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A STUDY OF THYROID FUNCTION TESTS IN PATIENTS WITH CHRONIC LIVER DISEASE, ADMITTED IN A TERTIARY CARE HOSPITAL, KOLKATA

Biochemistry

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ABSTRACT

objective: To evaluate thyroid function tests in chronic liver disease(CLD) patients and to find out whether the thyroid functions tests abnormalities if any correlate with the clinical severity or stage of CLD patients.

Method: Cross sectional study, spanning over a period of one and half years involving one hundred CLD patients, carried out in a tertiary hospital in Kolkata.

Results: The mean values of serum FT3 and FT4 showed a tendency to fall with progressive chronic liver disease and was statistically significant, more marked with FT3 (Child A vs B, p-<0.001; A vs C, p-<0.001; CLD stage 1 vs stage 2,p <0.001) than with FT4(Child A vs B, p 0.556; A vs C, p < 0.001, stage 1 vs stage 2, p 0.020). Changes of serum TSH with chronic liver disease was found not statistically significant . The fall of mean serum FT3 and FT4 values were also significant when compared independently in respect of ascites and no ascites (p-<0.001 & p-<0.007 respectively) and hepatic encephalopathy(HE) and no HE (p <0.001; p 0.001 respectively). Significant changes of serum FT3 and FT4 values were noted with regard to rise of serum bilirubin(p-<0.001 & p-<0.001 respectively) and prothrombin prolongation time (p-<0.001 & p-0.001 resp.) but with regard to serum albumin significant changes was observed only with changes of serum FT4 but not with serum FT3 or TSH.

Conclusion: Serum FT3 can be considered as a sensitive marker of hepatic function in chronic liver disease. However thyroid function tests with etiology based chronic liver disease would perhaps help better to understand thyroid dysfunction in chronic liver disease.

KEYWORDS

Chronic liver disease(CLD), Hepatic encephalopathy(HE), Thyroid dysfunction.

INTRODUCTION:

Liver plays an important role in thyroid hormone metabolism such as the syn-thesis of carrier proteins viz. thyroxin binding globulin (TBG), prealbumin, and albumin that binds thyroid hormones. It is also the major site of thyroid hormones' peripheral metabolism and is involved in its conjugated biliary excretion, oxidation, deamination and extrathyroidal deiodination of thyroxin (T_4) to tri-iodothyronine(T3) and reverse T_3 (rT_3).[1] Thyroid hormones on the other hand are essential for normal development, growth and function of liver.[1] Keeping aside a variety of systemic diseases that affect both organs such as the association of chronic auto-immune hepatitis and primary biliary cirrhosis with autoimmune thyroid disease,[2,3] and the incidence of liver or thyroid disorders in relation to the therapy of either the thyroid or liver disease[4,5] , liver diseases are also frequently associated with thyroid dysfunctions or thyroid function tests abnormalities.[6,7,8,10] With this background we conducted a study evaluating thyroid function tests in a large number of CLD patients.

MATERIALS AND METHODS:

This was a cross sectional study conducted over a period of one and half years (2016-2017) in a tertiary hospital, Institute of Post Graduate Medical Education & Research (IPGME & R) , Kolkata ,West Bengal. With prior Institutional Ethical Committee approval,100 patients (> 14 years) of chronic liver disease were enrolled after getting them informed and having written consent for participation. Patients with thyroid disease or dysfunction on treat-ment and having alcoholic liver disease were excluded from the study. All patients underwent detailed history taking and physical examination; estimation of liver function tests, P.Time, serum FT3,FT4,TSH measurement by chemiluminescence method, tests such as USG upper abdomen and upper GI endoscopy were carried out in each patient.

Cirrhosis of liver is mainly a tissue diagnosis and is characterized by diffuse hepatic fibrosis and nodule formation . Chronic liver disease is the clinical correlate of cirrhosis of liver and is a very useful clinical surrogate that does not always need the cumbersome biopsy and histopathology examination. The diagnosis of chronic liver disease was arrived at by past h/o jaundice, clinical features suggestive of portal hypertension and heaptocellular failure, laboratory parameters such as hypoalbuminaemia (<3gm/dL) with or without reversal of albumin globulin ratio, per-sistently raised prothrombin time and history suggestive of one or more episodes of hepatic encephalopathy (HE). ultrasonographic suggestions and upper GI endoscopic evidences.

Based on West Haven Criteria hepatic encephalopathy (HE) was graded as: Minimal hepatic encephalopathy(MHE) - No clinical manifestations of encephalopathic features. Diagnosis depends on psychometric and electrophysiological testing. Grade I – Mild cognitive changes. The patient is oriented to time and space.Inversion of sleep pattern, No asterixis. Grade II - Confusion,lethargy or apathy; disorienttation to time(at least three of the following are wrong e.g-day of the week; day of the month; month, season or year), Asterixis. Grade III - Disorientation to place and person in addi-tion to time, Somnolence , Asterixis generally absent. Grade IV- Stupor and Coma.

Covert HE : MHE + Grade I HE, Overt HE : Grade II-IV. Covert HE is scarcely symptomatic or asymptomatic and does not require hospital admission. Overt HE : undoubtedly symptomatic and require hospital admission

The subjects of chronic liver disease selected were further classified as per Child Pugh score. Here Child Pugh Class –A (Score of < 7) was grouped as CLD Stage 1 (Compensated cirrhosis). Child Class B and C combined together(score >7) were grouped as CLD Stage 2 (Decompens Cirrhosis).

CLD patients with ascites were graded as no ascites, mild ascites, and moderate to severe ascites. [Mild ascites- ascites only by USG, Moderate ascites – symmetrical distension of abdomen with flank dullness and positive shifting dullness, Severe ascites - ascites causing marked abdominal distension].

Statistical Methods: The statistical software SPSS version 20 was used for data storage and analysis. Categorical variables were expressed as number and percentage of patients and compared across the groups using Pearson's Chi Square Tests. The continuous variables were expressed as mean ± standard deviation. Association between continuous variables were tested using Spearman's Rank correlation coefficient. Statistical significance was set at p value of ≤ 0.05, p value of ≤ 0.005 was leveled as highly significant.

RESULTS AND ANALYSIS:

Out of total of 100 CLD patients studied, 63 were male and 37 were fem- ale patients. As per Child Pugh Class and CLD Stage the age and sex distribution of the CLD patients are given in Table 1 & 2.

Regarding etiology of CLD, 42 patient were isolated Hepatitis B related, 15 patients isolated hepatitis C related, 4 patients having both hep B and hep C positive CLD, 8 were autoimmune CLD ,3 had Wilson disease induced CLD and in rest 28 cause was cryptogenic. However as the study was not etiology based we considered only severity of liver disease (Child pugh A,B and C or CLD-1 and CLD-2) irrespective of etiology.

Table 1

			CHILD PUGH CLASS		Total	Overall	
		Class A	Class B	Class C		p Value	Significance
AGE IN YEAR	16-30	6(21.43)	8(16.33)	3(13.04)	17(17)	0.648	Not significant
	31-45	12(42.86)	18(36.73)	7(30.43)	37(37)		
	46-60	6(21.43)	15(30.61)	11(47.83)	32(32)		
	>60	4(14.29)	8(16.33)	2(8.7)	14(14)		
Total		28(100)	49(100)	23(100)	100(100)		

Table 2

		CLD STAGE		Total		
		Stage 1	Stage 2		p Value	Significance
AGE IN YEAR	16-30	6(21.43)	11(15.28)	17(17)	0.519	Not Significant
	31-45	12(42.86)	25(34.72)	37(37)		
	46-60	6(21.43)	26(36.11)	32(32)		
	>60	4(14.29)	10(13.89)	14(14)		
Total		28(100)	72(100)	100(100)		

The mean values of serum FT3, FT4 and TSH with respect to Child Pugh Class and CLD stage were depicted in Table 3 and 4.

Table3

Child Pugh Class		Ft3 pg/ml	Ft4 ng/dl	TSH MIU/L
Class A	Mean	3.06±0.78	1.47±.31	2.54±1.06
Class B	Mean	1.98±0.86	1.42±0.27	2.72±2.14
Class C	Mean	1.37±0.82	1.08±0.29	3.41±1.72
A vs. B	p Value	<0.001	0.556	0.658
	Significance	Significant	Not Significant	Not Significant
A vs. C	p Value	<0.001	<0.001	0.036
	Significance	Significant	Significant	Significant
B vs. C	p Value	0.006	<0.001	0.042
	Significance	Significant	Significant	Significant

Table 4

CLD STAGE		Ft3 pg/ml	Ft4 ng/dl	TSH MIU/L
Stage 1	Mean	3.06±0.78	1.47±0.31	2.54±1.06
Stage 2	Mean	1.79±0.89	1.31±0.32	2.94±2.03
	p Value	<0.001	0.020	0.920
	Significance	Significant	Significant	Not Significant

Serum FT3 level showed a tendency to fall with progression of chronic liver disease and the change was statistically highly significant (Child Class A vs B and A vs C , p <0.001; Child B vs C , p 0.006; CLD stage 1 vs CLD stage 2, p <0.001). Serum FT4 level also registered a tendency to fall and the changes of FT4 with respect to progressive CLD was statistically significant (Child A vs B, p 0.556; Child A vs C, p < 0.001; Child B vs C, p <0.001; CLD stage 1 vs CLD stage 2, p 0.020) . Serum TSH did not show any significant changes with severity of liver dysfunction in CLD patients (Child A vs B, p 0.658; Child A vs C, p 0.036; CLD stage 1 vs CLD stage 2, p 0.920)

With regard to ascites, 40 patients had grade 1 (no ascites), 16 patients had grade 2 (mild ascites) and 44 patients had grade 3 (moderate to severe) ascites. Serum FT3 and FT4 had a tendency to fall with progression of ascites and their mean level at different grades of ascites when compared was found statistically significant (p- <0.001 &0.007 respectively). Serum TSH value did not show any significant changes with progressive ascites (p-0.758).

Ascites		Ft3 pg/ml	Ft4 ng/dl	TSH MIU/L
No ascites	Mean	2.64±1.00	1.46±1.00	2.62±1.00
Mild	Mean	2.24±0.92	1.38±0.37	2.71±1.79
Moderate to Severe	Mean	1.66±0.88	1.25±0.33	3.06±2.14
	p Value	<0.001	0.007	0.758
	Significance	Significant	Significant	Not Significant

Among 100 CLD patients 75 patients had no hepatic encephalopathy (No HE), 16 patients had Covert HE and 9 patients had Overt HE. This study showed that the mean serum FT3 and FT4 levels tend to fall with progressive severity or grade of HE and the changes of mean values of FT3 and FT4 with respect to different grades of HE when compared was highly significant (p-<0.001 &0.001 respectively). Serum TSH level at different grades of HE showed no significant changes (p-0.150).

Hepatic encephalopathy		Ft3 pg/ml	Ft4 ng/dl	TSH MIU/L
No HE	Mean	2.44±0.96	1.43±0.29	2.62±1.62
Covert HE	Mean	1.49±0.76	1.22±0.31	3.80±2.52
Overt HE	Mean	0.88±0.41	0.98±0.27	2.84±1.57
	p Value	<0.001	0.001	0.150
	Significance	Significant	Significant	Not Significant

Significant changes of serum FT3 and FT4 values were noted with regard to rise of serum bilirubin (p-<0.001 & p-<0.001 respectively) and prothrombin prolongation time (p-<0.001 & p-0.001 respectively) but with regard to serum albumin significant changes was observed only with of serum FT4 but not with serum FT3 or TSH.

The serum bilirubin level were <2mg/dl in 54 patients, 2-3mg/dl in 28 patients and >3mg/dl in 18 patients out of 100 patients studied. Mean serum FT3 and FT4 with reference to rising bilirubin level when compared was statistically highly significant (p <0.001 & <0.001 respec-tively), but no significant change of serum TSH with rising serum bilirubin was found. (p 0.161).

Among 100 patients,13 patients had albumin >3.5gm/dL, 48 had 3.5-2.8gm/dL and 39 has less than 2.8 gm/dL. The fall of serum FT4 with decrease of serum albumin in CLD patients was statistically significant.(p - 0.008). Whereas serum FT3 and TSH did not show any statistically significant Changes with albumin in CLD patients(p-0.073 & 0.051).

The Prothrombin time (PT) prolongation was <4 secs in 66 patients, 4-6 secs in 16 patients and >6 secs in 18 patients. The changes of mean TSH with different levels of PT prolongation in CLD patients was statistically significant(p-0.020) whereas the changes of both serum FT3 and FT4 at the same level of PT prolongation was highly significant. (p-<0.001 & p-0.001 respectively).]

Normal value of FT3 was taken as 1.5-4.1 pg/dl, normal FT4 value 0.8-2 ng/dl and normal TSH level 0.4-4.mIU/L. Among 28 patients with CLD grade-1, only 4 patients(14.28%) had TSH value above normal range but their FT3 and FT4 values were within normal range. Among 72 patients with CLD grade- 2, fifteen patients (20.83%) had TSH value above normal. Among them,only 4 patient had low FT4 also and 3 patients had both low FT3 and FT4.No patients had TSH below normal range. No patients had clinical manifestation of hyperthyroidism

DISCUSSION.

Several past Investigators reported various thyroid function tests abnormalities in patients with acute and chronic liver diseases and the abnormalities reported seemed inconsistent sometimes.[6-10] The total(T4) and free thyroxine (FT4) serum concentrations reported were normal , increased or decreased in various liver disease.[6,8,12] The most consistent findings were elevation of T4 but normal free T4 (FT4) and thyroid stimulating hormone (TSH) both in acute and chronic liver diseases.[6-10] The elevation of T4, as reported by past investigators was secondary to thyroxine binding globulin (TBG) elevation. The finding of increased rather than decreased serum TBG concentration in chronic hepatitis and cirrhosis is due to several factors such as i) increased TBG synthesis in regenerating hepatocytes ii) decreased TBG degradation and iii) release of TBG by damaged hepatocytes. [13] Total and free triiodothyronine (T3 and FT3) concentrations were often decreased , sometimes profoundly and their levels correlated well with the severity of liver dysfunction [12,15] The inconsistencies reported in different studies might possibly be due to selection of patients at different stages of the disease process and the different analytical methods used.[11]

In our study, we found that serum FT4 level decreased with CLD severity and this change was statistically significant (Child A vs C, p <0.001; CLD1 vs CLD2, p < 0.020). Our study also showed that serum FT3 level tend to fall with progressive severity of chronic liver disease and the change was statistically highly significant (Child A vs B, p-<0.001; A vs C, p-<0.001; CLD stage 1 vs stage 2,p <0.001). This findings corroborated with several other previous studies that showed that the total (T3) and free triiodothyronine (FT3) concentrations were often decreased sometime markedly and correlated negatively with the severity of the liver disease.[6,12] Patients with advanced decompensated liver disease, as in other nonthyroidal illness (NTIS) may even have the 'low T3 syndrome' characterised by low total T3 with normal total T4 and thyrotropin (TSH) concentration in the absence of clinical hypothyroidism [6,7,8,14]

Israel et al [15] ,in a group of alcoholic patients reported a progressive increase of T3 in those subjects eventually displaying a favourable outcome, suggesting T3 concentration in patients with advanced liver disease may be considered as helpful prognostic indicator.

Our study did not show any significant change of serum TSH with progressive CLD stages (Child A vs B, p 0.658; Child A vs C, p 0.036; CLD stage 1 vs CLD stage 2, p 0.920). Slightly increased serum thyrotropin concentration in liver cirrhosis was previously reported [7,8] but the possibility of this finding being due to the existence of hypothyroidism was unlikely in view of the normal or even reduced thyrotropin response to thyrotropin releasing hormone(TRH), a finding also confirmed by M. Borzio et al. [9]

The fall of mean serum FT3 and FT4 values were also significant when compared indepen-dently in respect to ascites and no ascites (p-<0.001 & p-<0.007 respectively) and hepatic encephalopathy (HE) and no HE (p <0.001; p 0.001 respectively).

Significant changes of serum FT3 and FT4 values were noted with regard to rise of serum bilirubin and prothrombin prolongation time but with regard to serum albumin significant changes was observed only with changes of serum FT4 but not with serum FT3 or TSH. M. Borzio et al also found a good correlation between serum T3 and serum albumin, bilirubin and prothrombine time but no correlation with the hepatic inflammatory markers like the transami-nases and Y globulins suggesting that T3 concentrations should be considered a sensitive index of hepatic function in liver disease.[9]

It appears that thyroid function tests may be difficult to interpret in the presence of liver disease. As FT4 and TSH are usually normal in euthyroid patients with liver disease, these should be measured to rule out or to establish the presence of associated thyroid dysfunctions. Because of the frequently raised TBG in those patients one could have falsely raised T4 and T3 despite being hypothyroid. Finding of normal or low normal T4 in these patient population should alert the physicians to the possibility of coexistent hypothyroidism.[16] Wheras determin-ation of free hormone concentration will readily distinguish these patients from those with hyperthyroidism.[17]

The strengths of this study were in the assessment of thyroid functions at various stages of liver disease and exclusion of patients with alcoholic liver disease because alcohol was known to affect hypothalamopituitarythyroid axis.[18]

The present study confirmed the existence of several thyroid function tests abnormalities in patients with chronic liver disease, althoughit it showed that euthyroidism was almost always maintained, probably as a result of low-normal FT3. Furthermore, serum FT3 levels appear to parallel the severity of liver dysfunction. Low free T3 levels may be regarded as an adaptive hypothyroid state that serves to reduce the basal metabolic rate within hepatocytes and prese-rve liver functions and total body proteins stores. Indeed, a recent study in cirrhotic patients showed that onset of hypothyroidism from intrinsic thyroid disease of various etiologies during cirrhosis resulting in a biochemical improvement in liver function (e.g. coagulation profile) as compared to controls. [19] Hypothyroidism was also associated with lesser degree of decompen-sation in cirrhosis.[20] As serum FT3 level fall with progression of chronic liver disease , it can be a useful marker to assess the severity of CLD.

CONCLUSION:

A statistically significant changes of serum FT3 and FT4 levels that tend to fall with progressive severity of chronic liver disease irrespective of aetiology, more marked with FT3 than with FT4 was found. Thyroid function tests with aetiology based chronic liver disease would perhaps help better to understand thyroid dysfunction in chronic liver disease. We can conclude that serum FT3 can be considered as a sensitive marker of hepatic function in chronic liver disease

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