Journal of Medicine in Scientific Research

Volume 1 | Issue 4 Article 2

Subject Area:

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Recommended Citation

Shaheen, El-Saied; Elshazly, Helmy M.; and Allah, Noha Abd (2018) "Hepatic encephalopathy in patients with diabetes mellitus," *Journal of Medicine in Scientific Research*: Vol. 1: Iss. 4, Article 2.
DOI: https://doi.org/10.4103/JMISR.JMISR_88_18

Original Article

Hepatic encephalopathy in patients with diabetes mellitus

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Abstract

Background and aim of the work

Hepatic encephalopathy (HE) is a complex frequent neuropsychiatric manifestation of chronic and acute liver disease with disturbance of psychomotor, intellectual, cognitive, behavioral, and fine motor function of varying severity. Diabetes mellitus (DM) exacerbates progression of hepatic fibrosis. Recently, a meta-analysis study concluded that type 2 DM was associated with relative 1.5-fold increased risk for clinically defined Alzheimer disease and 2.5 for vascular dementia compared with nondiabetic individuals; furthermore, one recent prospective study showed that elevated blood glucose in the absence of DM increased the risk of dementia. Given the high prevalence of DM in the liver cirrhosis population, a better understanding of the effect of DM offers significant opportunities to improve patient outcome.

Aim of the work

To determine the relationship between duration of DM and blood sugar level and increase risk of the occurrence of HE in patients with liver cirrhosis.

Patients and methods

This study was carried out on 100 patients with cirrhosis with DM admitted between July 2017 and July 2018 in Internal Medicine Department, Shebin Elkom Teaching Hospital, Menoufia, Egypt. They were categorized into two groups according to the presence or absence of HE. Group 1 included 50 cirrhotic diabetic patients with HE and group 2 included 50 cirrhotic diabetic patients without HE. All patients in the study were subjected to a thorough physical examination; laboratory investigations, including complete blood picture, liver function tests, hepatitis B virus surface antigen, hepatitis C virus antibody, renal function tests, serum ammonia level, fasting and postprandial blood sugar, and glycated hemoglobin; tests to detect the presence of autonomic neuropathy (tilt-table test and diurnal variation of blood pressure measurement); and abdominal ultrasonography.

Results

The present study found a significant increase in fasting and postprandial blood glucose, glycated hemoglobin, and duration of DM in group 1 versus group 2. Positive tilt-table test and positive posture hypotension were highly significant in group 1 versus group 2.

Conclusion

Patients with cirrhosis with long-standing and uncontrolled DM are more likely to developed HE. Autonomic neuropathy, which may complicate patients with cirrhosis with long-standing uncontrolled diabetes, may play a role in the pathogenesis of HE in these patients.

Keywords: Autonomic neuropathy, diabetes mellitus, hepatic encephalopathy, hepatitis C, liver cirrhosis

Introduction

Hepatic encephalopathy (HE) is a complex, frequent neuropsychiatric manifestation of chronic and acute liver disease with disturbance of psychomotor, intellectual, cognitive, behavioral, and fine motor functions of varying severity (*https://en.wikipedia.org/wki/Hepatic encephalopathy)*. It is one of the most common and serious complications of liver cirrhosis, affecting almost one-third of patients with cirrhosis. This spectrum of neuropsychiatric abnormalities with advanced liver disease is associated with significant morbidity and mortality. It is functional in nature and potentially reversible, and symptoms range from personality change to deep coma [1].

Access this article online

Quick Response Code:

Website: www.jmsr.eg.net

DOI: 10.4103/JMISR.JMISR_88_18

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How to cite this article: Shaheen ES, Elshazly HM, Allah NA. Hepatic encephalopathy in patients with diabetes mellitus. J Med Sci Res 2018;1:227-30.

HE may arise spontaneously owing to liver failure but more commonly will develop as a result of one or more precipitating factors in course of chronic liver disease or it could happen as a result of prolonged porto-systemic shunting, leading to chronic portal systemic encephalopathy (PSE). Outcome of patients depends upon timely and early identification of precipitating factors in diagnosis and treatment of the fatal condition [2]. Common precipitating factors of HE include sepsis/infection, upper gastrointestinal bleeding, constipation, and over usage of drugs such as sedatives, diuretics, tranquilizers, and NSAIDS [1].

Pathogenesis of HE is not clearly elucidated because of less clinical study in this aspect. However, it is said that diminished hepatic reserve results in impaired ability of liver to detoxify nitrogenous compounds, for example, ammonia, manganese, GABA, phenols, and mercaptans that are absorbed from the bowel [3]. They gain access to the systemic circulation as a result of poor porto-systemic shunting of blood. Furthermore, they alter amino acid metabolism in neurons resulting in astrocyte swelling and cerebral edema [1].

The survival of patients having chronic PSE is better than those who develop HE acutely, and prognosis of chronic PSE is better than those who present with increased severity of disease. Approximately 30% of patients with cirrhosis usually die in hepatic coma [4]. This study has been done to study the common precipitating factors and clinical outcome of cirrhotic patients who need hospitalization owing to HE on the basis of Child–Pugh score [1].

Liver cirrhosis is a common metabolic disease that leads to multisystem lesions. Brain is one of the affected organs. Numerous studies have reported the adverse effects of liver cirrhosis on structural and functional brain reorganization, thus leading to cognitive dysfunction in these patients [5]. Moreover, Garcia-Compean *et al.* [6] reported that up to 96% of patients with cirrhosis may be glucose intolerant and 30% of patients may have type 2 diabetes mellitus (T2DM). Another study has demonstrated that coexistent diabetes exacerbates progression of hepatic fibrosis [7]. Recently, a meta-analysis study concluded that T2DM was associated with relative 1.5-fold increased risk for clinically defined Alzheimer disease and 2.5 for vascular dementia compared with nondiabetic individuals. Furthermore, one recent prospective study showed that elevated blood glucose in the absence of DM increased the risk of dementia [8]. Given the high prevalence of DM in the liver cirrhosis population, a better understanding of the effect of DM offers significant opportunities to improve patient's outcome.

Patients and methods

This study was carried out on 100 cirrhotic patients with DM admitted between July 2017 and July 2018 in Internal Medicine Department, Shebin Elkom Teaching Hospital, Menoufia, Egypt. They were categorized into two groups according to the presence or absence of HE. Group 1 included 50 cirrhotic diabetic patients with HE and group 2 included 50 cirrhotic diabetic patients without HE.

Exclusion criteria

Patients with heart failure, COPD, endocrinal disease, neurotic, or psychiatric disorders; patients taking drugs that can alter gastrointestinal motility; and patients taking benzodiazepine and narcotics were excluded. All patients were enrolled during the same period and provided consent to participate in the study, which was approved by the investigations and Ethics Committee of the Hospital.

All patients were subjected to the following: thorough assessment of history and physical examination; laboratory investigations including hepatitis B virus surface antigen and hepatitis C virus antibody, aspartate aminotransferase, alanine aminotransferase, serum albumin, total and direct serum bilirubin, prothrombin time, complete blood count, fasting and postprandial blood glucose, glycated hemoglobin (HbA1C), blood urea, serum creatinine, serum sodium and potassium level, and serum ammonia level; abdominal ultrasound; and applicable tests to detect autonomic neuropathy (tilt-table test and postural hypotension).

Statistical analysis

Results were collected, tabulated, and statistically analyzed using an IBM personal computer and statistical package SPSS (version 16; SPSS Inc., Chicago, Illinois, USA). Two type of statistics were determined [9].

Results

Table 1 shows the grade of HE in group 1. Grade 4 HE is common found in 32% of the patients in group 1.

Table 2 shows precipitating factors of HE. Hematemesis and melena was found in 14%, hypokalemia was found in 18%, and unknown (30%) was common precipitating factor.

Table 3 shows the demographic and laboratory investigations in the studied groups, with a significant increase in serum ammonia in group 1 (125 ± 32.1) versus in group 2 (75.3 ± 25.2).

There was a highly significant increase in fasting and postprandial blood glucose, HbA1C, and duration of DM in group 1 versus group 2 (Table 4).

Table 5 shows positive tilt-table test and positive posture hypotension were highly significant in group 1 versus group 2.

Discussion

The present study showed the serum ammonia level was significant increase in patients with HE. Hyperammonemia has been considered a crucial factor to trigger HE. However, frequently the arterial concentration of ammonia can be found elevated in the absence of symptoms of HE. Moreover, inflammatory systemic response has been proposed as coexisting and necessary factor [10]. Ammonia can reach the systemic circulation directly from kidney and through

Table 1: Grade of hepatic encephalopathy in group 1

Grades of hepatic encephalopathy	*n* (%)
Grade 1	10 (20)
Grade 2	11 (22)
Grade 3	13 (26)
Grade 4	16 (32%)

Table 2: Precipitating factors for hepatic encephalopathy

Precipitating factors of the present attack	*n* (%)
Infection	7 (1)
High-protein diet	5 (10)
Hematemesis and melena	7 (14)
Diuretics overdosage and hypokalemia	9 (18)
Vomiting and diarrhea	2 (4)
Paracentesis	4 (8)
Sedatives	1 (2)
Unknown	15 (30)

Table 3: Demographic and laboratory investigations in the studied groups

Variables	Group 1	Group 2	*P*
Age (years)	55.4±7.8	53.2±6.4	>0.05
Sex (M/F)	28/22	27/23	>0.05
AST (U/dl)	52±10.2	55±11.2	>0.05
ALT (U/dl)	50±12.4	51±11.4	>0.05
Serum albumin (g/dl)	2.8±0.3	3±0.4	>0.05
Serum bilirubin (mg/dl)	2.1±0.5	2.3±0.6	>0.05
PT activity (%)	65±10	67±12.5	>0.05
Serum ammonia	125±32.1	75.3±25.2	<0.05

ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, female; M, male; PT, prothrombin time.

portacaval shunt from small intestine and ultimately promotes brain dysfunction mainly by astrocyte edema and impairment in the neurotransmission [11]. In patients with cirrhosis, there is increased evidence about the role of inflammation in HE, bacterial translocation, and risk of spontaneous bacterial peritonitis. Indeed focal calprotectin was correlated with critical flicker frequency and HE grading [12]. The pathophysiology of HE is closely linked to changes in the blood–brain barrier. Endothelial cells and astrocytes are major constituents of the blood–brain barrier. During infection, activated microglial cells and astrocytes have the ability to produce proinflammatory cytokines (interleukin-6, tumor necrosis factor-α), which are able to exacerbate the neuropsychological alterations induced by hyperammonemia [13].

The present study found a highly significant increase in fasting and postprandial blood sugar levels, HbA1C, and duration of DM in encephalopathy group in comparison with the other group. These results are in agreement with Abo El Soud *et al*. [14] who reported increased risk of HE in patients with DM, with increased blood sugar level, HbA1C, and duration of DM. Chow *et al*. [15] reported that T2DM is characterized

Table 4: Blood sugar level, glycated hemoglobin, and duration of diabetes mellitus in the studied groups

Variables	Group 1	Group 2	*P*
Fasting blood glucose	230±31.2	140.3±20.5	<0.01
Postprandial blood glucose	280±40.3	182.5±18.4	<0.01
HbA1C	10.8±3.5	7.5±0.9	<0.01
Duration (years)	12.4±4.5	7.5±3.4	<0.01

HbA1C, glycated hemoglobin.

Table 5: Tilt-table test and postural hypotension measurement in the studied groups

Test group	Group 1 [*n* (%)]	Group 2 [*n* (%)]	*P*
Tilt-table test			
Positive	35 (70)	6 (12)	<0.01
Negative	15 (30)	44 (88)	<0.01
Postural hypotension			
Positive	35 (70)	8 (16)	
Negative	15 (30)	42 (84)	

Table 6: Relation between ammonia level and grades of hepatic encephalopathy

Serum ammonia level	G1	G2	G3	G4
23-43	6	4	0	0
44-64	3	4	3	0
65-85	1	2	5	6
86-106	0	1	1	3
107-127	0	0	2	3
128-148	0	0	2	4

by the presence of insulin resistance, which generates a hyperinsulinemia state that could promote an increase in protein catabolism and finally, ammonia production [Table 6].

The present study also showed that autonomic neuropathy was significantly higher in group 1 patients as evidenced by a significant increase in the number of patients with positive tilt-table test and positive diurnal variation in BP measurement compared with group 2. These results are in agreement with Abo El Soud *et al*. [14] and Javier *et al*. [13] who reported that in DM, it has been well documented the presence of autonomic dysfunction, and as a result, prolonged duodenum-cecal transit time is common and could promote small intestine bacterial overgrowth. In fact, small intestine bacterial overgrowth was found in 60% of patients with cirrhosis being related to bacterial translocation [13]. Zhang *et al*. [16] reported that continuation of metformin in patients with newly diagnosed cirrhosis is associated with longer survival, and the occurrence of HE was significantly lower in patients receiving metformin.

Conclusion

Patients with cirrhosis with long-standing and uncontrolled DM are more likely to developed HE. Autonomic neuropathy, which

may complicate patients with cirrhosis with long-standing uncontrolled diabetes, may play a role in the pathogenesis of HE in these patients.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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