Original Article APMC-336

Analysis of Identifiable Risk Factors Precipitating Acute Encephalopathy in Chronic Liver Disease, At PNS Shifa Karachi

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Submitted for Publication
07-09-2016
Accepted for Publication
21-09-2016

ABSTRACT

Background: Hepatic encephalopathy is one of the most debilitating manifestations and frequent complication in patients suffering from chronic liver disease. **Objective:** To determine the frequency of identifiable risk factors precipitating hepatic encephalopathy in patients with chronic liver disease, at PNS Shifa Karachi and their correlation with grades of hepatic encephalopathy, length of hospital stay and mortality. **Study Design:** It was a cross sectional study **Period:** 24 Oct 2014 to 31 Aug 2015. **Methods:** during which 96 patients of clinically diagnosed hepatic encephalopathy associated with CLD were enrolled. Hepatic encephalopathy was graded and precipitating factors identified based on history, clinical examination and relevant laboratory investigations. Management was carried out according to the latest guidelines. Patients were followed up till discharge/death from the hospital and duration of hospital stay. Mortality was recorded. **Results:** Majority of patients (57.3%) had one precipitating factor; more than one factor was found in 43.5%. Gastrointestinal bleed was the most common precipitating factor identified in 42 (44%) patients followed by Infection in 36 patients (38%), diuretic therapy in 10 patients associated with electrolyte imbalance (11%), constipation in 8 (9%) patients, use of high protein diet in 7(6.72%), sedative /tranquilizers in 4(3.84 %) and large volume paracentesis in 4 (3.84%) were least common factors, Mean hospital stay was 11 ± 1.8 days. Mortality was 15 % with 14 patients expiring during the hospital stay. There was no statistically significant correlation between the various precipitating factors and grade of hepatic encephalopathy, length of hospital stay and mortality ($p > 0.05$). **Conclusion:** Commonest precipitating factors of hepatic encephalopathy in patients of liver cirrhosis are, gastrointestinal bleed, infection, electrolyte imbalance and constipation. There is no correlation between the various precipitating factors and grade of hepatic encephalopathy, length of hospital stay and mortality. There is a need to improve the awareness of patients and attendants about the precipitating factors and their avoidance. This also includes effective control measures against rising cases of hepatitis C and hepatitis B as it is the leading cause of liver cirrhosis in Pakistan.

Keywords: Hepatic encephalopathy; liver cirrhosis; identifiable precipitating factors; hospital stay; mortality.

Article Citation: Iqbal J, Parvez MA, Alam MM. Analysis of Identifiable Risk Factors Precipitating Acute Encephalopathy in Chronic Liver Disease, At PNS Shifa Karachi. APMC 2016;10(4):222-227.

INTRODUCTION

Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction after exclusion of brain disease.[1] In developing country like Pakistan where cost of the health care has always been an issue, chronic diseases like cirrhosis and its various complications are a big burden on health economy. Inadequate education , poverty, poor hygienic environment, inadequate nutrition and lack of counselling are important factors, due to which number of cirrhotic patients are increasing and also causing increased mortality in these patients due to various complications.[2-7] Hepatic encephalopathy is characterized by personality changes like confusion, forgetfulness, speech and handwriting impairment, agitation, stupor, intellectual impairment and depressed level of consciousness is one of the bad prognostic indicator in patients with cirrhosis as is

evidenced in Child Pugh scoring system.[2-3,8-12] An important prerequisite for the syndrome is diversion of portal blood into the systemic circulation through portosystemic collateral vessels.[13] The development of hepatic encephalopathy is explained, to some extent, by the effect of neurotoxic substances, which occurs in the setting of cirrhosis and portal hypertension. Overt hepatic encephalopathy occurs in about 30-45% of patients with cirrhosis.[14,35]

Due to a very high prevalence of hepatitis B and C, Cirrhosis liver (CLD) is becoming an epidemic in Pakistan. Associated with poor survival and a high risk of recurrence,[15] Hepatic encephalopathy is also the most common, possibly preventable, cause for readmission.[16] In most of the patients presenting in hepatic encephalopathy, one or the other precipitating factor has been found to be the culprit and responsible for the morbidity and mortality.[12,17,18-20] Common precipitating factors include gastrointestinal bleeding, infections, azotemia, constipation, electrolyte imbalance, and high protein diet[2,21-27] and their identification is of paramount importance. Firstly, because avoidance of these precipitating factors is still the cornerstone of management and nearly 91% of patients can be treated with just correction of the precipitating factors.[28,33] Secondly, because hepatic encephalopathy is a diagnosis of Exclusion[1] and recognition of precipitating factors supports the diagnosis. Prognosis can be improved if the precipitating factors are recognized early and managed accordingly.[31] This study was aimed at ascertaining the common precipitating factors and their frequency in patients presenting with HE.

METHODOLOGY

Study Design: It was a cross sectional study.

Setting: Department of Medicine, PNS Shifa, a tertiary care hospital of Karachi Pakistan.

Period: 24 Oct 2014 to 31 August 2015 (about 9 months).

Methods: During this study period, 96 patients of clinically diagnosed acute hepatic encephalopathy associated with liver cirrhosis were enrolled. Patents with age above 20 years were included from both the genders. Patients with intracranial lesions such as subdural hematoma, cerebral infarction, meningitis, encephalitis, brain abscess, hypoxia, hypercarbia, ketoacidosis, uraemia, post seizure encephalopathy and neuropsychiatric disorders were excluded from the study.

Diagnosis of cirrhosis was based on history, physical examination and full blood count, liver function tests, renal function tests, random blood sugar, serum electrolytes, serum albumin, coagulation profile, hepatitis B & C serology and abdominal ultrasound was done to look for liver and splenic size, parenchymal echogenicity, portal vein diameter, and ascites. In case of ascites, an ascitic tap was also done to look for spontaneous bacterial peritonitis. Any evidence of the presence of other co-existent complications of cirrhosis liver was also recorded. Hepatic encephalopathy was graded according to the severity of manifestations (Table 1). Precipitating factors sought were infections, gastrointestinal bleeding, infections, diuretic overdose associated with electrolie imbalance, constipation, high protein diet (>1.5 g/kg/day), cough syrups, sedatives, paracentesis and unidentified/no precipitating factors. Data was collected on a specially designed proforma. Data were analyzed using descriptive statistics.

RESULTS

Ninety six patients were included in this study. Maximum age was 70 years and minimum was 20 years. The mean was 45.3 years. 80 were males and 16 were females. Majority of patients (63.75%) had one precipitating factor. More than one factor was found in 27.5%. Patients 39(40.6%) were in grade IV, 29(30.2%) were in grade III and 28 (29.1 %) patients were in grade II of hepatic encephalopathy. Gastrointestinal bleed was the most common precipitating factor identified in 42 (44%) patients, followed by infection in 36 patients (38%) and electrolyte imbalance associated with diuretics use in 10(11%) patients. Other precipitating factors in descending order of frequency were constipation in 8(9%) patients, use of high protein diet in 7(6.72%) sedative /tranquilizers in 4(3.84 %) and large volume paracentesis in 4(3.84%).

Mean hospital stay was 11 ± 1.8 days. Mortality was 11.4 % with 11 patients expiring during the hospital stay. 85 (88.5%) patients were discharged. Most of them 74 (87%) fully recovered and 11 (12.9%) patients in grade I hepatic encephalopathy.

This study concludes that, gastro-intestinal bleed, infection, diuretic therapy associated with electrolyte imbalance, constipation, high protein diet were the commonest precipitating factors of hepatic encephalopathy

Table 1: Risk Factors Precipitating Acute Encephalopathy in Chronic Liver Disease

Upper gastrointestinal bleed	42
Infections including spontaneous bacterial	38
Drugs specifically diuretics / Electrolyte imbalance like hypokalemia and hyponatremia	11
Constipation.	9
Dietary protein	7
Fulminant hepatitis	4
Paracentesis	4
Tranquilizers	4
Hypoglycemia	3
No precipitating factor found.	2

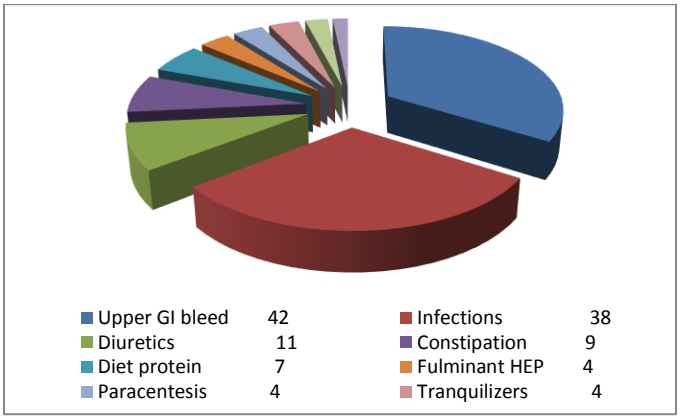

Figure 1: Precipitating risk factors

Note: In certain patients, there were multiple factors, so percentages do not add to 100.

Table 2: Result and comparison of our study with other studies done on same subject

Studies	GI bleed (%)	Infection (%)	Constipation (%)	Diuretic use	Large prot. Diet (%)	No factor
Conn 2	18		3	9	9	
Niger37	24	29		13		
Intekhab42`	22	24	32	56	4	
Manzar23	56	27	7	19	1.3	9
Saad 26	38	44	38	12	12	
Atif 22	51	53	49		47	
Devrajani BR27	45	67	49			
khalid mum29		35.8	18.3			12
Suresh25	51	22	41			
Ijaz 28	24	80	32			12
Abiid40	37.3	12	42.7			
Tariq41	29	30	30	0.5		
Present study	44	38	9	11	6.7	

Table 3: Age and gender distribution in different clinical presentation grades of patients with HE

Grades	No& %	No of patients according to Age group/years					
		20-35		35-50		>50	
		M	F	M	F	M	F
I	7 (7.29%)	0	0	0	0	4	0
II	21(21.8%)	4	2	11	2	5	2
III	29 (30.2%)	8	0	19	5	16	4
IV	39 (40.6%)	7	0	13	0	9	1

Table 4: Patients characteristics (n=96)

Age. Years		Sex		Hepatitis Serology	
Range	Mean	Male%	Female%	HbsAg%	HCV%
20-70	45.31	80	16	20	69
7 (7.29%) patients were positive for both hepatitis B and C serology					

Table 5: Grading of Hepatic Encephalopathy

Grades	Detailed Description
I	Mild confusion, euphoria, anxiety or depression, reverse sleep rhythm, slurred speech.
II	Drowsiness, lethargy, gross deficits in the ability to perform mental tasks, relatively moderate confusion.
III	Somnolent but arousable, severe confusion, inability to perform mental tasks
IV	Coma with (IVa) or without (IVb) response to painful stimuli.

DISCUSSION

Patients of cirrhosis having hepatic encephalopathy at time of admission were selected. Precipitating factors leading to encephalopathy were ascertained. Males outnumbered females. This is probably because males are given preference for

hospitalization and treatment. Strauss in a similar study reported that male–female ratio was 3:1.14.[29] The male preponderance in west is explained by patterns of alcohol consumption where 77% cases of chronic liver disease are related to alcoholism.[30] Interestingly all 96 patients had viral etiology of cirrhosis in this study is supported by another study in Lahore.[22] 1n a study by Khalid Mumtaz, at Aga Khan Hospital, 70% patients were having hepatitis C, close to our Study 28. Khokhar in his study in northern areas of Pakistan described incidence of hepatitis C 86%, thus reiterating the significant disease burden posed by this infection, which is on a rising trend in Pakistan.[32] Most of our patients were males i.e. 83% as compared to 16.6% females. This is close to to Hayat et al,[30] who reported 74% males, Devrajani et al[31] reported 65% males and Mumtaz et al[32] who reported 62% males. Upper GI bleed was the most common precipitating factor identified in 44% patients followed by infection 38% and diuretic associated with electrolyte imbalance in 11% patients. According to a study conducted by Manzar et al combined military hospital Lahore, gastrointestinal bleeding 56%, infection 27% stood out as the most common factors,[28] In one paper published by Mina Shaker, in June 2014 gastrointestinal bleed was the top precipitating in hepatic encephalopathy,[24] followed by infection as in our case. Similarly in other studies conducted by Conn, Atif, Tariq, GIT bleed was the leading factor close to our study. According to Tromn A, the most common precipitant identified is gastrointestinal bleeding, which is responsible for upto 34% cases of HE.[35] 1n another article by morillasl et al, GIT bleeding is the most common preventable factor.[42] In one study GIT bleeding associated with varices is documented significant predictive factor leading to hepatic encephalopathy.[43] It is to be stressed that gastrointestinal bleeding had significant association with mortality (37% vs 92%; p=0.001.[44]

In studies carried out at Islamabad and Hyderabad, infection, constipation and gastrointestinal bleeding stood out as the most common factors.[25-28,36] Infection in our study ranked 2nd most common factor. The infections included peritonitis, urinary tract, lower respiratory tract and other infections.

Other precipitating factors in descending order of frequency were constipation 11%, diuretic therapy associated with electrolyte imbalance in 9%, high protein diet in 6.7%, paracentesis in 3.8% and sedatives in 3.8% patients.

Diuretic therapy associated electrolyte imbalance was the precipitating factor in 9 % of our patients that progressed to hepatic encephalopathy. Patients of cirrhosis are frequently prescribed diuretics to treat ascites. Dehydration and electrolyte imbalance induced by diuretics may be the cause for hepatic encephalopathy however mechanism in this situation is not fully understood.[37] Caution must be exercised while prescribing diuretics and these patients need to be followed vigilantly with frequent monitoring of serum electrolytes.[2,38] It was also identified in many other studies that included hyponatremia, hypokalemia, alkalosis and hypovolemia.[2,5,23,26,39] According to Devrajani et al,[26] most of their subjects with electrolyte imbalance had history of diarrhea/vomiting or were already on diuretic therapy. Pathogenesis of this is still not fully understood however Hyponatremia is associated with low concentration of brain osmolytes, particularly myo-inositol, which has been shown to increase the risk of developing hepatic encephalopathy. Drietay protein overload was an infrequent cause of HE documented in a paper published in 2014 by mina shaker,[38] as also, in our study, only 6.7% have history of excessive protein intake precipitating HE. This was close to study conducted by intekhab, manzar and saad.[22,25,40] It was mostly because of the fact that patients and their attendants were unaware of protein restriction advice. This percentage was even higher in another study that was carried out at a remote hospital in interior Sindh that didn't have a nutritionist and most of their patients were illiterate.[41] At our hospital this highlighted the need for improvement in counseling/guidance regarding patients' diet. We have decided to introduce regular visits of nutritionist at the bed side, diet charts for the patient and information leaflets for the patients and attendants.

Mean hospital stay of our patients was 5 ± 1.8 days and mortality was 21%. In our subjects individual precipitating factors didn't significantly affect the length of hospital stay and mortality. Mumtaz et al had similar findings however he noted that patients having 2 or more participants were more likely to have a prolonged hospital stay and high mortality.

In our study hospital stay was prolonged and mortality was high in patients who reported to the hospital with grade III or IV hepatic encephalopathy at initial presentation. Mumtaz et al and Strauss et al in their studies found the same trend.[28,29]

CONCLUSION

Commonest precipitating factors of hepatic encephalopathy in patients of liver cirrhosis are gastrointestinal bleed, infection and constipation. There is no statistically significant correlation between the various precipitating factors and grade of hepatic encephalopathy, length of hospital stay and mortality. There is a need to improve the awareness of patients and attendants about the precipitating factors, their avoidance and dietary restrictions. Patients on diuretics should be followed regularly with frequent monitoring of serum electrolytes.

REFERENCES

1. Butterworth RF. Neurosteroids in hepatic encephalopathy: Novel insights and new therapeutic opportunities. J Steroid Biochem Mol Biol. 2016;160:94-7.
2. Conn HO. Quantifying the severity of hepatic encephalopathy. In: conn HO, Bircher J, editors. Hepatic encephalopathy: syndromes and therapies. West Lansing, MI: Medi-ed Press;1993.p.13.
3. Maqsood S, Saleem A, Iqbal A, Butt JA. Precipitating factors of hepatic encephalopathy: Experience at Pakistan Institute of Medical Sciences Islamabad. J Ayub Med Coll Abbottabad 2006;18:58-62.
4. Faloon WW, Evans GL, Precipitating factors in the genesis of hepatic coma. NY State J Med. 1970;70:2891-6.
5. Alam I, Razaullah, Haider I, Humayun M, Taqweem MA, Nisar M. Spectrum of precipitating factors of hepatic encepahalopathy in liver cirrhosis. Pak J Med Res. 2005;44:96-100.
6. Mehbbob F. frequency of risk factors for hepatic encephalopathy in patients of chronic liver disease. Ann King Edward Med Coll. 2003;9:29-30.
7. Ahmed I, Amin ZA, Ashraf HM, Determination of factors precipitating encephalopathy in patients with liver cirrhosis. Pak Armed Forces Med J 2006;56:284-8.
8. Gerber T, Shomerus H. Hepatic encephalopathy in liver cirrhosis: pathogenesis, diagnosis and management. Drugs. 2000;60:1353-70.
9. Ahmed H, Rehman M, Saeedi I, Shah D. Factors precipitating hepatic encephalopathy in cirrhosis liver. J Poastgrad Med Inst. 2001;15:91-7.
10. Nadeem MA, Waseem T, Sheikh AM, Grumman M, Irfan K, Hussnain SS. Hepatitis C virus: An alarmingly increasing cause of liver cirrhosis in Pakistan. Pak-J-Gastroenterol. 2002;16:3-8.
11. Chatauret N, Butterworth RF. Effects of liver failure on inter organ trafficking of ammonia; Implications for the treatment of hepatic encephalopathy. J Gastroenterol, Hepatol. 2004;19:219-23.
12. O'Beirne JP, Chouhan M, Hughes RD. The role of infection and inflammation in the pathogenesis of hepatic encephalopathy and cerebral edema in acute liver failure. Nat ClinPract Gastroenterol Hepatol. 2006;3:118-9.
13. Riggio O, Efrati C, Catalano C, et al. High prevalence of spontaneous portal-systemic shunts in persistent hepatic encephalopathy: a case-control study. Hepatology. 2005;42(5):1158-65.
14. Poordad FF. Review article: the burden of hepatic encephalopathy. Aliment Pharmacol Ther. 2007;1:3-9.
15. Kaplan PW, Rossetti AO. EEG patterns and imaging correlations in encephalopathy: encephalopathy part II. J Clin Neurophysiol. 2011;28:233-51.
16. Volk ML, Tocco RS, Bazick J, Rakoski MO, Lok AS. Hospital readmissions among patients with decompensated cirrhosis. Am J Gastroenterol. 2012;107(2):247-52.
17. Bustamante L, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hapatol. 1999;30:890-52.
18. Prasad S, Dhiman RK, Duseja A, Chawla YK, Sharma A, Agarwal R. Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy. Hepatology. 2007;45:549-59.
19. Weissenborn K, Ennen JC, Schomerus H, Ruckert N, Hecker H. Neuropsychological characterization of hepatic encephalopathy. J Hepatol. 2001;34:768-73.
20. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46:922-38.
21. Hayat AS, Shaikh N, Memon F. Identification of Precipitating Factors in Hepatic Encephalopathy Patients at Liaquat University Hospital Jamshoro. World Applied Sciences Journal. 2010;8(6):661-6.
22. Zakaria M, Hussain SR, Rehman M, Butt A, Rana GF, Precipitating factors in patients with cirrhosis. Professional Med J. 2008;15(3):375-9.
23. Tariq M, Iqbal S, Khan Nu, Basri R. Precipitating Factors of Hepatic Encephalopathy. RMJ. 2009;34(1):95-7.
24. Suresh B N, M. Viswanathan Poster Presentation – Hepatology, JAPI, Clinical spectrum of precipitating factors of hepatic encephalopathy in cirrhosis of liver; JJM Medical College. Davanagere. 2016;1:64-8:
25. Maqsood S, Saleem A, Iqbal A, Butt JA. Precipitating Factors of Hepatic Encephalopathy: experience at Pakistan Institute of Medical Sciences Islamabad. J Ayub Med Coll Abbottabad. 2006;18(4):58-62.

26. Devrajani BR, Shah SZ, Devrajani T, Kumar D. Precipitating factors of hepatic encephalopathy at a tertiary care hospital Jamshoro, Hyderabad. J Pak Med Assoc. 2009;59(10):683-6.
27. Taseer I, Mahmood MA, Naeem M, Safdar S, Ijaz A. Frequency of Precipitating Factors of Hepatic Encephalopathy in Patients with Chronic Liver Disease (CLD), PJMHS. 2014;8(4):900.
28. Mumtaz K, Ahmed US, Abid S, Baig N, Hamid S, Jafri W. Precipitating factors and the outcome of hepatic encephalopathy in liver cirrhosis. J Coll Physicians Surg Pak. 2010;20(8):514-8.
29. Strauss E, da Costa MF. The importance of bacterial infection as precipitating factor of chronic hepatic encephalopathy. Hepatogastroenterology. 1998;45:900-4.
30. Mennon KV. Pathogenesis, diagnosis and treatment of alcoholic liver disease. Mayo Clin Proc 2001;76:1021.
31. Lizardi-Cervera J, Almeda P, Guevara L, Uribe M. Hepatic encephalopathy: a review. Ann Hepatol 2003; 2:122-30.
32. N. Khokhar ;Spectrum of Chronic Liver Disease in a Tertiary Care Hospital; J Pak Med Assoc. 2002;52(2):56-8.
33. Vilstrupetall H, Recommendation 16, Identification of precipitating factors and their correction, Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by AASLD and EASL.
34. Patidar KR, Bajaj JS. Covert and Overt Hepatic Encephalopathy: Diagnosis and Management. Clin Gastroenterol Hepatol. 2015;13(12):2048-61.
35. Tromn A, Griga T, Greving I, Hilden H, Schwegler H. Hepatic encephalopathy in patients with cirrhosis and upper GI bleeding. Hepatology 2000;47:473-7.
36. Onyekwere CA, Ogbera AO, Hameed L Chronic liver disease and hepatic encephalopathy: clinical profile and outcomes. Niger J Clin Pract. 2011;14(2):181-5.
37. Jalan R, Kapoor D. Reversal of diuretic-induced hepatic encephalopathy with infusion of albumin but not colloid. Clin Sci Lond. 2004;106(5):467-74.
38. Shaker M, Carey WD. Common Precipitants of Hepatic Encephalopathy, The Cleveland Clinic Foundation. Center for Continuing Education, 1950 Richmond Road, TR204, Lyndhurst, OH 44124. Published: June 2014
39. Khan A, Iqbal M, Yasmeen R, Ahmed W. Determination of Various Precipitating Factors of Hepatic Encephalopathy in Patients of Chronic Liver Disease at Military Hospital Rawalpindi. PAFMJ 2011;61(4).
40. Alam I, Razaullah, Haider I, Humayun M, Taqweem MA, Nisar M. Spectrum of Precipitating factors of Hepatic Encephalopathy in liver cirrhosis Department of Medicine, PGMI, Lady Reading Hospital Peshawar Pakistan J. Med. Res. 2005;44(2):145-9.
41. Hayat AS, Shaikh N, Memon F. Identification of precipitating factors in hepatic encephalopathy patients at Liaquat university hospital Jamshoro. World Applied Sciences Journal. 2010;8(6):661-6.
42. Morillas RM, Sala M, Planas R. [Prevention of hepatic encephalopathy]. Med Clin (Barc). 2014;142(11):512-4.
43. Rattanasupar A, Tiawijit N, Rachatapantanakorn B. Predictive factor for hepatic encephalopathy in cirrhotic patients who presented with acute variceal bleeding. J Med Assoc Thai. 2014;97(6):567-73.
44. Dehghani SM, Mosavat SH, Bordbar MR. Risk Factors of Mortality in Children with Hepatic Encephalopathy. J Ped Sci. 2013;5:e191.

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