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RESEARCH ARTICLE

PRECIPITATING FACTORS OF HEPATIC ENCEPHALOPATHY IN CIRRHOSIS OF LIVER AT A TERTIARY CARE HOSPITAL IN NORTH EAST INDIA

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ABSTRACT

Hepatic encephalopathy is a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, characterized by personality changes, intellectual impairment and altered consciousness. A hospital based observational descriptive study was conducted from June 2013 to May 2014 in Gauhati Medical College, Guwahati, India with an objective to evaluate different precipitating factors of hepatic encephalopathy in patients with liver cirrhosis. Among 112 patients enrolled 86 (76.78%) were male and 26 (23.22%) female with male and female ratio 3.3: 1. 73 (65.17 %) patients were above 40 years of age, 37 (33%) in grade IV, 32 (28.6%) grade III and grade I hepatic encephalopathy. 74 (66%) out of 112 patients had alcoholic cirrhosis. The most common precipitating factors were upper GastroIntestinal bleeding 56 (50%), infection 49 (43.75%), constipation 45 (40.18%) and hypernatremia 45 (40.18%). Single precipitating factor was found in 42 (38%) and more than three factors in 35 (31%). 80 patients recovered while 32 patients expired. Majority of expired patients had Child-Pugh score C, grade IV hepatic encephalopathy and multiple precipitating factors.The study concluded that different precipitating factors play key role in development of hepatic encephalopathy. Upper gastrointestinal bleeding was the most common factor in this study, higher grade of hepatic encephalopathy with multiple precipitating factors having poor prognosis.

INTRODUCTION

Hepatic encephalopathy (HE) is a serious complication of both acute liver failure (ALF) and chronic liver failure with the potential to affect health-related quality of life, clinical management strategies, liver transplant priority, and patient survival (Bustamante J *et al*, 1999). The neuropathological features of HE primarily include changes in the morphology and function of cells of the glial lineage rather than neuronal and have led to the suggestion that HE is a primary gliopathy (Butterworth RF, 2003).

Hepatic encephalopathy (HE) is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of other known causes of brain disease. It is characterized by personality changes, intellectual impairment and a depressed level of consciousness (Shawcross DL *et al*, 2015). An important prerequisite for the syndrome is diversion of portal blood into the systemic circulation through portosystemic collateral vessels (Riggio O *et al*, 2005). The development of hepatic encephalopathy is explained, to some extent, by the effect of neurotoxic substances, which occur in patients with cirrhosis and portal hypertension. Overt hepatic encephalopathy occurred in 30 to 45 % patients of cirrhosis (Butterworth RF, 1996) .The development of hepatic encephalopathy negatively impacts patient survival. The occurrence of encephalopathy severe enough to lead to hospitalization is associated with a survival probability of 42% at 1 year of follow-up and 23% at 3 years (Bustamante J *et al*, 1999). Approximately 30% of patients dying of end-stage liver disease experience significant encephalopathy, approaching coma (Ferenci P *et al*, 1995). The nitrogenous substances derived from the gut adversely affect brain function and play a role in its pathogenesis (Donovan JP *et al*, 1998).These compounds gain access to the systemic circulation as a result of decreased hepatic function or Porto-systemic shunts. In the brain these compounds produce alterations of neurotransmission that affect consciousness and behaviour. Abnormalities in glutamatergic, serotoninergic, gaminobutyric acid-ergic (GABA-ergic) and catecholamine pathways have been described in experimental HE. Ammonia is a key factor in the pathogenesis of HE (Butterworth RF, 2003). In acute and chronic liver disease increased arterial levels of ammonia is seen. The blood-brain barrier permeability to ammonia is

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increased in patients with HE. Furthermore, the alterations in neurotransmission induced by ammonia also occurs after the metabolism of this toxin into astrocytes resulting in neurochemical events caused by the function alteration of this cell (Butterworth RF *et al*, 2003). Other gut-derived toxins have been proposed e.g. benzodiazepine like substances, products of colonic bacterial metabolism such as neurotoxic short and medium chain fatty acids, phenols and mercaptans and manganese which is deposited in basal ganglia and induces extrapyramidal symptomatology. All of these compounds may interact with ammonia and result in additional neurochemical changes which reactivate peripheral type benzodiazepine receptors with subsequent stimulation of the GABA-ergic system, an effect also induced directly by ammonia (Chatauret N *et al*, 2004).

Working party on hepatic encephalopathy World Congress of Gastroenterology, Viena 1998, classify hepatic encephalopathy in three types, type-A HE related with acute liver failure, B-related with portosystemic shunt surgery and type- C related cirrhosis with portal hypertension (Ferenci P *et al*, 2002). The hepatic encephalopathy has four grades. There are several precipitating factors for HE such as infection, gastrointestinal bleeding, constipation, diarrhoea/vomiting, hypoxia and hypoglycaemia. The treatment of Hepatic encephalopathy has two parts, one is to avoid the precipitating factors and the second is to treat the precipitating factor.

Therefore, considering the increasing incidence of liver disease and hepatic encephalopathy with time, this study was carried out with the main objective of ascertaining the frequency of various precipitating factors and to assess their outcome in cirrhosis patients presenting with hepatic encephalopathy at Guahati Medical College and Hospital, Guwahati, Assam, a 1500 bedded tertiary care teaching hospital which covers both urban as well as rural population of entire North East India. Early diagnosis and treatment of precipitating factors will reduce the mortality due to hepatic coma. Furthermore, this study will also open a new forum of discussion regarding demographical distribution of patient, knowledge and protocol regarding the medical workup of the patients with hepatic encephalopathy.

PATIENT AND METHODS

A hospital based observational descriptive study conducted on 112 patients in the Department of Gastroenterology and Medicine, Gauhati Medical College and Hospital, Guwahati, Assam, from June 2013 to May 2014. All patients who were above 18 years and had signs and symptoms of HE, both at presentation or during the course of hospital stay were evaluated and studied.Hepatic encephalopathy is diagnosed patient with altered mental function with existing liver dysfunction after exclusion of metabolic disorders, infectious diseases, intracranial vascular events and intracranial space occupying lesions, different precipitating factors, and/or a prior diagnosis of hepatic encephalopathy and aetiology of liver disease were determined by history and relevant specific investigations. A proforma was designed and used for data collection. A detailed clinical history of the patient was taken regarding the present and past illnesses. Inquiry was made regarding upper GI bleeding, including hematemesis and melaena, fever, cough, pain abdomen, urinary symptoms, altered bowel habit (constipation/ diarrhoea), vomiting, high protein diet and any trauma or surgery. The drug history, particularly, recent increased dose of diuretics, history of intake of sedative or tranquilizer and non steroid anti-inflammatory drugs (NSAID). All patients were examined carefully for presence of fever, anaemia, jaundice, dehydration, asterixis, abdominal tenderness and documented.

The routine and relevant investigations like complete blood count, urine routine examination, urine culture and sensitivity, blood urea, serum creatinine, electrolyte,blood sugar, chest radiograph, liver function test, coagulation profile, ascitic fluid examination, venous blood ammonia, ultrasound of abdomen, HbsAg, Anti-HCV and antinuclear antibody were carried out. Grading of hepatic encephalopathy were determined using West Haven classification and severity of liver disease assessed by calculating CTP score.

RESULTS

Total 112 patients with cirrhosis of liver suffering from hepatic encephalopathy were included in the study. The different precipitating factors in each patient were evaluated during hospitalization. There were 86 male and 26 female with male female ratio 3.3: 1.(Figure-1) Total 73 patient above age of 40yrs.

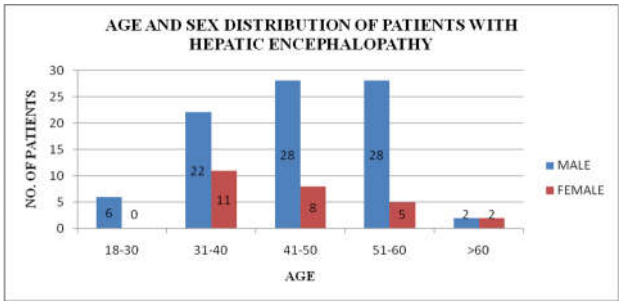

Figure 1 Bar diagram showing the age and sex distribution of the patients

37(33%) grade IV, 32(28.6%) grade III, 11(9.8%) grade II and 32(28.6%) Grade I hepatic encephalopathy. In this study 74(66.08%) patient alcohol related cirrhosis, 15(13.39%) patient hepatitis B, 5(4.46%) patient hepatitis C and 18(16.07%) patient had cirrhosis due to other cause.The most common precipitating factor of hepatic encephalopathy found in our study are upper gastrointestinal bleeding 56(50%), infection 49(43.75%), Constipation 45(40.17%) and hypernatremia 45(40.17%). Super added infection of acute hepatitis- A in 2 patient (1.79%) and new diagnosis HCC found in 2 cases(1.79%).(Figure-2)

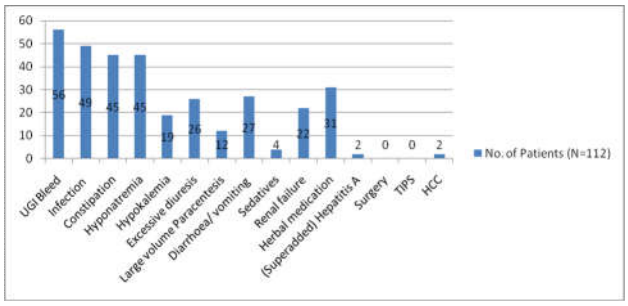

Figure-2 precipitating factors of hepatic encephalopathy

Among infection spontaneous bacterial peritonitis was most common infection 20(40.81%) followed by urinary tract infection and Chest infection 11(27.5%), Leg infection(cellulitis) found in 7(22.5%) patient. No cases of hepaticencephalopathy found following TIPS and surgery.Out of 112 hepatic encephalopathy patient 42(38%) had one, 35(31%) had two and 35(31%) had three precipitating factors, 60% of patient with more than two precipitating factors of hepatic encephalopathy presented with grade IV hepatic encephalopathy.(Figure-3)

Grade	Number of precipitating factors		
	1(n=42)	**2(n=35)**	**>=3(n=35)**
I(n=32)	20(47%)	11(31%)	1(3%)
II(n=11)	5(12%)	5(14%)	1(3%)
III(n=32)	10(24%)	10(29%)	12 (34%)
IV(n=37)	7(17%)	9(6%)	21 (60%)
TOTAL	42	35	35

Figure 3 precipitating factors correlated with grades of hepatic encephalopathy

After recovery from hepatic encephalopathy upper GI endoscopy was done in 85 patient, 77(90.59%) had esophageal varices, 11(12.94%) portal hypertensive gastropathy, erosive gastropathy in 16(18.82%), Peptic ulcer in 14(16.47%) and endoscopy was normal in 4(4.70%0 patient.76(67.85%) recovered and discharge from hospital, 32(28.57%) patient died in hospital and 4 (3.58%) lost follow up because leave hospital on request against medical advice. Of the total death 8(25%) patient died had one precipitating factor, 11(34%) died had two and 13(41%) died had more than two precipitating factors(Figure-4).

no. of precipitating factors (per patient)	mortality (%)(n=32)
1(n=42)	8 (25%)
2(n=35)	11 (34%)
>=3(n=35)	13 (41%)
TOTAL	32 (100%)

Figure 4 no. of precipitating factors and mortality

On univariable analysis upper GI bleeding as a precipitating factor had highest mortality irrespective of whether associated with one or more than one precipitating factor (62%) in both cases. In contrast infection results in greater mortality when associated with more than one precipitating factor (25% with one compared to 45% with more than two precipitating factors).(Figure-5)

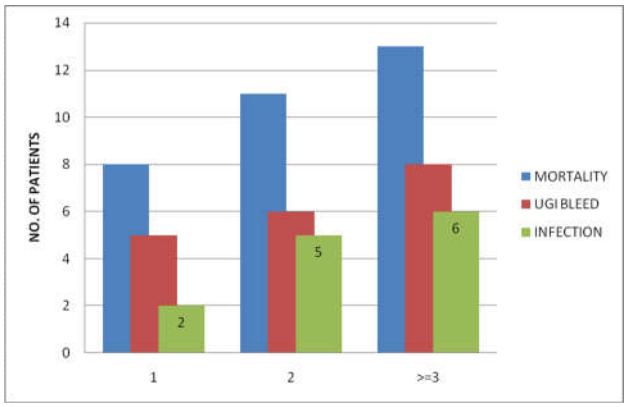

Figure5 univariable analysis of ugi bleed and infection with respect to mortality

DISCUSSION

Hepatic encephalopathy is a well-recognized clinical complication of cirrhosis of liver (CL) and the presence and prompt identification of well-defined precipitating factors is extremely important in early treatment and better outcome of this fatal condition. It is a major neuropsychiatric complication of cirrhosis of liver and its appearance is indicative of a poor prognosis. Patients with cirrhosis of liver may have either a chronic neuropsychiatric state due to portal-systemic shunting (portosystemic encephalopathy) or have an acute episode with some precipitating factor labeled as HE.

The clinical manifestations of this syndrome range from subtle abnormalities detectable only by psychometric testing to overt hepatic encephalopathy. However, most manifestations of hepatic encephalopathy are reversible with medical treatment. Therefore early diagnosis, detection of precipitating factors and effective treatment of HE have important prognostic implication in cirrhotic patients. In keeping with this, the present study was undertaken comprising of 112 patients of chronic liver disease presenting with overt hepatic encephalopathy, who were admitted in the Departments of Medicine and Gastroenterology in Gauhati Medical College and Hospital, Guwahati.In our study we found 86 males, 26 females with a male to female ratio of 3.3:1 out of 112 patient cirrhosis of liver with hepatic encephalopathy. Higher incidence of liver disease with HE were seen amongst males in other study by Mital *et al* (1967), Dhiman *et al* (2000) and Das *et al* (2001) found male to female ratios of 38: 19(2:1), 33 : 7(4.7:1) and 139 : 26(5.3:1), respectively. Majority of our patients above age of 40years and highest number of patient found in grade IV hepatic encephalopathy. Similar findings in the past were reported by Dhiman *et al* (2000) and Weissenborn (2001).

In our study, predominant cause of cirrhosis is alcoholic cirrhosis 66.08%, followed by cryptogenic (16.07%), Hepatitis B (13.39%) and Hepatitis C (4.46%). Menon K.V. N. (2001) found that alcoholism is the main cause of liver cirrhosis, the fourth commonest cause of death in males in USA. Most of alcoholic cirrhosis in the present series was found to be male alcoholics with consumption of alcohol for a mean duration of 18 yrs. It has been documented that liver disease occurs more commonly with consumption of illicit liquor despite its lower alcohol content and liver involvement appears earlier in Indians. This may be due to smaller built and possibly unknown individual susceptibility factors or adulterants in the alcohol consumed here as reported by Singh *et al*(1959) and Parikh *et al*(1998). Gastro intestinal bleeding (50%), infection (43.75%), constipation (40.17%) were the common precipitating factors found in this study. Other causes included dyselectrolytemia (hyponatremia in 40.17% and hypokalemia in 16.96%), drugs (overuse of diuretics in 23.21% and sedatives in 3.57%). Most of the patients with electrolyte imbalance had history of diarrhea or vomiting or were already on diuretic therapy Similar finding were also observed by different authors e.g. Conn *et. al.*[17] reported GI Bleeding (18%), Constipation(3%), Infection(4%), hypokalmia (9%), excess dietary protein(9%) . Mumtaz K *et.al*(2010)- spontaneous bacterial peritonitis (SBP) (20.5%), Constipation (18.3%),urinary tract infections(15.3%) and upper gastrointestinal bleeding (13.6%) hypokalemia (6.4%) and hyponatremia in (3%) patients.

In this study, 42 out of 112 patients (37.5%) had one precipitating factor of hepatic encephalopathy, 35 (31.25%) patients had two precipitating factors and 35 (31.25%) patients had more than two precipitating factors of hepatic encephalopathy. The occurrence of more than one precipitating factors was also noted by Mumtaz K *et al* (2010) and found that about 35% had more than one precipitating factor while 53% had only one precipitating factor In our study higher incidence of mortality and longer hospital stay (more than 4 days) were observed in patients having more than two precipitating factors. 25% of the expired patients had only one precipitating factor, 34% had two and 41% had more than two precipitating factors of hepatic encephalopathy. Mumtaz K,*et al* (2010) also had a similar observation and noted that lesser the number of precipitating factors , lesser the grade of hepatic encephalopathy

On univariable analysis of UGI bleed and infection with respect to mortality, our study revealed that UGI bleeding as a precipitating factor resulted in higher mortality rate irrespective of whether associated with one or more than one precipitating factor (62% in both cases). In contrast, Infection results in greater mortality when associated with more than one precipitating factor (25% with one precipitating factor compared to 45% with more than 2 precipitating factors). Similar findings were noted in a recent study carried out in Egypt by Gad. YZ (2012).

CONCLUSION

Our study concluded that different precipitating factors play major role in development of hepatic encephalopathy, common precipitating factors being upper GI bleeding, infection, dyselectrolytemia and over use of diuretics. Mortality is more in those having upper GI bleeding and higher number of precipitating factors.

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