PORTO-SYSTEMIC ENCEPHALOPATHY (PSE); STUDY TO EVALUATE COMMON PRECIPITATING FACTORS IN PATIENTS WITH CHRONIC LIVER DISEASE

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ABSTRACT... Background: Porto-systemic encephalopathy (PSE) is a common medical emergency at our settings due to increased prevalence of chronic liver disease. **Objective:** To determine frequency of common precipitating factors in patients having porto-systemic encephalopathy (PSE) at tertiary care settings in Hyderabad. **Study design:** Descriptive case series study. Setting: Department of Medicine Isra University Hospital Hyderabad. Period: 1st April 2011 to 31st December 2011. **Methods:** A total 100 patients manifesting clinical features of PSE were included in this study by non-probability convenience sampling. The data was evaluated in statistical program SPSS version 16. **Results:** As 100 patients with PSE were enrolled in the current study, out of these 96 patients have precipitating factors involved while only 4 patients have no such factors. Out of these 96 patients, 36 patients have only single risk factor found while in 64 cases multiple factors were implicated. Constipation, infections (except SBP) and renal impairment were noted in 36%, 24% and 22% respectively. **Conclusions:** Constipation, infections (except SBP) and renal impairment were the most common precipitating factors of porto-systemic encephalopathy in our study. Hence priority should be given to them in terms of hospital funds, medicines and human efforts.

Key words: Porto-systemic encephalopathy, cirrhosis, chronic liver disease, precipitating factors.

Porto-systemic encephalopathy (PSE) or Hepatic encephalopathy (HE) is a potentially-reversible neuropsychiatric abnormality in the setting of liver failure, whether chronic (as in cirrhosis), or acute[1].

It results from failure of the liver to detoxify noxious agents of gut origin because of hepato-cellular dysfunction and porto-systemic shunting. The clinical spectrum ranges from mild intellectual impairment to coma. Patients with minimal porto-systemic encephalopathy have no recognizable clinical symptoms but demonstrate mild cognitive and psychomotor deficits and attention deficit on standardized tests. The stages of overt encephalopathy are (1) mild confusion, (2) drowsiness, (3) stupor, and (4) coma, while the porto-systemic encephalopathy was classified into episodic, persistent, and minimal[2].

Ammonia is the most readily identified and measurable toxin but is not solely responsible for the disturbed mental status[3]. Development of porto-systemic encephalopathy heralds a bad prognosis in cirrhosis[4]. Exact cause of porto-systemic encephalopathy still not clear but it is widely accepted to be due to the failure of hepatic clearance of toxic products from the gut[5]. Following important factors are implicated in development of PSE:

Ammonia is the most important toxin[6]

False neurotransmitter's production[7]

Increase production of inhibitory neurotransmitters like Gamma-amino butyric acid (GABA)[8].
Increased in circulatory levels of endogenous benzodiazepines[9]

In the majority of patients with porto-systemic encephalopathy, a clearly defined precipitating factor usually identified. Following are the known precipitating factors.

- Bleeding into the intestinal tract significantly

increases the proteins in the bowel and precipitate rapid development of encephalopathy[10]

- Constipation[8]
- Metabolic Alkalosis[11]
- Potassium deficiency induced by diuretics.
- Sedative and hypnotics[7]
- Medicine containing ammonium or amino compounds[11]
- Paracentesis with attendant hypovolemia[11]
- Hepatic or systemic infections[7]
- Porto-systemic shunts including TIPS[7]
- As most of the cases of porto-systemic encephalopathy are precipitated by known factors, so early recognition and prompt treatment of the precipitating factors can lead to better final outcomes of these patients[12]

MATERIAL AND METHODS

The descriptive case series study on 100 patients of PSE, who were admitted at Isra University Hospital Hyderabad, during 9 months study period from 1st April 2011 to 31st December 2011. In this study patients were recurited by non-probability convenience sampling. Only those patients were included who met inclusion criteria for the study, age above 12 years irrespective of sex, race, community and have manifested signs of PSE.

The diagnosis of PSE was done in detailed history (like altered behavior, conscious level, sleep pattern, speech) and also history regarding precipitating factors like constipation, GIT blood loss, fluid and electrolytes loss by diarrhea/ vomiting, history of concomitant illness like diabetes mellitus, fever, drugs, benzodiazepine alcohol, diuretics, nutritional history and once the diagnosis was made, it was confirmed by laboratory investigation like CBC, LFT, viral profile, protein AG ratio, serum albumin, PT, APPT, serum ammonia, serum electrolytes, blood urea, blood glucose and U/S abdomen.

The data were evaluated in statistical program SPSS version 16. Qualitative data (frequency and percentage) like GI bleeding, infections, constipation etc were presented as n (%) – Numerical parameters i.e age was presented as mean ± standard deviation. All the data was calculated on 95% confidence interval. As it was descriptive study, hence no statistical test was applied to compare proportion.

RESULTS

The data obtained from 100 patients of chronic liver disease with features of porto-systemic encephalopathy were admitted in hospital. Male and female ratio was 2:1 and there were 68(68.0%) males and 32(32.0%) females patients with mean + SD of age 48.36+13.1(Table I).

Table-I. Demographic characteristics of the patients of porto-systemic encephalopathy (n = 100)

Age (in years),	48.36 ± 13.10 (20-95)
Gender	**n (%)**
Male	68 (68.0)
Female	32 (32.0)

The minimum age of the patients was 20 and maximum was 95 years. The maximum number of patients i.e. 33 was between ages 41 to 50 years (Table II).

Table-II. Groups of age in years (n = 100)

Age group	n (%)
21 to 30	12 (12.0)
31 to 40	15 (15.0)
41 to 50	33 (33.0)
51 to 60	32 (32.0)
60 to 70	07 (7.0)
Above 70	01 (1.0)

There were 9(33.3%) patients of HBsAg positive in age group 21 to 30 (Table III), while 29(39.2%) of HCV positive in age group 51 to 60(Table IV).

The different precipitating factors found in patients. Constipation was present on top of list and was found in 36(36.0%) patients. Infection included, spontaneous bacterial peritonitis in 17(17.0%) patients, Infection other than SBP was found in 24 (24.0%) patients. Upper GI bleeding was in 19(19.0%) patients. Hypokalemia in 15(15.0%) patients, renal impairment in 22(22.0%)

Table-III. Groups of age in years with HbsAg (n = 100)

	HbsAg (n=100)	
	Reactive n=27 (%)	Non-reactive n=73 (%)
Age group		
21 to 30	9 (33.3%)	3 (4.1%)
31 to 40	6 (22.2%)	9 (12.3%)
41 to 50	8 (29.6%)	25 (34.2%)
51 to 60	3 (11.1%)	29 (39.7%)
60 to 70	-	7 (9.6%)
Above 70	1 (3.7%)	-

Table-IV. Groups of age in years with Anti-HCV (n = 100)

	HCV	
	Reactive n=74 (%)	Non-reactive n=26 (%)
Age group		
21 to 30	3 (4.1%)	9 (34.6%)
31 to 40	9 (12.2%)	6 (23.1%)
41 to 50	26 (35.1%)	7 (26.9%)
51 to 60	29 (39.2%)	3 (11.5%)
60 to 70	7 (9.5%)	-
Above 70	-	1 (3.8%)

patients, hyponatremia in 18(18.0%) patients. However there was no precipitating factor found in 4(4.0%) patients. The summary of different identified precipitating factors of porto-systemic encephalopathy are shown in (Table V).

Regarding viral marker, anti-HCV antibodies were detected in 74(74.0%) patients and HbsAg positive in 27(27.0%) patients. One patient having both anti-HCV antibodies and HbsAg (Fig-1).

Table-V. Precipitating factors of porto-systemic encephalopathy (n = 100)

Causes	n (%)
Volume depletion secondary to diuretics	4 (4.0%)
Volume depletion other than diuretics	5 (5.0%)
Renal impairment other than volume deplete	22 (22.0%)
SBP (Documented / Suspected)	17 (17.0%)
Infection other than SBP	24 (24.0%)
Upper GI bleeding	19 (19.0%)
Constipation	36 (36.0%)
Sedative of hypnotics	2 (2.0%)
Recent liver failure (recent increase)	7 (7.0%)
Huge paracentesis	3 (3.0%)
Hyponatremia	18 (18.0%)
Hypokalemia	15 (15.0%)
Hypoglycemia	4 (4.0%)
Unknown cause	4 (4.0%)

Among 68(68.0%) male patients, anti-HCV positive in 52(70.3%) patients (Fig-2), HbsAg positive in 17(63.0%) patients (Graph: 03), both anti-HCV and HbsAg positive in 1(1.0%) patient. However in 4 (4.0%) no cause was detected.

Among 32(32.0%) female patients, anti-HCV was positive in 22(29.7%) patients (Fig-2), HBsAg was positive in 10(37.0%) patients (Fig-3).

DISCUSSION

Porto-systemic encephalopathy (PSE) is brain and nervous system damage that occurs as a complication of liver disorders. It causes different nervous system symptoms including changes in reflexes, changes in consciousness, and behavior changes that can range from mild to severe[13]. In cirrhotic patients PSE has been reported in 19% to 50%[14].

The present study focused on the evaluation of precipitating factors of porto-systemic encephalopathy in

Fig-1. Viral markers noticed in 100 patients of porto-systemic encephalopathy (n = 100)

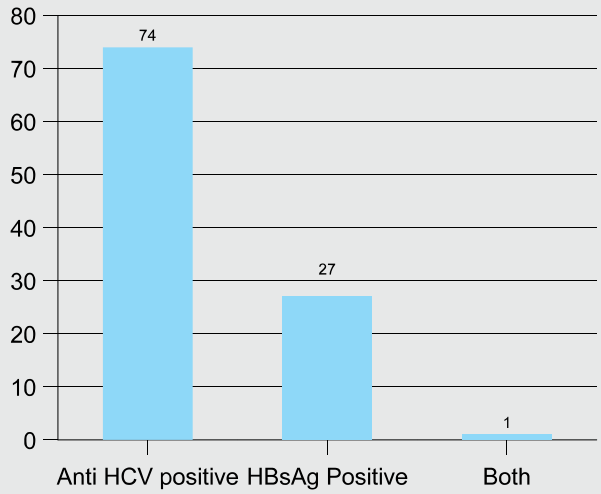
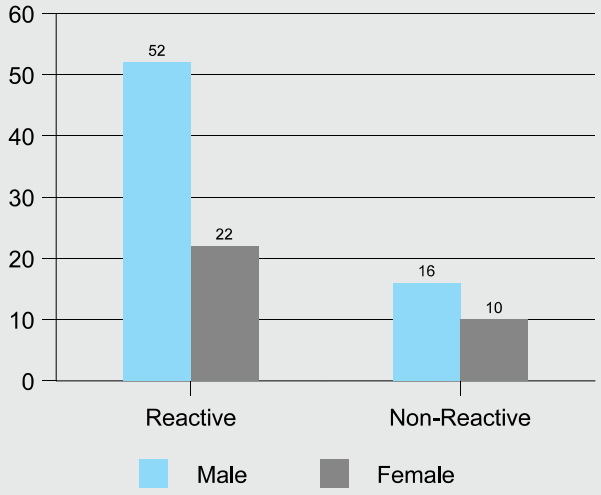
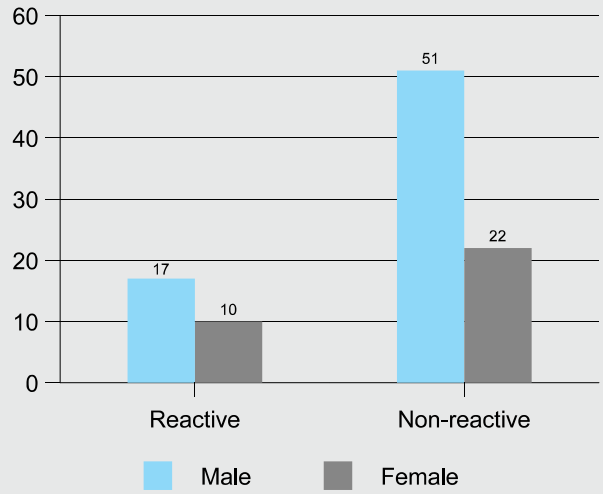


Fig-2. Male and female patients having HCV positive (n = 100)



patients with chronic liver disease. The majority of patients recruited in our study were males (68%), however our such observation is resembled with the study of Tan et al[15]. Similarly another study conducted on "Development of a clinical hepatic encephalopathy staging scale" also shown the male predominance[16]. In my study the mean age of patients with hepatic encephalopathy was 48.36± 13.1, however a study conducted by Shavakhi et al also displayed similar finding[17].

Fig-3. Male and female patients having HBV positive (n = 100)



Pakistan carries one of the world's highest burdens of chronic hepatitis and mortality due to liver failure[18]. The present study identified hepatitis C viral infection found in 74% patients. However two other studies also identified that viral hepatitis is the common cause of cirrhosis and hepatic encephalopathy[19,20].

Over a million die annually due to HBV induced hepatic encephalopathy[21]. Majority of the patients in my study were villagers living in remote areas 78% i.e. rural population while remaining 22% were from Hyderabad city i.e. urban population. The drawback for rural population is that they reached in tertiary care hospital usually in late phase and lack of health education to them regarding precipitating factors may be a contributory factor.

Common precipitating factors are:[22-23] (a) Constipation that increases intestinal production and absorption of ammonia, (b) Renal failure that leads to decreased clearance of urea, ammonia, and other nitrogenous compounds, (c) Gastrointestinal bleeding that leads to presence of blood in the upper gastrointestinal tract results in increased ammonia and nitrogen absorption from the gut. (d) Bleeding may predispose to kidney hypoperfusion and impaired renal function. (e) Blood transfusions may result in mild hemolysis, with resulting

elevated blood ammonia levels, (f) Infection that may predispose to impaired renal function and to increased tissue catabolism, both of which increase blood ammonia levels and (g) medications (drugs) that act upon the central nervous system such as opiates, benzodiazepines, antidepressants, and antipsychotic agents may worsen hepatic encephalopathy; diuretic therapy that decrease serum potassium levels and alkalosis may facilitate the conversion of NH4+ to NH3 and dietary protein overload that is an infrequent cause of hepatic encephalopathy. The most precipitating factors of porto-systemic encephalopathy observed in our study were constipation (36%), infection (24%), renal impairment (22%), volume depletion (5%), gastrointestinal bleeding (19%), hypokalemia (15%), hyponatremia (18%), hypoglycemia (4%), sedative or hypnotics (2%) and huge paracentesis (3%);however various studies conducted in different setup and hospitals shown the similar precipitating factors with different frequencies[24,25,26]. In our study the most common precipitating factor found was constipation, however a recent study published in Rawal Medical Journal 2009 conducted by Tariq et al has shown the similar results[27].

In present study the volume depletion was observed in 4% and it is similar with the study by Richards et al[28]. The spontaneous bacterial peritonitis was identified in 17% of patients as an precipitating factor, where as it is detected by Fernández, et al in his study conducted on "Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis"[29]. The bleeding was observed in 19% of patients and similar finding was identified by Halsted et al[30]. In present study the history of use of sedative and hypnotics was observed in 2% of patients, however it is similar with the statements of Iversen et al[31]. The hyponatremia was identified in 18% of patients as a precipitating factor, where as Guevara et al conducted a study on "Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analysis" shown similar observation[32]. The hypokalemia was identified in 15% patients, however it was 12% in the study by Maqsood et al[24]. The hypoglycemia usually observed in cirrhosis, it is one of the precipitating factor for developing hepatic encephalopathy[33] and in our study it was identified in 4% of patients.

There is a definite need for health education in cirrhotic patients regarding risk of porto-systemic encephalopathy and its precipitating factors and a constant need and effort to avert them at all costs. Proper dietary advice must be an integral part of all counseling protocols to chronic liver disease patients.

CONCLUSION AND RECOMENDATIONS

Constipation, Infection, renal impairment, gastrointestinal bleeding and electrolyte disturbances are the most common identified precipitating factors of hepatic encephalopathy. Priority should be given to these factors in terms of hospital funds, medicines and human efforts. Caution must be exercised in putting cirrhotic patients on diuretics. Early and effective infection control measures and better hygienic conditions in government hospitals are needed to be maintained. Consistent use of lactulose and fibre should be encouraged to prevent constipation. More and more endoscopic facilities should be made available nationwide for prompt control of gastrointestinal bleeding and most importantly, a more committed effort is needed to control increasing incidence of hepatitis C. Only then we stand any chance of combating cirrhosis and even worse hepatic encephalopathy.

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