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To study the prevalence of hyperprolactinemia in liver cirrhosis patients at tertiary care hospital Bikaner, Rajasthan

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Abstract

Background: Hyperprolactinemia is a frequent endocrine disorder with well known harmful effects on the reproductive system and bone metabolism. Besides prolactinomas several drugs and disorders such as renal failure and hypothyroidism have been shown to cause hyperprolactinemia. Based on former studies, liver cirrhosis has also been suggested to cause hyperprolactinemia, while mechanisms have not been identified yet. In this study, we find out the prevalence of hyperprolactinemia in liver cirrhosis patients at tertiary care hospital Bikaner, Rajasthan.

Methods: The present study is a cross-sectional study planned in consecutive cases of liver cirrhosis from different etiologies, who were admitted in different wards in the Department of Medicine, S.P. Medical College, P.B.M. and Associated group of Hospitals, Bikaner, from 1st June 2019 to 30th November 2019. One hundred cases of liver cirrhosis were taken up for the study.

Results: In the present study, out of the total 100 cirrhotic patients taken up for the study, 62 patients had elevated prolactin levels while in 38 patients it was found to be within the normal range.

Conclusion: Hyperprolactinemia is a common finding seen among the patients of liver cirrhosis. It was present in a significant number of the patients of liver cirrhosis irrespective of the etiology of cirrhosis. Prolactin levels increase significantly with severity and duration of liver disease.

Keywords: Hyperprolactinemia, liver cirrhosis, etiology.

Introduction

Cirrhosis, a final pathway for a variety of chronic liver diseases, is a pathologic entity defined as diffuse hepatic fibrosis with the replacement of the normal liver architecture by nodules[1].

Most deaths in patients with cirrhosis occur as a result of hepatic decompensation; however, in the compensated stages, the most common cause of death is cardiovascular disease, followed by stroke, malignancy and renal disease[2]. Complications of portal hypertension, hepatocellular carcinoma (HCC) and sepsis[3] are the usual causes of mortality in patients with decompensated cirrhosis.

The complications of cirrhosis are basically the same regardless of the etiology. Nonetheless, it is useful to classify patients by their cause of the liver disease[4].

Prolactin levels in patients with hepatic dysfunction have been debated in detail. Elevation of prolactin occurs mainly due to the drop in dopamine levels in the tuberoinfundibular tract[5]. Prolactin secretion is mainly regulated by tonic hypothalamic inhibition through dopamine and the stimulatory influences of hypothalamic releasing factors and circulating estrogens are elevated in liver cirrhosis due to increased peripheral aromatization of testosterone via androstenedione and to a lesser extent through a decreased elimination by liver[6-9]. These estrogens stimulate prolactin release by interfering with dopamine secretion from the hypothalamus and through a direct effect on anterior pituitary[6]. Decompensated liver function leads to a change in the type of aminoacids entering the central nervous system. Circulating concentrations of aromatic aminoacids have been found to increase leading to an increase in the synthesis of false neurotransmitters such as octapamine and phenylethanolamine[10]. These false neurotransmitters may inhibit dopamine release contributing to hyperprolactinemia[11].

Materials and Method

The present study is a cross-sectional study planned in consecutive cases of liver cirrhosis from different etiologies, who were admitted in different wards in the Department of Medicine, S.P. Medical College, P.B.M. and Associated group of Hospitals, Bikaner, from 1st June 2019 to 30th November 2019. One hundred cases of liver cirrhosis were taken up for the study.

Inclusion Criteria

All patients of liver cirrhosis above the age of 18 years, including both sexes admitted in different wards of the Department of Medicine. Patients who consented to participate in the study.

Exclusion Criteria

1. History of cranial surgery or irradiation
2. Chest wall trauma
3. History of pituitary or hypothalamic disease
4. Chronic renal failure
5. Herpes zoster
6. Pregnant and lactating women
7. Patients on medications known to cause hyperprolactinemia

a. Atypical anti psychotics (risperidone)
b. Phenothiazines (chlorpromazine, perfenazine)
c. Butyrophenones (haloperidol)
d. Thioxanthines
e. Metoclopramide
f. Dopamine synthesis inhibitors (alpha methyldopa)
g. Catecholamine depletors (reserpine)
h. Opiates
i. H2 antagonists (cimetidine, ranitidine)
j. Imipramines (amitryptyline, amoxapine)
k. Serotonin reuptake inhibitors (fluoxetine)
l. Calcium channel blockers (verapamil, estrogens, thyrotropin releasing hormone)

8. Seizure disorders
9. Hypothyroidism
10. Patients less than 18 years age
11. Patients not willing to participate in the study.

Method of data collection

1. All patients were evaluated as per the proforma including demographic profile, clinical evaluation and laboratory tests. Various laboratory tests like CBC, RFT, LFT, PT-INR, HBsAg, Anti-HCV, were done in all cases. Underlying etiology and reason to hospitalize was also evaluated by clinical and laboratory examinations as per the proforma.
2. All cases were subjected to USG abdomen and pelvis and esophago-gastroduodenoscopy (OGD). Cases were treated and followed up as per standard protocol.
3. Evaluation of prolactin levels-prolactin (PRL) chemiluminescence immunoassay (CLIA).

Statistical Analysis

Descriptive statistical measures (mean, median, standard deviation and range) were estimated for summarizing the quantitative variables. Student 't' test and ANOVA test were applied for quantitative data and Chi-Square test was applied for qualitative data. The data analysis was performed by using Statistical Package for the Social Sciences (SPSS) software 17.0 version. The two sided $p<0.05$ considered as statistically significant.

Observations

Table 1: Distribution of Cases According To Age In Relation To Etiology Of Liver Cirrhosis

Age Class (Years)	Alcohol	NASH	HBV	HCV	Cryptogenic	Autoimmune	Total
≤20	0	1	0	0	0	0	1
21-30	2	3	0	0	0	1	5
31-40	19	7	1	2	0	0	29
41-50	17	6	1	0	0	0	24
51-60	9	4	0	2	3	0	18
61-70	9	4	2	0	0	0	15
>70	2	5	0	0	0	0	7
Mean	47.82	50.00	53.25	44.50	51.00	23.00	48.41
SD	13.35	17.37	13.62	13.08	0.00	0.00	14.53
Range	22-75	19-78	40-65	32-59	51-51	23-23	19-78

The mean age of the total cases in the study was 48.41±14.53 (age range = 19-78). The majority of total cases included in the study belonged to 31-40 years of age class. In the present study, out of total 58 alcoholic patients, majority of cases belonged to middle aged class, that is, 19 cases in age class of 31-40 years and 17 cases in age class of 41-50 years. 9 cases each belonged to 51-60 years and 61-70 years age class and 2 patients each belonged to extremes of age class, that is, 21-30 and >70. Out of 4 cases in HBV class, 1 case each belonged to 31-40 years and 41-50 years age class while 2 cases belonged to age class 61-70 years. Out of 4 cases of HCV class, 2 cases each belonged to age class 31-40 years and 51-60 years. NASH was present in 30 cases and out of them 7 cases belonged to age class 31-40, 6 cases belonged to 41-50 years age class, 5 cases belonged to >70 years of age class, 4 cases each belonged to 51-60 and 61-70 years age class, 3 cases belonged to 21-30 years of age class while only 1 case belonged to age class ≤20 years. All the 3 cases of cryptogenic cirrhosis were found to belong to higher age class, that is, 51-60 years. Single case of autoimmune etiology was 23 years old.

Table 2: Distribution of cases according to gender in relation to etiology of liver cirrhosis

Gender	Alcohol	NASH	HBV	HCV	Cryptogenic	Autoimmune	Total
Female	0	17	0	0	3	1	25
Male	58	13	4	4	0	0	75

All 58 alcoholic patients were males, while 1 case of autoimmune etiology was female. 4 cases each of HBV and HCV related cirrhosis were males. Out of total 30 NASH cases, 17 cases were females and 13 cases were males and all 3 cases of cryptogenic cirrhosis were females.

Table 3: Frequency of hyperprolactinemia in liver cirrhosis patients

Prolactin level	No.	%
Normal	38	38.0
Elevated	62	62.0
Total	100	100

In the present study, out of the total 100 cirrhotic patients taken up for the study, 62 patients had elevated prolactin levels while in 38 patients it was found to be within the normal range.

Table 4.Correlation of serum prolactin level to age of liver cirrhosis patient

Age Group	Prolactin Group				Total
	Normal		Elevated		
	No.	%	No.	%	
≤20	1	100	0	-	1
21-30	1	17.8	5	93.3	6
31-40	10	34.5	19	65.5	29
41-50	5	20.8	19	79.2	24

51-60	10	55.6	8	44.4	18
61-70	6	40.0	9	60.0	15
>70	5	71.4	2	28.6	7
Total	38	38.0	62	62.0	100
Mean	52.00		46.21		
SD	15.49		13.57		
t	1.962				
p	0.053				

The above table describes correlation between serum prolactin level and age of the cirrhotic patients. The mean age in the group of patients with normal prolactin level was found to be 52±15.49 years and that in the group of patients with increased prolactin level was 46.21±13.57 years. There was no significant correlation found between the prolactin level and age of cirrhotic patient ($p>0.05$).

Table 5.Correlation of serum prolactin level to gender of liver cirrhosis patient

Characteristics	Gender	
	Female	Male
Mean prolactin	46.42	35.71
SD	52.15	29.71
Range	7.51-199.00	1.60-159.98
t	1.270	
p	0.207	

Mean prolactin level in female patients was 46.42±52.15 (range 7.51-199.00) while in males it was calculated to be 35.71±29.71 (range 1.60-159.98) and the correlation between prolactin level and gender of cirrhotic patient was found statistically insignificant ($p>0.05$).

Table 6.Correlation of serum prolactin level to duration of liver cirrhosis

Characteristics	Liver Cirrhosis		
	Newly Diagnosed	≤5 years	>5 years
Mean prolactin	21.91	34.74	69.77
SD	7.97	22.66	69.06
Range	7.51-31.72	1.60-96.00	5.16-199.00
t	9.896		
p	<0.001		

Mean prolactin level in newly diagnosed liver cirrhosis patients was 21.91±7.97 (range 7.51-31.72) whereas mean prolactin level in patients who had duration of liver cirrhosis ≤5 years was 34.74±22.66 (range 1.60-96.00) and mean prolactin level in patients who had duration of liver cirrhosis >5 years was 69.77±69.06 (range 5.16-199.0) and this difference was found statistically highly significant (p<0.001).

Table 7.Correlation of serum prolactin level to etiology of liver cirrhosis

Characteristics	etiology					
	Alcohol	NASH	HBV	HCV	Cryptogenic	Autoimmune
Mean prolactin	39.02	39.61	29.36	45.46	19.88	28.00
SD	31.87	48.49	28.59	28.81	0.00	-
Range	1.60-159.98	7.51-199.00	5.16-69.71	15.93-81.50	19.88-19.88	28.00-28.00
f	0.248					
p	0.940					

In the present study, the mean prolactin level was 39.02±31.87 (range 1.60-159.99) in alcoholic patients, 39.61±48.49 (range 7.51-199.00) in NASH patients, 29.36±28.59 (range 5.16-69.71) in HBV patients, 45.46±28.81 (range 15.93-81.50) in HCV patients, 19.88±0.00 (range 19.88-19.88) in cryptogenic cases and 28.00±0.00 (range 28.00-28.00) in autoimmune cases. The correlation between the etiology of liver disease and prolactin level was found to be insignificant (p>0.05).

Discussion

The present study was conducted in the Department of Medicine, S.P. Medical College and PBM group of Hospitals and Research Centre, Bikaner from 1st June 2019 to 30th November 2019. This study is a cross-sectional study and one hundred cases of liver cirrhosis were taken up for the study after applying the exclusion and inclusion criteria and taking consent from the patients.

Prolactin levels in patients with hepatic dysfunction have been controversial. Many authors have reported hyperprolactinemia and few have debated the same. Elevation of prolactin is attributed to fall in dopamine levels in the tuberoinfundibular tract. Decompensated liver function also leads to alteration in the type of aminoacids entering the central nervous system. Circulating levels of aromatic amino acids have been found to be increased leading to increase in synthesis of false neurotransmitters like octopamine and phenylethanolamine which inhibit dopamine release and lead to hyperprolactinemia. Cases of hypogonadism have also been reported in cirrhotic patients attributable to hyperprolactinemia. In our study, out of the total 100 cirrhotic patients taken up for the study, 62 patients had elevated prolactin levels while in 38 patients it was found to be within the normal range. Hence a large number of cirrhotic patients were found to have hyperprolactinemia. In a study by Balakrishnan et al[12] out 60 patients, 44 (73.33%) had elevated serum prolactin levels. This showed that the results of our study were consistent with the high number of cirrhotic patients with elevated serum prolactin levels as seen in previously done studies.

The mean age in the group of patients with normal prolactin level was found to be 52±15.49 years and that in the group of patients with increased prolactin level was 46.21±13.57 years. There was no significant correlation found between the prolactin level and age of cirrhotic patient. Similarly, in a study done by Khalil et al[13] in 2017, no correlation was found between the age and prolactin levels. Mean prolactin level in female patients was 46.42±52.15 (range 7.51-199.00) while in males it was calculated to be 35.71±29.71 (range 1.60-159.98) and the correlation between prolactin level and gender of cirrhotic patient was found statistically insignificant (p>0.05).

In our study, mean prolactin level in newly diagnosed liver cirrhosis patients was 21.91±7.97 (range 7.51-31.72) whereas mean prolactin level in patients who had duration of liver cirrhosis ≤5 years was 34.74±22.66 (range 1.60-96.00) and mean prolactin level in patients who had duration of liver cirrhosis >5 years was 69.77±69.06 (range 5.16-199.0) and this difference was found statistically highly significant (p<0.001) and this correlation has not been published in any literature as of now.

In the present study, the mean prolactin level was 39.02±31.87 (range 1.60-159.99) in alcoholic patients, 39.61±48.49 (range 7.51-199.00) in NASH patients, 29.36±28.59 (range 5.16-69.71) in HBV patients, 45.46±28.81 (range 15.93-81.50) in HCV patients, 19.88±0.00 (range 19.88-19.88) in cryptogenic cases and 28.00±0.00 (range 28.00-28.00) in autoimmune cases. The correlation between the etiology of liver disease and prolactin level was found to be insignificant (p>0.05). The results of our study are consistent with another study done by Payer et al, who also found that there was no impact of gender or etiology of cirrhosis on prolactin levels.[14]

Conclusion

Hyperprolactinemia is a common finding seen among the patients of liver cirrhosis. It was present in a significant number of the patients of liver cirrhosis irrespective of the etiology of cirrhosis. Prolactin levels increase significantly with severity and duration of liver disease.

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