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ORIGINAL ARTICLE

Features of Hormonal Disturbances in Cirrhotic Patients with Hepatic Encephalopathy

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ABSTRACT

Background: Features of hormone disturbances in patients suffering from chronic hepatic failure have been documented for many years.

Objective: To evaluate the possible diagnostic and prognostic values of cortisol, total T3, thyroid-stimulating hormone (TSH) and prolactin concentrations in cirrhotic patients for prediction of hepatic encephalopathy (HE) and severity of hepatic diseases.

Materials and methods: Study was carried out on 75 (40 males, 35 females) cirrhotic patients (HCV positive) with HE and 50 (28 males, 22 females) cirrhotic patients without HE (HCV positive). Patients underwent clinical evaluation with determination of the degree of HE. The severity of cirrhosis was assessed according to Child-Pugh classification. Immulite 1000 chemiluminescent immunometric assay was used for determination of cortisol, total T3, TSH and prolactin.

Results: Cortisol, total T3 concentrations were significantly decreased in cirrhotic patients with HE compared to those without HE. Cutoff value for cortisol was less than 18.3 mg/dl could predict HE in cirrhotic patients according to AUROC curve showing a sensitivity of 52% and a specificity of 61%. Cutoff value for total T3 of less than 45.5 ng/dl could predict HE in cirrhotic patients showing a sensitivity of 64% and a specificity of 80.6%. Whereas prolactin concentration in cirrhotic patients with HE was significantly increased compared to patients without HE and its cutoff value was more than 18.85 ng/dl could predict HE in cirrhotic patients showing a sensitivity of 88% and a specificity of 90.3%. TSH concentration showed no significant difference in patients with HE *vs* patients without HE.

Conclusion: Hormonal abnormalities of cortisol, total T3 and prolactin may represent risk factors and early indicators of impending hepatic encephalopathy and progression of liver disease severity.

Keywords: Liver cirrhosis, Cortisol, Hepatic encephalopathy, Prolactin, Total T3, TSH.

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INTRODUCTION

Hepatic encephalopathy (HE), a major complication of cirrhosis, is a clinical syndrome characterized by mental status changes in patients with severe hepatic insufficiency.[1] Features of hormone disturbances in patients suffering from chronic hepatic failure have been documented for many years.[2] The hypothalamic-pituitary-gonadal axis is affected in most patients,[3] but also other hormones are altered by hepatic insufficiency as described for thyroid hormones[4] and growth hormone.[5]

Liver is the primary site of metabolism of adrenal steroid hormone and synthesis of cholesterol, which is the major precursor of steroid.[6] The adrenal insufficiency is extremely frequent in patients with advanced cirrhosis and septic shock and that treatment with low doses of hydrocortisone is associated with a marked increase in shock reversal and hospital survival.[7]

The liver plays an important role in the metabolism of thyroid hormones, being involved in their conjugation, excretion and peripheral deiodination and in synthesizing thyroid binding globulin (TBG).[8] 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 nonalcoholic cirrhotic patients with HE.[9] Malik and Hodgson[10] reported that the most common thyroid function test abnormalities in cirrhosis are low total T3, low free T3 and elevated rT3.

In cirrhosis, hypogonadism can be primary or central, resulting from the inhibition of the hypothalamus-pituitary-gonadal axis,[11] with studies showing simultaneous (gonadal and central) damage.[12] Hyperprolactinemia is often present in these patients, as well as hyperestrogenemia, both responsible for the clinical characteristics of feminization. Hyperprolactinemia and hyperestrogenemia can contribute to the genesis of hypogonadism.[13]

The main goal of the present study was to evaluate the possibility of diagnostic and prognostic values of cortisol, total T3, thyroid stimulating hormone (TSH) and prolactin concentrations in cirrhotic patients to predict HE and the severity of hepatic disease as measured by the Child-Pugh score.

MATERIALS AND METHODS

This study was carried out on 75 (40 males, 35 females) cirrhotic patients with HE and 50 (28 males, 22 females) cirrhotic without HE (all patients positive for anti-HCV antibodies). They were age and sex matched with their mean age (49.22 ± 5.62 years) recruited from Inpatient and Outpatient Clinic of Tropical Medicine Department and Specialized Medical Hospital, Mansoura University, Egypt. Cirrhosis was diagnosed on a clinical basis involving laboratory tests, endoscopic evidence, sonographic findings

and/or by liver biopsy, and regular follow-up in our Liver Outpatient Clinic. The exclusion criteria were the presence of significant comorbid illness such as heart, respiratory or renal failure; and history of any neurologic disease, such as Alzheimer's disease, Parkinson's disease or nonhepatic metabolic encephalopathies, patients on psychoactive drugs, such as antidepressants or sedatives and patients receiving drugs known to cause hyperprolactinemia.

All study participants underwent comprehensive biochemical, clinical evaluation with determination of the degree of encephalopathy. The severity of cirrhosis was assessed according to Child-Pugh classification into Child A (n = 40), B (n = 40) and C (n = 45). For the calculation of the Child-Turcotte-Pugh score **(**CTP score) we used the Pugh score modification.[14] The degree of encephalopathy was defined on the basis of previously reported criteria[15] ranked between grade 1 and grade 4. Informed consent was taken and the protocol was approved by the hospital ethical committee in accordance with the ethical guidelines of the 1975 declaration of Helsinki.

Routine laboratory tests include liver function tests (albumin, total bilirubin, ALT, AST), serum creatinine (Chemistry autoanalyzer) and INR were done. Special investigations included serum cortisol, total T3, TSH and prolactin. Immulite 1000 (competitive chemiluminescent immunometric assay) was used for determination of serum cortisol[16] and total T3[17] and solid phase 2-site chemiluminescent immunometric assay was used for determination of serum TSH[18] and prolactin.[19]

Statistical Analysis

Data were analyzed using SPSS (statistical package for social sciences) version 10. Qualitative data were presented as number and percent. Comparison between groups was done by Chi-square test. Quantitative data were tested for normality by Kolmogrov-Smirnov test. Normally distributed data were presented as mean ± SD. Student t-test was used to compare between two groups. Nonparametric data were presented as min-max and median. Mann-Whitney and Kruskal-Wallis tests were used for comparison between groups. Spearman's correlation coefficient was used to test correlation between variables. Receiver operating curve (ROC) was done to determine a cutoff point; sensitivity and specificity were calculated for this cutoff point. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

This study was carried out on 75 cirrhotic patients with HE and 50 cirrhotic patients without HE. The severity of cirrhosis was assessed according to Child-Pugh classification in all patients into Child A (n = 40), B (n = 40) and C (n = 45). Patients with HE ranked between grade I [n = 21 (28%)], grade II [n = 20 (26.7%)], grade III [n = 19 (25.3%)] and grade IV [n = 15 (20%)] (Table 1).

Cortisol, total T3 concentrations in cirrhotic patients with HE were significantly decreased compared to those in patients without HE ($p = 0.001$ and $p = 0.002$). Cutoff value for cortisol was less than 18.3 mg/dl that can predict HE in cirrhotic patients according to AUROC curve showing a sensitivity of 52% and a specificity of 61% (Fig. 1). Cutoff value for total T3 was less than 45.5 ng/dl could predict HE in cirrhotic patients according to AUROC curve showing a sensitivity of 64% and a specificity of 80.6% (Fig. 2), whereas prolactin concentration in cirrhotic patients with HE was significantly increased *vs* patients without HE ($p = 0.007$) and more than 18.85 ng/dl could predict HE in

Table 1: Patients' demographic and laboratory data

	Patients with HE (n = 75)		*Patients without HE (n = 50)*	
	Mean	*SD*	*Mean*	*SD*
Age (years)	49.22	5.62	51.38	7.56
Gender (M/F)	40/35		28/22	
S. albumin (g/dl)	3.24	0.60	3.38	0.46
S. bilirubin (mg/dl)	2.73	1.57	1.58	0.53
Creatinine (mg/dl)	1.19	0.49	1.09	0.45
INR	1.48	0.29	1.43	0.42
AST (U/l)	65	12	71	14
ALT (U/l)	49	6	52	7
Child class				
A	25 (33.3%)		15 (30%)	
B	23 (30.7%)		17 (34%)	
C	27 (36%)		18 (36%)	
HE				
I	21 (28%)		0	
II	20 (26.7%)		0	
III	19 (25.3%)		0	
IV	15 (20%)		0	

cirrhotic patients according to AUROC curve showing a sensitivity of 88% and a specificity of 90.3% (Fig. 3). However, TSH concentration showed no significant difference in patients with HE versus patients without HE (p = 0.15) (Tables 2 and 6).

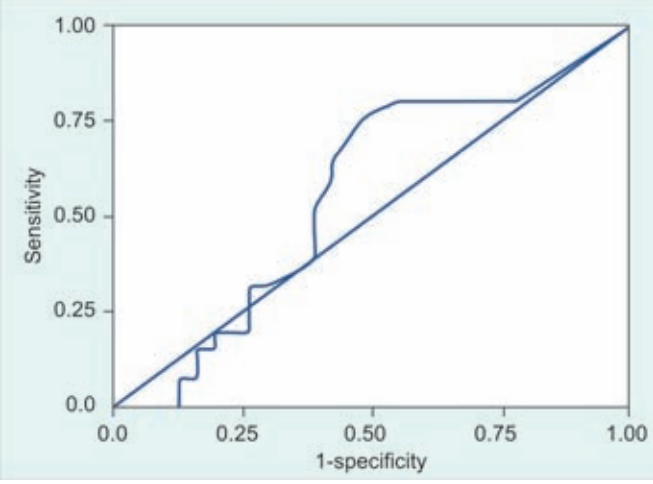

Fig. 1: ROC curve for cortisol

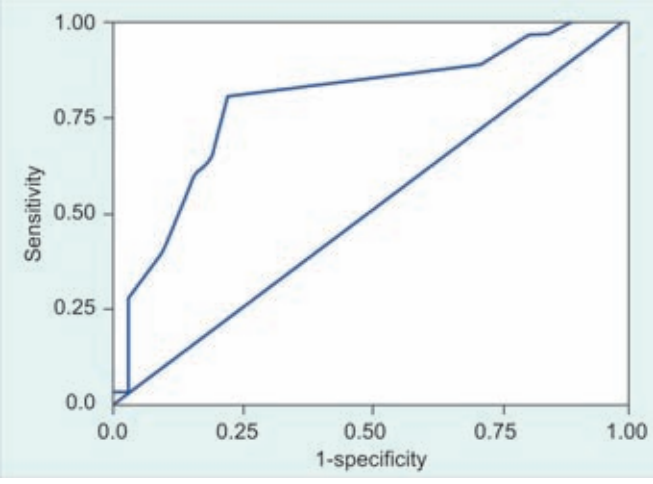

Fig. 2: ROC curve for T3

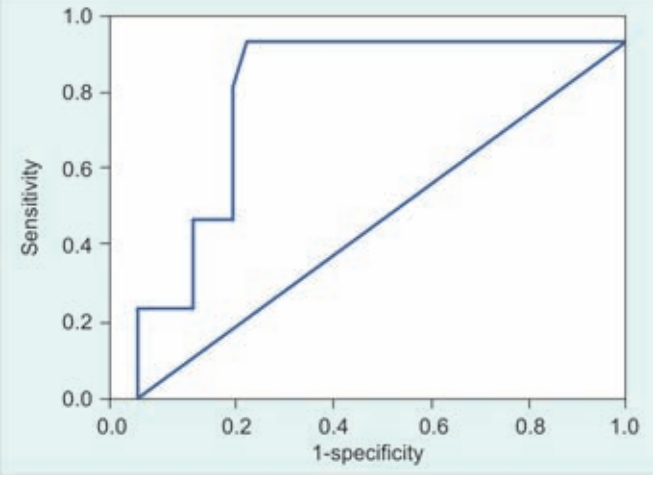

Fig. 3: ROC curve for prolactin

Serum cortisol and total T3 concentrations were significantly decreased with progression of liver disease according to Child-Pugh classification (A *vs* B, A *vs* C and B *vs* C) (p = 0.014, p = 0.007 and p = 0.006 respectively for cortisol) and (p = 0.029, p = 0.000 and p = 0.002 respectively for total T3). In contrast, serum prolactin level was significantly increased with progression of liver diseases from Child A to C (p = 0.023, p = 0.000 and p = 0.007 respectively). In addition, no significant difference was observed on serum TSH level among Child A, B and C groups (p = 0.063, p = 0.081 and p = 0.073) (Table 3).

Cortisol, total T3 concentrations were significantly decreased with progression of HE from grades I to IV (p = 0.004 and p = 0.003). Whereas, prolactin concentratiosn in HE was increased with progression of HE from grades I to IV (p = 0.000) and TSH concentration showed no significant difference with progression of HE from grades I to IV (p = 0.08) (Table 4).

The present study demonstrated positive significant correlation between serum total T3, serum cortisol concentrations and serum albumin, prothrombin time. However, there was negative significant correlation between serum prolactin concentration, serum albumin and prothrombin time. In addition, there was no correlation between serum TSH concentration and serum albumin and prothrombin time (Table 5).

DISCUSSION

HE is a neurocognitive disorder in which brain function is impaired and is associated with both acute and chronic liver dysfunction. HE occurs in the presence of liver injury or when the liver is bypassed in the presence of a portosystemic shunt.[20] Features of hormone disturbances in patients suffering from chronic hepatic failure have been documented for many years.[2]

Patients with cirrhosis are susceptible to bacterial infection[21,22] which can lead to circulatory dysfunction, renal failure, hepatic encephalopathy and decreased survival. Actually, cirrhosis is associated with an increased risk of sepsis and sepsis-related death.[23]

Patients with cirrhosis are characterized by hyperdynamic circulation, which is closely related to the complications of liver cirrhosis. The hemodynamic impairment can be made worse during sepsis, leading to multiple organ failure and mortality system dysfunction and may have contributed to mortality. In this regard, our results showed that serum level of cortisol was significantly decreased in patients with HE *vs* cirrhotic patient without HE and cortisol level was significantly decreased with

Table 2: Serum cortisol, TSH, total T3, prolactin concentrations in cirrhotic patients with HE *vs* patients without HE

	Patients with HE (n = 75)		*Patients without HE (n = 50)*		*p-value*
	Median	*Range*	*Median*	*Range*	
Cortisol (µg/dl)	11	4-33	23.15	21-37	0.001
TSH (µIU/ml)	2.17	0.27-5.27	2.05	0.49-4.49	0.15
T3 (ng/dl)	42.5	35-57.8	88	72.4-112	0.002
Prolactin (ng/ml)	22.25	7.35-71.2	9.11	8-12.9	0.007

Table 3: Serum cortisol, TSH, total T3, prolactin concentrations in cirrhotic patients with HE according to the severity of hepatic disease as measured by the Child-Pugh score

	Cortisol (µg/dl) Median (range)	*TSH (µIU/ml) Median (range)*	*Total T3 (ng/dl) Median (range)*	*Prolactin (ng/dl) Median (range)*
Child A (n = 25)	24 (13.4-33)	1.63 (0.27-3.5)	52 (44-57.8)	13.2 (7.35-19)
Child B (n = 23)	13.7 (9-23)	2.42 (0.42-4.38)	43 (41-52)	18 (13-28)
Child C (n = 27)	9.85 (4-16)	2.8 (1.56 -5.27)	39.5 (35-45)	28.6 (15-71.2)
A *vs* B	p = 0.014	p = 0.063	p = 0.029	p = 0.023
A *vs* C	p = 0.007	p = 0.081	p < 0.000	p < 0.000
B *vs* C	p = 0.006	p = 0.073	p = 0.002	p = 0.007

Table 4: Serum cortisol, TSH, total T3, prolactin concentrations in cirrhotic patients with different grades of hepatic encephalopathy

	Grade I (n = 19) Median (range)	*Grade II (n = 16) Median (range)*	*Grade III (n = 23) Median (range)*	*Grade IV (n = 17) Median (range)*	*p-value*
Cortisol (µg/dl)	19.5 (10.3-33)	19.6 (10-25)	11 (8.8-15.3)	8.8 (4-9.7)	0.004
TSH (µIU/ml)	0.99 (0.27-2.24)	1.85 (0.4-2.14)	2.80 (0.97-4.25)	3.39 (4.1-5.27)	0.08
Total T3 (ng/dl)	48.5 (43.8-57)	52 (40-53.2)	42 (37-44)	39 (35-41)	0.003
Prolactin (ng/dl)	14.55 (7.35-20)	14.2 (12-25.6)	22.25 (15-33)	35 (26.6-71.2)	0.00

Table 5: Correlation between serum albumin and INR with serum cortisol, TSH, total T3 and prolactin

	Albumin (g/dl)		*INR*	
	r	*p*	*r*	*p*
Cortisol (µg/dl)	0.445	0.006	–0.628	0.003*
TSH (µIU/ml)	–0.244	0.151	0.250	0.06
Total T3 (ng/dl)	0.453	0.006*	–0.657	0.002*
Prolactin (ng/dl)	–0.565	0.000*	0.658	0.000*

*p < 0.05

Table 6: Diagnostic performance of cortisol (µg/dl) total T3 (ng/dl) and prolactin (ng/dl) in studied cases according to ROC curves to differentiate cirrhotic with HE from cirrhotic without HE cases

	Cutoff	*Sensitivity*	*Specificity*	*Accuracy*
Cortisol (µg/dl)	18.3	52%	61%	56.2%
Total T3 (ng/dl)	45.5	64%	80.6%	78.5%
Prolactin (ng/dl)	18.85	88%	90.3%	95.9%

progression of liver disease from Child A to C and decreased with severity of HE.

Consistent with these results from this study, Tsai et al[24] reported that adrenal dysfunction was related to the degree of liver failure and multiple organ system dysfunction and may have contributed to mortality. Fernández et al[7] found that adrenal dysfunction was frequent in patients with advanced cirrhosis (Child C: 76% *vs* Child B: 25%, p = 0.08). Harry et al[25] recently showed that adrenal insufficiency is common and may contribute to hemodynamic instability and mortality in patients with acute liver failure.

It is plausible that liver disease *per se* may cause relative adrenal insufficiency (RAI) by a number of mechanisms. These include low levels of HDL cholesterol central to cortisol production,[26] increased conversion of cortisol to the inactive cortisone and the negative effect of cytokines, such as tumor necrosis factor (TNF-α) on hypothalamic function.[27]

Our study differs from Sterczer et al[28] who concluded that there is a close relation between portosystemic encephalopathy and hypercortisolism in dogs with portosystemic shunts (PSS) and that both deviations resolve completely within 4 weeks of closure of the shunt and this difference could be attributed to that Sterczer et al investigated hypercortisolism in dogs with congenital portosystemic shunts without liver cell failure.

Thyroid dysfunction has been reported previously in a variety of nonthyroidal illnesses including liver, pulmonary and renal neoplastic disease, severe systemic illness, fasting, malnutrition, postoperative state, physical trauma and acute infections. Low total and free T3 with normal total T4 and thyrotropin concentrations in the absence of clinical hypothyroidism have been frequently reported in patients with nonthyroidal illnesses.[29]

The present study revealed a significant reduction in serum total T3 in patients with HE than cirrhotic patient without HE, the lowest values being found in patients with grade IV hepatic encephalopathy and Child C. Whereas, TSH showed no significant difference in patients with HE *vs* cirrhotic patient without HE. These phenomena can be explained by a reduced hepatic conversion of T4 to T3, also described as 'low T3 syndrome' in liver cirrhosis.[30,31] The mechanism being inversely related to the degree of hepatic dysfunction. It completely resolved after orthotopic liver transplantation (OLT) in accordance with observations of Van Thiel et al.[32] Hepner and Chopra reported a significant inverse correlation between serum T3 concentrations and the severity of liver dysfunction. A progressive decrease in T3 levels in chronic liver diseases has been described as indicative of a poor prognosis.[33] Kayacetin et al[9] demonstrated a fall in FT3 and T3 parallel to severity of the disease.

Prolactin secretion follows a pulsatile pattern, with a characteristic nocturnal rise, but cirrhosis is associated with elevated 24-hour prolactin levels and loss of circadian prolactin rhythm.[34] These finding were in consistent with the present study that showed significantly increased serum level of prolactin in patients with HE more than cirrhotic patients without HE and its level was significantly increased with progression of liver disease from Child A to Child C (Table 3) and increased with severity of HE (Table 4). Koller et al[35] found that 16.7% of patients had elevated serum prolactin levels, and had significantly higher Child-Pugh and the model for end-stage liver disease (MELD) scores as well as higher ascites and encephalopathy stage, they also found that ascites, higher INR, jaundice and higher Child-Pugh and MELD scores were more often with increasing prolactin concentrations.

The present study revealed a fall in serum total T3, serum cortisol parallel to severity of the disease and HE and a good correlation between serum total T3, serum cortisol concentrations, serum albumin and prothrombin time. Whereas there was a significant negative correlation between serum prolactin concentration and serum albumin and prothrombin time. These results suggest that serum total T3, serum cortisol and serum prolactin concentrations may be considered a sensitive index of hepatic function in liver disease and severity of HE.

Limitations of the study include the relatively small number of patients so results obtained from this study can't be disseminated, further studies with larger sample size are required. On the other hand short synacthen (corticotrophin) stimulation test (SST) was not used to evaluate the appropriateness of the adrenal response in this setting due to ethical consideration.

CONCLUSION

Patients with liver cirrhosis complicated by HE were found to have low serum total T3, serum cortisol and high serum prolactin levels and are associated with disease severity and progressing grades of HE. Depressed serum total T3, serum cortisol and increasing serum prolactin levels, together with a prolonged prothrombin time and decreased serum albumin, therefore appear to be characteristic of cirrhotic patients prone to develop HE. So, hormonal abnormalities of cortisol, total T3 and prolactin may represent risk factors and early indicators of impending HE and progression of liver disease severity.

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