Research Article

Assessment of Adrenal Function in Chronic Hepatitis C Patients

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Abstract
Background: Adrenal insufficiency (AI) was demonstrated in patients with cirrhosis and liver failure. 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:** was to Detection of serum cortisol level and ACTH level in patients with Chronic hepatitis C and liver cirrhosis and Correlation between severity of liver disease and Adrenal insufficiency.
Methods: this cross-sectional hospital-based study was conducted in Internal Medicine Department, Minia University Hospital from June 2018 to June 2019, and included 240 patients divided into the following groups: First group: It included 60 patients with chronic HCV. Second group: It included 60 patients with HCV-related compensated cirrhosis. Third group: it includes 60 patients with HCV decompensated cirrhosis. fourth group: 60 people (healthy volunteers) with matched age and sex to patients' group. **Results**: increase in percentage of patients with adrenal dysfunction with progression of liver disease. Also, we found significantly higher level of INR, RBS, Alt and Total bilirubin in AI group than normal one and significantly lower Hb level, Serum albumin and Platelet count in group with AI Vs normal one. **Conclusion**: serum albumin level was lower, and INR was higher in patients with AI than in those without adrenal insufficiency, Adrenal function worsens with progression of 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 population, 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 cholesterol 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 including complete blood count, INR and complete liver and renal function tests and viral markers.

**Assessment of Adrenal Function in
Chronic Hepatitis C Patients**

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:

Causes of chronic hepatitis rather than HCV infection.

Patients with autoimmune diseases, patients received corticosteroids and other causes of adrenal dysfunction rather than CHC.

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=60)	(n=60)	(n=60)	(n=60)	
INR *Mean±SD* *(Range)*	1.12±0.19 (1-1.76)	1.18±0.17 (1-1.8)	1.46±0.36 (1-2.2)	0.99±0.05 (0.9-1.1)	**<0.001***
Serum albumin *Mean±SD* *(Range)*	4.5±0.5 (3.5-5.9)	3.7±0.1 (3.5-3.9)	2.6±0. 6(1.6-3.8)	4.5±0.6 (3.5-5.7)	**<0.001***
ALT *Mean±SD* *(Range)*	45.5±26.3 (20-128)	72.9±28.2 (18-99)	46.3±26.3 (15-111)	16.6±2.9 (11-20)	**<0.001***
AST *Mean±SD* *(Range)*	45.3±24.5 (18-103)	75.7±24.8 (29-98)	50±24.9 (16-115)	15.7±3.4 (10-20)	**<0.001***
T.BIL *Mean±SD* *(Range)*	0.68±0.22 (0.11-1.2)	0.93±0.06 (0.87-1)	1.45±0.56 (0.4-2.1)	0.51±0.2gv8 (0.18-1.2)	**<0.001***
D.BIL *Mean±SD* *(Range)*	0.23±0.16 (0.1-0.7)	0.37±0.19 (0.1-0.6)	0.92±0.44 (0.1-1.8)	0.28±0.24 (0.1-0.9)	**<0.001***
AFP *Mean±SD* *(Range)*	5.4±3 (1.7-13.4)	5.4±3 (1.7-13.4)	7.3±2.7 (3.2-12.9)	….	**<0.001***

The results in **Table (1)** showed that there was statistically significant difference between groups regarding liver function tests (P<0.001).

The results of Hormonal profile of study groups showed that that there was a statistically significant difference when measuring ACTH level and delta cortisol among different study groups.
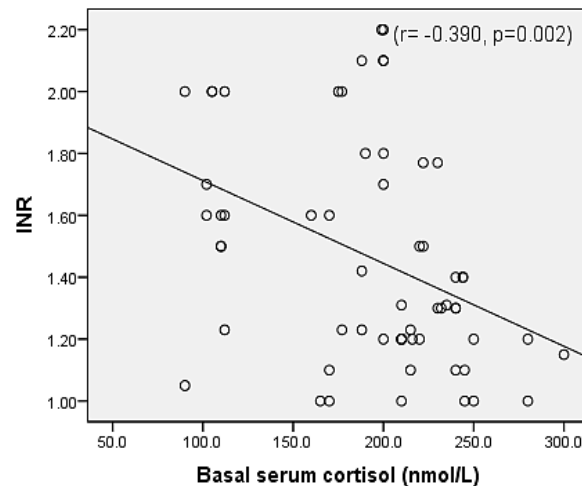
Figure (1):shows that there was significant negative correlation between (baseline morning serum cortisol and INR).

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 a statistical significant difference between different liver function as regard serum albumin, INR, Total and direct bilirubin which were more affected in decompensated patients than other groups, 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.

Our results showed that there was a statistically significant difference between ACTH level in different studied groups (p<0.001), also a statistically significant difference in delta cortisol between different studied groups (p=0.021). with no statistically significant difference between baseline cortisol and peak cortisol in different studied groups. AI was predicted by lower levels of serum protein, serum albumin, total cholesterol and HDL cholesterol and higher levels of serum bilirubin and INR.

In our results we found significantly higher level of INR, RBS, Alt and Total bilirubin in AI group than normal one and significantly lower Hb level, Serum albumin and Platelet count in group with AI Vs normal one. This in agreement 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, 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

Our study indicates that AI is a common feature in patients with cirrhosis without evidence of sepsis, hemodynamic derangement. AI should be actively sought in patients of cirrhosis.

Our result revealed that Adrenal insufficiency (AI) was demonstrated in patients with chronic hepatitis C, cirrhosis and liver failure.

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 insufficiency 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.

References

1. Bornstein, S. R., Allolio, B., Arlt, W., Barthel, A., Don-Wauchope, A., Hammer, G. D., Husebye, E. S., Merke, D. P., Murad, M. H., & Stratakis, C. A. (2016). Diagnosis and treatment of primary adrenal insufficiency: An endocrine society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism, 101(2), 364–389.

2. de Mattos, A. A. (2016). Current indications for the use of albumin in the treatment of cirrhosis. Annals of Hepatology, 10(S1), 15–20.

3. Grune, T., & Berger, M. M. (2007). Markers of oxidative stress in ICU clinical settings: Present and future. Current Opinion in Clinical Nutrition & Metabolic Care, 10(6), 712–717.

4. Kharb, S., Garg, M. K., Puri, P., Nandi, B., Brar, K., Gundgurthi, A., & Pandit, A. (2013). Assessment of adrenal function in liver diseases. Indian Journal of Endocrinology and Metabolism, 17, 465–471. https://doi.org/10.4103/2230-8210. 111643

5. O'Beirne, J., Holmes, M., Agarwal, B., Bouloux, P., Shaw, S., Patch, D., & Burroughs, A. (2007). Adrenal insufficiency in liver disease–what is the evidence? Journal of Hepatology, 47(3), 418-423.

6. Orozco, F., Anders, M., Mella, J., Antinucci, F., Pagano, P., Esteban, P., Cartier, M., Romero, G., Francini, B., & Mastai, R. (2016). Adrenal insufficiency in cirrhotic patients. Medicina,76(4),208-212.

7. Park, S. H., Joo, M. S., Kim, B. H., Yoo, H. N., Kim, S. E., Kim, J. B., Jang, M. K., Kim, D. J., & Lee, M. S. (2018). Clinical characteristics and prevalence of adrenal insufficiency in hemodynamically stable patients with cirrhosis. Medicine, 97(26), e11046. https://doi.org/ 10.1097/MD. 0000000000011046

8. Trifan, A., Chiriac, S., & Stanciu, C. (2013). Update on adrenal insufficiency in patients with liver cirrhosis. World Journal of Gastroenterology: WJG, 19(4), 445.

9. Vos, T., Barber, R. M., Bell, B., Bertozzi-Villa, A., Biryukov, S., Bolliger, I., Charlson, F., Davis, A., Degenhardt, L., Dicker, D., Duan, L., Erskine, H., Feigin, V. L., Ferrari, A. J., Fitzmaurice, C., Fleming, T., Graetz, N., Guinovart, C., Haagsma, J.,… Murray, C. J. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. The Lancet, 386 (9995),743–800.https://doi.org/ 10.1016/ S0140-6736(15)60692-4

10. Wasmuth, H. E., Kunz, D., Yagmur, E., Timmer-Stranghöner, A., Vidacek, D., Siewert, E., Bach, J., Geier, A., Purucker, E. A., & Gressner, A. M. (2005). Patients with acute on chronic liver failure display 'sepsis-like'immune paralysis. Journal of Hepatology, 42(2), 195–201.