Research Article

Assessment of Adrenal Function in Chronic Hepatitis C Patients

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Abstract
Background: Chronic hepatitis C virus (HCV) infection is a public health problem. A relationship appears to exist between the severity of the liver disease and the presence of RAI**.** AI has been shown to correlate with progression of liver disease**.** It can be seen in both stable and critically ill (sepsis, septic shock, and gastrointestinal system bleeding) cirrhotic patients. RAI is a feature of liver disease per se, leading to what is termed hepatoadrenal syndrome. **The aim of our study:** measurement of cortisone in liver disease patient and study the effect of adrenal function change on liver function. **Methods:** this cross-sectional hospital-based study was done in Internal Medicine Department, Minia University Hospital. It lasts one year duration, and included 120 patients divided into the following groups: First group: It contained 30 patients with hepatitis c. Second group: It contained 30 persons with hepatic cirrhosis and hepatitis c. Third group: it includes 30 patients with liver failure cirrhosis. fourth group: 30 people control with matched age and sex to patients' group. **Results**: corticosteroid binding globulin was found to be significantly decreased in cirrhotic patients compared to healthy controls. In this setting, in case of hypoalbuminemia or reduced CBG, the total cortisol is reduced while free cortisol, responsible for glucocorticoid activity on peripheral organs remains unchanged. **Conclusion**: Total cortisol, as a marker of adrenal function, may lead to overestimation of AI in patients with cirrhosis, high levels of serum free cortisol are associated with a poor prognosis in liver disease.
Key Words: HCV, liver cirrhosis, severity of liver disease, Relative Adrenal insufficiency.

Introduction
Hepatitis C viral infection is endemic in Egypt with the highest prevalence rate in the world. Although around 30% of patients may clear the virus spontaneously, the main health burden occurs from the majority of patients who develop chronic HCV. In this patient popu-lation, cirrhosis may develop within 20 years of infection, with hepatic decompensation and hepatocellular carcinoma (Vos et al., 2015). AI in cirrhosis is an issue that has recently gained momentum. It can be seen in both stable and critically ill (sepsis, septic shock, and gastrointestinal system bleeding) cirrhotic patients. AI was frequent even in hemo-dynamically stable patients with cirrhosis and tended to be associated with liver disease severity (Park et al., 2018).

The term hepato-adrenal syndrome defines AI in patients with advanced liver disease with sepsis and/or other complications, and it suggests that it could be a feature of liver disease per se, with a different pathogenesis from that of septic shock. Relative AI is the term given to inadequate cortisol response to stress. More recently, another term is used, namely "critical illness related corticosteroid insufficiency" to define "an inadequate cellular corticosteroid activity for the severity of the patient's illness" (Trifan et al., 2013).

Although the reason for AI is not definite, it is attributed to decreased synthesis of total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein chole-sterol in the liver in cirrhosis and increased level of circulating endotoxins, such as proinflammatory cytokines and lipopoly-saccharides (Bornstein et al., 2016).

Material and Methods
Routine laboratory Investigations: Using the commercially available kits, all patients underwent full laboratory investigation includ-ding complete blood count, INR and complete liver and renal function tests and viral markers.
Specific investigation: Serum basal cortisol level and ACTH level, post SST.

Imaging studies: Abdominal ultrasound was performed by the ultrasound machine, Toshiba alpio 500, Japan with 3-5MHz tranceducer, elastography with Toshiba alpio 500 and adrenal CT using CT bright speed GE.

Statistical analysis
Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS software version 25).

Inclusion criteria:
All patients were infected by HCV that proved by + ve HCV antibody and quantitative PCR for HCV RNA and underwent to receive new direct acting antiviral drugs.
Selection of patients were known cirrhotic compensated and decompensated.

Exclusion criteria:
Other causes of chronic liver disease and liver cirrhosis.
Patients taken drugs and patients who had Addison without hepatic disease or liver cirrhosis weather complicated or not.

Ethical considerations:
The study was approved by research ethics committee of Minia faculty of medicine.

Results
Table (1): Liver function tests of different study groups.

	Chronic hepatitis C (I)	Compensated cirrhosis (II)	Decompensated cirrhosis (III)	Control (C)	p value
	(n=30)	(n=30)	(n=30)	(n=30)	
INR *Mean±SD (Range)*	1.13±0.18 (1.1-1.77)	1.19±0.19 (1.1-1.78)	1.66±0.37 (1.1-2.3)	0.98±0.06 (0.97-1.11)	<**0.05***
Serum albumin *Mean±SD (Range)*	4.6±0.7 (3.2-5.8)	3.8±0.2 (3.6-3.6)	2.7±0.1 6(1.4-3.2)	5.5±0.7 (3.8-5.4)	<**0.05***
ALT *Mean±SD (Range)*	66±12.3 (50-165)	34.9±128.2 (99-200)	55.3±33.3 (115-100)	16.6±3.9 (22-42)	<**0.05***
AST *Mean±SD (Range)*	63.3±23.5 (18-103)	48.7±124.9 (33-198)	150±124.9 (66-105)	12.7±3.3 (20-30)	<**0.05***
T.BIL *Mean±SD (Range)*	0.99±0.72 (0.133-1.22)	0.99±0.86 (0.44-1.5)	33.45±0.76 (14-12.1)	01.51±0.22 (0.11-11.2)	<**0.05***
D.BIL *Mean±SD (Range)*	01.1±0.34 (0.11-1.7)	0.78±0.99 (0.11-0.16)	0.99±0.65 (0.11-1.18)	1.28±0.124 (0.11-0.39)	<**0.05***
AFP *Mean±SD (Range)*	25.4±13 (11.7-33.4)	15.4±13 (2.7-23.4)	17.3±12.7 (13.2-11.9)	….	<**0.05***

The results in **Table (1)** showed that there was some difference between groups regarding liver function tests (P<0.05).

The results of Hormonal profile of study groups showed that that there was a statistically significant difference when measuring ACTH level and total cortisol among different study groups.

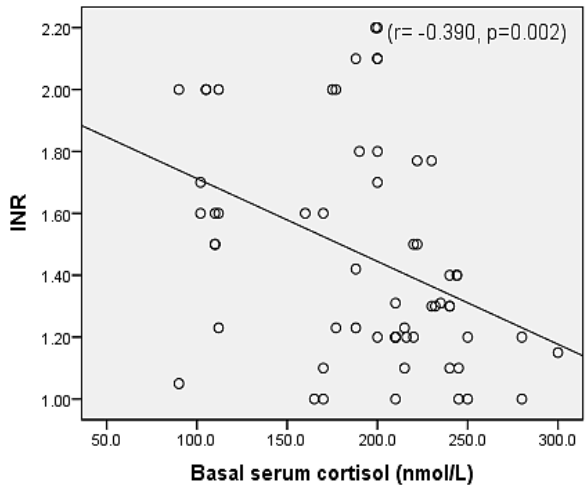

Figure (1): shows some relations= between (total serum cortisol level and INR).

Discussion

Liver failure shares many clinical similarities to septic shock. Both conditions are characterized by the presence of hyperdynamic circulatory failure, with a low mean arterial pressure, decreased systemic vascular resistance, and increased cardiac output (Grune & Berger, 2007). Elevated cytokine levels, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, can be observed in both conditions, and liver failure also leads to decreased monocyte function and immunoparalysis, a finding first noted in patients with septic shock (Wasmuth et al., 2005) Therefore, many studies of AI in liver failure have been reported based on the similarity between liver failure and sepsis. They reported that AI prevalence in liver failure was 52% to 63% (O'Beirne et al., 2007).

Orozco et al., (2016) recently reported that AI is frequent in patients with stable cirrhosis and that it is related to the liver disease severity.

We found Approximately 80% of circulating cortisol is synthesized both at rest and during stress from plasma cholesterol (particularly in the form of HDL cholesterol), this goes with de Mattos et al., (2016) who declared that Patients with cirrhosis have impaired hepatocellular function and reduced albumin synthesis, which can reach a 60-80% reduction in advanced cirrhosis**.**

After the release in the blood, cortisol circulates in "free" form (~5–6% of the total plasma cortisol, which diffuses into the cells exerting its biological effects on target tissues) or bound primarily to two proteins. Cortisol can significantly bind to the "low affinity-high capacity protein" albumin when its secretion rate is high; in physiological secretion rates, cortisol has a specific carrier, the "high affinity-low capacity" corticosteroid binding globulin (CBG or transcortin) produced by the liver. So this mechanism affected in liver disease.

The prevalence of AI in patients with liver disease varies widely according to the study population: critically ill patients (33-92%)**,** stable cirrhosis (31-60%) or decompensated cirrhosis, This in agree-ment with Park et al., (2018) who found that serum albumin level was lower, and INR was higher in patients with AI than in those without adrenal insufficiency and Kharb et al., (2013) who concluded that deterioration of synthetic functions of liver disease predicts presence of AI in chronic liver disease patients, and these patients should be evaluated for adrenal dysfunction periodically as, Adrenal function worsens with progression of liver disease. Also, presence of AI may predict survival of CLD patients. Though adrenal function shows recovery with liver transplant.

Conclusions

Adrenal Insufficiency (RAI), which is an inadequate glucocorticoid activity relative to the severity of illness. This term replaced by critical illness related corticosteroid insufficiency.
define inadequate corticosteroid activity for the severity of the patient's illness. some authors proposed the term "hepato adrenal syndrome

Recommendations

Further studies should be done on large number of patients.
Further studies are needed to validate our results and to detect effect of hydrocortisone in liver disease with adrenal insufficiency.
follow up of CLD patients with adrenal insuffiiciency is recommended.

Limitations of the study

There are potential limitations of our study which include relatively small sample size, and also the use of total cortisol levels for determining the occurrence of AI.

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