prohibitively high.

Although only one in every five patients with fulminant hepatic failure obtains a transplant, the survival rate is more than 70% in the first five years after transplantation [6, 7]. Hepatic encephalopathy is not only diagnosed and graded by experts in chronic liver failure. Patients may first consult a regular practitioner, an emergency physician, or a hospitalist.

Early identification of triggering causes is critical in the diagnosis and treatment of this deadly illness. Controlling the triggering causes can halt the clinical course of hepatic encephalopathy in the majority of patients [8]. Thus, the purpose of this study is to investigate the clinical profile and spectrum of precipitating causes for hepatic

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encephalopathy. As a result, early and correct diagnosis, as well as proper identification of triggering causes, will aid in the initiation of appropriate therapy, reducing morbidity and mortality.

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Material & Methods

Study design: Hospital-based, cross-sectional study.

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Sample size: The study consisted of a total of 50 subjects.

Sampling technique: Simple Random technique.

Inclusion criteria

1. Patients with clinical symptoms and signs of hepatic encephalopathy.
2. Patients with an age of more than 18 years irrespective of sex.

Exclusion criteria

1. The cases of hepatic encephalopathy arising due to obstructive jaundice because of surgical causes like stones, strictures, mass lesions, etc.
2. All cases of cirrhosis due to cardiovascular causes.

Study tools and Data collection procedure

Tools

- Clinical proforma.
- West Haven classification for grading of hepatic encephalopathy.

On admission, a detailed history was noted and a thorough clinical examination was done. For data collection, a questionnaire was developed. History of previous episodes of jaundice, blood transfusions, IV abuse, drug intake, and alcoholism concerning the type, duration, amount & frequency was elicited. History regarding alteration in sleep pattern & neurological symptoms were enquired into. A complete history regarding precipitating events of hepatic encephalopathy like GI bleeding, high protein intake & overzealous use of diuretics, or vigorous paracentesis was noted.

A detailed systemic examination was carried out including a general examination pertinent to the stigmata of chronic liver disease like anaemia, clubbing, jaundice, testicular atrophy, loss of axillary hair & gynecomastia. The skin was carefully examined to detect purpuric spots, ecchymoses, bruises, palmar erythema, and spider angiomas. Examination of the abdomen was carried out to detect any distention, dilated veins, signs of free fluid, organomegaly & other palpable mass lesions. The abdomen

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was carefully auscultated to detect any venous hum. Evaluation of the mental status and neurological examination were done to know the presence of flapping tremors, level of consciousness, and personality changes. Evidence of any constructional apraxia was recorded using a simple number connecting test.

Routine haematological investigations, biochemical parameters, and specific investigations such as liver function tests, viral markers, etc were performed. Special investigations like serum iron levels, ceruloplasmin levels, and levels of alpha-1 antitrypsin were also performed as and when required. An abdominal ultrasound was performed to look for liver size, parenchymal echogenicity, portal vein diameter, splenomegaly, and free fluid. In patients with ascites, paracentesis was done and fluid was sent for biochemical and microbiological analysis to find out any evidence of infection. Upper GI endoscopy was done to detect any bleeding varices. Any evidence of other co-existent complications of cirrhosis liver like portal hypertension, hepato-renal syndrome, and hepato-pulmonary syndrome was also recorded.

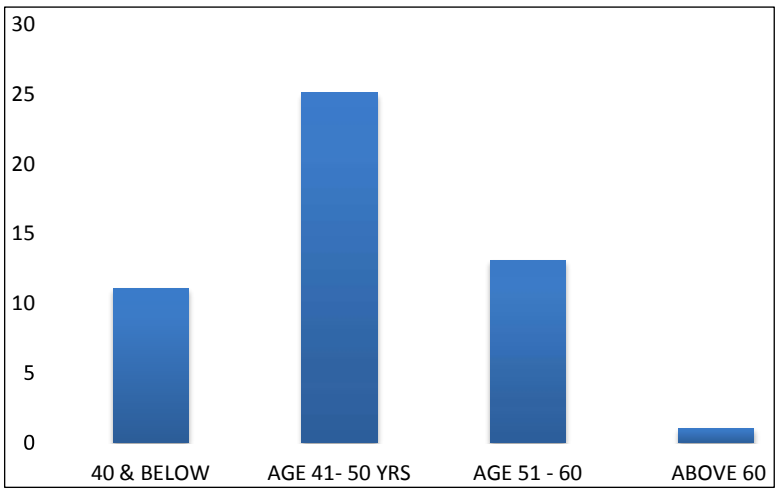
Diagnosis of hepatic encephalopathy was done on clinical grounds only in most of the cases. The use of neuroimaging modalities was limited to circumstances where there were strong clinical indicators for other diagnoses. Neuropsychiatric assessment along with EEG was done if the diagnosis was in doubt. Hepatic encephalopathy was graded according to the West Haven criteria.

Statistical analysis

The data has been entered into MS Excel and statistical analysis has been done by using IBM SPSS Version 25.0. For categorical variables, the data values are represented in terms of numbers and percentages. The chi-square test was used to assess group association. For continuous variables, the mean and standard deviation of the data are displayed. The student's t-test was used to compare the mean differences between the two groups. All p-values less than 0.05 are regarded as statistically significant.

Observations & Results

In the present study which included 50 patients, there was a male preponderance with 43 (86%) to 7(14%) females.



Graph 1: Age Distribution

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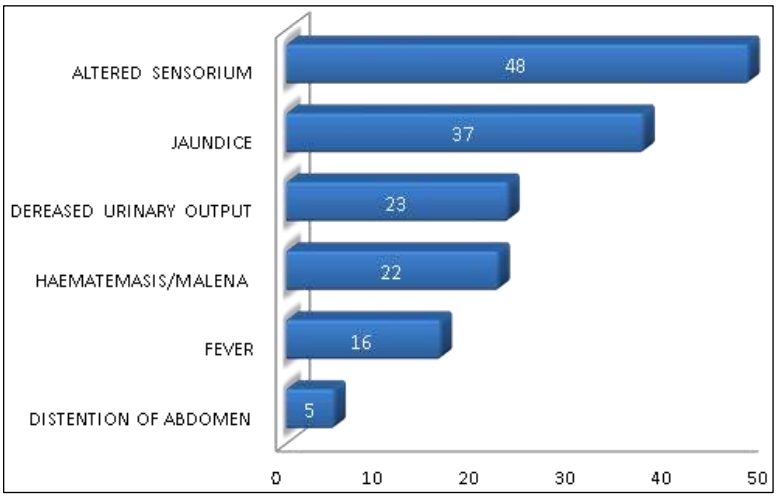
Most of the patients i.e. 25 (50%) are in the age group between 41-50 yrs, out of these 24 (96%) were males, and 1(4%) was female. Eleven (22%) patients were in the age group 40 and below, of these eight (73%) were males and 3 (27%) were females. There were 13 (26%) patients in the age group 51-60 years and only one patient above 60 years.

Precipitating factors

In the present study, the most common precipitating factors of Hepatic encephalopathy were GI bleeding 22 (44%), dehydration with diuretic overuse 20 (40%), and hypokalaemia 14 (28%). However, in about 28 (56%) patients precipitating cause was multifactorial which predominantly included sepsis (LRTI), constipation, and increased protein intake. In about 13 (26%) patients no precipitating cause could be elicited. Of the 11 (22%) patients who had evidence of acute Fulminant Hepatitis Plasmodium Falciparum was found to be positive in 7 (63%) patients.



Graph 2: Analysis of symptoms

In the present study, altered sensorium ranging from drowsiness to coma was seen at presentation in 48 (96%) patients, the other two developed hepatic encephalopathy during hospital stay. About 74% of patients had jaundice at the time of presentation. Twenty-three (46%) patients complained of decreased urine output at presentation. Fever was documented in 16 (32%) of patients. Although only 5 patients complained of distention of the abdomen, ascites were clinically documented in 10 (20%) patients. Symptoms of GI bleeding in the form of hematemesis and malena were seen in 22 (44%) patients.

Analysis of signs: Grade IV hepatic encephalopathy was seen in 26 (52%) patients at presentation. Signs of dehydration were evident in 27 (54%) patients. The flapping tremor was elicited in 60% of patients, if not at presentation, later during their hospital course. Constructional apraxia could be elicited only in 24% of patients whereas inversion of sleep rhythm was observed in up to 95% of patients. The other signs are charted below.

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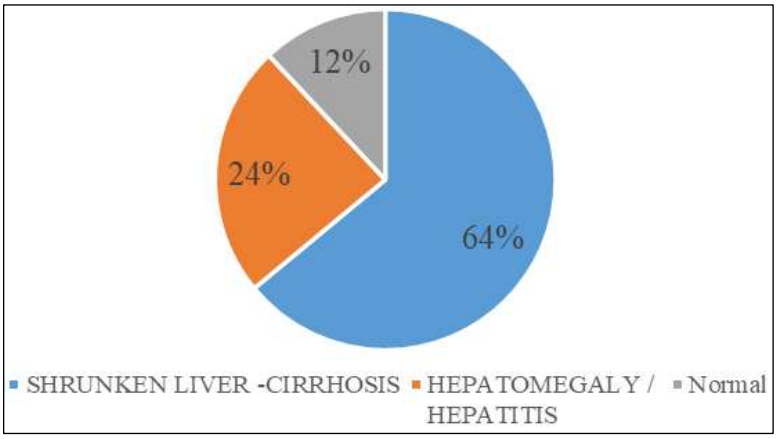

Graph 3: Liver-Ultrasound Abdomen Findings

USG abdomen findings: Liver size was shrunken in 32 (64%) patients. Hepatomegaly has been seen in 12 (24%) patients majority of them presented with acute fulminant hepatitis.

Aetiology: In the present study hepatic encephalopathy was most commonly associated with cirrhosis / chronic liver disease in 37 (74%) patients. One patient developed hepatic encephalopathy after 20 days following the TIPPS procedure. Acute liver cell failure was seen in 12 (24%) patients of whom 9 cases were due to malaria.

Table 1: West Haven Classification

Stage	No. of Patients
I	11
II	5
III	16
IV	18

The majority of patients of hepatic encephalopathy in the present study belong to Grade IV (36%) and Grade III (31%) of West Haven classification followed by 22% in Grade I and 11% in Grade II.

Table 2: Type of Hepatic Encephalopathy

Type of Hepatic Encephalopathy	No. of Patients
Type-A	12
Type-B	1
Type-C	37
Total	50

Among 50 patients, 9 patients (24%) belong to type A, and 37 patients (74%) belong to

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type C. There was 1 patient (2%) in type B.

Risk factors for chronic liver disease: About 61% of patients in the study had a history of consumption of alcohol in significant amounts. Hepatitis B virus infection was found in 12 (24%) patients, of them 4 (8%) were also positive for hepatitis C. Hepatitis C virus infection was found in 6 (12%) patients.

Outcome: In the present study, a total mortality of 54% was observed. Out of them 22 (81%) were males and 5 (19%) females.

Table 3: Prognosis and Outcome in Males and Females

Outcome	Males	Females	Total
Survived	17	6	23
Expired	22	5	27

Table 4: West Haven Classification and Mortality

West Haven Classification	No. of Cases	Mortality	Percentage
I	11	0	**0%**
II	5	1	**20%**
III	16	11	**68%**
IV	18	15	**84%**

Discussion

In the present study, the maximum incidence of hepatic encephalopathy is seen in the age group between 41 -50 years, followed by the age group between 51-60 years. The majority (64%) of patients were more than forty years by Saira Afzal *et al.* [9] Most common age group affected by hepatic encephalopathy was 41-60 in Bikham Ram Devrajani *et al*., [10] whereas 64% were in the age group of 45-60 years by Alam *et al*. [11] The mean age of the present study subjects was 47 years, and the mean age of the males and females were comparable (47.4 years and 47.6 years respectively) Onyekwere CA *et al.* [12] Reported that there was no significant difference in the mean ages of males and females in patients with hepatic encephalopathy.

Most of the patients i.e. 25 (50%) are in the age group between 41-50 yrs., out of these 24 (96%) were males, and 1(4%) was female. Eleven (22%) patients were in the age group 40 and below, of these eight (73%) were males and 3 (27%) were females. There were 13 (26%) patients in the age group 51-60 years and only one patient above 60 years. In the present study male to male-to-female ratio is about 6:1. The preponderance of hepatic encephalopathy in men is parallel with the fact that alcoholism is very common in males, easier access to alcohol in men, and high-risk behaviour in men than in women. This fact is in keeping with the reports by Binesh *et al.* [13], and Marcus CD *et al.* [14].

In the present study, GI bleeding was the main precipitating factor seen in 22 (44%) patients, which was also the predominant factor reported in other studies. Most of the

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patients had a history of similar complaints in the past & most of them were alcoholics. Of the 22 patients who had GI bleed 20 (90%) succumbed despite aggressive efforts indicating that GI bleeding, as a precipitating factor, has the worst prognosis. The incidence of infection was 14% in our study. Hypokalemia was found in 28% of patients which was similar to other studies, out of which 85% recovered. The present study also highlights the fact that dehydration secondary to diuretic overuse is a common reversible precipitating factor for hepatic encephalopathy. At the time of presentation, 27 (54%) patients had dehydration and 20 (74%) had diuretic overuse. Gastrointestinal bleeding and infections were the most common precipitating factors for hepatic encephalopathy. This is especially true for the province of Punjab where Aisha [15] and Khurram [16] revealed gastrointestinal bleeding, infection, and constipation as the main factors precipitating HE.

The most common precipitating factors for hepatic encephalopathy detected were infection (67%), constipation (49%) and gastrointestinal bleeding (45%) by Bikha Ram Devrajani *et al*. [10] Most common precipitants of hepatic encephalopathy were infections (20.5%) and constipation (18.3%) by Mumtaz K *et al*. [17] The identified precipitants for hepatic encephalopathy were sepsis (29%), electrolyte imbalance (14%), gastrointestinal bleed (24%) and drugs (5%) by Onyekwere CA *et al*. [12] Infection (44%), gastrointestinal bleeding (38%) and constipation (38%) stood out as the most common precipitating factors for hepatic encephalopathy by Maqsood S *et al*., [18] Islamabad. Souheil *et al*. [19] found that infections were responsible in only 3% of cases and Conn reported infections were responsible in only 4% of cases.

In the present study, altered sensorium ranging from drowsiness to coma was seen at presentation in 48 (96%) patients, the other two developed hepatic encephalopathy during hospital stay. About 74% of patients had jaundice at the time of presentation. Twenty-three (46%) patients complained of decreased urine output at presentation. Fever was documented in 16(32%) of patients. Although only 5 patients complained of distention of the abdomen, ascites were clinically documented in 10 (20%) patients. Symptoms of GI bleeding in the form of hematemesis and Malena were seen in 22(44%) patients.

Grade IV hepatic encephalopathy was seen in 26(52%) patients at presentation. Signs of dehydration were evident in 27(54%) patients. The flapping tremor was elicited in 60% of patients, if not at presentation, later during their hospital course. Constructional apraxia could be elicited only in 24% of patients whereas inversion of sleep rhythm was observed in up to 95% of patients. In the present study, hepatic encephalopathy was most commonly associated with cirrhosis/chronic liver disease in 37 (74%) patients. One patient developed hepatic encephalopathy after 20 days following the TIPPS procedure. Acute liver cell failure was seen in 12 (24%) patients of whom 9 cases were due to malaria. In the present study, alcoholic liver disease was not observed in females, whereas in another local study, it was seen in 3.5% of female cases. This may be because patients denied alcoholic consumption. Alcoholic liver disease (68%) was the most common CLD by Dhiman RK *et al*., Chandigarh [20].

In our study, there was a lower prevalence of hepatitis B and HCV infection among ALD patients with only (5 patients) 10% of ALD were positive for HBsAg. These findings correlate with Gautham Ray *et al*. [21] In the present study among the 27 patients who expired 21 (42%) patients were alcoholics, showing the importance of

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alcohol in the secondary prevention of hepatic encephalopathy. HCV is the dominant cause of non-alcoholic Chronic Liver Disease (CLD) in several parts of the world, whereas in India there are conflicting reports. Some report hepatitis B, while others hepatitis C viruses as the most important infection in CLD patients. HBV was the most prevalent viral infection than HCV in chronic liver disease patients in North India as reported by Sarin SK *et al*. [22].

Out of 50 patients, in the present study, a total mortality of 54% was observed. Out of them 22 (81%) were males and 5 (19%) females. A higher fatality rate was recorded with increasing severity of encephalopathy. According to West Haven classification out of the 18 patients, 15 expired in Grade IV. Out of the 11 patients, there was no mortality in Grade I hepatic encephalopathy. In Grade IV hepatic encephalopathy, the mortality was more than 80%. Mortality with AHF was seen in 3 patients, of them one was with hepatitis B infection positive.

There is a definite need for health education in patients who are diagnosed with cirrhosis of the liver regarding the risk of hepatic encephalopathy and its precipitating factors. Priority should be given to these factors in terms of hospital funds, blood banks, medicines, and human efforts. No stone should be left unturned in providing better and more effective infection control measures and better hygienic conditions in hospitals. The proper disposal of infected hospital waste especially syringes, and blades should be performed. Consistent use of lactulose and fibre, lifestyle modifications like exercise, a low-fat diet, and activity should be encouraged to prevent constipation. Emergency endoscopic facilities should be made available nationwide in public sector hospitals for prompt control of gastrointestinal bleeding. Every effort should be made to control the increasing incidence of hepatitis B and C through health education, prevention and immunization. Judicial use of sedatives and diuretics and proper advice regarding diet must be an integral part of all counselling protocols for cirrhotic patients. Hence, the early detection and diagnosis of these precipitating factors help in starting treatment of this fatal condition, reducing mortality.

Conclusion

From this study, it was concluded that in most of the cases, different factors play a key role in precipitating hepatic encephalopathy which is a common phenomenon in patients with liver disease. Infections, upper GI bleeding, constipation and electrolyte imbalance were the most common precipitating factors. There is a definite need for health education in patients who are diagnosed with cirrhosis of the liver regarding the risk of hepatic encephalopathy and its precipitating factors.

References

1. Liere V, Sandhu G, DeMorrow S. Recent advances in hepatic encephalopathy F1000Res. 2017;6:16-37.
2. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, *et al*. Hepatic encephalopathy in chronic liver disease: 2014 Practice guideline by the American Association for the Study of Liver Diseases and the EUROPEAN association for the study of the liver Hepatology. 2014;60:715-35.
3. Wijdicks EF. Hepatic encephalopathy N Engl J Med. 2016;375:1660-70.
4. Bajaj JS. Review article: The modern management of hepatic encephalopathy

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 03, 2024

Aliment Pharmacol Ther. 2010;31:537-47.

5. Prognostic Significance of Hepatic Encephalopathy in Patients with Cirrhosis-Science Direct, Available from: https://www.sciencedirect.com/science/article/pii/S0168827899801445.
6. Bernal W, Hyyrylainen A, Gera A, *et al*. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. J Hepatol. 2013;59:74-80.
7. Reuben A, Tillman H, Fontana RJ, *et al*. Outcomes in adults with acute liver failure between 1998 and 2013: an observational cohort study. Ann Intern Med. 2016;164:724-32.
8. Mullen KD, Dasarathy S. Hepatic encephalopathy. Schiff ER, Sorrell MF, Maddrey WC, editors. Schiff's Diseases of the liver. 11th ed. Philadelphia: Lippincott-Raven Publishers, 2012, p. 545-81.
9. Afzal S, Ahmad M. Precitating factors of hepatic coma. Annals. 2011;17(3):2013-217.
10. Devrajani BR, Shah SZ, Devrajani T, *et al*. Precipitating factors of hepatic encephalopathy at a tertiary care hospital Jamshoro. Hyderabad. J Pak Med Assoc. 2009;59(10):683-686.
11. Alam I, Razaullah, Haider I, *et al*. The spectrum of precipitating factors of hepatic encephalopathy in liver cirrhosis. Pakistan J Med Res. 2005;44(2):96-100.
12. Onyekwere CA, Ogbera AO, Hameed L SO. Chronic liver disease and hepatic encephalopathy: clinical profile and outcomes. Niger J Clin. Pract. 2011;14(2):181-185.
13. Binesh N, Huda A, Thomas MA, Wyckoff N, Bugbee M, Han S, *et al*. Hepatic encephalopathy: A neurochemical, neuroanatomical, and neuropsychological study. J Appl. Clin. Med Phys. 2006 Dec;7(1):86-96.
14. Marcus CD, Sargentoni J, Bryant DJ, Taylor-Robinson SD. 1H MRS in patients with chronic hepatic encephalopathy-Regional variations. Book of abstracts. Society of Magnetic Resonance, 1994, 571.
15. Sheikh Isha A, Ahmed SI, Naseemullah M. Etiology of hepatic encephalopathy and importance of upper gastrointestinal bleeding and infections as precipitating factors. J Rawal Med Coll. 2001;5:10.
16. Khurram M, Khaar HB, Minhas Z, *et al*. An experience of cirrhotic hepatic encephalopathy at DHQ Teaching Hospital. J Rawal Med Coll. 2001;5:60-64.
17. Mumtaz K, Ahmed US, Abid S, *et al*. Precipitating factors and the outcome of hepatic encephalopathy in liver cirrhosis. J Coll Physicians Surg. Pak. 2010;20(8):514-519.
18. Maqsood S, Saleem A, Lqbal A, *et al*. Precipitating factors of hepatic encephalopathy: experience at Pakistan Institute of Medical Sciences Islamabad. J Ayub Med Coll Abbottabad. 2006;18(4):58-62.
19. Souheil Abu-Assi, Vlaeevie ZR. Hepatic encephalopathy: metabolic consequences of cirrhosis are often reversible. Postgraduate Med., 2001, 109. http://www.postgradmed.com/ issues/2001/02_01/assi.html
20. Dhiman RK, Agrawal S, Gupta T, *et al*. CLIF-SOFA vs APASL criteria for ACLF. World Journal of Gastroenterology. 2014;20:14934-14941.
21. Ray G. Trends of chronic liver disease in a tertiary care referral hospital in Eastern India. Indian J Public Health. 2014;58:186-94.

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 03, 2024

22. Sarin SK, Guptan RC, Banerjee K, *et al*. Low prevalence of hepatitis C viral infection in patients with non-alcoholic chronic liver disease in India. J Assoc Physicians India. 1996;44(4):243-245.