

Original Research Article

Assessment of serum prolactin level in hepatic encephalopathy patient

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ABSTRACT

Background: Hepatic encephalopathy (HE) is a complex neuropsychiatric disorder that arises in both acute and chronic liver disease. It is typified by the disturbance in consciousness and behavior, personality changes fluctuating neurological signs, asterisks or flapping tremors and distinctive EEG changes. This study was established to assess and evaluate the serum prolactin level in hepatic encephalopathy (HE) patient.

Methods: The present cross-sectional study consisted a total 70 patients, out of those 35 were having HE and the rest 35 had no clinical evidence of HE. Those patients without clinical evidence of HE but having cirrhosis of liver, acute viral hepatitis and normal healthy controls.

Results: Serum prolactin levels of patients of cirrhosis of liver with hepatic encephalopathy ranged from 37.6-210.7 ng/ml with a mean of 73.63 ± 43.85 ng/ml. In patients, Prolactin levels were found significantly high in cirrhosis of liver patients with HE then cirrhosis of liver without HE patients ($p < 0.001$). Level of serum prolactin in patients with hepatic encephalopathy with Fulminant hepatic failure (FHF) ranged from 30.6-119.7 ng/ml with a mean of 71.24 ± 26.87 ng/ml. The values obtained from these are significantly higher as compared to those in normal healthy controls and those in acute viral hepatitis ($p < 0.001$). Level of serum prolactin in patients of liver cirrhosis without hepatic encephalopathy ranged from 18.6-26.4 ng/ml with a mean of 21.48 ± 2.43 ng/ml. These values are significantly higher than those found in normal healthy controls and those found in acute viral hepatitis ($p < 0.001$). Mortality rate was 70% in patients of cirrhosis of liver with HE.

Conclusions: Serum prolactin levels (SPL) are significantly higher in patients with complications such as hepatic encephalopathy and higher the levels, greater the severity. Hence, we conclude that level of serum prolactin can be used as a useful prognostic marker in patients with cirrhosis of the liver as well as an early indicator of its complications.

Keywords: Hepatic encephalopathy, Serum prolactin, Liver cirrhosis, Acute viral hepatitis, Fulminant hepatic failure

INTRODUCTION

Hepatic encephalopathy (HE) is a syndrome usually found in patients with cirrhosis. HE is well-defined as a range of neuropsychiatric abnormalities in patients with liver dysfunction, after elimination of brain disease.¹ It is characterized by the disturbance in consciousness and behavior, personality changes fluctuating neurological signs, asterisks or flapping tremors and distinctive EEG changes.² Although the precise pathophysiological mechanisms responsible for hepatic encephalopathy are

not fully understood, a defect in neurotransmission rather than a primary shortfall in cerebral energy metabolism seems to be involved.³ HE establishes by broad range of neuropsychiatric disturbances such as: defects in cognitive, emotional, behavioral, psychomotor, and locomotive functions.⁴ The diagnosis of overt HE is founded on clinical examination. Symptoms of overt HE is reported in around 30-45% of patients with liver cirrhosis and 10-50% of patients with trans jugular intrahepatic portosystemic shunts.⁵ Inclining factors for the expansion of HE are elevated levels of ammonia, zinc,

alcohol intake, and the existence of esophageal varices, branched chain amino acids, and minimal hepatic encephalopathy.⁶ Electrolyte anomalies, high protein diet, bleeding in the gastrointestinal tract, diuretics, infections, and sedatives may arouse the development of HE.⁷

According to preceding studies, hyperammonemia remains prime factor responsible for the brain related abnormalities in HE.^{8,9} Several mechanisms that describe the effect of ammonia on central nervous system (CNS) have been anticipated such as: specific relations among brain endothelium and astrocytes, adjustment of transport across the blood-brain barrier, fluctuations in energy metabolism, a straight neurotoxic effect on astrocytes, and neuronal membranes, reducing the production of free glutamate with glutamatergic neurotransmission disorder.¹⁰⁻¹² Among the neurotransmitter modification, main was dopamine. But dopamine is restricted by the fact that it cannot be determined in any of the body fluids or brain. Since dopamine puts negative control on prolactin, few studies shown prolactin to be a predictive marker.^{13,14}

Considering voids from Indian context, current study was aimed to assess and evaluate serum prolactin level (SPL) in hepatic encephalopathy patients with liver cirrhosis.

METHODS

This hospital based prospective cross-sectional study has been carried out in department of medicine, KPS institute, GSVM medical college, Kanpur, Uttar Pradesh, India during January 2020 to December 2020 on 70 patients. The study was approved by ethical committee of GSVM medical college Kanpur. Patients above the age of 15 years to 50 years with diagnosis of liver cirrhosis and/or its complications, disturbance of awareness and mentation progressing from reduced alertness, poor concentration, forgetfulness, confusion to stupor, and finally coma, shifting combination of neurological signs like asterixis, rigidity, hyper reflexia, and extensor plantar responses, past history of infective hepatitis, alcoholism, malabsorption and poor nutrition, nonspecific digestive symptoms such as anorexia, nausea vomiting and upper abdominal; discomfort and who have consented to participate in this study were included in this study. Pregnant women, lactating women, patients with chronic renal failure, hypothyroid patients, patients on following drugs-e.g., phenothiazines, thioxanthene, haloperidol, SSRI, estrogen, anti-androgen, opiates and metoclopramide, patients with no previous documentation of pituitary tumour were excluded from the study.

The cases were clinically evaluated and thoroughly investigated. All 70 patients were divided into 3 groups. Group A: consisted of normal healthy controls; Group B: were cases of viral hepatitis which were again sub grouped into patients with clinical evidence of hepatic encephalopathy (15 cases) and patients without hepatic failure (10 cases); Group C: consisted of patients of cirrhosis of liver without clinical evidence of hepatic

encephalopathy (15 cases) and cirrhosis of liver with hepatic encephalopathy (20 cases).

The patients underwent a detailed history including past, treatment and personal history to identify possible etiologies and a thorough clinical examination to identify the evidence of cirrhosis of the liver and the presence of its complications including portal hypertension, ascites, and hepatic encephalopathy. The findings were logged in a specially prepared proforma. The cases were subjected to following investigations: Hb, TLC, DLC, ESR, urine routine and microscopy, random blood sugar, SGPT/SGOT, serum bilirubin total and differential, prothrombin time, serum total protein, albumin and globulin, upper GI, endoscopy, USG whole abdomen, ascitic fluid examination cytology, biochemical examination and AFB/gram staining, ELISA for HBsAg., serum prolactin assay C. L. I. A. method (chemiluminescent immuno assay).

The patients were then scored based on the modified child Pugh scoring system and divided into classes A, B or C based on the score obtained.¹⁵ The complications of cirrhosis such as ascites, portal hypertension, esophageal varices, hepatic encephalopathy, hepatorenal syndrome and spontaneous bacterial peritonitis were identified.

Statistical analysis

Data analysis was done using Statistical Package for Social Science (SPSS version 10.5) package. The collected data was summarized in the form of mean±standard deviation (SD) and range for measurable data and frequency and percentage for qualitative data. Comparisons between the various study groups were done using student t test. Association between variables was considered statistically significant if $p < 0.05$.

RESULTS

Out of the 70 cases 43 (61.4%) were male and 27 (38.6%) were female (Figure 1). Gender distribution among groups was shown in Figure 2. The presenting symptoms of Fulminant hepatic failure (FHF) were 80% of patients had yellowness of eyes and urine, 66.67% of patients had complaints of fever, while 53.33% patients came to us in the state of altered sensorium. Common symptoms of patients of liver cirrhosis presenting with hepatic encephalopathy 40% patients had noticed yellowish of sclera and urine. Other complaints were hematemesis (45%) melena (50%) and seizures (20%). The total duration of illness of the patients of cirrhosis of liver was majority (65.71%) of the patients had illness of more than 1 year of duration, while 28.57% patients gave the history of duration of illness of more than one and a half year.

In respect of HBsAg positivity, it was more positive in the acute hepatitis group (13/25, i.e., 52%) while in the patients of liver cirrhosis, the positivity was only 17.14%. None of the healthy control was HBsAg positive. Overall,

the HBsAg positivity was 27.1% in the study group (Table 1). The causes of liver cirrhosis in the studied patients were chronic alcoholic (45.7%), hepatitis B virus (22.8%) and

hepatitis C virus (14.3%) etc. (Figure 3). Cause in 5 (14.3%) could not be determined.

Table 1: HBsAg positivity in study subjects.

Study group		No. of HBsAg positive cases, (n=19)	Percentage of positivity (%)
Group A, (n=10)	Normal healthy controls	0	0
Group B, (n=25)	Acute viral hepatitis with no clinical evidence of HE, (n=10)	4	40
	Acute viral hepatitis with clinical evidence of HE, (n=15)	9	60
Group C, (n=35)	Cirrhosis of liver without HE, (n=15)	3	20
	Cirrhosis of liver with HE, (n=20)	3	15

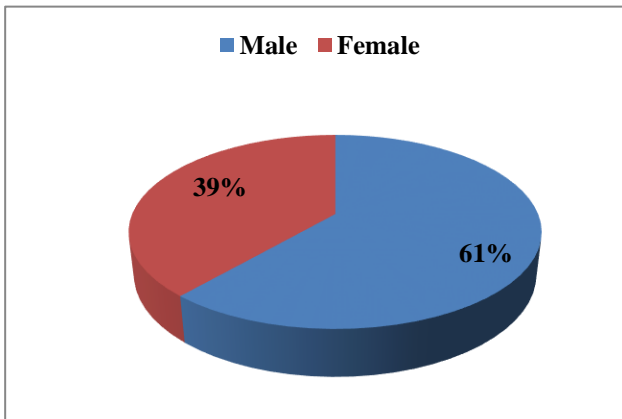


Figure 1: Overall gender distribution.

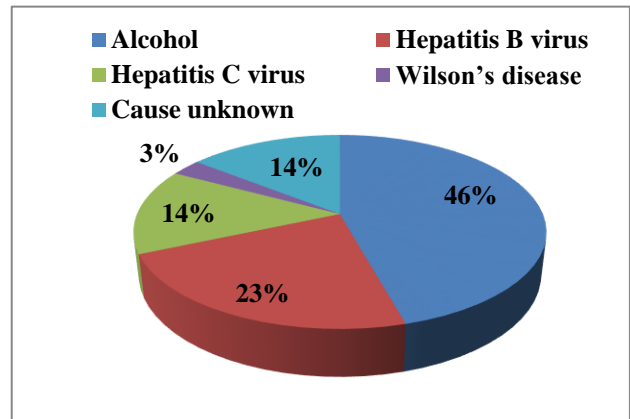


Figure 3: Causes of cirrhosis of liver in the study population.

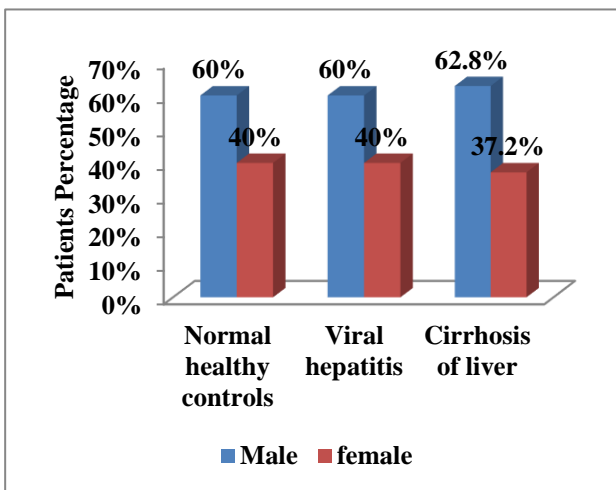


Figure 2: Gender in groups.

Gastrointestinal bleeding (40%) and infection (30%) were the prominent causes of HE in patients of liver cirrhosis. The other causes of precipitation of hepatic encephalopathy were alcohol intake (15%), hypokalemia (10%) and constipation (5%) (Figure 4).

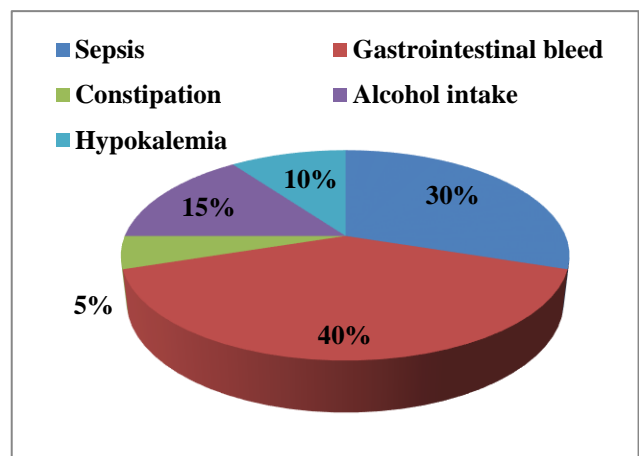


Figure 4: Precipitating cause of HE in patients of cirrhosis of liver.

The severity of cirrhosis of liver was estimated according to child Pugh scoring system (Group A, B and C) where 34.29% of patients were of class A group (Score of 5-6). 22.86% of patients fell under group B (score of 7-9) while

rest 42.85% patients were in the most severe group C (score of 10 or above). A 66.6% of patients of FHF had demonstrable flapping tremor, while 60% of patients of

liver cirrhosis with clinical evidence of hepatic encephalopathy showed flapping tremors.

Table 2: Serum prolactin levels in studied patients.

Study group	Serum prolactin levels (ng/ml)	
	Mean±SD	Range
Group A: Normal, (n=10)	Healthy controls	11.22±3.54 6.2-18.6
Group B: Patients of viral hepatitis, (n=25)	Patients without clinical evidence of HE, (n=10)	9.68±3.66 5.8-19.6
	Patients with clinical evidence of HE, (n=15)	71.24±26.87 30.6-119.7
Group C: Patients of cirrhosis of liver, (n=35)	Without clinical evidence of HE, (n=15)	21.48±2.43 18.6-26.4
	With clinical evidence of HE, (n=20)	73.63±43.85 37.6-210.7

Table 3: Comparison between serum prolactin levels in patients of cirrhosis of liver with hepatic encephalopathy with other study groups without clinical evidence of hepatic encephalopathy.

Study group	Serum prolactin means (ng/ml)	Serum prolactin range (ng/dl)
Normal healthy controls, (n=10)	11.22±3.54	6.2-18.6
Acute viral hepatitis, (n=10)	9.68±3.66	5.8-19.6
Cirrhosis of liver, (n=15)	21.4±2.43	18.6-26.4
Cirrhosis of liver with hepatic encephalopathy, (n=20)	73.63±43.85	37.6-210.7

For 4th vs. 1st: $t=4.45$, $p<0.001$ (highly significant); For 4th vs. 2nd: $t=6.67$, $p<0.001$ (highly significant); For 4th vs. 3rd: $t=4.17$, $p<0.001$ (highly significant).

Table 4: Comparison of serum prolactin levels in patients of hepatic encephalopathy with fulminant hepatic failure with normal healthy controls and acute viral hepatitis.

Study group	Serum prolactin means (ng/ml)	Serum prolactin range (ng/dl)
Normal healthy controls, (n=10)	11.22±3.54	6.2-18.6
Acute viral hepatitis, (n=10)	9.68±3.66	5.8-19.6
Fulminant hepatic failure with hepatic encephalopathy, (n=15)	71.24±26.87	30.6-119.7

For 3rd vs. 1st: $t=6.97$, $p<0.001$ (highly significant); For 3rd vs. 2nd: $t=7.15$, $p<0.001$ (highly significant).

Table 5: Correlation of serum prolactin levels to mortality in patients of cirrhosis of liver with hepatic encephalopathy and hepatic encephalopathy with Fulminant hepatic failure.

Type of patients		Serum prolactin levels (ng/ml)		P value
		<50	>50	
Cirrhosis of liver with hepatic encephalopathy	No. of patient, (n=20)	8	12	<0.05
	No. of patients expired (%)	4 (50)	10 (83.3)	
Hepatic encephalopathy with Fulminant hepatic failure	No. of patient, (n=15)	3	12	<0.05
	No. of patients expired (%)	1 (33.3)	10 (66.6)	

Serum prolactin values are slightly on the higher side in patients of cirrhosis of liver without clinical evidence of hepatic encephalopathy (Table 2).

higher than those in patients of cirrhosis of liver without hepatic encephalopathy, acute viral hepatitis and normal healthy controls ($p<0.001$) (Table 3).

The level of serum prolactin in patients of liver cirrhosis with hepatic encephalopathy are statistically significantly

The serum prolactin levels in patients of FHF with hepatic encephalopathy are statistically significantly higher than

those in patients of acute viral hepatitis and normal healthy controls ($p < 0.001$) (Table 4).

The level of serum prolactin in patients of hepatic encephalopathy with cirrhosis of liver were found elevated, out of the 20 cases, 8 cases (40%) had level of serum prolactin below 50 ng/ml, while rest 12 (60%) had more marked elevated in level of serum prolactin (> 50 ng/ml). The level of serum prolactin in patients of FHF was found as out of the 15 cases studied 3 cases (20%) had mildly elevated serum prolactin levels (< 50 ng/ml), whereas rest 12 (80%) had more marked elevation of serum prolactin levels (> 50 ng/ml). Mortality was reported in 24 patients out of total studied patients. There is statistically significant correlation between level of serum prolactin and mortality of the patients in patients of cirrhosis of liver with hepatic encephalopathy, with mortality increasing at higher level of serum prolactin ($p < 0.05$). There is statistically significant correlation of level of serum prolactin to mortality in patients of hepatic encephalopathy with FHF we observed that with mortality increasing significantly at serum prolactin levels > 50 ng/ml (Table 5).

DISCUSSION

Prolactin levels in patients with hepatic dysfunction have been debated. Various authors have conveyed hyperprolactinemia although few have debated the same. Hormonal interruption in cirrhosis has been assessed by very less researchers, and the studies have concluded lower T3 and cortisol levels with elevated prolactin in the serum.¹⁶ The present study has been undertaken with 25 cases of viral hepatitis and 35 patients of cirrhosis of liver with matching healthy controls of 10 patients. Out of total 43 (61.4%) were males and 27 (38.6%) were females. As far as HBsAg positivity is concerned, 19 out of 70 (27.1%) were HBsAg positive and the positivity was more in acute hepatitis group (13/25, i.e., 52%). 30% (21) of the study population were alcoholic, majority (17/ 21 i.e., 81% of alcoholics) of which coming from the group of patients with cirrhosis of liver. Similar observation was reported by Jha et al, in their study among 60 patients with liver disease, 19 were found to be positive for HBsAg (13 with viral hepatitis and 6 with cirrhosis liver).³

The most common cause of cirrhosis of liver was alcoholic liver disease (45.71%). Viral hepatitis, both hepatitis B virus (22.85 %) and hepatitis C virus (14.29%) were the next common causes. Jha et al reported among the 25 patients of acute viral hepatitis, 15 (60%) had symptoms and signs of encephalopathy, and among the 35 patients with liver cirrhosis, 20 (57.1%) had such features.³ In our study, of the 35 case of cirrhosis of liver, 12 (34.2%) were in child Pugh class A group (score of 5-6), i.e., in the compensated phase of cirrhosis, whereas 23 (65.8%) cases had child Pugh score of 7 or more, i.e., in the decompensated phase of cirrhosis. In Jha et al study, 12/35 (34.3%) patients were found with liver cirrhosis belonged to category A of Child-Pugh classification, 8/35 (22.9%)

were B and the remaining (15/35, 42.9%) were C type.³ In the present study, the most common precipitating cause of hepatic encephalopathy in patients of cirrhosis of liver in the study population was acute G. I. bleed (40%) followed by sepsis (30%).

Prolactin release in human beings is normally associated with a pulsatile pattern, but a constant 24 hours elevation has been found in patients with cirrhosis liver.¹⁶ In our study, it is clear from the table that serum prolactin levels are markedly raised in patients of hepatic encephalopathy irrespective of the cause. But levels of serum prolactin are comparable in normal healthy controls and in those with acute viral hepatitis. Serum prolactin values are slightly on the higher side in patients of cirrhosis of liver without clinical evidence of HE.

Serum prolactin levels were comparable in patients of normal healthy controls) and cases of acute viral hepatitis. But the level of serum prolactin level was statistically significantly higher in patients of cirrhosis of liver even without hepatic encephalopathy. The study also showed that there was statistically-significant rise of level of serum prolactin in patients of hepatic encephalopathy irrespective of the cause. The differences in mean serum prolactin levels in patients of hepatic encephalopathy with cirrhosis of liver and in those with FHF are not statistically significant. The significant elevation of serum prolactin levels in patients of cirrhosis of liver without hepatic encephalopathy as compared to normal healthy controls and in acute viral hepatitis is due to the fact that there is continuation of damage to hepatocytes progressing from normal liver function to cirrhosis of liver, progressing ultimately to hepatic encephalopathy.

Correlation between serum prolactin levels and mortality

There was a single (10%) expiry in patients of acute viral hepatitis, as compared to 10 (66.67%) mortality in patients of FHF (71.24 26.87). Similarly, in patients of cirrhosis of liver, only one patient died (6.67%) without clinical evidence of hepatic encephalopathy (21.48 2.43), while 14 (70%) patients expired with clinical evidence of hepatic encephalopathy.

In the patients of hepatic encephalopathy with cirrhosis of liver 8 patients had level of serum prolactin less than 50 ng/ml, and 4 of them (50%) expired. But in those patients with level of serum prolactin more than 50 ng/ml, 10 out of 12 (i.e., 83.33%) expired. The correlation between level of serum prolactin and mortality was significant ($z = 1.65$, $p < 0.05$). So, our findings suggest that serum prolactin levels are increased in patients of hepatic encephalopathy and that the mortality is more when serum prolactin levels are > 50 ng/ml i.e., moderate to markedly raised.

We know that serum prolactin is regarded as a sensitive indicator of functional dopamine activity in brain, and dopamine is a hypothalamic prolactin inhibitor factor.¹⁷ So increased prolactin levels indicate depletion of dopamine

and other catecholamine levels (true neurotransmitters). The levels of these neurotransmitters are also related to the severity of liver disease. So, lesser the level of these true neurotransmitters, (i.e., more the level of serum prolactin), more is the severity of liver disease, and hence more the mortality.

Similar correlation of mortality to level of serum prolactin were observed by previous workers. McClain et al in his study observed that 21 patients of alcoholic liver disease with PSE were divisible into two groups, 12 patients were having mildly increased serum prolactin values and 9 patients were having markedly increased level of serum prolactin. Patients of latter group not only had greater derangement of liver functions but also higher mortality (100%).¹⁸

Sharma et al also observed that 20 patients of liver cirrhosis with hepatic encephalopathy were divisible into two groups.¹⁹ In current study, 8 patients had serum prolactin levels less than 50 ng/ml and 12 patient had serum prolactin levels more than 50 ng/ml. Similar trend was seen in patients of hepatic encephalopathy with FHF. The expiry was much less (1 out of 3, i.e., 33.3%) in patients with serum prolactin levels less than 50 ng/ml as compared to those in whom level of serum prolactin were more than 50 ng/ml (10 out of 15, i.e., 66.67%) This observation shows that serum prolactin may be seen as a prognostic indicator in patients of hepatic encephalopathy. Thus, our observation of higher mortality in patients of hepatic encephalopathy having higher prolactin levels is consistent with the previous workers like McClain et al and Sharma et al.^{18,19}

Results of the present study showed significant elevation of prolactin levels in patients of cirrhosis of liver with or without hepatic encephalopathy in comparison to those patients with no clinical evidence of hepatic encephalopathy. It is well recognized that serum prolactin is a sensitive indicator of dopamine activity in the brain. Further it has been observed that elevated prolactin concentrations in cirrhosis with hepatic encephalopathy and in FHF were associated with significant alteration of hepatic functions.

Similar observations were also made by McClain et al in patients of alcoholic liver disease with Porto systemic Encephalopathy in whom a disturbance of pituitary hypothalamic axis was postulated to be underlying mechanism of the altered prolactin status.¹⁸ A critical concentration of these pseudo neurotransmitters in the brain accompanying other metabolic derangements may be responsible for Porto Systemic Encephalopathy. So, mild to moderate release of prolactin levels as seen in our patients of cirrhosis without hepatic encephalopathy may indicate pseudo euro transmitters like activity below the critical level necessary to induce hepatic encephalopathy or might be requiring other pathogenic factor to induce hepatic encephalopathy.¹⁹ Sharma et al suggested that level of serum prolactin can be treated as a prognostic

indicator in patients having cirrhosis of liver with hepatic encephalopathy. With above discussion it can be concluded that in patients of hepatic encephalopathy elevation of serum prolactin, a known marker of functional dopamine activity, supports the hypothesis that elevation of pseudo transmitters like octopamine with depletion of true neurotransmitters like dopamine play a role in the pathogenesis of hepatic encephalopathy.¹⁹

Mukherjee et al analyzed the prolactin levels in patients with hepatic cirrhosis and reported a higher level in both patients with encephalopathy and mortality. Also, they found out a direct correlation between the clinico-biochemical severities of the condition and mortality.²⁰

CONCLUSION

We found that serum prolactin levels are increased in cases of hepatic encephalopathy. We also found that patients with more severe liver damage had proportional increase in serum prolactin levels. Higher serum prolactin levels were associated with high mortality in the patients as well. So, we can conclude that serum prolactin can be exercised as an indicator of severity of hepatic encephalopathy, which means that the patients of hepatic encephalopathy with higher serum prolactin levels need urgent and intensive medical care. From the present study another conclusion can be made that serum prolactin level may be used as prognostic indicator for patients of hepatic encephalopathy. Serum prolactin levels and mortality of patients studied groups shows that higher the serum prolactin level, poorer the prognosis. Higher levels of serum prolactin were associated with higher mortality rates in patients of hepatic encephalopathy.

The limitation of the present study was small sample size. Future studies have to be directed in a larger group of patients with different indications and their severity states.

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