

Original Article

FREQUENCY OF HEPATIC ENCEPHALOPATHY IN HCV CIRRHOTIC PATIENTS WITH AND WITHOUT DIABETES MELLITUS

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Objective: To compare the frequency of hepatic encephalopathy (HE) in HCV cirrhotic patients with and without Diabetes Mellitus.

Material and Methods: This cross sectional survey of 100 patients was conducted in all medical units of Mayo Hospital Lahore after meeting the inclusion criteria. Patients were classified as diabetic if they were on oral hypoglycemic agents or insulin or have BSF>126mg/dl and non diabetic if they had BSF<126 mg/dl. The assessment for presence or absence of hepatic encephalopathy was determined using criteria defined in operational definition. HCV LIVER CIRRHOSIS is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrosis, scar tissue and regenerative nodules. Cirrhosis was confirmed by Ultrasonography abdomen and hepatitis C was confirmed with ELISA test.

Results: Mean age of patient was 44.43 ± 10.16 years with minimum and maximum ages 18 & 60 years respectively. Frequency of DM was determined as 34% among HCV cirrhosis patients while in 66% patients the diabetes was not seen. Hepatic encephalopathy was seen in 31(91.2%) of diabetics and in 48(72.7%) of non-diabetic patients. HE was not seen in 21% of patients in which 3 were diabetics & 18 were non diabetic. In this study frequency of HE was higher in diabetic group as compared to non diabetic group i.e. P- value=0.032.

Conclusion: According to this study, frequency of Hepatic encephalopathy (HE) is significantly higher in diabetic patients as compared to non-diabetic patients i.e. P value 0.032. Frequency of HE was seen in 91.2% of the diabetic patients and in 72.7% of non-diabetic patients.

Keywords: Hepatic encephalopathy (HE), Diabetes Mellitus (DM), Liver cirrhosis (LC)

Introduction

Hepatic encephalopathy is a reversible syndrome of impaired brain function with advanced liver disease.¹ It presents with clinical findings that range from abnormal Psychometric tests to coma in patients with liver cirrhosis. Approximately 30% of patients dying of end stage liver disease have significant encephalopathy approaching to coma.² Due to high prevalence of hepatitis C in our community i.e. (3.0%) liver cirrhosis is attaining epidemic proportion in Pakistan.³ Hepatic encephalopathy is a major neuropsychometric complication of liver cirrhosis, and its appearance is an indicator of poor prognosis.⁴

Diabetes Mellitus is very common in chronic liver disease (32%) and there is a strong association of DM with hepatitis C.^{5,6} In cirrhosis gastro paresis and intestinal motility dysfunction is very common due to autonomic neuropathy and it worsens with advancing stages of cirrhosis. Among multiple pathological factors increased Ammonia level of gut bacteria is considered to be the most important in development of hepatic encephalopathy. Therefore this autonomic dysfunction may contribute in

developing hepatic encephalopathy by increasing exposure to GI bacteria due to constipation.⁷

In Diabetic patients 50% have delayed gastric emptying and also duodenal transit time is prolonged and small intestinal motility is sluggish. These factors may lead to bacterial overgrowth in gut of Diabetic patients. Therefore frequency of hepatic encephalopathy in HCV cirrhotic patients is 95% in diabetics and 78% in non diabetic patients.⁸ Because of these adverse effects of diabetes on GI motility, it is expected that patients with cirrhosis having comorbidity with diabetes are associated with higher frequency of hepatic encephalopathy. Improved glycemic control in these patients will have positive effect on overall survival of cirrhotic patients.

Operational Definition

1. HCV liver cirrhosis: is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrosis, scar tissue and regenerative nodules. Cirrhosis was confirmed with Ultrasonography abdomen and Hepatitis C was confirmed with ELISA test (cut-off value varies according to the test device used).

- 2. Hepatic Encephalopathy (HE):** Patients were diagnosed clinically on presence of any of the symptoms/signs of Insomnia, Day night reversal of sleep rythm, Poor concentration, Irritability, Asterix is associated with impaired Neuropsychometric test: (number connection test). Test was considered impaired if the Time taken by the subject is more than 30 seconds.¹⁸
- 3. Diabetes Mellitus:** All patients receiving treatment with oral hypoglycemic agents or insulin or having elevated fasting blood glucose level >126 mg/dl and BSR> 200 mg/dl.

Material & Method

This cross sectional study was conducted at medicine department (all four medical units). Mayo Hospital Lahore. This study was completed in 06 months from 15-01-2012 to 15-06-2012. The sampling technique was non probability purposive sampling.

100 patients who fulfilled inclusion/exclusion criteria were recruited from all medical units of medicine department of Mayo Hospital Lahore. Informed consent was taken and patient's demographic profile was also obtained. All patients with HCV cirrhosis (as per operational), with age from 16-60 years of both genders were enrolled. Following patients were excluded from the study.

- 1) Patients with active gastrointestinal bleeding (hematemesis & melena) assessed clinically.
- 2) Active infections like urinary tract infection diagnosed by the presence of pus cells in urine complete examination, respiratory tract infection diagnosed by productive cough or increased white blood cells count (>11000/mm³) on complete blood count.
- 3) Renal failure with creatinine > 2mg/dl.
- 4) History of taking sedatives/hypnotics like benzodiazepine, methadone, narcotics.

Data Analysis

All the data were entered in SPSS version 12 and were analyzed using same software. The quantitative variable like age was presented as mean±SD. The qualitative variables like gender, diabetes and HE in diabetic and non diabetic group were calculated as frequency & percentage. Chi-square test was used to compare the frequency of HE in DM & non DM patients A P- value < 0.05 was considered as significant.

Results

All patients with HCV Cirrhosis were taking in this

study to determine the frequency of hepatic encephalopathy in diabetic and non-diabetic group. Mean age of patients was 44.43± 10.16 with minimum and maximum ages 18 years and 60 years respectively. In this study the frequency of diabetes was determined as 34% among HCV cirrhosis patients while in 66% patients the diabetes was not seen.

- İ Insomnia was seen in 65% of the patients. Among diabetic patients the frequency of Insomnia was 22(64.7) while in non-diabetic patients the frequency of insomnia was 43(65.2%). Thirty-five patients did not have insomnia in which 12 were diabetic and 23 were non-diabetic.
- İ Frequency of day night reversal was present in 58% of the patients. Among diabetic patients the frequency of day night reversal was 23(67.6%) while in non-diabetic patients the frequency of day night reversal was 35(53%). There were 42% patients who did not have the history of day night reversal in which 11 were diabetic and 31 were non-diabetic.
- İ Poor concentration was assessed in 81% of the patients in which 26 were diabetic and 55 were non-diabetic. There were 8 diabetic patients and 11 non-diabetic patients with good concentration.
- İ The frequency of irritability was 26 in diabetic group and 40 in non-diabetic patients. There were 8 patients with diabetes and 26 non-diabetic patients who do not have irritability.
- İ Asterixis was also seen in 29% of the patients and in 71% patients it was absent. Among diabetic group there were 19(55.9%) patients having

Table-1: General distribution of age.

Age/Years	Mean	%
Mean		44.43
Standard deviation (SD)		10.16
Minimum		18
Maximum		60

Table-2: Frequency distribution of diabetes.

	Mean	%
	Yes	34
Diabetes	No	66
	Total	100

asterixis while 15(44.1%) did not have asterixis. In non-diabetic group 10(15.2%) have asterixis and 56(84.8%) asterixis was not seen.

Moreover 3(8.8%) diabetic patients had normal neuropsychometric test while 31(91.2%) had abnormal neuropsychometric test. In 18(27.3%) non-diabetic patients neuropsychometric test was normal while in 48(72.7%) non-diabetic patients neuropsychometric test was abnormal. The diabetic

patients had higher frequency of abnormal neuropsychometric test as compare to non-diabetic, p -value=0.032. Hepatic encephalopathy (HE) was seen in 31(91.2%) of diabetic patients and in 48(72.7%) of non-diabetic patients. HE was not seen in 21% of the patients in which 3 were diabetic and 18 were non-diabetic. In this study the frequency of HE was higher in diabetic group as compare to non-diabetic group, i.e p -value=0.032.

Table-3: Shows the frequency distribution of various symptoms in liver cirrhosis with respect to diabetes.

Symptoms		Diabetes		Total
		Yes	No	
Insomnia	Yes	22 (64.7%)	43 (65.2%)	65 (65%)
	No	12 (35.3%)	23 (34.8%)	35 (35%)
	Total	34 (100%)	66 (100)	100 (100%)
Day night reversal	Yes	23 (67.6%)	35 (53%)	58 (58%)
	No	23 (67.6%)	31 (47%)	42 (42%)
	Total	34 (100%)	66 (100)	100 (100%)
Poor conentration	Yes	26 (76.5%)	55(83.3%)	81 (81%)
	No	08 (23.5%)	11 (16.7%)	19 (19%)
	Total	34 (100%)	66 (100)	100 (100%)
Irritability	Yes	26 (76.5%)	40 (60.6%)	66 (66%)
	No	08 (23.5%)	26 (39.4%)	34 (34%)
	Total	34 (100%)	66 (100)	100 (100%)
Asterixis	Yes	19 (55.9%)	56 (84.8%)	29 (49%)
	No	15 (44.1%)	56 (84.8%)	71 (71%)
	Total	34 (100%)	66 (100)	100 (100%)

Table-4: Frequency of distribution of Neuropsychometric test with respect to diabetes.

		Diabetes		Total
		Yes	No	
Neuropsychometric test	Normal	03 (8.8%)	18 (27.3%)	21 (21%)
	No	31 (91.2%)	48 (72.7%)	79 (79%)
	Total	34 (100%)	66 (100)	100 (100%)

Chi-square test=4.60, p-value=0.032

Table-5: Frequency distribution of hepatic encephalopathy with respect to diabetes.

		Diabetes		Total
		Yes	No	
Hepatic Encephalopathy	Yes	31 (91.2%)	48 (72.7%)	79 (79%)
	No	3 (8.8%)	18 (27.3%)	21 (21%)
	Total	34 (100%)	66 (100)	100 (100%)

Chi-square test = 4.60, p-value= 0.032

Discussion

Hepatic Encephalopathy is a well recognized clinical complication of liver cirrhosis and prompt identification of well defined precipitating factor is extremely important in diagnosis and treatment of this fatal condition. About 30% of patients with cirrhosis die in hepatic coma.⁹ Encephalopathy is a major neuropsychiatric complication of liver cirrhosis and its appearance is indicative of poor prognosis. Moreover the patients with specific condition of cirrhosis are at more risk to exhibit psychometric impairment, especially cirrhotic hepatitis.¹⁰ The prevalence of Hepatic Encephalopathy in HCV cirrhotic patients is 95% in Diabetic and 78% in non-diabetic patients.⁸

The mean age of patients in this study was 44.43 ± 10.16 years with minimum and maximum ages 18 years and 60 years respectively. The mean age in this study was lower as compared to sigal SH et al, they reported the mean age 52 years with age range of 20-75 years.

In this study the frequency of diabetes was determined as 34% among HCV cirrhosis patients while in 66% patients the diabetes was not seen. According to Sigal SH et al 31% patients were diabetic in HCV group which is smaller than to our study.¹¹ Many authors reported that, DM associates to a decreased life expectancy in cirrhotic patients, as well as an earlier progression to more severe hepatic encephalopathy.¹² The mechanism that favors encephalopathy is not clear but may be dependent on diabetes-related autonomic neuropathy and subsequent constipation and/or impairment in ammonia metabolism.¹³

According our findings HE was seen in 31(91.2%) of the diabetic patients and in 48(72.7%) of non-diabetic patients. HE was not seen in 21% of the patients in which 3 were diabetic and 18 were non-diabetic. In this study the frequency of HE was higher in diabetic group as compare to non-diabetic group, i.e p-value=0.32. Our findings are comparable to another study in which fifty-four patients (83%) had HE. Twenty patients (31%) had DM.

He was present in 19(95%) patients with diabetes and 35(78%) patients without diabetes ($p=0.087$). Severity of HE was greater in diabetic patients (35% mild, 60% severe) than in non-diabetic patients (58% mild, 20% severe) ($p=0.007$). In both the mild and severe HE categories, severity of liver disease in diabetic patients was otherwise milder than in the non-diabetic patients,¹¹ According to sigal SH, the

association between diabetes and the presence of any degree of HE did not reach statistical significance, the diabetic patients had significantly more severe HE compare with no diabetic. Diabetic patients also had severe HE at earlier stages of biochemical decomposition and portal hypertension compared with non-diabetic patients.

DM is very common in the cirrhotic population because of shared etiologies such as obesity, chronic HCV, iron overload, alcohol as well as insulin resistance associated with cirrhosis.¹⁴ Recent studies have emphasized the importance of steatohepatitis that is commonly associated with DM in the pathogenesis of most cases of cryptogenic cirrhosis and the progression of chronic HCV,¹⁵ Diabetes is a risk factor for decreased long-term survival in patients with cirrhosis.

Kalaitzakis E et al also reported that DM was more common in patients with hepatocellular cirrhosis compared to those with cholestatic cirrhosis but the two groups did not differ in cirrhosis or the prevalence of hepatic encephalopathy ($p>0.05$).¹⁶

Finally it is important to discuss that various studies gave a positive and significant association of HE with DM so we need to emphasize the importance of optimizing diabetic control. Although the intestinal motility dysfunction in diabetic patients is commonly attributed to autonomic neuropathy and long-standing insulin-dependent DM, acute and reversible metabolic derangements related to elevated glucose levels and hyperinsulinemia also contribute, and it occurs frequently in non-insulin dependent DM as well.¹⁷

Conclusion

According to this study the frequency of Hepatic encephalopathy is significantly higher in diabetic's patients as compare to non-diabetic patients i.e. p-value 0.032. In this study the frequency of HE was seen in 91.2% of the diabetic patients and in 72.7% of non-diabetic patients. Therefore it is recommended that patients with liver cirrhosis should have a good control of diabetes mellitus which may decrease incidence of hepatic encephalopathy.

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References

1. Ferenci P, Runyon BA, Bonis PA. Clinical Manifestations and diagnosis of hepatic encephalopathy, Uptodate, Last literature review version 16.3 2008. [Http://www.uptodateinc.com/patients/content/topic.do?topickey=EP22NnT7FcJqt](http://www.uptodateinc.com/patients/content/topic.do?topickey=EP22NnT7FcJqt).
2. Wolf DC Encephalopathy, Hepatic. 2009. [Http://emedicine.medscape.com/article/186101-overview](http://emedicine.medscape.com/article/186101-overview).
3. Ali S, Donahue R, Qureshi H, Vermund S. Hepatitis Band hepatitis C in Pakistan: prevalence and risk factors. *Int J Infect Dis* 2009; 13(1): 9-19.
4. Alam I, Razaullah, Haider I, Humayun M, Taqweem MA, Nisar M. Spectrum of precipitating factors of hepatic encephalopathy in liver cirrhosis. *Pak J Med Res* 2005;44(2):96-100.
5. Rathore R, Butt NF, Shoaib S, Iqbal A, Khan Z. Diabetes Mellitus in J Services Inst Med Sci 2008; 3(4):6-9.
6. Moscatiello S, Manini R, Marchesini G. Diabetes and liver disease: An ominous association. *Nutri Metab Cardiovas Dis* 2007; 17 (1) 63-70.
7. Maheshwari A, Thuluvath PJ. Automic neuropathy may be associated with delayed orocaecal transit time in patients with cirrhosis. *Auton Neurosci* 2005;118:135-9.
8. Thuluvath PJ. Higher prevalence and severity of hepatic encephalopathy in patients with HCV cirrhosis and diabetes mellitus: *Am J Gastroentrol* 2006; 101 (10):2244-6.
9. Butterworth RF. The neurobiology of hepatic encephalopathy. *Semin liver Dis* 1996; 16: 235-44.
10. Amodio P, Del Piccolo F, Marchetti P. Clinical features and survival of cirrhotic patients with subclinical cognitive alterations detected by the number connection test and computerized psychometric test. *Hepatology* 1999;29:1662.
11. Sigal SH, Stanca CM, Kontorinis N, Bodian C, Ryan E, Diabetes Mellitus is associated with Hepatic Encephalopathy in patients with HCV Cirrhosis, *Am J Gastro- enterol* 2006;101 (7):1490-6.
12. Marchesini G, Bianchi G, Amodio P, et al. Factors associated with poor health-related quality of life of patients with cirrhosis. *Gastroenterology* 200;120L170.
13. Alam I, Razaullah, Haider I, Humayun M, Taqweem MA, Nasir M, Spectrum of Precipitating factors of Hepatic Encephalopathy in liver cirrhosis. *Pakistan J Med Res.* 2005;44(2):96-100.
14. Merli M, Leoneti F, Riggio O. Glucose intolerance and insulin resistance in cirrhosis are normalized after liver transplantation. *Hepatology* 1999;30:649-54.
15. Clark JM, Diehl AM. Nonalcoholic fatty liver disease: An under recognized cause of cryptogenic cirrhosis. *JAMA* 2003; 289:3000-4.
16. Bajaj JS. Minimal hepatic encephalopathy matters in dialy life. *World J Gastroenterol* 2008; 14(23): 3609-15.
17. Abrahamsson, H. Gastrointestinal motility disorders in patients with diabetes mellitus. *J Intern Med* 1995;237:403-9.
18. Connect the number test. Psycho diagnostic procedure for quantitative detection of (latent) portosystemic encephalopathy (PSE). [Www.apef.compt /download](http://www.apef.compt/download).