

Association of Diabetes Mellitus with Minimal Hepatic Encephalopathy in patients with Liver Cirrhosis

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ABSTRACT

Aim: To evaluate the role of diabetes mellitus as a risk factor for minimal hepatic encephalopathy in patients with liver cirrhosis.

Setting: Medical outpatients department of Mayo Hospital Lahore for six months.

Study Design: Case control study

Results: Majority of the patients in both groups were between 41-50 years of age i.e., 33(30%) in Cases and 34(30.91%) in controls, mean and sd was calculated as 42.35 ± 2.54 in cases and 47.65 ± 3.65 years in controls, 73(66.36%) in cases and 81(73.64%) in controls were male while rest of 37(33.64%) in cases and 29(26.36%) in controls were females, frequency of diabetes in both groups was recorded as 28(25.45%) in cases and 8(7.27%) in controls had findings of this morbidity while rest of 82(74.55) in cases and 102(92.73%) in controls had no findings of diabetes mellitus, odds ratio was recorded as 4.35, p value was calculated as 0.000 which shows a significant difference in both groups.

Conclusion: There is a significant role of diabetes mellitus as a risk factor for minimal hepatic encephalopathy in patients with liver cirrhosis.

Keywords: Minimal hepatic encephalopathy, liver cirrhosis, diabetes, risk factor

INTRODUCTION

Minimal hepatic encephalopathy (MHE), also called sub-clinical HE, is a mild neurocognitive impairment seen in those patients with cirrhosis of liver whose clinical examination fails to identify mental state abnormalities. It is present in 30-84% of cirrhotic patients¹. MHE has important implications in a patient's life. There is no ideal test for the diagnosis of MHE, however, diagnosis of MHE requires a normal mental status examination and impairment in the performance of at least two of the following tests: trail making test-A, trail making test-B, block design test (BDT) and digit symbol test (DST)². MHE & overt hepatic encephalopathy share common causes. Raised serum ammonia derived either from gut or kidneys is mainly implicated in pathogenesis of MHE¹.

Glucose intolerance and diabetes mellitus are common in chronic liver disease (CLD) because of altered glucose metabolism. Glucose intolerance is seen in up to 80% and frank diabetes is present in 30-60% of chronic liver disease patients³. There is bidirectional relationship between diabetes mellitus and cirrhosis of liver. Diabetic patients, due to high prevalence of non-alcoholic fatty liver disease, have increased risk of developing cirrhosis and patients with cirrhosis are at risk of developing insulin resistance and diabetes because of disturbed carbohydrate metabolism and hyperinsulinemia⁴.

Patients with diabetes often have autonomic neuropathy, increased intestinal bacterial flora, increased colonic transit time and constipation, which are potential risk factors for development of minimal and overt hepatic encephalopathy⁵.

The association between diabetes mellitus and overt (clinical) hepatic encephalopathy is well established^{1,4,5}. However less work has been done on association of diabetes mellitus with minimal (sub-clinical) hepatic encephalopathy. In one study involving cirrhotic patients, diabetes was associated with MHE (P value=0.02) as patients with diabetes took longer time to complete number connection test-A as compared to patients without diabetes⁶. In another study, 21% of patients with MHE had diabetes compared to 9% of patients without MHE (odds ratio=2.7), but it was not statistically significant⁷. We could not find any local study on association of diabetes and MHE.

MATERIALS AND METHODS

It was conducted in medical outpatients department of Mayo Hospital Lahore for six months. It was a Case-Control Study. Non-probability sampling method was used. Sample size of 220 patients (110 in each group) was calculated with 80% power of test, 5% level of significance and taking expected percentage of diabetes in both groups i.e., 21% in cases(with MHE) versus 9% in controls (without MHE) in patients of liver cirrhosis. Patients of liver

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cirrhosis with minimal hepatic encephalopathy defined as both trail making-A and -B scores more than 2 SD from mean score for that age, category of population, both males and females of any age who were literate and presented in outpatient department only were included for cases. Patients of liver cirrhosis without minimal hepatic encephalopathy defined as both trail making-A and -B scores less than 2 SD from mean score for that age category of normal population, both males and females of any age, and literate patients who presented in OPD were included for controls. Patients with overt hepatic encephalopathy, on anxiolytics, sedatives, morphine or other drugs that slow intestinal motility or affect alertness, with severe co-morbid medical illness like CRF, COPD, parkinsonism or psychiatric illnesses, who were illiterate or had vision problems restricting reading were excluded. Data was collected on a structured questionnaire after obtaining informed consent. Name, age, gender were recorded. Number connection test A and B was administered to all patients in a quiet and comfortable room. Time taken to perform these tests was noted. Before administering the test detailed instructions were given to all patients on how to perform the tests. As defined in the operational definitions, patients whose scores on these tests was more than 2 standard deviations of the scores normal for that age, was labeled as cases (having MHE) and controls (without MHE) were those whose scores was less than 2 standard deviations of scores normal for that age. For both cases and controls, the risk factor (diabetes) was assessed as defined in the operational definitions. To define the normal range of NCT-A and -B, these tests were administered to one hundred normal and healthy individuals. Data was entered in SPSS version 17 and analyzed. Mean \pm SD was calculated for continuous variables, like age and frequencies were calculated for categorical variables, like diabetes, gender. Cases (with MHE) and controls (without MHE) were compared with each other regarding risk factor (diabetes). Odd's ratio was calculated to see the strength of association between diabetes and minimal hepatic encephalopathy in patients with liver cirrhosis. Odd's ratio $>$ 2 was considered as statistically significant.

RESULTS

Age distribution of the patients showed that majority of the patients in both groups were between 41-50 years of age i.e., 33(30%) in Cases and 34(30.91%) in controls, followed by 26(23.64%) in cases and 27(24.55%) in controls between 51-60 years, 15(13.64%) in cases and 19(17.27%) in controls between 20-30 years, while only 15(13.63%) in cases

and 7(6.36%) in controls had $>$ 60 years of age, mean and sd was calculated as 42.35 \pm 2.54 in cases and 47.65 \pm 3.65 years in controls. Gender distribution of the patients was done which shows 73(66.36%) in cases and 81(73.64%) in controls were male while rest of 37(33.64%) in cases and 29(26.36%) in controls were females. Frequency of diabetes in both groups was recorded and compared, where 28(25.45%) in cases and 8(7.27%) in controls had findings of this morbidity while rest of 82(74.55%) in cases and 102(92.73%) in controls had no findings of diabetes mellitus, odds ratios was recorded as 4.35, p value was calculated as 0.000 which shows a significant difference in both groups. Stratification for gender in patients having diabetes mellitus was done which shows out of 28 patients in cases 17(60.71%) were male while 11(39.29%) were females, in controls out of 8 cases 5(62.5%) were male while 3(37.5%) were females.

DISCUSSION

The pathogenesis of hepatic encephalopathy (HE), a common complication of liver cirrhosis, remains incompletely understood but it is probably multifactorial in most cases⁸. Malnutrition is also commonly encountered in patients with cirrhosis and it has been reported to have an effect on health related quality of life⁹. Although experimental studies suggest that low energy intake and poor nutritional status may facilitate the development of HE¹⁰, there are scarce data on the potential role of malnutrition in HE in patients with liver cirrhosis.

In our study we recorded frequency of diabetes in both groups as 28(25.45%) in cases and 8(7.27%) in controls while rest of 82(74.55) in cases and 102(92.73%) in controls had no findings of diabetes mellitus, odds ratios was recorded as 4.35 which shows a significant difference in both groups. The findings of the study are in agreement with Sigal H who recorded 21% of patients with MHE had diabetes compared to 9% of patients without MHE (odds ratio=2.7)⁷. In the paper of Soros et al¹¹ they did not report how many patients had diabetes mellitus. However, the risk of diabetes mellitus has been reported to be increased in patients with cirrhosis due to hepatitis C¹² and the majority of patients enrolled in the study of Soros et al¹¹ (56%) had viral cirrhosis¹¹. It is therefore unknown whether patients with HE had a higher proportion of diabetes mellitus compared with patients without HE. This might have had an effect on the median BMI in the two groups as diabetes mellitus is more prevalent in patients with increased BMI, thus accounting for the lack of difference in median BMI between patients with HE and those without HE¹¹. In fact, the BMI of

patients with HE ranged from 14.5 to 36.3 kg/m² as compared to 17.5-28.4 kg/m² in those without HE¹¹.

But according to findings of the current study in accordance with Sigal H⁷ it is determined that diabetes mellitus has an independent role as a risk factor for minimal hepatic encephalopathy in patients with liver cirrhosis. However, the limitation of the study was that we did not include BMI measurements in our study which also indicates malnourishment as a risk factor for minimal hepatic encephalopathy. The results of the study justify our hypothesis that diabetes mellitus may be associated with MHE, as it is associated with overt hepatic encephalopathy.

CONCLUSION

The results of study revealed a significant role of diabetes mellitus as a risk factor for minimal hepatic encephalopathy in patients with liver cirrhosis.

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