FACTORS PRECIPITATING HEPATIC ENCEPHALOPATHY IN CIRRHOSIS LIVER

Hameed Ahmed, Masoodur Rehman, M Ilyas Saeedi and Dilawar Shah

Department of Medicine,
Postgraduate Medical Institute,
Lady Reading Hospital, Peshawar.

SUMMARY

We surveyed 50 patients admitted with clinical diagnosis of hepatic encephalopathy, for one or more factors responsible for encephalopathy. The commonest precipitating factors were, hypokalaemia 68%, Haematemesis 56%, constipation 52%, high protein intake 52%, hyponatraemia 28%, diarrhoea 22%, infections including spontaneous bacterial peritonitis and septicaemia 28%, Benzodiazepine intake 2% surgical procedure 2%. Oesophageal varices were present in 60%. Hypokalaemia and Electrolytes imbalance must be considered as an important precipitating factor in causation of encephalopathy in cirrhotics.

INTRODUCTION

Cirrhosis liver is a common, usually progressive and fatal disorder of our community,[1] as well as of the western society.[2]

Hepatic encephalopathy is a complication of cirrhosis. It is generally regarded as due to biochemical disturbances of the blood brain barrier. The pathogenesis of hepatic encephalopathy is still unclear. Variety of mechanisms such as action of ammonia and other neurotoxins, disturbances of the blood-brain barrier and alteration of various neurotransmitter systems and their receptors has been implicated.

Acute attacks of hepatic decompensation are frequently precipitated by gastrointestinal bleeding, diuretic therapy, electrolyte imbalance, use of sedatives, tranquilizers, narcotic analgerics, alcohol and therapeutic paracentesis. Infections, specially with bacteria and spontaneous bacterial peritonitics are important precipitating factors.[6,7]

Identification, correction and treatment of these precipitating factors are important steps in the management of chronic liver failure with hepatic encephalopathy.[8,9,10]

MATERIAL AND METHODS

The study was conducted in Medical 'C' Unit, Lady Reading Hospital, Peshawar. All patients (male/female) between the ages of 12 to 70 admitted with features of encephalopathy were selected for the study.

Criteria for inclusions of cirrhotic patients:

Known cirrhotic patients, having various neurological symptoms including changes in consciousness, behaviour changes and personality changes, changes in mental state, forgetfulness, confusion, disorientation, delerium, acute confusion with fluctuating level of consciousness, "dementia" loss of memory, intellect, reasoning and other functions, changes in mood, decreased alertness, daytime sleepiness, decreased responsiveness, progressive stupor, coma, decreased self-care ability, deterioration of handwriting or loss of other small hand movements, course muscle tremors, asterexis (coarse "flapping muscle tremors) were all included.

Criteria newly diagnosed patients with cirrhosis liver:

New patients were being diagnosed and were included in our study. The criteria for diagnosing cirrhosis liver was based on clinical signs and symptoms, laboratory investigations and ultrasonography of the abdomen. The laboratory findings included prothrombin time (PT), serum albumin and albumin-globulin ratio (A/G ratio).

Abdominal ultrasonography was done for each patient, as it is highly suggestive and non-invasive technique, commenting on the size, echogenicity of the liver, splenic enlargement and fluid collection in the abdominal cavity.

The following types of patients were excluded from our study:–

Patients who had taken antibiotics, orally or parenterally about a week preceding their illnesses, and had signs and symptoms, suggestive of hepatic encephalopathy were excluded.

NO. OF CIRRHOSIS

Cirrhosis	No. of cases	Percentage (%)
Known cirrhotics	06	12
Newly diagnosed cirrhotics	44	88
Total	**50**	**100**

TABLE – 1

AGE DISTRIBUTION

Age group	No. of cases	Percentage (%)
11–20 years	02	04
21–30 years	02	04
31–40 years	12	24
41–50 years	16	32
51–60 years	08	16
61–70 years	10	20
Total	**50**	**100**

TABLE – 2

SYMPTOMS & SIGNS

Signs & symptoms	No. of cases	Percentage (%)
Jaundice	38	76
Abdominal distortion	36	72
Ascites	36	72
Splenomegaly	34	68
Haematemesis	28	56
Constipation	26	52
Foetor hepaticus	26	52
Oedema feet	20	40
Palmar erythema	10	20
Fever	10	20

TABLE – 3

PRECIPITATING FACTORS

Precipitating Factors	No. of cases	Percentage (%)
Hypokalaemia	34	68
Haematemesis	28	56
Constipation	26	52
High protein diet	26	52
Hyponatraemia	14	28
Diarrhoea	11	22
S.B.P.	08	16
Septicaemia	06	12
Benzodiazepine usage	01	02
Surgical procedure	01	02

TABLE – 4

Cases presenting with jaundice or ascites, which on routine investigations, were found not to be suffering from cirrhosis liver, and the fluid collection were due to some other diseases.

Patient with acute fulminant or subfulminant hepatic failure due to viral hepatitis, drugs and some other poisoning were excluded.

CAUSES

Causes	Conn and Lieber-thal (n=1000)	Faloon and Evans (n=39)	Leevy and David-son
Azotaemia	30	33	16
G.I Bleeding	18	33	34
Dietary protein	09	0	07
Constipation	03	0	0
Tranquilizers, sedatives analgesic drugs	22	0	11
Hypokalaemic alkalosis	09	18	0
Infection	04	0	27
Hepatic parenchymal injury	03	00	0
Miscellaneous	0	13	5
Unknown	02	03	00

TABLE – 5

History based on the presenting complaints, its durations, drugs intake, surgery, blood transfusion and therapeutic paracentesis was obtained.

Past history of any major illness, comprising jaundice, history of cytotoxic drugs (methotrexate) intake, blood transfusion and surgery was recorded on a proforma, patients family and personal histories were obtained and recorded on a proforma. Routine laboratory investigations like haemoglobin (Hb) total leucocyte count (TLC) differential leucocytes count (DLC) were performed. Stool for naked eye examination and routine examination was done on each patient for malaena or occult blood. Investigations relating to cirrhosis liver and its complications, like liver function test's (LFT's), HbsAg, anti-HCV antibodies, prothrombin time (PT), activated partial thromboplastin time (APTT), serum albumin and albumin globulin ratio (A/G ratio), blood urea, serum creatinine, serum electrolytes and ascitic fluid for routine examination, gram staining and culture sensitivity were done.

Barium swallow was performed on each patient after initial stabilization. Oesophagogastroduodenoscopy (OGD) was performed on urgent basis on those patients who presented with G.I bleeding.

Hb was determined by Sahle's method. Erythrocyte sedimentation rate (ESR) was measured by westergren's method. TLC in ascitic fluid was determined by neubar counting chamber.

Slides were stained with giemsa reaction for obtaining DLC values. X-ray's chest were being done for each patient. Biuret method was used for obtaining ascitic fluid concentration. Blood and ascitic fluid cultures were done in blood agar medium. Ascitic fluid was cultured in blood culture bottle at the bed side. Serum bilirubin level was measured by Vanden Berg reaction.

Serum glutamate pyruvate transminase (SGPT) was measured by Karmel reaction using wiener kit. For serum albumin and globulin (A/G) ratio, Bromocresy. Green method (BCG) was used. Sigma kit was used for PT/APT. HbsAg was detected by the enzyme linked immuno-sorbent assay (ELISA). Anti-HVC antibodies were detected by using the ELISA.

Barium swallow was done on a fluoroscopy machine. Serum creatinine was determined by jaffe reaction. Ion selective electrode (ISE) were used for estimation of serum electrolytes. Stool for occult blood was determined by benzirin method. Blood and urine cultures were done and organisms being identified.

RESULTS

Fifty patients of cirrhosis liver were selected for our study, 40 males (80%) and 10 females (20%). Previously known cirrhotics were 6 cases (12%) and 44 cases (88%) were newly diagnosed Table 1. Grading of encephalopathy was done as follows:–

38 (76%) patients were in grade-IV encephalopathy, 4 (8%) patients were in grade-III, 4 (8%) patients in grade-II and 4 (8%) patients in grade-I encephalopathy. Most of the patients were in the age group of 41-50 years ranging from 12-70 years.

The patients suffering from hepatic encephalopathy were being admitted to the hospital from all districts and tribal agencies attached to NWFP and therefore no particular geographical distribution was observed in collecting the cases. The commonest signs observed as shown in Table No. 3.

Clubbing, cyanosis, lymphadenopathy, duputryen's contractures and Xanthoma or Xanthelasma were not seen in our patients. None of the patient was suffering from alcoholic cirrhosis, spider naevi, gynaecomastia, testicular atrophy and parotid swellings were not seen. Most of the patients in the study had more than one factor involved. These precipitating factors were in the range of 1-5.

Precipitating factors observed for hepatic encephalopathy in patients suffering from cirrhosis liver as shown table 4.

DISCUSSION

Cirrhosis liver is on the rise in Pakistan and a very common health problem challenging the medical profession. HBV, HCV and HDV are transmitted through parenteral routes like transfusions of infective blood or blood products, sharing needles by drug addicts, quacks, tattoist, dentist, acupunturist, hair dressers, close personal contacts, sexual intercourse, particularly in homosexuals and maternofetal transmission. There are more than 400 millions carriers of HBV. HCV was identified late and was thought to be responsible for 70-90% of post-transfusion hepatitis in all countries, where blood was not screened for HCV markers.

In western societies roughly 50% of all cases of liver cirrhosis are related to alcohol abuse.[12] We have compared our study with other studies performed on both national and international levels.

We found hypokalaemia in 68% of patients, which was almost nearer to 70% in the study done at Nawabshah Sindh. This similarity was probably due to the same geographical conditions and might have been due to nutritional disturbances, gastro-intestinal loss and injudicious use of diuretic therapy. In other series from the west,[5] hypokalaemia was found to be 9% and 18%. These figures do not coincide with our study. These differences were probably due to facts that peoples in the West were more educated, and had better health system facilities and avail them in time witout any delay.

Haematemesis being the second most important factor in our study detected in 56% of patients, which was the same as that detected in the study done at Nawabshah Sindh. In other series,[5] G.I bleedings were seen in 18%, 33% and 34%. The increase in the incidence of G.I bleeding in our country had been due to the excessive use of intake of non-steroidal inflammatory drugs (NASAIDs) probably prescribed by quacks, and delayed consultation on the part of the patients.

Constipation was the third most important factor observed in 52% of patients. It was consistent with the study performed in Nawabshah Sindh, because of the same geographical conditions. In other series,[5] it was found to be 3 percent. The increase incidence of constipation in our country was probably due to the fact that peoples of our country were probably less aware of the significance of constipation, precipitating hepatic encephalopathy. High protein intake was also found to be in 52%, of patients but none had been found in the study done at Nawabshah Sindh. In the other studies done in the west,[5] it was found to be 9% and 7%. This high percentage of dietary protein intake was probably due to the fact that, peoples of our province were very fond of eating animal proteins. In western countries, it was probably due to their higher socio-economic status.

In cases of G.I bleeding, high protein diet and constipation, there is an increased production of amonia in the gut and thereby precipitate hepatic encephalopathy[5]. Hypokalaemia also directly stimulates renal ammonia production.

We found hyponatraemia in 28% of patients in our study, which was consistent with the study done at Sindh. The hyponatraemia in cirrhosis liver is due to the concomitant increase of plasma renin activity and decrease of plasma atrial natriuretic factor (ANF) that decreased effective plasma volume, generates non-osmotic stimuli for vasopressin hypersecretion in these patients. Sodium could be increased or normal.

We found infections in 28% of patients, which were the same as that in the other study at Sindh. This high rate of infections could be due to poor health education and ignorance on the part of patients and their relatives in this part of the world.

In other studies from the western countries,[5] it was found to be 4% and 27%. These two studies from the west also have a great difference among themselves. Cirrhotics are more prone to infections because of the decreased serum albumin. Infections anywhere, including SBP can precipitate hepatic encephalopathy. Patients with advanced liver cell dysfunction and jaundice are probably more prone to various infections including SBP, and itself can cause further deterioration of liver cell function and deepening of jaundice.

Secondary bacterial peritonitis should be suspected when the ascitic leukocyte count is greater than 10,000/mm 3, cultures of the fluid are positive for anaerobes or multiple organisms, the ascitic fluid protein concentration exceeds 1 gms/dl, or a follow up paracentesis 48 hours after initiation of treatment for presumed SBP reveals persistently positive cultures or a rising ascitic Leukocyte (PMN) count. We found diarrhoea in 22% of our patients. It was nearer to the 24% in the study done at Sindh. None had been found in other studies. It was probably due to poor hygiene and bad sanitation in our country. We found benzodiazepine intake (tranquilizers) in 2% of our patients, none had been found in the study. This could be due to the fact that patients might had taken sedatives for sleeplessness or their attendants had been giving them for irritability and restlessness. Moreover, quacks might have ben prescribing these medications.

In other studies,[5] it were 22% and 11%. But this large percentages were collectively meant for tranquilizers, sedatives and analgesics abuse. If one would have deducted analgesic drugs from this list, then it would probably have fallen to a very low percentage of only tranquilizer intake. Both GABA and benzodiazepines bind to adjacent sites on a common receptor complex and thereby leading to inhibitory neurotransmission and precipitate hepatic encephalopathy.

We found history of surgery precipitating hepatic encephalopathy in 2% of our patients, none have been found in the study and other studies.[5] This have been probably misdiagnosis of symptomatic piles due to anorectal varices as ordinary sentinal piles.

Patients with cirrhosis have a variety of haematological, vascular and other defects that increase their morbidity and mortality rates for surgery. In all of our patients PT was prolonged and serum albumin levels were low. The PT may be prolonged due to failure to absorb fat-soluble vitamin K as a result of cholestasis, or due to reduced synthesis of prothrombin, and other liver derived factors that contribute to the prothrombin time, as a result of hepatocellular damage. A prolonged PT due to malabsorption is corrected by parenteral administration of vitamin K, but an abnormal value due to hepatocellular disease is not. A lengthened PT is a relatively late manifestation of hepatic disease but changes are then rapid because of the short half lives of the proteins involved. Fluid retention any lower albumin, concentration by dilution nevertheless, low albumin levels do occur, especially in chronic liver disease such as cirrhosis.

We found hepatitis B alone in 44% of patients, hepatitis C alone in 32% and both hepatitis B & C in 4% of patients. Chronic hepatitis B is the most frequent cause of chronic hepatitis/cirrhosis of liver. Hepatitis C virus is the second most frequent case of chronic liver disease. Hepatic encephalopathy is the most common cause of death[11]. We found jaundice in 76% of our patients. Patients can present with chronic liver disease without jaundice. Ascitic fluid culture was positive in 22.2%, urine culture in 6% and blood culture in 12% of cases. X-ray's chest revealed foci of infections in 4% of cases. Infection anywhere can precipitate hepatic encephalopathy. We found oesophageal varices in 60% of patients. The risk of bleeding from oesophageal varices is high when the portal venous pressure is above 12 mmHg. Not all bleeding in cirrhotics come from oesophageal varices. Upto 50% of patients with documented oesophageal varices have a non-variceal source of bleeding. Variceal bleeding cannot be differentiated from a non-variceal haemorrhage on clinical examination. Bleeding may come from portal hypertensive gastropathy, patients with portal hypertension are at increased risk of massive bleeding from mallory weiss tears and the frequency of peptic ulcer disease ranges from 9.5% to 16.7%.

In all of our patients, ultrasonography findings were suggestive of cirrhosis. All patients had small shrunken hyperechogenic livers. The ultrasonography of abdomen is used to assess the bile ducts, gall bladder, liver and pancreas.

Ultrasonography is also used for the examination of both the liver parenchyma and the biliary tree[3]. Previous history of blood transfusion was present in 4% of cases. In Pakistan HB is usually transmitted through parenteral route, like transfusion of infective blood or blood products. HCV was identified late and was thought to be responsible for 70-90% of post-transfusion hepatitis in all countries, where blood was not screened for HCV markers.[11] Community acquired HCV infection is less common

than post-transfusion HCV hepatitis. The community acquired risk factors are hospitalization, use of barber razors, dental work, tattooing, ear piercing and acupuncture. Past history of jaundice was present in 70% of patients. Chronic hepatitis (B and C) occurs mainly in men and it is often not preceded by an acute attack.

CONCLUSION

Cirrhosis liver is a common problem in our country. We are receiving several cases of chronic hepatic encephalopathy each week in our Medical Units. Patients and their attendants have limited knowledge about cirrhosis liver and hepatic encephalopathy. (Lack of information about the causes is also an important factor in acquiring cirrhosis liver and hepatic encephalopathy). In our country hepatitis-B virus (HBV) and hepatitis-C virus (HCV) and (HDV) are mainly responsible for cirrhosis liver.

There are world wide more than 400 millions carriers of HBV. HCV was identified later and was thought to be responsible for 70-90% of post transfusion hepatitis in all countries, where blood was not screened. By screening blood and blood products for HBV and HCV. We can prevent the incidence of viral hepatitis and cirrhosis liver. Chronic liver disease is associated with persistent antigenaemia. It is observed that approximately half the sufferers of post transfusion hepatitis will have raised transaminase levels, most of them will have chronic active hepatitis (CAH) and out of those twenty percent (20%) will develop cirrhosis of the liver.

REFERENCES

1. Qureshi H, Shahid A, Moza F. and Zuberi SJ. Portal systemic encephalopathy. JPMA, 1987; 37: 25.
2. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension. A meta-analysis review. Hepatology, 1995; 22: 332.
3. Haussinger D, Laubenberger J, Dehl SV, Ernst T, Bayer S, Lager M et al. Proton-magnetic spectroscopy studies on human brain myo-inositol in hypo-osmolarity and hepatic encephalopathy. Gastroenterology, 1994; 107: 1475.
4. Mink GY. Gamma-amino-hutyric acid and the liver. Dig. Dis., 1993; 11 (1): 45.
5. Jensen DM. Portal-systemic encephalopathy and hepatic coma. Med. Clin. North. Am. Sept. 1986; 70 (5): 1081.
6. Gilbert JA, Kamath PS. Spontaneous bacterial peritonitis (SBP). An update mayo clinic proc. 1995; 70: 365.
7. Runyon BA. Management of adult patients with ascites caused by cirrhosis. Hepatology, 1998; 27: 264.
8. Kamath PS, MC Musick MA. Transvenous intra-hepatic porto-systemic shunts. Gastroenterology, 1996; 111: 1700.
9. Riordan SM, Williams R. Current concepts and treatment of hepatic encephalopathy. N. Engl. J. Med. 1997; 337.
10. Lawrence S, Friedman. Liver, biliary tract and pancreas. Tierney Jm LM, Mcphee SJ, Papadakis MA. Current medical diagnosis and treatment 38 ed. Appleton and Lange, 1999; 639.
11. Naheed T. Antigenaemia in chronic liver disease. Pakistan's Med. Sci, Jul-Sept. 1998; 14 (4): 303.