Study of Thyroid Function in Alcoholic Liver Cirrhosis and Its Correlation with Child Pugh Score

Sanjay Neeralagi[1], Praveen N.[2], Anil Kumar[3], Chethan T. L.[4], Geetha[5], Sathish R.[6]

[1]Professor and Unit Chief, Department of General Medicine, Karnataka Institute of Medical Sciences, Hubli, Karnataka. [2]Senior Resident, Department of General Medicine, Adichunchanagiri Institute of Medical Sciences, B. G. Nagar, Karnataka. [3]Junior Resident, Department of General Medicine, Karnataka Institute of Medical Sciences, Hubli, Karnataka. [4]Junior Resident, Department of General Medicine, Karnataka Institute of Medical Sciences, Hubli, Karnataka. [5]Junior Resident, Department of General Medicine, Karnataka Institute of Medical Sciences, Hubli, Karnataka. [6]Junior Resident, Department of General Medicine, Karnataka Institute of Medical Sciences, Hubli, Karnataka.

ABSTRACT

BACKGROUND

Liver plays an important role in the metabolism of thyroid hormone. Hence, thyroid dysfunction has been reported in various liver diseases and is dependent on the severity of liver disease. We wanted to study thyroid dysfunction in patients with alcoholic liver cirrhosis and it's correlation with Child Pugh (CTP) score.

METHODS

110 patients with alcoholic liver cirrhosis were included in the study. CTP score is calculated and classified into class A, B and C. Prevalence of thyroid dysfunction was calculated and its relationship with CTP was noted.

RESULTS

In the study 3.6%, 5.5%, 13.6% and 77.3% were overt hypothyroidism, subclinical hypothyroidism, sick euthyroid syndrome and euthyroid respectively. Higher the child pugh score, higher will be chance of patient having hypothyroidism.

CONCLUSIONS

Thyroid dysfunction is an important part of spectrum of chronic liver disease. Patients with chronic liver disease should be evaluated for thyroid dysfunction periodically.

KEYWORDS

Alcoholic Liver Cirrhosis, Child Pugh Score, Thyroid Dysfunction, Free T3, Free T4, TSH, Sick Euthyroid Syndrome

Corresponding Author:
Dr. Praveen N,
Senior Resident,
Department of General Medicine, Adichunchanagiri Institute of Medical Sciences, B. G. Nagar- 571448, Karnataka.
E-mail: drpraveenn1991@gmail.com

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BACKGROUND

Liver is an important organ in the human body. Among the various functions of the liver, one important function is the synthesis of carrier proteins and metabolism of hormones. Liver diseases are extremely common worldwide and also in India and the prevalence of liver disease is likely to increase in even more in the future.[1] Liver diseases are associated with various endocrinal disturbances. The liver plays an important role in metabolism of thyroid hormones, being involved in their conjugation, excretion, peripheral de-iodination and the synthesis of thyroxine binding-globulin (TBG). Alterations in thyroid function can lead to liver dysfunction, and conversely, various liver diseases can have differing effects on thyroid hormone metabolism.[2,3] Liver dysfunction leads to a secondary dysfunction of the endocrine glands directly due to the toxic effects and indirectly by the alteration of the carrier protein synthesis. Therefore, chronic liver disease may be accompanied by signs of apparent hormonal imbalance. Thyroxine and Tri-iodothyronine are essential for normal organ growth, development and function. These hormones regulate the basal metabolic rate of all cells, including hepatocytes, and thereby modulate hepatic function. Liver plays an important role in the metabolism of thyroid hormones, like conjugation, peripheral deiodination and synthesis of thyroid binding globulin.[4-6] Hence, it is not surprising that thyroid dysfunction has been reported in various spectra of liver disease and has been associated with the severity of liver disease.[7,8] Even though Thyroxine is secreted at a higher rate quantitatively, it is regarded as a pro hormone that requires de-iodination of T4 and conversion to T3 to become biologically active.

This reaction occurs in the thyroid and extra-thyroidal system. T3 is released from the thyroid, but approximately 80% of it is derived from the peripheral tissues by the enzymatic removal of a single 5′ iodine atom (outer ring or 5′ mono deiodination) from T4. Out of this about 30-40 percent of extra-thyroidal conversion occurs in the liver.[9] Apart from this, the liver also plays an important role in the inactivation of thyroid hormones by D3. In addition to the central role in de-iodination to activate and deactivate thyroid hormones, the liver performs specific functions relating to thyroid hormone transport. The slow clearance, prolonged half-life, and high serum concentration of thyroxine (T4) are largely due to a strong binding by the principal plasma thyroid hormone binding proteins, thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin.[10] several studies indicate that during the various phases of liver disease the serum T4 concentration alters accordingly and this is related also to the disease progression. T3 can be used as good laboratory index in evaluating the status of liver disease. The serum T3 concentration and liver factors, such as bilirubin are now can be regarded as a valuable index in Thyroid-liver pathophysiology. It is vital to measure the free T4 and Thyroid Stimulating Hormone (TSH) and any other laboratory test which may be in anyway helpful to avoid misdiagnosis of a hypothyroid patients suffering from liver diseases. A few endocrine disorders associated with chronic liver disease are even reported to reverse after liver transplantation.[5] the low total and FT3 levels may be regarded as an adaptive hypothyroid state that serves to reduce the basal metabolic rate within the hepatocytes and preserve liver function and total body protein stores[4]. It has been suggested that this adaptation may confer a survival advantage, which adapts an organism to chronic illness by reducing the basal metabolic rate within cells and thereby reducing caloric requirements. Hence the present study has been conducted to establish the concrete relationship between hypothyroidism (by measuring FT3, FT4, and TSH) and alcoholic liver cirrhosis and correlation of thyroid dysfunction with Child-Pugh score by using clinical and biochemical parameters available in our hospital.

METHODS

This study was conducted in the Department of Medicine at Karnataka Institute of Medical Sciences, Hubballi. After obtaining clearance and approval from the institutional ethical committee and written informed consent, patients with cirrhosis of liver fulfilling inclusion and exclusion criteria were enrolled in the study. Demographic data, history, clinical examination and details of investigations were recorded in the study proforma.

Method of Collection of Data

a) Period of study: December 2016 to May 2018
b) Design of study: A Prospective study
c) Size of the study sample: 110
d) Place of study: Karnataka Institute of Medical Sciences, Hubballi.

Inclusion Criteria

a) Patients willing to give written informed consent.
b) Age >18 years.
c) Male and female patients with evidence of alcoholic liver cirrhosis.

Exclusion Criteria

a) Any thyroid illness in past.
b) Pregnant women.
c) Patients with sepsis.
d) Drugs causing hypothyroidism- amiodarone, lithium.

Investigations: Complete Hemogram, Liver function tests, renal function tests, Serum electrolytes, Ultra-Sonography of Abdomen, Prothrombin time, International Normalized Ratio, Thyroid function tests. After all investigations, alcoholic liver cirrhosis were divided according to Child Pugh score child into A, B, C groups.

Statistical Analysis

4 Data was entered into Microsoft excel data sheet and was analysed using SPSS 22 version software. Categorical data

was represented in the form of frequencies and proportions. Chi-square test was used as a test of significance for qualitative data. Continuous data was represented as mean and standard deviation. ANOVA (analysis of variance) or Kruskal Wallis test was the test of significance to identify the mean difference between more than two groups for quantitative data. p value (probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests. MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) were used to analyse data.

RESULTS

In Child A group, 100% were males, in Child B group, 97.6% were males and 2.4% were females and in Child C, 98.4% were males and 1.6% were females. There was no significant difference in sex distribution with respect to Child Pugh Grade. In Child A group, mean age of subjects was 40.3 ± 9.5 years, in Child B, mean age of subjects was 42.2 ± 10.6 years and in Child C, mean age of subjects was 44.1 ± 11.4 years. There was no significant difference in mean age with respect to Child Pugh Grade. In the study 10.9% had increased TSH levels, 41.8% had decreased T3 and 3.6% had decreased T4 levels.

		Count	%
Class	Class A	7	6.3%
	Class B	41	37.3%
	Class C	62	56.4%
	Total	110	100%

Table 1. Distribution of Alcoholic Cirrhosis Patients According to Child Pugh Grade

		Child Pugh Score					
		Class A		Class B		Class C	
		Count	%	Count	%	Count	%
Sex	Female	0	0%	1	2.4%	1	1.6%
	Male	7	100%	40	97.6%	61	98.4%

Table 2. Sex Distribution with Regard to Child Pugh Grade

		Age in Yrs.	
		Mean	S.D.
Child Pugh Grade	Child A	40.3	9.5
	Child B	42.3	10.6
	Child C	44.1	11.5
	P value	0.551	

Table 3. Age Distribution Comparison with Regard to Child Pugh Grade

		Count	%
TSH	Normal (0.5 to 5.5 IU/ml)	100	90.9%
	Increased (>5.5 IU/ml)	10	9.1%
Free T3	Normal (2 to 5 pg/dl)	90	81.8%
	Decreased (<2 pg/dl)	20	18.2%
Free T4	Normal (0.7 to 2 ng/dl)	106	96.4%
	Decreased (<0.7 ng/dl)	4	3.6%

Table 4. Prevalence of Thyroid Dysfunction among Patients of Alcoholic Liver Cirrhosis

	Child Pugh Score						p
	Child A		Child B		Child C		
	Mean	SD	Mean	SD	Mean	SD	
TSH (µIU/ml)	3.3	1.2	2.8	1.4	6.5	15.4	<0.001
FT3 (pg/ml)	3.2	0.4	2.9	0.7	2.3	0.6	<0.001
FT4 (ng/dl)	1.1	0.2	1.3	0.3	1.1	0.3	0.011

Table 5. Mean TSH, T3 and T4 Comparison with Regard to Child Pugh Grade

		Class					
		Class A		Class B		Class C	
		Count	%	Count	%	Count	%
Thyroid Status	Hypothyroidism	0	00%	0	00%	4	6.5%
	Sub Clinical Hypothyroidism	0	00%	1	2.4%	5	8.1%
	Sick Euthyroid syndrome	0	00%	2	4.9%	13	20.9%
	Euthyroidism	7	100%	38	92.7%	40	64.5%

Table 6. Association between Thyroid Status and Child Pugh Grade

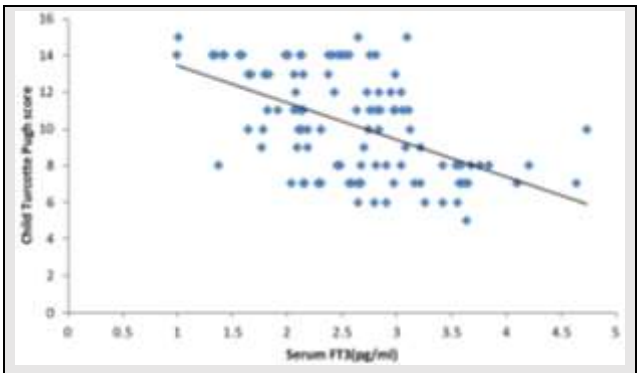

Figure 1. Scatter plot showing Child-Turcotte Pugh Score and Free

In Child A group, mean TSH was 3.3 ± 1.2, in Child B group, 2.8 ± 1.4 and in Child C group, 6.4 ± 15.4. There was significant difference in TSH with respect to Child Pugh grade. In Child A group, mean Free T3 was 3.2 ± 0.4, in Child B group, 2.9 ± 0.7 and in Child C group, 2.3 ± 0.6. There was significant difference in Free T3 with respect to Child Pugh grade. In Child A group, mean Free T4 was 1.1 ± 0.2, in Child B group, 1.3 ± 0.3 and in Child C group, 1.1 ± 0.3. There was significant difference in Free T4 with respect to Child Pugh grade.

In Subjects with Child A grade, 100% were Euthyroid. In Subjects with Child B grade, 92.7% were Euthyroid, 4.9% were Sick Euthyroid, and 2.4% were Subclinical Hypothyroid. In Subjects with Child C grade, 64.5% were Euthyroid, 20.9% were Sick Euthyroid, 8.1% were Subclinical Hypothyroid and 6.5% were Hypothyroid. There was significant association between Child Pugh Grade with Thyroid Status.

Scatter plot graph showing negative correction of child Pugh score and FT3, as higher child Pugh score lower FT3 levels in patients with Liver Cirrhosis.

DISCUSSION

In our study 110 patients with alcoholic liver cirrhosis were enrolled and they underwent a detailed history, clinical examination, haematological and biochemical investigations, ultrasonography and thyroid profile.

In practical clinical terms diagnosis of alcoholic liver cirrhosis was made in the presence of clinical features of liver cirrhosis and portal hypertension, with blood and imaging results. Therefore, the utilisation of clinical (signs and symptoms of liver cell failure), bio-chemical (raised bilirubin, SGOT, SGPT, low albumin), haematological (low haemoglobin, platelets and leucocyte count) and radiological

(nodular liver cirrhosis, contracted, signs of portal hypertension) tools is vital in diagnosis of alcoholic liver cirrhosis.

Patient Characteristics

110 patients with alcoholic liver cirrhosis were enrolled in this study with a mean age of 43.2±10.9 years (range 25-84 years). In this study female cases were less compared to male cases, this difference in gender distribution maybe to decreased prevalence of alcoholism among females in this geographic area. Among them 98.2% (108 patients) were males and 1.8% (2 patients) were females. Out of 110 patients 7 (6.3%) patients were in Child Pugh class A, 41 (37.3%) in class B and 62 (56.4%) in class C. In study done by Verma S K et al[11] 3.9% were in Child Pugh class A, 39.2% were in Child Pugh class B and 56.9% were in Child Pugh class C and study done by Kharb S et al 68 23.3% in Child Pugh class A and 35.3% in Child Pugh class B and C. In Child a group, mean age of subjects was 40.3 ± 9.5 years, in Child B, mean age of subjects was 42.2 ± 10.6 years and in Child C, mean age of subjects was 44.1 ± 11.4 years. Our study revealed, that there is a significant occurrence of hypothyroidism, subclinical hypothyroidism and sick euthyroidism with increased severity of cirrhosis of liver i.e. these finding are more patients with Child Pugh Class C.

In our study 9.1% found to be hypothyroidism, among them 3.6% had Overt Hypothyroidism and 5.5% had Subclinical Hypothyroidism, further 13.6% had Sick Euthyroid syndrome and 77.3% had Euthyroidism. In many studies thyroid hormone dysfunction ranged from 13% to 61% in patients with chronic liver disease. In patients with cirrhosis, hypothyroidism was more frequently seen, and hyperthyroidism has also been reported.[12] this is due to varied aetiology and severity. In a study by Kharb S et al[13] 4(5.33%) patients out of 75 patients of liver disease found to be hypothyroid, in which 3(3.5%) were subclinical and 1(1.3%) patient is overt hypothyroid. Out of 30 patients of liver cirrhosis in a study conducted by Kumar KH et al[14] shows subclinical hypothyroidism is present in 10%(3 patients), central hypothyroidism in 6.66%(2 patients) and primary hypothyroidism in 3.3%(1 patient).

According to Deepika G et al[15] in a study on 310 cirrhotic patients revealed that cirrhotic patients were more prevalence thyroid dysfunction specially hypothyroidism because of many reasons. In a study done by Patira NK et al[16] 31(62%) patients out of 50 patients found to be hypothyroid and among them 23(46%) had subclinical hypothyroidism. This study shows that statistically significant difference in mean FT3, FT4 and TSH with respect to Child Pugh grade with p value of <0.001, 0.011 and <0.001 respectively. Similar results found in the study done by Patira NK et al.[16]

In our study there was significant decrease in FT3 levels with p value of <0.001 and insignificant decrease in FT4 levels with p value of 0.455 and insignificant increase in TSH value with p value of 0.124. However, study conducted by Deepika G et al[15] showed that there was a significantly increased TSH between cirrhotic patients and non-cirrhotic subjects and slightly decreased T3 and T4 where the p value is 0.039, 0.014 and 0.245 respectively and also study done El-Feki MA et who found that in chronic hepatitis C concluded that decrease in the FT3 and FT4 levels and increase in the TSH levels in patients with chronic hepatitis C with cirrhosis when compared to patients with chronic hepatitis C without cirrhosis, whereas study done by Mousa HA[17] who found that a significant decrease level of T3 and an insignificant change in TSH and T4 levels than control groups The loss of peripheral deiodination is cause of decreased free T3 levels, the so called sick euthyroid syndrome. Poor nutrition in cases of liver cirrhosis has been linked to decrease in free T3. Release of cytokines such as Interleukin-6 might also be responsible for the syndrome of sick euthyroid syndrome[18] In the study there was negative correlation -0.516 and -0.130 between Child Pugh score and Free T3 and Free T4 respectively. i.e. with increase in Child Pugh score there was decrease in Free T3 and Free T4 and vice versa. This goes with Borzio M et al[8] who evaluated thyroid function in 33 patients with liver disease and found that T3, FT3 and T3/thyroxine binding globulin and thyrotropin after thyrotropin releasing hormone were significantly reduced.

According to Takahashi H et al[19] conducted a study on thyroid hormones in different categories of liver disease like acute hepatitis, chronic persistent hepatitis and chronic aggressive hepatitis concluded that serum Free T3 (FT3) levels reduced in chronic liver disease in order of chronic persistent hepatitis and chronic aggressive hepatitis and liver cirrhosis, and were low levels in acute hepatitis with the same degree as liver cirrhosis. The decreased FT3 in this study is probably reflects a decrease in deiodinase activity in the liver of cirrhotic patients.[20,21] Although some T3 is produced in the thyroid, approximately 80-85 percent is generated outside the thyroid, primarily by conversion of T4 in the liver and kidneys.[22,23] Several studies concluded that the most consistent thyroid hormone profile in patient with cirrhosis is low total and FT3 and elevated rT3 levels, similar to changes in patients with sick euthyroid syndrome. This results in a decrease in conversion of T4 to T3 and increase in rT3.[24-26]

The liver plays important role in thyroid hormone metabolism because it synthesis protein that bind thyroid hormone, like thyroid-binding globulin (TBG), albumin and pre-albumin. It is also the major site of thyroid hormone peripheral metabolism and is involved in its conjugation, biliary excretion, oxidative deamination and the extra thyroidal deiodination of thyroxin (T4) to triiodothyronine (T3) and to reverse T3. On the other hand the level of thyroid hormone is also important to normal hepatic function and bilirubin metabolism.

CONCLUSIONS

Thyroid dysfunction forms an important part of the spectrum of chronic liver disease. Patients with chronic liver disease should be evaluated for thyroid dysfunction periodically. Our study revealed, that there is a significant occurrence of

hypothyroidism and sick euthyroid syndrome in Child Pugh class C.

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