August 2010

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ORIGINAL ARTICLE

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ABSTRACT

Objective: To determine precipitants of hepatic encephalopathy (HE) and their impact on hospital stay and mortality.
Study Design: Cross-sectional, analytical study.
Place and Duration of Study: The Aga Khan University Hospital, from January 2005 to December 2007.
Methodology: Consecutive patients admitted with different grades of HE were evaluated between January 2005 and December 2007. The precipitants of HE were correlated with the different grades of HE, and length of hospital stay and mortality. Chi-square test was used to compare the proportion of precipitating factors versus hospital stay and grade with significance at $p < 0.05$.
Results: Of the 404 patients 252 (62%) were males. Hepatitis C virus was the cause of cirrhosis in 283 (70%); Child Turcotte Pugh (CTP) class C was present in 317 (78%) patients. On presentation, 17% patients had grade 1 HE while 44%, 29% and 10% had grades 2, 3 and 4 respectively. The most common precipitant of HE was spontaneous bacterial peritonitis in 83 (20.5%), constipation in 74 (18.3%) and urinary tract infection in 62 (15.3%). One hundred and forty (35%) patients had ≥ 2 precipitating factors while no precipitant was noted in 50 (12%) patients. Mean hospital stay was 4±3 days. The lesser the number of precipitants, shorter was the length of stay ($p < 0.01$) and lesser was the grade of HE ($p=0.025$). Complete reversal of HE was noted in 366 patients (91%) while the remaining had grade 1 HE on discharge. Nine (2.2%) patients died during the hospital stay. No mortality was noted in patients without precipitants.
Conclusion: Patients presenting with ≥ 2 precipitating factors and advanced grade of HE had a prolonged hospital stay. Moreover, patients without precipitants had better outcomes.

Key words: *Hepatic encephalopathy. Cirrhosis. Hepatitis C. Precipitant. Outcome.*

INTRODUCTION

Hepatic encephalopathy (HE) is present in upto 70% of all patients with cirrhosis, including patients with abnormalities demonstrable only by psychometric testing.[1,2] It accompanies portal-systemic shunting of venous blood that occurs either spontaneously, due to portal hypertension, or surgically following porto-caval anastomosis surgery or trans-jugular intra-hepatic porto-systemic stent shunt (TIPS) aimed at relieving portal hypertension. Patients with HE characteristically present with the development of acute encephalopathy with an abrupt decline in the level of consciousness, often manifested as confusion or coma. A precipitating factor can be usually identified, and the treatment of the episode is directed towards the correction of this precipitant. Once the precipitating condition has been resolved, the encephalopathy also subsides usually.[3]

The most common precipitant identified is gastro-intestinal bleeding,[4] which is responsible for upto 34% cases of HE.[5] Gastrointestinal bleeding contributes approximately 20 grams of proteins per 100 ml of blood,[5] leading to an increased production of nitrogenous products especially ammonia from the gut. Other precipitants include constipation, excessive dietary protein, especially animal protein hypovolemia, shock, hypokalemia and alkalosis.[6,7] Use of medications acting on the CNS such as opiates and benzodiazepine, presence of infections and shunt procedures have also been implicated in the precipitation of HE.[8-10]

Neurological deficits in patients with HE secondary to a precipitating event are usually completely reversible following correction of the cause, and these patients have a good prognosis.[3] However, it is imperative that such precipitating events are identified earlier, and patients' attendants counseled regarding their identification to ensure that medical care is provided promptly, and thus subsequently ensuring better patient outcomes.

The aims of this study were to evaluate the precipitant factors of hepatic encephalopathy and their impact on hospital stay and mortality.

METHODOLOGY

A hospital based cross-sectional study of patients presenting to The Aga Khan University Hospital, Karachi, between January 2005 and December 2007 with hepatic encephalopathy was carried out. All patients with liver disease who were diagnosed as

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Received November 18, 2009; accepted June 07, 2010.

having acute HE secondary to liver cirrhosis and portal hypertension and classified as type C HE according to the working party classification of HE by Fereci *et al.*[11] were included. The diagnosis of acute HE being made on the basis of a detailed history and physical examination, West Haven criteria and Number Connection Test (NCT). Patients classified as type A HE (acute liver failure) and type B HE (secondary to portal systemic bypass without intrinsic hepatocellular disease)[11] were excluded. Also excluded were patients with concomitant uremic, cerebral, septic, and anoxic encephalopathy. Renal impairment was defined as serum creatinine level ≥ 2 mg/dl on admission and treated with intravenous fluids and albumin whenever indicated. Liver cirrhosis was diagnosed on the basis of clinical, biochemical and ultrasonological examination. Data related to present and past medical history at the time of admission was collected from the medical records. The clinical findings on examination including presence of jaundice, pallor, fever, asterixis, and ascites were recorded. Demographics and laboratory parameters (complete blood count, liver function tests, renal function tests, serum albumin levels, coagulation profile, urine analysis, and blood cultures) were collected. The findings of abdominal ultrasound including liver and spleen size, parenchymal echogenicity, portal vein diameter, and ascites was noted in the questionnaire. An ascitic tap was performed in all patients with ascites and sent for detailed report and culture in order to diagnose spontaneous bacterial peritonitis. Urine detailed report and culture was also sent in all patients, along with blood culture in order to diagnose any infection. A chest X-ray was also performed in all patients on arrival in Emergency Department.

Patients were classified according to the Child Turcotte Pugh (CTP) criteria and etiology of cirrhosis and grade of hepatic encephalopathy on admission was noted. Grading of hepatic encephalopathy was performed according to the West Haven Criteria.[11] All the patients were assessed with these criteria and the Number Connection Tests-A (NCT-A) on daily basis for noting an improvement/deterioration in HE grade. Improvement of HE was defined as complete reversal of clinical symptoms on the basis of the West Haven criteria and NCT-A. Patients with HE of ≥ grade 1 on discharge were considered as 'did not show improvement'.

All patients underwent standard management during their hospital stay which included use of ammonia lowering and gut cleansing agents such as lactulose and metronidazole, along with dietary protein restriction to 60 gms/day until HE improved. Placement of a nasogastric tube for feeding was considered in all patients with HE grade > 2. Proton pump inhibitors, vitamin K and fresh frozen plasma were used in patients with upper gastrointestinal bleeding and deranged coagulation. Patients who presented with upper gastrointestinal bleeding subsequently underwent an upper gastrointestinal endoscopy upon improvement of HE or earlier in cases of continuing bleeding.

The outcomes assessed were the hospital stay and death during the hospital admission.

Statistical analysis was performed using the Statistical Package for Social Science (SPSS) [15.0, standard version, copyright © SPSS; 1989-02]. Descriptive analysis of patients with hepatic encephalopathy was performed for demographic and laboratory parameters and results presented as mean ± standard deviation for quantitative variables. Length of duration of hospital stay was divided into two categories; less than 4 days and more than and equal to 4 days and compared with number of precipitating factors, child's Pugh class and grades of encephalopathy using χ^2 test for categorical variables. Relationship of number of precipitating factors was categorized into 2 categories; one precipitating factor, and more than and equal to 2 precipitating factors and compared it with different parameters using χ^2 chi-square test. All p-values were two sided and considered as statistically significant if < 0.05.

RESULTS

A total of 404 patients of cirrhosis with HE were studied, of whom 252 (62%) were males. Mean age was 55 ± 9 years; other demographic and laboratory parameters are shown in Table I. There were 291 (72%) patients with cirrhosis due to hepatitis C infection, while 32 (8%) had hepatitis B, non-B, non-C cirrhosis was seen in 73 (18%) patients. Hepatitis B and D related cirrhosis was noted in 7 (1.7%) patients while one patient (0.3%) had hepatitis B, C and D infections simultaneously.

Table I: Demographics and laboratory parameters of all patients with hepatic encephalopathy.

Variables	Mean ± Standard Deviation
Age (years)	55 ± 9
Hemoglobin (g/dl)	11.0 ± 2.0
WBC count (x10^9/l)	9.1 ± 5.4
Platelet count (x10^9/l)	109.5 ± 60.8
Total bilirubin (mg/dl)	4.3 ± 5.3
Albumin (g/l)	2.3 ± 0.5
Prothrombin time (seconds)	21.4 ± 6.4
Sodium (mEq/l)	132 ± 7.3
Potassium (mEq/l)	4.2 ± 0.8
Creatinine (mg/dl)	1.6 ± 1.6

Three hundred and seventeen (78%) patients had CTP class C cirrhosis, while 76 (19%) and 11 (3%) patients had CTP class B and A cirrhosis respectively. Seventy (17%) patients were in grade 1 hepatic encephalopathy, while 178 (44%) had grade 2, 118 (29%) grade 3 and 38 (10%) had grade 4 HE on presentation based on the West Haven criteria and NCT-A. The common comorbid conditions present were Diabetes mellitus in 165 (41%), hypertension in 67 (17%) and ischemic heart disease in 28 (7%).

Different precipitants of HE were identified in 354/404 (88%) patients while none could be found in 50 (12%) patients. The most common precipitant identified was spontaneous bacterial peritonitis (SBP) which was seen in 83 (20.5%) patients. Constipation in 74 (18.3%), urinary tract infections in 62 (15.3%) and upper gastrointestinal bleeding in 55 (13.6%) patients were the other precipitating factors identified. Electrolyte abnormality including hypokalemia were seen in 26 (6.4%) while hyponatremia was present in 12 (3%) patients. Acute HE secondary to benzodiazepine use such as midazolam was noted in 3 patients. Two hundred and fourteen (53%) patients had one identifiable precipitant, while 122 (30%) patients had 2 and 18 (5%) patients had three precipitating factors respectively at the time of presentation.

Mean hospital stay was 4 ± 3 days; the duration of hospital stay of 210 (52%) patients was < 4 days, of which 110 patients (55%) were found out to have only one precipitating factor. There were 194 patients (48%) who had a mean stay of > 4 days, out of which 85 (44%) had ≥ 2 precipitating factors contributing to development of HE ($p < 0.05$). Forty (80%) patients, without any identifiable precipitants had a stay of < 4 days (Table II). Out of the 210 patients with a hospital stay of < 4 days, 142/210 (67%) had grade 1 or 2 HE on presentation, while 88/194 patients (45%) with a stay of > 4 days had stages 3 or 4 HE respectively on presentation (p-value < 0.05). Additionally advanced grades of HE were noted in patients with ≥ 2 precipitants on presentation ($p < 0.01$).

Table II: Relationship of number of precipitants and grades of hepatic encephalopathy with the hospital stay.

Factors	Duration of hospitalization		p-value
	< 4 days (n= 210)	≥ 4 days (n=194)	
Number of precipitating factor			
None	40 (19%)	10 (5%)	
One	115 (55%)	99 (51%)	< 0.001
Two	50 (24%)	72 (37%)	
Three	5 (2%)	13 (7%)	
Child's Pugh classification			
A	6 (3%)	5 (3%)	
B	46 (22%)	30 (15%)	0.243
C	158 (75%)	159 (82%)	
Clinical grades of encephalopathy			
Grade 1	36 (17%)	34 (18%)	
Grade 2	106 (50%)	72 (37%)	0.009
Grade 3	56 (27%)	62 (32%)	
Grade 4	12 (6%)	26 (13%)	

Improvement of HE defined as complete reversal of clinical symptoms, was noted in 367/404 (91%) patients. Out of these 50 patients without any identifiable precipitant on admission, 49 (98%) had an improvement in HE on discharge.

Similarly, 191 patients (89%) with one precipitant showed an improvement in HE while improvements were also noted in 113 patients (93%) with 2 precipitants and 14 patients (77%) with 3 precipitating factors ($p < 0.01$).

Nine (2.2%) patients died during the hospital stay, of whom 3 had ≤ 1 precipitating factor and 6 had ≥ 2 precipitating factor (p=0.06, Table III). There was no mortality found in patients without any precipitating factor. There was no significant association between the number of precipitating factors and severity of cirrhosis on the basis of CTP score (Table III).

Table III: Relationship of numbers of precipitating factors with different parameters.

	≤ 1 precipitant n=264	≥ 2 precipitant n=140	p-value
Childs class			
A	7 (3%)	4 (3%)	
B	53 (20%)	23 (16%)	0.66
C	204 (77%)	113 (81%)	
Grades of HE			
Grade 1	49 (19%)	21 (15%)	
Grade 2	127 (48%)	51 (36%)	0.025
Grade 3	68 (26%)	50 (36%)	
Grade 4	20 (7%)	18 (13%)	
Duration of stay			
< 4 days	155 (59%)	55 (39%)	< 0.01
≥ 4 days	109 (41%)	85 (61%)	
Outcome			
Alive	261 (99%)	134 (95%)	0.06
Dead	3 (1%)	6 (5%)	

DISCUSSION

Patients with chronic HE are known to have better long term (5 years) survival than those who develop HE acutely (100% vs. 70% survival).[13] However, prognosis in the latter group can be improved if the precipitating factors are recognized early and managed accordingly.[14] This study was aimed at identifying precipitating factors in patients presenting to the centre with an acute onset of HE, type C.

It is the largest study on hepatic encephalopathy about its precipitating factors and predictors from our region. The results showed that 70% patients suffered from hepatitis C, which is consistent with other studies,[15,16] thus reiterating the significant disease burden posed by this infection, which is on a rising trend in Pakistan. Infection was identified as the main precipitant of HE in upto 35% patients, with around 20% patients suffering from SBP and 15% from urinary infection which is previously reported in patients with cirrhosis from Pakistan.[17] Literature from developed countries however, has not identified infections as amongst the most common precipitating events,[18] possibly due to more awareness and better nutrition status in their patients. Patients in local setting are usually severely malnourished not only because of their disease but also because of food faddism and taboos regarding their diet.[19] Strict dietary restrictions on these patients lead to anorexia

and malnutrition, and eventually lowering their immunity and making them more susceptible to infections. In the developing world, gastrointestinal bleeding and constipation have been identified as major precipitating events of HE.[18] This is considered to be secondary to increased ammonia production and absorption, and were noted in 13.6% patients.

Well-recognized factors, which tend to precipitate hepatic encephalopathy in patients with underlying liver cirrhosis, include an increased dietary protein load, constipation, and gastrointestinal hemorrhage, which can be classified as gut factors, and are consistent with the hypothesis that gut-derived nitrogenous constituents of portal venous blood contribute to HE. Some of these are neuroactive and can traverse the blood-brain barrier, subsequently resulting in altered brain function. The importance of gut factors in the pathogenesis of HE is also suggested by improvement in symptoms following evacuation of the bowel and by dietary protein restriction.[20] Any factor that increases portal-systemic shunting may also precipitate or exacerbate HE.[21] Factors other than liver failure, such as uremia, hypoglycemia, and use of sedative or hypnotic drugs, may also contribute to encephalopathy in such patients.

Electrolyte imbalances, also correlate with the severity of the liver disease,[22] was also found. It is explained by the use of diuretics in patients who have ascites secondary to decompensated liver disease. Therefore, caution must be exercised and these patients need to be followed vigilantly with frequent monitoring of serum electrolytes to avoid any precipitation of HE.

In patients with low reserves of hepatic function, the hepatic encephalopathy can be a chronic condition and no precipitants can be established. The low reserve predisposes the patient to development of spontaneous hepatic encephalopathy, which was noted in 11.4% patients, in whom no precipitating factors could be identified. Interestingly the improvement in HE in this group of patients without any precipitant was best as compared to those with the precipitant induced HE.

This study identified a longer hospital stay in patients with ≥ 2 precipitating factor, and in those who presented with grades 3 or 4 HE. Two-thirds of our patients who died during the hospital stay had ≥ 2 precipitating factors, while patients with no identifiable precipitating event had no mortalities during their hospital stay. Similarly, patients with ≥ 2 precipitant were mostly suffering from grade 3 and 4 HE on initial presentation and have a prolonged hospital stay. In a study by Strauss *et al.*[9] higher mortality rates were noted in acute HE, associated with grades 3 and 4 of HE and more precipitating factors. This indicates that patients with increased number of precipitants tend to have a worse outcome in terms of both duration of hospital stay and mortality. Moreover, the improvement in HE was better in patients with less number of precipitants and early grades of HE.

It is, therefore, crucial that precipitating factors are identified earlier, especially in patients with severe liver disease, and appropriate treatment initiated soon, with an aim to treat and manage them, and subsequently ensuring better outcomes. It is also important to educate the patients and their families about these precipitants to ensure earlier presentation, diagnosis, and management of acute HE.

CONCLUSION

Precipitant-induced hepatic encephalopathy is a common complication of cirrhosis. Infections, constipation and gastrointestinal bleeding were identified as the major precipitants in this study. Once the precipitating condition is resolved the encephalopathy also typically disappears, with the patient recovering to his or her previous state. Patients with ≥ 2 precipitating factors and grades 3 or 4 HE on admission was associated with worse outcomes.

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