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Low serum total thyroxine and free triiodothyronine in patients with hepatic encephalopathy due to non-alcoholic cirrhosis

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Summary

Principles: We evaluated serum thyroid hormone levels in non-alcoholic cirrhotic patients with and without hepatic encephalopathy.

Methods: 15 consecutive patients with hepatic encephalopathy secondary to non-alcoholic cirrhosis (8 males and 7 females, age 37–75 years) and 33 non-alcoholic cirrhotic patients without encephalopathy (22 males and 11 females, age 36–74 years) were investigated. A control group consisted of 20 healthy subjects (10 men and 10 women aged 26–69 years). The levels of serum triiodothyronine (T_3), thyroxine (T_4), thyrotropin (TSH), free T_3 (FT_3) and free T_4 (FT_4) were studied in serum samples drawn in the morning. Thyroid function tests were set in relation to the severity of hepatic dysfunction and to the presence or absence of hepatic encephalopathy.

Results: Serum levels of FT_3 and total T_4 (but not total T_3 and FT_4) were significantly lower in patients with hepatic encephalopathy compared to decompensated cirrhotic patients without encephalopathy ($p = 0.006$ for T_4, $P < 0.05$ for FT_3). Prothrombin-time also differed significantly between decompensated cirrhotic patients (Child C) with and without encephalopathy groups ($p = 0.002$).

Conclusions: These results suggest that patients with hepatic encephalopathy secondary to decompensated non-alcoholic cirrhosis are typified by low FT_3 and low total T_4, as well as by a prolonged prothrombin time. Low FT_3 does not obviously put patients at risk for hepatic encephalopathy, and thyroid parameters are secondary and late events.

Key words: cirrhosis; hepatic encephalopathy; thyroid function tests

Introduction

The liver plays an important role in the metabolism of thyroid hormones, being involved in their conjugation, excretion and peripheral deiodination, and in synthesising thyroid binding globulin (TBG) [1, 2]. Evidence of an association between chronic diseases of the liver and thyroid alterations have often been reported, but limited information is available on thyroid function tests in non-alcoholic cirrhotic patients with hepatic encephalopathy. Most studies have been carried out in patients with cirrhosis of alcoholic origin. Studies have revealed that T_4 levels are usually within normal limits, but, as cirrhosis progresses, FT_4 levels increase secondary to decreased serum levels of thyroxine-binding protein [3]. T_3 and FT_3 concentrations are usually decreased in correlation with the severity of the disease, but this is still controverted [4]. To our knowledge, there has been no previous study comparing thyroid hormone levels in patients with non-alcoholic decompensated cirrhosis and those with cirrhosis complicated with hepatic encephalopathy.

In this study we investigated thyroid hormone levels in non-alcoholic decompensated cirrhotic patients with and without hepatic encephalopathy. We also attempted to determine whether or not thyroid function tests may be a useful prognostic indicator for the development of hepatic encephalopathy in decompensated cirrhotic patients.

No financial support declared.

Material and methods

This study was carried out in 15 patients (mean age 51 ± 8.74 years, range 37–75 years) with hepatic encephalopathy due to non-alcoholic cirrhosis, consecutively admitted to the Division of Gastroenterology, and in 33 non-alcoholic cirrhotic patients (mean age 55 ± 7.71, range 36–74 years) without encephalopathy. 20 healthy subjects (10 male, 10 female, aged 49.7 ± 8.45 years, range 26–69 years) matched for age, height and sex served as control group. None of the patients or controls had a history of alcohol consumption. All the subjects were clinically euthyroid, none was known to have a present or past history of thyroid disease and none was taking any drug known to affect thyroid function. The main characteristics of the patients are summarised in table 1.

The diagnosis of cirrhosis was based on case history, clinical examination, biochemical, endoscopic and ultrasound findings, or liver biopsy. Liver biopsies were not performed if coma, reduced coagulability or extensive ascites was present. The functional severity of the liver injury was determined on the basis of the Child-Pugh grading system [5]. The size of the groups were as follows: Child A: 9 patients, mean age 51.33 ± 8.81 years (range 37–65 years), Child B: 11 patients, mean age 52.72 ± 7.80 years (range 44–75 years), Child C: 13 patients, mean age 57.21 ± 9.40 years (range 51–72 years). 27 patients had positive serological markers for viral hepatitis (19 hepatitis B surface antigen-associated and 8 hepatitis C virus antibody-associated), the remaining 6 having cirrhosis of unknown origin.

The degree of encephalopathy was defined on the basis of previously reported criteria [6] ranked between grade 1 and grade 4. Encephalopathy was related to hepatitis B virus in 10 patients and to hepatitis C virus in 5. Hepatitis B virus infection was assumed if hepatitis B surface antigen was detected in the sera, whereas hepatitis C virus infection was diagnosed when anti-HCV antibodies were found in an enzyme immunosorbent assay (Anti-HCV Enzyme Immunoassay kit, Diasorin S.A., Madrid, Spain). Encephalopathic patients were further divided into two groups, survivors and non-survivors.

On admission, the following parameters for evaluation of the severity of liver dysfunction were recorded: albumin (n: 3.5–5.2 g/dl); bilirubin (n: 1.3–3.1 mg/dl); serum aspartate transaminase (AST) (n: 10–30 U/L); serum alkaline phosphatase (ALP) (n: 44–155 U/l) and prothrombin time (n: 1.04–1.5 [INR]). These biochemical tests were performed by standard auto-analyser methods. Plasma prothrombin ratios were measured with human brain thromboplastin tissue (STA-Neoplastine CI Plus kits, France). In all cases, blood samples for hormone determinations were drawn in the morning after overnight fasting. FT_3, FT_4, T_3, and T_4 were measured by competitive radioimmunoassay using DPC kit (Diagnostic Products Corporation, United Kingdom). TSH was measured by an immunometric assay method (DPC-UK). On the basis of the patients' and control subjects' thyroid function values we calculated a 95% confidence interval for this parameter.

Statistical analysis

Student's t test was used to compare the continued variables between two groups. The analysis of variance (ANOVA) was used to test the significance of continued variables within groups. All values are reported as mean ± standard deviation. The correlation between serum albumin bilirubin levels, prothrombin time and T_3, T_4, FT_3 levels in both groups was assessed by Pearson's correlation coefficient. P value <0.05 was considered statistically significant. Normal values in our laboratory are as follows: FT_3: 1.57–4.71 pg/ml; FT_4: 0.85–1.78 ng/dl: T_3: 60–164 mg/dl; T_4: 4.5–12.1 µg/dl; TSH: 0.4–4 µIU/ml.

Table 1

Main features of patients and control subjects.

	cirrhotic patients with hepatic encephalopathy		all cirrhotic patients		control subjects	
	survivors	non-survivors	Child A	Child B	Child C	
Number	9	6	9	11	13	20
Males/females	5/4	3/3	6/3	8/3	10/3	10/10
Age (yr) *	53.4 ± 9.45	57.14 ± 6.95	51.33 ± 8.81	52.72 ± 7.80	57.21 ± 9.40	49.7 ± 8.45
Duration of disease (yr) *	3.8 ± 0.9	4.7 ± 1.4	3.1 ± 0.7	3.4 ± 0.91	3.8 ± 0.52	–

*Data given as mean ± SEM

Results

The thyroid function tests in non-alcoholic cirrhotic patients with encephalopathy, in non-alcoholic cirrhotic patients without encephalopathy and in control patients are shown in table 2. Compared to controls, patients with hepatic encephalopathy and decompensated cirrhotic patients (Child C group) showed a significant decrease in T_3 and FT_3 levels (98.7 ± 17.4 ng/dl vs 40.66 ± 9.6, 51.96 ± 8.21 for T_3 and 2.76 ± 0.45 pg/ml vs 1.61 ± 0.38 and 1.15 ± 0.25 for FT_3 respectively; $p < 0.05$), whereas there was no difference in serum T_4, TSH and FT_4 levels.

Cirrhotic patients with hepatic encephalopathy had significantly reduced serum levels of T_4, FT_3 and T_3 compared to all cirrhotic patients ($p = 0.003$ for T_4, $p < 0.001$ for FT_3 and $p = 0.004$ for T_3), whereas there was no difference in FT_4 and TSH levels. No significant differences in T_3, T_4, TSH, FT_3 and FT_4 levels were observed between survivors and non-survivors with hepatic en-

Table 2

Thyroid hormone levels in patients and control subjects.

Hormone	non-alcoholic cirrhotic patients with encephalopathy			cirrhotic patients				control subjects (n = 20)
	all patients (n = 15)	survivors (n = 9)	non-survivors (n = 6)	all patients (n = 33)	Child A (n = 9)	Child B (n = 11)	Child C (n = 13)	
T3 (ng/dl)	40.66 ± 9.6[a d]	43.4 ± 8.22	49.2 ± 6.9	69.28 ± 20.8	88.13 ± 17.59	74 ± 10.06	51.96 ± 8.21*	98.7 ± 17.4
T4 (µg/dl)	4.28 ± 1.53[b e]	4.36 ± 1.22	4.18 ± 1.1	6.96 ± 1.6	7.04 ± 2.67	6.7 ± 1.45	6.38 ± 1.51	7.33 ± 2.68
TSH (µU/ml)	1.22 ± 0.83	1.23 ± 0.74	1.2 ± 0.86	1.22 ± 0.17	0.96 ± 0.74	1.35 ± 0.69	1.53 ± 0.63	
FT3 (pg/ml)	1.15 ± 0.25[c f *]	1.14 ± 0.21	1.17 ± 0.14	2.08 ± 0.67	2.40 ± 0.79	2.36 ± 0.56	1.61 ± 0.38 [g *]	2.76 ± 0.45
FT4 (g/dl)	0.85 ± 0.28	0.87 ± 0.23	0.83 ± 0.74	0.96 ± 0.28	1.14 ± 0.22	1.04 ± 0.25	0.93 ± 0.21	1.27 ± 0.42

[a] p <0.05 (Child C and hepatic encephalopathy vs controls)
[b] p = 0.003 (Hepatic encephalopathy vs all cirrhotic patients)
[c] p <0.001 (Hepatic encephalopathy vs all cirrhotic patients)
[d] p = 0.004 (Hepatic encephalopathy vs all cirrhotic patients)
[e] p = 0.006 (Hepatic encephalopathy vs Child C)
[f] p <0.05 (Hepatic encephalopathy vs Child C)
[g] p <0.05 (Child C vs Child A and Child B)

Table 3

Laboratory data in control subjects and in patients with cirrhosis.

	non-alcoholic cirrhotic patients with encephalopathy			cirrhotic patients				control subjects (n = 20)
	all patients (n = 15)	survivors (n = 9)	non-survivors (n = 6)	all patients (n = 33)	Child A (n = 9)	Child B (n = 11)	Child C (n = 13)	
HBV related	10	7	3	19	6	5	8	
HCV related	5	3	2	8	2	3	3	
Cryptogenic				6	1	3	2	
Albumin (g/dl)	2.61 ± 0.39	2.63 ± 0.42	2.54 ± 0.33	3.17 ± 0.59	3.72 ± 0.5[a]	3.29 ± 0.54[a]	2.74 ± 031	4.1 ± 0.29
Bilirubin (mg/dl)	3.68 ± 1.8	3.57 ± 1.83	3.71 ± 1.62	2.66 ± 0.39	0.97 ± 0.28[b]	2.61 ± 1.25	3.8 ± 2.11	0.95 ± 0.18
ALP (U/L)	220 ± 17	214 ± 30	225 ± 32	252 ± 34	265 ± 28	236 ± 19	250 ± 39	145 ± 12
AST (U/L)	47 ± 8	43 ± 6	54 ± 8	54 ± 9	49 ± 12	6 ± 11	51 ± 8	17 ± 6
Prothrombin time (INR)	2.21 ± 0.53	2.19 ± 0.24	2.24 ± 0.42	1.6 ± 0.41	1.21 ± 0.22[c]	1.58 ± 0.25[c]	1.86 ± 0.42[c]	1.12 ± 0.19

[a] P <0.03 (Child A and Child B vs encephalopathy)
[b] P <0.05 (Child A vs encephalopathy)
[c] P <0.001 (Child A, Child B and Child C vs encephalopathy)

cephalopathy (p <0.375). Serum T_4 and FT_3 levels were significantly decreased in patients with encephalopathy compared with decompensated (Child C) cirrhotic patients (p = 0.006 for T_4, p <0.05 for FT_3 respectively). Decompensated cirrhotic patients had significantly lower serum T_3 and FT_3 levels than Child A and Child B groups (p <0.05). No significant differences were observed when serum T_4, TSH and FT_4 levels were compared among Child A, Child B and Child C groups. Cirrhotic patients' and controls' biochemical data which reflect the severity of the liver disease are presented in table 3.

Of cirrhotic patients with encephalopathy, 11 belonged to Child C group and 4 to Child B group. Routine laboratory tests did not significantly differ between survivors and non-survivors.

Statistical analysis revealed a significant inverse correlation between serum FT_3 concentrations and the severity of liver dysfunction. An inverse correlation was observed between serum bilirubin and T_3, T_4 levels (r = –0.65, p = 0.014 for T_3, r = –0.298, p = 0.047 for T_4) as well as between prothrombin time and T_3, T_4 and FT_3 levels in both groups (r = –0.594, p <0.01 for T_3, r = 0.476, p = 0.001 for T_4, r = –0.515, p = 0.001 for FT_3). On the other hand, a positive correlation was found between serum albumin levels and T_3, T_4 and FT_3 levels (r = 0.634, p <0.001 for T_3, r = 0.397, p = 0.007 for T_4, r = 0.394, p = 0.011 for FT_3.

Prothrombin time was significantly longer in patients with hepatic encephalopathy than in Child C patients without encephalopathy (p = 0.002). However, no difference was observed between albumin and bilirubin levels.

Discussion

Thyroid dysfunction has been reported previously in a variety of non-thyroid illnesses including liver, pulmonary and renal neoplastic disease, severe systemic illness, fasting, malnutrition, postoperative state, physical trauma and acute infections. Low total and free T_3 with normal total T_4 and thyrotropin concentrations in the absence of clinical hypothyroidism have been frequently reported in patients with non-thyroidal illnesses [7, 8, 9]. Several investigations have been performed to assess the relationship between liver disease and thyroid hormones [1, 2, 7, 10]. Hepner and Walfish reported a significant inverse correlation between serum T_3 concentrations and the severity of liver dysfunction. A progressive decrease in T_3 levels in chronic liver diseases has been described as indicative of a poor prognosis [10–12]. Authors ascribed this finding to diminished conversion of T_4 to T_3 and impaired metabolism of thyroxine-binding proteins. In the present study we demonstrated a fall in FT_3 and T_3 parallel to severity of the disease, and a good correlation between T_3 concentrations, serum albumin and prothrombin time. These results suggest that serum T_3 and FT_3 concentrations may be considered a sensitive index of hepatic function in liver disease. We chose non-alcoholic patients because alcohol is considered to have a direct toxic effect on thyroid parenchyma, as previously described in chronic alcoholics [13].

Borzio et al. compared cirrhotics with normal subjects and chronic hepatitis patients. They suggested that T_3 serum levels inversely paralleled severity of liver dysfunction [2]. Thyroid function tests have also been performed in acute hepatitis [14]. T_4 has been found to be elevated in patients with acute viral hepatitis due to elevation of TBG (possibly secondary to release from injured hepatocytes).

Our study differs from previous investigations in that we determined the alterations of thyroid hormone level in non-alcoholic decompensated cirrhotic patients with and without hepatic encephalopathy. We found a significant reduction in serum FT_3 in non-alcoholic cirrhotic patients compared with a control group, the lowest values being found in patients with hepatic encephalopathy. Low FT_3 levels may be due to reduced extra-thyroidal T_4-to-T_3 conversion, the mechanism being inversely related to the degree of hepatic dysfunction.

We found no significant difference in functional thyroid parameters between patients surviving and not surviving hepatic encephalopathy ($p < 0.375$), but Guven et al. have reported lower T_3 levels in patients who died than in patients who survived [7, 10, 15]. The reason for this difference is not clear.

In conclusion, patients with decompensated liver disease complicated by hepatic encephalopathy subsequent to non-alcoholic cirrhosis were found to have exceedingly low serum FT_3 and T_4 levels. Depressed serum FT_3 and T_4 levels, together with a prolonged prothrombin-time, therefore appear to be characteristic of a subgroup of decompensated cirrhotic patients prone to develop hepatic encephalopathy.

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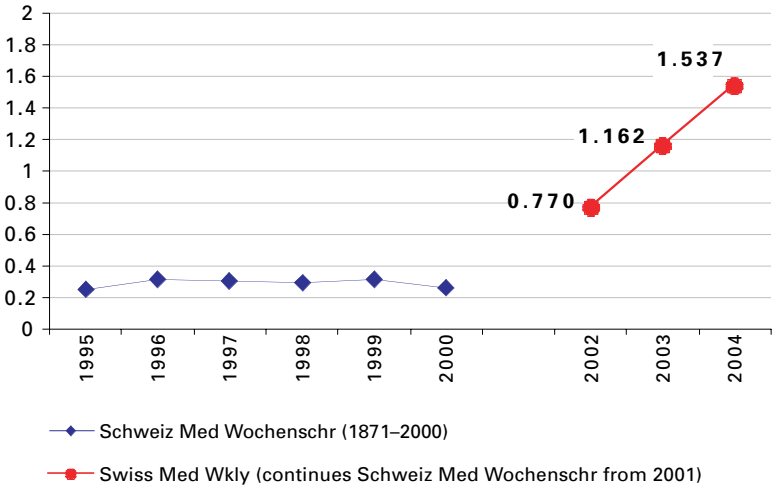

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