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Hepatic Encephalopathy; Prevalence, Precipitating Factors and Challenges of Management in a Resource-Limited Setting

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Abstract

Background and Aims: Hepatic encephalopathy, a neuropsychiatric syndrome caused by portosystemic venous shunting, clinical presentation ranges from minimal to overt H.E. It is a common complication of advanced liver disease with significant morbidity and mortality The aim of this study was to assess the prevalence, common precipitating factors, and outcomes of hepatic encephalopathy in patients with preexisting liver disease.

Methods: A hospital based, retrospective chart review study was conducted at Bugando Medical Centre a tertiary hospital in Mwanza region. The target population included all patients aged > 18 years admitted with Hepatic encephalopathy from January 2009 to June 2015. Patients were enrolled using a detailed checklist, personal identifications were removed and analysis was done using the SPSS version 17.0.

Results: A population of 88 patients with Hepatic encephalopathy were enrolled with a mean of 47 years (SD +/-17 years). Among patients admitted to the medical ward, the prevalence was 0.4% (88/23942). Most common liver disease and complications including alcoholic cirrhosis, hepatitis B infection, and hepatocellular carcinoma were present in 47.7% of (42/88), 22.7% (20/88), and 23.9% (21/88) patients, respectively. Majority had West Haven grade 3, 36.4% (32/88), and grade 4, 18.2% (16/88).

Precipitating factors included diuretic therapy on patients with ascites 27.2% (44/162), infections 21.6% (35/162), blood transfusions, 16.7% (27/162), and upper gastrointestinal bleeding 17.3% (28/162). Most died during their hospitalization, 75% (66/88). The remaining 25% (22/88) were discharged. Majority of the cohort, 72.7% (64/88), had less than 3 months survival after diagnosis, while 27.3% (24/88) survived more than 1 year.

Conclusions: We found severe Hepatic encephalopathy presenting in patients with preexisting liver disease associated with poor outcomes, posing challenges in management and survival. The use of newer and superior agents like polyethylene glycol, identification of subclinical Hepatic encephalopathy and targeting early removal of precipitating factors is imperative. Screening those at risk of developing Hepatic encephalopathy would likely improve outcomes.

Keywords: Hepatic encephalopathy; West Haven; Tanzania

Introduction

Background

Hepatic Encephalopathy (H.E), defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction after exclusion of brain disease, is a common complication of advanced liver disease with significant morbidity and mortality [1]. The exact worldwide prevalence of hepatic encephalopathy remains unknown, and is possibly a result of differences in etiological factors, severity of the disease, and challenges in diagnosing minimal or sub-clinical H.E [2]. Studies in developed countries reveal minimal hepatic encephalopathy affects the quality of life in 70% of patients with liver cirrhosis [3]. Other studies report on overt H.E occurring in 30% to 45% of patients with cirrhosis and 10 to 20% of patients with Transjugular Porto Systemic Shunts (TIPS) [4]. Local data in Nigeria reported a prevalence of H.E in 6% of patients admitted to the gastroenterology medical ward [5].

Common H.E precipitating factors include sepsis, gastrointestinal (GI) bleeding, constipation, and diuretic use, and once treated, H.E usually subsides significantly [6]. However, patient outcome relies on early identification.

Treatment of H.E targets reducing the ammonia load in the body. Commonly this is achieved with lactulose use, though polyethylene glycol (PEG) was recently shown to be superior to lactulose in treating H.E of hospitalized patients [7]. Targeting broad-spectrum activity against urease producing bacteria with Rifaximin is not yet available especially in resource-limited settings [8].

Rationale

Decreases in H.E mortality and recurrence has been linked with timely identification and correction of potential causes and early H.E treatment. In resource limited areas, most patients outcomes are poor and thought to be due to later stage presentation and limited treatment options. This study provides information on the magnitude of H.E in patients with existing liver disease and creates a field for analyzing and improving current treatment guidelines targeting improved clinical outcomes to the population at risk.

Objectives

Broad objective

To determine the prevalence, precipitating factors and management of patients admitted with H.E at BMC Mwanza from 2012-2015.

Specific objectives

- To determine the prevalence of H.E in patients admitted with liver diseases at BMC Mwanza from 2012-2015.
- To determine the commonest precipitating factors for HE in patients admitted with HE at BMC Mwanza from 2012-2015.
- To determine the outcomes of patients after management following the present local guidelines inpatients admitted with H.E at BMC Mwanza from 2012-2015.

Methodology

Study site

The study was conducted at Bugando Medical Centre located in the northwest region of Tanzania. It is a tertiary and teaching hospital serving 900 beds equivalent to one third of the country's total population.

Study design

Hospital based retrospective cross sectional chart review study was employed in all patients above 18 years with liver disease. All patients with clinical symptoms and signs of H.E were evaluated using the West Haven classification which was formulated by Harold Conn and colleagues [9].

Sampling procedures

The sample size obtained was a population of 145 were files were serially selected and 88 patients met inclusion criteria. Those with little or inconclusive information about liver disease or symptoms suggestive of hepatic encephalopathy were excluded. Data collection procedures were done using a detailed check-list.

Data analysis

Data obtained was first entered in the Microsoft Excel sheet to generate data base which was exported in the SPSS version 17.0. A series of tabulations was formed that gave the results of the study.

Ethical consideration

Permission was obtained from the Catholic University of Health and allied sciences (CUHAS) review committee and all personal identification was removed.

Results

Social demographic characteristics of the study population

A total population of 88 subjects met inclusion criteria, and Table 1 summaries the demographic characteristics of the participants. The mean age was 47 years with a SD of ±17 years; males were predominantly more represented than females, 78.4% (69/88) and 21.6% (19/88), respectively. Majority of patients were aged between 36 to 60 years 52.3% (46/88), though younger and older aged patients were represented, 22.7% (20/88) aged 18-35 and 25% (22/88) aged greater than 60 years.

Variables	Frequency	Percentage
Age in years		
18-35	20	22.7
36-60	46	52.3
>60	22	25
Gender		
Male	69	78.4
Female	19	21.6

Table 1: Social demographic characteristics of the study population.

The incidence and prevalence of H.E

The overall prevalence of hepatic encephalopathy of all patients admitted to the medical ward was 0.4% (88/23,942) (Table 2). The incidence of hepatic encephalopathy increased slightly from 0.3% in 2009-2012 to 0.4% in 2013-2015.

Year	Total admissions	Hepatic encephalopathy	Incidence (%)
2009- 2012	15016	49	0.3
2013- 2015	8926	39	0.4
Total	23942	88	0.4

Table 2: Incidence and prevalence of H.E.

Severity of H.E (according to West Haven classification), type of H.E and etiology of liver disease

Details of H.E and causes of liver disease were reported in Table 3. The majority of patients admitted had H.E Grade 2, 34% (30/88), and Grade 3, 36.4% (32/88) severity. Most had type C H.E 77.3% (68/88). Causes of chronic liver disease included liver cirrhosis 47.7% (42/88), hepatoma 23.9% (21/88), hepatitis b virus infection 22.7% (20/88), cardiac hepatopathy 3.4% (3/88), and liver abscess 2.3% (2/88). HCC (Hepatocellular carcinoma).

Variable	Frequency	Percentage
Severity of H.E		
Grade 1	10	11.6
Grade 2	30	34
Grade 3	32	36.4
Grade 4	16	18.2
Type of H.E		
A	20	22.9
B	0	0
C	68	77.3
Liver disease		
Alcoholic Cirrhosis	42	47.7
Hepatocellular c.a	21	23.9
Acute on chronic Hepatitis B	20	22.7
Cardiac Hepatopathy	3	3.4
Liver abscess	2	2.3

Table 3: Severity of Hepatic encephalopathy (according to West Haven classification), type of hepatic encephalopathy and etiology of liver disease. c.a: Carcinoma.

Precipitating factors for H.E and underlying comorbidities

Most patients admitted with H.E had more than one precipitating factor. Commonly observed was use of diuretics in massive ascites, 27.2% (44/162), infectious, 21.6% (35/162), GI bleeding, 17.3% (28/162), and blood transfusion, 16.7% (27/162) (Table 4). The most commonly encountered comorbidity in the population was severe anemia, 36.4% (16/44), and HIV infection WHO clinical stage IV, 27.3% (12/44) (Table 4).

Variables	Frequency	Percentage
Precipitants		
Ascites on Diuretics	44	27.2
Infections	35	21.6
Blood Transfusion	27	16.7
GI Bleeding	28	17.3
Renal Failure	9	5.6
CNS Drugs (BDZ)	9	5.6
Constipation	10	6.2
Comorbidities		
HIV – IDS	12	27.3
Diabetes Mellitus	3	6.8
Hypovolemic Shock	2	4.5
Septic Shock	1	2.3
Severe Anemia	16	36.4
CCF	4	9.1
Obstructive Uropathy	2	4.5
Cerebral Abscess	1	2.3
Hypertension	3	6.8

Table 4: Precipitating factors for H.E and underlying comorbidities. GI: Gastro Intestinal; CNS: Central Nervous System; BDZ: Benzodiazepines; HIDS:Human Immunodeficiency Virus; IDS: Immunodeficiency Syndrome; CCF: Congestive Cardiac Failure.

Treatment, duration of hospital stay, primary outcomes and survival rate after diagnosis

Treatment offered to the patients while admitted in the wards, their duration of stay, and their primary outcome after initiating treatment, and survival time after diagnosis was presented in Table 5.

Variables	Frequency	Percentages
Treatment		
Diet protein restriction	9	10.2
Lactulose	72	81.8
Neomycin	7	8
Lactilol	0	0
PEG	0	0
Sodium benzoate	0	0
Hospital stay(Days)		
0-5	57	64.8
6-10	17	19.3
11-15	8	9.1
16-20	3	3.4
21-25	3	3.4
P.outcomes		
Discharge	22	25
Death	66	75
Survival		
<3 months	64	72.7
>12 months	24	27.3

Table 5: Treatment, duration of hospital stay, primary outcomes and survival rate after diagnosis. P: Primary; PEG: Polyethylene glycol.

Majority of patients with H.E were treated with lactulose, 81.8% (72/88), protein diet restriction, 10.2% (9/88), and use of neomycin antibiotics, 8.0% (7/88). After initiating treatment the mortality of

patients was high, 75% (66/88), with 72.7% (64/88) of all patient deaths in less than 3 months. One in four, 25% (22/88) of patients was discharged. There was an average hospital stay of 5 days for majority of patients 64.8% (57/88). 27.3% (24/88) survived past 12 months.

Discussion

The current study was conducted at Bugando Medical Centre in Mwanza region, Tanzania among inpatients with liver disease. The mean age of the study population was 47 years with male predominance in more than half of the subjects. The overall prevalence of H.E in this study was relatively low, less than one percentage, which is in contrast with other studies in China which had a higher prevalence of the disease [10]. This may be due to differences in etiology, disease severity, and the diagnostic methods used to detect minimal H.E that are not entirely practical in our setting.

Majority of patients found to have H.E were in their 3rd and 4th decades of life, which is younger as compared to other studies were most patients were in their 5th decades of life [11]. This could partly be explained due to high prevalence of viral hepatitis B infection in the younger adults which is among the commonest causes of acute and chronic liver failure to both the general and health care worker populations in Tanzania [12,13]. The male predominant population in this study is likely due to the risk of chronic alcohol use as a cause of liver disease which was consistent with other studies [11].

The majority of patients admitted had West Haven classification grade 3 and 4 H.E and died within less than 3 months. Alcoholic cirrhosis, hepatocellular carcinoma, and hepatitis B infection, were the frequent causes of liver disease. In contrast, a similar study in South Asia reported a severity of grade 2 and 3 H.E with hepatitis C infection accounting for more than 50% of the etiology of liver disease [14].

The precipitants encountered in the current study were constipation, hypokalemia due to the use of diuretics, CNS drugs like benzodiazepines, infections and Upper GI bleeding which were in line with other studies [5,11]. In contrast blood transfusion and renal failure were the new entities observed in our study as precipitants.

HIV infection was a common comorbidity associated with very poor outcomes and majority had WHO clinical stage 4 diseases. No clear association was seen between HIV and development H.E. Although, current studies have shown an increased association between the risk of developing H.E in patients co infected with HIV/viral hepatitis B/C with increasing levels of hyaluronic acid [15]. Similarly, the risk of hepatic decompensation increases significantly in patients' co infected with HIV/viral hepatitis C as compared to mono infection of viral hepatitis C treatment naïve patients on Anti retro viral therapy [16].

Lactulose was the main standard of treatment for H.E from this current study. Although, PEG has been shown to be more superior in resolving signs and symptoms of H.E especially in hospitalized patients [7], its availability is limited. More emphasis and recommendations should be made to the use of PEG which may result in improved outcomes.

The overall mortality of patients with H.E was high, but this cannot be attributed to H.E alone. Most of the patients had severe complications of end stage liver disease and associated comorbid conditions like severe anemia and HIV/AIDS stage 4 diseases which could account for poor outcomes. The exact cause of death in most patients could not be ascertained as either a result of associated comorbid conditions, primary liver disease or solely H.E.

In addition to the late presentation of patients with advanced liver disease and the severity of H.E, key factors also contributing to poor outcomes includes the lack of proper training and facilities to diagnose subclinical H.E through neuropsychological examinations, standard psychometric batteries, neuropsychological testing, and computerized testing [10].

Conclusion

There is high prevalence of H.E in patients with preexisting liver disease usually associated with poor outcomes. Late presentation of these patients poses challenges in management and survival. Lactulose is commonly used in the treatment of H.E in contrast to more superior and potent drugs like PEG that cause early remission of symptoms. It is unfortunate that such drugs are not easily accessible in our setting. Therefore, screening should be done to those at risk of developing H.E (preexisting liver disease) to identify subclinical H.E, enabling early identification and removal of different precipitating factors.

Limitations

The study involved a small sample size and may have some context specificity since it involved only one tertiary hospital in Mwanza region, Tanzania. This may also be attributed to the missed cases with minimal H.E due to the challenges in diagnosis. Neuro scanning using CT SCAN of the head, EEG and ammonia levels were not performed.

Competing Interests

The authors have declared that no competing interests exist.

Author Contributions

KCR did designing and data collections, SSM and NTS did the analysis while ACL wrote the manuscript and HJ was the supervisor of the study and she is the corresponding Author.

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