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A STUDY OF THYROID PROFILE IN CIRRHOSIS OF LIVER AND THEIR CORRELATION WITH SEVERITY OF LIVER DISEASE

General Medicine

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ABSTRACT

Introduction: Cirrhosis is one of the leading cause of morbidity and mortality worldwide. The levels of thyroid hormone and thyroid binding proteins are altered in patients of chronic liver disease1. Low free T3 and T4 levels, increased reversed T3 level and decreased T3 to T4 ratio (Sick euthyroid syndrome or low free T3 syndrome) are the common alterations observed in cirrhotics2. Almost all patients with liver disease are clinically euthyroid3. So it is important to assess thyroid profile in patients of CLD or cirrhosis and tend any correlation of severity of CLD with thyroid profile in our state population as it could be an important biochemical indicator of severity or prognosis in patients of CLD. **Material And Methods:** It was an observational study conducted over a period of 1 and a half year with a total of 60patients diagnosed as cirrhosis of liver (based on a combination of clinical, laboratory and Imaging features)95 enrolled for the study.All subjects had their free T3, free T4 and TSH measured using CLIA and the severity of Cirrhosis was determined by using the Child-Turcotte-Pugh Scoring system and MELD Scoring System. **Results:** Thyroid profile of the study population revealed that mean FT3 was 2.92±0.79 ng/dl, FT4 was 1.37±0.75 ug/dl and TSH was 4.32±2.18 mIU/mL.Correlation of thyroid profile with Child Turcotte Pugh scoring system revealed a significant correlation between Class B vs C in T3 ($p<0.05$), significant correlation between Class B vs C ($p<0.001$) AND class A vs C ($p<0.05$) in TSH. No significant difference was observed in any class A, B and C with respect to T4 ($p>0.05$, NS).On statistical analysis, the difference among MELD score between <20 and >20 was found to be significant ($p<0.05$) while comparing with thyroid parameters viz. T3, T4 and TSH. **Conclusion:** The study showed a low FT3 levels (sick euthyroid syndrome) with high T4 and TSH levels with increasing severity of liver disease as graded by the Child Turcotte Pugh score and MELD score.

KEYWORDS

Liver Cirrhosis, thyroid profile, Child Turcotte Pugh score, MELD score

INTRODUCTION

Cirrhosis is one of the major causes of health issues in the world. It is a leading cause of morbidity and mortality worldwide. The levels of thyroid hormone and thyroid binding proteins are altered in patients of chronic liver disease[1]. The total and free thyroxine have been reported as normal, increased or decreased in various liver diseases; abnormalities in thyroxine binding globulin serum concentration and a reduced thyroid hormone binding capacity, perhaps because of a hypothetical circulating inhibitor, have also been reported[4]. Moreover, total and free triiodothyronine concentration are often decreased, sometimes profoundly and their levels correlate well with severity of liver dysfunction. In order to further evaluate the thyroid function in liver disease, this study measures FT3, FT4 and TSH serum levels in patients with chronic liver disease.

The mortality related to cirrhotic liver disease in India has been progressively increasing. This may be due to the fact that India is passing presently through a cultural lifestyle transition. This sedentary habits, fast food culture and excessive and frequent use of alcohol in the society in India is responsible for increasing incidents of alcoholic liver disease (ALD) and non alcoholic fatty liver disease (NAFLD) as courses of chronic liver disease (CLD)[2]. CLD and cirrhosis has been reported to account for 2.1 percentage of all diseases in India in the year 2016[5]

Liver is involved in the conjugation, excretion, peripheral deiodinization and synthesis of thyroid binding globulin (TBG). Liver is the most important organ in the peripheral conversion of tetra iodothyroxine T4 to T3, by the action of selenium dependent 5'deiodinase.Liver also metabolises the TSH and regulates their systemic endocrine effects. Low free T3 and T4 levels, increased reversed T3 level and decreased T3 to T4 ratio. (Sick euthyroid syndrome or low free T3 syndrome) are the common alterations observed in cirrhotics and is due to associated poor nutrition and release of cytokines, especially Interleukin 6[7].

A significant inverse correlation between serum levels of free T3 and Severity of liver cirrhosis have been observed in various studies. Hormonal abnormalities of total T3 is one of the risk factor and early indicator of impending hepatic encephalopathy (HE) and progression of liver disease severity as per CPS class or MELD score.

MATERIALS AND METHOD

Sixty patients diagnosed as cirrhosis of liver (based on a combination of clinical, laboratory and Imaging features)were enrolled for the study All the demographic data, detailed history, clinical examination and relevant investigations were collected on predesigned semi-structured proforma and written informed consent was taken.

Inclusion Criteria

1. Newly diagnosed or Old cases of cirrhosis of liver under treatment.
2. Age > 18 yrs

Exclusion Criteria

1) Patient with sepsis, cardiac failure, renal failure, nephrotic syndrome
2) Pregnant Females.
3) Personal or family History of Thyroid Disorders
4) Patients on any drug that alters thyroid functions (eg Lithium, Amiodarone and Gamma Interferon etc)
5) Cases < 18 years of age.

The cases were diagnosed as cirrhosis with clinical and radiological evidences

The severity of Cirrhosis was determined by using the Child-Turcotte-Pugh Scoring system and MELD Scoring System. The Subjects were Classified in 3 groups based on Child-Turcotte-Pugh Score as Child A, B and C and 2 groups based on MELD Score (as MELD < 20 and MELD > 20)

OBSERVATIONS AND RESULTS

The present observational study was conducted in Faculty of Medicine & Health Sciences, SGT Medical College, Hospital & Research Institute (a Tertiary care Hospital) Budhera, Gurgaon, Haryana. All the sixty subjects were enrolled through Outdoor Patient Department (OPD) and Indoor Patient Department (IPD) after taking the consent and as per inclusion and exclusion criteria. This study was conducted over a period of one and half year.

Majority of patients were in the age range of 31-40 years i.e. 21(35%) followed by 17(28.33%) patients in age group of 41-50 years. A total of 10(16.66%) patients each were in the age range of 20-30 and 51-60 years respectively. Only 1(1.66%) patient each was in elderly age group i.e. 61-70 and >70 years age. Mean age of the study population was 41.80±11.51 years with age range of 20-80 years.

Presenting features of study population shows that 38 (63.33%) patients had pallor, 27 (45%) had icterus and 44 (73.33%) had pedal edema at the time of enrollment in the study.

The mean systolic blood pressure of the patients was 113.3±13.66 mmHg, mean diastolic blood pressure was 71.8±9.88 mmHg, pulse rate was 84.91±13.36 beats/min, respiratory was 16.25±1.98 cycles/min and oxygen saturation was 94.85±2.45%.

Mean random blood sugar of study participants was 188.98±150.59 mg/dl.

Splenomegaly was present in 22 (36.66%) patients and caput medusa and haemorrhoids was present in 8 (13.33%) patients each as signs of portal hypertension. None of the subjects had an enlarged thyroid gland or nodules.

Mean hemoglobin in the present study was 8.74±2.17 gm%, Total Leukocyte Count was 7044.16±3876.15 per cmm, Platelet was 171766.66±39919.23/microlitre, mean corpuscular volume was 97.74±10.13fl and mean corpuscular hemoglobin was 32.71±7.85 pg.

Mean cholesterol was 144.48±9.38 mg/dl, triglycerides was 120.46±10.18 mg/dl, LDL was 84.36±8.01 mg/dl and HDL was 38.83±1.96 mg/dl. Mean total bilirubin was 2.49±0.93 mg/dl, mean direct bilirubin was 1.47±0.83 mg/dl, SGOT was 90.86±45.05 units/litre, SGPT was 79.93±40.97 units/litre, Alkaline phosphatase was 126.81±53.67 U/L and S. Albumin was 2.62±0.57 g/dl. Mean urea was 51.1±25.84 mg/dL, creatinine 1.22±0.35 mg/dL, uric acid 5.84±1.18 mg/dL, calcium 7.70±0.52 mg/dl, sodium 132.86±4.39 mEq/L, potassium 4.03±0.45 mEq/L and chloride was 102.13±4.54 mEq/L.

PT was 15.91±1.96 seconds with a range of 13.2-22.4 and INR 1.71±0.43 with a range of 1.1-1.28. Mean FT3 was 2.92±0.79 pg/dl, FT4 was 1.37±0.75 ng/dl and TSH was 4.32±2.18 mIU/L.

USG findings revealed that all the patients i.e. 60 (100%) had altered or coarse echotextue of the liver with a mean portal vein diameter of 15.03± 1.57 mm. Mean size of liver was 11.56±2.76 cm. Mild to moderate ascitic fluid was found in 47(78.33%) patients and gross ascitic fluid was found in 13(21.66%) patients.

Using Child-Turcotte-Pugh Scoring system, 5(8.33%) patients were in Class A, 32(53.33%) in Class B and 23(38.33%) in Class C. (Table 1).

MELD score of the patients revealed that a total of 24(40%) had MELD score <20 and 36(60%) had >20. Mean MELD score of the study population was 20.71±6.34 with a range of 9-37. (Table 2).

When we correlated thyroid profile according to Child-Turcotte-Pugh grading system, we observed significant correlation between Class B vs C in T3, significant correlation between Class B vs C and class A vs C in TSH. No significant difference was observed in any class A, B and C with respect to T4 (p >0.05, NS).(Table3).

In the present study a total of 24 patients (40%) had MELD score <20 and 36(60%) had >20. On statistical analysis, the difference among MELD score between <20 and >20 found to be significant (p <0.05) while comparing with thyroid parameters viz. T3, T4 and TSH. (Table 4)

DISCUSSION

Liver has an important role to play in the metabolism of thyroid hormones. It is involved in the conjugation, excretion, peripheral deiodination and synthesis of thyroid hormone binding proteins[5]. Cirrhosis leads to derangement in thyroid hormone profile. The two main enzymes responsible for extrathyroidal production of T3 and inactivation of thyroid hormones are Type 1 deiodinase and Type 3 deiodinase respectively. Two minor enzymes i.e. Type 2 deiodinase and 5' deiodinase are also responsible for T3 production from T4. In Cirrhotic patients, there is a decrease in type 1 deiodinase activity which leads to a decrease in total T3. The type 3 deiodinase activity is increased in cirrhosis of liver which is found in liver, skin and CNS and catalyses the conversion of T4 to rT3 and T3 to T2 which are inactive metabolites[1,12,13,14]. Cirrhosis also affects thyroid hormone transport in blood significantly because of its affect on the synthesis of 3 binding proteins i.e thyroid binding globulin, thyroid binding pre albumin and albumin to which 99% on thyroid hormones are bound[15-16]. Therefore, cirrhosis leads to impairement in thyroid hormone metabolism due to decrease in type 1 deiodinase activity, increase in type 3 deiodinase activity and changes in plasma concentrations of thyroid hormone binding proteins as well as free fatty acids (which displace thyroid hormones from binding proteins). All these lead to what is called the Sick Euthyroid syndrome.

Cirrhosis also leads to an increase in the release of cytokines as a proinflammatory markers which cause a decrease in the activity of type I deiodinase and decrease the binding capacity of T3 nuclear receptors[11,17,18,19].

Diminished enzyme activity accounts for decreased deiodination of T4 to T3. This may account for increased secretion of thyroid stimulating hormone (TSH) due to the positive feedback mechanism via the hypothalamus pituitary axis.

The decreased deiodination of T4 to T3 may explain the higher levels of T4 which is further aided by a decrease in the levels of thyroid hormone binding proteins leading to increased free T4 levels.

The available studies till date have shown that most frequent change in the plasma level of thyroid hormone associated with severity of hepatic dysfunction is decreased total T3 and free T4 concentration. Serum thyroid hormones levels were found to be altered in patients of acute on chronic liver failure and there exists a relation between the levels of thyroid hormones and severity of disease. Low free T3 and T4 levels are associated with more severe Liver injury in patients with cirrhosis of liver. Despite the derangements in the thyroid hormone metabolism in cirrhotics, almost all patients with liver diseases are clinically euthyroid. So it is important to assess thyroid profile in patients of CLD or cirrhosis and tend any correlation of severity of CLD with thyroid profile in our state population as it could be an important biochemical indicator of severity or prognosis in patients of CLD.

The present observational study was conducted on 60 patients diagnosed as cirrhosis of liver.Early morning fasting serum thyroid stimulating hormone (TSH), serum total free thyroxine (FT4) and free triiodothyronine (FT3) was measured by radioimmunoassays along with other routine investigations to study thyroid functions in patients with cirrhosis of liver and to find their correlation with severity of liver disease. The cause of Cirrhosis in all the subjects was alcohol and all subjects were male due to the prevalence of alcoholism predominantly in males in this part of the society.

In the present study, serum free T3 values decreased significantly with severity of liver disease as graded by Child Turcotte Pugh scoring system (based on total bilirubin, albumin, INR, ascites and encephaloathy) and MELD score (based on s.creatinine, total bilirubin, INR and s.sodium levels).These results were in concordance with the other studies[1,12,13,14,20,21,22]which showed a significant inverse correlation between serum levels of free T3 and severity of liver disease as graded by Child Pugh Score and MELD score.

In the present study, S.TSH levels were higher in severe liver disease as scored on Child Turcotte Pugh score and MELD score. Similar observations of positive correlation with advancing liver disease severity based on CTP and MELD score has been observed in other studies[1,21,23,24]except two studies which did not show a positive correlation[22,25].

Serum TSH levels have been found to be useful indicator for assessing severity and prognosis in patients with acute on chronic failure[26].

In our study, there was an increase in FT4 levels with increasing

severity of liver disease as graded by CTP and MELD score. This finding was not in concordance with the previous studies[1,13,21,22].

Table 1 Distribution Of The Cases According To Child-turcotte-pugh Scoring System

Child-Turcotte-Pugh Scoring system	No. of patients	Percentage
Class A	5	8.33%
Class B	32	53.33%
Class C	23	38.33%

Class A = None, Class B = Mild to moderate, Class C = Severe

Table 2 Distribution Of The Cases According To Meld Score

MELD score	No. of patients	Percentage
<20	24	40%
>20	36	60%
Mean±SD	20.71±6.34	
Range	9-37	

Table 3 Correlation Of Thyroid Profile According To Severity Of Cirrhosis And Grading

	T3	T4	TSH
Class A (n=5)	3.12±0.33	1.37±0.57	4.66±1.27
Class B (n=32)	3.12±0.63	1.47±0.79	3.34±1.51
Class C (n=23)	2.59±0.93	1.24±0.69	5.59±2.44
Statistical analysis			
Class A vs B	p=1	p=0.794	p=0.07
Class B vs C	<0.01 Sig.	p=0.277	p <0.001
Class C vs A	p=0.236	p=0.705	p <0.05

Class A = None, Class B = Mild to moderate, Class C = Severe

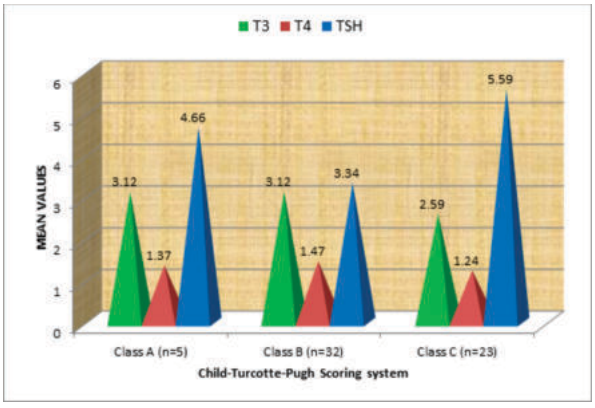

Figure 1 Showing Correlation Of Thyroid Profile According To Severity Of Cirrhosis And Grading

Table 4 Comparison Of Meld Score According To Thyroid Profile

MELD score	T3	T4	TSH
<20 (n=24)	3.07±0.61	1.42±0.63	3.76±1.58
>20 (n=36)	2.63±0.95	1.80±0.79	4.84±2.56
Statistical analysis	p=0.03 (<0.05Sig.)	p=0.04 (<0.05 Sig.)	p=0.05 (<0.05 Sig.)

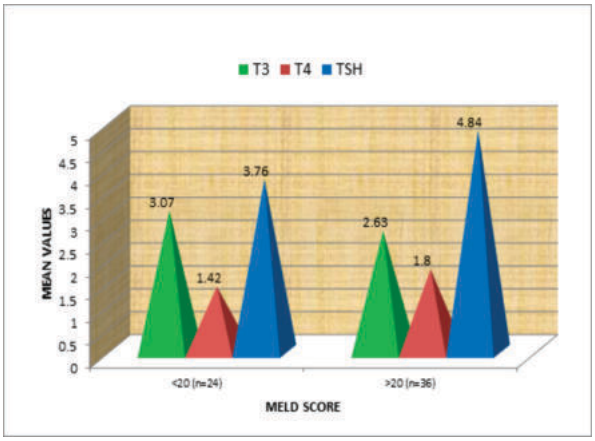

Figure 2 Comparison Of Meld Score According To Thyroid Profile

CONCLUSION

The study showed a low FT3 levels (sick euthyroid syndrome) with high T4 and TSH levels with increasing severity of liver disease as graded by the Child Turcotte Pugh score[27] and MELD score[28]. It is suggested that serum FT3 level be an index for liver status, as well as a marker for prognosis in hospitalized liver cirrhosis patients. So it is suggested that the estimation of thyroid function test may be included as a part of protocol in the evaluation of patients with chronic liver disease. However larger and longer studies are desired to study the correlation and progression of thyroid dysfunction with increasing severity of liver disease.

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