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Fakhar Qazi

Aga Khan University, fakhhar.qazi@aku.edu

Shameem Behram Khan

Jinnah Post Graduate Medical Centre

Anam Umar

Jinnah Post Graduate Medical Centre, Karachi

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Hepatic encephalopathy in chronic liver disease; predisposing factors in a developing country

Fakhar Ali Qazi Arisar¹, Shameem Behram Khan², Anam Umar²

¹Department of Medicine, Section of Gastroenterology, Aga Khan University Hospital, Karachi, Sindh, Pakistan, ²Department of Medicine, Ward-5, Jinnah Post Graduate Medical Centre, Karachi, Sindh, Pakistan

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ABSTRACT

Objective: To find out the risk factors for developing Hepatic Encephalopathy in patients suffering from Chronic liver disease. **Background:** Hepatic encephalopathy (HE) is a neuropsychiatric disorder that is caused by liver damage. In its pathology, alterations in normal brain function are associated with an increase in blood ammonia, benzodiazepine like substances, products of neurotoxic fatty acids, and other gut derived toxins, which gain access to the brain as a result of liver dysfunction. **Study Design:** Hospital based descriptive, cross sectional study. **Settings:** Medical Unit 1, Ward- 5, Jinnah Post Graduate Medical Centre, Karachi. **Duration:** July 2013 to December 2013. **Patients and Methods:** About 150 patients admitted in medical unit 1 with a diagnosis of chronic liver disease in a state of hepatic encephalopathy were included in this study. Patients suffering from viral or bacterial encephalitis, stroke, brain tumor, Wernicke's encephalopathy were excluded from the study. **Results and Observations:** There were 96 (64%) female and 54 (36%) were male patients. Mean age of the patients was 52.45 (\pm 12.271) years. 80 (53.33%) patients were having constipation. Infection was found in 55 (36.66%) cases. Upper GI Bleed was present in 51 (34%) patients. 44 (29.33%) patients had moderate to severe electrolyte imbalance as the cause. Constipation alone was the cause in 11.33% of cases. More than one factor was found to be responsible in around 56% of patients while in 6.6% of cases none of these precipitating factors was isolated. **Conclusion:** Constipation is the commonest cause of hepatic encephalopathy followed by infection, upper GI bleed and electrolyte imbalance.

Key words: Hepatic encephalopathy, Precipitating factors, Cirrhosis of liver, Outcome

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INTRODUCTION

Chronic liver disease is a worldwide major problem and alcohol is the leading cause of chronic liver disease in western societies, while hepatitis B and C viruses are the major in Pakistan. The prevalence of hepatitis B is over 10% in the Asia-pacific region where as the prevalence of chronic hepatitis C in the Asia-pacific region is variable between 4 to 12%.^{1,2}

It causes significant morbidity and mortality, mainly due to complications like hepatic encephalopathy, ascites, hepatorenal syndrome (HRS) and esophageal variceal hemorrhage (EVH).³ Hepatic encephalopathy (HE) is present in up to 70% of all patients with cirrhosis,

including patients with abnormalities demonstrable only by psychometric testing,^{4,5} out of which about 30% patients of chronic liver disease die of hepatic encephalopathy.^{6,7}

Hepatic encephalopathy describes a range of neuropsychiatric oddities that occur as a result of liver failure. The most primitive known paper to date on HE is by Giovanni Battista Morgagni in eighteenth century. Morgagni's book of medicine reported the case of a man with liver cirrhosis who had coma and subsequently died, whose gross brain examination did not show any alteration (Morgagni 1765).⁸ Many ideas generated and struggles are made to find out the exact pathophysiology of H.E. The diversion of portal blood into the systemic circulation through Porto systemic collateral vessels is found to be an imperative requirement

Address for Correspondence:

Dr. Fakhar Ali Qazi Arisar, Resident (Gastroenterology), Fellows Room, Faculty offices building, The Aga Khan University Hospital, Stadium Road, P.O. Box 3500, Karachi-74800, Pakistan. **E-mail:** dr_ar_lumhs@yahoo.com; **Phone:** +923332724599. © Copyright AJMS

for the syndrome. It accompanies portal-systemic shunting of venous blood that occurs either spontaneously, due to cirrhosis, or non-cirrhotic portal hypertension, or surgically following porto-caval anastomosis surgery or trans-jugular intra-hepatic porto-systemic shunt (TIPS) aimed at relieving portal hypertension.⁹

A relationship between portal-systemic shunting of blood and behavioral alterations, including coma, was clearly proven in porto-caval shunted dogs (i.e., submitted to Eck fistula) by Hahn et al. (1893)¹⁰ who demonstrated that meat-rich meals could cause 'encephalitis'.

Many studies also emphasize the role of neurotoxic agents in H.E. Van Caulet in 1932¹¹ declared that Ammonia is the principal neurotoxin in instigating coma and disturbed brain function in patients of cirrhosis, the same was then proven by Sthal in 1936.¹² Although many critics focused strictly on the involvement of neurotoxins and it remained controversial for a long period of time but now it is widely accepted that they have a certain role in the pathogenesis of H.E and among them ammonia is the toxin of interest. Ammonia formed by the colonic bacteria is carried to the liver via portal vein after absorption, where it is incorporated in the urea cycle for detoxification. Other gut-derived toxins have also 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. Ammonia and the other substances gain access to the systemic circulation as a result of decreased hepatic function or porto-systemic shunts and harmfully disturbs brain function and theaters a role in the pathogenesis of H. E. In the brain these compounds produce alterations of neurotransmission that affect cognizance and behavior. Abnormalities in glutamatergic, serotonergic, gaminobutyric acid-ergic (GABA-ergic) and catecholamine pathways have been described in experimental hepatic encephalopathy. The role of ammonia in hepatic encephalopathy is supported by the finding of high arterial ammonia level. The permeability of blood-brain barrier for ammonia is increased in patients with hepatic encephalopathy. Furthermore, ammonia after entering into the astrocytes, is metabolized and leads to changes in neurotransmission and hence alters the cellular functions. Manganese is deposited in basal ganglia and induces extra pyramidal symptomatology. It's also been proposed that an alteration in the ratio of branch chain amino acids and aliphatic amino acids can also predisposes to hepatic encephalopathy.¹³

PATIENTS AND PROCEDURES

Study design and setting

It was a hospital based descriptive, cross sectional study, carried out at department of medicine, ward 5,

Jinnah Postgraduate Medical Centre, Karachi, from July 2013 to December 2013. 150 consecutive patients of Chronic Liver Disease diagnosed previously or newly diagnosed after admission, between the ages of 14 to 83 years, presenting with encephalopathy were enrolled in the study.

Data collection

A Performa was structured and check list was used for data collection. Detailed history was obtained with special consideration to fever, GI bleed, Burning micturition, Diarrhea, vomiting, constipation, abdominal pain and distension, jaundice, diet and drugs like sedatives, diuretics and cough syrups. Patients were examined with special attention to fever, anemia, jaundice, palmar erythema, spider nevi, gynaecomastia, asterixis, dehydration, edema, splenomegaly and ascites. Relevant hematological, biochemical and radiological investigations were ordered including complete blood count, urea, creatinine and electrolytes, liver function tests, coagulation profile, serum proteins, serum albumin and globulin ratio, HBsAg, Anti HCV Antibody, urine D/R, ascitic fluid D/R, serum ammonia, chest X-Ray, ultrasound abdomen, CT Brain and upper GI endoscopy. All patients underwent standard management during their hospital stay which included use of lactulose, metronidazole, 3rd generation cephalosporin, proton pump inhibitor, and vitamin K and FFP in patient with deranged coagulation profile or GI bleed. Ryle's tube for feeding purposes was placed in patients with hepatic encephalopathy grade > 2. Outcomes assessed were the discharge or death during admission period.

Inclusion criteria

Cirrhosis was diagnosed on the basis of clinical signs & symptoms, laboratory findings (deranged coagulation profile and reversal of albumin/globulin ratio) and ultrasound findings (size and echogenicity of liver, portal vein diameter, splenomegaly), and patients were categorized according to Child Pugh classification (Table 1). Diagnosis of hepatic encephalopathy was made on the basis of history, physical examination and number connection test, and was graded from I to IV according to the West Haven criteria (Table 2).

Exclusion criteria

Patients suffering from acute liver failure, non cirrhotic portal hypertension, intracranial lesions such as subdural

Table 1: Child pugh classification

	1	2	3
Bilirubin (mg/dl)	<2	2-3	>3
Serum Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Grade of Encephalopathy	None	Mild	Moderate to severe
Grade of Ascites	None	Mild	Moderate to severe
INR	<1.2	1.2-1.7	>1.7

Child A: 5-6, Child B: 7-9, Child C: 10-15

hematoma, cerebral infarction or bleed, meningitis, encephalitis, brain abscess, hypoxia, hypercarbia, ketoacidosis, neuropsychiatric disorders or post-epileptic confusion were excluded from the study.

Operational definitions

Constipation was defined as failure to pass stool in 48 hours, **infection** as presence of fever, raised leukocyte count, significant pyuria (at greater than or equal to 10 leucocytes/mm³), >500 TLC or >250 neutrophils in ascitic D/R, **electrolyte imbalance** as high or low level of serum sodium or serum potassium as per the reference levels, **upper gastrointestinal bleed** as history of hematemesis or melena, **dehydration** as presence of dry tongue and loss of skin turgor, **high protein diet** as recent unrestricted high intake of proteins consumed in any form, **renal impairment** as creatinine of >2.

Data analysis

Statistical analysis was done using SPSS version 19 and the results were obtained in the terms of frequencies and percentages for descriptive analysis. Chi-Square and student t tests were used to analyze the numerical data and p value of <0.05 was considered statistically significant.

RESULTS

A total number of one hundred and fifty (n = 150) adults diagnosed cases of chronic liver disease who presented with hepatic encephalopathy irrespective of cause were included, out of them ninety six (n = 96, 64%) were females and fifty four (n = 54, 36%) were males. Majority (n = 106, 70%) of the patients in our study belong from middle age group (i.e., 40-60 years of age), with mean age of 52.45 (±12.271) years. The age and gender distribution of the patients is shown in Figure 1 & 2.

The most common cause of chronic liver disease was found to be HCV in our patients. Frequency of viral hepatitis as a cause of chronic liver disease is mentioned in Figure 3.

Out of 150 admitted patients, 107 (71.3%) were discharged, while 43 (28.7%) passed away. The frequency of grade of hepatic encephalopathy in our patients is shown in Figure 4.

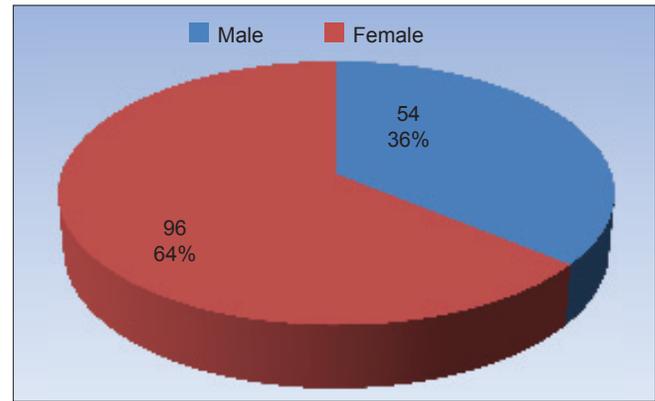


Figure 1: Gender distribution of patients included in the study

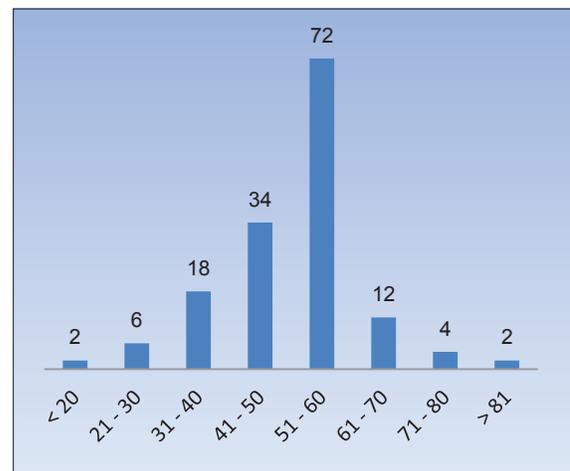


Figure 2: Age frequency of the patients enrolled in the study

Table 2: West haven criteria	
Grade 1	Mild confusion Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition
Grade 2	Drowsiness Lethargy or apathy Minimal disorientation for time or place Subtle personality change Inappropriate behavior
Grade 3	Impaired performance of subtraction Somnolence but arousable Marked confusion
Grade 4	Gross disorientation Coma (unresponsive to verbal or noxious stimuli)

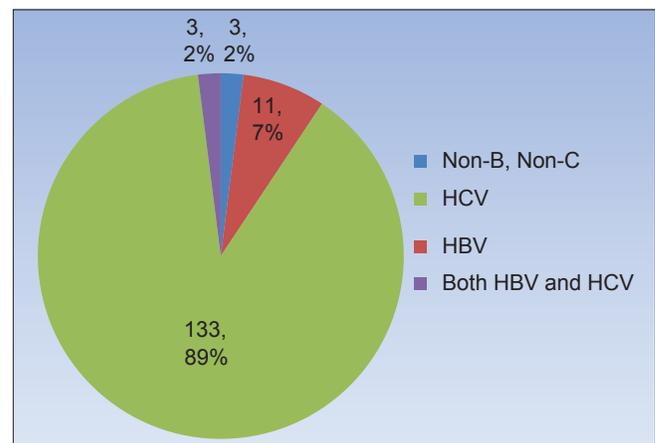


Figure 3: Frequency of viral hepatitis as a cause of chronic liver disease

Sign & symptoms (in the decreasing order of frequency) and the laboratory parameters of our patients are mentioned in the Figure 5 and Table 3.

TLC count was low in 13 (8.66%), normal in 94 (62.66%) and high in 43 (28.66%) of our patients. Urea was deranged in 78 (52%), while creatinine was high in 20 (13.33%) of the cases. Hypoalbuminemia was recorded in 118 (78.66%), while deranged coagulation profile was found in 85 (56.66%) of subjects. Fifty one (51) patients in our study presented with GI Bleed comprising of 34% of total cases.

Out of 150 patients, 07 (4.6%) had hypernatremia while 62 (41.33%) had normal sodium level. Hyponatremia was present in 81 (54%) patients. Of those having hyponatremia, 51 patients fall in the category of mild,

23 in moderate and 7 had severely low serum sodium. Similarly, out of total 150 patients 07 (4.6%) had hyperkalemia while 92 (61.33%) had normal potassium level. Hypokalemia was present in 51 (34%) patients. Of those having hypokalemia, 42 patients fall in the category of mild, and 9 had moderately low serum potassium. Frequency of infections and electrolyte imbalances is mentioned in the Table 4.

Eighty (53.33%) patients were having constipation. Infection was found in 55 (36.66%) cases. Upper GI Bleed was present in 51 (34%) patients. 44 (29.33%) patients had moderate to severe electrolyte imbalance as the cause. Constipation alone was the cause in 11.33% of cases. More than one factor was found to be responsible in around 56% of patients while in 6.6% of cases none of these precipitating factors was isolated.

Grade of hepatic encephalopathy in our patients was directly related with the number of predisposing factors as shown in Table 5.

Table 3: Laboratory parameters of all patients with hepatic encephalopathy

	Minimum	Maximum	Mean	Std. deviation
Hemoglobin (mg/dl)	1.7	13.2	8.417	2.1582
TLC (x10 ⁹ /L)	1.8	33.0	9.291	5.9084
Neutrophils (% of WBC)	5	94	75.04	18.562
Platelets	15	388	96.19	63.906
RBS (mg/dl)	61	591	149.63	88.079
Urea (mg/dl)	15	201	61.56	46.069
Creatinine (mg/dl)	0.10	5.20	1.3939	0.97563
Serum Sodium (meq/l)	83.0	153.0	131.840	10.1431
Serum Potassium (meq/l)	1.70	5.94	3.8703	0.96595
Serum Chloride (meq/l)	81.0	127.8	102.518	9.1711
Total Bilirubin (mg/dl)	0.60	26.00	4.3302	4.93379
ALT (u/l)	12	113	37.34	20.899
AST (u/l)	22	304	80.02	60.401
Serum Albumin (mg/dl)	1.6	33.0	3.574	4.0016
A/G ratio	0.4	1.2	0.816	0.1536
PT (sec)	13.0	38.6	20.171	6.5844
INR	1.00	4.10	1.5506	0.63901
Serum Ammonia (µg/dl)	31	388	191.29	94.566
Liver span (cm)	7.3	14.6	11.115	1.9717
Portal vein diameter	0.7	2.0	1.19	0.3210
Spleen size	8.8	18.9	13.43	2.1089

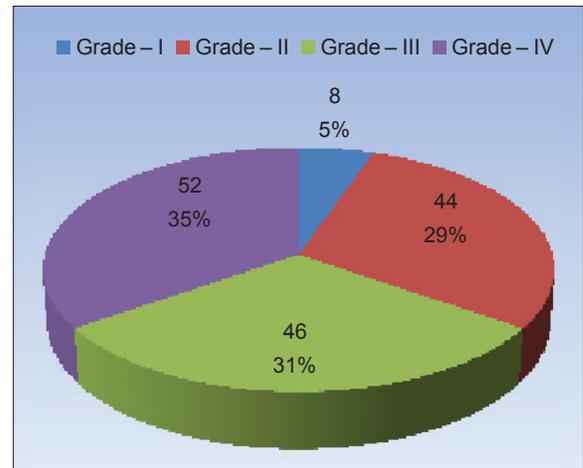


Figure 4: Classification of patients according to the grades of encephalopathy

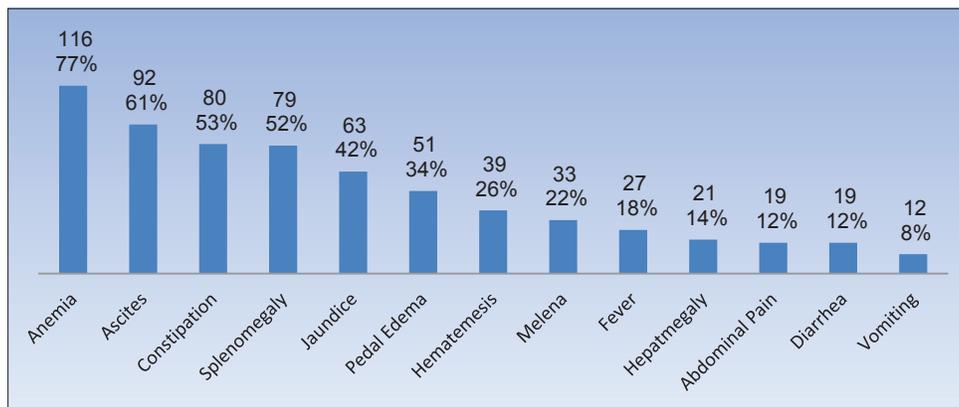


Figure 5: Sign and symptoms of the patients included in the study

	Frequency	Percentage
Absent	95	63.33
Present	55	36.66
Malaria	2	3.63
SBP	5	9.09
Gastroenteritis	6	10.9
Others (UTI, RTI)	42	76.36

Cause	Grade of hepatic encephalopathy				Total
	I	II	III	IV	
None	0	3	2	5	10
Single cause					
Bleed	0	0	3	3	6
Infection	0	3	3	4	10
Constipation	0	7	2	8	17
Electrolyte Imbalance	0	2	5	16	23
More than 1 cause	8	29	31	16	84
Total	8	44	46	52	150

Spearman correlation: P value=0.012

Outcome	Child-pugh class			Total
	A	B	C	
Discharge	9	53	45	107
Expire	0	11	32	43
Total	9	64	77	150

Pearson's R=0.022, Spearman correlation: P value=0.022

To assess the severity of liver disease in our patients, Child-Pugh and MELD scoring systems were applied. The mean MELD score of our patients was 17.2 while mean Child-Pugh Score was 9.65.

Chi-square test was used to determine the relation of child's class with mortality rate, and it was found that mortality rate was significantly high in child class C patients as shown in Tables 6.

The grade of hepatic encephalopathy at the time of presentation was directly related with the outcome (P value < 0.001) and is summarized in the Figure 6.

DISCUSSION

A clearly defined precipitating factor is usually identified in most patients with hepatic encephalopathy and the reversal or control of these factors is a key step in the management. The results of our study showed that 133 patients (88.66%) were suffering from Hepatitis C, and 11 patients (7.33%)

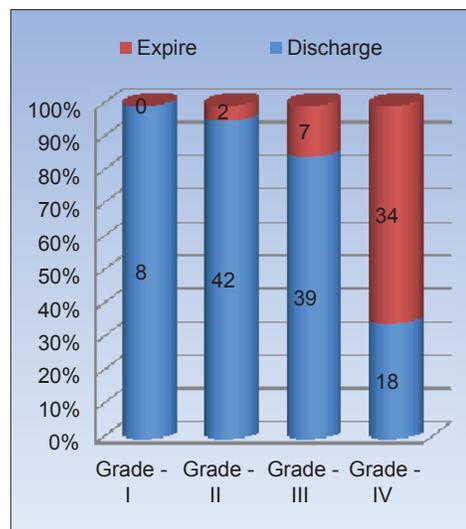


Figure 6: Grade of hepatic encephalopathy relating with outcome in terms of mortality

were of hepatitis B. Since it was a consecutive type of sampling, avoiding selection bias, so our findings are in conformation with other studies, which also emphasize the fact that HCV is a rapidly growing problem and has already overtaken HBV in the etiogenesis of hepatic encephalopathy in Pakistan.^{14,15} A review article by Jafri described a rise in frequency of HCV as a cause of CLD in Pakistan from 16.67% in early nineties to 51-86% over a period of time.¹⁶

Constipation was the commonest factor responsible for 53% cases of Hepatic encephalopathy in our patients, which is close to earlier published studies (as summarized in Table 7),¹⁷⁻²⁰ however contradictory with some of national and international reports.²¹⁻²⁸ High frequency of constipation in our population was perhaps due to the fact that people of our country were probably less aware of the importance of constipation, precipitating hepatic encephalopathy.¹⁹ Other factors responsible for prevalence of constipation among our setup include dietary restriction, poverty, lack of use or inappropriate dosing of lactulose due to financial constrains, and lack of education regarding role of diet in chornic liver disease.^{18,20} Also most of the patient in our study belong middle age group, and that increasing age effects the bowel habits, it may partly be the reason of high prevalence of constipation in our study.^{21,22} Liver and brain biopsies were not taken in our study.

Proper guidance about a healthy diet which consists of plenty of fresh fruits and vegetable, foods high in fiber content (including whole-meal bread, whole-wheat cereal and some raw bran in cereal or yoghurt), foods that are high in Omega-3 fatty acids and adequate fluid intake to avoid dehydration should be provided to all the patients of Chronic liver disease. Exercise is an integral feature of

Table 7: Comparison of our study with past literature (figures in percentages)

Author/Place/Year	n	Constipation	INF	SBP	Diarrhea	Malaria	Other infections (RTI, UTI)	GI Bleed	Low Na+	Low K+	Low Azotemia	None	1 cause	>1 cause
Present Study/JPMC Karachi/2013	150	53	36.66	3.33	12	1.33	28	34	54	34	52	6.66	37	56
Mahboob ⁶	-	19	47	-	5	-	-	30	-	-	-	-	-	-
Bikha Ram Devrajani ¹³ /LUMHS Jamshoro/2007	87	49	67	-	-	-	-	45	-	33	-	6	-	-
Akhtar Ali Baloch ¹⁷ /CHK/2009	190	49.5	38.9	-	-	-	-	32.6	-	-	-	-	-	-
Naila Masood ¹⁸ /LUMHS Jamshoro/2009	90	31.1	27.8	-	-	-	-	10	13.3	37.8	-	13.3	-	-
Hameed Ahmed ¹⁹ /Lady Reading Hosp. Peshawar	50	52	-	-	22	-	-	56	28	68	-	-	-	-
Saira Afzal ²⁰ /KEMU Lahore/2005-06	50	60	10	-	-	-	-	18	-	-	-	-	-	-
Col. Dr. Manzar Zakaria ²¹ /CMH Lahore/2007	80	6.3	27.5	-	-	-	-	56.3	-	-	-	8.8	-	-
Khalid Mumtaz ²² /AKUH Karachi/2005-07	404	18.3	-	20.5	-	-	15.3	13.6	3	6.4	-	-	53	35
Dileep k. Rohra ²³ /CHK/2006	256	12.1	-	10.9	-	-	9	15.2	-	-	-	50.8	-	-
Intekhab Alam ²⁴ /Lady Reading Hospital Peshawar/2005	50	32	24	-	40	-	-	22	38	18	-	-	-	-
Imran Ahmed ²⁵ /CMH Okara/2005	43	20.9	7	-	-	-	-	37.2	-	14	-	9.3	-	-
Souheil ²⁶	100	3	3	-	-	-	-	18	-	11	-	-	-	-
Faloon & Evans ²⁷	39	6	-	-	-	-	-	33	-	18	33	3	-	-
Conn & Liebertha ²⁸	1000	3	4	-	-	-	-	18	-	9	30	2	-	-
M. Tariq ³² /Khyber Teaching Hospital Peshawar/2006	200	30	30	8	3	-	22	29	1.5	4.5	-	-	-	-

bowel management programs, and a lack of physical activity is a factor in the development of constipation in some people. Its effectiveness as an intervention to prevent or treat constipation, however, has yet to be demonstrated.²⁹

Lactulose is a commonly prescribed agent to relieve constipation in patients with chronic liver disease. It has an added advantage as a non-absorbable disaccharide inhibiting intestinal ammonia production by number of mechanisms.^{30,31}

Infections like SBP, urinary tract infection and lower respiratory tract infection were the 2nd most common factor present in 37% of cases corresponds to the study of Mohammad Tariq (2006).³² In West however the infection as a cause of hepatic encephalopathy is not very common, possibly due to more awareness and better nutrition status in their patients.

GI bleed was the third most important factor and was found in 34% of patients in our study, which is similar to 30% found in Mehboob F (2003),⁶ although lower than that reported by zakaria.²¹

Electrolyte imbalance was found in 29% patients. Among electrolytes, hyponatremia was much more common than

hypokalemia in our patients which was consistent with the findings of Alam,²⁴ but contradicts with those of Ahmed.¹⁹ Electrolyte imbalances also correlate with the severity of the liver disease.³³

In our study, sedatives and Tranquilizers were not in use of any patient, and the history taken from the attendants and patients themselves were not suggestive of any self prescription of such drugs. In this study the majority of patients are in age group of 50 to 60 and the female were dominant, which is contradictory with the findings observed in a retrospective study, of hepatic encephalopathy in Saudi Arabia³⁴ and in civil hospital Hyderabad.¹³

When grading of encephalopathy is considered, in grade 3 and 4 electrolyte imbalance is the single most common precipitating factor involved.

The mortality rate of hepatic encephalopathy is high as shown by the study of Sargent et al³⁵ whereas, in our study the mortality was 29% and the majority were, Class C, Child- Pugh classification. Patients with chronic HE are known to have better long term (5 years) survival than those who develop HE acutely (100% vs. 70% survival).³⁶ But this

survival can be improved as appropriate treatment and care can cause complete recovery especially if encephalopathy is elicited by a rescindable cause. So there is a definite need for health education in patients regarding the risk of HE and its precipitating factors, as lack of awareness about this life threatening complication of CLD is itself a cause of acquiring hepatic encephalopathy. So a constant need and effort to obviate them by all possible measures is necessary. Proper dietary advice must be an important part of all counseling practices to chronic liver disease patients.

CONCLUSION

Constipation is the commonest cause of hepatic encephalopathy followed by infection, upper GI bleed and electrolyte imbalance. Control of constipation is very imperative in the avoidance of hepatic encephalopathy in our setup. The leading cause of constipation is a poor diet – poor choice of foods, or irregular eating. Patient counseling is a key competency element in its prevention. In most cases, simple changes in diet and lifestyle as described above can help relieve symptoms and manage constipation, and so very effectively prevent the development of this life threatening complication of cirrhosis.

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Authors Contribution:

FAQA – designed the study, collected and analyzed the data, drafted the manuscript, & reviewed the manuscript; **SBK** – Contributed to the study design and collection of data; **AU** – Contributed in collection of data, writing of manuscript.

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