PREVALENCE AND PRECIPITATING FACTORS OF HEPATIC ENCEPHALOPATHY IN PATIENTS WITH LIVER CIRRHOSIS AND ASCITES ADMITTED AT KORLE BU TEACHING HOSPITAL IN GHANA.

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Abstract

Background: Hepatic encephalopathy (HE) is one of the most debilitating complications of cirrhosis leading to death and severely affects the lives of patients and their caregivers. Decreases in HE mortality and recurrence have been linked with timely identification and correction of potential precipitating factors and early treatment. The aim of this study was therefore to determine the prevalence and precipitating factors of patients with cirrhotic ascites admitted with overt hepatic encephalopathy at KBTH Accra, Ghana.

Materials and Methods: A cross-sectional study was conducted involving one hundred and three (103) patients admitted at medical block in the Korle-Bu Teaching Hospital (KBTH) with cirrhotic ascites from 25th March 2016 to 25th November, 2016. Demographic and clinical features including features of overt hepatic encephalopathy and possible precipitant were collected using a standardized questionnaire.

Results One hundred and three patients with cirrhotic ascites were recruited for the study with a mean age of 43.5 ± 12.2 years. Fifty-eight (56.3%) patients were males. The prevalence of hepatic encephalopathy was 25.24%. Precipitating factors were infections (53.8%), gastrointestinal bleeding (19.2%), electrolyte imbalance (9.2%) and constipation (3.9%). No precipitant was identified for one patient with hepatic encephalopathy.

Conclusion: Prevalence of overt hepatic encephalopathy in patients with liver cirrhosis and ascites is not uncommon in our setting and precipitants were identified for almost all of them except one patient. A similar study should be done on a larger scale in multiple centres and regions to get a well-balanced prevalence of hepatic encephalopathy and its precipitating factors.

Key Words: *hepatic encephalopathy, liver cirrhosis, precipitating factors, Ghana.*

Introduction

Hepatic encephalopathy (HE) describes a broad range of neuropsychiatric abnormalities caused by advance hepatic insufficiency or portosystemic shunting in the absence of neurological disorders.[1-2] HE is one of the most debilitating complications of cirrhosis and severely affects the lives of patients and their caregivers.[3] Based on the underlying hepatic abnormality, encephalopathy is subdivided into three types;[2] type A (associated with acute liver disease), type B (associated with portosystemic bypass and no intrinsic hepatocellular disease), and type C (associated with chronic liver disease). Type C HE can be further divided into three categories: i. Episodic HE (Spontaneous; recurrent; precipitated) ii. Persistent HE (Mild; Severe; Treatment dependent) and iii. Minimal or Overt HE. Overt HE (OHE) is a syndrome of neuropsychiatric abnormalities that can be detected by bedside clinical tests in contrast to minimal HE (MHE) that requires specific psychometric tests for detection.[4] The likelihood of developing hepatic encephalopathy correlates with the severity of the liver disease. Generally, at the time of diagnosis of liver cirrhosis, there is a 10-14% chance of OHE,[5-7] 16-21% in those with decompensated cirrhosis[8-9] and 10-50% in patients with transjugular intrahepatic portosystemic shunt.[10-11] The cumulated number indicates that OHE will occur in 30-45% of those with cirrhosis at some time during their clinical course and in the survivors in most cases repeatedly.[12] The risk for the first bout of OHE is 5-25% within 5 years after cirrhosis diagnosis, depending on the presence of risk factors such as other complications of cirrhosis and probably diabetes and hepatitis C.[3] The pathogenesis of HE in cirrhosis is complex and multifactorial, but the key role is thought to be played by circulating gut-derived toxins of the nitrogenous compound, most notable ammonia. Management of HE primary involves providing supportive care, identifying and treating any precipitating causes, reducing nitrogenous load in the gut, and assessing the need for long term therapy and liver transplant evaluation. Ammonia lowering therapies such as non-absorbable disaccharides (lactulose, lactitol etc.) and selected antimicrobial (metronidazole, rifaximin etc.) are the main agents used to treat OHE.

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Common HE precipitating factors include sepsis, gastrointestinal (GI) bleeding, constipation, and diuretic use, and once treated, H.E usually subsides significantly.[13] Decreases in H.E mortality and recurrence have been linked with timely identification and correction of potential causes and early HE treatment. There is a need to document the pattern of hepatic encephalopathy in adult population with liver cirrhosis in our setting as only reports from resource-endowed countries abound in the literature. This will no doubt allow a more appropriate management guideline, taking cognizance of resource availability. The aim of this study was therefore to determine the prevalence and precipitating factors of patients with cirrhotic ascites admitted with OHE at KBTH Accra, Ghana.

Methods

Formal approval of this study was obtained from the Ethical and Protocol Committee of the University of Ghana School of Medicine and Dentistry. This study was conducted in accordance with the Helsinki Declaration. The research design was a cross -sectional hospital-based study, carried out at the Department of Medicine, Korle-Bu Teaching Hospital (KBTH), Accra, from 25th March, 2016 to 25th November, 2016.

One hundred and three (103) patients with cirrhotic ascites admitted to the medical block of KBTH were consecutively recruited. All adult patients above 18 years with cirrhotic ascites who provided informed consent were included. Diagnosis of liver cirrhosis was made based on the clinical features, laboratory investigations and abdominal ultrasound findings suggestive of liver cirrhosis. After thoroughly explaining the study to patients, individuals who gave informed consent were recruited and a questionnaire was administered to obtain socio-demographic data and clinical history. For those patients with stage 3 and 4 HE, written consent was obtained from caregivers. Relevant history including alcohol use and clinical features of liver cirrhosis (spider angioma, palmar erythema, ascites, asterixis, hepatomegaly, splenomegaly and abdominal vein collaterals) were obtained. A diagnosis of hepatic encephalopathy was made when patient had impaired consciousness with a background liver disease in the absence of any neurological disorder or other causes of impaired consciousness. The West Haven criteria was used in grading the encephalopathy.[14] The West Haven criteria is a semi-quantitative grading of mental state from trivial lack of awareness (grade 1) to coma (unresponsive to verbal or noxious stimuli (grade 4). The Child-Pugh scoring system was used for assessing the severity of liver disease on patient presentation.[15] The scoring system takes into account the serum albumin, serum prothrombin time, and bilirubin as well as presence of fluid retention and encephalopathy; each of which is given a numerical score. There are 3 grades: A, B, and C depending on the total scores.

A sample of 15mls of venous blood was taken for haematological, biochemical and serological investigations. Abdominal paracentesis was performed using an aseptic technique at the right or left iliac fossa, 3cm above and 3cm medial to the anterior superior iliac spine. Exactly 15mls of ascitic fluid was collected using a sterile syringe for culture, cell count and differentials, albumin and protein. Diagnosis of spontaneous bacterial peritonitis was based on demonstration of more than 250 neutrophils/cm^3 or positive fluid culture in ascitic fluid. Urine analysis (Proteins, leucocytes, erythrocytes, pus cell and other urine abnormalities) were done for all patients. All patients were tested for HBsAg and anti-HCV antibodies to determine the cause of liver cirrhosis. Chest X- ray was done for all patients with clinical diagnosis of pneumonia, mainly to look for areas of consolidation.

Furthermore, an abdominal ultrasound scan was performed for all patients. The following details were recorded: maximum vertical span of the liver; nodularity of liver surface; spleen size (length of its longest axis); and presence of ascites.

Data analysis: Data obtained were analysed using STATA 15 statistical software. Descriptive statistics was run for all the variables. The prevalence of OHE and other categorical variables were expressed as proportions. Biochemical parameters and Child-Pugh Score were reported as Mean ± SD (normal data) and median (IQR) (non-normal data). The Student t-test or Mann Whitney U test were used to test the difference in means. Chi-squared test and the Fishers exact tests were used to determine the association of categorical variables and OHE. For all analysis, p-values < 0.05 were considered statistically significant.

Results

One hundred and three patients with cirrhotic ascites were recruited for the study with a mean age of 43.5 ± 12.2 years (age range 18 to 74) years. Fifty-eight (58, 56.3%) patients were males and 44 (43.4%) were females with male to female ratio of 1.7:1. HBV infection was the commonest cause (53.4%, 54/103) of liver cirrhosis and alcohol alone accounted for 21.4% of causes of liver cirrhosis. HCV infection accounted for 8.9% of cases and HBV infection in combination with alcohol accounted for 6.9% of the cases. Autoimmune hepatitis, fatty liver disease and congenital atresia were uncommon causes (Table 1).

Most patients admitted had H.E Grade 3, 38.5% (10/26), and Grade 4, 30.8% (8/26) severity (Table 2).

The prevalence of hepatic encephalopathy was 25.24%. The major precipitating factors of hepatic encephalopathy were infections (14/26, 53.8%) [(spontaneous bacterial peritonitis (26.9%), pneumonia (15.4%) and urinary tract infection (11.5%)], gastrointestinal bleeding (5/26, 19.2%), electrolyte imbalance (5/26, 19.2%) [hypokaelemia (3/26, 11.5%) and hyponatraemia (2/26, 7.7%)]. Constipation and

unknown precipitants accounted for 1/26 (3.9%) each (Table 3).

The clinical feature significantly associated with hepatic encephalopathy were jaundice, fever and splenomegaly and the laboratory parameters associated with hepatic encephalopathy were high bilirubin mainly conjugated bilirubin, high INR and Child-Pugh score and low haemoglobin (Table 4, 5).

Table 1: Causes of liver cirrhosis

Causes	**Encephalopathy**		**Total (%)**
	Present (%)	Absent (%)	
Hepatitis B virus	12(11.6)	42(40.8)	54(52.4)
Alcohol	6(5.8)	16(15.6)	22(21.4)
Hepatitis C Virus	6(5.8)	3(2.9)	9(8.7)
Alcohol + Hepatitis B virus	2(1.9)	5(4.9)	7(6.8)
Autoimmune Hepatitis	0(0.0)	4(3.9)	4(3.9)
Congenital Biliary Atresia	0(0.0)	1(1.0)	1(1.0)
Unknown	0(0.0)	6(5.8)	6(5.8)

Table 2: Severity of Hepatic Encephalopathy

Severity of Encephalopathy (n=26)	Frequency (%)
Grade 1	3 (11.5)
Grade 2	5 (19.2)
Grade 3	10 (38.5)
Grade 4	8 (30.8)

Table 3: Precipitating Factors for Hepatic Encephalopathy

Precipitants	**Frequency (%)**
Infections	
Spontaneous Bacterial Peritonitis	7 (26.9%)
Pneumonia	4 (15.4%)
Urinary tract infections	3 (11.5%)
Upper GIB	5 (19.2%)
Electrolyte imbalance	5 (19.2%)
Constipations	1 (3.9%)
No precipitant found	1 (3.9%)

Table 4: Clinical Features of the Study Participants

Clinical symptoms and signs	Encephalopathy (Absent)	Encephalopathy (Present)	Total	p-value
	N (%)			
Ascites				0.252
Moderate	40 (51.9)	9 (34.6)	49	
Severe	37 (48.1)	17 (65.4)	53	
Jaundice	36 (46.8)	21 (80.8)	57	**0.003**
Abdominal Pain	39 (50.7)	15 (57.7)	54	0.534
Fever	27 (35.1)	15 (57.7)	42	**0.042**
Chills	20 (26.0)	11 (42.3)	31	0.116
Weight loss	64 (83.1)	20 (76.9)	84	0.481
Hematemesis	11 (14.3)	3 (11.5)	14	0.508
Clubbing	9 (11.7)	5 (19.2)	14	0.332
Palmar erythema	25 (32.5)	5 (19.2)	30	0.199
Pedal edema	61 (79.2)	17 (65.4)	78	0.155
Hepatomegaly	20 (26)	4 (15.4)	24	0.421
Splenomegaly	12 (15.6)	0 (0)	12	**0.034**

Table 5: Laboratory Parameters of the Study Participants

Liver function	Encephalopathy (Absent) (n=77)	Encephalopathy (Present) (n=26)	p-value
AST (U/L)	**126** (66, 250)	**142** (83, 287)	0.414
ALT (U/L)	**58** (36, 94)	**51** (40, 78)	0.529
ALP (U/L)	**222** (147, 305)	**209** (112, 294)	0.573
GGT (U/L)	**152** (92, 298)	**133** (63, 387)	0.501
Total Bilirubin (umol/l)	**32** (18.9, 115)	**130.7** (46, 314)	**0.003**
Direct Bilirubin (umol/l)	**20.1** (8.3, 81.2)	**105.2** (22, 260)	**0.001**
Total Protein (g/l)	**70** (62, 76.6)	**74.5** (61, 80)	0.398
Serum Albumin (g/l)	**26** (22, 30)	**24** (20,28)	0.08
INR	2 (1.4, 2.2)	**7.5** (4, 10)	**0.034**
Child-Pugh Score	**10** (8, 12)	**13** (12, 13)	< **0.001**
Full Blood Count			
Haemoglobin (g/dl)	**10.8** (9.3, 12.1)	**9.1** (7.5, 10.9)	**0.001**
WBC (10^9/l)	**7.9** (5.6, 13.1)	**12.5** (8, 16.4)	0.063
Platelet (10^9/l)	**112** (71, 204)	**124.5** (87, 176)	0.391
Renal Function Test			
Sodium (mmol/l)	**134** (131, 139)	**131.5** (127, 140)	0.150
Potassium (mmol/l)	**4.1** (3.7, 4.6)	**4.8** (3.7, 5.2)	0.206
Urea (umol/l)	**5.4** (3.6, 8.5)	**5.1** (3.8, 11.3)	0.395
Creatinine (umol/l)	**80** (67, 106)	**93** (73, 200)	0.050

Variables presented as median (IQR) p-values (Mann Whitney U test) WBC- white cell count
ALT- Alanine transaminase, AST- Aspartate transaminase, ALP- Alanine transaminase, GGT- Gamma glutamyl transaminase, INR- International normalize ratio.

Discussion

Hepatic encephalopathy is a serious complication of decompensated cirrhosis with a significantly high mortality if not managed appropriately and in a timely manner. Hence, there is an urgency to accurately diagnose these conditions, start appropriate therapy, and to maintain remission. Management of HE primarily involves providing supportive care, identifying and treating any precipitating causes, reducing nitrogenous load in the gut, and assessing the need for long term therapy and liver transplant evaluation. The aim of this study was therefore to determine the prevalence and precipitating factors of patients with cirrhotic ascites admitted with OHE at KBTH Accra, Ghana. To the best of our knowledge this study represents the first ever report of HE and its precipitating factors in cirrhotic patients in Ghana. This will go a long way in formulating rational strategies in its management including prophylaxis in view of the reported poor outcome.

In this study 25.2% of the participants had HE. The exact worldwide prevalence of HE remains unknown, and is possibly a result of differences in aetiological factors, severity of the disease, and challenges in diagnosing minimal or sub-clinical HE.[16] Studies in developed countries have revealed that the prevalence of OHE at the time of diagnosis of cirrhosis is 10%–14% in general,[5,6,7] 16%–21% in those with decompensated cirrhosis.[8,9] The cumulated numbers indicate that OHE will occur in 30%–45% of those with cirrhosis at some time during their clinical course and in the survivors in most cases repeatedly.[12] This shows that hepatic encephalopathy in patient with decompensated liver cirrhosis is uncommon in our patients.

In this study clinical features associated with HE included high fever, jaundice and splenomegaly and laboratory parameters consist of high INR, high Child-Pugh score and bilirubin. These features are associated with advance liver cirrhosis and the prevalence of hepatic encephalopathy has been found to be higher in these patients. High bilirubin and INR are among five markers used to stage the severity of liver disease according to Child-Pugh rankings.[15] Jaundice is a clinical indication of decompensated liver cirrhosis; fever is a sign of infection which is a common precipitant of HE and splenomegaly is a sign of portal hypertension. Incidence of HE was found to be high among those with portal hypertension.[17]

The precipitants encountered in the current study were infections, electrolyte imbalance, gastrointestinal bleeding and constipation. No precipitant was identified in only one patient. This confirmed the fact that in most cases of liver cirrhosis with acute or chronic HE, a precipitating factor is found.[14] Previous studies have shown that infections and gastrointestinal bleeding are the most frequent precipitants of HE.[18-19] A similar trend of precipitants of HE was also found in Nigeria study.[20] Identified upper gastrointestinal bleeding (47%), constipation (18%) and spontaneous bacterial peritonitis

(12%) as the commonest precipitating event of HE, but precipitants was not found in 21% of their study population.[5] Another study also identified dehydration, acute kidney injury, constipation, and infection as the most frequent precipitants of HE.[21] The precipitating factors of HE is globally similar, but the predominant precipitants vary from one study to another. The reasons for these variations may be as a result of the aetiology and severity of liver disease and the drugs (Diuretics, Benzodiazepines, Lactulose or Lactitol etc.) the patients were taking before the studies.

Majority of the patients in our study had Hepatitis B-related liver disease, while significant alcohol consumption was noted to be the second commonest caused. This is in keeping with earlier reports about the role of hepatitis B in causation of liver disease in Ghana.[22] Efforts at improving the coverage of current immunization campaign against Hepatitis B certainly will help reduce the burden of Hepatitis B virus infection, whilst education on harmful alcohol use should be encouraged to prevent its effect on the liver in addition to other vital organs.

This study is not without limitations, due to the high cost of imaging patients in this study, we did not have brain computerized tomographic scan (CT scan) to exclude primary neurological disease. However, most of these patients already had pre-existing liver disease.

Conclusion and recommendations

Prevalence of HE in patients with liver cirrhosis and ascites is not uncommon in our setting and precipitants were identified for almost all of them except one patient. Therefore, clinicians should do proper examination to identify OHE early in patients with decompensated liver cirrhosis and identification of different precipitating factors for early treatment. A large scale multi-center study will provide a well-balanced prevalence of hepatic encephalopathy and its precipitating factors. Moreover, study to determine treatment outcomes will be essential in our setting.

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