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ORIGINAL ARTICLE

Determine the Frequency of Factors Leading to Hepatic Encephalopathy in Patients with Liver Cirrhosis

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ABSTRACT

Aim: To determine the frequency of factors leading to hepatic encephalopathy in patients with liver cirrhosis.
Study design: Retrospective study
Place and duration of study: Department of Internal Medicine, Rawalpindi Medical Universityfrom 01-07-2021 to 30-06-2022
Methodology: One hundred patients were included and divided into two groups. One group was those which developed hepatic encephalopathy while the other group was of those which did not develop any hepatic encephalopathy. Various risk factors and their frequencies were measured through a modelled hepatic encephalopathy pharmacological, clinical as well as demographic data. Comparison on the frequency of the variable seen in hepatic encephalopathy patients with non-hepatic encephalopathy was conducted for better assessment of the frequency of risk factors.
Results: Seventy patients did not develop hepatic encephalopathy while 30 patients did develop hepatic encephalopathy. Fifteen patients had developed alcoholic liver cirrhosis followed by hepatitis C and non-alcoholic cirrhosis. Age greater than 60 years had a percentage of 60% within cases of hepatic encephalopathy only. Prevalence of hepatitis C cirrhosis in 36.6%, diabetes in 49%, cardiovascular disease in 51%, hepatocellular carcinoma in 6.6%, use of proton pump inhibitor in 63.3% were presented and were higher than who did not develop hepatic encephalopathy. Benzodiazepines, gamma aminobutyric acid [GABA]ergics, opioids and proton pump inhibitors each of them was associated with increased chances of hepatic encephalopathy.
Conclusion: Hepatic encephalopathy was more commonly observed in older patients (60%) and more specifically in male population. Higher frequency of comorbidities (hypertension, diabetes, cardiovascular disease, ascites, alcoholic cirrhosis), CCI score and pharmacological drugs were identifiable risk factors for hepatic encephalopathy.
Key words: Neurotoxicity; Cirrhosis, Complications, Hepatitis C, Deteriorate

INTRODUCTION

Hepatic encephalopathy (HE) is a serious nervous disorder occurred due to severe or end stage liver failure. In liver cirrhosis, toxins build up in blood and then these toxins travel to brain and cause deteriorate brain function. It is considered as a critical complication causing cirrhosis. Developing and advancement of HE exacerbate the chances of mortality as well as increase the risk of hospitalizations, psychosocial burden, accidents and confusion among the patients.[1-4] Various risk factors have been associated with the progression of hepatic encephalopathy development including alcoholic and non-alcoholic related liver diseases.

Major factors of the liver cirrhosis are hepatitis C, hepatitis B and fatty liver diseases. Mortality with liver cirrhosis has drastically risen within the last few years despite of the formation and innovation of new anti-viral therapies to curing the diseases.[5-8] Aging proved to be an additional risk factor for HE. Studies have suggested that aging provoke other risk factors including renal insufficiency, diabetes mellitus, sarcopenia, hypertension and cardiovascular problems which in return increase the chances of liver diseases.[9,10] Certain medication which are more commonly prescribed to older patients may escalate ammonia' neurotoxicity and neuro-depressant effects such as benzodiazepines and gabapentin.[11]

Limited data is available for the association of role of medication and risk of liver cirrhosis. It was also highlighted in few studies that; proton pump inhibitors also cause dysbiosis which could be the cause of HE. In this study, association between various risk factors for hepatic encephalopathy in liver cirrhotic patients was determined. For better assessment of individual risk variable, comparison was made between hepatic encephalopathy patients with non-hepatic encephalopathy patients

MATERIALS AND METHODS

This retrospective study was performed at Department of Internal Medicine, Rawalpindi Medical University Rawalpindi from 1st July 2021 to 30th June 2022. All the required demographic details as well as clinical history and medical assessment including diagnosis as well as disease prognosis history were taken from the available medical files of patients. A total of 100 patients were enrolled. Sample size was calculated through WHO sample size calculator using 80% power of test and 95% confidence interval with 5%. All the patients were divided into two groups. One group was those which developed hepatic encephalopathy while the other group was of those which did not develop any hepatic encephalopathy. The incident of various risk factors and their frequencies were measured through a modelled hepatic encephalopathy pharmacological, clinical as well as demographic data. The risk factors for hepatic encephalopathy were completely evaluated through demographic, socioeconomic as well as cirrhosis presence. Severity of the liver disease and pharmacopathy was also evaluated. A well-structured questionnaire was prepared for documenting all the details. Comparison on the frequency of the variable seen in Hepatic Encephalopathy patients with non-hepatic Encephalopathy was conducted for better assessment of the frequency of risk variable involved in formation of hepatic encephalopathy. Data was analyzed by using SPSS version 25.0. Chi square tool as well as IQR and odd ration with 95% CI were used for data analysis. P value <0.001 was taken as significant.

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RESULTS

In present study, majority of study participants were old patients between 50-70 years and 70 patients did not develop HE while 30 patients did develop HE. Gastroenterology symptoms were also assessed in present study (Table 1).

Most of the patients develop alcoholic liver cirrhosis (15) followed by hepatitis C and non-alcoholic cirrhosis. Ascites, HCC and varices were found in patients who did not develop hepatic encephalopathy. Ascites and varices were developed in 12 and 5 patients respectively. Charlson comorbidity score showed that moderate score for comorbidity in HE patients was 20%, with CCI scores of 3–4; while 10% had a severe, CCI scores with a score ≥5. These score were much significantly higher than cases who did not develop HE (Table 2).

The results showed that percentage of developing hypertension, diabetes, sarcopenia and cardiovascular disease

was significantly higher in HE group than those who did not develop HE (Fig. 1).

Adjusted analysis results of clinical and demographic factors are also calculated. Strongest association was determined with alcohol related cirrhosis and portal hypertension. Urban patients were more likely to develop HE. Hepatitis C prevalence was found increase in participants who did not have HE as compared to the HE group (Table 3).

Effects related to use of certain medications with HE was also described. Benzodiazepines, GABAergics, Opioids and Proton pump inhibitors each of them was associated with increased chances of HE. Estimate of these variables were adjusted according to aetiology of cirrhosis, demographic factors and comorbidities (Table 4).

Table 1: Baseline characteristics of the patients

Variable	Total(n=100)	Did not Develop HE (n=70)	Developed HE (n=30)	*P* Value
Age, median (IQR)	65 (57, 72)	65 (58, 73)	63 (55, 71)	P<0.001
Age in years				
50-60 n(%)	47 (47)	35 (50)	12 (40)	P<0.001
61-70 n(%)	53 (53)	35 (50)	18 (60)	P<0.001
Male	54 (54%)	37 (52.8%)	17(56.6%)	P<0.001
Urban/rural status: urban	81 (81%)	57(81.4%)	24 (80%)	P=0.147
Gastroenterology/hepatology consult	29 (29%)	27 (38.5%)	2 (6.6%)	P<0.001

Table 2: Severity of cirrhosis and disease symptoms variance

Characteristic	Total (n=100)	Did not Develop HE (n=70)	Developed HE (n=30)	*P* Value
Charlson comorbidity index				
0	31 (31%)	21 (30%)	10 (33.3%)	P<0.001
1-2	46 (46%)	35 (50%)	11 (36.6%)	
3-4	16 (16%)	10(14.2%)	6 (20%)	
5 or more	7 (7%)	4 (5.7%)	3 (10%)	
ESRD	4 (4%)	3 (4.2%)	1 (3.3%)	P=0.118
Disabled	40 (40%)	30 (42.8%)	13 (43.3%)	P<0.001
Cirrhosis Features				
Alcoholic-cirrhosis	33 (33%)	18 (25.7%)	15 (50)	P<0.001
Hepatitis C cirrhosis	30 (30%)	19 (27.1%)	11 (36.6)	P<0.001
Nonalcoholic nonviral cirrhosis	24 (24%)	10 (14.2)	14 (46.6%)	P<0.001
Ascites	17 (17%)	12 (17.1%)	5 (16.6 %)	P=0.145
Varices	7 (7%)	5 (7.1%)	2 (6.6%)	P=0.123
HCC	4 (4%)	2 (2.8 %)	2 (6.6%)	P<0.001

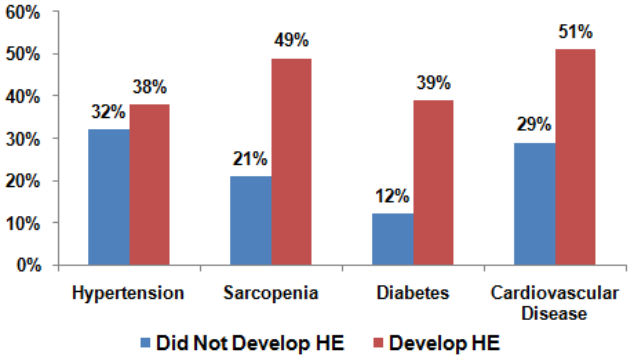
Table 3: Association between incident HE and clinical and demographic factors

Baseline Variable	AHR (95% CI)	*P* Value
Age in years	1.00 (1.00, 1.02)	*P*<0.001
Male	0.97 (0.95, 1.01)	*P*=0.166
Gastroenterology consult (within 1 year before diagnosis)	0.14 (0.13, 0.15)	*P*<0.001
ESRD	1.06 (1.00, 1.14)	*P*<0.046
Disability	1.06 (1.05, 1.11)	*P*<0.001
Urban	1.04 (1.03, 1.08)	*P*=0.003
Cirrhosis grading class (non-alcoholic and non-viral)		
Alcoholic-cirrhosis	1.45 (1.41, 1.47)	*P*<0.001
HCV	1.27 (1.22, 1.30)	*P*<0.001
HBV	0.90 (0.85, 0.95)	*P*<0.001
Covariation of time		
Gastroenterology consultancy post cirrhosis diagnosis	2.07 (2.04, 2.14)	*P*<0.001
Portal-hypertension	3.43 (3.35, 3.51)	*P*<0.001
CCI (relatable to CCI 0)		
CCI = 1	0.84 (0.80, 0.87)	*P*<0.001
CCI = 2	0.96 (0.92, 0.98)	*P*=0.008
CCI ≥ 3	1.08 (1.07, 1.13)	*P*<0.002

Table 4: Influence of application of chronic medication on the incidence of HE

Medication Type	N=30 (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Plausible influence on the pathophysiology of HE			
Benzodiazepines	10(33.3)	1.24(1.21, 1.25)	1.19(1.16, 1.22)
GABAergics	10(33.3)	1.25(1.22, 1.26)	1.17(1.14, 1.21)
Opioids	15(50)	1.38(1.35, 1.39)	1.24(1.21, 1.27)
Proton pump inhibitors	19(63.3)	1.57(1.56, 1.61)	1.42(1.39, 1.45)
Mental-health treatment markers			
Antipsychotics	7 (23.3)	1.15 (1.11, 1.19)	1.12(1.07, 1.18)
Antidepressants	20 (66.6)	1.32 (1.30, 1.35)	1.24(1.22, 1.27)
Tricyclic antidepressants	16 (53.3)	1.20 (1.16, 1.24)	1.11(1.06, 1.14)
Hepatic disease severity related markers			
Diuretics	16(53.3)	2.71(2.70, 2.76)	2.08(2.03, 2.13)
Nonselective beta blockers	14 (46.6)	2.02(1.98, 2.06)	1.40(1.35, 1.43)
Indirect effect causing medication pathophysiology of HE			
Statins	12(40)	1.03(1.01, 1.04)	1.09(1.05, 1.14)

Fig. 1: Comaprison within comrobidites in cases who develop HE and who did not develop HE



DISCUSSION

Hepatic encephalopathy proved to be turning point in the history of liver diseases. Mortality and comorbidity risk escalates many times in recent years due to number of causes. HE stand as the potent risk factor for frequent hospital admissions, accidental traumas, transplantation and even death in fatal liver disease patients[12,13]. Data regarding long term consequences of HE is currently unavailable. Present study was designed to find out the potential risk factors of HE in liver cirrhosis patients. Medicinal affects were determined which could be the main cause of further worsening of present disease state.

Present study describes the distinct differences and variances in HE risk factors according to aetiology of liver diseases. Incidence rate of hepatic encephalopathy was higher among patients who had alcoholic liver cirrhosis. Many studies also suggested the similar findings in which liver cirrhosis turned

out to be main marker for HE development in liver cirrhosis patients[14-18]. Non-alcoholic non-viral cirrhosis was also determined in present study. Although no strong association was found with HE development in present study but previous studies had proved its significant relation[19]. Medicinal association with increased chances of liver cirrhosis was also found in present study. Benzodiazepines, opioids, GABAergics and proton pump inhibitors are appeared to be the main drugs in increased risk group and positive association was found among study participants. Similar results have been reported elsewhere[20,21].

To validate these results, large prospective, multicenter studies should be conducted for better evaluation and drawing the conclusion especially in case of medicinal administration and treatment plan. Trials can be a safe and suitable option in which alternatives of benzodiazepines, PPIs, opiates and GABAergics are used to determine the difference in disease outcome.

CONCLUSION

Hepatic encephalopathy was more commonly observed in older patients (60%) and more specifically in male population. Higher frequency of comorbidities (hypertension, diabetes, cardiovascular disease, ascites, alcoholic cirrhosis), CCI score and pharmacological drugs were identifiable risk factors for hepatic encephalopathy.

Conflict of interest: Nil

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