Clinical and Experimental
HEPATOLOGY

Original paper

Evaluation of adrenal function in hemodynamically stable patients with liver cirrhosis

Rania Naguib[1,2], Amel Fayed[1], Shady Abouelnaga[3], Hend Naguib[4]

[1]Clinical Science Department, College of Medicine, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia
[2]Internal Medicine Department, Endocrinology Unit, Faculty of Medicine, Alexandria University, Alexandria, Egypt
[3]Alexandria University Hospitals, Alexandria, Egypt
[4]Internal Medicine Department, Hepatology Unit, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Abstract

Aim of the study: To estimate the prevalence of adrenal insufficiency (AI) in hemodynamically stable cirrhotic patients and to evaluate the potential association with patients' clinical characteristics, cirrhosis etiology and liver disease severity.

Material and methods: The cross-sectional study included 132 stable liver cirrhosis patients. Severity of liver disease was graded using the Child-Pugh classification and Model for End-stage Liver Disease (MELD) score. The adrenal function was evaluated by measuring basal and peak cortisol after 60 minutes following the short Synacthen test (SST). Differences in terms of demographic data, clinical information and liver disease severity were compared between cirrhotic patients with and without AI.

Results: Out of 132 cirrhotic patients, 86 patients had evidence of AI based on the peak serum cortisol value while the prevalence was lower (67 patients out of 132) when basal cortisol level was taken as the basis. A total of 82 patients were classified as Child-Pugh class C, with an average MELD score of 20 ±7.1. Most patients with AI had Child-Pugh class C. Patients with AI had a higher prevalence of ascites, gastrointestinal hemorrhage, and hepatic encephalopathy, a higher MELD score and a lower serum sodium level compared to patients with normal adrenal function. AI was not related to the etiology of cirrhosis but was related to the severity of liver disease and the degree of hyponatremia.

Conclusions: Adrenal insufficiency is common among hemodynamically stable patients with cirrhosis. It is related to the severity of liver disease and the degree of hyponatremia.

Key words: liver cirrhosis, adrenal insufficiency (AI), Child-Pugh class, Model for End-stage Liver Disease (MELD) score.

Address for correspondence

Rania Naguib, Clinical Science Department, College of Medicine, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia; Internal Medicine Department, Endocrinology Unit, Faculty of Medicine, Alexandria University, Alexandria, Egypt, e-mail: ranianaguib2000@yahoo.com

Introduction

Liver cirrhosis is a common disease that has increasingly become an important cause of mortality and mortality worldwide [1, 2]. Extrahepatic organ malfunction in the setting of liver cirrhosis can lead to a wide range of complications. Hemodynamic disturbances, which are common in advanced stages of liver cirrhosis, are among the most difficult to treat [3]. Liver cirrhosis has been associated with adrenal insufficiency (AI) for a long time. Cirrhosis of the liver is now one of the most common high-risk diseases associated with an increased risk of AI, a condition which is known as hepatoadrenal syndrome [4]. The prevalence of AI is shown to be quite diverse in studies of patients with liver illness, possibly due to the heteroge-

neity of studied cases, as well as different definitional criteria and techniques of diagnosis. The majority of these studies were conducted on critically ill or decompensated cirrhotic patients during hospitalization [5].

It is sometimes difficult to differentiate between AI and hemodynamic alterations seen in terminal events of advanced cirrhosis such as circulatory collapse resulting from reduced peripheral vascular resistance and systemic vasodilation, low mean arterial pressure, and poor responsiveness to vasopressors [5]. Evidence suggests that AI is related to the severity of the liver disease [4] and is linked to a worse prognosis and a significantly high mortality rate in patients with cirrhosis [6]. Cirrhotic patients with AI have been shown to have a higher risk of circulatory derangement, severe sepsis, renal function impairment, and even hepatorenal syndrome (HRS) type 1 [5, 7, 8]. Treatment with low doses of hydrocortisone is associated with a significant increase in shock reversal and hospital survival in these patients [3, 4].

The aim of this study was to estimate the AI prevalence in hemodynamically stable cirrhotic patients and evaluate the potential association with patients' clinical characteristics, cirrhosis etiology and liver disease severity.

Material and methods

Study design, data collection and analysis

This is a cross sectional study, which was conducted between February and June 2021 at a tertiary care hospital. The study was authorized by the Institute's Ethical Committee (approval number 21/167), and all subjects gave written informed consent.

The study included 132 individuals with liver cirrhosis who were recruited from Alexandria Main University Hospital, Internal Medicine Department, Hepatology Outpatient Clinic. All patients were hemodynamically stable. Cirrhosis was diagnosed based on clinical manifestations, examination, presence of complications, laboratory results, liver histology and imaging findings.

Patients were considered for the study if they met the following criteria: age 18 years and above, hemodynamically stable with a mean arterial pressure (MAP) > 70 mm Hg and not on vasopressors.

The following were the criteria for exclusion: history of pituitary or adrenal disease, taking steroids or other medicines that affect cortisol production (e.g., etomidate, ketoconazole), severe cardiopulmonary and kidney disease, hepatocellular carcinoma, critical illness, sepsis, active infection, receiving oral or parenteral antibiotic therapy within the last 30 days before enrolment and pregnancy.

The clinical information of the patients, including basic demographics, clinical features, additional comorbidities and the results of routine laboratory tests, was recorded. Patients were questioned about manifestations of hepatic decompensations such as history of ascites, variceal bleeding, or encephalopathy and the findings were documented. Severity of liver disease was graded using the Child-Pugh classification and Model for End-stage Liver Disease (MELD) score [8]. Patients were then categorized into two groups based on the results of adrenal function evaluation – cirrhosis with AI and cirrhosis without AI – and their differences in terms of demographic data, clinical information and liver disease severity were compared.

Biological assays

The adrenal function of all subjects was evaluated by measuring basal and peak cortisol after 60 minutes following the short Synacthen test (SST). To avoid a stress-induced cortisol increase, samples were taken at least 15 minutes after the indwelling intravenous catheter was inserted. Synthetic adrenocorticotropic hormone (ACTH; Synacthen, 250 μg, Novartis Pharma, Switzerland) was injected intravenously, after an overnight fast, immediately after blood samples were obtained (at 8-9 a.m.) to measure baseline levels of cortisol then another sample was collected 60 minutes later to measure the peak cortisol. Serum was separated and stored at –80˚C. Measurement of serum cortisol was performed with a standard chemiluminescent immunoassay (CLIA). The tests were performed using the ADVIA Centaur XPT immunoassay system Cortisol kit (ADVIA Centaur Cortisol assay (REF: 10994924) according to the manufacturer's recommendations (Siemens Health Care Diagnostics, USA) [9].

Diagnostic criteria and definitions

The severity of liver disease was estimated by the Child-Pugh classification and MELD score [8].

Child-Pugh class and MELD score were calculated from the required parameters. A MELD score of 15 was taken as dividing line between mild and severe disease [10]. Basal cortisol was defined as the morning cortisol concentration (between 8:00 and 9:00 a.m.) before Synacthen administration. The highest cortisol concentration at 60 minutes after Synacthen injection was considered as peak cortisol [4]. A normal response to the Synacthen stimulation test (SST) was defined as a peak total serum cortisol concentration of at least

Rania Naguib, Amel Fayed, Shady Abouelnaga, Hend Naguib

Table 1. Distribution of the studied cases according to adrenal function ($N = 132$)

Adrenal function	n (%)
Adrenal insufficiency	86 (65.2)
Normal adrenal function	46 (34.8)

18 μg/dl. For the purposes of this study, AI was defined as having a basal cortisol of less than 9 μg/dl and/or a peak cortisol of less than 18 μg/dl [11].

Statistical analysis

Data were analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Description of quantitative study variables was reported in forms of mean ± standard deviation and median (minimum-maximum) while qualitative variables were reported as frequency and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution of variables. Comparisons between groups for categorical variables were assessed using the χ^2 test (Monte Carlo correction). Student's t-test or the Mann-Whitney test was used to compare quantitative variables according to the normality distribution. A p-value of less than 0.05 was considered statistically significant.

Results

Out of 132 cirrhotic patients who were enrolled in the study, 67 patients (50.7%) had evidence of AI based on a basal serum cortisol value of less than 9 μg/dl, while the prevalence was higher (65.2%) (86 out of 132) when a peak cortisol level of less than 18 μg/dl was taken as the basis (Table 1). 77.9% (67 out of 86) of those with AI had basal cortisol less than 9 μg/dl. Males (84 patients) outnumbered females in the study sample (63.6%); however, no statistically significant difference in adrenal function was found between males and females. The mean age of the study group was 55.2 ±8.9 years and patients with AI were significantly older (56.5 ±8.8) than those with normal adrenal function (52.8 ±8.8), p-value = 0.02.

Cirrhosis was most frequently caused by hepatitis C virus in 77 (58.3%) patients, followed by autoimmune hepatitis (AIH) in 21 (15.9%), non-alcoholic steatohepatitis (NASH) in 16 (12.1%) patients and hepatitis B virus in 7 (5.3%) patients, whereas alcoholic cirrhosis and hemochromatosis were reported in just four cases each.

A total of 82 (62.1%) patients were classified as Child-Pugh class C, with an average MELD score of 20 ±7.1.

Most patients with AI [67 (77.9%)] had Child-Pugh class C, which was much higher than the rate observed in individuals with normal adrenal function [15 (32.6%)]. Similarly, patients with AI had a considerably higher MELD score (23 ±6.5) than those with normal adrenal function (14.5 ±4.3). Severe hepatic cirrhosis (MELD 15+) was prominent in the patients with AI (79.1%, 68 out of 86), which was significantly more than that noted in patients with normal adrenal function (43.5%, 20 out of 46).

Ascites, gastrointestinal hemorrhage, and hepatic encephalopathy were found in 107 (81.1%), 76 (57.6%), and 54 (40.9%) patients, respectively. When compared to patients with normal adrenal function, those with AI consistently had a higher prevalence of these complications.

Serum sodium levels in the studied sample averaged 136.7 ±4.8 mEq/l; however, patients with AI had a significantly lower serum sodium level (135.8 ±5.4 mEq/l) compared to patients with normal adrenal function (138.2 ±3.1 mEq/l); additionally, hyponatremia was confirmed in 32 (37.2%) patients with AI compared to only 4 (8.7%) patients with normal adrenal function (Table 2).

Discussion

Cirrhosis-related AI, or hepatoadrenal syndrome, is a topic that has recently gained attraction. However, the lack of definite diagnostic standards, the disease's indefinite physiopathology, and the difficulties in diagnosing and treating it trigger a contentious debate. Both stable cirrhosis and cirrhosis with critical disease (sepsis, septic shock, variceal bleeding) can show signs of AI and this is associated with bad prognosis [8, 12-14]. The prevalence has been observed in various studies to range from 10% to 87% in critically ill cirrhotic patients to 7% to 83% in stable cirrhotic patients [2, 3, 7, 8, 10]. In the current study, the prevalence of AI was 50.7% when basal cortisol levels were used as the baseline and 65.2% when peak cortisol levels were used as the baseline. The diversity in the prevalence of AI compared to other studies may be attributed to different patient selection criteria, presence of infection, critical illness, hemodynamic instability or performing the study during hospitalization. It may also be attributed to the heterogeneity of the method of stimulation of cortisol secretion used, diverse techniques of diagnosis, use of serum or salivary cortisol, use of free or total cortisol as well as the cutoff value for cortisol as a definition of AI [8]. The higher prevalence in our study compared to some studies, although our patients were hemodynamically stable, might be

Table 2. Comparison between adrenal insufficiency and normal adrenal function according to different parameters

Variable	Total (N = 132)	Adrenal insufficiency (n = 86)	Normal adrenal function (n = 46)	Test of Sig.	p
Age (years)					
Mean ±SD	55.2 ±8.9	56.5 ±8.8	52.8 ±8.8	t = 2.307*	0.023*
Median (min.-max.)	56 (35-75)	57 (39-75)	53.5 (35-69)		
Sex, n (%)					
Male	84 (63.6)	57 (66.3)	27 (58.7)	χ^2 = 0.745	0.388
Female	48 (36.4)	29 (33.7)	19 (41.3)		
Cirrhosis etiology, n (%)					
AIH	21 (15.9)	12 (14)	9 (19.6)	χ^2 = 7.326	MCp = 0.258
HBV	7 (5.3)	2 (2.3)	5 (10.9)		
HCV	77 (58.3)	52 (60.5)	25 (54.3)		
Alcohol	4 (3)	2 (2.3)	2 (4.3)		
Wilson's disease	3 (2.3)	2 (2.3)	1 (2.2)		
NASH	16 (12.1)	13 (15.1)	3 (6.5)		
Hemochromatosis	4 (3)	3 (3.5)	1 (2.2)		
Child-Pugh class, n (%)					
A	14 (10.6)	0 (0)	14 (30.4)	χ^2 = 38.501*	< 0.001*
B	36 (27.3)	19 (22.1)	17 (37)		
C	82 (62.1)	67 (77.9)	15 (32.6)		
GIT bleeding, n (%)	76 (57.6)	58 (67.4)	18 (39.1)	χ^2 = 9.834*	0.002*
Hepatic encephalopathy (HE), n (%)	54 (40.9)	47 (54.7)	7 (15.2)	χ^2 = 19.279*	< 0.001*
Ascites, n (%)	107 (81.1)	79 (91.9)	28 (60.9)	χ^2 = 18.749*	< 0.001*
Serum sodium (Na) (mEq/l)					
Hyponatremia < 135, n (%)	36 (27.3)	32 (37.2)	4 (8.7)	χ^2 = 12.285*	< 0.001*
Mean ±SD	136.7 ±4.8	135.8 ±5.4	138.2 ± 3.1	t = 3.223*	0.002*
Median (min.-max.)	137 (127-145)	136 (127-145)	138 (129-143)		
MELD score					
≥ 15, n (%)	88 (66.7)	68 (79.1)	20 (43.5)	χ^2 = 17.084*	< 0.001*
Mean ±SD	20 ±7.1	23 ±6.5	14.5 ±4.3	t = 9.026*	< 0.001*
Median (min.-max.)	19.5 (9-31)	26 (10-31)	13.5 (9-26)		
Basal serum cortisol (µg/dl)					
< 9, n (%)	67 (50.8)	67 (77.9)	0 (0)	χ^2 = 72.777*	< 0.001*
Mean ±SD	9 ±3.5	7.1 ±2.5	12.5 ±2	t = 12.678*	< 0.001*
Median (min.-max.)	8 (4-17)	6 (4-13)	12 (10-17)		
Peak serum cortisol (µg/dl)					
< 18, n (%)	86 (65.2)	86 (100)	0 (0)	χ^2 = 132.0*	< 0.001*
Mean ±SD	16.5 ±6	12.5 ±2.3	24 ±2.4	t = 27.190*	< 0.001*
Median (min.-max.)	14 (6-29)	12 (6-17)	24 (19-29)		

*SD – standard deviation, t – Student's t-test, χ^2 – chi square test, MC – Monte Carlo, p – p value for comparing between the studied groups, *statistically significant at p ≤ 0.05*

explained by the fact that our patients had severe liver disease as evidenced by high prevalence of Child-Pugh class C and high MELD scores. Another possible explanation of the higher prevalence of AI in our patients is that we measured the total cortisol rather than the free cortisol level. Only free cortisol is biologically active, while the bulk of cortisol is bound to corticosteroid-binding globulin (CBG) and albumin and hence

is physiologically inactive [15]. The serum level of albumin and CBG falls as the severity of cirrhosis increases. This leads to lowering of the total cortisol level and results in overdiagnosis of AI. Multiple studies have found that utilizing total cortisol rather than free cortisol yields much higher estimates of AI but detection of free cortisol is not used in routine practice since it is both expensive and difficult [3].

The mechanism behind the occurrence of AI in patients with liver cirrhosis is still unknown. Several mechanisms, however, have been proposed. The role of cholesterol and its impaired synthesis in liver disease is one of these hypothesized pathways. A low cholesterol level can lead to decreased cortisol production by the adrenal glands in cirrhosis with subsequent low total cholesterol levels, high-density lipoprotein levels and low-density lipoprotein levels especially in stressful conditions. Another possible explanation is the increased levels of proinflammatory cytokines and circulating endotoxin in patients with liver cirrhosis, which have a negative feedback effect on the hypothalamic-pituitary-adrenal axis. Adrenal hemorrhage in the context of liver disease-related coagulation problems has also been suggested as an uncommon cause of AI [3-5].

In this study the indicators of severity of liver disease, MELD and Child-Pugh classification, were significantly greater in the group with AI compared to those with normal adrenal function. Park et al. reported a negative correlation between the Child-Pugh class and basal cortisol levels that was significant. This corresponds with the findings of our study [4]. Another study by Nandish *et al.* reported that more severe liver disease was associated with AI [6]. A comparable finding was obtained by Galbois *et al.* [16], who reported that AI was linked to the severity of liver disease, and that AI would alter the prognosis of patients with liver cirrhosis, which is why early detection of AI and use of glucocorticoids might improve patients' symptoms and reduce mortality [2]. These results are contradictory to Acevedo *et al.*, who did not find any relation between disease severity and AI in hospitalized patients with decompensated cirrhosis [7].

A major finding of our study is that patients with AI had a significantly lower serum sodium level compared to those with normal adrenal function. This high rate of hyponatremia in patients with cirrhosis and AI could be attributed to adrenal dysfunction rather than just a symptom of patients' more advanced circulatory dysfunction. Hyponatremia is a well-known consequence of advanced cirrhosis that is associated with a poor prognosis. The mechanism of hyponatremia in liver cirrhosis is similar to that of heart failure [17].

The compensatory activation of the neurohormonal system in cirrhosis is triggered by arterial underfilling caused by systemic vasodilation [18]. These compensatory mechanisms include non-osmotic release of arginine vasopressin (AVP), sympathetic nervous system activation, and the renin-angiotensin system [17, 18]. These pathways cause sodium and water retention, as well as dilutional hyponatremia. Hyponatremia may also be attributed to glucocorticoid deficiency [5]. Similar results of some recent studies were reported [5, 7, 8] while other studies [2, 6] failed to find a correlation between sodium level and AI. According to our findings and those of other researchers, AI could be one of the elements contributing to the pathophysiology of cirrhosis-related hemodynamic changes.

The effects of steroid therapy in cirrhotic individuals with AI are still controversial. Corticosteroid therapy is said to lower the need for vasopressors in critical illness, shorten the time spent in the intensive care unit, and improve shock resolution, but it also raises the risk of infection and bleeding [4]. Several trials have demonstrated that administration of corticosteroids to patients with cirrhosis who were in septic shock improved their survival while other studies found no benefit [3, 19-21]. We did not aim to evaluate the effect of corticosteroid medication since all of the patients in this trial were stable. To assess the impact of corticosteroid therapy in cirrhotic patients with AI, more prospective randomized clinical trials are needed.

Strengths of the current study include the relatively large sample size with different etiologies for cirrhosis. It is also one of the few studies to evaluate the adrenal function and associated variables in stable cirrhotic patients in the outpatient setting.

Our study's main limitation is that we tested total cortisol rather than free cortisol in response to Synacthen stimulation, which may have led to overestimation of AI in our patients with low albumin.

Conclusions

Adrenal insufficiency is common among cirrhotic patients even in hemodynamically stable individuals. It is not related to the etiology of cirrhosis but is related to the severity of liver disease and the degree of hyponatremia. These results could provide a wider research field for improving the treatment modalities of hemodynamically stable patients with liver cirrhosis. We recommend measuring free cortisol levels for more accurate estimation of the prevalence of AI. Further research should look into the impact of medical treatment for AI on the management of hyponatremia, circulatory failure, and the avoidance of cirrhosis-related

comorbidities such as hepatorenal syndrome. More studies are recommended to determine the impact of AI on clinical outcomes in stable cirrhotic patients.

Data sharing statement

Data for this study are available for sharing on reasonable request from the primary investigator R.N.

Funding source

Disclosure

The authors declare no conflict of interest.

References

1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014; 383: 1749-1761.
2. Rinaldi L, Milione S, Fascione MC, et al. Clinical analysis of patients of cirrhosis complicated with adrenal insufficiency. Eur Rev Med Pharmacol Sci 2016; 20: 4183-4184.
3. Rakici H. Adrenal insufficiency in cirrhosis patients: evaluation of 108 case series. Euroasian J Hepatogastroenterol 2017; 7: 150-153.
4. Park SH, Joo MS, Kim BH, et al. Clinical characteristics and prevalence of adrenal insufficiency in hemodynamically stable patients with cirrhosis. Med (United States) 2018; 97: 1-5.
5. Moini M, Yazdani Sarvestani M, Shams M, et al. Evaluation of adrenal function in nonhospitalized patients with cirrhosis. Can J Gastroenterol Hepatol 2017; 2017: 2354253.
6. Nandish HK, Arun CS, Nair HR, et al. Adrenal insufficiency in decompensated cirrhotic patients without infection: Prevalence, predictors and impact on mortality. J R Coll Physicians Edinb 2019; 49: 277-281.
7. Acevedo J, Fernández J, Prado V, et al. Relative adrenal insufficiency in decompensated cirrhosis: Relationship to short-term risk of severe sepsis, hepatorenal syndrome, and death. Hepatology 2013; 58: 1757-1765.
8. Singh RR, Walia R, Sachdeva N, et al. Relative adrenal insufficiency in cirrhotic patients with ascites (hepatoadrenal syndrome). Dig Liver Dis 2018; 50: 1232-1237.
9. Hawley JM, Owen LJ, Lockhart SJ, et al. Serum cortisol: An up-to-date assessment of routine assay performance. Clin Chem 2016; 62: 1220-1229.
10. Ray G, Bhargav PM. A study of hormonal abnormalities in chronic liver disease. J Assoc Physicians India 2019; 67 (June): 47-52.
11. Galbois A, Rudler M, Massard J, et al. Assessment of adrenal function in cirrhotic patients: Salivary cortisol should be preferred. J Hepatol 2010; 52: 839-845.
12. Thevenot T, Dorin R, Monnet E, et al. High serum levels of free cortisol indicate severity of cirrhosis in hemodynamically stable patients. J Gastroenterol Hepatol 2012; 27: 1596-1601.
13. Thevenot T, Borot S, Remy-Martin A, et al. Assessment of adrenal function in cirrhotic patients using concentration of serum-free and salivary cortisol. Liver Int 2011; 31: 425-433.
14. Fede G, Spadaro L, Tomaselli T, et al. Assessment of adrenocortical reserve in stable patients with cirrhosis. J Hepatol 2011; 54: 243-250.
15. Levick C, Aspinall RJ. Prevalence and clinical significance of relative adrenal insufficiency in decompensated cirrhosis. J R Coll Physicians Edinb 2019; 49: 274-276.
16. Galbois A, Rudler M, Massard J, et al. Assessment of adrenal function in cirrhotic patients: Salivary cortisol should be preferred. J Hepatol 2010; 52: 839-845.
17. Schrier RW, Sharma S, Shchekochikhin D. Hyponatraemia: More than just a marker of disease severity? Nat Rev Nephrol 2013; 9: 37-50.
18. John S, Thuluvath PJ. Hyponatremia in cirrhosis: Pathophysiology and management. World J Gastroenterol 2015; 21: 3197-3205.
19. Trifan A, Chiriac S, Stanciu C. Update on adrenal insufficiency in patients with liver cirrhosis. World J Gastroenterol 2013; 19: 445-456.
20. Fede G, Spadaro L, Tomaselli T, et al. Adrenocortical dysfunction in liver disease: A systematic review. Hepatology 2012; 55: 1282-1291.
21. Arabi YM, Aljumah A, Dabbagh O, et al. Low-dose hydrocortisone in patients with cirrhosis and septic shock: A randomized controlled trial. CMAJ 2010; 182: 1971-1977.