Original Article

Occult endocrine dysfunction in patients with cirrhosis of liver

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Abstract

Background: Liver dysfunction leads to endocrine disturbance due to the alteration in protein metabolism or synthesis. We studied the presence of occult endocrine dysfunction in liver cirrhosis and compared the same with underlying etiology. **Materials and Methods:** We evaluated thirty patients with liver cirrhosis in this cross-sectional, observational study. All subjects were assessed for pituitary, thyroid, adrenal, and gonadal function. The patients were divided into Group 1 (cirrhosis, $n = 30$) and Group 2 (controls, $n = 15$) and the data were analyzed with appropriate statistical tests. **Results:** The study participants (20 males, 10 females) had a mean age of 54.5 ± 12.4 years and duration of the cirrhosis 5.1 ± 2.7 years. Four patients were in Child Class A, 11 and 15 patients were in Child Classes B and C, respectively. Eleven out of thirty patients (37%) had endocrine disorders, that include subclinical hypothyroidism ($n = 3$), primary hypothyroidism ($n = 1$), Sick Euthyroid syndrome ($n = 3$), central hypothyroidism ($n = 2$), secondary hypogonadism ($n = 3$) and growth hormone deficiency in three patients. Two patients had partial hypopituitarism and one patient had complete hypopituitarism. **Conclusion:** Occult endocrine dysfunction of thyroid and gonadal axes is common in patients with cirrhosis of the liver. The hormonal abnormalities are not different based on the etiology of the cirrhosis.

Keywords: Alcoholism, cirrhosis, hypogonadism, hypopituitarism, hypothyroidism

Introduction

Endocrine and liver disorders are increasing in frequency among the general population. The most common endocrine disorders include diabetes, thyroid and gonadal disorders; whereas liver disorders include chronic hepatitis and cirrhosis of the liver. The simultaneous occurrence of disorders involving these two major systems is not an uncommon finding in current day medical practice.[1,2] Liver is a major organ involved in the metabolism and is the seat for synthesis of proteins and various hormones. Liver is also a site of internal detoxification processes and chronic liver dysfunction leads to accumulation of the systemic toxins.[3] The liver is the site of synthesis for most of the hormone binding proteins such as sex hormone binding globulin (SHBG) and thyroid binding globulin (TBG).[4] The chronic liver disorders commonly associated with endocrinopathies include chronic hepatitis, primary biliary cirrhosis and autoimmune hepatitis.[5] The liver dysfunction leads to secondary dysfunction of endocrine glands directly due to the toxic effects and indirectly by the alteration of the carrier protein synthesis.[6]

Cirrhosis of the liver is one of the commonest forms of chronic liver disease (CLD) characterized by replacement of normal hepatic architecture with fibrosis and regenerating nodules. The two most common causes of cirrhosis in our country include alcoholic liver disease and infection of hepatotropic viruses such as hepatitis B and hepatitis C (HBV and HCV).[7] CLD may lead to dysfunction of most of the endocrine organs, including pituitary, thyroid, and other glands. The commonly observed endocrine manifestations in CLD are short stature, hepatic

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osteodystrophy, delayed puberty, hypogonadism, relative adrenal insufficiency and Sick Euthyroid syndrome.[8,9] Few endocrine disorders associated with CLD are even reported to reverse after liver transplantation.[10] The literature is limited on in this subject from India and also about the endocrine dysfunction with respect to the etiology of cirrhosis. Hence, we conducted this study to assess the endocrine dysfunction in patients with liver cirrhosis of postnecrotic and postviral etiology.

Materials and Methods

We conducted this cross-sectional, observational study at a tertiary level referral hospital in India. All patients with a known diagnosis of liver cirrhosis (aged 18–70) for more than 2 years, under follow-up at our hospital and admitted to the Intensive Care Unit for cirrhosis related complications were included in the study. Liver cirrhosis was diagnosed based on meeting any three of the following four criteria: (1) CLD lasting for more than 6 months (2) coarse echo texture of the liver on sonography (3) evidence of portal hypertension on upper gastrointestinal endoscopy (4) liver biopsy findings consistent with cirrhosis. The patients with known diabetes, thyroid or endocrine disorders, previous radiation exposure, intake of drugs such as glucocorticoids, thyroxine, estrogen or testosterone, and cryptogenic cirrhosis were excluded from the study.

The patients were divided into two groups for the comparison: Group 1 (cirrhosis) and Group 2 (controls). The patients in Group 1 are further subdivided into two groups based on the underlying etiology of the cirrhosis into Group A (alcoholic) and Group B (postviral). The age and sex matched control population was derived from the attendants of the patients admitted to the hospital. The participants in the control group denied history of any known medical ailment and were in good health. Alcoholic liver disease was diagnosed with a history of alcohol consumption more than 40 g/day for more than 10 years duration. Postviral etiology of cirrhosis is confirmed by the presence of viral markers (HCV RNA, hepatitis B antigen and HBV DNA) and treatment with antiviral agents. All patients were explained about the aims and objectives of the study and the severity of liver disease was scored as per Child-Pugh criteria. The Local Ethics Committee approved the trial protocol and all patients provided written informed consent.

A fasting blood sample was collected from each participant at 08:00 h in fasting state and the serum was separated and stored at −80°C. All the samples were analyzed for pituitary profile (growth hormone [GH], insulin like growth factor-1 [IGF-1], luteinizing hormone [LH], follicle stimulating hormone [FSH], prolactin, adrenocorticotrophic hormone [ACTH]), thyroid profile (free triiodothyronine [FT3], free thyroxine [FT4], total triiodothyronine [T3], total thyroxine [T4], thyroid stimulating hormone [TSH]) and adrenogonadal profile (cortisol, total testosterone, estradiol [E2], dehydroepiandrosterone [DHEA], DHEA sulfate). Patients with morning cortisol <200 nmol/L were subjected to modified ACTH stimulation test and the cortisol response was noted.[11] We did not perform dynamic testing for the gonadal and thyroid axes evaluation. The samples of estradiol were not assessed in relation to the menstrual and menopausal status of the females. The samples were also analyzed for the biochemical and hematological parameters including bilirubin, aspartate transaminases, alanine transaminase, International Normalized Ratio, total protein, albumin, glucose, creatinine, lipids, and electrolytes. The entire hormonal panel was evaluated using electrochemiluminescence assay barring IGF-1 and testosterone, which were measured by the enzyme immunoassay method.

Primary hypothyroidism is defined as low FT4 (normal, 0.8–2.1 ng/ml) with elevated TSH (normal, 0.5–5.5 μIU/ml) and subclinical hypothyroidism as normal FT4 with raised TSH. The Sick Euthyroid syndrome is defined by the presence of low T3 or low T4 along with normal TSH levels. Secondary hypothyroidism is defined as low FT4 or FT3 with normal or low TSH levels. Primary hyperthyroidism is defined as elevated FT4 with low TSH and subclinical hyperthyroidism as normal FT4 with suppressed TSH. Hypogonadism is defined in males with testosterone <300 ng/dL (normal 310–1200 ng/dL) and amenorrhea along with estradiol <30 pg/mL in females. The hypogonadism was termed as primary (elevated LH and FSH) or secondary (low or normal LH/FSH). Adrenal insufficiency is diagnosed when 8 am and stimulated cortisol are below 100 and 500 nmol/L, respectively. We did not study the relative adrenal insufficiency in the subjects, and all the patients were tested with the modified ACTH stimulation test.[11] An IGF-1 level below the range specific for the age is considered as diagnostic of GH deficiency and we did not do GH stimulation test in these individuals. A diagnosis of complete hypopituitarism was made with dysfunction of more than or equal to three hormonal axes and partial hypopituitarism with two hormonal axes abnormalities.

Data are presented as mean ± standard deviation and a comparison between the groups was done using nonparametric (Mann–Whitney U-test) and Fisher's exact tests. Spearman's correlation test was used for correlation between numerical variables, and a $P < 0.05$ was considered significant. The statistical analysis and graph generation were done using the GraphPad Prism Software, Version 6 (GraphPad Software, San Deigo, CA, USA).

Results

The study participants consist of 20 males and 10 females with a mean age of 54.5 ± 12.4 years, the mean duration of the cirrhosis was 5.1 ± 2.7 years and body weight of 57.2 ± 6.4 kg. A total of 16 patients had alcoholic cirrhosis, and the remaining 14 had postnecrotic cirrhosis with male predominance in Group 1. A total of 4 patients were in Child Class A, 11 and 15 patients were in Child Classes B and C, respectively. The baseline details about the liver function and the endocrine disorders of cases and controls are given in Table 1. Out of total 14 postviral cirrhosis

nine patients had chronic hepatitis B and the remaining was infected with HCV. The comparison between both the groups regarding their baseline parameters and the endocrine disorders is shown in Table 2.

Eleven out of thirty (37%) patients showed results consistent with an endocrine disorder. They include subclinical hypothyroidism (n = 3), primary hypothyroidism (n = 1), Sick Euthyroid syndrome (n = 3), central hypothyroidism (n = 2), secondary hypogonadism (n = 3) and GH deficiency in three patients. Two patients had partial hypopituitarism and one patient had a loss of 3 hormonal axes suggesting a diagnosis of complete hypopituitarism. The endocrine conditions did not differ significantly between the individual groups as shown in Table 2. None of the patients had hyperthyroidism, hypocortisolism and primary hypogonadism.

The comparison between the groups regarding the hormonal profile is given in Table 3. Briefly, the findings include low IGF-1 and high LH in postnecrotic cirrhosis. Thyroid panel did not show any alteration in both the groups and adrenogonadal panel reported in decreased cortisol and DHEA in alcoholic cirrhosis and low testosterone in postviral cirrhosis. We performed a univariate correlation analysis between severity of liver disease as assessed by Child-Pugh score and all hormonal parameters. Child-Pugh score is not correlated with any of the hormonal parameters except for an inverse correlation with the IGF-1 level as shown in Figure 1.

Table 1: Comparison between two groups regarding the baseline parameters and diagnoses

Feature	Units	Group 1 (cirrhosis) (n=30)	Group 2 (controls) (n=15)	P
Demographic parameters				
Age	Years	52.3 (11.9)	50.4 (9.6)	0.5945
Sex	Male: female	20:10	12:3	0.4917
Endocrine disorder				
Primary hypothyroidism	Number	1	0	1.0000
Central hypothyroidism	Number	2	0	1.0000
Sick euthyroid syndrome	Number	3	0	0.5402
Subclinical hypothyroidism	Number	3	1	1.0000
Hyperthyroidism	Number	0	0	1.0000
Hypogonadism	Number	3	0	0.5402
Hypocortisolism	Number	0	0	1.0000
Growth hormone deficiency	Number	3	0	0.5402
Liver function parameters				
Total bilirubin	mg/dL	9.1 (5.5)	0.7 (0.1)	<0.0001
Serum albumin	g/dL	2.8 (0.7)	4.3 (1.1)	<0.0001
INR*	Value	1.9 (0.8)	1.1 (0.2)	0.0005
Ascites	Number	23	0	<0.0001
Hepatic encephalopathy	Number	14	0	<0.0001

Mean (standard deviation). *International Normalized Ratio

Table 2: Baseline parameters and endocrine disorders in two groups of cirrhosis

Feature	Units	Group A (alcohol) (n=16)	Group B (postviral) (n=14)	P
Age	Years	55.4 (11.9)	50 (13.6)	0.2641
Sex	Male/female	15/1	5/9	0.0029
Duration of cirrhosis	Years	4.8 (2.5)	5.6 (2.2)	0.2043
Child-Pugh score	Score	9.9 (2.6)	9.7 (2.1)	0.3211
Endocrine disorders				
Primary hypothyroidism	Number	1	0	1.0000
Central hypothyroidism	Number	1	1	1.0000
Sick euthyroid syndrome	Number	1	2	0.5862
Subclinical hypothyroidism	Number	1	2	0.5862
Hyperthyroidism	Number	0	0	1.0000
Hypogonadism	Number	2	1	1.0000
Hypocortisolism	Number	0	0	1.0000
Growth hormone deficiency	Number	1	2	0.5862

Mean (standard deviation)

Discussion

Our pilot study showed that occult endocrine dysfunction is seen in one-third (11 out of 30) of patients with liver cirrhosis and only in one control patient. Occult endocrine dysfunction is commonly seen in chronic liver disorders, and they have a direct correlation with the severity of liver dysfunction.[12] Previous reports suggest that 10–25% of patients with cirrhosis have thyroid disorders.[13] Our study data derived from a small group of patients do not give enough evidence to suggest that the observed endocrinopathies are merely coincidental or due to the underlying cirrhosis. Thyroid disorders are the commonest abnormalities identified which includes subclinical hypothyroidism and Sick Euthyroid syndrome. All our patients were admitted to hospital with a complication of cirrhosis and they are likely to be in different phases of the Sick Euthyroid syndrome. CLD due autoimmune etiology is known to be associated autoimmune thyroid disease like Grave's disease and Hashimoto's thyroiditis.[14] Chronic hepatitis C infection may lead to subclinical hypothyroidism due to the direct cytopathic effect of HCV on thyroid cells or with the use of interferon.[15] Liver disease is also associated with an increase in inflammatory cytokines, which negatively affect the

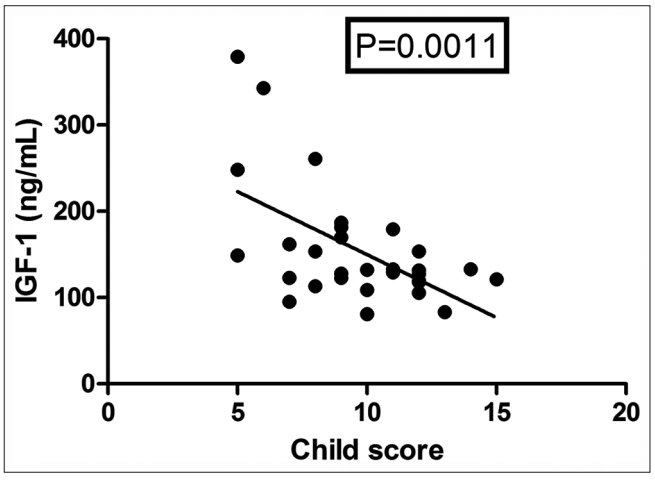

Figure 1: Correlation between insulin like growth factor-1 and child score in study participants

Table 3: Comparison between alcoholic (Group A) and postviral (Group B) cirrhosis

Feature	Units	Group A (alcohol) (*n*=16)	Group B (postviral) (*n*=14)	*P*
Pituitary profile				
Growth hormone	ng/mL	10.5 (9.9)	10.4 (12.3)	0.9975
IGF-1	µg/L	216.1 (102.7)	138.5 (98.6)	0.0313
LH	IU/L	7.8 (5.1)	4.7 (6.3)	0.4673
FSH	IU/L	4.2 (4.6)	9.2 (11.2)	0.1160
Prolactin	mIU/L	465.8 (186)	428 (97.4)	0.5008
ACTH	pmol/L	5.3 (3.8)	4.6 (3.7)	0.6209
Thyroid profile				
Total triiodothyronine	nmol/L	0.68 (0.28)	0.63 (0.27)	0.6608
Total thyroxine	µg/dL	3.8 (1.2)	4.4 (1.3)	0.5682
Free triiodothyronine	pmol/L	2 (0.6)	1.8 (0.5)	0.3997
Free thyroxine	ng/dL	0.78 (0.18)	0.8 (0.1)	0.2371
Thyroid stimulating hormone	mIU/L	2.2 (3.4)	1.2 (0.7)	0.3077
Adrenogonadal profile				
Cortisol (8 am)	nmol/L	191.1 (61.5)	257.3 (94.2)	0.0275
DHEA	ng/dL	268 (135.6)	460.3 (283)	0.0221
DHEAS	µg/dL	204.7 (134.8)	153 (96.8)	0.2440
Total testosterone (8 am)*	ng/dL	383.9 (217.2)	198.6 (210.7)	0.0253
Estradiol*	pmol/L	138.4 (110.3)	102.2 (134)	0.7193

Mean (standard deviation). *Testosterone levels pertains to only males and estradiol for females. DHEA: Dehydroepiandrosterone; DHEAS: Dehydroepiandrosterone sulfate; FSH: Follicle stimulating hormone; LH: Luteinizing hormone, IGF-1: Insulin like growth factor-1; ACTH: Adrenocorticotrophic hormone

hypothalamus-pituitary-thyroid axis, leading to suppressed TSH levels in some patients.[16]

Hypogonadism is observed in 20–65% of patients with cirrhosis and is seen in three out of thirty patients in our study. The higher prevalence observed in the previous studies could be due to the higher age of the patients and also sampling variation. Few studies have also reported the presence of primary hypogonadism, especially in alcoholic liver disease.[17] However, none of our study participants had features of primary hypogonadism. Previous reports suggest the involvement of the gonadal axis in patients with Child-Pugh class B and C, whereas others suggest hypothalamo-pituitary-gonadal dysfunction at all stages of the cirrhosis.[18,19] GH deficiency in adults results in obesity, metabolic syndrome and increased risk of fatty liver disease. IGF-1 is synthesized mainly in the liver, and the presence of CLD may result in the low levels of IGF-1.[20] Three patients had low IGF-1 in our study suggestive of GH deficiency. Twelve patients had morning cortisol <200 nmol/L and all of them showed robust cortisol response after ACTH stimulation.

Our data, when subdivided based on the etiology of cirrhosis, showed interesting findings. Cirrhosis patients with postviral etiology showed low IGF-1 and testosterone when compared with postalcoholic etiology. This could be explained by the central effect of the hepatotropic viral infection.[21] Our data, derived from a small sample size, may not give enough evidence to suggest the relation between the severity of the liver disease and the hypogonadism. Neuroimaging of the hypothalamo-pituitary region is the ideal modality to label the patients of hypogonadism. Patients with alcoholic cirrhosis had marked suppression of adrenal hormones such as cortisol and DHEA. Previous reports suggest the presence of adrenal insufficiency in 30–60% of patients with liver cell failure.[22] The underlying etiology could be due to direct toxic effects of the alcohol on the adrenal tissues.

The strength of our study includes assessment of all hormonal axes in cirrhosis and no such study has been conducted earlier from our country. The limitations of our study include small sample size, failure to measure free testosterone, TBG, SHBG, and lack of dynamic testing for GH deficiency. The cross-sectional nature of our study limits the usefulness in predicting the cause and effect relation between the endocrine dysfunction and underlying cirrhosis. We did not present the data according to the severity of the liver disease due to the small sample size. Our pilot data from a small sample precludes the representation of the findings in the general population.

Conclusion

Occult endocrine dysfunction is common in patients with cirrhosis of the liver and is seen in one-third of patients. Thyroid and gonadal axes abnormalities are identified in the majority of patients. The endocrine dysfunction is not different between the alcoholic or postviral etiology of the cirrhosis. Further large scale studies with more number of patients are required to confirm the findings observed in our study.

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Conflicts of interest

There are no conflicts of interest.

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