

Precipitating factors of hepatic encephalopathy at a tertiary care hospital Jamshoro, Hyderabad

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Abstract

Objective: To determine the precipitating factors of hepatic encephalopathy (HE) in patients with liver cirrhosis at Liaquat University Hospital Hyderabad/Jamshoro.

Methods: This hospital based descriptive study was conducted from April 2007 to September 2007. All the patients who were more than 12 years of age and were diagnosed as hepatic encephalopathy were studied. During this period, 87 patients of hepatic encephalopathy were admitted. All patients were carefully examined, relevant investigations were performed and data was collected through pre-designed proforma.

Results: Male patients were 65 (75%), above 40 years of age 58 (67%), belonging to interior/periphery of Sindh 54 (62%), in grade IV of hepatic encephalopathy 70 (80%) and Anti-HCV positive were 52 (60%). The most common precipitating factors detected were infection 58 (67%), constipation 43 (49%) and gastrointestinal bleeding 39 (45%). Out of 87 patients, 68 had increased total leucocytes count, 09 patients had hypokalaemia, 24 patients, hyponatraemia, 64 hypoalbuminaemia and 54 patients had a disturbed coagulation profile. Fifty nine patients recovered and were discharged while 20 patients expired. Majority of expired patients had Child-Pugh score 10-15 and were in grade IV of hepatic encephalopathy.

Conclusion: The study concluded that there were different factors which play a key role in hepatic encephalopathy. In these factors, infection was the most common (JPMA 59:683; 2009).

Introduction

Hepatic encephalopathy (HE) is a syndrome observed in patients with cirrhosis. It is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of other known causes of brain disease.¹ It is characterized by personality changes, intellectual impairment and a depressed level of consciousness. An important prerequisite for the syndrome is diversion of portal blood into the systemic circulation through portosystemic collateral vessels. Hepatic encephalopathy may develop in patients without cirrhosis who have undergone portocaval shunt surgery. 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. About 30% of patients with cirrhosis die due to hepatic coma (Hepatic Encephalopathy). Cirrhosis of liver is a common cause of mortality amongst Pakistani population and a frequent cause of admission in our hospitals² and majority of patients with chronic liver disease have evidence of hepatitis B (22%), hepatitis C (28%) viral infection.³

The nitrogenous substances derived from the gut adversely affect brain function and play a role in its pathogenesis. These compounds gain access to the systemic circulation as a result of decreased hepatic function or portal-systemic shunts. In the brain these compounds produce

alterations of neurotransmission that affect consciousness and behaviour. Abnormalities in glutamatergic, serotonergic, g-aminobutyric acid-ergic (GABA-ergic) and catecholamine pathways have been described in experimental HE. Ammonia is a key factor in the pathogenesis of HE.⁴ In acute and chronic liver disease increased arterial levels of ammonia is seen. The blood-brain barrier permeability to ammonia is 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.⁵ 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.

According to auspices of the World Congress of Gastroenterology, there are four types of hepatic encephalopathy (a) Acute, (b) Recurrent (c) Persistent (d) Minimal or sub-clinical. The hepatic encephalopathy is a diagnosis of exclusion⁶ and 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 parameters, one is to avoid the precipitating factor and the second is to treat the precipitating factor.

Therefore, considering the increasing incidence of hepatitis and hepatic coma with time, this study was carried out with the main objective of ascertaining the frequency of various precipitating factors and to assess their disease severity according to Child-Pugh classification in patients presenting with hepatic encephalopathy at Liaquat University Hospital Hyderabad, a 1500 bedded tertiary care teaching hospital which covers both urban as well as rural population of Sindh province, Pakistan. Early diagnosis and treatment of precipitating factor/s 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 descriptive study conducted on 87 patients in the Department of Medicine, Liaquat University Hyderabad/Jamshoro from April 2007 to September 2007. All patients who were above 12 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 a diagnosis of exclusion.⁷ Therefore, HE was diagnosed after excluding metabolic disorders, infectious diseases, intracranial vascular events and intracranial space occupying lesions, knowledge of existing acute or chronic liver disease, the history of precipitating factors, and/or a prior diagnosis of hepatic encephalopathy 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 about fever, GI bleeding, including haematemesis and malaena, constipation / diarrhoea / vomiting, diet and any trauma or surgery. The drug history, particularly, use of diuretics, sedatives or tranquilizers, non steroid anti-inflammatory drugs (NSAID), anti-tussives and past history of hospital admission was also inquired. All patients were examined carefully and presence of fever, anaemia, jaundice, dehydration and asterixis was noted.

The routine and relevant investigations carried out were, full blood count, urine examination, blood urea and creatinine, blood glucose, chest radiograph, serum electrolytes, serum albumin, coagulation profile, ultrasound of abdomen, liver function test (LFT), HbsAg and Anti-HCV (if not previously diagnosed and not a known case). Due to the lack of facility for testing the serum ammonia level in the laboratory of Liaquat University Hospital, we were unable to

perform ammonia levels and also an elevated blood ammonia level does not always detect and indicate hepatic encephalopathy.⁸ Therefore the method of exclusion to detect hepatic encephalopathy were used. The hepatic encephalopathy was graded according to the West Haven classification system.⁹ The severity of liver cirrhosis was assessed through Child-Pugh score system (Table-1).¹⁰

Table-1: Child-pugh score chart.

Parameter	Numerical Score		
	1	2	3
Ascites	None	Slight	Moderate to severe
Serum bilirubin (mg/dl)	<2	2 - 3	>3
Albumin (gm/dl)	>3.5	2.8 - 3.5	<2.8
Prothrombin time (sec)	1 - 3	4 - 6	>6
Encephalopathy	None	Slight to moderate	Moderate to severe

Results

During our study period 87 patients were diagnosed as hepatic encephalopathy, 70 (80%) grade IV, 08 (9%) grade-III, 05 (6%) grade-II and 04 (5%) were in grade I. Out of 87 patients 65 (75%) were males and 22 (25%) were females. The majority of the patients 54 (62%) were from interior / periphery of Sindh Province while 33 (38%) belonged to Hyderabad City. About 58 (67%) were more than 40 years old except 09 (10%) patients who were less than 20 years of age and 20 (23%) were between 20-40 years of age.

Anti-HCV was positive in 52 (60%) patients in which 32 were known cases, while 20 were detected during hospital admission. HBsAg was positive in 18 (16%) patients in which 12 were known cases while 05 were diagnosed during hospital admission, 06 (5%) patients were positive for both hepatitis B and hepatitis C. while 11 (13%) patients were B and C negative.

The most common precipitating factor of hepatic encephalopathy found in our study was infection, however, other factors such as, constipation, GI bleeding, electrolyte imbalance, high protein diet, hypoglycaemia, drugs (sedatives / tranquilizers / diuretics), hypoxia and trauma / surgery were also identified (Table-2). In 05 (6%) patients no factor was found.

The biochemical analysis of blood count showed low haemoglobin levels in 53/87(61%) patients, increase in total leukocyte count (TLC) in 68/87 (78%) patients and thrombocytopenia in 57/87 (66%) patients. The levels of serum electrolyte showed hypokalaemia in 29 (33%) patients and hyponatraemia in 24/87 (26%) patients. Hypoglycaemia was found in 20 (23%) patients. In 46 (53%) patients the urea was high and creatinine was above normal limits in 40 (46%) patients. Hypoalbuminaemia (serum albumin <3 mg/dl) was found

Table-2: Frequency of precipitating factors (n = 87).

Precipitating Factor	n (87)	%
Infection	58	67
Constipation	43	49
GI Bleeding	39	45
Hypokalaemia	29	33
Dietary Protein	24	26
Hypoglycaemia	20	23
Sedatives	05	06
Tranquilizers	03	03
Trauma / Surgery	04	05
Hypoxia	03	03
Diuretics	18	21
No Factor	05	06

in 51 (59%) patients. The coagulation profile was > 5 seconds in 47 (54%) patients.

Out of 87 patients 59 (68%) recovered and were discharged, 05 were insistent for discharge on request from hospital and 03 left the hospital against medical advice while 20 (23%) expired in which 13 were males. The child - Pugh score of 16 expired patients was between 10 -15 (class C) while 4 patients had a score range between 7-9 (Class B). Out of 20 patients which expired 15 were in grade-IV while 05 were in grade III of hepatic encephalopathy.

Discussion

Hepatic Encephalopathy is a life threatening complication of liver cirrhosis. A recent conference proposed nomenclature for categorizing hepatic encephalopathy. Type A, HE describes encephalopathy associated with acute liver failure. Type B, HE describes encephalopathy associated with portal-systemic Bypass and no intrinsic hepatocellular disease. Type C, hepatic encephalopathy describes encephalopathy associated with Cirrhosis and portal hypertension or portal-systemic shunts. Type C, hepatic encephalopathy is, in turn, subcategorized as episodic, persistent, or minimal.

According to our study, majority of patients were from interior / periphery of Sindh province and this may be because of poor hygiene, lack of awareness, motivational deficiency and improper counseling. We also found that majority of the patients were more than 40 years of age, however a study conducted in Balouchistan, Pakistan on spectrum of chronic liver disease, also had similar observations.¹¹ About gender, the male were dominant in our study, while similar findings were observed in a retrospective study, of hepatic encephalopathy in Saudi Arabia.¹²

In our study, the majority of patients were HCV positive and in our country this is a common cause of liver cirrhosis. On the other hand, in the western world alcoholism is the main cause of liver cirrhosis where there is definite male preponderance to the extent of 77:33, making it the

fourth commonest cause of death in males in USA.¹³

Infection, gastrointestinal bleeding and constipation were common precipitating factors detected in our study. On the other hand, Gastrointestinal bleeding (GIB) and infections remained the most common precipitating factors in a study conducted in the province of Punjab¹⁴ and some other studies.¹⁵ However, infection, was a less precipitating factor of HE in the study of Faloon.¹³

The present study also identified electrolyte imbalance in patients with hepatic encephalopathy and this is similar to the study by Hassanein et al.¹⁶ Most of the subjects with electrolyte imbalance had history of diarrhoea/vomiting or were already on diuretic therapy. Constipation is the second precipitating factor of HE in our study, similar to the study of Gómez et al.¹⁷ In our study we identified low haemoglobin, thrombocytopenia and hypoalbuminaemia in patients with hepatic encephalopathy which is suggestive of advanced liver cirrhosis.¹⁸ Increased total leukocyte count (TLC) suggests infection which was the common precipitating factor in our study. In the present study there was also a disturbance in the level of serum urea and creatinine similar to the study by Dasarathy et al.¹⁹

Our study, found 04 patients who used sedatives and tranquilizers and the history taken from the attendants and patients themselves (when recovered from hepatic coma or in a hepatic encephalopathy grade 0 or 1) were suggestive of self prescription of such drugs and this shows the lack of proper counseling and knowledge in these patients. The hypoglycaemia was also a precipitating factor detected in our study; two patients were diabetic, already on oral hypoglycemic therapy and in these patients the hypoglycaemic attacks may be due to lack of guidance regarding drug and nutrition. In these patients the dose must be adjusted or drug should be withdrawn because of development of hepatorenal syndrome (complication of liver cirrhosis) in which the kidney function becomes compromised. The recovered patients usually became depressed or tense and have a poor intake due to fear of recurrent attacks of hepatic encephalopathy. The intake of high protein diet was also a precipitating factor found in our study due to lack of guidance regarding nutritional supplements for the patient or unavailability of a nutritionist.

Hepatic encephalopathy is a diagnosis of exclusion²⁰ hence, such a tool was used in our study to detect hepatic encephalopathy and this correlates with the study of Alam et al,²¹ who studied the precipitating factors of hepatic encephalopathy without considering the serum ammonia levels as a diagnostic tool.²¹ Evidence exists that serum ammonia has low sensitivity in hepatic encephalopathy and is not always raised in HE therefore, it is not a good screening tool.²²

The mortality rate of hepatic encephalopathy is high

as shown by the study of Sargent et al²³ whereas, in our study mortality was 23% and the majority were, Class C, Child-Pugh classification. In 6% patients we did not find any predisposing factors. However, we can predict other factors, such as porto-systemic shunts, sodium valproate (as in our study, one patient was already on Valproic acid) and zinc deficiency.²⁴

Specific precipitating factors have specific treatment and with proper treatment and care hepatic encephalopathy is frequently reversible. In fact, complete recovery is possible, especially if the encephalopathy was triggered by a reversible cause. However, people with chronic liver disorders are susceptible to future episodes of encephalopathy. Therefore, our goal should be to identify and manage the particular precipitating factor and effective measures and steps must be taken especially in remote areas where there is lack of medical facilities. Therefore, in this context we can prolong the life expectancy and improve the quality of life in patients with hepatic encephalopathy.

Conclusion

From our study it was concluded that there are different factors which play a key role in precipitating hepatic encephalopathy. Among these factors, infection, constipation and gastrointestinal bleeding are predominant. Hepatic encephalopathy was more common in patients from interior/peripheral part of province Sindh, Pakistan. There is a definite need for health education and proper counseling in patients who were diagnosed as liver cirrhosis in relation to hepatic encephalopathy.

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