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SERUM PROLACTIN LEVEL IN PATIENTS WITH CIRRHOSIS OF LIVER: A TERTIARY CARE CENTRE STUDY

Biochemistry

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ABSTRACT

Introduction: Cirrhosis is the final step in progression of chronic liver disease which depends on aetiology and duration of chronicity. The liver is a major site for metabolism of various hormones including Prolactin. Chronic liver disease leads to alterations in serum levels of Prolactin. Elevated serum level of Prolactin in cirrhosis leads to hypogonadism and feminisation features.

Material and Methods: we enrolled 50 patients of chronic liver disease as case group and 50 healthy subjects as control group. Blood samples were taken for routine investigations and hormonal analysis and serum Prolactin levels were measured using electrochemiluminescence immunoassay. Results were analysed and compared with the control group. Statistical analysis was done using SPSS software version 20. A statistical value of $p<0.05$ was considered significant. Majority of patients in our study had decompensate cirrhosis.

Results: Mean age of patients was 40.98±50.5 years. Most common cause of cirrhosis was ethanol intake in 64% patients. As cites and oliguria were major presenting features in 86% and 76% patients respectively. Serum levels of Prolactin were elevated in 92% patients with mean 66.58±28.30 ng/ml. Mean serum Prolactin levels were significantly elevated in case group as compared to control group ($p<0.001$). Elevated serum levels of estradiol and low serum levels of testosterone were associated with gonadal hormonal abnormalities in the case group. Serum Prolactin levels were higher in moderate to severe chronic liver disease.

Conclusion: Elevated serum Prolactin levels were seen in the majority of patients of cirrhosis which is statistically significant as compared to the control group. Patients with decompensated liver disease had higher serum Prolactin levels. Elevated serum Prolactin along with hyperestrogenemia and low serum testosterone levels were responsible for hypogonadism and feminization features in cirrhotic patients.

KEYWORDS

Cirrhosis; Serum Prolactin; Hypogonadism; Dopamine

INTRODUCTION

Liver cirrhosis clinically manifested in the form of ascites, hepatic encephalopathy , variceal bleed and hepatocellular carcinoma. Progression of liver cirrhosis from compensated to decompensated depends on aetiology,stage of fibrosis and duration . As endocrine system works by secretion of hormones in the bloodstream and acts at distant sites. Liver is the major site for synthesis and metabolism of various hormone binding proteins and cytokines. Therefore dysfunction of the liver leads to alterations in functions of the endocrine system and its manifestations. Prolactin (PRL), a polypeptide hormone is secreted from pituitary and causes breast development and lactation in women. Release of Prolactin from the pituitary is regulated by hypothalamus through PRL releasing factors and PRL inhibitory factors (1,2). Raised serum Prolactin levels are found in patients of pituitary tumours, head injury, renal failure, Cushing syndrome, severe liver disease and celiac disease (3,4). Raised levels of prolactin in liver cirrhosis are mainly attributed to decreased levels of dopamine in central nervous system. Raised serum Prolactin levels are commonly associated with lower T3 and cortisol levels in cirrhosis (5). In patients with decompensated liver disease there is increase in synthesis of false neurotransmitters such as phenyl ethanolamine and octopamine (6). These false neurotransmitters inhibit dopamine release leading to hypogonadism in cirrhosis (7). Therefore based on previous literature we planned a study to find out abnormality in serum Prolactin levels in cirrhotic patients. The main aim of our study is to find out abnormalities of Prolactin in patients with chronic liver disease. Secondary aim was to correlate with disease severity.

MATERIALAND METHOD

This case control study was conducted at Sawai Man Singh Medical College and Hospitals, Jaipur which is one of the largest tertiary care centres of North India. We enrolled 50 patients diagnosed with cirrhosis admitted in the gastroenterology department and taken as a case group. Fifty healthy subjects were enrolled as a control group. Cirrhotic patients with age between 18-45 years were included as cases in the study. Cirrhosis was diagnosed based on biochemical, radiological and clinical features and liver biopsy if needed. Cirrhotic patients who are critically ill, hepatocellular carcinoma, associated endocrinological disorders such as diabetes mellitus and thyroid disorder, pregnancy, post organ transplant were excluded. The study period was from September 2018 to August 2020.The study protocol was approved by the ethical and research committee of the institute. Data were collected after the patient's informed and written consent. Patients were categorized into groups based on functional severity of the liver disease. Severity of liver cirrhosis was graded on the basis of the Child Pugh Turcotte score (CTP) and model for end stage liver disease score (MELD). Normal values of serum prolactin were 1.9 - 25 ng/ml. Selection of subjects is done on the basis of inclusion and exclusion criteria. Detailed clinical history related to demographic parameters and liver disease along with anthropometry was taken at the time of enrolment. Patient's blood samples were collected for routine laboratory investigations along with samples for serum hormonal assay after an overnight fasting in appropriate vials from ante-cubital vein puncture. Collected samples were analysed for hemogram , renal function tests, prothrombin time (PT).Standard liver function tests like serum albumin, serum bilirubin (total/direct), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and serum alkaline phosphatase were measured on the same day on AU 680 auto-analyser using IFCC approved methods. Rest sample used for measurement of hormonal analysis including serum Prolactin.

STATISTICALANALYSIS

Detailed data of all subjects of case and control group were collected. After complete evaluation, all the data were expressed in terms of Mean ± SD. Comparison between cases and control group was done using paired "t" tests. All statistical analysis was done using SPSS software version 20. A statistical value of $p<0.05$ was considered significant.

RESULTS

As per study protocol we took 50 patients of chronic liver disease as a case group and 50 healthy subjects as control. Mean age of all study patients was 40.98±5.05 years. Out of 50 cases, the most common cause of cirrhosis was ethanol intake in 64% patients followed by hepatitis B virus (HBV), hepatitis C virus (HCV) and autoimmune hepatitis in 20%, 8%, 4% patients respectively. Ascites (86% patients) and oliguria (76% patients) were major presenting features. Most of the patients (72%) had decompensated cirrhosis. Majority of patients in case group 43(86%) were anaemic with mean haemoglobin level was 8.09 ±1.44 gm/dl; most common type of anaemia was macrocytic. Serum calcium level was significantly lower in cases group (8.31±0.97 mg/dl) as compared to control group ((9.98± 0.88 mg/dl) (p<0.001). Serum bilirubin levels were significantly high in the case group (3.54±2.42 mg/dl) as compared to the control group (1.00± 0.40 mg/dl) (p<0.001). Endocrine assessment revealed that the majority of endocrine function were affected up to variable extent as shown in (table no.2).Prevalence of thyroid hormone abnormalities was seen in 70% cases. Sex hormone abnormalities were seen in majority (70%-90%) of patients. High oestrogen and low serum testosterone levels were found in the case group as compared to the control group, which was statistically significant (p<0.001). (Table no.2). Elevated serum Prolactin level was observed in 46(92%) of patients. Serum Prolactin levels were significantly elevated in the case group (66.58± 28.30) as compared to the control group (13.47± 17.16) with p<0.001.

OBSERVATION TABLES

Table no. 1: Demographic Profile & Clinical Characteristics of Patients

	N	Mean	SD	Median	Min.	Max.
Age (years)	50	40.98	5.05	41	28	55
Dose per week	32	53.91	10.22	50	40	80
Duration	32	15.75	3.42	15	10	25
Duration of CLD	50	3.07	1.24	3	1	6
PT/INR	50	2.06	0.70	1.85	1.1	4
GGT	50	107.60	26.18	103	62	175
Total Cell N/L	49	521.18	683.46	150	85	2650
MELD	50	23.30	6.40	24.5	11	32
APRI	50	3.16	1.25	2.85	1.02	6.74
GPRI	50	2.13	0.77	2.055	0.88	4.64
oesophageal Vx grade	49	2.25	0.66	2	1	3
Duration of hospital stay (in days)	50	5.92	1.85	6	3	10

Table no. 2: Comparison of Hormonal Abnormalities in case and control groups

Parameters	Group	N	Mean	SD	Median	Min.	Max.	'p' value*
Ft3	Case	50	2.17	1.37	1.805	0.78	8.8	<0.001
	Control	50	2.91	0.66	2.9	1.1	5.2	
Ft4	Case	50	0.96	0.53	0.825	0.45	3.8	0.005
	Control	50	1.21	0.32	1.27	0.3	1.95	
TSH	Case	50	3.33	2.77	2.42	0.07	12.5	0.036
	Control	50	4.96	4.66	3.5	0.21	27.5	
Serum Vit.D3	Case	50	18.30	14.38	13	5	61	<0.001
	Control	50	40.85	23.63	39	5.6	98	
Serum Cortisol	Case	50	12.47	11.32	11.56	0.65	56.8	0.614
	Control	50	11.39	10.00	8.4	1.35	52.8	
Serum Estradiol	Case	50	107.24	54.67	105.5	15	205	<0.001
	Control	50	13.21	12.11	9.8	3.1	67	
Serum GH	Case	50	5.80	4.29	5.2	0.8	25.7	<0.001
	Control	50	1.81	4.02	0.63	0.15	23.6	
Serum IGF-1	Case	50	68.16	60.14	50	14	315	<0.001
	Control	50	182.62	129.41	147	18	633	
Serum Insulin	Case	50	46.66	29.90	48	5	103	<0.001
	Control	50	12.50	16.31	7.75	0.9	84.1	
Serum Prolactin	Case	50	66.58	28.30	65.8	15.7	200	<0.001
	Control	50	13.47	17.16	7.65	1.3	74	
Serum PTH	Case	50	48.11	48.25	26.75	0.2	229	0.082
	Control	50	63.54	39.09	57.5	18	210	
Serum Testosterone	Case	50	48.79	69.25	25.45	7.1	382	0.005
	Control	50	78.02	21.88	80.5	18	129	

Unpaired't' tests

Table No. 3: Sex Hormone Abnormalities in case & control group

Serum Testosterone	Case		Control		Total	
	No.	%	No.	%	No.	%
Low	40	80.00	4	8.00	44	44.00
Normal	10	20.00	46	92.00	56	56.00
Total	50	100.00	50	100.00	100	100.00

Fisher Exact Test P<0.001

Serum Estradiol	Case		Control		Total	
	No.	%	No.	%	No.	%
Low	0	0.00	3	6.00	3	3.00
Normal	11	22.00	44	88.00	55	55.00
High	39	78.00	3	6.00	42	42.00
Total	50	100.00	50	100.00	100	100.00

Chi-square = 53.657 with 2 degrees of freedom; P<0.001

Serum Prolactin	Case		Control		Total	
	No.	%	No.	%	No.	%
Low	0	0.00	2	4.00	2	2.00
Normal	3	6.00	41	82.00	44	44.00
High	47	94.00	7	14.00	54	54.00
Total	50	100.00	50	100.00	100	100.00

Chi-square = 64.448 with 2 degrees of freedom; P<0.001

DISCUSSION

Cirrhosis is the final stage in the progression in chronic liver disease. . As the disease progresses, Cirrhosis progresses from compensated to decompensated stage. Liver is involved in synthesis and metabolism of various hormone binding proteins and cytokines. Therefore abnormalities of endocrine functions are seen in these patients which may be subclinical in some patients. As liver is involved in metabolism of sex hormones, hyperestrogenemia and hyperprolactinemia are seen in patients with cirrhosis. Low serum testosterone levels are also common features of these patients. Hyperprolactinemia and hyperestrogenemia are responsible for clinical manifestations of feminization and genesis of hypogonadism (8). Prolactin is a polypeptide hormone of 199 amino acids with three intermolecular disulfide bonds (9). Decompensated liver disease leads to increased concentration of aromatic amino acids which is responsible for increased synthesis of false neurotransmitters such as octopamine and phenyl ethanolamine. Elevated levels of false neurotransmitters in the central nervous system leads to inhibition of dopamine release and contributes to hyperprolactinemia . Normally secretion of Prolactin from pituitary in humans occurs in pulsatile pattern but in patients with cirrhosis there is constant 24 hours elevation of Prolactin levels (10). In our study we found that elevated serum Prolactin levels were present in 92% patients of CLD. Serum Prolactin levels were significantly elevated in the case group as compared to the control group with p value <0.001. Mean serum Prolactin level in CLD patients was 66.58± 28.30. Majority of patients with moderate to severe liver disease had elevated Prolactin levels. Similar study done by Simon et al in cirrhotic patients found that hyperprolactinemia was present in the majority of patients and may involve hypogonadism by an inhibitory effect on gonadotropins (11). Features of hypogonadism were more severe in patients with higher CTP score (12). Another study done by Mukherjee et al and found higher Prolactin levels in patients of encephalopathy and mortality (13). In studies done by Mc clain et al (14) and Sharma et al (15) found a correlation of higher risk of mortality with serum Prolactin levels of > 50 ng/ml. Similar to all previous studies , we also found that elevated serum Prolactin levels were found in the majority of patients of cirrhosis and these levels were higher in moderate to severe disease.

CONCLUSION

In conclusion patients of cirrhosis had abnormal endocrine functions. Majority of patients had hyperprolactinemia associated with hyperestrogenemia. Elevated Prolactin levels in these patients leads to hypogonadism with clinical features of feminization. Serum Prolactin levels were higher in moderate to severe liver disease.

DISCLOSURE STATEMENT

This study is investigator initiated. The authors declare that they have no competing/conflict of interests in relation to this article.

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CONSENT FOR PUBLICATION

- Ethics approval and consent to participate.
- The study protocol was approved by the medical ethics committee of the Rajasthan University of Health Sciences, Jaipur, Rajasthan(State), India.

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