ORIGINAL ARTICLE

Chronic liver disease and hepatic encephalopathy: Clinical profile and outcomes

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Abstract

Background: Hepatic encephalopathy (HE) is an important neuropsychiatry complication of liver disease causing significant morbidity and mortality worldwide. Efforts at improving the outcome have resulted in development of new strategies in the management given the background of new insights in the pathogenesis of this disease entity. Understanding the disease profile including precipitants as well as prognostic factors will contribute in this regard as new strategies are yet to be widely applied. The aim of this report is to document the profile of patients with HE, the precipitants, prognostic factors as well as the scope of the burden associated with it.

Materials and Methods: In this prospective study, all patients managed for HE from January to December 2008 were recruited. A questionnaire was used to extract their basic demographics, clinical features noting any possible precipitants, complications, management protocol as well as outcome.

Results: A total of 21 subjects (11 females and 10 males) within the age range of 16–83 years were seen during the period under review. (mean age 57.9 ± 13). There was no significant difference in the mean ages of males and females. Two patients had acute encephalopathy, while others had acute-on chronic encephalopathy. The risk factors for liver disease included significant alcohol ingestion, hepatitis B virus infection, and previous jaundice, while other complications of liver disease noted were deepening jaundice, ascites, bleeding tendencies, and renal failure. The identified precipitants for HE were sepsis 6 (29%), electrolyte inbalance 3 (14%), gastrointestinal bleed 5 (24%), drugs (5%), and possible malignant transformation 6 (29%). Focus of sepsis was bacterial peritonitis in two cases. Majority of our patients (61%) came during advanced stage of liver disease (Child-Pugh class C). Length of hospital stay ranged from 1 to 7 weeks and a mortality of 48% was observed. Predictors of mortality were a history of significant alcohol ingestion, previous blood transfusion, Hepatitis B and C infections, and severe liver dysfunction on presentation (Child-Pugh class C).

Conclusions: HE is associated with a high mortality rate and this scenario is associated with a history of previous blood transfusion, Hepatitis B and C infections, and severe liver dysfunction on presentation. Measures to reduce the burden of viral Hepatitis B and C, safe blood transfusion, and responsible use of alcohol should be promoted. Screening of those at risk of encephalopathy (liver disease patients) with a psychometric test of good predictability should be part of their routine evaluation in daily practice so as to detect cases of latent encephalopathy. Intensive care facilities and necessary personnel should be provided.

Key words: Hepatic encephalopathy, Liver failure, Nigeria.

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Introduction

Hepatic encephalopathy (HE) is a common neuropsychiatric syndrome seen in patients with

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significant hepatic dysfunction in the absence of neurological disorders.[1] It is seen in upto 30-45% of patients with cirrhosis and its latent or sub clinical form (minimal hepatic encephalopathy can affect upto 60% of patients with liver disease.[2] Although controversy about the exact pathogenetic mechanism exists, certain factors like hyper ammonia and increased blood-brain permeability to ammonia, increased brain concentration of manganese and inhibitory neurosteroids (allopregnanolone) have been documented.[3] Based on the underlying hepatic abnormality, encephalopathy is subdivided into three types;[1] 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).

Current recommendation[1] of the working party on its definition suggest guidelines that would allow even the diagnosis of the sub clinical form (latent encephalopathy) and the use of the newer neuroimaging techniques. However, this is yet to be widely applied in clinical practice as some report indicates.[4] Available reports[4-6] have identified factors such as sepsis, gastrointestinal bleeding, constipation, and diuretic use as common precipitating factors of encephalopathy in patients with liver disease. Identification of these precipitants and other prognostic indices would enable institution of more rationale measures in the management of this condition, which has been associated with poor outcome.[7] This is even worse in resource poor countries that often lack necessary manpower, newer imaging techniques, and dedicated specialized care unit. The cornerstone of therapy is still the nonabsorbable disaccharides, since the new therapeutic agents with broad-spectrum activity against urease producing bacteria are yet to be available. Also, dietary manipulation is still protein restriction and not protein maintenance with glutein and casein-free diet (GCFD), which has recently been recommended in view of its role in lowering opioid peptides that have been implicated in the pathogenesis.

An earlier report[6] from this locality in children had shown a very poor outcome (95% mortality), although these were mostly fulminant cases (type A encephalopathy). There is a need to document the pattern of hepatic encephalopathy in adult population 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. We therefore set out to redress this issue in our study. The aim of this report is documenting the profile of patients admitted with features of HE from January to December 2008 and note possible precipitants, complications, and management outcome.

Materials and Methods

This was a prospective and observational study and was conducted in line with the principle of the Declaration of Helsinki as amended in Tokyo (1975), Venice (1983), and Hong Kong (1989). All patients with HE admitted into the Medical Wards of the Lagos State University Teaching Hospital, Ikeja from January to December 2008 were recruited. A patient was included if he had impaired consciousness with a background liver disease (acute or chronic on basis of clinical findings, liver biochemistry, and sonographic findings) in the absence of any neurological disorder or other cause of impaired consciousness. A questionnaire was used to extract the following: Bio data, clinical features including laboratory findings, any identified precipitants, complications as well as management and outcome. Brain imaging with computerized tomographic scan was done where possible to exclude primary neurological cause. Diagnosis of spontaneous bacterial peritonitis was based on demonstration of more than 250 WBC/cm^3 in ascitic fluid. The presence of elevated serum creatinine (>1.5 mg/dl) in the absence of shock, hematuria, or proteinuria with a normal renal sonogram was taken to be indicative of hepatorenal syndrome. The Child-Pugh scoring system[7] was used for assessing the severity of liver disease on patient presentation. 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. The West Haven criteria[8] was used in grading the encephalopathy. It 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).

Results

There were 21 subjects (11 females and 10 males) with HE seen within the period of study. Age ranged from 16 to 83 years with a median age of 61 years. The mean age of the study subjects was 57.9 ± 13 years, and the mean age of the males and females were comparable [(57.7 (±18) years vs. 58 (±8) years; $P = 0.7$]. Total emergency admission for the gastroenterology/liver unit during this period was 362, thus, HE accounted for 6% of this.

Two patients had acute encephalopathy (type A), while 19 had acute on chronic liver disease (type C). The two acute encephalopathy were drug induced, one of whom survived.

Risk factors for chronic liver disease

Significant alcohol and previous blood transfusion histories were documented in 10 (48%) and 2 (10%), respectively, of the study subjects. Also, a history of previous jaundice and use of herbal medications was documented in 9 (43%) and

2 (10%), respectively, of the subjects under study.

These and other risk factors are shown in Table 1.

Clinical presentation

Of the stigmata of chronic liver disease, 4 (40%) of the males had testicular atrophy. The distribution of stigmata of chronic liver disease (CLI) is shown in Figure 1.

Some of the patients presented with complications of CLD and the distribution of these are shown in Figure 2.

Severity of liver disease on presentation as assessed using the Child-Pugh's classification is shown in Figure 3.

Grading of HE

Table 2 shows the distribution of the grade of encephalopathy and outcome of management among study participants.

Precipitating factors

Identified precipitants of encephalopathy in the patients were sepsis 6 (29%), electrolyte inbalance 3 (14%), gastrointestinal bleed 5 (24%), drug induced (5%), and possible malignant transformation 6 (29%). Focus of sepsis was bacterial peritonitis in two cases.

Table 1: Clinical characteristics of the study subjects

Variable	Frequency (%)
Previous blood transfusion	2 (10)
Alcohol history	10 (48%)
Hep C antibody	2 (10)
Hep B surface antigen	10 (48)
Previous jaundice	9 (43)
Elevated alpha feto protein	(>100) 5 (29)
Use of herbs	2 (10)

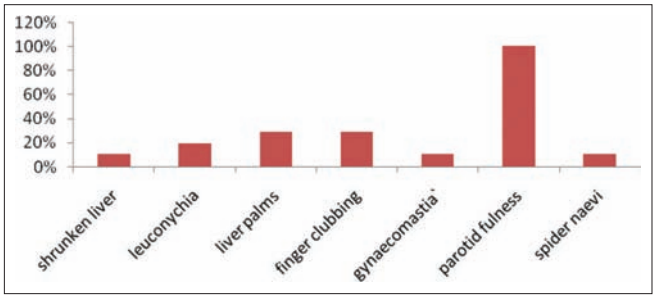

Figure 1: Prevalence of stigmata of CLD

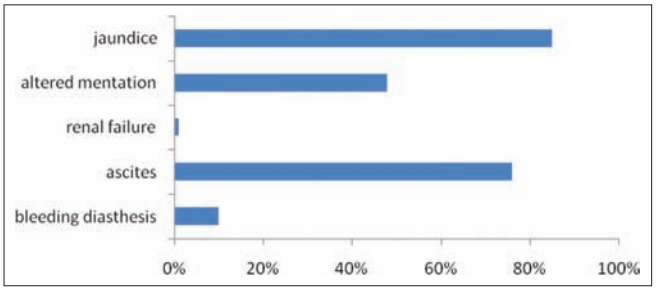

Figure 2: Distribution of complications of CLD

Treatment and duration of hospitalization

Treatment type varied and included the use of mannitol, especially in acute encephalopathy. Various treatment types are shown in Table 3. The duration of hospitalization is shown in Table 4.

Outcome of management

In all, 10 (48%) of the subjects expired. The number of females who passed away was more than males, with the female: Male ratio being 7:3. Possible determinants of mortality are shown in Table 5. A history of significant alcohol ingestion, previous blood transfusion, Hepatitis B and C infections, and severe liver dysfunction on presentation (Child-Pugh class C) are highly predictive of mortality from encephalopathy.

Discussion

HE remains an important complication of liver disease associated with high mortality even in developed nations.

Table 2: Grade of hepatic encephalopathy using West Haven criteria and outcome

Grade	Frequency (%)	Recovered (%)	Died
1	11 (52.4)	7 (64)	4 (36%)
2	6 (28.6)	4 (67)	2 (33)
3	1 (4.8)	0	1 (100%)
4	3 (14.3)	0	3 (100%)

Table 3: Treatment modalities for hepatic encephalopathy

Variable	Frequency (%)
Protein restriction	21 (100)
Lactulose	18 (86)
Metronidazole	18 (86)
Neomycin	4 (19)
Mannitol	18 (86)

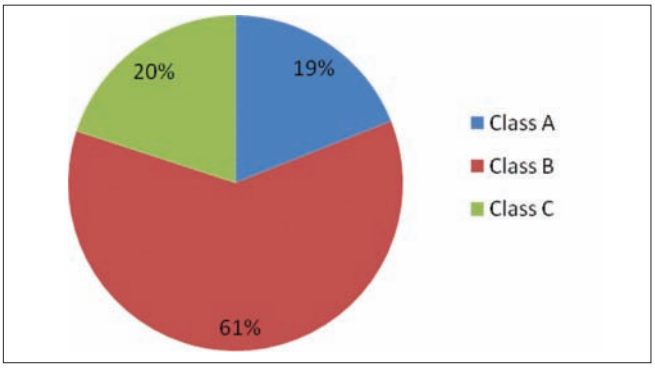

Figure 3: Child-Pugh's classification in study subjects

Table 4: Duration of hospitalization and survival

Duration in weeks	No. of subject (dead)
<1	6 (3)
>1<2	4 (1)
>2<3	4 (2)
>3	7 (4)

Table 5: Predictive factors of mortality from hepatic encephalopathy

Variable	Odds ratio	95% CI
Female sex	0.31	0.04-3.8
Alcohol intake	1.4	0.18-8.1
Jaundice	0.26	0.02-48.6
Previous blood transfusion	2.6	0.06-22.8
Grade of encephalopathy	5.1	0.7-33.9
Child-Pugh class C	2.7	0.56-13.28
Elevated and-fetoprotein	(>100) 0.62	0.063-6.12
HBsAg	1.03	0.03-30.8
HCV antibody	1.09	0.08-22.1

Newer insight into its pathogenesis[4] has led to newer approaches[9,10] in its management, though these are yet to be widely applied particularly in the resource poor nations.[3] Documentation of its profile including precipitating factors will go a long way in formulating rational strategies in its management including prophylaxis in view of the reported poor outcome.[11]

Majority of the patients in our study had encephalopathy complicating underlying chronic liver disease with only two having fulminant failure, one of whom survived. About half of study subjects had Hepatitis B-related liver disease, while significant alcohol consumption was noted in majority, which may have contributed to the progression of liver disease. This is in keeping with earlier reports[12] about the role of hepatitis B in causation of liver disease in our setting. Efforts at improving the coverage of current immunization campaign[13] against Hepatitis B certainly will help reduce the burden of Hepatitis B virus infection, whilst promotion of sensible use of alcohol should be encouraged.

The observed precipitants in this study, sepsis (29%), electrolyte inbalance (14%), gastrointestinal bleed (24%), drug induced (5%), and possible malignant transformation (29%), do not differ from those in previous reports.[3,5] No other precipitants were found in 5 (29%) with sonographic features of PLCC as well as elevated alpha fetoprotein and were considered as having PLCC.[14] Majority of our patients came in fairly advanced stage of liver dysfunction (Child-pugh class B and C), which may have contributed to observed mortality [Odds ratio (OR) 2.7 (95% CI) 0.56-13.28). Higher fatality rate were recorded with increasing severity of encephalopathy (OR 5.1, 95% CI).

It is noteworthy that our management protocol (nonabsorbable disaccharides, antibiotics, and protein restriction) did not involve any of the newer therapeutic regime (antibiotics with broad spectrum activity against urease producing bacteria as well as GCFD). The patients in this study were nursed in the open ward and this was largely due to financial constraints. In our setting, usually healthcare costs are borne by the patients and payment often has to be made before some facilities are made available for use. Management in an intensive care unit as well as employment of the newer therapeutic measures may have improved the outcome.

Apart from advanced stage presentation, other predictors of fatal outcome are; severe grade of encephalopathy, a history of significant alcohol ingestion, previous blood transfusion, Hepatitis B and C infections. Identification of early encephalopathy by screening of those at risk (patients with pre-existing liver disease) using the psychometric tests[15,16] will go a long way in reducing the fatal outcome since advanced stage presentation as was documented in this study is associated with less favourable outcome.

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.

The limitations of this report include a small sample size.

Conclusions

The disease burden of HE is high and the contributory factors of this scenario are potentially remediable. Possible measures that may ameliorate the dismal statistics associated with HE include routine vaccination against viral Hepatitis B and C, ensuring safe blood transfusion as well as responsible use of alcohol. Screening of those at risk of encephalopathy (liver disease patients) with a psychometric test of good predictability should be part of their routine evaluation in daily practice so as to detect cases of latent encephalopathy. Intensive care facilities and necessary personnel should be provided for the care of these patients in health institution.

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